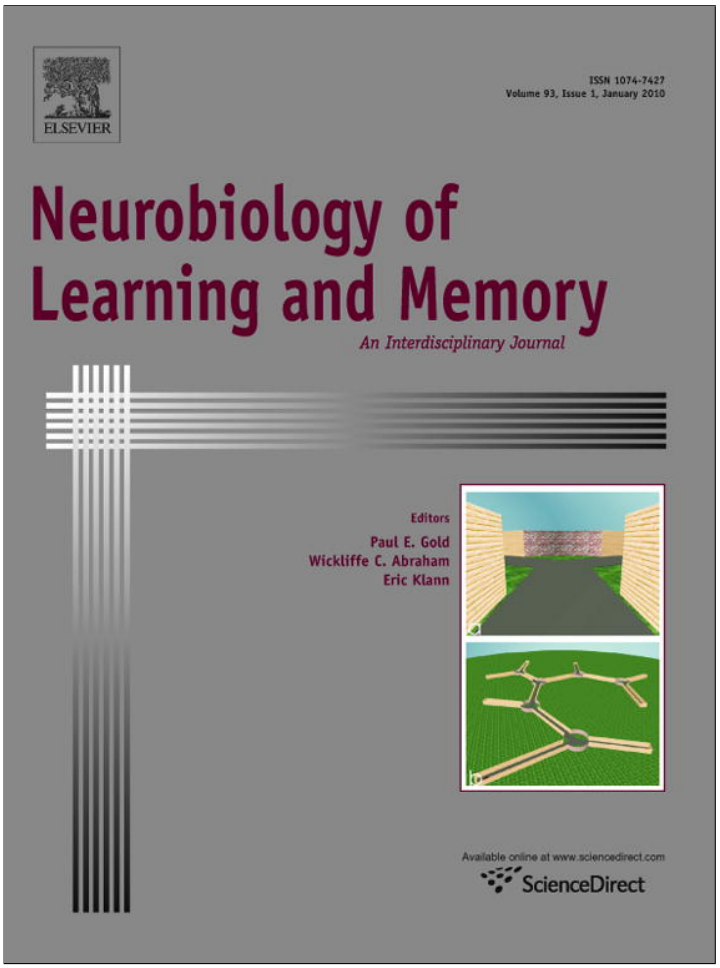

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Interacting noradrenergic and corticosteroid systems shift human brain activation patterns during encoding

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ABSTRACT

Emotionally arousing experiences are usually well retained, an effect that depends on the release of adrenal stress hormones. Animal studies have shown that corticosterone and noradrenaline – representing the two main stress hormone systems – act in concert to enhance memory formation by actions involving the amygdala, hippocampus and prefrontal cortex (PFC). Here we test whether interactions between these two stress hormone systems also affect human memory formation as well as the associated pattern of brain activation. To this end, forty-eight male human subjects received hydrocortisone, yohimbine or both before presentation of emotional and neutral pictures. Activity in the amygdala, hippocampus and PFC was monitored with functional Magnetic Resonance Imaging (fMRI) during encoding of these stimuli, when hormonal levels were elevated. Memory performance was tested 1 week later. We investigated whether an increased level of one of the two hormone systems would lead to differential effects compared to the combined application of the drugs on brain activation and memory performance. We report that the application of cortisol led to an overall enhancing effect on recognition memory, with no significant additional effect of yohimbine. However, during encoding the brain switched from amygdala/hippocampus activation with either hormone alone, to a strong deactivation of prefrontal areas under the influence of the combination of both exogenous hormones. Although we did not find evidence that exogenous stimulation of the noradrenergic and corticosteroid systems led to significant interaction effects on memory performance in this experiment, we conclude that stress hormone levels during encoding did differentially determine the activation pattern of the brain circuits here involved.

1. Introduction

Exposure to stressful or emotionally arousing experiences affects cognitive function in humans and animals (McGaugh, 2000). Stress exposure either shortly before or after learning particularly enhances memory of emotionally arousing information (Buchanan & Lovallo, 2001; Cahill & Alkire, 2003; Cahill, Gorski, & Le, 2003; Kuhlmann & Wolf, 2006; Payne et al., 2007), although this has not always been found (Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, 2003). The involvement of corticosteroid and adrenergic hormones in human memory has been investigated by either activating or blocking these stress hormones. For example, post-training administration of adrenaline to humans enhances memory consolidation for emotionally arousing material (Cahill & Alkire, 2003). Conversely, blocking (nor)adrenergic function with propranolol selectively impairs memory performance for emotionally arousing, but not emotionally neutral, material (Cahill, Prins, Weber, & McGaugh, 1994; Hurlemann et al., 2005; van Stegeren, 2008; van Stegeren, Everaerd, Cahill, McGaugh, & Gooren, 1998). Imaging studies show that the amygdala as well as the hippocampus (HC) play important roles in the consolidation of memory of emotional information and that this process is noradrenaline dependent. Emotional pictures evoked a noradrenergic response that was associated with increased amygdala activity (van Stegeren et al., 2005) and human emotional memory is associated with a β-adrenergic-dependent modulation of amygdala-HC interactions (Strange & Dolan, 2004).

Corticosteroid hormones also dose-dependently enhance memory consolidation when administered shortly before or after learning. Comparable to the effects of noradrenergic antagonism, steroid-synthesis inhibitors or corticosteroid receptor antagonists or genetic modification of the glucocorticoid receptor impair memory consolidation and block stress- and epinephrine-induced memory enhancement in rodents and humans (de Kloet, Oitzl, & Joëls, 1999; Kellendonk, Gass, Kretz, Schutz, & Tronche, 2002;

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Lupien et al., 2002; Maheu, Joober, Beaulieu, & Lupien, 2004; Maheu, Joober, & Lupien, 2005; Oitzl, Reichardt, Joëls, & de Kloet, 2001; Roozendaal, 2000; Roozendaal, Carmi, & McGaugh, 1996).

Importantly, recent studies indicate that particularly the *combined* action of noradrenaline and corticosteroid hormones potently affects memory function (Hurlemann et al., 2007; McGaugh & Roozendaal, 2002; Pu, Krugers, & Joëls, 2007; Roozendaal, Okuda, Van der Zee, & McGaugh, 2006; Roozendaal, Quirarte, & McGaugh, 2002). Blockade of β-adrenoceptors in the amygdala with propranolol prevents glucocorticoid-induced memory enhancement for emotionally arousing training (Quirarte, Roozendaal, & McGaugh, 1997; Roozendaal et al., 2006). In a recent functional Magnetic Resonance Imaging (fMRI) study we found support for an interactive effect of these two hormones in influencing arousal-induced amygdala activity in healthy humans. Interestingly, in this study we found that subjects with higher endogenous cortisol levels had a significantly stronger amygdala response to emotional pictures compared to participants with lower cortisol levels, whereas administration of the noradrenergic antagonist propranolol blocked this cortisol-dependent amygdala activation (van Stegeren et al., 2007). However, to our knowledge, pharmacological activation of the noradrenergic and corticosteroid systems and its effect on human memory formation and related brain activity has not been reported.

