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The effect of exogenous cortisol during sleep on the behavioral and neural correlates of emotional memory consolidation in humans

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Summary A host of animal work demonstrates that the retention benefit for emotionally aversive over neutral memories is regulated by glucocorticoid action during memory consolidation. Particularly, glucocorticoids may affect systems-level processes that promote the gradual reorganization of emotional memory traces. These effects remain largely uninvestigated in humans. Therefore, in this functional magnetic resonance imaging study we administered hydrocortisone during a polysomnographically monitored night of sleep directly after healthy volunteers studied negative and neutral pictures in a double-blind, placebo-controlled, between-subjects design. The following evening memory consolidation was probed during a recognition memory test in the MR scanner by assessing the difference in brain activity associated with memory for the consolidated items studied before sleep and new, unconsolidated items studied shortly before test (remote vs. recent memory paradigm). Hydrocortisone administration resulted in elevated cortisol levels throughout the experimental night with no group difference at recent encoding or test. Behaviorally, we showed that cortisol enhanced the difference between emotional and neutral consolidated memory, effectively prioritizing emotional memory consolidation. On a neural level, we found that cortisol reduced amygdala reactivity related to the retrieval of these same consolidated, negative items. These findings show that cortisol administration during first post-encoding sleep had a twofold effect on the first 24 h of emotional memory consolidation. While cortisol prioritized recognition memory for emotional items, it reduced reactivation of the neural circuitry underlying emotional responsiveness during retrieval. These findings fit recent theories on emotional depotentiation following consolidation during sleep, although future research should establish the sleep-dependence of this effect. Moreover, our data may shed light on mechanisms underlying potential therapeutic effects of cortisol administration following psychological trauma.

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1. Introduction

A striking and adaptive feature of human memory is its propensity to prioritize biologically salient over emotionally neutral information (Hamann, 2001; LaBar and Cabeza, 2006). An established animal literature posits that this emotional enhancement effect is at least partly related to neuromodulatory action during memory consolidation (McGaugh and Roozendaal, 2002). Stress hormones like cortisol (corticosterone in rats) are, together with stress-related neurotransmitters like norepinephrine, thought to exert their modulatory effect through potentiation of the amygdala. The amygdala subsequently modulates mnemonic processing in the hippocampus and other brain regions (McGaugh, 2004). Although well established in animals, these effects remain relatively uninvestigated in humans, despite recent reports on a possible role for glucocorticoids in the prevention of traumatic memory (de Quervain et al., 2009).

During memory consolidation, initially fragile memory traces are reorganized and integrated into long-term storage (Müller and Pilzecker, 1900; Marr, 1970; McGaugh, 2000). This process occurs when awake, but is particularly facilitated during sleep (Stickgold, 2005; Diekelmann and Born, 2010). In case of emotional memory, current theories suggest that this consolidation process additionally serves to reduce the affective tone of the memory trace by integrating it into conceptualized, semantic networks (Walker and van der Helm, 2009). Within neuroimaging, memory consolidation is often probed by measuring the outcome of consolidation during retrieval, for instance using a remote versus recent memory paradigm (Takashima et al., 2006).

Previous studies using similar designs have shown that the emotional enhancement effect of memory develops progressively over consolidation (Nishida et al., 2009), and that the retrieval of consolidated emotional memories engages the amygdala and hippocampus (Dolcos et al., 2005; Sterpenich et al., 2009). However, none of these studies consider the role of cortisol. On a behavioral level, several studies have suggested a facilitatory role of cortisol in (emotional) memory consolidation (Buchanan and Lovallo, 2001; Cahill et al., 2003; Maheu et al., 2004; Abercrombie et al., 2006; Kuhlmann and Wolf, 2006; Payne et al., 2007, but see: Wagner et al., 2005b, and see Lupien et al., 2007; de Quervain et al., 2009 for reviews). However, these findings are either complicated by concomitant drug effects on encoding, or related to other stress-induced neuromodulatory changes in addition to cortisol, most importantly norepinephrine. A recent study by Wilhelm and colleagues did study the isolated effect of cortisol on consolidation, but only found an effect on relational (and not item) memory of neutral text material (Wilhelm et al., 2011). Thus, it remains unknown to what extent the reorganization of emotional memory traces as a result of prioritized memory consolidation directly depends on cortisol.

We assessed the effect of hydrocortisone administration on the consolidation of negative and neutral pictures studied just prior to polysomnographically monitored sleep (remote set), in a double-blind, placebo-controlled, between-subjects design. Memory consolidation was probed the following evening during a recognition memory test in the MR scanner by assessing the difference in memory performance and brain activity for the 'remote' items and new, 'recent' items studied just prior to test. We administered hydrocortisone after learning and just before sleep, because processes underlying memory consolidation are thought to take place most prominently, although not exclusively, during sleep (Diekelmann and Born, 2010). Remote items thus transitioned through a phase of memory consolidation during sleep, which in the cortisol group was accompanied by elevated cortisol levels. In contrast, recent items were neither consolidated, nor affected by the cortisol manipulation. Note that although this experimental setup targets memory consolidation during sleep, it cannot establish sleep dependence. We did not include a non-sleep condition at a different time of day or a sleep deprivation condition because such controls would be confounded by cortisol differences resulting respectively from the diurnal cycle of cortisol or sleep deprivation itself (Balbo et al., 2010).

Based on extensive animal literature concerning the facilitatory role of glucocorticoids in the memory consolidation of emotionally arousing events (McGaugh and Roozendaal, 2002), we hypothesized that hydrocortisone administration during post-encoding sleep would enhance the consolidation benefit for emotional (vs. neutral) memory, which would be reflected in altered reactivation patterns of limbic circuitry during retrieval.

2. Materials and methods

2.1. Participants

Forty-two healthy male volunteers participated in this study, which was approved by the local ethics committee (CMO region Arnhem-Nijmegen, The Netherlands) in accordance with the declaration of Helsinki. Only men were included to minimize heterogeneity related to gender differences in HPA-axis activity (Wang et al., 2007). Volunteers were screened before entering the study. Prior to screening, they were informed about all procedures and risks and asked to sign informed consent. At screening, all individuals that met any of the following criteria were excluded from participation: history of head trauma; history of psychiatric, neurological, endocrine, metabolic, or sleep disorders; current use of psychoactive or corticosteroid drugs, or any other drug that affects the central nervous and endocrine systems; acute peptic or duodenal ulcers; medical illness within the three weeks prior to testing; daily tobacco or alcohol use; current stressful episode or major life event; a body-mass-index outside the range of 18.5—25; or standard contra-indications for participation in an MRI experiment. Furthermore, all participants were right-handed, and had normal or corrected to normal vision. Participants had no complaints of excessive daytime sleepiness as assessed with the Dutch version of the Epworth Sleepiness Scale (Johns, 1991), or any sleep disturbances as determined by the Pittburgh Sleep Quality Index (Buysse et al., 1989). Additionally, we screened for extreme morning and evening chronotypes using the Horne—Ostberg Questionnaire (Horne and Ostberg, 1976). Finally, a venous blood sample was taken, which was analyzed for serum cortisol with an inclusion range between 150 and 700 mmol/L. Participants were randomly assigned to the *hydrocortisone* group (CORT) or the *placebo* group (PLAC). Data of three participants were excluded: two due to excessive head movement during scanning and one

(in the placebo group) due to very high cortisol levels during the test session (>3 × SD above the mean), resulting in thirty-nine participants used in the below analysis (CORT, $n = 20$; mean age: 21 ± 2.7, range: 19–31; PLAC, $n = 19$; mean age: 21 ± 2.1, range: 19–26). There were no differences between experimental groups in any of the sleep-related questionnaires (all $T_{(37)} < 1.2$, *n.s.*).

