Psychoneuroendocrinology (2008) xxx, xxx–xxx

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

True or false? Memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval

Tom Smeets [a,b,*], Henry Otgaar [b], Ingrid Candel [b], Oliver T. Wolf [a]

[a] Department of Cognitive Psychology, Ruhr-Universität Bochum, Germany
[b] Faculty of Psychology and Neuroscience, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands

Received 2 June 2008; received in revised form 21 July 2008; accepted 23 July 2008

KEYWORDS
True recall;
False recall;
Cold pressor stress (CPS);
Glucocorticoids (GCs);
Salivary alpha-amylase (sAA)

Summary Adrenal stress hormones released in response to acute stress may yield memory-enhancing effects when released post-learning and impairing effects at memory retrieval, especially for emotional memory material. However, so far these differential effects of stress hormones on the various memory phases for neutral and emotional memory material have not been demonstrated within one experiment. This study investigated whether, in line with their effects on true memory, stress and stress-induced adrenal stress hormones affect the encoding, consolidation, and retrieval of emotional and neutral false memories. Participants (N = 90) were exposed to a stressor before encoding, during consolidation, before retrieval, or were not stressed and then were subjected to neutral and emotional versions of the Deese–Roediger–McDermott word list learning paradigm. Twenty-four hours later, recall of presented words (true recall) and non-presented critical lure words (false recall) was assessed. Results show that stress exposure resulted in superior true memory performance in the consolidation stress group and reduced true memory performance in the retrieval stress group compared to the other groups, predominantly for emotional words. These memory-enhancing and memory-impairing effects were strongly related to stress-induced cortisol and sympathetic activity measured via salivary alpha-amylase levels. Neutral and emotional false recall, on the other hand, was neither affected by stress exposure, nor related to cortisol and sympathetic activity following stress. These results demonstrate the importance of stress-induced hormone-related activity in enhancing memory consolidation and in impairing memory retrieval, in particular for emotional memory material.

1. Introduction

A plethora of research has shown that emotional events are better remembered than neutral ones (LaBar and Cabeza, 2006), an effect driven by adrenal stress hormones that act on brain structures central to memory (e.g., McGaugh and

* Corresponding author at: Faculty of Psychology and Neuroscience, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands. Tel.: +31 43 3884506; fax: +31 43 3884196.
E-mail address: tom.smeets@psychology.unimaas.nl (T. Smeets).

0306-4530/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psyneuen.2008.07.009

Roozendaal, 2002). That is, noradrenaline release and β-adrenoceptor activation within the basolateral amygdala (BLA) modulates memory consolidation. One important issue is that adrenal stress hormones such as noradrenaline and glucocorticoids (GCs) may encompass differential effects on the various memory phases. Specifically, while stress hormones impair retrieval (e.g., de Quervain et al., 2000; Kuhlmann et al., 2005a,b; Buchanan and Tranel, 2008), they can enhance memory when released post-learning (i.e., during consolidation; e.g., Cahill et al., 2003; Andreano and Cahill, 2006). So far, the differential effects of stress hormones on the various memory phases for neutral and emotional memory material have not been demonstrated within a single study.

In contrast to the massive amount of studies on the effects of stress hormones on true memory (for reviews, see Het et al., 2005; Lupien et al., 2005; Wolf, 2008), only few studies have looked at the effects of stress on false memories. One paradigm aimed at eliciting false memories is the Deese–Roediger–McDermott paradigm (DRM; Deese, 1959; Roediger and McDermott, 1995). Here, participants are presented with lists of semantic associates (e.g., ''bed'', ''tired'', ''dream'') after which recall performance is assessed. Typically, people often falsely recall the semantically related, non-presented theme words (termed ''critical lures''; in this case ''sleep''). In a study by Payne et al. (2002), participants were exposed to the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) or a non-stressful filler task after which they had to listen to 20 DRM word lists, each followed by a computerized recognition task. Compared to controls, participants exposed to the TSST showed elevated rates of false recognition for the critical lures. Thus, the Payne et al. (2002) findings imply that people under stressful circumstances are more vulnerable to false recollections. In contrast, Smeets et al. (2006a) showed that neither stress-exposure (Study 1) nor stress-induced GC (i.e., cortisol) responses (Study 2) are sufficient to potentiate false recollections in a DRM paradigm. One explanation for these divergent findings would be that Payne et al.'s findings showing increased levels of false memories are not GC driven, but rather relate to the Sympatho-Adrenal Medullary (SAM) axis driven memory effects. Many studies indeed revealed that GCs interact with adrenergic hormones and noradrenergic activation in the BLA in modulating memory performance (i.e., enhanced memory consolidation and exacerbated memory retrieval; e.g., McGaugh, 2000; Roozendaal, 2000; Roozendaal et al., 2004, 2006; Kuhlmann and Wolf, 2006; de Quervain et al., 2007).

The primary aim of this study was to assess the effects of stress-induced activity of the SAM and HPA axes on false recall following exposure to an acute stressor, in comparison to their effects on true recall. A secondary aim of this study was to specifically look at how stress-induced hormonal changes affect the encoding, consolidation, and retrieval phase of the DRM paradigm. To the best of our knowledge there are no studies that have looked at whether, in line with their effects on true memory, adrenal stress hormones have differential effects on false memories for emotional versus neutral stimuli. Thus, another aim of this study was to investigate this issue by concurrently looking at adrenergic activity and GC involvement in stress-induced neutral and emotional false recall.

2. Materials and methods

2.1. Participants

Ninety undergraduate students (84 women[1]) with a mean age of 20.6 years (S.D. = 1.4; range: 18–25) participated in this study. All were right-handed, non-smoking individuals with a normal Body Mass Index (BMI; Mean ± S.D.: 21.8 ± 2.5; range: 17.4–28.5). Suffering from cardiovascular diseases, severe physical illnesses (e.g., fybromyalgia), hypertension, endocrine disorders, or being on any kind of medication served as additional exclusion criteria. Test protocols were approved by the standing ethics committee of the Psychology Faculty of Maastricht University. All participants signed a written informed consent and were financially compensated (12.5€; approximately 18$) in return for their participation.

