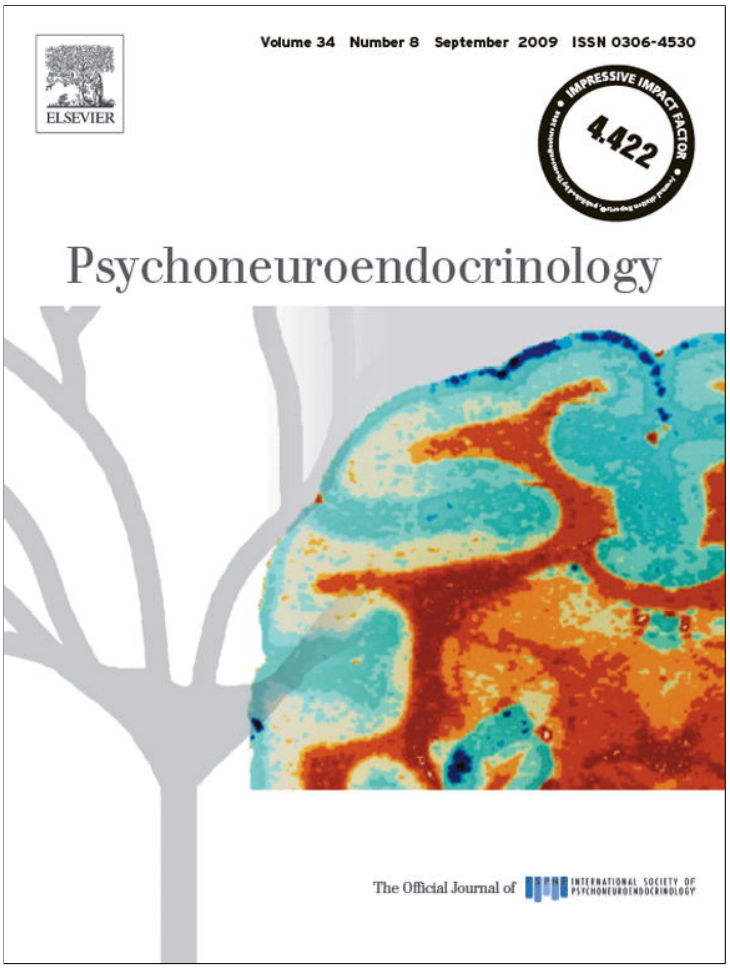

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Stress selectively and lastingly promotes learning of context-related high arousing information

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Summary The secretion of adrenal stress hormones in response to acute stress is known to affect learning and memory, particularly for emotionally arousing memory material. Here, we investigated whether stress-induced modulation of learning and memory performance depends on (i) the conceptual relatedness between the material to be learned/remembered and the stressor and (ii) the timing of stress exposure versus learning phase. Participants learned stressor-related and stressor-unrelated words of varying arousal 1 h prior to, immediately following, or 2 h after exposure to the Trier Social Stress Test (all groups $n = 16$). Twenty-four hours later, delayed free recall was assessed. Cortisol and alpha-amylase were sampled to evaluate if concurrent stress-induced raised glucocorticoid levels and high adrenergic activity are implicated in modulating learning performance. Our results demonstrate that immediate and delayed post-stress learning selectively enhanced the learning and delayed recall of stressor-related high arousing words. This enhancing effect was strongly associated with concurrent stress-induced cortisol and sympathetic activity. Our data suggest that when to-be-learned information is conceptually related to a stressor and considered important (i.e., arousing) by the individual, learning under stressful circumstances results in improved memorability afterwards.

1. Introduction

Exposure to stressful events is known to activate the sympathetic branches of the autonomic nervous system (ANS) and the hypothalamic—pituitary—adrenal (HPA) axis. The activation of these systems causes the release of adrenaline by the adrenal medulla and glucocorticoids (GCs) by the adrenal cortex, respectively. It is well established that in rodents as well as humans such adrenal stress hormones can influence learning and memory performance in various ways, in part depending on which phase (for instance consolidation versus retrieval) is targeted (see e.g. de Kloet et al., 1999; Roozendaal, 2002; Wolf, 2008).

Animal studies have consistently shown that GCs interact with noradrenergic activity in the basolateral part of the amygdala (BLA), thereby resulting in optimal emotional

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memory consolidation (e.g., de Kloet et al., 1999; Roozendaal, 2000, 2002; McGaugh and Roozendaal, 2002). Noradrenergic activity is essential for GCs to affect learning and memory performance, as β-adrenoceptor blockade within the BLA of rodents is known to block the memory-enhancing effects of GCs during consolidation (Roozendaal et al., 2006). Correspondingly, studies involving humans have found that learning and memory can be enhanced when adrenal stress hormones are released post-learning (e.g., Buchanan and Lovallo, 2001; Cahill et al., 2003; Andreano and Cahill, 2006; Kuhlmann and Wolf, 2006; Payne et al., 2007). For example, one of our previous studies (Smeets et al., 2008) showed that post-learning exposure to cold pressor stress and the ensuing GC and sympathetic activity improves consolidation, especially for emotional material.