2.2. Design and general procedure

To study emotional memory consolidation, participants performed two study sessions (remote and recent, see Fig. 1). At the first study session (day 1) participants encoded a set of negative and neutral pictures (10.45 PM, ***remote set***) outside the scanner before they went to bed at 11.45 PM to allow 8 h of polysomnographically monitored sleep. After awaking (day 2), participants left the lab to follow their normal daily routine with the instruction not to engage in excessive physical exercise or have any daytime sleep (monitored by an Actigraph activity monitor (Actigraph, Pensacola, Florida)). Participants returned to the lab on the afternoon for a second study session (5.15 PM, ***recent set***) that was directly followed by a recognition memory test in the MR scanner (6 PM), which included both the remote and recent sets and a set of new pictures never seen before. The role of cortisol in emotional memory consolidation was investigated by orally administering capsules containing either 10 mg of hydrocortisone + cellulose (CORT group) or cellulose alone (PLAC group) directly after encoding the remote set (11 PM) and at 2 AM when participants were briefly awakened by an alarm clock. The total dosage of 20 mg of hydrocortisone was chosen based on previous studies showing clear effects of similar dosages on memory function (Buchanan and Lovallo, 2001; Kuhlmann and Wolf, 2006). The timing of the second capsule was chosen to ensure an elevated level of cortisol throughout the night (hydrocortisone is absorbed rapidly and well when administered orally with a t_{max} of 60 min and a $t_{1/2}$ of approximately 8–12 h). The timing of the memory test on the evening of day 2 excluded any effects of the drug on recent encoding and retrieval. Both behavioral and imaging data were analyzed using a 2 (picture valence) × 2 (picture remoteness) × 2 (drug) factorial ANOVA with picture valence and picture remoteness as within subjects factors and drug as between subjects factor. The emotional enhancement effect was indexed as the difference between negative versus neutral pictures, offline consolidation as the difference between remote versus recent pictures, and the relative consolidation benefit for emotional versus neutral items as the difference between these two difference scores ([negative remote–neutral remote] – [negative recent–neutral recent]).

2.3. Memory paradigm

2.3.1. Stimulus materials

Three unique sets of 160 pictures each (80 negative and 80 neutral) were formed from a selection of a standard set of affective pictures (Lang et al., 2008), supplemented with a small additional set of newly rated pictures (Henckens et al., 2009). Negative pictures were selected based on their moderate to high arousal (mean ± SD, 5.4 ± 0.7), and negative valence (mean ± SD, 3.0 ± 0.7), as rated on the Self-Assessment Manikin (SAM) scales (Bradley and Lang, 1994). Neutral pictures were selected based on their relatively low arousal (mean ± SD, 2.5 ± 0.8) and neutral valence (mean ± SD, 5.2 ± 0.3). All pictures were equalized in luminance and

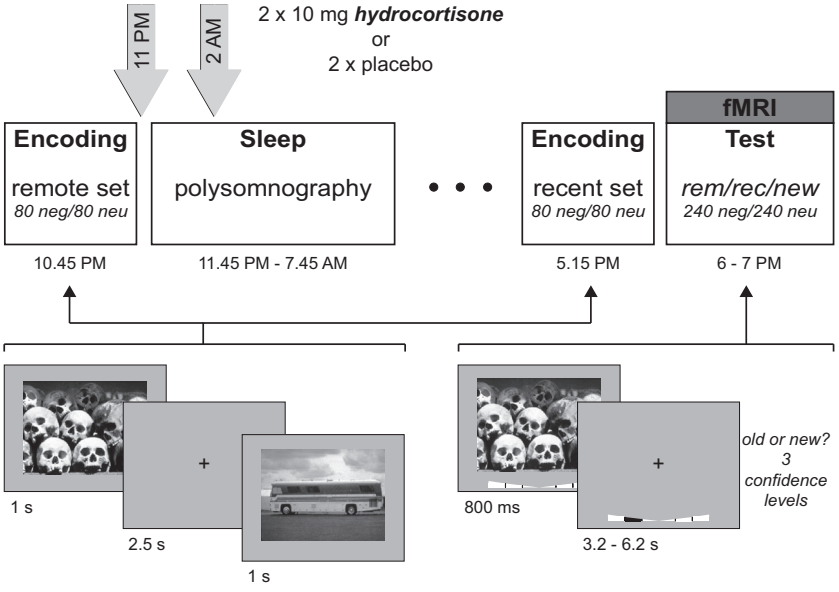

Figure 1 Experimental design. Participants encoded two sets of negative and neutral IAPS with varying time delays to a recognition memory test in the MR scanner: a *remote* set (±20 h before test, and followed by nocturnal sleep), and a ***recent*** set (shortly before to test, with no sleep in between). At retrieval, memory was tested for both sets (plus foils), and offline memory consolidation was indexed as the difference between remote and recent memory. To assess the role of cortisol in emotional memory consolidation hydrocortisone was administered (2 × 10 mg) in half of the participants during the post-encoding night of sleep. Neg, negative; Neu, neutral; Rem, remote; Rec, recent.

presented centrally on a background with the averaged gray-value of all pictures. The sets were matched in mean arousal and valence ratings, while content overlap within one set was minimized. The order of pictures within each set was pseudorandomized with no more than two pictures of the same valence presented consecutively. Each set could serve as either a remote, recent, or new set following a fully counterbalanced scheme across participants.

2.3.2. Study sessions

At the remote and recent study sessions pictures were presented on a computer screen for 1 s with a fixed ITI of 2.5 s during which a fixation cross was shown (Fig. 1). Participants were instructed to view attentively and memorize each picture and rate its valence as negative or neutral by keyboard button press (ensuring deep encoding). Practice sessions familiarized participants with the task and response options.

