

## Complementary Roles of Slow-Wave Sleep and Rapid Eye Movement Sleep in Emotional Memory Consolidation

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**Although rapid eye movement sleep (REM) is regularly implicated in emotional memory consolidation, the role of slow-wave sleep (SWS) in this process is largely uncharacterized. In the present study, we investigated the relative impacts of nocturnal SWS and REM upon the consolidation of emotional memories using functional magnetic resonance imaging (fMRI) and polysomnography (PSG). Participants encoded emotionally positive, negative, and neutral images (remote memories) before a night of PSG-monitored sleep. Twenty-four hours later, they encoded a second set of images (recent memories) immediately before a recognition test in an MRI scanner. SWS predicted superior memory for remote negative images and a reduction in right hippocampal responses during the recollection of these items. REM, however, predicted an overnight increase in hippocampal–neocortical connectivity associated with negative remote memory. These findings provide physiological support for sequential views of sleep-dependent memory processing, demonstrating that SWS and REM serve distinct but complementary functions in consolidation. Furthermore, these findings extend those ideas to emotional memory by showing that, once selectively reorganized away from the hippocampus during SWS, emotionally aversive representations undergo a comparably targeted process during subsequent REM.**

**Keywords:** hippocampus, neocortex, reorganization, sleep

### Introduction

In recent years, a surge of experimental evidence has led to the general consensus that memory consolidation processes are supported by sleep (Maquet 2001; Gais and Born 2004; Stickgold 2005; Gais et al. 2006; Tucker et al. 2006; Walker 2008; Diekelmann and Born 2010; Cairney et al. 2011). The active systems model of consolidation suggests that newly formed memories are actively reorganized during slow-wave sleep (SWS), such that the retrieval of consolidated representations no longer depends upon the hippocampus, but instead draws more directly upon neocortical networks (Born et al. 2006, Born 2010; Diekelmann et al. 2009, 2011; Born 2010; ; Born and Wilhelm 2012; Rasch and Born 2013). Despite support for this model at behavioral (Plihal and Born 1997, 1999; Marshall et al. 2004, 2006; Peigneux et al. 2004) and functional levels (Takashima et al. 2006), the precise mechanisms underpinning sleep-specific memory processes remain a matter of intense debate, with some suggesting that overnight consolidation may actually depend on the sequential influences of both SWS and rapid eye movement sleep (REM) (Giuditta et al. 1995; Ambrosini and Giuditta 2001; Walker and Stickgold 2010).

Several studies have suggested that emotional memories are preferentially consolidated during sleep (Wagner et al. 2001, 2006; Hu et al. 2006; Payne et al. 2008), and that the brain

regions supporting such memories undergo distinct changes overnight, when compared with their neutral counterparts (Sterpenich et al. 2007, 2009; Lewis et al. 2011; Payne and Kensinger 2011). Although some work has implicated REM in emotional memory consolidation (Wagner et al. 2001; Nishida et al. 2009; Payne et al. 2012; Groch et al. 2013), other studies have failed to demonstrate such a relationship (Baran et al. 2012), and research addressing the role of SWS in this process is particularly limited (Groch et al. 2011). Moreover, since recent work has suggested that highly salient memories are selectively supported by slow oscillation activity (Wilhelm et al. 2011), it is possible that SWS may facilitate the consolidation of inherently salient emotional information.

The current study aimed to examine the roles of both SWS and REM in the overnight consolidation of emotional memories. We used a picture-learning task, in which participants encoded emotionally positive, negative, and neutral images before a night of polysomnographically monitored sleep (remote memories). Twenty-four hours later, participants encoded a second equivalent set of images (recent memories) immediately before a recognition test with functional magnetic resonance imaging (fMRI). In previous work, Takashima et al. (2006) revealed a SWS-related reduction of hippocampal responses during the retrieval of emotionally neutral images. Drawing upon both this finding and work suggesting that SWS supports the targeted consolidation of highly salient information (Wilhelm et al. 2011; Born and Wilhelm 2012), we predicted that SWS would be associated with a reduction in hippocampal responses during the retrieval of emotionally negative images, reflecting a selective systems-level reorganization of these intrinsically relevant representations. In keeping with sequential views of consolidation (Giuditta et al. 1995; Ambrosini and Giuditta 2001; Walker and Stickgold 2010), we expected that REM would offer complementary support to the consolidation processes in SWS, and that this would be apparent from REM-related changes in the responses of areas where activity had been mediated by SWS.

### Materials and Methods

#### Participants

Twenty-two (12 males) healthy participants aged 19–28 years (mean age = 22.47 years, SD ± 2.37) were recruited on a voluntary basis. Six participants were excluded from the study for reasons including: poor task performance (3), insufficient overnight sleep (2), and failing the prescan medical (1). Therefore, we present data from the remaining 16 participants (10 males) aged 19–28 years (mean age = 22.67 years, SD ± 2.47). As evaluated with prestudy screening questionnaires and telephone interviews, participants had no history of neurological, depressive, or sleep disorders, and reported a regular sleep pattern over the

month preceding the study. Aside from females using the contraceptive pill, participants were also free from any form of medication. Participants followed a standardized sleep schedule for 3 days prior to the experiment during which they went to bed before 11 PM and rose the following morning at 7 AM. To ensure compliance, participants recorded lights out and wake times on each day of the scheduled period, together with subjective estimations of hours slept throughout the night and information relating to any acute sleep disturbances, in laboratory-issued sleep diaries. All participants were native English speakers and were right handed, as indicated by a score of 80% or higher on the Edinburgh Handedness Inventory (Oldfield 1971). Written informed consent was acquired from all participants in accordance with the research ethics committees of the University of Manchester and the University of Liverpool. Participants were paid £50 for their time and were required to remain alcohol and caffeine free from 24 h prior to the study start and throughout the study period. Before any scanning took place, participants were assessed by a qualified radiographer to ensure their safety within an MR environment. Participants were asked not to nap on experiment days, and the Stanford Sleepiness Scale (Hoddes et al. 1973) was used to check for differences in alertness between the experimental sessions. Because time spent in SWS predicts homeostatic sleep pressure, it was also important to ensure that any observed relationship between SWS and memory consolidation was not simply the result of varying levels of sleep pressure. Therefore, using an approach adopted in previous work (Durrant et al. 2011, 2013), we examined correlations between the amount of SWS obtained by participants overnight and their response times (RTs) during subsequent memory testing, with an absence of relationship between these measures indicating that SWS-related effects could not be attributed to participant differences in sleep pressure.

### Stimuli

Two hundred seventy images were selected from the International Affective Picture System (IAPS) (Lang et al. 2005) for use in this study. IAPS images range from everyday scenes to images of injury, violence, and contaminated foods, and each are rated on 9-point scales for emotional valence (1 = negative; 5 = neutral; 9 = positive) and arousal (1 = calm; 9 = exciting). Images were selected on the basis of their valence rating and placed into 1 of 3 sets: “positive,” “negative,” or “neutral,” which each contained 90 images. Thus, the mean valence rating of each image set was significantly different (positive: 7.55 [SD  $\pm$  0.36], negative: 2.40 [SD  $\pm$  0.34], neutral: 5.03 [SD  $\pm$  0.19],  $F_{2,267} = 6355.03$ ;  $P < 0.0001$ ). Although the mean arousal rating of the neutral

image set was significantly different from that of the emotional image sets (positive: 5.35 [SD  $\pm$  0.80], negative: 5.39 [SD  $\pm$  0.48], neutral: 3.10 [SD  $\pm$  0.52],  $F_{2,267} = 405.40$ ;  $P < 0.0001$ ), the difference in arousal rating between positive and negative image sets alone was not significant ( $t_{(89)} = 0.34$ ;  $P = 0.73$ ).