2.2. Cold pressor stress

Stress was induced by exposing participants to cold pressor stress (CPS). The CPS is a widely used, low-risk technique in medical research to expose participants to painful stressors and is known to induce robust and reliable stress responses (e.g., Lovallo, 1975; Bohus et al., 2000; Cahill et al., 2003; Mitchell et al., 2004). As is typical in research employing CPS, participants were instructed to immerse their dominant arm up to the elbow in ice-cold (0–1 °C) water for as long as possible with a maximum of 3 min. They were explicitly told that, as the procedure could be very uncomfortable, they could remove their arm from the ice-cold water at their own discretion without consequences. Participants who fully endured CPS were told to remove their arm after 3 min. In the control condition, participants were instructed to place their arm in warm (37–40 °C) water until they were instructed to remove their arm. This instruction was given pseudo-randomly across participants after 1, 2, or 3 min following arm immersion. Arm immersion always occurred single-blind. That is, participants were not informed beforehand to which group they were assigned until immediately before arm immersion, even though they did know at the outset that they could be asked to put their arm in ice-cold water. During the CPS or control test, the experimenter always remained in the test room to monitor participants' compliance with the test instructions. Following CPS, all participants had to rest their arm covered by a blanket for 3 min. In line with Cahill et al. (2003), participants were asked to rate the level of discomfort they experienced during water immersion. To this end, they first were asked to think back at the most intense physical pain they had ever experienced and rate this experience by appropriately marking a 0–100 scale (anchors: 0 = *no pain or discomfort*; 100 = *the worst pain or discomfort imaginable*). After this ''calibration'' scale, participants rated the peak level of discomfort they had experienced during the CPS on an analogous scale.

[1] Of the six men that participated in this study, three were in the encoding stress group, two were in the retrieval stress group, and one was in the control group.

Please cite this article in press as: Smeets, T., et al., True or false? Memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.07.009

2.3. Deese—Roediger—McDermott paradigm

This study used a Dutch version of the Deese—Roediger—McDermott paradigm (DRM; Deese, 1959; Roediger and McDermott, 1995) in which participants were presented with 10 semantically related wordlists. Each list contained 10 presented words that all converged on 1 non-presented word (i.e., the critical lure). Five of the DRM lists concentrated around a neutral lure word (i.e., "bread", "foot", "smoke", "sweet", and "window") while the other lists referred to emotionally negative lure words (i.e., "cry", "dead", "murder", "pain", and "punishment"). DRM lists were audiotaped and played back on a CD player, thus ensuring that all participants heard the words at the same pace, tone of voice, volume, and intonation. DRM lists were counterbalanced in such a way that half of the participants first heard the emotional DRM lists followed by the neutral lists, while the other half received the reverse order. Mean word frequency of neutral and emotional critical lures did not differ [$t(8) = 0.22$; *ns*]. Furthermore, mean associative strength between the neutral list words and their critical lures and the mean associative strength between the emotional list words and their critical lures did not differ [$t(8) = 1.69$; *ns*]. Presentation order of the emotional and neutral DRM lists was counterbalanced within and across groups, and participants were explicitly told to pay close attention to all words as their memory for the words would be tested the next day.

Twenty-four hours later, participants were probed for true and false recall by means of a stem-cued recall test (e.g., McKone and Murphy, 2000; McBride et al., 2006). Preference was given to the stem-cued recall test over a more standard free recall test because a 24-h retention interval might lead to floor effects (see also McDermott, 1996, who used a 2-day retention interval). For the same reason, we included 3 of the 10 previously presented words of each list to cue the words pertaining to that particular list. In constructing the stem-cued recall test, we used two-letter stems that had many different word completions and were not words in themselves (e.g., "soft" was not used). Participants were clearly informed that some of the stems could be completed with words from the previously presented lists and were instructed to complete stems only with words they could remember being on the lists. Additionally, they were told that perhaps not all stems had appeared at study and that if they could not recall a completion from the presented words, they should leave them blank. No time limit on completion of stems was enforced. Four dependent measures were derived from the DRM paradigm: (1) percentage recall of presented neutral words (*neutral true recall*), (2) percentage recall of presented emotional words (*emotional true recall*), (3) percentage falsely recalled neutral critical lures (*neutral false recall*), and (4) percentage falsely recalled emotional critical lures (*emotional false recall*).