Animal (McGaugh, 2000, 2004; Quirarte et al., 1997; Roozendaal, Barsegyan, & Lee, 2008; Roozendaal, Nguyen, Power, & McGaugh, 1999) as well as human studies (Dolcos, LaBar, & Cabeza, 2004b; Labar & Cabeza, 2006; Phan, Wager, Taylor, & Liberzon, 2002) have shown that amygdala activity is critically involved in memory enhancement of emotionally arousing experiences by strengthening consolidation processes in other brain regions such as the HC. This processing of emotional information in the amygdala is noradrenaline dependent (Strange & Dolan, 2004; van Stegeren et al., 2005). Other studies indicated that the prefrontal cortex (PFC) is also involved in mediating stress effects on memory consolidation (Kern et al., 2008; Kilpatrick & Cahill, 2003; Stark et al., 2006; Wang et al., 2007). Studies on the role of the PFC in emotion and memory not only showed that PFC activity is sensitive to stress and emotional arousal (Grimm et al., 2006), but also that successful encoding activity in the left ventrolateral and dorsolateral PFC is greater for arousing than for neutral pictures (Dolcos, LaBar, & Cabeza, 2004a). Most likely, the PFC interacts with other brain regions, including the amygdala and HC, in mediating these arousal effects on memory (Cerqueira, Mailliet, Almeida, Jay, & Sousa, 2007; Diamond, Campbell, Park, Halonen, & Zoladz, 2007; Goldin, McRae, Ramel, & Gross, 2008; Kensinger & Schacter, 2006; Nomura et al., 2004; Urry et al., 2006).

So far, it is unknown to what extent the circuit of amygdala, HC and PFC shows altered activation during encoding of arousing information under the influence of the two interacting hormonal systems (van Stegeren, 2009). To address this issue, 48 healthy male participants were allocated to one of four drug conditions. They received either the noradrenergic stimulant yohimbine (20 mg) (=YOH/PL) or hydrocortisone 20 mg (=CORT/PL) or a combination of both (YOH/CORT) versus placebo (PL/PL). At peak plasma times of both drugs, subjects entered an fMRI scanning procedure in which they were asked to rate randomly presented emotionally arousing (EMO) and neutral (NEU) pictures on emotional intensity (Fig. 1). Brain activation was monitored during picture viewing, i.e. at a time that stress hormone levels (YOH and CORT) were elevated. Memory of the pictures was tested by surprise 1 week later without any drugs. In this study we specifically investigated YOH and CORT effects on changes in brain activation during encoding and/or consolidation, and related this to memory performance at a point in time where stress levels were no longer elevated.

2. Materials and methods

2.1. Subjects

Forty-eight male students applied for the study. One participant left the study after the first session. All forty-seven participants (mean age = 22.3 ± 3.8 years, ranging from 18 to 39 years) included in the final analyses were healthy, without medication or substance abuse and had no experience with experiments of this kind. They received course credit for their participation or a small finan-

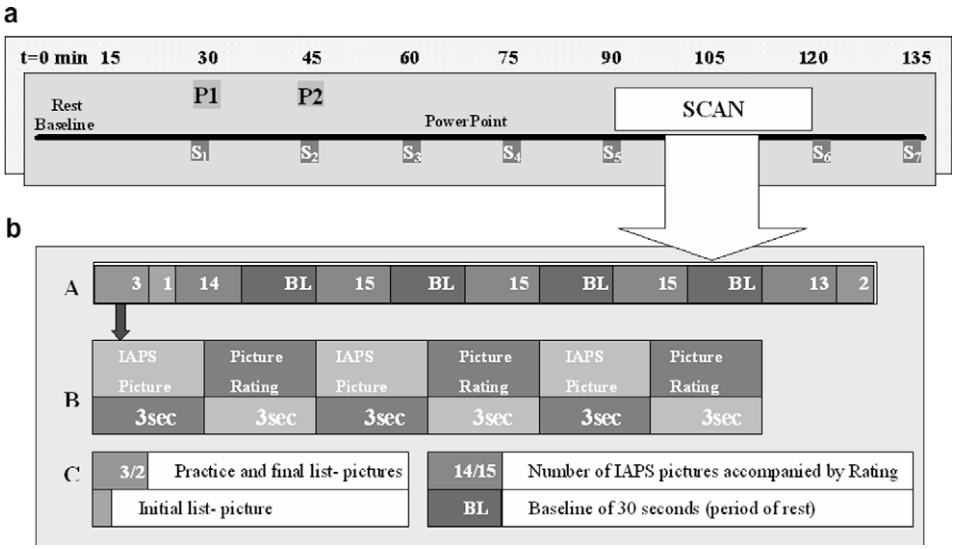

Fig. 1. Timeline (a) and stimulus presentation paradigm (b) in the scanner. (a) Timeline of experimental procedure during session 1. Subjects entered the experiment and were seated during a 30-min acclimatization period, during which they were informed on the procedure of that day. Salivary sampling (S1–S7) took place for the first time (S1) before the first drug (P1) was taken at 30 min after baseline, just before the second drug (P2) was applied (S2 = 45 min after baseline) and then at 15-min intervals. Only just before and after scanning there was a 30 min interval. Before entering the MRI-room the participants were properly informed about the scanning procedure by use of a PowerPoint presentation. (b) Stimulus presentation paradigm in the scanner: every grey block in panel A is presented in a format shown in panel B. Practice, initial- and final-list pictures were excluded from the analysis of the final memory results to prevent primacy and recency effects. Panel C explains the various blocks and numbers in panel A and B.

cial compensation. The study was approved by the ethical committee of the University of Amsterdam and informed consent was obtained from all participants.

2.2. Drugs and design

The fMRI study applied a randomized double-blind placebo controlled design in which participants received a combination of the noradrenergic agonist Yohimbine (YOH) 20 mg, Hydrocortisone (CORT) 20 mg and/or placebo. Yohimbine stimulates central noradrenergic activity via blockade of the α-2 adrenergic receptor. The choice for 20 mg of yohimbine is based on findings that this dose successfully increases peripheral noradrenaline levels in healthy males (O'Carroll, Drysdale, Cahill, Shajahan, & Ebmeier, 1999). Cortisol levels were manipulated by administration of 20 mg of hydrocortisone (Buchanan & Lovallo, 2001). All drugs were taken orally. Participants were randomly allocated to one of four drug groups with 12 participants in each group: placebo/placebo (PL/PL), placebo/Hydrocortisone (PL/CORT), Yohimbine/placebo (YOH/PL) or Yohimbine/Hydrocortisone (YOH/CORT). Drugs were administered at two different time points: YOH at 1 h and CORT at 45 min before scanning, respectively, (P1 = 30 min after baseline and P2 = 45 min after baseline, Fig. 1) in order to reach peak plasma levels at the time of entering the MRI-scanning procedure. As cortisol has a circadian rhythm characterized by relatively high morning levels, the starting time for the experiment was set at 12.00 h when free cortisol levels are descending to a low steady-level.