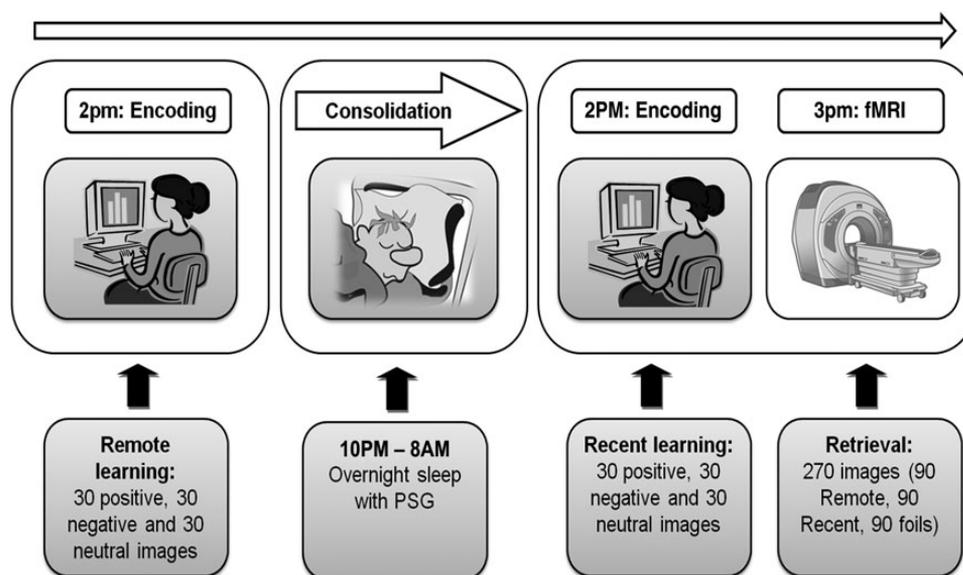
One hundred eighty images (60 positive, 60 negative, 60 neutral) were used for the encoding and retrieval phase, while the remaining 90 images (30 positive, 30 negative, 30 neutral) were used as foils in the retrieval phase alone. Of those images used for encoding, half were presented 24 h prior to retrieval and referred to as “remote” images while the other half, known as “recent” images, were presented 30 min prior to retrieval. The order in which these subsets were used (i.e., as remote images or recent images) was counterbalanced across participants.

### Experimental Protocol

All participants undertook 2 experimental sessions, separated by a period of 24 ( $\pm$ 1.5) h. The first took place at the Manchester Sleep Laboratory, University of Manchester, while the second took place at the Magnetic Resonance and Image Analysis Research Centre (MARIARC), University of Liverpool. Before arriving for the first study session, participants were explicitly informed of all the experimental procedures, including the memory tests. The experimental design is summarized in Figure 1.

#### Session 1 (Remote Encoding)

The first experimental session began at 2 PM ( $\pm$ 30 min) and lasted ~25 min. Here, participants were presented with 90 photographic images on a computer screen (30 positive, 30 negative, and 30 neutral) in random order twice, with a short interval (<1 min) between encoding runs. At the beginning of the encoding task, participants saw a black screen with a white crosshair in the center for 2000 ms. They were then presented with the first image for 3000 ms, which was followed by the black screen and white crosshair for another 2000 ms until the next image was presented. This pattern continued for each remaining image until the end of the task. In 1 encoding run, using the corresponding keys on the keyboard, participants were asked to rate the images in terms of their emotional valence on a scale of 1–7 (1 = highly negative, 4 = neutral, and 7 = highly positive), while in the other, participants were asked to rate the same images for emotional arousal, again on a scale of 1–7 (1 = nonarousing or calm and 7 = highly arousing or exciting). Participants were asked to respond as quickly and



**Figure 1.** Study procedures. In the first session, participants encoded 90 (30 positive, 30 negative, and 30 neutral) images and then returned in the evening for overnight sleep with PSG monitoring. The next day, participants encoded another 90 images before completing a recognition task for all previously learned images in the MRI scanner.

accurately as possible, and were advised that they could make their responses during either the presentation of the image or the subsequent crosshair. The order of rating type (i.e., valence or arousal rating in the first or second encoding run) was counterbalanced across participants. On completing session 1, participants were free to go about their usual daily activities.

#### Overnight Sleep

Participants returned to the Manchester Sleep Laboratory at 10 PM, where they were connected to a polysomnography (PSG) unit before being left to sleep in a darkened bedroom until 8 AM the next morning. After waking, participants were disconnected from the PSG unit and given a 2-h break before traveling to the MRI scanner for the second experimental session.

#### Session 2 (Recent Encoding and Retrieval)

At 2 PM ( $\pm 1$  h) the next day, participants repeated the procedures of session 1 but with a new batch of 90 images. Approximately 30 min after completing encoding ( $3\text{pm} \pm 1$  h), participants began the retrieval phase, which took place inside the MRI scanner. The retrieval test was in the form of a recognition task, which encompassed all previously encoded remote and recent images and an additional 90 unseen foils (30 positive, 30 negative, and 30 neutral), making a total of 270 images. The retrieval phase was divided into 2 scanning sessions, with a short ( $<1$  min) break placed between each. Thus, both sessions consisted of 90 encoded images and 45 foils presented in a randomized order. At the beginning of the retrieval task, participants saw a black screen with a white crosshair in the center for 2000 ms. They were then presented with the first image for 1000 ms, which was followed by the black screen and white crosshair for another 2000 ms until the next image was presented. This pattern continued for each remaining image until the end of the task. For each presented image, participants were required to make a remember/know/new judgment (Tulving 1985) using a 3-button keypad which they held in their right hand. A “remember” (R) response indicated that participants could consciously recollect seeing the image in one of the previous encoding sessions. A “know” (K) response indicated that participants knew that they had seen the image at encoding, but could not retrieve any contextual details about its occurrence. Finally, a “new” (N) response indicated that participants believed they had not seen the image in either encoding session. Participants were asked to respond as quickly and accurately as possible, and were advised that they could make their responses during either the presentation of the image or the subsequent crosshair. The encoding and retrieval tasks are illustrated in Figure 2.

In keeping with similar work (Takashima et al. 2006), all remote and recent images were seen only twice, once in the encoding session and once in the retrieval test. This methodology ensures that memory bias cannot arise from unbalanced stimuli exposure, as would result from an immediate retrieval test in session 1. However, it also meant we were unable to obtain a measure of immediate memory for the remote images, and must therefore assume that these were encoded in an identical manner to their recent counterparts.

#### Equipment

##### Experimental Task

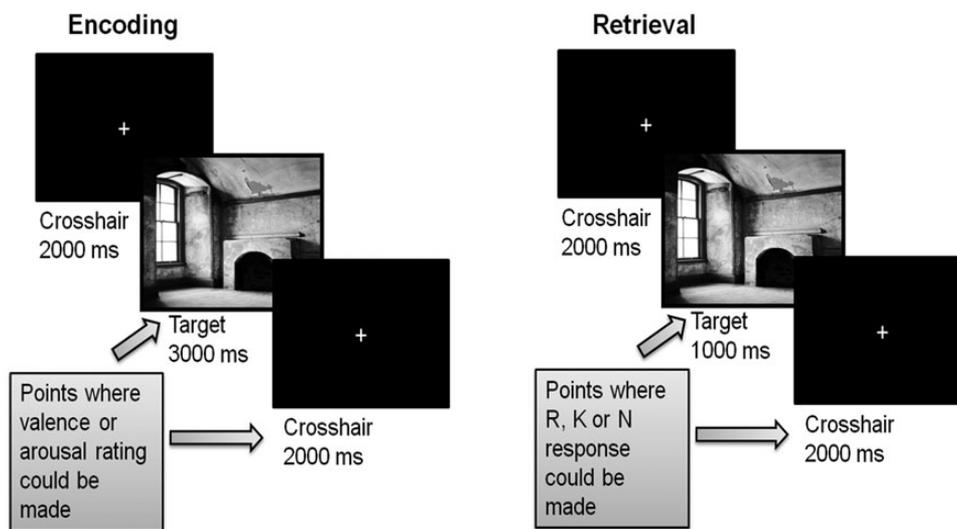
The experimental tasks were created using Cogent 2000 developed at the functional imaging laboratory (FIL), University College London. The tasks were written and implemented using MatLab© version 6.5 on a Toshiba Satellite Pro laptop with a 13” screen. During the encoding sessions, participant responses were recorded using the laptop keyboard, while retrieval session responses were recorded with a serial multibutton box attached to a Domino 2 microcontroller from Micromint© with a temporal resolution of  $\sim 1$  ms. The order of buttons used in the retrieval task was counterbalanced across participants.

##### Polysomnography

Sleep monitoring was carried out using an Embla© N7000 PSG system, with silver–silver chloride (Ag–AgCl) electrodes attached using EC2© electrogel after the scalp was cleaned using NuPrep© exfoliating agent. Scalp electrodes were attached according to the international 10–20 system at 6 standardized locations: central (C3 and C4), frontal (F3 and F4), and occipital (O1 and O2), and each was referenced to the contralateral mastoid (A1 or A2). Left and right electrooculogram, mentalis, and bilateral submentalis electromyogram, and a ground electrode were also attached. All electrodes were verified to have a connection impedance of  $<5$  k $\Omega$ . All signals were digitally sampled at a rate of 200 Hz.