2.4. Saliva sampling and biochemical analyses

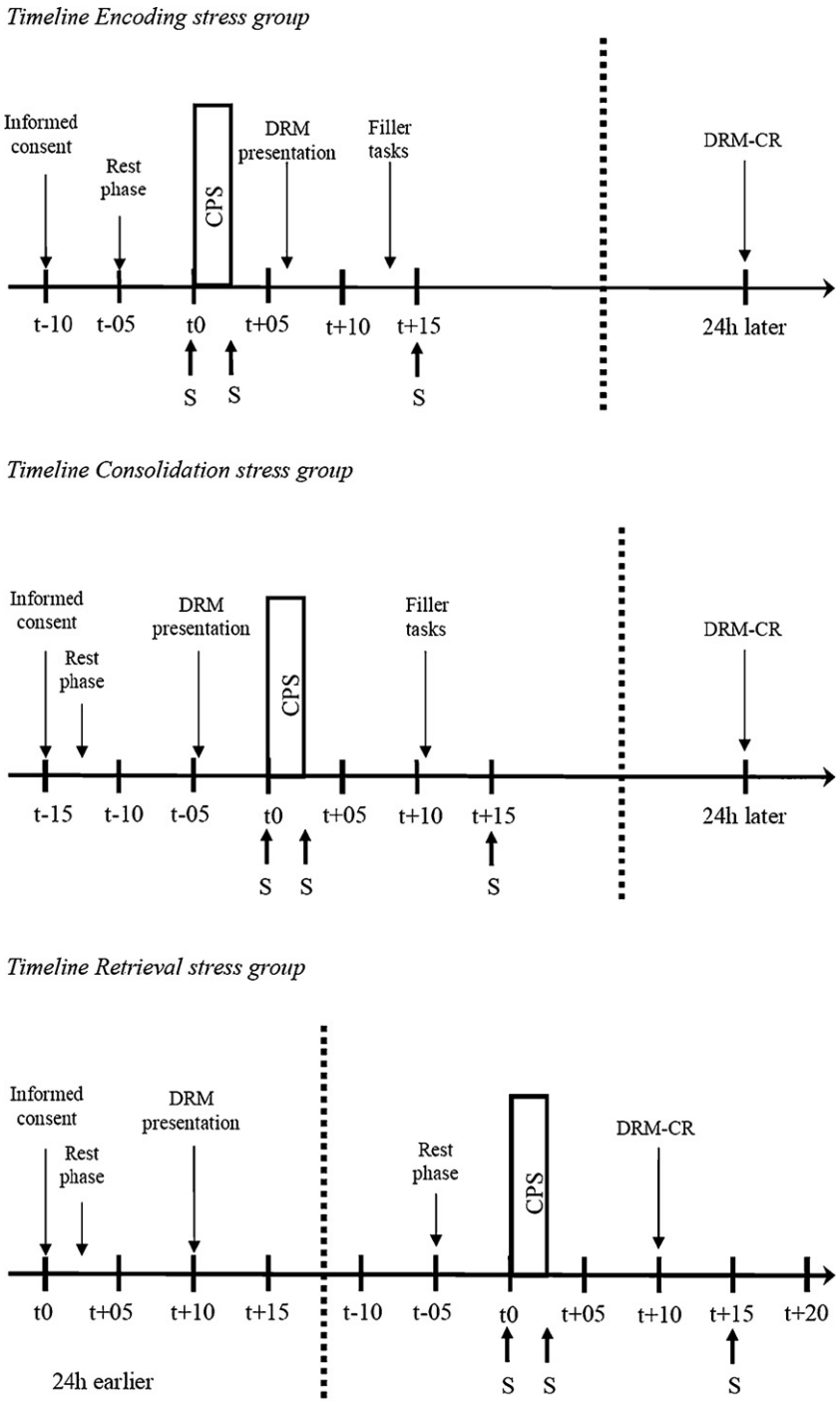
Salivary alpha-amylase (sAA) and cortisol (CORT) was measured in response to the CPS as a measure of activity of the stress-responsive SAM- and HPA-axes, respectively. Salivary sAA and CORT data were obtained with cotton Salivette (Sarstedt®, Etten-Leur, the Netherlands) devices. The saliva samples were stored at −40 °C immediately on collection. Free CORT levels were determined by a commercially available luminescence immuno assay (IBL, Hamburg, Germany; see Westermann et al., 2004). Mean intra- and inter-assay coefficients of variation are typically less than 8% and 12%, respectively, and the lower and upper detection limits were 0.015 μg/dl (0.41 nmol/l) and 4.0 μg/dl (110.4 nmol/l), respectively. sAA levels were determined from the saliva samples using a commercially available kinetic reaction assay (Salimetrics, Penn State, PA; see, for example, Granger et al., 2007). Mean intra- and inter-assay coefficients of variation of the sAA analyses are typically less than 8% and 6%, respectively.

2.5. Design and procedure

A 4(Group: encoding stress vs. consolidation stress vs. retrieval stress vs. no-stress control) × 2(Valence: neutral vs. emotional) mixed-model was employed, with the latter factor being a repeated measure. Thus, participants were randomly assigned to one of four groups and were administered both neutral as well as emotional DRM lists. Participants were tested in individual sessions run between 1300 and 1800 hours. To allow for controlled saliva collection, participants were asked not to brush their teeth and were deprived of food, drinks, and heavy exercise at least 1 h prior to the test phase. After arrival in the laboratory, they were informed about the CPS and memory tests and subsequently gave written informed consent. Afterwards, participants were asked to wash their hands and rinse their mouths with water to ensure non-contaminated saliva sampling, and were seated in a comfortable chair.

Participants in the first group (i.e., the *encoding stress* group; $n = 22$) were then exposed to the CPS and asked to rate the level of discomfort they experienced during water immersion (cf. supra). Afterwards, they were instructed to listen to the 5 neutral and 5 emotional DRM lists. Participants were instructed that they should try to memorize each word that would be presented to them as they would have to undergo a recall test in a second session scheduled 24 h later. Upon arriving for the second session, these participants were subjected to the stem-cued recall test probing for their memory of all words presented during the first session as well as false recall. Participants in the second group (i.e., the *consolidation stress* group; $n = 22$) first had to listen to the DRM lists and then were exposed to the CPS. Similar to the first group, these participants underwent the stem-cued recall test in a second session 24 h later. Participants in the third, *retrieval stress* group ($n = 22$) simply listened to the DRM lists during the first session and were exposed to the CPS in a 24-h delayed second session, which was then followed by the stem-cued recall test. Alternatively, those in the fourth, *no-stress control* group ($n = 24$), were never exposed to the CPS but instead had to immerse their arm in warm water instead of ice-cold water (cf. supra). A third of the no-stress control participants were exposed to the control task prior to encoding the DRM word lists, a third during consolidation of the DRM lists, and the final third before retrieval of the DRM lists (i.e., before the second session's stem-cued recall test). Fig. 1 shows the time lines.

Please cite this article in press as: Smeets, T., et al., True or false? Memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.07.009



Notes: S= Salivette; DRM presentation = Deese-Roediger-McDermott word list presentation phase (10 min); DRM-CR= Delayed cued recall test pertaining to the DRM words lists that were presented 24h earlier (20 min); CPS= Cold Pressor Stress; Filler tasks consisted of unrelated memory tasks.