2.3. Experimental protocol

Participants entered the experiment and were seated during a 30-min acclimatization period, during which they were informed on the procedure of that day. Salivary sampling (S1–S7) took place for the first time (at S1) before the first drug (P1) was taken, just before the second drug (P2) was applied and then at 15-min intervals (Fig. 1a). Presentation of pictures was accomplished using stimulus presentation software (Presentation v9.90). During the stimulus task, pictures were projected on a screen in front of the MRI scanner. Pictures were derived from the International Affective Picture System (Lang, Bradley, & Cuthbert, 1997). In an earlier fMRI study of our group (van Stegeren et al., 2005), EMO pictures evoked significantly more amygdala activation than NEU pictures under placebo condition and led to better memory performance for EMO than NEU pictures. The stimulus set consisted of 36 NEU and 36 aversive EMO pictures that were randomly presented. Each picture was shown for 3 s, followed by a screen that asked for a personal dichotomous rating of the preceding picture (Fig. 1b). Participants pressed one out of two buttons to indicate whether they felt the image was 'neutral' or 'emotional'. Pictures were randomly presented and jittered (500 ms-2 s).

2.4. Memory task

Exactly 1 week later, participants returned for an unannounced memory test outside the scanner. During this second session long-term memory was assessed with a free recall and recognition test. To avoid intentional rehearsal of the stimuli, participants were unaware of the purpose of this second session until that time. First the participants were instructed to recall as many pictures as possible from the stimulus task. Their answers were recorded and scored afterwards. There was no time limit and participants were encouraged to remember as much as they could. Answers were judged by two experimenters, blind for the drug condition, and compared to a list describing all 72 stimuli in detail. Free recall performance was scored as the number of correctly recalled items. The recognition task consisted of the presentation of the 72 (36 EMO + 36 NEU) 'old' pictures mixed with 48 (24 EMO + 24 NEU) 'new' filler pictures with comparable emotional intensity. Participants were instructed to indicate whether they had seen the picture before or not by pressing one out of two buttons. Recognition scores were calculated as the percentage correctly recognized pictures ('hits'). False alarm rates were calculated as the percentage of 'new' filler pictures that were erroneously judged as 'seen before'. Corrected recognition scores were calculated by subtracting false alarm rates from the original recognition scores (hits – false alarms).

2.5. Salivary sampling

Both salivary CORT and alpha-amylase (sAA) levels were determined, being representative markers for cortisol levels and noradrenergic activity, respectively, in humans (Kirschbaum & Hellhammer, 1994; Nater, Rohleder, Schlotz, Ehlert, & Kirschbaum, 2007). Salivary samples were collected at seven different time points with a baseline (S1) measurement, immediately after an acclimatization period of 30 min, using commercially available salivettes (Sarstedt, Nümbrecht, Germany) (Fig. 1a). Salivary samples S5 at $t = 90$ and S6 at $t = 120$ were collected immediately before and after the scanning procedure, respectively. Free cortisol levels were measured using a commercially available immunoassay (IBL, Hamburg, Germany). sAA levels were determined with methods identical to the procedure used in a previous study (van Stegeren, Rohleder, Everaerd, & Wolf, 2006).

2.6. Scanning procedure/fMRI acquisition

Participants were prepared for scanning and placed in the scanner (3T, Philips, Eindhoven, the Netherlands) with the subjects' head fixed in the head-coil. The response device was placed in their dominant hand and they could practice how to press the buttons. A structural scan was made first (3D-T1 TFE, FA 8, TR 9.7 ms, FOV 250 × 250, matrix size 256 × 256, 182 slices, slice thickness 1.2 mm) and hereafter the event-related fMRI procedure began (T2 GE-EPI, TR 2298 ms, TE 28 ms, FA 90, FOV 220 × 220, matrix size 96 × 96, 35 slices, slice thickness 3 mm, slice gap 0.3 mm). The functional images were positioned perpendicular to the long axis of the HC and completely covering the left (L) and right (R), the L and R HC and PFC.

2.7. fMRI data analysis

All analyses were carried out using FEAT (FMRI Expert Analysis Tool) Version 5.92, part of FSL 4.0 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). All pre-statistics processes were applied conform previous studies (van Stegeren et al., 2005, 2007). To model the events a double gamma hemodynamic response function (HRF) and its temporal derivative was applied to the basic waveform. Functional images were co-registered to high-resolution scans (7 DOF) and subsequently to standard images (12 DOF), using FLIRT (for references see FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl).

Two analyses were carried out. The first analysis was directed at brain activity related to arousal effects of the stimulus material (EMO versus NEU) during presentation and encoding. At first level two predictors were coded 'EMO' and 'NEU', respectively, representing mean activation during presentation of EMO and NEU pictures. This label was provided in retrospective by the personal rating of each participant of the pictures during the experiment. This procedure has been shown to improve sensitivity for detecting activation in regions including the amygdala when using arousing material (Phan et al., 2003). Mean brain activation was analyzed by

a general linear model contrasting these predictors to baseline. Furthermore both predictors were contrasted to each other in two ways: EMO > NEU and NEU > EMO. At higher-level analysis a two-way ANCOVA model was used for each of the first level contrasts with drug condition as between-subjects factor. One subject was excluded from the drug group analysis because of poor image quality. In the higher-level whole brain analysis average activation was determined for each drug group as well as the difference between the groups for forty-six (46) participants (one from the PL/PL group and one from the YOH/CORT group was missing). Additionally, drug effects interacting with the arousal component (EMO-NEU) were calculated.

The second analysis was directed at brain activation and deactivation during presentation of later successfully encoded pictures. Four separate predictors were created at first level for EMO and NEU pictures that were later correctly recognized (Ehits and Nhits) or forgotten (Eforg and Nforg) during the recognition task. In a second higher-level analysis a main effect of 'Memory' on brain activation was analyzed by contrasting activation during Ehits + Nhits with Eforg + Nforg and finally a two-way interaction effect of memory × drugs was analyzed at higher level.

The analysis was carried out using FLAME (FSL) stage 1 only. Z (Gaussian T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a cluster-corrected significance threshold of $p = .05$. After the whole brain analysis specific analyses were carried out with a priori chosen anatomically based Regions of Interests (ROIs) as masks: amygdala, HC, anterior cingulate cortex, and dorsolateral part (BA46) and inferior frontal gyrus (BA47) of the PFC. Mean activation in every ROI was calculated using Feat-query (FSL) resulting in mean activation values in ROIs chosen for this study.