2.3.3. Recognition test

Participants lay supine in the scanner and viewed the screen through a mirror positioned on the head coil. At recognition test all pictures (remote, recent, and new) were presented for 800 ms with an ITI ranging from 3.2 to 6.2 s (mean 4.7 s) (Fig. 1). The order of presentation was pseudorandomized with no more than three pictures of the same set presented consecutively, and 60 null events (fixation cross) were added as implicit baseline for later analysis. Participants were instructed to make old/new judgments with simultaneous confidence ratings, in which both remote and recent pictures were classified as old. Using two button boxes, participants had the following response options: Old/very sure, Old/sure, and Old/unsure as separate buttons for one hand, and New/very sure, New/sure, and New/unsure for the other. Across participants Old and New responses were randomly assigned to the right and the left button box. The response options were graphically depicted at the bottom of the screen and participants were instructed to respond as quickly as possible, but could respond until the appearance of the next picture. The total of 480 pictures (+60 null events) was divided over two sessions of approximately 25 min with a very short break in between during which the participants stayed in the scanner. Practice sessions in the scanner ensured participants were familiarized with the task and response options. Using this set-up, 4 response categories were possible: hits (correct old judgments), misses (incorrect old judgments), correct rejections (CR, correct new judgments), and false alarms (FA, incorrect new judgments). Accuracy was calculated as hit rate (hits/hits + misses) minus false alarm rate (FA/FA + CR). For both the behavioral and fMRI analysis all Old/unsure responses were discarded since the number of unsure hits and unsure FAs did not significantly differ indicating that participants were operating at chance level. Thus hits and FAs included only very sure and sure responses, and misses and CRs included all confidence levels.

2.4. Sleep/polysomnography

Sleep was assessed by standard polysomnographical recordings acquired with a Brainvision system (Brain Products, Gilching, Germany) (sampling rate: 500 Hz, high- and low-pass filter 0.016 and 125 Hz, respectively). A mastoid referenced electrode montage was used with electroencephalography recordings from F3/F4, C3/C4, and O3/O4 with a recommended derivation to the contralateral mastoid electrodes (A1/A2), electromyography recordings from a chin electrode, and electrooculography recordings from above and next to the right eye. Sleep scoring (blind to drug group and memory performance) was performed using Somnologica software (Somnologica Studio 5.0, Embla, Broomfield, Colorado), and consisted of visual categorization of each 30 s epoch as either NREM stages 1–3, REM sleep or wake according to standard criteria (Iber et al., 2007). Participants were instructed to keep to their normal sleep rhythm on the three nights prior to the experimental night. Sleep registration failed in one subject in the PLAC group due to technical problems. This subject is included in all other analysis.

2.5. Cortisol measurements

To monitor the cortisol manipulation, saliva was sampled throughout the experiment using saliva collection devices (Salivette, Sarstedt, Rommelsdorf, Germany) to determine the level of free cortisol. Saliva was sampled seven times during the experimental night: 9.30 PM (baseline, 30 min after entry), 11 PM (directly following remote encoding and prior to drug intake 1), 11.45 PM (prior to going to bed), 2 AM (prior to drug intake 2), 7.45 AM (at awakening), 8.15 AM (30 min after awakening), 8.45 AM (1 h after awakening), and three times during the afternoon session on day 2: 5.15 PM (prior to recent encoding and 30 min after entry), 5.30 PM (directly following recent encoding), and 7.30 PM (15 min after finishing the MRI session). For a detailed description on the biochemical analysis of the cortisol samples see (van Marle et al., 2009). To minimize differences in baseline cortisol levels, we instructed participants to refrain from drinking alcohol, exercising, and smoking for 24 h prior to the experiment. Furthermore, participants were requested not to brush their teeth, floss, or eat and drink anything but water for 30 min prior to arrival until the end of the experimental session on both days to enable adequate saliva sampling for cortisol assessment. Group differences in total cortisol concentration were tested by performing independent *T*-tests on the area under the curve with respect to the ground (AUCg) (Pruessner et al., 2003), separately for the experimental night (samples 1–7) and the afternoon session on day 2 (samples 8–10). Alpha was set at 0.05 throughout.

2.6. Image acquisition

Whole brain T2* weighted gradient echo EPI BOLD-fMRI images were acquired with a Siemens (Erlangen, Germany) TIM Trio 3.0 T MR-scanner equipped with an eight channel phased-array head coil, using an ascending slice acquisition (37 axial-slices, TE/TR: 25/2180 ms, flip angle 80°, FOV: 212 mm × 212 mm, matrix 64 × 64, 3.0 mm slice thickness, .3 mm slice gap). 687 images were acquired during the task. In order to reduce artifacts caused by inhomogeneity around air-tissue interfaces, we used a relatively short TE, and an oblique axial angulation. High-resolution structural images (1 mm × 1 mm × 1 mm) were obtained using a t1-weighted MP-RAGE sequence (TE/TR: 2.96/2300 ms, flip angle: 8°,

FOV: 256 mm × 256 mm × 192 mm, GRAPPA acceleration factor 2).

2.7. Image analysis

Image processing and statistical analyses were performed using SPM5 (www.fil.ion.ucl.ac.uk/spm). The first five EPI volumes were discarded to allow for T1 equilibration, and the remaining images were realigned using rigid body transformations. The mean image was then coregistered to the structural MR-image. Subsequently, images were transformed into common stereotactic space (MNI152 T1-template), and resampled into 2 mm isotropic voxels. Spatial smoothing was performed using a Gaussian kernel of 8 mm full-width at half-maximum. Statistical analysis was performed within the framework of the general linear model (Friston et al., 1995). The four hit types (*negative remote hits, negative recent hits, neutral remote hits and neutral recent hits*) were modeled separately as boxcar regressors and convolved with the canonical hemodynamic response function of SPM5. Negative CRs, neutral CRs, and grouped FAs and misses were additionally modeled in separate categories. Additionally, realignment parameters, consisting of six parameter rigid body transformations (3 translations and 3 rotations) used for motion correction, were included to model potential movement artifacts. Contrast parameter images generated at the single subject level (each hit type -> null events/implicit baseline) were then submitted to 2nd level random effects analysis. Statistical parametric maps were created within SPM5 using a factorial ANOVA with picture valence (negative vs. neutral) and picture remoteness (remote vs. recent) as within subject factors and drug (CORT vs. PLAC) as between subject factor. Our statistical threshold was set at $p < 0.05$, family-wise-error (FWE) rate corrected for multiple comparisons across regions of interest (ROI) using a small volume correction. Given their role in emotional memory retrieval, the amygdala and hippocampus were targeted as ROIs. Specifically, for both regions, the search volumes were anatomically defined using the Talairach Daemon database atlas (Lancaster et al., 2000). For all other regions we report effects after FWE-correction for multiple comparisons across the whole brain.

3. Results

3.1. Cortisol measurements

Hydrocortisone administration resulted in a significant increase in total cortisol concentration during the post-encoding night as compared to placebo (measured as AUCg, $T_{(37)} = 3.2$, $p < 0.005$), while not affecting cortisol levels during the recent encoding and retrieval on day 2 ($T_{(37)} = 0.1$, $p = 0.9$) (Table 1). Baseline cortisol levels were not different between groups ($T_{(37)} = 0.9$, $p = 0.4$).

Table 1 Cortisol measurements.

	Hydrocortisone	Placebo
Experimental night		
AUCg of samples 1–7***	6594.9 (547.7)	4466.1 (372.4)
Study session 2/test		
AUCg of samples 8–10	667.4 (52.7)	660.3 (43.3)

Data are shown as mean (SEM), AUCg, area under the curve with respect to ground.
*** $p < 0.005$ for difference between hydrocortisone and placebo.