##### fMRI Data Acquisition

Event-related fMRI data were attained using a Siemens MAGNETOM Trio 3 T Allegra MR scanner with an 8-channel head coil. Stimuli were projected onto a screen at the rear of the magnet bore and comfortably viewed with an angled mirror attached to the head coil. Blood oxygen level-dependent (BOLD) signal was recorded using  $T_2^*$ -weighted fMRI images obtained with a gradient echo-planar sequence (EPI). Fifty oblique transaxial slices tilted at  $15^\circ$  were acquired in an ascending



**Figure 2.** Encoding and retrieval tasks. At encoding, participants were required to rate each image in terms of its emotional valence (unpleasant–pleasant) and emotional arousal (calm–exciting). At retrieval, participants were required to indicate if they recognized the image with recollection (R response) or familiarity (K response), or if they thought that the image was new (N response).

sequence with a voxel size of  $3 \times 3 \times 2.8 \text{ mm}^3$  including an interslice gap of 40%, matrix size of  $64 \times 64$ , TR of 2960 ms, TE of 30 ms, and a flip angle of  $80^\circ$ . A  $T_1$ -weighted structural image was also acquired in the same session for each participant using a 3D IR/GR sequence with a matrix size of  $224 \times 256 \times 176$ , cubic isovoxels of  $1 \text{ mm}^3$ , TR of 2040 ms, TE of 5.57 ms, and a flip angle of  $8^\circ$ .

### Data Analysis

Although our experimental task provided an index of both recollection (R responses) and familiarity (K responses) (Tulving 1985), we were particularly interested in recollection as this has previously shown emotion-specific sensitivity to sleep (Sterpenich et al. 2007), and we therefore made this the primary focus of our investigation. To ensure a high proportion of correct R responses, we used a deep encoding task, with participants viewing all images twice, rating them once for valence and once for arousal. A high proportion of R responses is necessarily associated with a low proportion of K responses, as the 2 are mutually exclusive (Yonelinas 2002). One-sample *t*-tests revealed that, while recollection performance (R hits – R false alarms) was above chance for both remote and recent images, irrespective of emotional valence (all  $P < 0.0001$ ), familiarity performance (K hits – K false alarms) was not (all  $P > 0.2$ ). When R and K responses were combined, memory performance remained above chance for both remote and recent images across all emotional valences (all  $P < 0.0001$ ). Unless otherwise stated, our analyses were therefore focused on recollection.

### Behavior

The sensitivity index ( $d'$ ) [Normalized (hits/(hits + misses)) – Normalized (false alarms/(false alarms + correct rejections))] was calculated for remote and recent images and used as a measure of memory performance. A combination of 2 retention types and 3 emotional valences produced a  $2 \times 3$  repeated-measures ANOVA design with factors “Retention Type” (remote/recent) and “Valence” (positive/negative/neutral).

To further examine the time course of memory consolidation, we created a difference measure, which we refer to as “behavioral consolidation,” by subtracting recent from remote memory performance ( $d'$ ) for positive, negative, and neutral images. The resulting behavioral consolidation scores provide indices of the emotional memory processes taking place across the 24-h retention delay. These were used to examine relationships between sleep parameters and behavioral change. All behavioral data were analyzed with SPSS version 16.0, and a two-tailed  $P < 0.05$  was considered significant.

### Sleep Scoring

PSG sleep recordings were independently scored by 2 experienced sleep researchers using RemLogic© 1.1 software. Sleep data were categorized into 30-s epochs and scored on the referenced central electrodes (C3–A2 and C4–A1) according to the standardized sleep scoring criteria of Rechtschaffen and Kales (1968), with sleep stages 3 and 4 grouped together as SWS. Scored data were then partitioned in terms of the percentage of total sleep time spent in stage 1 sleep (S1), stage 2 sleep (S2), SWS, and REM. To examine how SWS and REM, which have been previously implicated in the respective consolidation of neutral and emotional declarative memory (Wagner et al. 2001; Hu et al. 2006; Born and Wilhelm 2012), impacted upon subsequent remote memory performance, we separately correlated these sleep parameters with our scores of behavioral consolidation for positive, negative, and neutral images.

### Functional Magnetic Resonance Imaging

Functional imaging data were processed using the Statistical Parametric Mapping 8 software (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK, <http://www.fil.ion.ucl.ac.uk/spm>). To allow for  $T_1$  equilibration effects, the first 3 volumes of each retrieval session were discarded from our analysis. Single-subject EPI volumes were realigned to correct for minor motion artifacts before slice-timing correction, referenced to the middle slice, was carried out. Images were then transformed into standard stereotaxic space, corresponding to the Montreal Neurological Institute (MNI) canonical brain. This was

accomplished by registering the mean EPI volume (acquired during realignment) to SPM8's EPI template and applying the subsequent transform to all image volumes. A spherical Gaussian smoothing kernel with a full-width half-maximum of 8 mm was then applied to the normalized data to attenuate variations in intersubject localization.

Data analysis was conducted with a 2-level, random effects general linear model (GLM) (Friston et al. 1995). To minimize the impact of guessing, we focused on successful recollection (correct R responses) alone. At the first level, our design matrix contained 27 regressors. These were remote recollection (remote-positive-R, remote-negative-R, remote-neutral-R), recent recollection (recent-positive-R, recent-negative-R, recent-neutral-R), remote familiarity (remote-positive-K, remote-negative-K, remote-neutral-K), recent familiarity (recent-positive-K, recent-negative-K, recent-neutral-K), correct rejections (new-positive-N, new-negative-N, new-neutral-N), misses (remote-positive-N, remote-negative-N, remote-neutral-N, recent-positive-N, recent-negative-N, recent-neutral-N), and false alarms (new-positive-R, new-negative-R, new-neutral-R, new-positive-K, new-negative-K, new-neutral-K). Each regressor was convolved with a canonical hemodynamic response function. Movement parameters were included as 6 nonconvolved regressors of no interest. To ensure that our fMRI analysis contained sufficient statistical power, participants with fewer than 10 successful recollection trials for each image combination of retention type (remote/recent) and emotional valence (positive/negative/neutral) were excluded from the study. Three participants were excluded on these grounds. For the 16 participants included in our analysis, mean frequencies of successful remote and recent recollection trials were as follows: remote positive:  $26.06$  [SD  $\pm 2.86$ ], remote negative:  $26.13$  [SD  $\pm 3.01$ ], remote neutral:  $25.63$  [SD  $\pm 3.77$ ], recent positive:  $25.31$  [SD  $\pm 4.38$ ], recent negative:  $26.50$  [SD  $\pm 3.14$ ], recent neutral:  $25.31$  [SD  $\pm 3.59$ ].

Linear *t*-contrasts were calculated at the first level to examine overnight changes in recollection-related brain responses for positive images [positive remote hits <> positive recent hits], negative images [negative remote hits <> negative recent hits], and neutral images [neutral remote hits <> neutral recent hits]. To assess group effects, the resulting contrast images were carried forward to separate second-level one-sample *t*-tests. In order to examine how postlearning SWS or REM influenced overnight changes in recollection-related activity, the contrast images acquired from our first-level analyses were also carried forward to 2 additional sets of second-level one-sample *t*-tests where SWS was included as a covariate in one set, and REM as a covariate in the other set. Accordingly, activation changes represented a SWS- or REM-dependent modification in the neural architecture of emotionally positive, negative, or neutral memory recollection.

Data were thresholded at a whole-brain-corrected significance level of  $P < 0.05$ . This was achieved by using an uncorrected voxel-level threshold of  $P < 0.001$  in combination with a cluster extent threshold of  $k = 16$  voxels, as determined by a Monte-Carlo Simulation with 1000 iterations (Slotnick et al. 2003). Because the hippocampus has been previously implicated in sleep-dependent changes to the associative neural trace of declarative memory (Takashima et al. 2006; Gais et al. 2007; Sterpenich et al. 2007), we were specifically interested in responses within this structure. We therefore conducted additional voxel-wise bilateral region of interest (ROI) analyses to examine responses in the hippocampus in more detail [ $P < 0.05$  family-wise error (FWE) corrected;  $k = 5$  voxels]. These were carried out using hippocampal masks from the automated anatomical labeling templates (Tzourio-Mazoyer et al. 2002), as implemented within the Wake Forest University (WFU) pickatlas software version 3.0 (Maldjian et al. 2003).