Figure 1 Sequence of filler tasks, CPS or control task, saliva sampling, and performing DRM memory tests for encoding stress, consolidation stress, and retrieval stress groups.

Please cite this article in press as: Smeets, T., et al., True or false? Memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.07.009

Table 1 CORT and sAA levels before (pre) and after (post) arm immersion in warm (filler) or cold (CPS) water as well as duration of arm immersion and subjective rating of the painfulness of CPS/filler task for all groups

	Encoding stress group	Consolidation stress group	Retrieval stress group	No-stress control group
CORT (nmol/l)				
Pre	5.92 ± 0.53	6.58 ± 0.44	5.84 ± 0.60	6.12 ± 0.54
Post	**9.14 ± 0.60***	**9.04 ± 0.68***	**9.39 ± 1.11***	5.83 ± 0.47
sAA (U/ml)				
Pre	48.94 ± 15.63	58.59 ± 9.11	61.48 ± 9.81	60.29 ± 8.28
Post	**88.15 ± 10.96***	**85.82 ± 9.59***	**87.97 ± 12.54***	53.10 ± 6.92
Duration (s)	122.50 ± 10.52	135.09 ± 12.23	147.27 ± 8.91	142.50 ± 10.87
Subjective pain rating (max = 100)	52.86 ± 3.70*	46.00 ± 5.38*	46.50 ± 4.98*	1.54 ± 0.45

Values represent Means ± S.E.M. Values printed in bold denote significant within-group differences from pre to post measures. Saliva samples were collected prior to (CORT *Pre* and sAA *Pre*) and immediately following (sAA *Post*) or 15 min following (CORT *Post*) the CPS or control test.
* $p < 0.01$ for CPS groups compared to no-stress control group.

To collect the samples needed for sAA and CORT analysis, participants were asked to provide a saliva sample via the Salivette devices prior to (sAA and CORT) and immediately following (sAA) or 15 min following (CORT) the CPS or control test. After all measures were completed, participants were debriefed, paid, and thanked for their participation.

2.6. Statistical analyses

One-way Analysis of Variance (ANOVA) was used to check whether the three control subgroups differed on any of the primary outcome variables (i.e., memory, CORT and sAA data). The absence of significant main or interactive effects (all p's > 0.10) allowed us to collapse the data from these groups. All subsequent statistical analyses will thus include one overall control group ($n = 24$). Shapiro–Wilk tests of normality showed skewness of CORT and sAA data and, therefore, these data were log-transformed before use in subsequent analyses. CORT and sAA responses were evaluated using a 4(Group: encoding stress vs. consolidation stress vs. retrieval stress vs. no-stress controls) × 2(Time: pre-stress vs. post-stress) ANOVA, with Time being a repeated measure. For each participant individually, we also computed a CORT and sAA response (i.e., delta increase in CORT/sAA) defined as CORT/sAA concentration after the CPS or control task minus pre-stress CORT/sAA concentration. Delta responses were analyzed using univariate ANOVAs. Delayed true recall performance for presented words and delayed false recall of critical lures was evaluated using 4(Group: encoding stress vs. consolidation stress vs. retrieval stress vs. no-stress controls) × 2(Valence: neutral vs. emotional) ANOVAs, with the latter factor being a repeated measure. Finally, Spearman's *Rho* correlations were computed between true and false recall and delta CORT and sAA increases. When sphericity assumptions were violated, Greenhouse–Geisser corrected p-values are reported. Alpha was set at 0.05 and adjusted (Bonferroni) for multiple comparisons where necessary, unless specified otherwise. In case of (borderline) significant results, ANOVAs are supplemented with Mean Square Error (MSE) and Partial Eta Squared (η_p^2) values as a measure of effect size.

3. Results[2]

3.1. CORT and sAA stress responses

Mean CORT and sAA levels prior to and following CPS are shown in Table 1. Pre-stress CORT concentrations did not differ between the encoding stress, consolidation stress, retrieval stress and control groups [$F(3, 86) = 0.75$; $p = 0.52$] nor did pre-stress sAA levels [$F(3, 86) = 1.41$; $p = 0.25$]. Participants in the encoding stress, consolidation stress, and retrieval stress group rated the CPS as more painful than the control task [$F(3, 86) = 36.09$; $p < 0.001$; MSE = 363.72; $\eta_p^2 = 0.56$], yet both groups did not differ regarding the time they kept their arm in ice-cold (CPS) or warm (control) water [$F(3, 86) = 1.05$; $p = 0.38$]. Follow-up t-tests showed that the control group experienced the warm water task as less painful than the CPS in the three stress groups (all p's < 0.01), who did not differ from each other (all p's > 0.99). Mean ratings of the painfulness of the CPS/control task as well as the duration of the tasks can also be found in Table 1.

As expected, for CORT the ANOVA yielded a significant Group × Time interaction [$F(3, 86) = 12.96$; $p < 0.001$; MSE = 0.05; $\eta_p^2 = 0.31$] and a significant main effect of Time [$F(1, 86) = 84.26$; $p < 0.001$; MSE = 0.05; $\eta_p^2 = 0.50$], in the absence of a main effect of Group [$F(3, 86) = 2.25$; $p = 0.088$; MSE = 0.30; $\eta_p^2 = 0.07$]. Similarly, for sAA there was a significant Group × Time interaction [$F(3, 86) = 9.20$; $p < 0.001$; MSE = 0.28; $\eta_p^2 = 0.24$], a significant main effect of Time [$F(1, 86) = 40.39$; $p < 0.001$; MSE = 0.28; $\eta_p^2 = 0.32$], but no main effect of Group [$F(3, 86) = 1.18$; $p = 0.32$]. Follow-up t-tests showed that while all three CPS groups displayed CORT and sAA increases from pre-stress to the post-stress measurement (all p's < 0.01), the control group remained stable over time (p's > 0.22). Moreover, delta increases in CORT and sAA differed significantly between groups [CORT: $F(3, 86) = 12.96$; $p < 0.001$; MSE = 0.10; $\eta_p^2 = 0.31$]; [sAA: $F(3, 86) = 9.20$; $p < 0.001$; MSE = 0.55; $\eta_p^2 = 0.24$]. Follow-up t-tests confirmed that for delta

[2] Because there were only few male participants, specific sex effects could not be investigated. However, when the analyses were restricted to only the female participants, the same conclusions were reached.