2.8. Statistical analysis

Memory data were analyzed with a MANOVA – General linear model, repeated measures, with "Arousal" (EMO versus NEU pictures) as within-subjects variable and drug condition (2 × 2) (pill 1: Yoh versus PL and pill 2: Cort versus PL) as between-subjects variable. Main and interaction effects were calculated. Since we had specific predictions on the interaction of YOH/CORT versus PL/PL, we carried out an additional analysis with drug group (4) as between-subject variable, with a specific a priori contrast between PL/PL and YOH/CORT, in which we expected better memory performance for YOH/CORT than PL/PL.

3. Results

3.1. Hormone measures

Baseline sAA levels (used as a marker for noradrenergic and sympathetic activation (van Stegeren et al., 2006)) as well as cortisol levels before drug administration did not differ between the four groups: sAA levels were around 30 u/ml and cortisol levels around 7 nmol/L ($p > .10$; Fig. 2). Drug manipulation was successful. sAA levels were significantly higher ($F(1, 16) = 7.75$; $p < .05$) in the groups receiving (20 mg) YOH (i.e., the YOH/PL and YOH/CORT groups) compared to the groups receiving PL (PL/PL or PL/CORT) from 30 min after drug intake throughout session 1 (Fig. 2a). Subjects who received CORT (20 mg) (combined PL/CORT and YOH/CORT groups) showed manifold and significantly ($F(1, 22) = 12.52$, $p < .01$) higher cortisol levels than did the PL groups (PL/PL and YOH/PL) from 30 min after drug intake throughout the entire experimental procedure of session 1 (Fig. 2b). Administration of YOH did not affect cortisol levels and CORT administration did not affect sAA levels (all $p > .10$). We conclude that hormone levels were elevated during scanning at the time participants were exposed to the EMO and NEU pictures. One week later during session 2, at the time of retention testing, hormone levels were completely comparable to baseline levels of session 1.

3.2. Brain activity during picture viewing

A whole brain analysis, followed by the specified ROI analysis, compared mean brain activation during presentation of EMO and NEU pictures, irrespective of drug condition. Results of the ROI analysis are presented here. Overall, EMO pictures evoked significantly more activation than NEU pictures in the right (R) and left (L) amygdala, R and L HC and several areas of the PFC, predomi-

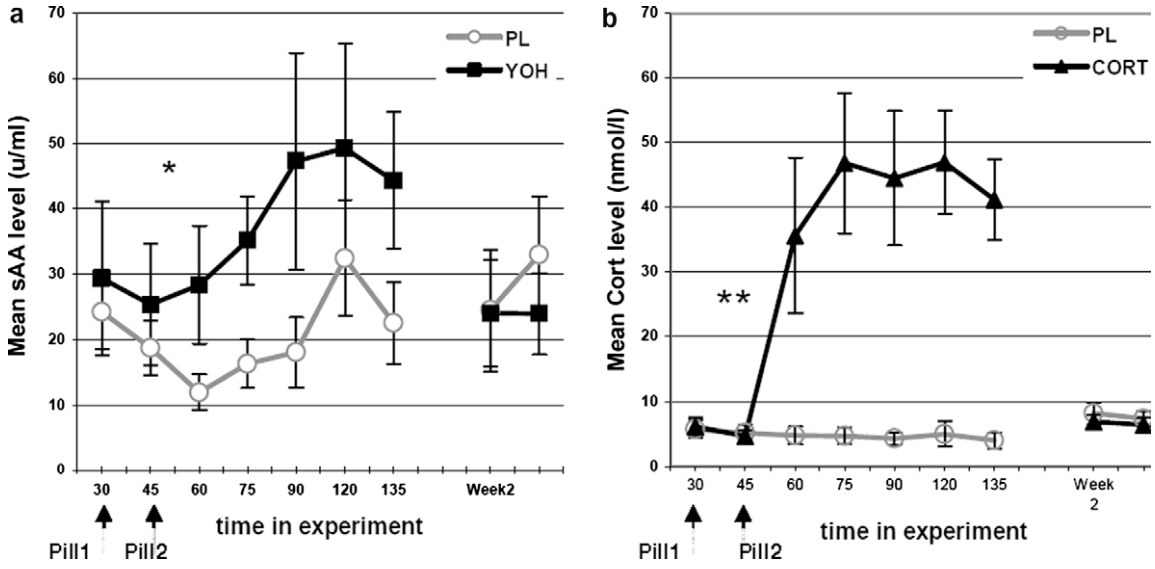

Fig. 2. Neuroendocrine responses to drug intake and experimental procedure. (a) Mean salivary alpha amylase (sAA) level in response to pill 1 (left arrow). The first pill was applied at $t = 30$ min. Subjects received either yohimbine (YOH) (20 mg) or placebo (PL). Drug manipulation by 20 mg YOH was successful: YOH led to a significantly ($* = p < .05$) higher sAA level than PL from $t = 60$ min onwards and throughout the experiment during session1. (b) Mean cortisol (CORT) level in response to pill 2 (right arrow), that was applied at $t = 45$ min. Subjects who received CORT showed manifold and significantly ($** = p < .01$) higher CORT levels than the placebo group from 15 min after drug intake throughout the whole experimental procedure during session 1. Note that hormones were at baseline levels during session 2, one week later. So, at the time of retrieval hormone levels were comparably low in all groups.

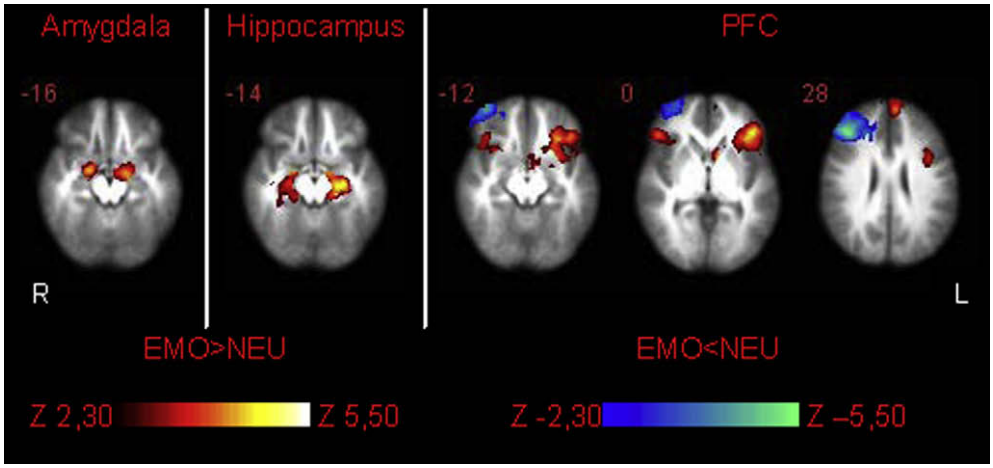

Fig. 3. Brain (de)activation during presentation of emotional (EMO) versus neutral (NEU) stimuli. Arousal effects of the stimulus material during presentation and encoding was compared by contrasting mean activation during NEU pictures with mean activation during EMO pictures. Transversal images at various levels (e.g. for amygdala at *z*-coordinate = −16) are depicted for the specific regions of interest (ROIs). EMO pictures evoked significantly more activation than NEU pictures in R and L Amygdala, R and L hippocampus and areas in predominantly the L prefrontal cortex (PFC). Also deactivation was found in the R BA46 of the PFC.