### Functional Connectivity

We used a psychophysiological interaction (PPI) to examine SWS- or REM-related changes in connectivity between areas of the hippocampus that had already shown strong sensitivity to SWS in local functional activations and other regions of the brain. Accordingly, the peak hippocampal coordinates from the previous ROI analysis that had yielded the strongest SWS-related change in hippocampal activity [Negative Remote hits > Negative Recent hits  $\times$  SWS] were used to create a 6-mm-radius volume of interest in the right hippocampus ( $x, y, z$  (mm): 27, –10, –17) of each participant, from which the time series was extracted. The deconvolved time series were then multiplied by contrasts for the effect of remote recollection for positive images

[positive remote hits > positive recent hits], negative images [negative remote hits > negative recent hits], and neutral images [neutral remote hits > neutral recent hits], forming 3 PPIs. As such, the resulting first-level GLM analyses contained a psychological factor (remote > recent recollection), a physiological factor (the deconvolved time series), and the interaction of these (psychological  $\times$  physiological) as regressors. The 6 movement parameters were also included as nonconvolved regressors of no interest. Linear *t*-contrasts were calculated at the first level to assess how recollection-related patterns of connectivity between the right hippocampus and other regions of the brain changed over sleep for positive images [positive remote hits <> positive recent hits], negative images [negative remote hits <> negative recent hits], and neutral images [neutral remote hits <> neutral recent hits]. The resulting interaction contrast maps were then taken forward to separate second-level one-sample *t*-tests for an examination of group effects. To investigate how postlearning SWS or REM influenced overnight changes in hippocampal connectivity, the first-level contrast maps were also carried forward to 2 additional sets of second-level, one-sample *t*-tests, where one set included SWS as a covariate and the other set included REM as a covariate. Activation changes therefore, represented a SWS- or a REM-related alteration of hippocampal connectivity associated with emotionally positive, negative, or neutral memory recollection. As with our localized analyses, our connectivity analyses were thresholded at a whole-brain corrected significance level of  $P < 0.05$ , achieved by combining an uncorrected voxel-level threshold of  $P < 0.001$  with a cluster extent threshold of  $k = 16$  voxels, as determined by a Monte-Carlo Simulation with 1000 iterations (Slotnick et al. 2003).

## Results

### Sleep Patterns and Alertness

Sleep diaries revealed that participants had adhered to our standardized sleep schedule throughout the 3 days prior to the experiment and had not suffered any major acute sleep disturbance. The mean number of hours slept on the night preceding the first experimental session was 7.84 [SD  $\pm$  0.85], and the mean estimation of hours sleep obtained in a typical night was 7.47 [SD  $\pm$  0.50]. The difference between these 2 measures was not significant ( $t_{(15)} = 1.54$ ;  $P = 0.15$ ), confirming that participants' prestudy sleep had not deviated from their usual practices. Mean alertness scores, as obtained with the Stanford Sleepiness Scale, showed no significant difference between session 1 (2.25 [SD  $\pm$  0.77]) and session 2 (2.00 [SD  $\pm$  0.52]) ( $t_{(15)} = 1.00$ ;  $P = 0.33$ ). In addition, no significant correlation was found between the SWS obtained overnight and RTs for remote or recent images in the subsequent retrieval test, irrespective of image valence (remote positive:  $r = -0.13$ ;  $P = 0.64$ , remote negative:  $r = -0.20$ ;  $P = 0.46$ , remote neutral:  $r = -0.13$ ;  $P = 0.64$ , recent positive:  $r = -0.14$ ;  $P = 0.62$ , recent negative:  $r = -0.22$ ;  $P = 0.41$ , recent neutral:  $r = -0.12$ ;  $P = 0.66$ ). Taken together with the data obtained from participant sleep diaries, these results indicate that any sleep-related effects were unlikely to have occurred as a result of participant differences in sleep pressure.

### Subjective Ratings of Valence and Arousal

The image ratings obtained at encoding were also examined to ensure that subjective ratings of valence and arousal were in keeping with those used to initially categorize images as positive, negative, or neutral (Lang et al. 2005). The mean valence ratings were significantly different for each image set (positive: 5.60 [SD  $\pm$  0.35], negative: 2.04 [SD  $\pm$  0.54], neutral: 3.94 [SD  $\pm$  0.40],  $F_{2,118} = 1045.78$ ;  $P < 0.0001$ ), as were mean arousal

ratings (positive: 4.69 [SD  $\pm$  0.71], negative: 5.30 [SD  $\pm$  0.78], neutral: 2.34 [SD  $\pm$  0.89],  $F_{2,118} = 233.15$ ;  $P < 0.0001$ ). Participant ratings also revealed that negative images were associated with a significantly greater degree of arousal than positive images ( $t_{(59)} = 4.44$ ;  $P < 0.0001$ ).

### Experimental Findings

As described in the Materials and Methods, familiarity performance (K responses) for both remote and recent images did not differ from chance, irrespective of emotional valence (all  $P > 0.2$ ), indicating that recognition performance was driven by recollection (R responses). Therefore, unless otherwise stated, the results described in this section are exclusively focused on recollection.

### Memory Performance

A  $2 \times 3$  repeated-measures ANOVA, with factors "Retention Type" (remote/recent) and "Valence" (positive/negative/neutral) showed equivalent memory performance ( $d'$ ) for images encoded 24 h (remote) or 30 min (recent) before retrieval ( $F_{1,15} = 0.02$ ;  $P = 0.89$ ). Memory performance was also unaffected by image valence ( $F_{2,30} = 0.42$ ;  $P = 0.66$ ), and there was no interaction between factors ( $F_{2,30} = 0.07$ ;  $P = 0.94$ ). The ANOVA was repeated with R and K responses combined. Again, this revealed no main effect of Retention Type ( $F_{1,15} = 0.12$ ;  $P = 0.74$ ), no main effect of Valence ( $F_{2,30} = 0.88$ ;  $P = 0.43$ ), and no interaction between factors ( $F_{2,30} = 0.02$ ;  $P = 0.98$ ). Behavioral data are available in Table 1.

### Sleep Parameters

PSG data revealed that participants spent the following percentages of total sleep time in each stage of sleep (mean): S1 = 14.31 [SD  $\pm$  8.87], S2 = 44.44 [SD  $\pm$  8.83], SWS = 20.26 [SD  $\pm$  4.05], REM = 20.98 [SD  $\pm$  5.01]. SWS predicted the behavioral consolidation of negative memories ( $r = 0.57$ ;  $P = 0.02$ ), suggesting that the offline processing of such memories may have been mediated by this sleep stage (see Fig. 3A). In contrast, REM was associated with less behavioral consolidation of positive memories ( $r = -0.58$ ;  $P = 0.018$ ), suggesting that mnemonic processes unique to this sleep stage may have inhibited the stabilization of emotionally positive material (see Fig. 3B). Care should be taken when drawing interpretations from these correlations; however, as one-sample *t*-tests revealed no group-level effect of behavioral consolidation (remote  $d'$  - recent  $d'$ ) for positive, negative, or neutral images (all  $P > 0.8$ ), and no significant difference in this measure was found between valences ( $F_{2,30} = 0.07$ ;  $P = 0.94$ ).