Please cite this article in press as: Smeets, T., et al., True or false? Memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.07.009

CORT and sAA responses, the CPS groups differed from the control group (all p's < 0.01), but not from each other (all p's > 0.64).

3.2. DRM true and false memories

Mean percentage delayed recall of neutral and emotional presented (i.e., true recall) and non-presented (i.e., false recall) words is shown in Figs. 2 and 3. As expected, for true recall there were main effects of Group [$F(3, 86) = 7.47$; $p < 0.001$; MSE = 0.03; $\eta_p^2 = 0.21$] and Valence [$F(1, 86) = 14.92$; $p < 0.001$; MSE = 0.01; $\eta_p^2 = 0.15$], as well as a significant Group × Valence interaction [$F(3, 86) = 5.58$; $p < 0.001$; MSE = 0.01; $\eta_p^2 = 0.16$]. Further exploring this interaction, univariate ANOVAs with Group (encoding stress vs. consolidation stress vs. retrieval stress vs. no-stress controls) as between subjects factor was run for neutral true recall and emotional true recall separately. For recall of emotional true recall, the follow-up ANOVA yielded a significant effect of Group [$F(3, 86) = 11.29$; $p < 0.001$; MSE = 0.02; $\eta_p^2 = 0.28$]. Bonferroni-corrected follow-up t-tests showed that while the consolidation stress group outperformed the encoding stress and control group (both p's < 0.05), the retrieval stress group was significantly impaired in true recall of emotional words compared to the encoding stress and control groups (p's < 0.03). For neutral true recall, a borderline significant effect of Group [$F(3, 86) = 2.62$; $p = 0.056$; MSE = 0.02; $\eta_p^2 = 0.08$] appeared. Exploratory uncorrected follow-up t-tests indicated that the retrieval stress group recalled fewer neutral presented words than the encoding stress and control group (both p's < 0.02), but did not differ from the consolidation stress group ($p = 0.09$). Finally, specific contrast analyses confirmed that the memory impairing effect of retrieval stress for emotional true recall was larger than for neutral true recall ($p < 0.01$).

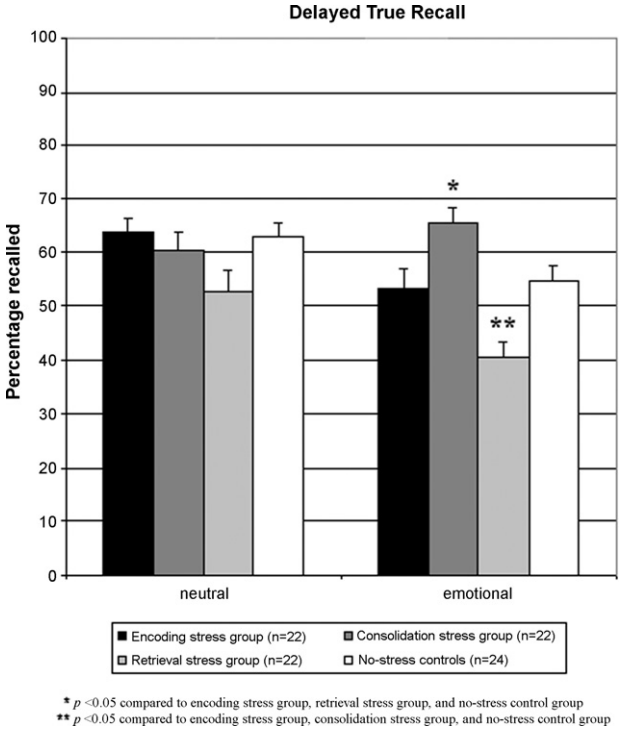


Figure 2 Delayed true recall of neutral and emotional words. Error bars represent standard error of mean (S.E.).

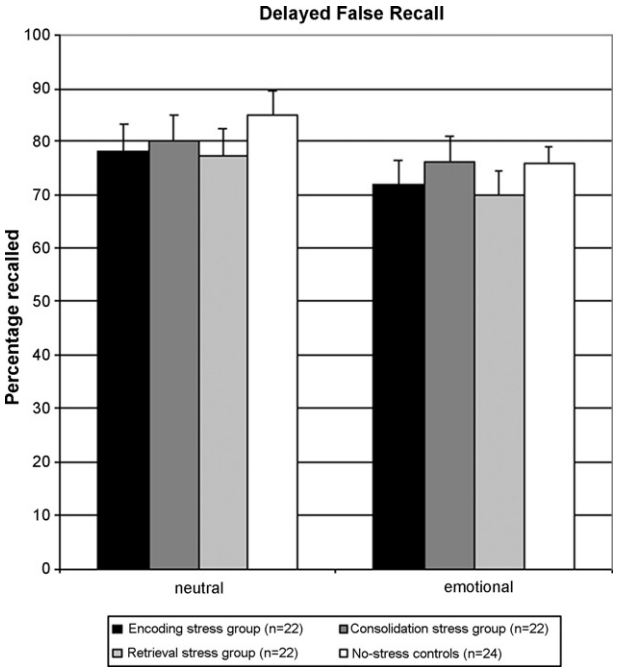


Figure 3 Delayed false recall of neutral and emotional words. Error bars represent standard error of mean (S.E.).

When evaluating delayed false recall, ANOVA yielded a main effect of Valence [$F(1, 86) = 6.07$; $p = 0.016$; MSE = 0.03; $\eta_p^2 = 0.07$], yet no effect of Group [$F(3, 86) = 0.68$; $p = 0.57$] or a Group × Valence interaction [$F(3, 86) = 0.19$; $p = 0.90$] was found. Follow-up analyses indicated that across groups, false recall of neutral non-presented words occurred more often than false recall of emotional non-presented words ($p < 0.02$).