nantly on the L side (Fig. 3). On the other hand EMO pictures contrasted with NEU pictures induced a deactivation in the R BA46 of the PFC.

Subsequently, we analyzed drug effects on brain activity while viewing EMO versus NEU pictures. No significant effects were found with either of the drugs alone (YOH/PL or PL/CORT, data not shown) compared to PL/PL. The combination of YOH/CORT versus PL/PL led to slightly more activation in the L amygdala/parahippocampal region (x, y, $z = 26, -8, -14$; $Z = 2.97$, $p = .07$), but this was seen only when allowing an uncorrected voxel-based specific ROI analysis. Thus the overall higher-level activity during the perception of EMO versus NEU stimuli – particularly in the amygdala and hippocampus – were not further modulated by the drugs.

3.3. Arousal and drug effects on memory performance

One week later outside the scanner, EMO pictures were not only better recalled ($p < .01$; Fig. 4a), they were also significantly better recognized than NEU pictures ($p < .01$) over all drug conditions (Fig. 4b). Main effects of drugs on free recall and recognition performance were calculated. As YOH or CORT given either alone or in combination did not affect free recall, we further confined ourselves to drug effects on recognition memory. No main effect of pill 1 could be found: YOH did not have a main effect on recognition memory (Fig. 4c1), compared to placebo (PL). However, a main effect of pill 2 was found: CORT significantly enhanced recognition memory of both EMO and NEU pictures compared with PL (Fig. 4c2). No interaction effect of pill 1 × pill 2 on memory was found. In the additional analysis the effect of the four specific drug groups on memory was calculated. The combined application of YOH/CORT also led to an overall (main) enhancing effect on recognition memory ($p < .05$), but particularly for EMO pictures (with a trend for the drug × arousal interaction effect: $p < .10$, Fig. 4c3) with a medium effect size ($\eta^2 = .099$) compared to PL/PL. When contrasting the YOH/CORT with the PL/CORT group separately, the drug × arousal interaction effect was not significant, indicating that YOH did not modify CORT-induced memory enhancement.

False alarm rates were significantly higher ($p < .01$) for EMO than for NEU pictures. Drugs also increased false alarm rates: YOH/PL and PL/CORT as well as the combined YOH/CORT condition led to more EMO false alarms than in the PL/PL control condition. Because such drug effects on false alarm rates indicate an emotional or arousal bias at the time of retention testing, we calculated corrected recognition scores (hits – false alarms) to account for this differential arousal and drug effect on false alarms. Analyzing our findings with these corrected recognition scores did not alter the main findings: a main effect of 'arousal' remained statistically significant (Emo > Neu) ($F(1, 42) = 38.28$; $p < .001$; $\eta^2 = .48$). Also a significant main effect of 'drug condition' was found ($F(3, 42) = 3.40$; $p < .05$; $\eta^2 = .20$): both cortisol groups (PL/CORT and YOH/CORT) remembered significantly more EMO and NEU pictures than did subjects in the PL/PL group. However, no interaction between arousal × drug condition was found. So, even if drugs were not present at the time of memory testing (see hormone levels in Fig. 2), subjects were affected by the drug condition of the previous week in their memory (recognition) performance, as well as in their false alarm rates. This indicates that the drugs had influenced encoding and/or consolidation of the pictures.

3.4. fMRI data: successful encoding effect on brain activity

We examined whether recognition memory performance during session 2 was related to specific brain activation patterns during encoding in the first session. To this end, we performed a higher-level analysis, detecting activation patterns of later successfully recognized pictures (emotional 'hits' = Ehits and neutral hits = Nhits) contrasted with activation of later not recognized emotional (Eforg) and neutral (Nforg) pictures. Successful encoding of EMO and NEU pictures together (i.e. Ehits + Nhits > Eforg + Nforg), regardless of drug condition, was linked to an activation of predominantly the R HC and amygdala and L frontal areas BA11, BA45, BA47 (orbitofrontal cortex) (Fig. 5). Deactivation was observed mainly in prefrontal areas, more specifically in L BA10 and 46 and R BA10, 11, 46 and 47 (Fig. 5, left panel).

3.5. fMRI data: interaction effect of drugs × memory on brain activity

Analyzing drug effects on activation during successfully encoded EMO + NEU pictures, the CORT alone (PL/CORT) condition showed activation clusters in the R HC and L frontal gyrus, when compared to PL/PL controls (Fig. 6a). Similarly, the YOH alone (YOH/PL) condition showed increased activation of the R HC and L superior frontal gyrus compared to PL/PL (Fig. 6b). However, the combination of these hormones (YOH/CORT) did not result in an activation of these areas, but instead led to a strong deactivation of the R orbitofrontal and insular cortex (BA47) as well as a