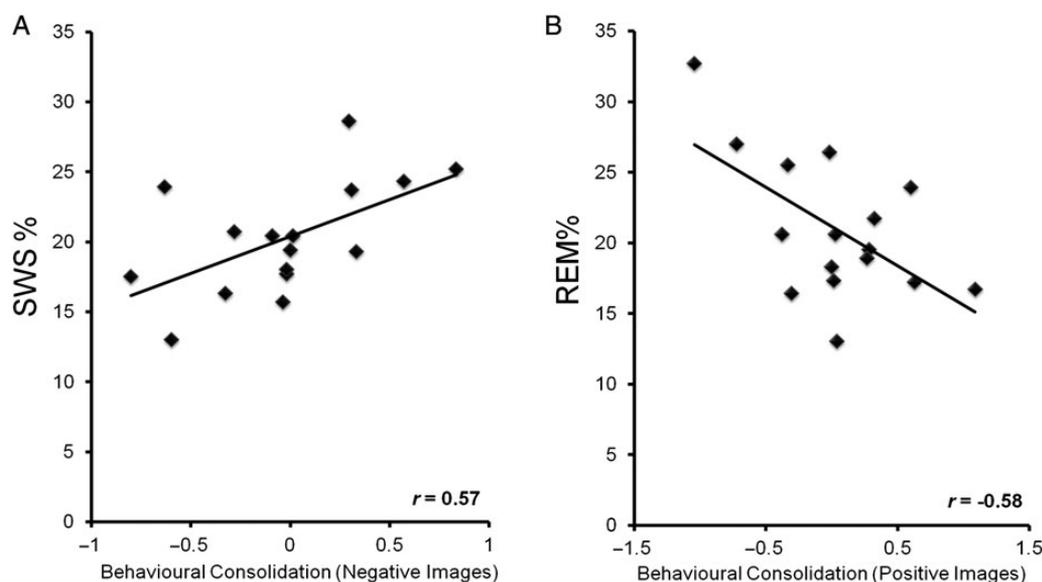
We found no evidence of a predictive relationship between SWS and the behavioral consolidation of positive ( $r = 0.04$ ;  $P = 0.88$ ) or neutral ( $r = -0.15$ ;  $P = 0.58$ ) memories, or between REM and the behavioral consolidation of negative ( $r = -0.25$ ;  $P = 0.35$ ) or neutral ( $r = 0.24$ ;  $P = 0.37$ ) memories, and no significant correlation was found between the percentages of total sleep time spent in SWS and REM ( $r = -0.22$ ;  $P = 0.41$ ).

### Functional Imaging

To determine how SWS and REM influenced the consolidation of emotionally positive, negative, and neutral memories, we included these sleep parameters as covariates in 2 separate whole-brain fMRI analyses [remote hits <> recent hits]. For emotionally negative images, SWS mediated a reduction of recollection-related activity in the right hippocampus (see

Table 1					
Behavioral data					
	Hits (%)	Miss (%)	CR (%)	FA (%)	$d'$
Positive images					
R: Remote	86.88 ( $\pm 9.54$ )	4.38 ( $\pm 5.54$ )	85.00 ( $\pm 9.74$ )	3.96 ( $\pm 3.89$ )	3.47 ( $\pm 0.46$ )
R: Recent	84.38 ( $\pm 14.59$ )	3.96 ( $\pm 2.78$ )			3.44 ( $\pm 0.36$ )
K: Remote	6.46 ( $\pm 7.65$ )			8.33 ( $\pm 8.34$ )	
K: Recent	9.17 ( $\pm 13.69$ )				
Negative images					
R: Remote	87.08 ( $\pm 10.03$ )	5.21 ( $\pm 5.57$ )	88.33 (10.54)	4.38 (4.34)	3.37 ( $\pm 0.45$ )
R: Recent	88.33 ( $\pm 10.47$ )	4.58 ( $\pm 4.19$ )			3.40 ( $\pm 0.53$ )
K: Remote	5.42 ( $\pm 7.59$ )			5.00 ( $\pm 7.50$ )	
K: Recent	4.38 ( $\pm 7.67$ )				
Neutral images					
R: Remote	85.42 ( $\pm 12.58$ )	4.79 ( $\pm 4.71$ )	85.42 ( $\pm 12.64$ )	3.13 ( $\pm 3.10$ )	3.45 ( $\pm 0.44$ )
R: Recent	84.38 ( $\pm 11.97$ )	4.38 ( $\pm 4.51$ )			3.48 ( $\pm 0.38$ )
K: Remote	6.88 ( $\pm 10.92$ )			9.17 ( $\pm 12.02$ )	
K: Recent	8.33 ( $\pm 12.05$ )				

Recollection (R) and familiarity (K) performance for remote and recent images (mean  $\pm$  standard deviation). Because images were not categorized as belonging to the first or second encoding session, false alarm (FA) and correct rejection (CR) values relate to both remote and recent items (Takashima et al. 2006). FAs that received an R or K response are shown separately. Because our analysis was focused on recollection,  $d'$  was only calculated for R responses.



**Figure 3.** Sleep stages and behavioral consolidation ( $d'$ ). (A) Correlation between slow-wave sleep (SWS) and the behavioral consolidation of negative images. (B) Inverse correlation between rapid eye movement sleep (REM) and the behavioral consolidation of positive images. Behavioral consolidation = remote recollection ( $d'$ ) – recent recollection ( $d'$ ).

Table 2A and Fig. 4). Our ROI analyses supported this finding, revealing SWS-related activity decreases in both the right anterior (27, -10, -17) and posterior (30, -28, -8) hippocampus ( $P < 0.05$  FWE corrected;  $k > 5$  voxels). No SWS-related alteration in hippocampal activity was observed for positive or neutral images. REM was not associated with any significant change in recollection-related activity for positive, negative, or neutral images. For completeness, we also conducted an analysis of brain responses associated with the consolidation of positive, negative, and neutral images, which did not include sleep stages as covariates. These results are available in Table 2B.

#### Functional Connectivity

To examine whether the region of the right hippocampus that had shown the strongest SWS-related functional response (27, -10, -17, see Table 2A) also showed SWS- or REM-related

alterations in functional connectivity during the retrieval of emotionally positive, negative, or neutral memories, we conducted 2 separate whole-brain PPI analyses [remote hits  $<>$  recent hits] with these sleep parameters as covariates. SWS predicted a reduction in connectivity between the right hippocampus and left caudate for remote negative images (see Table 3A), while REM predicted an increase in connectivity between the right hippocampus and the superior frontal gyrus for these same images (see Table 3B and Fig. 5). Neither SWS nor REM predicted connectivity changes associated with the consolidation of positive or neutral images.

#### Summary

Although we found no group-level behavioral evidence of emotional memory consolidation across 24 h, the time spent in

specific sleep stages during this retention interval predicted both neural responses and behavioral change. Notably, SWS predicted the behavioral consolidation of negative images and the extent to which functional responses in the right hippocampus during recollection of these items reduced across retention. In contrast, REM predicted less behavioral consolidation of positive images and an increase in hippocampal–neocortical connectivity during the recollection of remote negative memories. These findings provide strong evidence that SWS and

REM serve distinct roles in emotional memory consolidation, with SWS specifically influencing the extent to which the hippocampus is disengaged during emotional recollection, while REM is associated with increased connectivity between the hippocampus and prefrontal cortex.

## Discussion

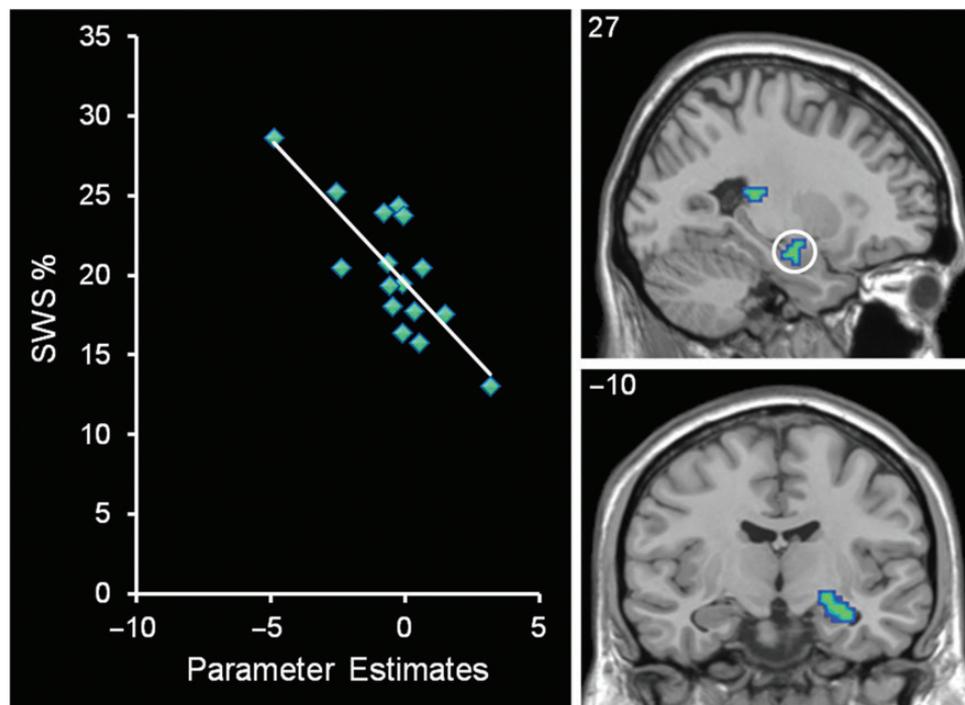
We investigated the roles of SWS and REM in the overnight consolidation of emotionally positive, negative, and neutral image memories. For negative images alone, SWS predicted a reduction of recollection-related activity in the right hippocampus, suggesting that SWS-specific memory processes selectively consolidated image memories with the highest degree of emotional salience. Moreover, REM predicted an increase in functional connectivity between this right hippocampal region and the superior frontal gyrus during the recollection of remote negative memories, suggesting that this sleep stage offered direct support to the selective processing during SWS. Building upon sequential views of sleep-dependent consolidation (Giuditta et al. 1995; Ambrosini and Giuditta 2001), these findings provide strong physiological support for the idea that SWS and REM work in synergy, with each playing a distinct but complementary role in emotional memory processing.