3.2. Behavioral results

As expected, we observed main effects of picture valence (negative > neutral, $F_{(1,37)} = 31.8$, $p < 0.0001$, $P\eta^2 = 0.46$), and picture remoteness (recent > remote, $F_{(1,37)} = 71.2$, $p < 0.0001$, $P\eta^2 = 0.66$). Additionally, we found interactions between drug and remoteness ($F_{(1,37)} = 5.0$, $p < 0.05$, $P\eta^2 = 0.12$), and between valence and remoteness ($F_{(1,37)} = 5.1$, $p < 0.05$, $P\eta^2 = 0.12$). More important for the topic at hand, these interactions were qualified by a three-way interaction between the factors drug, valence, and remoteness ($F_{(1,37)} = 6.7$, $p < 0.05$, $P\eta^2 = 0.15$). We followed-up on this three-way interaction by testing for a valence × remoteness interaction in each of the drug conditions separately using two two-way ANOVAs and found that the CORT group exhibited a valence × remoteness interaction ($F_{(1,19)} = 8.4$, $p < 0.05$, $P\eta^2 = 0.31$), whereas the PLAC group did not ($F_{(1,18)} < 1$, *n.s.*). This effect is visualized in Fig. 2. Within the CORT group both remote and recent items showed a main effect of valence (negative > neutral, $F_{(1,19)} = 24.7$, $p < 0.001$, $P\eta^2 = 0.57$; $F_{(1,19)} = 6.2$, $p < 0.05$, $P\eta^2 = 0.25$; respectively). Thus, by showing a larger emotional enhancement effect for remote than recent items in the CORT group, which is absent in the PLAC group, this analysis suggests that hydrocortisone during post-encoding sleep induces a shift toward relatively stronger consolidation

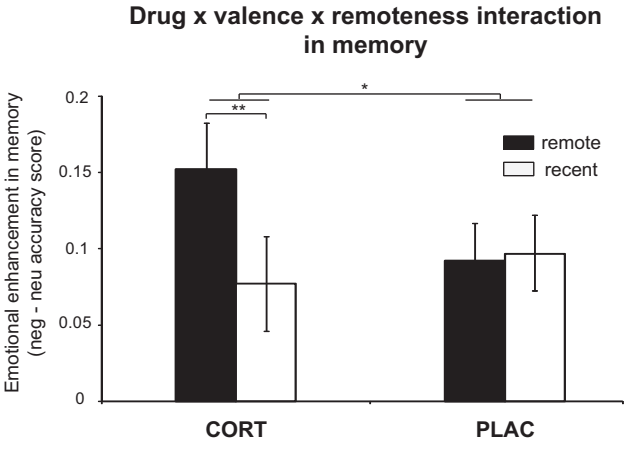

Figure 2 Drug × valence × remoteness interaction in memory. Hydrocortisone administration during post-encoding sleep affects emotional memory consolidation such that the emotional enhancement effect (difference between negative and neutral memory, as a pure measure of emotional memory) is increased for remote (vs. recent) items, effectively prioritizing emotional memory consolidation. Graphs represent difference scores for negative and neutral memory (calculated as accuracy). Neg, negative; Neu, neutral; CORT, hydrocortisone group; PLAC, placebo group. *$p < 0.05$; **$p < 0.01$.

Table 2 Memory (accuracy).

	Hydrocortisone	Placebo
Negative		
Remote	0.70 (0.02)	0.68 (0.03)
Recent	0.75 (0.03)	0.74 (0.03)
Neutral		
Remote	0.55 (0.04)	0.59 (0.04)
Recent	0.68 (0.04)	0.64 (0.04)
Negative—Neutral		
Remote	0.15 (0.03)	0.09 (0.02)
Recent	0.08 (0.03)	0.10 (0.03)

Data are shown as mean (SEM). None of the accuracy scores significantly differed between drug groups.

for emotional items. See Table 2 for direct comparisons of all categories of accuracy scores between drug groups.

3.3. Sleep parameters

Sleep data are presented in Table 3. On a subjective level, participants generally reported good sleep quality, and hydrocortisone administration did not affect total sleep time ($T_{(36)} = 1.3$, $p = 0.2$), sleep latency ($T_{(36)} = -0.9$, $p = 0.4$) or time spent awake ($T_{(36)} = -1.0$, $p = 0.3$). Hydrocortisone was associated with increased stage 2 sleep ($T_{(36)} = 2.7$, $p < 0.05$). The other sleep stages were not affected by hydrocortisone administration (S1: $T_{(36)} = 0.5$, $p = 0.6$; SWS: $T_{(36)} = -0.5$, $p = 0.6$; REM: $T_{(36)} = -1.7$, $p = 0.1$). Additional correlational analysis revealed no association between any of the sleep measures and behavioral indices of emotional memory consolidation.

3.4. fMRI results

As expected, fMRI analysis yielded a strong main effect of valence (Fig. 3A and Table 4), with retrieval activity being greater for negative than for neutral items in amygdala, posterior cingulate gyrus, precuneus, inferior parietal lobe, right inferior frontal gyrus, and medial frontal gyrus (regions typically activated during emotional memory retrieval or emotional processing tasks, Phan et al., 2002; Buchanan, 2007). Additionally, activations in bilateral fusiform gyrus and middle temporal gyrus were found (regions involved in higher order visual processing). Next, we identified brain regions showing larger responses to remote than recent items (reflecting the effect of systems-level consolidation). These included superior medial frontal gyrus, insula, and amygdala (Fig. 3B). The reverse contrast (recent > remote) revealed activations in precuneus and inferior parietal lobe. We found no main effect of drug. Given the timing of administration (only affecting remote items) this null finding was to be expected. A subsequent analysis, probing emotional memory consolidation, revealed a valence by remoteness interaction in bilateral amygdala, indicating enhanced amygdala activation during the retrieval of remote, negative items (negative > neutral × remote > recent) (Fig. 3C). Next, to assess the role of cortisol in emotional memory consolidation, we probed the three-way interaction between drug, valence, and remoteness. When contrasting the PLAC group with the CORT group this analysis revealed a trend-level significant effect in amygdala that seemed to overlap partly with anterior hippocampus (PLAC > CORT × negative > neutral × remote > recent, $p = 0.1$, svc-FWE). Since our hypothesis primarily concerned emotional memory, we continued to test this interaction by investigating the corresponding drug by remoteness interaction separately for negative and neutral items. For negative items this yielded reliable bilateral suprathreshold clusters in the amygdala/anterior hippocampus (PLAC > CORT × remote > recent, $p < 0.05$, svc-FWE, fitting both masks, Fig. 3D). The same analysis for neutral items revealed no significant suprathreshold clusters. Finally, testing remote and recent negative items separately between groups did not yield any significant activation clusters in amygdala, indicating that the observed interaction is carried by the difference for remote and recent (and not recent alone). Taken together, these data indicate that elevating cortisol levels during post-encoding sleep leads to an attenuation of amygdala/anterior hippocampus activation related to remote, emotional memory retrieval.

Table 3 Sleep.