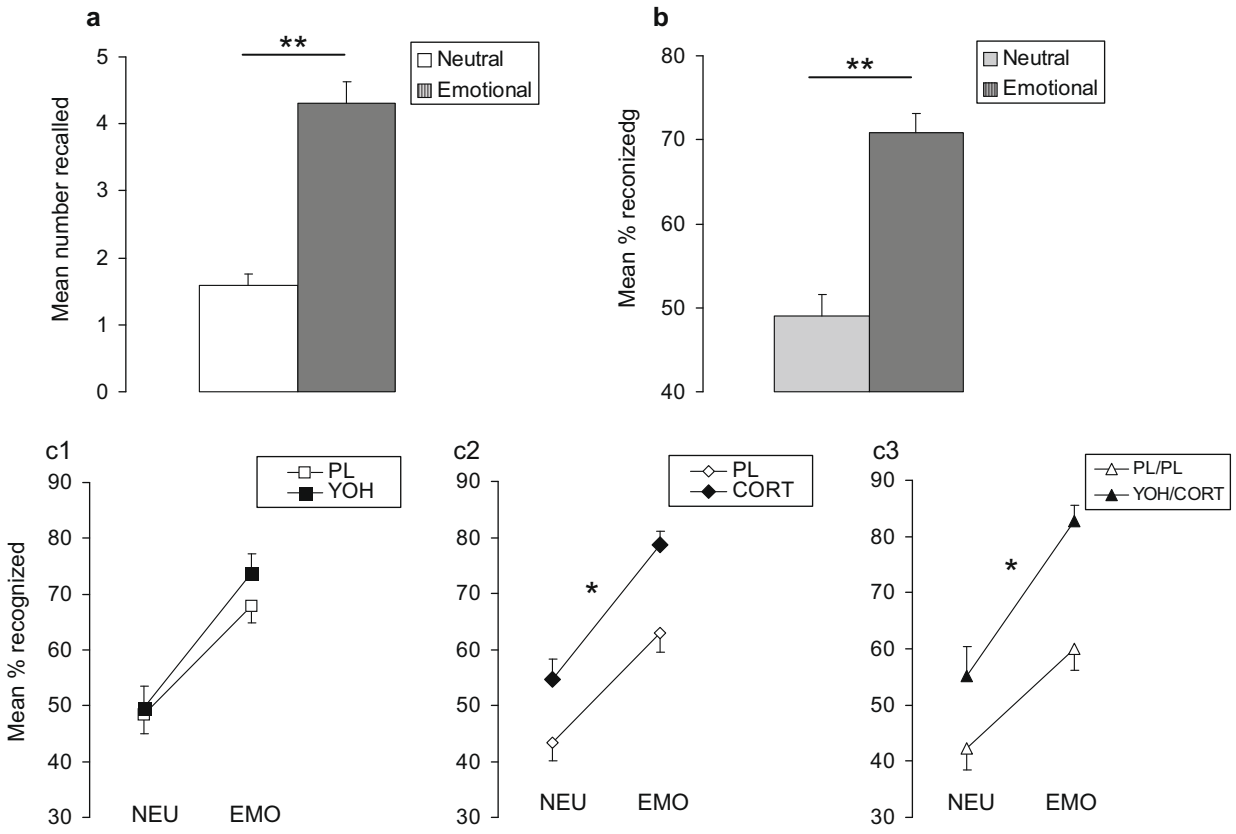

Fig. 4. Main effect of arousal and drug effects on free recall and recognition memory. Emotional pictures were significantly better recalled (a) and recognized (b) than neutral pictures over all groups (** = $p < .01$). We observed no main effect of pill 1 (YOH versus PL) on recognition memory performance (c1). By contrast, a significant main effect of pill 2 (CORT versus PL) was found on recognition memory (* = $p < .05$) (c2), independent of picture type. The specific analysis on recognition memory by drug groups revealed a significant main effect (* = $p < .05$) of YOH/CORT compared to PL/PL observed for recognition performance (c3). This effect of YOH/CORT was slightly stronger for recognition of EMO pictures compared to NEU pictures (interaction arousal × drug group showing a trend: +* = $p < .10$).

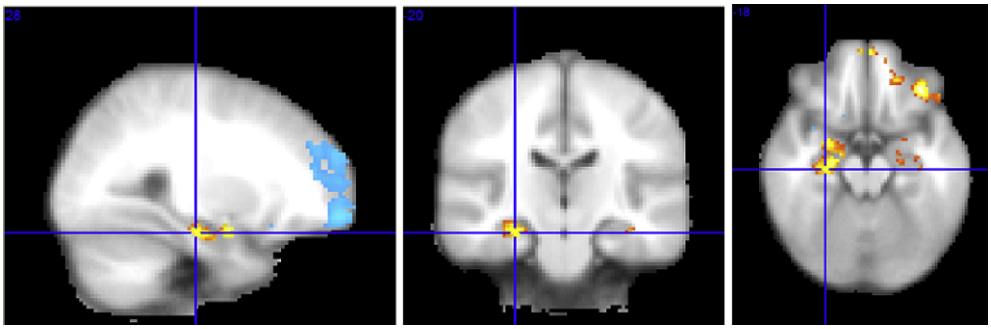

Fig. 5. Brain activation during successfully encoded emotional (EMO) and neutral (NEU) pictures. Contrasting activation of successfully encoded pictures (Ehits + Nhits) with later forgotten pictures (Eforg + Nforg) led to strong activation in the R HC (at the crosshair), R amygdala (all panels) and L frontal areas BA11, BA45, BA47 (orbitofrontal cortex) (visible in the right panel). Deactivation was seen in prefrontal areas, more specifically in the L BA10 and 46 and R BA10, 11, 46 and 47 (left panel).

deactivation of the L and R frontal pole compared to PL/PL (Fig. 6c). So, the combination of YOH/CORT versus PL/PL led to another brain activation pattern than YOH/PL or PL/CORT separately, a pattern that later appeared to be associated with very effective memory formation. Thus our findings indicate that the actions of the two hormones within the brain are not simply additive.

3.6. Correlation analysis between memory performance and brain activity

Finally, we analyzed activation levels in our ROIs during picture presentation and correlated this activation with later performance on the recognition memory task. YOH/CORT treatment-induced shifts in activation of networks, related to memory performance, were also evident from these correlational analyses. As expected based on previous studies, subjects who received PL/PL showed a significant positive correlation between later memory performance for EMO pictures and L amygdala activation ($r = .61$, $p < .05$), but no significant correlation with HC activity at the time of presentation. Also, there was no significant correlation between amygdala, HC or PFC activity and recognition scores for NEU pictures. By contrast, in the YOH/CORT condition we found a strong yet *negative* correlation between recognition scores of EMO pictures and L and R HC activation ($r = -.86$, $p < .001$; $r = -.54$, $p < .05$, respectively), but no correlation with amygdala activity. Apparently, in the YOH/CORT group deactivation of the L and R HC during encoding of EMO pictures

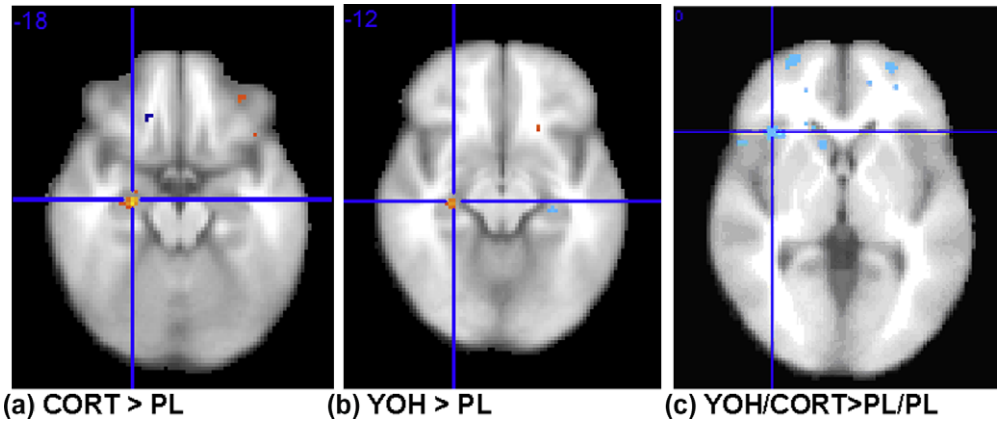

Fig. 6. Interaction effect of drugs with successfully encoded pictures. This depicts the two-way interaction effect of activation during successfully encoded pictures ('memory') with drug condition. PL/CORT (a) or YOH/PL (b) separately caused activation of the R hippocampus (HC) and a small activation cluster of the L superior frontal gyrus compared to PL/PL. However, the combined administration of YOH/CORT contrasted with the PL/PL group (c) did not activate the HC or amygdala region, but instead led to *de*activation of the R orbitofrontal and insular cortex (BA47) and of deactivation of the L and R frontal pole.