### Slow-Wave Sleep

According to classic consolidation theory (Marr 1971; McClelland et al. 1995; Frankland and Bontempi 2005), the coherent retrieval of recently acquired memories relies upon the hippocampus, which links together highly distributed neocortical memory modules, each coding for different components of an experience. Over time however, neocortical representations are thought to be linked together directly, such that retrieval

Table 2						
fMRI data						
No. of voxels	T	Z	Activation	x, y, z (mm)	Region (laterality)	
(A) Remote hits > Recent hits * SWS						
Positive images						
72	5.91	4.12	Decrease	-57, -64, 28	Angular gyrus (left)	
42	5.85	4.1	Decrease	-42, 14, 43	Middle frontal gyrus (left)	
22	5.75	4.05	Decrease	3, 26, 61	Medial superior frontal gyrus	
Negative images						
23	7.25	4.6	Decrease	-6, -55, -47	Cerebellum (left)	
121	5.38	3.9	Decrease	-15, -49, 4	Calcarine (left)	
32	5.26	3.84	Decrease	27, -10, -17	Hippocampus (right)	
23	4.43	3.45	Decrease	-27, -46, -11	Fusiform gyrus (left)	
Neutral images						
19	4.93	3.69	Decrease	51, 5, 31	Inferior frontal gyrus (right)	
(B) Remote hits > Recent hits						
Positive images						
25	6.26	4.33	Increase	36, 56, 7	Middle frontal gyrus (right)	
25	5.19	3.87	Increase	69, -37, 7	Superior temporal gyrus (right)	
Negative images						
n/a						
Neutral images						
n/a						

Notes: Activation changes associated with the contrast Remote hits > Recent hits. In part A, results are modulated by time spent in slow-wave sleep (SWS); in part B, they are not. All results listed reach a whole-brain-corrected significance level of  $P < 0.05$ , as achieved by combining an uncorrected voxel-level threshold of  $P < 0.001$  with a cluster extent threshold of  $k = 16$  voxels.



**Figure 4.** Slow-wave sleep and hippocampal activity. Slow-wave sleep (SWS) predicted a reduction of activity in the right hippocampus (white circle) during remote negative image recollection. Data are shown at an uncorrected voxel-level threshold of  $P < 0.001$  with a cluster extent threshold of  $k = 16$  voxels.

eventually becomes independent of the hippocampus. An adaptation of this theory, known as active systems consolidation (Born et al. 2006; Diekelmann et al. 2009; Born 2010; Diekelmann and Born 2010; Born and Wilhelm 2012; Rasch and Born 2013), proposes that memory replay during SWS facilitates the weakening of hippocampal–neocortical memory connections, and ultimately mediates a shift in retrieval dependency from the hippocampus to the neocortex. While this model is well supported by experimental research (Plihal and Born 1997, 1999; Marshall et al. 2004, 2006; Peigneux et al. 2004), it does not

consider how the emotionality of newly acquired information influences consolidation processes unique to SWS and research addressing this issue is limited, but see Groch et al. (2011).

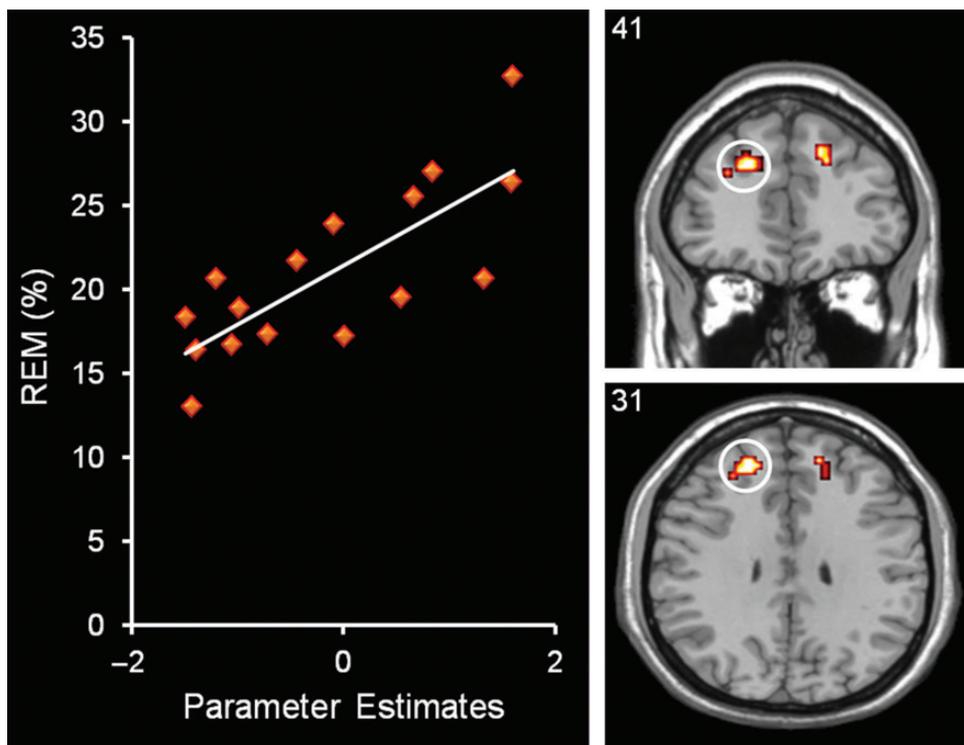
In the present study, we observed a SWS-mediated shift away from hippocampal retrieval dependency, as reflected in a reduction of activity in the right hippocampus during the recollection of emotionally negative images, but not positive or neutral images. This finding builds upon previous research showing that SWS predicts reduced hippocampal dependency during retrieval of purely neutral stimuli (Takashima et al. 2006) by suggesting that this SWS-specific consolidation preferentially targets aversive memory representations. Moreover, the fact that we observed reduced responses in the right hippocampus, rather than left hippocampus as observed previously (Takashima et al. 2006), may also relate to the emotional nature of these negative memories (Dolcos et al. 2005).

Our results relate closely to recent work suggesting that sleep-dependent memory processes operate in a highly selective manner, such that the most relevant or salient representations are consolidated ahead of their less significant counterparts (Born and Wilhelm 2012; Stickgold and Walker 2013). Several studies have reported enhanced consolidation across sleep when memories are manipulated to become more salient, suggesting that inherently valuable information is preferentially processed during offline periods (Fischer and Born 2009; Saletin et al. 2011; Wilhelm et al. 2011; van Dongen et al. 2012). Since unpleasant or aversive memories are highly salient by definition, we speculate that these representations may undergo a similarly selective consolidation process during SWS, which would explain why we observed SWS-related changes in the neural basis of negative, but not neutral, memories. In keeping with this idea, Wilhelm et al. (2011) showed that sleep slow

**Table 3**

PPI data					
No. of voxels	T	Z	Activation	x, y, z (mm)	Region (laterality)
(A) Remote hits > Recent hits × SWS					
Positive images					
n/a					
Negative images					
16	4.93	3.69	Decrease	−6, 8, 7	Caudate (left)
Neutral images					
n/a					
(B) Remote hits > Recent hits × REM					
Positive images					
n/a					
Negative images					
24	5.53	3.96	Increase	−18, 41, 31	Superior frontal gyrus (left)
Neutral images					
n/a					

Notes: (A) The influence of slow-wave sleep (SWS) and (B) rapid eye movement sleep (REM) on the effect of remote image recollection (6-mm-radius spherical seed centered in the right hippocampus: x, y, z (mm): 27, −10, −17). All results listed reach a whole-brain-corrected significance level of  $P < 0.05$ , as achieved by combining an uncorrected voxel-level threshold of  $P < 0.001$  with a cluster extent threshold of  $k = 16$  voxels.



