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Title: Complementary roles of slow-wave sleep and rapid eye movement sleep in emotional memory consolidation

Running Title: Sleep and emotional memory consolidation

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Abstract

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 uncharacterised. 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 reorganised away from the hippocampus during SWS, emotionally aversive representations undergo a comparably targeted process during subsequent REM.

Keywords: Hippocampus, Neocortex, Reorganisation, 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 reorganised 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; Diekelmann et al. 2009; Born 2010; Diekelmann et al. 2011; Born and Wilhelm 2012; Rasch and Born 2013). Despite support for this model at behavioural (Plihal and Born 1997; Plihal and Born 1999; Marshall et al. 2004; Peigneux et al. 2004; Marshall et al. 2006), 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; Hu et al. 2006; Wagner et al. 2006; Payne et al. 2008), and that the brain regions supporting such memories undergo distinct changes overnight, as compared to their neutral counterparts (Sterpenich et al. 2007; Sterpenich et al. 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 retrieval of emotionally negative images, reflecting a selective systems-level reorganisation 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 male) healthy participants aged 19-28 years (mean age = 22.47, S.D. ± 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 pre-scan medical (1). Therefore, we present data from the remaining 16 participants (10 male) aged 19-28 years (mean age = 22.67, S.D. ± 2.47). As evaluated with pre-study 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 standardised sleep schedule for three days prior to the experiment during which they went to bed before 11pm and rose the following morning at 7am. 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 hours 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; Durrant et al. 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 and 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 one of three 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 [S.D. ± 0.36], negative: 2.40 [S.D. ± 0.34], neutral: 5.03 [S.D. ± 0.19], $F(2,267) = 6355.03$; $p <0.0001$). Although the mean arousal rating of the neutral image set was significantly different to that of the emotional image sets (positive: 5.35 [S.D. ± 0.80], negative: 5.39 [S.D. ± 0.48], neutral: 3.10 [S.D. ± 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 and 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 hours prior to retrieval and referred to as 'remote' images whilst the other half, known as 'recent' images, were presented 30 minutes 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 two experimental sessions, separated by a period of 24 (± 1.5) hours. The first took place at the Manchester Sleep Laboratory, University of Manchester, whilst 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 summarised in figure 1.

Session one (remote encoding)

The first experimental session began at 2pm (± 30 minutes) and lasted approximately 25 minutes. 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 centre for 2000ms. They were then presented with the first image for 3000ms, which was followed by the black screen and white crosshair for another 2000ms until the next image was presented. This pattern continued for each remaining image until the end of the task. In one 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), whilst in the other, participants were asked to rate the same images for emotional arousal, again on a scale of 1-7 (1 = non-arousing or calm and 7 = highly arousing or exciting). 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 order of rating type (i.e. valence or arousal rating in the first or second encoding run) was counterbalanced across participants. Upon completing session one, participants were free to go about their usual daily activities.

Overnight sleep

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

Session two (recent encoding and retrieval)

At 2pm (± 1 hour) the next day, participants repeated the procedures of session one but with a new batch of 90 images. Approximately 30 minutes after completing encoding (3pm ± 1 hour), 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 two 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 randomised order. At the beginning of the retrieval task, participants saw a black screen with a white crosshair in the centre for 2000ms. They were then presented with the first image for 1000ms, which was followed by the black screen and white crosshair for another 2000ms 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 judgement (Tulving 1985) using a three-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 one. 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, whilst retrieval session responses were recorded with a serial multi-button box attached to a Domino 2 microcontroller from Micromint© with a temporal resolution of approximately 1ms. The order of buttons used in the retrieval task was counterbalanced across participants.

PSG

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 six standardised locations: central (C3 & C4), frontal (F3 & F4) and occipital (O1 & O2), and each was referenced to the contralateral mastoid (A1 or A2). Left and right electrooculagram, mentalis and bilateral submentalis electromyogram, and a ground electrode were also attached. All electrodes were verified to have a connection impedance of less than 5kOhms. All signals were digitally sampled at a rate of 200Hz.

fMRI data acquisition

Event-related fMRI data was attained using a Siemens MAGNETOM Trio 3T 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 T2*-weighted fMRI images obtained with a gradient echo-planar sequence (EPI). Fifty oblique transaxial slices tilted at 15° were acquired in an ascending sequence with a voxel size of 3 x 3 x 2.8 mm^3 including an interslice gap of 40%, matrix size of 64 x 64, TR of 2960ms, TE of 30ms and a flip angle of 80°. A T1-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 x 256 x 176, cubic isovoxels of 1mm^3, TR of 2040ms, TE of 5.57ms and a flip angle of 8°.