	Hydrocortisone	Placebo
Sleep time (min)	439.4 (7.3)	426.1 (7.4)
Sleep latency (min)	14.4 (2.1)	18.8 (4.4)
Wake (%)	5.1 (1.3)	7.0 (1.4)
S1 (%)	11.5 (1.1)	10.8 (0.8)
S2 (%)*	47.5 (1.7)	42.0 (1.1)
SWS (%)	19.1 (1.4)	20.2 (1.3)
REM (%)	16.8 (1.3)	20.2 (1.4)

Data are shown as mean (SEM). REM, rapid eye movement sleep; S1, stage 1 sleep; S2, stage 2 sleep; SWS, slow wave sleep; min, minutes; %, percentage of total sleep period.
* $p < 0.05$ for difference between hydrocortisone and placebo.

4. Discussion

We investigated the effect of cortisol on emotional memory consolidation using a remote/recent memory paradigm. Administration of 20 mg of hydrocortisone resulted in a substantial increase of cortisol levels during the night, with no group difference at recent encoding or test. In the CORT group we observed an increased relative retention benefit for emotional (vs. neutral) items. This prioritization of emotional memory consolidation by cortisol was accompanied by reduced activation in amygdala/anterior hippocampus during the retrieval of the same remote, negative items.

Behaviorally, we found that hydrocortisone administration resulted in an increase in emotional enhancement effect over the course of consolidation. Further testing showed that hydrocortisone administration did not significantly increase memory for negative, remote items or decrease memory for neutral, remote items when tested separately. These findings suggest a shift or prioritization in memory function by hydrocortisone toward emotional memory consolidation. This is consistent with previous studies

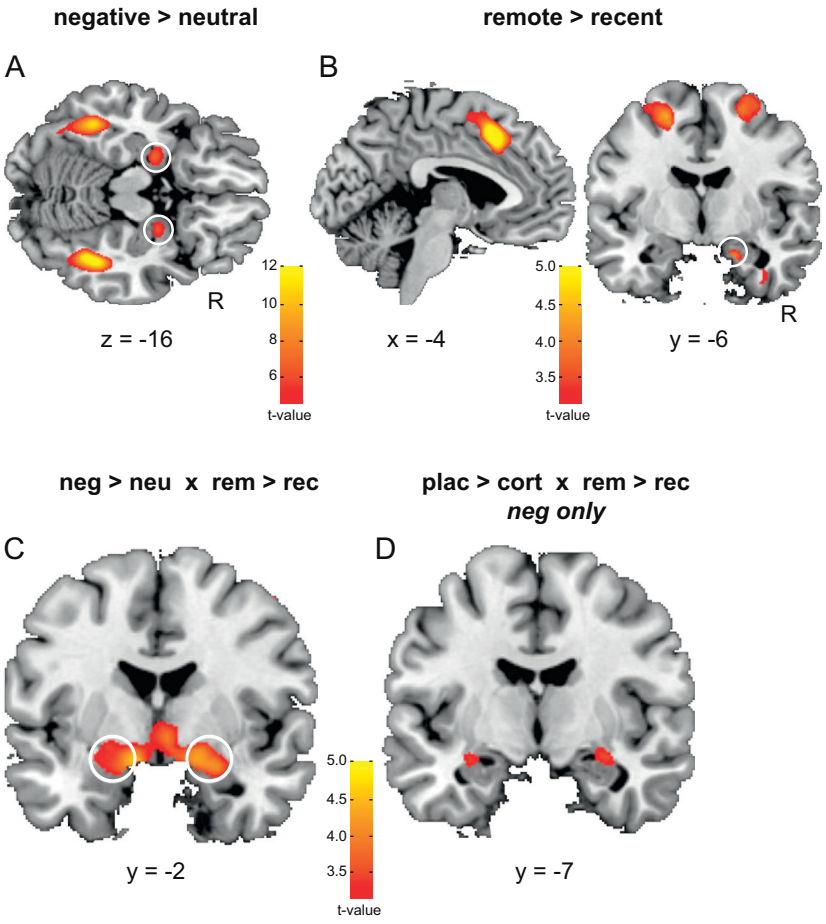

Figure 3 fMRI main effects of valence and remoteness and interaction effects. Statistical parametric maps illustrating the main effect of valence (neg > neu) in bilateral fusiform gyrus and amygdala (A), the main effect of remoteness (rem > rec) in superior medial frontal gyrus (left panel) and amygdala (right panel) (B), a valence × remoteness interaction (neg > neu × rem > rec) in amygdala (C), and a subsequent drug × remoteness interaction (plac > cort × rem > rec, tested for negative items only) in a border region of amygdala and anterior hippocampus (D). For display purposes the T-maps are thresholded at $p < 0.05$, *corrected* (A), and $p < 0.001$, *uncorrected* (B—D). For voxel-level statistics of all active clusters see Table 4. R, right; Neg, negative; Neu, neutral; Rem, remote; Rec, recent; CORT, hydrocortisone group; PLAC, placebo group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

that showed shifts in memory priority rather than increases in overall memory capacity after drug manipulations (Wagner et al., 2005a). Concerning cortisol, previous studies have suggested that exogenous hydrocortisone facilitates emotional memory (Buchanan and Lovallo, 2001; Kuhlmann and Wolf, 2006). Although these studies implemented sufficient study-test delays to allow consolidation, they cannot exclude concomitant effects on encoding since hydrocortisone was administered before learning. By administering after encoding just before sleep, we ensured that any findings at retrieval can result only from cortisol action during consolidation. Additional studies showed enhancing effects on emotional memory consolidation of a physiological (Cahill et al., 2003) and psychological (Abercrombie et al., 2006) stressor applied directly after encoding. These studies, however, cannot establish whether these effects are caused by cortisol specifically. A handful of studies did look specifically at the effect of cortisol during memory consolidation. Philal and Born found that hydrocortisone administration after learning inhibited memory consolidation for neutral material (word pairs) (Plihal and Born, 1999). By not directly comparing this to negative items, this study cannot, however, address a possible cortisol-induced prioritization of emotional versus neutral memory consolidation, as shown here. In another, more recent study Wilhelm and colleagues administered hydrocortisone after learning both negative and neutral texts, followed by either a wake or a sleep (nap) condition (Wilhelm et al., 2011). They found that cortisol affected only the memory for temporal order (and not content) of the neutral text, being enhanced in the wake and reduced in the sleep condition. There was no effect of cortisol on the negative text, irrespective of sleep condition. The discrepancy between our results and this relative null-finding concerning the effect of cortisol on emotional memory consolidation may be attributable to apparent differences in design. These include stimulus material (with negative IAPS material being generally considered more emotionally aversive than text material), type of memory test (free recall of content words and temporal sequence memory vs. item recognition), and most importantly timing

Table 4 Peak voxel and corresponding *t*-values of brain regions revealing significant main and interaction effects.