**Figure 5.** Rapid eye movement sleep and hippocampal–neocortical connectivity. Rapid eye movement sleep (REM) predicted an increase in connectivity between the right hippocampus and superior frontal gyrus (white circle) during remote negative image recollection. A 6-mm spherical seed was centered in the right hippocampus (x, y, z (mm): 27, −10, −17). Data are shown at a visualization threshold of  $P < 0.001$  (uncorrected);  $k > 10$  voxels.

oscillation activity increased after the salience of newly formed memories was augmented, and the extent of this increase predicted retrieval performance in a subsequent test. If this is correct however, then emotionally positive memories should be preferentially consolidated during SWS, just like their negative counterparts, but we found no evidence for this. One possible explanation relates to emotional arousal; because participants rated negative images as significantly more arousing than positive images at encoding, it is reasonable to assume that negative images were also most emotionally salient.

### **Rapid Eye Movement Sleep**

Research linking overnight memory benefits to time spent in both SWS and REM has supported the idea that these sleep stages play complementary roles in optimizing the potential efficacy of newly acquired information (Stickgold et al. 2000), an idea which is otherwise known as the sequential hypothesis (Giuditta et al. 1995; Ambrosini and Giuditta 2001). This hypothesis states that, after the consolidation processes of SWS have unfolded, representations are subject to an additional mnemonic process during REM, which further facilitates their storage. Our observation that REM predicts no functional change in localized neural responses but instead predicts increased connectivity in the hippocampal area where responses were modulated by SWS provides physiological support for this idea. Because these results were only observed within emotionally negative items, they also suggest that both SWS and REM target emotionally salient representations. This combined preferential processing could help to explain why emotional material is often selectively protected across a night of sleep (Hu et al. 2006; Payne et al. 2008).

Limbic and forebrain levels of the neurotransmitter acetylcholine are markedly elevated during REM, and are reportedly double the levels observed during quiet wakefulness (Marrosu et al. 1995). Because acetylcholine appears to co-regulate the effects of emotion on consolidation (Intorini-Collison et al. 1996; Power and McGaugh 2002), it has been suggested that REM-related increases in cholinergic activity may promote emotional plasticity (Walker and van der Helm 2009). Furthermore, theta oscillations, which prevail during REM and coordinate communication between the hippocampus and prefrontal cortex (Jones and Wilson 2005), have been suggested as a potential mechanism for the formation of new neural connections. Interestingly, recent work has revealed REM-related increases in creative insight (Cai et al. 2009), presumably through the formation of such connections, a finding that is in good keeping with our observation that REM predicts increased connectivity. Having said this, it is important to note that the brain responses observed during retrieval do not necessarily correspond to activity patterns in specific stages of sleep. For example, while our data revealed a REM-related increase in hippocampal–neocortical connectivity during retrieval, communication between these structures is actually reduced during REM (Axmacher et al. 2008).

In their recent adaptation of the sequential hypothesis, Walker and Stickgold (2010) proposed that REM supports the integration of recently acquired memories, strengthened during the preceding SWS, into rich and generalized networks of related knowledge. As effective integration can presumably be indexed by modifications in the associative neural trace at retrieval (Lewis and Durrant 2011), our observed REM-related

increase in hippocampal connectivity could potentially reflect a form of targeted integration. The experimental task adopted in this study however provides no behavioral metric of integration, and it is unclear why such integrative memory processes would depend on hippocampal connections to prefrontal regions, particularly when anterior temporal areas are most commonly associated with semantic knowledge (Binney et al. 2010; Lambon Ralph et al. 2012). Accordingly, this suggested role for REM in selective mnemonic integration is highly speculative and represents just one potential interpretation of our data. Future studies should examine this in more detail with a task that specifically tests for integration.

SWS was associated with the behavioral consolidation of negative images in the present study, but REM showed no such relationship, instead predicting less behavioral consolidation of positive images. This pattern fails to support the view that SWS and REM facilitate affective consolidation processes in a sequential manner, and is at odds with research linking REM to superior retention of emotional memories (Wagner et al. 2001; Nishida et al. 2009; Payne et al. 2012; Groch et al. 2013). That said, others have also failed to observe such a relationship (Baran et al. 2012), suggesting that these behavioral effects are fragile and may only emerge under very specific experimental conditions. Furthermore, although a number of reports have examined how emotionally negative memories are influenced by postlearning sleep (Hu et al. 2006; Payne et al. 2008; Lewis et al. 2011; Payne and Kensinger 2011), few have addressed the role of sleep in processing positive emotional representations (Sterpenich et al. 2007, 2009) and, to our knowledge, no prior study has revealed a specific link between REM and positive memory. Accordingly, while REM appears to affect emotional memory consolidation, the precise nature of these effects may depend on both the valence of the representation in question and the conditions of learning and retrieval. It is important to note, however, that individual differences in habitual sleep patterns may have affected the relative proportions of time spent in different sleep stages by each participant, meaning that habitual influences cannot be fully excluded when considering the results of this study.

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### **References**

Ambrosini MV, Giuditta A. 2001. Learning and sleep: the sequential hypothesis. *Sleep Med Rev.* 5:477–490.