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 two 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.

Behaviour

The sensitivity index (*d'*) [Normalised (hits / (hits + misses)) – Normalised (false alarms / (false alarms + correct rejections))] was calculated for remote and recent images and used as a measure of memory performance. A combination of two retention types and three emotional valences produced a 2x3 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 *behavioural consolidation,* by subtracting recent from remote memory performance (*d'*) for positive, negative and neutral images. The resulting behavioural consolidation scores provide indices of the emotional memory processes taking place across the 24 hour retention delay. These were used to examine relationships between sleep parameters and behavioural change. All behavioural data was analysed with SPSS version 16.0 and a two-tailed $p < 0.05$ was considered significant.

Sleep scoring

PSG sleep recordings were independently scored by two experienced sleep researchers using RemLogic© 1.1 software. Sleep data was categorised into 30s epochs and scored on the referenced central electrodes (C3-A2 and C4-A1) according

to the standardised sleep scoring criteria of Rechtschaffen and Kales (1968), with sleep stages three and four grouped together as SWS. Scored data was then partitioned in terms of the percentage of total sleep time spent in stage one sleep (S1), stage two 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 *behavioural consolidation* for positive, negative and neutral images.

fMRI

Functional imaging data was 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 T1 equilibration effects, the first three volumes of each retrieval session were discarded from our analysis. Single subject EPI volumes were realigned to correct for minor motion artefacts 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 8mm was then applied to the normalised data to attenuate variations in inter-subject localisation.

Data analysis was conducted with a two level, random effects general linear model (GLM) (Friston et al. 1995). To minimise 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 haemodynamic response function. Movement parameters were included as six non-convolved 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 [S.D. ± 2.86], remote negative: 26.13 [S.D. ± 3.01], remote neutral: 25.63 [S.D. ± 3.77], recent positive: 25.31 [S.D. ± 4.38], recent negative: 26.50 [S.D. ± 3.14], recent neutral: 25.31 [S.D. ± 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 post-learning SWS or REM influenced overnight changes in recollection-related activity, the contrast images acquired from our first-level analyses were also carried forward to two 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 labelling 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 * SWS] were used to create a 6mm 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 x physiological) as regressors. The six movement parameters were also included as non-convolved 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 post-learning SWS or REM influenced overnight changes in hippocampal connectivity, the first-level contrast maps were also carried forward to two 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 REM-related alteration of hippocampal connectivity associated with emotionally positive, negative or neutral memory recollection. As with our localised 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 standardised sleep schedule throughout the three 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 [S.D. ± 0.85], and the mean estimation of hours sleep obtained in a typical night was 7.47 [S.D. ± 0.50]. The difference between these two measures was not significant (t(15) = 1.54; p = 0.15), confirming that participants' pre-study sleep had not deviated from their usual practices. Mean alertness scores, as obtained with the Stanford Sleepiness Scale, showed no significant difference between session one (2.25 [S.D. ± 0.77]) and session two (2.00 [S.D. ± 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 categorise images as positive, negative or neutral (Lang et al. 2005). Mean valence ratings were significantly different for each image set (positive: 5.60 [S.D. ± 0.35], negative: 2.04 [S.D. ± 0.54], neutral: 3.94 [S.D. ± 0.40], $F(2,118) = 1045.78$; $p < 0.0001$), as were mean arousal ratings (positive: 4.69 [S.D. ± 0.71], negative: 5.30 [S.D. ± 0.78], neutral: 2.34 [S.D. ± 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 2x3 repeated measures ANOVA, with factors 'Retention Type' (remote/recent) and 'Valence' (positive/negative/neutral) showed equivalent memory performance (d') for images encoded 24 hours (remote) or 30 minutes (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). Behavioural data is available in table 1.