	Hemi	MNI coordinates				*t*-Value
		x	*y*	*Z*		
Main effect of valence						
Negative > neutral						
Fusiform gyrus	R	42	−48	−16		12.86***
	L	−44	−44	−18		11.53***
Inferior temporal gyrus	R	52	−64	6		10.61***
	L	−50	−68	8		10.87***
Inferior parietal lobe	R	68	−20	36		6.32***
	L	−64	−30	32		9.02***
Amygdala	R	24	−4	−16		6.56***
	L	−24	−4	−18		7.23***
Inferior frontal gyrus	R	52	36	4		7.19***
Precuneus	R	4	−46	28		6.63***
	L	−6	−52	32		5.92***
Medial frontal gyrus	R	6	54	24		6.11***
Posterior cingulate cortex		0	−10	38		6.10***
Main effect of remoteness						
Remote > recent						
Superior medial frontal gyrus	L	−4	14	48		5.75***
Insula	R	34	26	−4		4.34*
	L	−30	24	0		4.94***
Amygdala	R	20	−6	−22		4.01**
Recent > remote						
Precuneus	R	8	−62	38		6.13***
	L	−4	−70	40		5.66***
Inferior parietal lobe	R	48	−54	44		5.69***
Valence × remoteness interaction						
Negative > neutral × remote > recent						
Amygdala	R	22	−2	−16		4.16**
	L	−18	−2	−18		3.54**
Drug × valence × remoteness interaction						
PLAC>CORT × neg > neu × rem > rec						
Amygdala	R	26	−8	−14	($p = 0.10$)	2.65
	L	−22	−10	−10	($p = 0.16$)	2.43
Posterior hippocampus	L	−28	−26	−10	($p = 0.06$)	3.01
Drug × remoteness interaction						
Neg only, PLAC > CORT × rem > rec						
Amygdala	R	28	−8	−14		3.42**
	L	−26	−8	−14		3.14**
Anterior hippocampus	R	32	−16	−14	($p = 0.09$)	2.80
	L	−30	−14	−14		3.54**

R, right; L, left; Neg, negative; Neu, neutral; Rem, remote; Rec, recent; CORT, hydrocortisone; PLAC, placebo.
* $p < 0.001$, uncorr.
** $p < 0.05$, small volume FWE corr.
*** $p < 0.05$, whole brain FWE corr.

and duration of sleep, with our study having a much longer (whole-night) sleep interval. This results in a different duration of specific sleep stages, for instance longer REM sleep. Next, based on our findings one would predict that inhibiting cortisol action during sleep would impair emotional memory consolidation. However, the administration of metyrapone (a cortisol synthesis blocker) during sleep enhanced, rather than attenuated, the difference between emotional and neutral memory consolidation (Wagner et al., 2005). As the authors themselves mention, this discrepancy could potentially be explained by the fact that metyrapone in their study not only reduced cortisol, but also led to a strong elevation of corticotrophin releasing hormone (through decreased hypothalamo–pituitary feedback inhibition) that has also been found to enhance emotional memory consolidation (Roozendaal et al., 2008). Additionally, more obvious differences in design, including again stimulus material and type of memory test (see above) could

potentially underlie the different findings. We may add that a linear relationship between memory function and cortisol level, in this case ranging from an extremely low level caused by metyrapone and the physiologically elevated level in our study, is not to be expected (Lupien et al., 2007). Finally, we did not find a retrograde emotional enhancement effect in the PLAC group. Such effects are thought to develop progressively over time (Dolcos et al., 2005; Wagner et al., 2006), making them easier to detect over longer retention intervals than our 20 h (but see Hu et al., 2006; Payne et al., 2008). Also, we tested explicit instead of incidental memory, which is known to generate smaller emotional enhancement effects. Note however, that also the PLAC group showed strong valence effects for both remote and recent memory.

The primary fMRI finding is that hydrocortisone administration affects the system-level consolidation of emotional memory traces, which becomes apparent as attenuated amygdala/anterior hippocampus activation during the retrieval of remote, negative items. At present there is no consensus on the functional interpretation of amygdala activation during emotional retrieval and its presumed relationship to the preceding consolidation process. A widely held view is that amygdala facilitates the recollection of emotional memories by the hippocampus by re-instating the original arousal of encoding during retrieval (Buchanan, 2007). Subsequently, amygdala is further activated in response to the internally generated (retrieved) emotion. Following this re-instate and re-experience account, our findings suggests that cortisol may modulate the consolidation process by attenuating the intrinsic level of arousal that was linked to the emotional memory. Future studies may, in addition to amygdala reactivity, measure more direct indices of autonomic arousal, like skin conductance, to back up this interpretation. In combination with the behavioral results, these findings fit emerging theories on the interaction between sleep and emotional memory that propose that consolidation during sleep serves to preserve and solidify the declarative, factual aspect of an emotional memory trace, while at the same time depotentiating (and ultimately ameliorating) its affective charge (Walker, 2009; Walker and van der Helm, 2009). This progressive decoupling of emotion and memory during consolidation is thought to be achieved through integration of the emotional memory trace into pre-existing, neocortically stored memories. A recent study illustrated emotional depotentiation over sleep (albeit independent of memory) (van der Helm et al., 2011). Van der Helm and colleagues showed an overnight drop in subjective emotional ratings of previously seen negative items, including a reduction in corresponding amygdala reactivity (however see Baran et al., 2012 for an indication that behaviorally emotional reactivity is relatively preserved over sleep). We now propose that cortisol speeds up or facilitates the depotentiation of emotional memory. This results behaviorally in the observed relative consolidation benefit for emotional memory, in the presence of attenuated reactivity of the neural circuitry underlying emotional responsiveness centering on the amygdala. The emotional depotentiation theory of consolidation is often linked to REM sleep (Walker and van der Helm, 2009). Here, we did not find intra-subject correlations between amount of REM sleep (or any other sleep stage) and behavioral or neural indices of emotional memory consolidation. Instead we found a reduction of REM sleep by hydrocortisone (with concomitant increased S2 sleep) that just failed to reach significance ($T_{(36)} = -1.7$; $p = 0.1$). Hydrocortisone has been found before to reduce REM sleep (Born et al., 1989). Thus, together with our behavioral and imaging results, this suggests that emotional memory consolidation/depotentiation may be dependent on the integrated functions of REM neurophysiology and increased glucocorticoid action, as opposed to REM alone. Finally, future research may try to investigate the emergence of cortical representation areas for the increasingly consolidated memory traces. In this study however, the diverse content of the negative pictures may give rise to a more distributed rather than focal cortical representation (Takashima et al., 2009).

As stated before, we studied cortisol effects on emotional memory consolidation during sleep since that is when the targeted mechanisms are most likely to occur. Indeed, we demonstrated that exogenous cortisol during post-encoding sleep affects the systems-level consolidation of emotional memories. An important question that remains unanswered in this study is whether these findings are truly sleep-dependent. Alternative designs, implementing equal study-test intervals containing either sleep or no sleep (e.g. Payne and Kensinger, 2011), are better equipped to show sleep-dependence. Focusing on the role of cortisol in memory consolidation, however, we opted not to implement such a design because of the inherent confound of different circadian rhythm-determined levels of cortisol (in case of AM–PM paradigms), or likely increases in stress hormones due to sleep deprivation (in case of a simultaneous waking control condition) (Balbo et al., 2010). Thus, although the observed differences at test are mostly likely to result from cortisol action during the experimental night of sleep, we state clearly that our data show the effect of cortisol on emotional memory consolidation during sleep, and not on sleep-dependent memory consolidation.