- Axmacher N, Helmstaedter C, Elger CE, Fell J. 2008. Enhancement of neocortical-medial temporal EEG correlations during non-REM sleep. *Neural Plast.* 2008. Article ID 563028.
- Baran B, Pace-Schott EF, Ericson C, Spencer RMC. 2012. Processing of emotional reactivity and emotional memory over sleep. *J Neurosci.* 32:1035–1042.
- Binney RJ, Embleton KV, Jefferies E, Parker GJM, Lambon Ralph MA. 2010. The ventral and inferolateral aspects of the anterior temporal lobe are crucial in semantic memory: evidence from a novel direct comparison of distortion-corrected fMRI, rTMS, and semantic dementia. *Cereb Cortex.* 20:2728–2738.
- Born J. 2010. Slow-wave sleep and the consolidation of long-term memory. *World J Biol Psychiatry.* 11:16–21.
- Born J, Rasch B, Gais S. 2006. Sleep to remember. *Neuroscientist.* 12: 410–424.
- Born J, Wilhelm I. 2012. System consolidation of memory during sleep. *Psychol Res.* 76:192–203.
- Cai DJ, Mednick SA, Harrison EM, Kanady JC, Mednick SC. 2009. REM, not incubation, improves creativity by priming associative networks. *Proc Natl Acad Sci USA.* 106:10130–10134.
- Cairney SA, Durrant SJ, Musgrove H, Lewis PA. 2011. Sleep and environmental context: interactive effects for memory. *Exp Brain Res.* 214:83–92.
- Diekelmann S, Born J. 2010. The memory function of sleep. *Nat Rev Neurosci.* 11:114–126.
- Diekelmann S, Buchel C, Born J, Rasch B. 2011. Labile or stable: opposing consequences for memory when reactivated during waking and sleep. *Nat Neurosci.* 14:381–386.
- Diekelmann S, Wilhelm I, Born J. 2009. The whats and whens of sleep-dependent memory consolidation. *Sleep Med Rev.* 13:309–321.
- Dolcos F, LaBar KS, Cabeza R. 2005. Remembering one year later: role of the amygdala and the medial temporal lobe memory system in retrieving emotional memories. *Proc Natl Acad Sci USA.* 102:2626–2631.
- Durrant SJ, Cairney SA, Lewis PA. 2013. Overnight consolidation aids the transfer of statistical knowledge from the medial temporal lobe to the striatum. *Cereb Cortex.* 23:2467–2478.
- Durrant SJ, Taylor C, Cairney S, Lewis PA. 2011. Sleep-dependent consolidation of statistical learning. *Neuropsychologia.* 49:1322–1331.
- Fischer S, Born J. 2009. Anticipated reward enhances offline learning during sleep. *J Exp Psychol Learn Mem Cogn.* 35:1586–1593.
- Frankland PW, Bontempi B. 2005. The organization of recent and remote memories. *Nat Rev Neurosci.* 6:119–130.
- Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ. 1995. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp.* 1:153–171.
- Gais S, Albouy G, Boly M, Dang-Vu TT, Darsaud A, Desseilles M, Rauchs G, Schabus M, Sterpenich V, Vandewalle G et al. 2007. Sleep transforms the cerebral trace of declarative memories. *Proc Natl Acad Sci USA.* 104:18778–18783.
- Gais S, Born J. 2004. Declarative memory consolidation: mechanisms acting during human sleep. *Learn Mem.* 11:679–685.
- Gais S, Lucas B, Born J. 2006. Sleep after learning aids memory recall. *Learn Mem.* 13:259–262.
- Giuditta A, Ambrosini MV, Montagnese P, Mandile P, Cotugno M, Grassi Zucconi G, Vescia S. 1995. The sequential hypothesis of the function of sleep. *Behav Brain Res.* 69:157–166.
- Groch S, Wilhelm I, Diekelmann S, Born J. 2013. The role of REM sleep in the processing of emotional memories: evidence from behavior and event-related potentials. *Neurobiol Learn Mem.* 99:1–9.
- Groch S, Wilhelm I, Diekelmann S, Sayk F, Gais S, Born J. 2011. Contribution of norepinephrine to emotional memory consolidation during sleep. *Psychoneuroendocrinology.* 36:1342–1350.
- Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. 1973. Quantification of sleepiness: a new approach. *Psychophysiology.* 10:431–436.
- Hu P, Stylos-Allan M, Walker MP. 2006. Sleep facilitates consolidation of emotional declarative memory. *Psychol Sci.* 17:891–898.
- Introini-Collison IB, Dalmaz C, McGaugh JL. 1996. Amygdala  $\beta$ -noradrenergic influences on memory storage involve cholinergic activation. *Neurobiol Learn Mem.* 65:57–64.
- Jones MW, Wilson MA. 2005. Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. *PLoS Biol.* 3:e402.
- Lambon Ralph MA, Ehsan S, Baker GA, Rogers TT. 2012. Semantic memory is impaired in patients with unilateral anterior temporal lobe resection for temporal lobe epilepsy. *Brain.* 135:242–258.
- Lang PJ, Bradley MM, Cuthbert BN. 2005. International affective picture system (IAPS): affective ratings of pictures and instruction manual. Technical Report A-6. University of Florida, Gainesville, FL.
- Lewis PA, Cairney S, Manning L, Critchley HD. 2011. The impact of overnight consolidation upon memory for emotional and neutral encoding contexts. *Neuropsychologia.* 49:2619–2629.
- Lewis PA, Durrant SJ. 2011. Overlapping memory replay during sleep builds cognitive schemata. *Trends Cogn Sci.* 15:343–351.
- Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage.* 19:1233–1239.
- Maquet P. 2001. The role of sleep in learning and memory. *Science.* 294:1048–1052.
- Marr D. 1971. Simple memory: a theory for archicortex. *Philos Trans R Soc Lond B Biol Sci.* 262:23–81.
- Marrosu F, Portas C, Mascia MS, Casu MA, Fa M, Giagheddu M, Imperato A, Gessa GL. 1995. Microdialysis measurement of cortical and hippocampal acetylcholine release during sleep-wake cycle in freely moving cats. *Brain Res.* 671:329–332.
- Marshall L, Helgadottir H, Molle M, Born J. 2006. Boosting slow oscillations during sleep potentiates memory. *Nature.* 444:610–613.
- Marshall L, Molle M, Hallschmid M, Born J. 2004. Transcranial direct current stimulation during sleep improves declarative memory. *J Neurosci.* 24:9985–9992.
- McClelland JL, McNaughton BL, O'Reilly RC. 1995. Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol Rev.* 102:419–457.
- Nishida M, Pearsall J, Buckner RL, Walker MP. 2009. REM sleep, prefrontal theta, and the consolidation of human emotional memory. *Cereb Cortex.* 19:1158–1166.
- Oldfield RC. 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia.* 9:97–113.
- Payne JD, Chambers AM, Kensinger EA. 2012. Sleep promotes lasting changes in selective memory for emotional scenes. *Front Integr Neurosci.* 6:108.
- Payne JD, Kensinger EA. 2011. Sleep leads to changes in the emotional memory trace: evidence from fMRI. *J Cogn Neurosci.* 23:1285–1297.
- Payne JD, Stickgold R, Swanberg K, Kensinger EA. 2008. Sleep preferentially enhances memory for emotional components of scenes. *Psychol Sci.* 19:781–788.
- Peigneux P, Laureys S, Fuchs S, Collette F, Perrin F, Reggers J, Phillips C, Degueldre C, Del Fiore G, Aerts J et al. 2004. Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron.* 44:535–545.
- Plihal W, Born J. 1997. Effects of early and late nocturnal sleep on declarative and procedural memory. *J Cogn Neurosci.* 9:534–547.
- Plihal W, Born J. 1999. Effects of early and late nocturnal sleep on priming and spatial memory. *Psychophysiology.* 36:571–582.
- Power AE, McGaugh JL. 2002. Cholinergic activation of the basolateral amygdala regulates unlearned freezing behavior in rats. *Behav Brain Res.* 134:307–315.
- Rasch B, Born J. 2013. About sleep's role in memory. *Physiol Rev.* 93: 681–766.
- Rechtschaffen A, Kales A. 1968. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Bethesda (MD): US Department of Health.
- Saletin JM, Goldstein AN, Walker MP. 2011. The role of sleep in directed forgetting and remembering of human memories. *Cereb Cortex.* 21:2534–2541.
- Slotnick SD, Moo LR, Segal JB, Hart J. 2003. Distinct prefrontal cortex activity associated with item memory and source memory for visual shapes. *Brain Res Cogn Brain Res.* 17:75–82.
- Sterpenich V, Albouy G, Boly M, Vandewalle G, Darsaud A, Balteau E, Dang-Vu TT, Desseilles M, D'Argembeau A, Gais S et al. 2007. Sleep-related hippocampo-cortical interplay during emotional memory recollection. *PLoS Biol.* 5:e282.

- Sterpenich V, Albouy G, Darsaud A, Schmidt C, Vandewalle G, Dang Vu TT, Desseilles M, Phillips C, Degueldre C, Baiteau E et al. 2009. Sleep promotes the neural reorganization of remote emotional memory. *J Neurosci*. 29:5143–5152.
- Stickgold R. 2005. Sleep-dependent memory consolidation. *Nature*. 437:1272–1278.
- Stickgold R, Walker MP. 2013. Sleep-dependent memory triage: evolving generalization through selective processing. *Nat Neurosci*. 16:139–145.
- Stickgold R, Whidbee D, Schirmer B, Patel V, Hobson JA. 2000. Visual discrimination task improvement: a multi-step process occurring during sleep. *J Cogn Neurosci*. 12:246–254.
- Takashima A, Petersson KM, Rutters F, Tendolkar I, Jensen O, Zwarts MJ, McNaughton BL, Fernandez G. 2006. Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. *Proc Natl Acad Sci USA*. 103:756–761.
- Tucker MA, Hirota Y, Wamsley EJ, Lau H, Chaklader A, Fishbein W. 2006. A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. *Neurobiol Learn Mem*. 86:241–247.
- Tulving E. 1985. Memory and consciousness. *Can Psychol*. 26:1–12.
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 15:273–289.
- van Dongen EV, Thielen JW, Takashima A, Barth M, Fernández G. 2012. Sleep supports selective retention of associative memories based on relevance for future utilization. *PLoS ONE*. 7:e43426.
- Wagner U, Gais S, Born J. 2001. Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. *Learn Mem*. 8:112–119.
- Wagner U, Hallschmid M, Rasch B, Born J. 2006. Brief sleep after learning keeps emotional memories alive for years. *Biol Psychiatry*. 60:788–790.
- Walker MP. 2008. Sleep-dependent memory processing. *Harv Rev Psychiatry*. 16:287–298.
- Walker MP, Stickgold R. 2010. Overnight alchemy: sleep-dependent memory evolution. *Nat Rev Neurosci*. 11:218.
- Walker MP, van der Helm E. 2009. Overnight therapy? The role of sleep in emotional brain processing. *Psychol Bull*. 135:731–748.
- Wilhelm I, Diekelmann S, Mozlow I, Ayoub A, Mölle M, Born J. 2011. Sleep selectively enhances memory expected to be of future relevance. *J Neurosci*. 31:1563–1569.
- Yonelinas AP. 2002. The nature of recollection and familiarity: a review of 30 years of research. *J Mem Lang*. 46:441–517.