was related to better memory performance 1 week later. Moreover, in the YOH/CORT group, but not in the PL/PL group, (de)activation in the R HC significantly correlated with (de)activation in the R and L PFC (BA47) ($r = .66$ and $r = .69$, respectively, both $p < .01$) (Fig. 7).

So, memory enhancement induced by the combined administration of YOH and CORT, but not that by CORT alone, appears to be correlated with deactivation of a circuit of HC and area BA47 of the PFC during the encoding phase.

4. Discussion

The main findings of this study are that: (i) exogenous CORT at encoding (with or without extra stimulation of the noradrenergic system) enhances human memory and (ii) YOH and CORT in combination have a synergistic effect on the brain activation pattern during encoding.

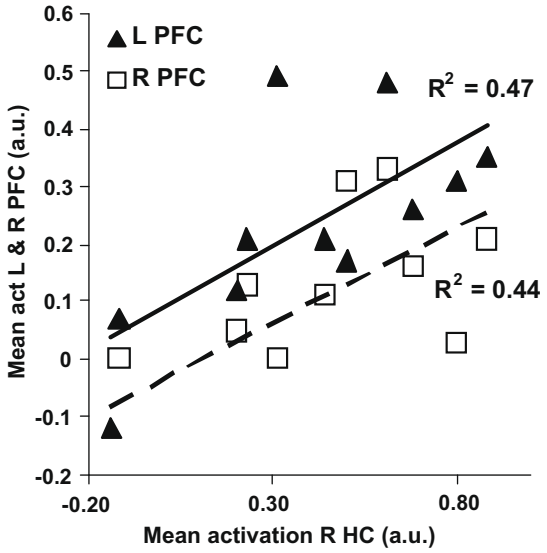

Fig. 7. Correlation between hippocampus (HC) and prefrontal cortex (PFC) during encoding. In the YOH/CORT group (de)activation (in arbitrary units = a.u.) in the R HC was strongly related to (de)activation in the R (□) and L PFC (BA47) (▲) ($r = .66$ and $r = .69$, respectively, $p < .01$), whereas no such correlation was found in the PL/PL group. We conclude that the memory-enhancing effect of YOH/CORT is correlated with deactivation of a circuit between HC and area BA47 in the PFC during encoding.

4.1. Stress hormones and memory performance

A first aim of our study was to examine whether elevations of noradrenaline (induced by YOH) and cortisol levels (induced by CORT) in interaction would facilitate memory consolidation of emotional information more than administration of each of these drugs separately. First, we found that EMO stimuli are remembered better than NEU pictures, as evidenced by the higher number of remembered EMO versus NEU pictures both with free recall and recognition memory tasks. This finding is in line with many previous studies (McGaugh, 2000). Application of CORT led to an overall enhancing effect on recognition memory. An effect of CORT on human memory has been found in several studies: one study (Abercrombie et al., 2003) reported that a 20 mg dose of CORT administered before encoding improved memory of both NEU and EMO pictures. In another study, metyrapone (a corticosteroid-synthesis inhibitor) was administered before the viewing of a story composed of EMO and NEU segments. Blocking cortisol release by metyrapone impaired memory consolidation irrespective of arousal (Maheu et al., 2004). Three other studies (Buchanan & Lovallo, 2001; Kuhlmann & Wolf, 2006; Payne et al., 2007) showed that CORT administration distinguishes between EMO and NEU memory performance, favoring memory formation of EMO over NEU information. However, in the last two studies this differential effect of better free recall for EMO than NEU stimuli was partly due to a negative effect of CORT on memory for NEU stimuli and was assessed with a recall task. Here we found an overall enhancing effect of CORT alone (PL/CORT) as well as for the combination of YOH/CORT on recognition memory. Also we found support (a trend) for an interaction of the YOH/CORT combination more on emotional than neutral memory performance compared to placebo.

A possible explanation why YOH alone did not enhance memory is that subjects in our study were tested in a scanner, a procedure known to evoke at least some degree of sympathetic arousal, as assessed by a rise in sAA levels in an earlier study (van Stegeren et al., 2006; Wolf, 2008). As was shown (Fig. 2a), sAA levels in the current study also rose in both placebo and YOH groups in response to the scanning procedure. Therefore, sympathetic activation of our subjects might have been higher than found outside a scanning environment. This could to some extent confound our intended sole administration of CORT or placebo. It is possible that the rise in endogenous noradrenaline levels was sufficient to mediate or enable the CORT effect on memory for both EMO and NEU pictures in the PL/CORT condition as well. It could also explain why, in con-

trast to earlier studies in humans (Cahill & Alkire, 2003; O'Carroll et al., 1999; Southwick et al., 2002), we did not find additional memory (enhancing) effects of the administration of an adrenergic agonist (YOH) compared to the PL condition.

The numbers of free recalled pictures were overall very low and no differential drug effects could be found. It is unclear why drug effects (if we interpret these as variation in arousal level) were not detectable with the free recall task. Several earlier studies showed that emotional arousal positively affects free recall (Cahill et al., 1996; Dolcos et al., 2004b) although the stimulus material was different (films versus pictures) (Cahill et al., 1996). Variation in stimulus material and the delay interval between stimulus presentation and recall varied between studies and also affect recall performance (Kensinger, Krendl, & Corkin, 2006). Free recall appeals to other brain areas and mechanisms than does recognition memory (Staresina & Davachi, 2006). We also cannot exclude that possible modulating drug effects on recall performance were not found due to floor effects, bearing in mind that in earlier studies CORT application led to negative effects on recall of NEU stimuli (Kuhlmann & Wolf, 2006; Payne et al., 2007).

Overall we can conclude that high cortisol levels during encoding (with or without exogenously manipulated high noradrenaline levels) have a beneficial effect on long-term memory performance in humans.