3.3. Associations between CORT/sAA responses and DRM true and false memories

Spearman's *Rho* correlational analyses between neutral true, emotional true, neutral false, and emotional false recall parameters on the one hand and CORT and sAA responses on the other were used to evaluate the role of CORT and sAA increases in modulating memory performance. In the consolidation stress group, both neutral as well as emotional true recall was positively correlated with increases in CORT ($r = 0.46$; $p = 0.03$ and $r = 0.77$; $p < 0.001$ for neutral and emotional true recall, respectively) and sAA ($r = 0.44$; $p = 0.04$ and $r = 0.60$; $p = 0.003$ for neutral and emotional true recall, respectively). Conversely, there were strong negative correlations between neutral true recall and emotional true recall and CORT ($r = -0.44$; $p = 0.04$ and $r = -0.69$; $p < 0.001$ for neutral and emotional true recall, respectively) and sAA ($r = -0.52$; $p = 0.01$ and $r = -0.46$; $p = 0.03$ for neutral and emotional true recall, respectively) responses in the retrieval stress group. No significant correlations emerged within the no-stress control group or the encoding stress group. Similarly, for false recall, none of the correlations reached statistical significance.

Please cite this article in press as: Smeets, T., et al., True or false? Memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.07.009

4. Discussion

This study has three main findings. First, compared to the encoding stress, retrieval stress, and no-stress control groups, the consolidation stress group displayed superior true recall of emotional, but not neutral, words. The retrieval stress group on the other hand demonstrated reduced true memory performance, especially for emotional words. This is the first study showing the differential effects of stress hormones on the various memory phases for neutral and emotional memory material within a single study that employed the same stressor and the same memory tests. Previous studies in humans have either only investigated one specific memory phase (e.g., Kuhlmann et al., 2005a,b; Buchanan et al., 2006) or have found effects only for one phase and not for the other (e.g., Beckner et al., 2006). Second, here we showed that stress-induced GC and sympathetic activity is associated with memory enhancing as well as memory impairing effects. That is, within the consolidation stress group positive associations between CORT and sAA increases following CPS and true recall were found. Within the retrieval stress group true recall was negatively correlated with CORT and sAA responses to CPS. Third, while participants falsely recalled the non-presented critical lures at rates similar to those reported elsewhere (e.g., Roediger and McDermott, 1995; Stadler et al., 1999), there were no differences in neutral or emotional false recall between the encoding stress, consolidation stress, retrieval stress, and no-stress control groups. However, across all groups neutral false recall rates were higher than false recall rates of emotional lure words.

Animal research has consistently demonstrated the beneficial effects of GCs on memory consolidation (e.g., De Kloet et al., 1999; Roozendaal, 2000). More precisely, GCs interact with noradrenergic activity in the BLA in modulating memory consolidation in other brain areas (Roozendaal, 2002). This noradrenergic activation in the BLA is a prerequisite for GCs to modulate memory performance, as blockade of β-adrenoceptors in the BLA of rodents block the memory-enhancing effects of GCs during memory consolidation (Roozendaal et al., 2006). Similarly, positive effects of CORT on emotional memory consolidation have also been reported in humans (e.g., Buchanan and Lovallo, 2001; Cahill et al., 2003; Kuhlmann and Wolf, 2006). For example, the study by Cahill et al. (2003) showed that post-learning CPS led to enhanced memory consolidation of emotional (but not neutral) pictures, eventually resulting in enhanced retrieval 1 week later. Well in line with these previous studies, results from the current study showed that the consolidation of memory traces is enhanced by stress and stress-induced CORT and sAA activity, even though it should be noted that neutral words were less affected than emotional ones. These results lend further support to the hypothesis that arousal-induced noradrenergic activity in the BLA is required for CORT elevations to result in beneficial effects on memory consolidation. A recent functional magnetic resonance imaging (fMRI) study confirmed that participants displaying higher endogenous CORT levels exhibited stronger amygdala responses to emotional slides than those with lower endogenous CORT levels (van Stegeren et al., 2007). All in all, the present results corroborate previous findings that showed that GCs lead to enhanced emotional memory consolidation. Nonetheless, it should be noted that some studies have shown that consolidation stress can also enhance memory for neutral memory material (e.g., Andreano and Cahill, 2006; Beckner et al., 2006; Smeets et al., 2007). Even though no overall memory-enhancing effect of consolidation stress for neutral words was found, this study did find that stress-induced CORT and sAA elevations during the consolidation phase were positively correlated with memory for neutral words. Overall, the issue of whether enhanced memory consolidation is restricted to emotional memory material or appears at the cost of neutral material remains somewhat equivocal.

In contrast to their beneficial effects on consolidation, we observed an impairing effect of CORT and sAA increases following stress exposure on retrieval of both neutral and emotional words. Thus, whereas stress triggers the BLA to turn the brain into a memory-consolidation state, thereby resulting in strong consolidation for ongoing events, it at the same time appears to undermine attempts at memory retrieval (Roozendaal, 2002). Our results accord well with studies showing that reduced retrieval performance following stress is of greater magnitude for emotional memory material than for neutral material (e.g., Domes et al., 2004; Kuhlmann et al., 2005a,b; Buchanan et al., 2006). Similar to their effects on memory consolidation, GCs require noradrenergic activation in the BLA in order to yield negative effects on memory retrieval processes (e.g., Buchanan et al., 2006; de Quervain et al., 2007). Thus, de Quervain and co-workers (2007) recently found that the central β-blocker propranolol blocked the detrimental effects of GC administration on the retrieval of emotionally arousing words. Also note that in line with studies by de Quervain et al. (2000) and Domes et al. (2004) but see Payne et al. (2007), we did not observe any effects of stress applied before the encoding phase with regard to neutral memory material.