TABLE 1 HERE

Sleep parameters

PSG data revealed that participants spent the following percentages of total sleep time in each stage of sleep (mean): S1 = 14.31 [S.D. ± 8.87], S2 = 44.44 [S.D. ± 8.83], SWS = 20.26 [S.D. ± 4.05], REM = 20.98 [S.D. ± 5.01]. SWS predicted the behavioural 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 figure 3A). By contrast, REM was associated with less behavioural consolidation of positive memories (r = -0.58; p = 0.018), suggesting that mnemonic processes unique to this sleep stage may have inhibited the stabilisation of emotionally positive material (see figure 3B). Care should be taken when drawing interpretations from these correlations however, as one sample t-tests revealed no group-level effect of *behavioural 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 behavioural consolidation of positive ($r = 0.04$; $p = 0.88$) or neutral ($r = -0.15$; $p = 0.58$) memories, or between REM and the behavioural 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 two 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 2A and figure 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.

<u>*TABLE 2 HERE*</u>

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 two 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), whilst REM predicted an increase in connectivity between the right hippocampus and the superior frontal gyrus for these same images (see table 3B and figure 5). Neither SWS nor REM predicted connectivity changes associated with the consolidation of positive or neutral images.

TABLE 3 HERE

Summary

Although we found no group-level behavioural evidence of emotional memory consolidation across 24 hours, the time spent in specific sleep stages during this retention interval predicted both neural responses and behavioural change. Notably, SWS predicted the behavioural consolidation of negative images and the extent to which functional responses in the right hippocampus during recollection of these items reduced across retention. By contrast, REM predicted less behavioural consolidation of positive images and an increase in hippocampal-neocortical connectivity during 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 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.

SWS

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 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; Plihal and Born 1999; Marshall et al. 2004; Peigneux et al. 2004; Marshall et al. 2006), 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 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.

REM

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 optimising 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 localised 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 (Introini-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 generalised networks of related knowledge. Since 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 behavioural 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 behavioural consolidation of negative images in the present study, but REM showed no such relationship, instead predicting less behavioural 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 behavioural 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 post-learning 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; Sterpenich et al. 2009) and, to our knowledge, no prior study has revealed a specific link between REM and positive memory. Accordingly, while REM appears to impact upon 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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Tables

Table 1: Behavioural data

Positive images

	Hits %	Miss %	CR %	FA %	d'
R: Remote	86.88 (±9.54)	4.38 (±5.54)	85.00 (±9.74)	3.96 (±3.89)	3.47 (±0.46)
R: Recent	84.38 (±14.59)	3.96 (±2.78)			3.44 (±0.36)
K: Remote	6.46 (±7.65)			8.33 (±8.34)	
K: Recent	9.17 (±13.69)				

Negative images

	Hits %	Miss %	CR %	FA %	d'
R: Remote	87.08 (±10.03)	5.21 (±5.57)	88.33 (10.54)	4.38 (4.34)	3.37 (±0.45)
R: Recent	88.33 (±10.47)	4.58 (±4.19)			3.40 (±0.53)
K: Remote	5.42 (±7.59)			5.00 (±7.50)	
K: Recent	4.38 (±7.67)				

Neutral images

	Hits %	Miss %	CR %	FA %	d'
R: Remote	85.42 (±12.58)	4.79 (±4.71)	85.42 (±12.64)	3.13 (±3.10)	3.45 (±0.44)
R: Recent	84.38 (±11.97)	4.38 (±4.51)			3.48 (±0.38)
K: Remote	6.88 (±10.92)			9.17 (±12.02)	
K: Recent	8.33 (±12.05)				

Recollection (R) and familiarity (K) performance for remote and recent images (mean

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					

± standard deviation). Because images were not categorised 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.

Table 2: fMRI data

Activation changes associated with the contrast Remote hits > Recent hits. In part A

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					

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.

Table 3: PPI data

A) The influence of slow-wave sleep (SWS) and B) rapid eye movement sleep (REM), on the effect of remote image recollection (6mm radius spherical seed centred 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.

Captions to Figures

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.

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 recognised the image with recollection (R response) or familiarity (K response), or if they thought that the image was new (N response).

Figure 3: Sleep stages and behavioural consolidation (*d'*)

(A) Correlation between slow-wave sleep (SWS) and the behavioural consolidation of negative images. (B) Inverse correlation between rapid eye movement sleep (REM) and the behavioural consolidation of positive images. Behavioural consolidation = remote recollection (*d'*) – recent recollection (*d'*).

Figure 4: Slow-wave sleep and hippocampal activity

Slow-wave sleep (SWS) predicted a reduction of activity in the right hippocampus (white ciricle) 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.

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 6mm spherical seed was centred in the right hippocampus (x, y, z, mm: 27, -10, -17). Data are shown at a visualisation threshold of $p < 0.001$ (uncorrected); k > 10 voxels.