4.2. Brain circuits activated during encoding

Facilitation of human memory performance induced by a combined activation of corticosteroid and adrenergic systems was examined and linked to differential activation of the HC, amygdala and PFC. These ROIs were selected based on extensive evidence that these brain regions are importantly involved in learning and memory and that stress alters the activity of these areas (Liberzon & Sripada, 2008; Shin, Rauch, & Pitman, 2006). We found that successful encoding of pictures in males was related to an increased activity of the R amygdala and HC as well as the L PFC network.

As expected CORT or YOH treatment alone slightly enhanced activation of this limbic network (activation in the R HC). Unexpectedly, the combination of YOH/CORT led to a completely different pattern of brain activity, most strikingly a relative deactivation of the HC, which strongly correlated to performance of EMO recognition memory as well as to deactivation of BA47 in the PFC. This brain activity pattern could fit to an inverted-u relationship between dose/arousal and brain activation, also found in an earlier study (van Stegeren et al., 2005). In that study medium levels of arousing stimuli led to increased amygdala activation but the lowest and highest level of arousing pictures led to less amygdala activation, fitting to an inverted u-shape (dose–response related) activation pattern (van Stegeren et al., 2005). In view of the important role of the HC in declarative memory, we were surprised to observe this shift from activation of the amygdala/HC complex to strong deactivation of HC and particularly of the PFC under drug (YOH/CORT) conditions that resulted in effective recognition memory formation. Interestingly, a very recent study (Pruessner et al., 2008) also reported hippocampal deactivation in human subjects exposed to an acute psychosocial stress situation. In line with our findings, they observed not only a profound deactivation of limbic system components but indeed also deactivation of the medio-orbitofrontal cortex and anterior cingulate cortex in subjects who reacted to the stressor with a significant increase of the endocrine stress marker cortisol (Pruessner et al., 2008). While several studies do find a pattern of stress (and cortisol) related deactivation in HC and PFC structures, hippocampal deactivation is usually related to a decrease in neuroplasticity and memory performance. Yet, in our study this pattern of deactivation (imaged during encoding) was correlated to better memory performance for the YOH/CORT group.

A crucial question is how PFC deactivation might enhance or be related to (emotional) memory formation. Firstly, the PFC appears to play a crucial role in emotion regulation in humans (Davidson, Fox, & Kalin, 2007; Ochsner & Gross, 2007). Several studies showed that deactivation of the PFC during emotional or stressful conditions results in activation (disinhibition) of other brain areas. Also, in several psychiatric disorders, such as depression or post-traumatic stress disorder (PTSD), a loss of top-down inhibition from the PFC on the medial temporal lobe has been associated with symptoms of increased arousal and memory deficits as well as intrusions (Bremner, 2006; Shin et al., 2006).

Secondly, the PFC is a brain area that is related to processes of attention and focusing (Dolcos, Miller, Kragel, Jha, & McCarthy, 2007). Increased attention has been repeatedly shown to be related to PFC activation and to better and more detailed memory performance. Perhaps the relative decrease in activation of BA47 of the PFC is not so much related to a decline in memory functioning in general, but more to a shift in the attention process, such as a shift in focus from detailed perception to perception of the core of the information presented. Under stressful circumstances it is ecologically valid to shift ones attention from a peripherally to a centrally focused view in order to make fast and appropriate decisions. So, stress specifically improves memory for the gist of the information. This concept has already been proposed in the late 50-ies as the 'weapon focus phenomenon': high emotional arousal can cause a "narrowing of attention" (Easterbrook, 1959) to only selected aspects of the scene. This is supported by studies in our laboratory (Cahill & van Stegeren, 2003) and others (Christianson & Loftus, 1987) where subjects viewed emotional and neutral slides. Later memory tests showed that emotional recognition memory for the central and critical aspects of these slides was better than for the peripheral aspects (Cahill & van Stegeren, 2003) as was shown earlier (Christianson & Loftus, 1991; Heuer & Reisberg, 1990). Perhaps the deactivation in the PFC area is related to a reallocation of resources (blood supply) that are related to attention for the stimuli that result in better memory performance. In this line of reasoning consolidation may mean not only strengthening but can also be viewed as a result of qualitative changes in memory. This has been shown from a completely different angle in studies on the role of sleep and daytime naps on the quality of memory (Gomez, Bootzin, & Nadel, 2006).

In agreement, increased brain activation appears to be reliably related to the task presented in the scanner, but deactivation or decreased activation should be interpreted with caution – as was the message of several publications (Gusnard, Akbudak, Shulman, & Raichle, 2001; Raichle & Snyder, 2007; Raichle et al., 2001). Deactivation could be understood as a reallocation of blood supply rather than 'less functioning' of the area under consideration (Gusnard et al., 2001; Raichle & Snyder, 2007; Raichle et al., 2001). A very relevant study in this respect was carried out by Daselaar and colleagues (Daselaar, Prince, & Cabeza, 2004). In event-related fMRI studies the Dm (Difference in memory) effect (i.e. greater activity for items that are subsequently remembered than for items that are subsequently forgotten) has been attributed to successful encoding operations. In contrast, regions showing a reverse Dm effect have been linked to detrimental processes leading to forgetting. They investigated whether this reverse Dm effect might reflect not only activations for the Forgotten items but also deactivations for the Remembered items (dR). Their results showed that dR effects were found in the dorsolateral prefrontal regions, very similar to our findings and were interpreted as the efficient reallocation of neurocognitive resources. Whereas most fMRI studies of encoding have focused on activation increases, these results indicate that activation decreases can also contribute to successful learning of new information.

Finally, the pattern of brain activity during picture exposure only represents the contribution of the encoding phase to improved memory performance. Animal studies have shown that corticosteroids and noradrenaline acting during the consolidation phase are also very important in determining the effects of stress hormones on memory (Bernabeu et al., 1997; Liang, Juler, & McGaugh, 1986; Roozendaal & McGaugh, 1997). Although we need to consider the possibility that YOH and CORT-induced changes in brain activity modulated later cognitive performance also by influencing consolidation, such consolidation processes were clearly outside our window of brain scanning. As consolidation is a process that takes place over several hours or days, it would be difficult with an fMRI procedure to select the right moment to selectively study this important process. However, in theory the possibility of a different activation pattern during consolidation, that might even be characterized by an increase or a rebound reaction in activation in the medial temporal lobe and/or PFC, could be considered and should be investigated in future studies.

In conclusion, we show here that the activation of central corticosteroid receptors is an effective manner to facilitate human memory. During encoding, the brain switches under the influence of the combination of these hormones from hippocampal/amygdalar activation to strong deactivation of prefrontal areas. We conclude that, in addition to the well-known role of the medial temporal lobe, the PFC is also critically involved in the effects of stress hormones on memory.

Disclosure/conflict of interest

None declared.

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