Our finding that encoding stress, consolidation stress, and retrieval stress failed to affect rates at which participants falsely recalled the (non-presented) critical lures, to some extent contradicts the work of Payne et al. (2002) showing increased vulnerability to false recollections following psychosocial stress (also see Payne et al., 2007). For sure, the methodology of the current study is substantially different from that of the Payne et al. (2002) study. Specifically, this study used a 24-h delayed stem-cued recall task while the Payne et al. study employed a single recognition task subsequent to each DRM list, which may have led to these opposing findings. The current findings do however confirm our earlier work (Smeets et al., 2006a) in which we showed that neither stressed (Study 1) nor high and low cortisol responders (Study 2) differed from controls in terms of false recollections. Furthermore, our results extend our previous findings by demonstrating that there is no relationship between stress-induced CORT or sAA activity and neutral or emotional false recall. In line with previous studies (e.g., Pesta et al., 2001; Geraerts et al., 2005; Howe, 2007), we observed that neutral false recollections were easier to elicit than emotional false recollections.

Some notes on the methodological limitations of this study are in order. First, we implemented a 24-h retention interval between DRM list learning and delayed recall. Therefore, we were compelled to use a cued recall test instead of a more conventional free recall test. Second, this study relied on an

Please cite this article in press as: Smeets, T., et al., True or false? Memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.07.009

almost entirely female undergraduate sample. There is substantial evidence suggesting that gender differences may moderate the link between stress and memory performance. For example, gender differences have been consistently reported in human fear conditioning studies (e.g., Jackson et al., 2006; Stark et al., 2006; Zorawski et al., 2006). On the other hand, there appear to be no such gender differences for memory retrieval following exogenously or stress-induced CORT elevations, with retrieval deficits occurring reliably in both men and women (e.g., de Quervain et al., 2000; Kuhlmann et al., 2005a,b; Smeets et al., 2006b; but see Wolf et al., 2001; Andreano and Cahill, 2006 for opposite findings). Nevertheless, future studies would benefit from taking gender differences into account when investigating the effects of stress on memory performance.

In sum, our results suggest an important role for stress-induced GC increases and noradrenergic activity in modulating memory performance. Specifically, this study suggests that CORT and sAA activity following consolidation stress results in superior true memory while similar processes at retrieval generally yield deteriorations in true memory performance. Moreover, these effects appear to be more pronounced for emotional than for neutral memory material. This study is the first to show both effects in a single study using the same stressor and the same memory tests, thus allowing a direct comparison of the different conditions. The current findings provide further evidence to suggest that both GC activity and noradrenergic activity in the BLA are crucial for stress to affect true memory. In contrast to its effect on true memory stress had no influence on false memory. Stress and the ensuing GC elevations and sympathetic activity did not interact either with the memory phase or with emotional arousal in influencing false memory.

Role of funding source

Supported in part by grants from the Netherlands Organization for Scientific Research (NWO) to Dr. T. Smeets (446-07-014) and Dr. I. Candel (451-03-013) and a German Research Foundation (DFG) Grant DFG WO 733/7-1 to Prof. Dr. O.T. Wolf. NWO and DFG had no further role in the study design; in the collection, analysis and interpretation of the data; in the writing of the report; and in the decision to submit the paper for publication.

Conflicts of interest

No conflicts of interest are declared.

Acknowledgments

We thank Kevin Sijstermans for his help in collecting the data. We also thank the anonymous reviewers for their insightful comments which helped to improve this paper.

References

Andreano, J.M., Cahill, L., 2006. Glucocorticoid release and memory consolidation in men and women. Psychol. Sci. 17, 466–470.

Beckner, V.E., Tucker, D.M., Delville, Y., Mohr, D.C., 2006. Stress facilitates consolidation of verbal memory for a film but does not affect retrieval. Behav. Neurosci. 120, 518–527.

Bohus, M., Limberger, M., Ebner, U., Glocker, F.X., Schwarz, B., Wernz, M., Lieb, K., 2000. Pain perception during self-reported distress and calmness in patients with borderline personality disorder and self-mutilating behavior. Psychiatry Res. 95, 251–260.

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

Buchanan, T.W., Tranel, D., Adolphs, R., 2006. Impaired memory retrieval correlates with individual differences in cortisol response but not autonomic response. Learn. Mem. 13, 382–387.

Buchanan, T.W., Tranel, D., 2008. Stress and emotional memory retrieval: effects of sex and cortisol response. Neurobiol. Learn. Mem. 89, 134–141.

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.

Deese, J., 1959. On the prediction of occurrence of particular verbal intrusions in immediate recall. J. Exp. Psychol. 58, 17–22.

De Kloet, E.R., Oitzl, M.S., Joels, M., 1999. Stress and cognition: Are corticosteroids good or bad guys? Trends Neurosci. 22, 422–426.

de Quervain, D.J.F., Roozendaal, B., Nitsch, R.M., McGaugh, J.L., Hock, C., 2000. Acute cortisone administration impairs retrieval of long-term declarative memory in humans. Nat. Neurosci. 3, 313–314.

de Quervain, D.J.F., Aerni, A., Roozendaal, B., 2007. Preventive effect of β-adrenoceptor blockade on glucocorticoid-induced memory retrieval deficits. Am. J. Psychiatry 164, 967–969.

Domes, G., Heinrichs, M., Rimmele, U., Reichwald, U., Hautzinger, M., 2004. Acute stress impairs recognition for positive words—association with stress-induced cortisol secretion. Stress 7, 173–181.

Geraerts, E., Smeets, E., Jelicic, M., van Heerden, J., Merckelbach, H., 2005. Fantasy proneness, but not self-reported trauma is related to DRM performance of women reporting recovered memories of childhood sexual abuse. Conscious. Cogn. 14, 602–612.

Granger, D.A., Kivlighan, K.T., El-Sheikh, M., Gordis, E., Stroud, L.R., 2007. Salivary alpha-amylase in biobehavioral research: recent developments and applications. Ann. N. Y. Acad. Sci. 1098, 122–144.