The enhanced amygdala activation for remote versus recent emotional memory across both groups (driven by lower activation for recent, negative items in the PLAC group) may fit an alternative interpretation. Although this remains a complex issue that relates to the generally debated functional interpretation of amygdala activity during emotional retrieval, we suggest that this effect reflects stronger habituation since recent negative items are repeated within 45 min between encoding and test (Breiter et al., 1996). Using emotional stimuli thus complicates the interpretation of the remote versus recent contrast, especially concerning amygdala activation. This can be overcome by introducing another factor, like drug. Importantly, this putative habituation effect is not different between groups, since the encoding/retrieval of recent items is unaffected by the drug. Difficulties surrounding this interpretation may also underlie inconsistencies with other neuroimaging studies on emotional memory consolidation. Although none of them specifically investigated cortisol, they mostly (Dolcos et al., 2005; Sterpenich et al., 2009; Payne and Kensinger, 2011), but not exclusively (Sterpenich et al., 2007) report increased rather than decreased amygdala activation with consolidation. Additional reasons for inconsistencies may be the lack of a recent condition (thus unable to track any progressive change in activation, (Dolcos et al., 2005)), or the use of sleep deprivation (Sterpenich et al., 2009). Furthermore, we implemented a study-test delay of one day rather than

months. Nonetheless, our primary focus was on cortisol, and we found that hydrocortisone administration reduced amygdala reactivity during the retrieval of consolidated negative items.

Prolonged hydrocortisone administration in intensive-care patients has been reported to reduce the subsequent risk to develop post traumatic stress disorder (PTSD) (Schelling et al., 2006). These preventive effects are typically interpreted to result from inhibiting effects of cortisol on memory retrieval, thereby interfering with a vicious cycle of spontaneous retrieval, re-experiencing, and (re)consolidation of aversive memories, effectively promoting forgetting (de Quervain et al., 2009). Speculatively, our findings now suggest that cortisol may additionally or alternatively prevent traumatic memory by facilitating the reorganization of emotional memory traces during consolidation resulting in a depotentiated memory at retrieval. This fits with several studies showing that reduced cortisol excretion after trauma (leading to diminished cortisol levels during consolidation) is associated with an increased risk for PTSD (McFarlane et al., 1997; Delahanty et al., 2000).

In conclusion, we show that exogenous cortisol during post-encoding sleep affects the system-level consolidation of emotional memory, resulting in both prioritized retention and attenuated reactivity of the neural circuitry underlying emotional responsiveness during memory retrieval. This combination of results is in line with recent theories on emotional depotentiation during consolidation/sleep. These data may further explicate the mechanism behind the reported therapeutic potential of cortisol in the prevention of traumatic memory.

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Conflict of interests

S.O. has received speaker fees from Boehringer, Ingelheim, UCB Pharma and Novartis. The other authors report no biomedical financial interests or potential conflicts of interest.

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References

Abercrombie, H.C., Speck, N.S., Monticelli, R.M., 2006. Endogenous cortisol elevations are related to memory facilitation only in individuals who are emotionally aroused. Psychoneuroendocrinology 31, 187—196.

Balbo, M., Leproult, R., Van Cauter, E., 2010. Impact of sleep and its disturbances on hypothalamo—pituitary—adrenal axis activity. Int. J. Endocrinol. 759234.

Baran, B., Pace-Schott, E.F., Ericson, C., Spencer, R.M., 2012. Processing of emotional reactivity and emotional memory over sleep. J. Neurosci. 32, 1035—1042.

Born, J., Spath-Schwalbe, E., Schwakenhofer, H., Kern, W., Fehm, H.L., 1989. Influences of corticotropin-releasing hormone, adrenocorticotropin, and cortisol on sleep in normal man. J. Clin. Endocrinol. Metab. 68, 904—911.

Bradley, M.M., Lang, P.J., 1994. Measuring emotion: the self-assessment manikin and the semantic differential. J. Behav. Ther. Exp. Psychiatr. 25, 49—59.

Breiter, H.C., Etcoff, N.L., Whalen, P.J., Kennedy, W.A., Rauch, S.L., Buckner, R.L., Strauss, M.M., Hyman, S.E., Rosen, B.R., 1996. Response and habituation of the human amygdala during visual processing of facial expression. Neuron 17, 875—887.

Buchanan, T.W., 2007. Retrieval of emotional memories. Psychol. Bull. 133, 761—779.

Buchanan, T.W., Lovallo, W.R., 2001. Enhanced memory for emotional material following stress-level cortisol treatment in humans. Psychoneuroendocrinology 26, 307—317.

Buysse, D.J., Reynolds III, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatr. Res. 28, 193—213.

Cahill, L., Gorski, L., Le, K., 2003. Enhanced human memory consolidation with post-learning stress: interaction with the degree of arousal at encoding. Learn. Mem. 10, 270—274.

de Quervain, D.J., Aerni, A., Schelling, G., Roozendaal, B., 2009. Glucocorticoids and the regulation of memory in health and disease. Front. Neuroendocrinol. 30, 358—370.

Delahanty, D.L., Raimonde, A.J., Spoonster, E., 2000. Initial posttraumatic urinary cortisol levels predict subsequent PTSD symptoms in motor vehicle accident victims. Biol. Psychiatr. 48, 940—947.

Diekelmann, S., Born, J., 2010. The memory function of sleep. Nat. Rev. Neurosci. 11, 114—126.

Dolcos, F., LaBar, K.S., 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. U. S. A. 102, 2626—2631.

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.B., Frith, C.D., Frackowiak, R.S.J., 1995. Statistical parametric maps in functional imaging: a general linear approach. Hum. Brain Mapp. 2, 189—210.

Hamann, S., 2001. Cognitive and neural mechanisms of emotional memory. Trends Cogn. Sci. 5, 394—400.

Henckens, M.J., Hermans, E.J., Pu, Z., Joels, M., Fernandez, G., 2009. Stressed memories: how acute stress affects memory formation in humans. J. Neurosci. 29, 10111—10119.

Horne, J.A., Ostberg, O., 1976. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int. J. Chronobiol. 4, 97—110.

Hu, P., Stylos-Allan, M., Walker, M.P., 2006. Sleep facilitates consolidation of emotional declarative memory. Psychol. Sci. 17, 891—898.

Iber, C., Ancoli-Israel, S., Chesson, A., Quan, S.F., 2007. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. American Academy of Sleep Medicine, Westchester, IL.

Johns, M.W., 1991. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14, 540—545.

Kuhlmann, S., Wolf, O.T., 2006. Arousal and cortisol interact in modulating memory consolidation in healthy young men. Behav. Neurosci. 120, 217—223.

LaBar, K.S., Cabeza, R., 2006. Cognitive neuroscience of emotional memory. Nat. Rev. Neurosci. 7, 54—64.