Het, S., Ramlow, G., Wolf, O.T., 2005. A meta-analytic review of the effects of acute cortisol administration on human memory. Psychoneuroendocrinology 30, 771–784.

Howe, M.L., 2007. Children's emotional false memories. Psychol. Sci. 18, 856–860.

Jackson, E.D., Payne, J.D., Nadel, L., Jacobs, W.J., 2006. Stress differentially modulates fear conditioning in healthy men and women. Biol. Psychiatry 59, 516–522.

Kirschbaum, C., Pirke, K.-M., Hellhammer, D.H., 1993. The 'Trier Social Stress Test': a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 28, 76–81.

Kuhlmann, S., Kirschbaum, C., Wolf, O.T., 2005a. Effects of oral cortisol treatment in healthy young women on memory retrieval of negative and neutral words. Neurobiol. Learn. Mem. 83, 158–162.

Kuhlmann, S., Piel, M., Wolf, O.T., 2005b. Impaired memory retrieval after psychosocial stress in healthy young men. J. Neurosci. 25, 2977–2982.

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.

Lovallo, W., 1975. The cold pressor test and autonomic function: a review and integration. Psychophysiology 12, 268–282.

Please cite this article in press as: Smeets, T., et al., True or false? Memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.07.009

Lupien, S.J., Fiocco, A., Wan, N., Maheu, F., Lord, C., Schramek, T., Thanh Tu, M., 2005. Stress hormones and human memory function across the lifespan. Psychoneuroendocrinology 30, 225—242.

McBride, D.M., Coane, J.H., Raulerson, B.A., 2006. An investigation of false memory in perceptual implicit tasks. Acta Pscychol. 123, 240—260.

McDermott, K.B., 1996. The persistence of false memories in list recall. J. Mem. Lang. 35, 212—230.

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

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

McKone, E., Murphy, B., 2000. Implicit false memory: effects of modality and multiple study presentations on long-lived semantic priming. J. Mem. Lang. 43, 89—109.

Mitchell, L.A., MacDonald, R.A., Brodie, E.E., 2004. Temperature and the cold pressor test. J. Pain 5, 233—237.

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.

Payne, J.D., Nadel, L., Allen, J.B., Thomas, K.G.F., Jacobs, W.J., 2002. The effects of experimentally induced stress on false recognition. Memory 10, 1—6.

Pesta, B.J., Murphy, M.D., Sanders, R.E., 2001. Are emotionally charged lures immune to false memory? J. Exp. Psychol. Learn. Mem. Cogn. 27, 328—338.

Roediger III, H.L., McDermott, K.B., 1995. Creating false memories: remembering words not presented in lists. J. Exp. Psychol. Learn. Mem. Cogn. 21, 803—814.

Roozendaal, B., 2000. Glucocorticoids and the regulation of memory consolidation. Psychoneuroendocrinology 25, 213—238.

Roozendaal, B., 2002. Stress and memory: opposing effects of glucocorticoids on memory consolidation and memory retrieval. Neurobiol. Learn. Mem. 78, 578—595.

Roozendaal, B., Hahn, E.L., Nathan, S.V., de Quervain, D.J., McGaugh, J.L., 2004. Glucocorticoid effects on memory retrieval require concurrent noradrenergic activity in the hippocampus and basolateral amygdala. J. Neurosci. 24, 8161—8169.

Roozendaal, B., Okuda, S., de Quervain, D.J., McGaugh, J.L., 2006. Glucocorticoids interact with emotion-induced noradrenergic activation in influencing different memory functions. Neuroscience 138, 901—910.

Stadler, M.A., Roediger III, H.L., McDermott, K.B., 1999. Norms for word lists that create false memories. Mem. Cognition 27, 494—500.

Smeets, T., Jelicic, M., Merckelbach, H., 2006a. Stress-induced cortisol responses, sex differences, and false recollections in a DRM-paradigm. Biol. Psychol. 72, 164—172.

Smeets, T., Jelicic, M., Merckelbach, H., 2006b. The effect of acute stress on memory depends on word valence. Int. J. Psychophysiol. 62, 30—37.

Smeets, T., Giesbrecht, T., Jelicic, M., Merckelbach, H., 2007. Context-dependent enhancement of declarative memory performance following acute psychosocial stress. Biol. Psychol. 76, 116—123.

Stark, R., Wolf, O.T., Tabbert, K., Kagerer, S., Zimmermann, M., Kirsch, P., Schienle, A., Vaitl, D., 2006. Influence of the stress hormone cortisol on fear conditioning in humans: evidence for sex differences in the response of the prefrontal cortex. Neuroimage 32, 1290—1298.

van Stegeren, A.H., Wolf, O.T., Everaerd, W., Scheltens, P., Barkhof, F., Rombouts, S.A., 2007. Endogenous cortisol level interacts with noradrenergic activation in the human amygdala. Neurobiol. Learn. Mem. 87, 57—66.

Westermann, J., Demir, A., Herbst, V., 2004. Determination of cortisol in saliva and serum by a luminescence-enhanced enzyme immunoassay. Clin. Lab. 50, 11—24.

Wolf, O.T., 2008. The influence of stress hormones on emotional memory: relevance for psychopathology. Acta Psychol. 127, 513—531.

Wolf, O.T., Schommer, N.C., Hellhammer, D.H., McEwen, B.S., Kirschbaum, C., 2001. The relationship between stress induced cortisol levels and memory differs between men and women. Psychoneuroendocrinology 26, 711—720.

Zorawski, M., Blanding, N.Q., Kuhn, C.M., LaBar, K.S., 2006. Effects of stress and sex on acquisition and consolidation of human fear conditioning. Learn. Mem. 13, 441—450.

Please cite this article in press as: Smeets, T., et al., True or false? Memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval. Psychoneuroendocrinology (2008), doi:10.1016/j.psyneuen.2008.07.009