Lancaster, J.L., Woldorff, M.G., Parsons, L.M., Liotti, M., Freitas, C.S., Rainey, L., Kochunov, P.V., Nickerson, D., Mikiten, S.A., Fox, P.T., 2000. Automated Talairach atlas labels for functional brain mapping. Hum. Brain Mapp. 10, 120—131.

Lang, P.J., Bradley, M.M., Cuthbert, B.N., 2008. International affective picture system (IAPS): affective ratings of pictures and

instruction manual. Technical Report A-8. University of Florida, Gainsville, FL.

Lupien, S.J., Maheu, F., Tu, M., Fiocco, A., Schramek, T.E., 2007. The effects of stress and stress hormones on human cognition: implications for the field of brain and cognition. Brain Cogn. 65, 209—237.

Maheu, F.S., Joober, R., Beaulieu, S., Lupien, S.J., 2004. Differential effects of adrenergic and corticosteroid hormonal systems on human short- and long-term declarative memory for emotionally arousing material. Behav. Neurosci. 118, 420—428.

Marr, D., 1970. A theory for cerebral neocortex. Proc. R. Soc. Lond. B: Biol. Sci. 176, 161—234.

McFarlane, A.C., Atchison, M., Yehuda, R., 1997. The acute stress response following motor vehicle accidents and its relation to PTSD. Ann. N. Y. Acad. Sci. 821, 437—441.

McGaugh, J.L., 2000. Memory—a century of consolidation. Science 287, 248—251.

McGaugh, J.L., 2004. The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu. Rev. Neurosci. 27, 1—28.

McGaugh, J.L., Roozendaal, B., 2002. Role of adrenal stress hormones in forming lasting memories in the brain. Curr. Opin. Neurobiol. 12, 205—210.

Müller, G.E., Pilzecker, A., 1900. Experimentelle beitrage zur lehre von Gedachtnis. Z. Psychol. 1, 1—288.

Nishida, M., Pearsall, J., Buckner, R.L., Walker, M.P., 2009. REM sleep, prefrontal theta, and the consolidation of human emotional memory. Cereb. Cortex 19, 1158—1166.

Payne, J.D., Kensinger, E.A., 2011. Sleep leads to changes in the emotional memory trace: evidence from FMRI. J. Cogn. Neurosci. 23, 1285—1297.

Payne, J.D., Stickgold, R., Swanberg, K., Kensinger, E.A., 2008. Sleep preferentially enhances memory for emotional components of scenes. Psychol. Sci. 19, 781—788.

Payne, J.D., Jackson, E.D., Hoscheidt, S., Ryan, L., Jacobs, W.J., Nadel, L., 2007. Stress administered prior to encoding impairs neutral but enhances emotional long-term episodic memories. Learn. Mem. 14, 861—868.

Phan, K.L., Wager, T., Taylor, S.F., Liberzon, I., 2002. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 16, 331—348.

Plihal, W., Born, J., 1999. Memory consolidation in human sleep depends on inhibition of glucocorticoid release. Neuroreport 10, 2741—2747.

Pruessner, J.C., Kirschbaum, C., Meinlschmid, G., Hellhammer, D.H., 2003. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 28, 916—931.

Roozendaal, B., Schelling, G., McGaugh, J.L., 2008. Corticotropin-releasing factor in the basolateral amygdala enhances memory consolidation via an interaction with the beta-adrenoceptor-cAMP pathway: dependence on glucocorticoid receptor activation. J. Neurosci. 28, 6642—6651.

Schelling, G., Roozendaal, B., Krauseneck, T., Schmoelz, M., DEQ, D., Briegel, J., 2006. Efficacy of hydrocortisone in preventing post-traumatic stress disorder following critical illness and major surgery. Ann. N. Y. Acad. Sci. 1071, 46—53.

Sterpenich, V., Albouy, G., Darsaud, A., Schmidt, C., Vandewalle, G., Dang Vu, T.T., Desseilles, M., Phillips, C., Degueldre, C., Balteau, E., Collette, F., Luxen, A., Maquet, P., 2009. Sleep promotes the neural reorganization of remote emotional memory. J. Neurosci. 29, 5143—5152.

Sterpenich, V., Albouy, G., Boly, M., Vandewalle, G., Darsaud, A., Balteau, E., Dang-Vu, T.T., Desseilles, M., D'Argembeau, A., Gais, S., Rauchs, G., Schabus, M., Degueldre, C., Luxen, A., Collette, F., Maquet, P., 2007. Sleep-related hippocampo-cortical interplay during emotional memory recollection. PLoS Biol. 5, e282.

Stickgold, R., 2005. Sleep-dependent memory consolidation. Nature 437, 1272—1278.

Takashima, A., Nieuwenhuis, I.L., Jensen, O., Talamini, L.M., Rijpkema, M., Fernandez, G., 2009. Shift from hippocampal to neocortical centered retrieval network with consolidation. J. Neurosci. 29, 10087—10093.

Takashima, A., Petersson, K.M., Rutters, F., Tendolkar, I., Jensen, O., Zwarts, M.J., McNaughton, B.L., Fernandez, G., 2006. Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. Proc. Natl. Acad. Sci. U. S. A. 103, 756—761.

van der Helm, E., Yao, J., Dutt, S., Rao, V., Saletin, J.M., Walker, M.P., 2011. REM sleep depotentiates amygdala activity to previous emotional experiences. Curr. Biol. 21, 2029—2032.

van Marle, H.J., Hermans, E.J., Qin, S., Fernandez, G., 2009. From specificity to sensitivity: how acute stress affects amygdala processing of biologically salient stimuli. Biol. Psychiatr. 66, 649—655.

Wagner, A.D., Shannon, B.J., Kahn, I., Buckner, R.L., 2005a. Parietal lobe contributions to episodic memory retrieval. Trends Cogn. Sci. 9, 445—453.

Wagner, U., Hallschmid, M., Rasch, B., Born, J., 2006. Brief sleep after learning keeps emotional memories alive for years. Biol. Psychiatr. 60, 788—790.

Wagner, U., Degirmenci, M., Drosopoulos, S., Perras, B., Born, J., 2005b. Effects of cortisol suppression on sleep-associated consolidation of neutral and emotional memory. Biol. Psychiatr. 58, 885—893.

Walker, M.P., 2009. The role of sleep in cognition and emotion. Ann. N. Y. Acad. Sci. 1156, 168—197.

Walker, M.P., van der Helm, E., 2009. Overnight therapy? The role of sleep in emotional brain processing. Psychol. Bull. 135, 731—748.

Wang, J., Korczykowski, M., Rao, H., Fan, Y., Pluta, J., Gur, R.C., McEwen, B.S., Detre, J.A., 2007. Gender difference in neural response to psychological stress. Soc. Cogn. Affect Neurosci. 2, 227—239.

Wilhelm, I., Wagner, U., Born, J., 2011. Opposite effects of cortisol on consolidation of temporal sequence memory during waking and sleep. J. Cogn. Neurosci. 23, 3703—3712.