The mnemonic effects of adrenal stress hormones thus occur when they act together in brain regions that are implicated in learning and memory. Importantly, GCs can exert their effects — at least in rodents — through rapid non-genomic or delayed genomic pathways (Joëls et al., 2007; de Kloet et al., 2008). To be precise, shortly after stress exposure when GCs are elevated, high levels of activity in the limbic areas but also in brainstem neurons are thought to produce high levels of arousal, focused attention, and enhanced encoding of relevant information (Joëls et al., 2007). These rapid non-genomic GC effects entail an increased capacity to induce Long-Term Potentiation (LTP) (Wiegert et al., 2006), rapid and reversible changes in the signalling of the hippocampus (Karst et al., 2005; Groc et al., 2008), and in part are dependent on a low-affinity membrane version of the mineralocorticoid receptor (MR) (Joëls et al., 2008). Several hours after stress exposure when GC levels have returned to their pre-stress concentrations genomic GC effects lead to optimal consolidation of previously encoded information by reversing and normalizing the enhanced excitability of the hippocampal pathways. These processes are gene-mediated and instigate a refractory period during which, e.g., the opportunity for LTP induction is reduced (Alfarez et al., 2002; Kim and Diamond, 2002; Wiegert et al., 2005). This implies that during the refractory period new memory material must be important enough to reach the activation threshold and, hence, for effective storage of the new information to occur.

Overall, the consensus view from the above-mentioned animal studies is that stress facilitates learning when the stressor is closely related to the learning context (i.e., when there is convergence in time and place; for review, see Joëls et al., 2006). The current study was set out to investigate for the first time in humans whether stress-induced modulation of learning/memory performance preferentially depends on (i) the conceptual relatedness between memory material and stressor and (ii) the timing of stress exposure versus learning phase. Based on our previous work in humans (Smeets et al., 2007) and rodents (see Wiegert et al., 2006; Joëls et al., 2007), we hypothesized that when learning *coincides* with stress exposure, high levels of the primary human GC cortisol (CORT) and concurrent sympathetic activity result in focused attention on and enhanced learning of relevant (i.e., stressor-related) but not irrelevant (i.e., stressor-unrelated) information, thereby also resulting in enhanced delayed recall. In contrast, earlier animal work showed that rises in corticosteroid hormones *after* the time of high-frequency stimulation was ineffective in facilitating synaptic strengthening (Wiegert et al., 2006); therefore, we anticipated that when learning precedes stress exposure of humans, no enhanced learning effect of stress for conceptually related memory material would occur. Finally, based on a diminished ability to induce LTP if corticosterone was applied several hours *in advance* of high-frequency stimulation (e.g., Wiegert et al., 2006; Pu et al., 2007), we expected that learning 2 h after stress exposure would result in impaired learning of new (i.e., stressor-unrelated) information. To test our hypotheses, we had participants learn stressor-related and stressor-unrelated words of varying arousal 1 h prior to (i.e., pre-stress learning), immediately following (i.e., post-stress immediate learning), or 2 h after (i.e., post-stress delayed learning) exposure to the Trier Social Stress Test, respectively. Twenty-four hours later, delayed free recall was assessed. CORT and salivary alpha-amylase (sAA; a measure of central adrenergic activity; see Ehlert et al., 2006; Nater et al., 2006) stress responses were measured to assess whether concomitantly elevated GC levels and high adrenergic activity are associated with pre- and post-stress learning performance.

2. Materials and methods

2.1. Participants

Forty-eight healthy young undergraduates with a mean age of 20.7 years (SD = 3.3; range: 18—39) participated in the current study. To rule out that gender differences could play a confounding role in CORT reactions to the stress task (Kudielka and Kirschbaum, 2005), only men were included in the present study. Eligibility of the volunteers was assessed using a self-report telephone interview. Suffering from cardiovascular diseases, severe physical illnesses (e.g., fibromyalgia), hypertension, current or lifetime psychopathology, endocrine disorders, or being on medication served as exclusion criteria. Note that although the current study involved healthy young men and self-reported medical or psychiatric problems served as exclusion criteria, we cannot entirely rule out that non-disclosed medical or psychiatric concerns may have influenced our data. Test protocols were approved by the standing ethics committee of the Faculty of Psychology and Neuroscience, Maastricht University. All participants signed a written informed consent and were given a small monetary reward (€12.5; approximately $18) in return for their participation.

2.2. Stress manipulation

The Trier Social Stress Test (TSST; Kirschbaum et al., 1993) is a valid and reliable procedure to induce neuroendocrine stress responses that basically consists of a 10 min preparation period, a 5 min mental arithmetic task, and a 5 min free speech in front of an audience while being video taped. The present study employed a modified TSST (see also Smeets et al., 2007) that was more personally relevant and ego-threatening. Specifically, participants were not asked to simulate a job interview as is typical in the TSST, but rather they had to critically describe their personality characteristics while standing in front of a live audience and being audio taped and video taped. Hence, the nature of the

worries elicited by the TSST was ego-threatening and highly personally relevant. To further increase the stressful nature of the TSST, participants had to deliver the speech in English (i.e., a non-native language).

2.3. Learning of stressor-related and stressor-unrelated words

During the learning phase, participants were presented with 12 stressor-related words (i.e., personality descriptors; e.g., romantic, insecure) and 12 stressor-unrelated words (i.e., other, non-personality descriptors; e.g., dirty, noisy). Stressor-related and stressor-unrelated words were chosen from the Affective Norms for English Words (ANEW; Bradley and Lang, 1999) and were unanimously categorized as personality descriptors or non-personality descriptors, respectively, in a pilot study ($N = 15$). Data drawn from the ANEW normative ratings showed that stressor-related and stressor-unrelated words did not differ with respect to mean valence, arousal, dominance, or word frequency (all $ts < 1.19$; all $ps > .24$). Words were audio taped and played back on a digital voice recorder, thus ensuring that all participants heard the words at the same pace, tone of voice, volume, and intonation. Synchronized with the aural presentation, words were also shown on a 15 in. computer screen using PowerPoint (Microsoft Corporation) in capitals with font type Times New Roman, font size 80. Presentation order of the words occurred pseudo-random so that no more than two stressor-related or stressor-unrelated words were presented in succession. Words were presented on three successive learning trials, with participants being explicitly told that their memory for the words would be tested immediately following each learning (i.e., presentation) trial by means of an immediate free recall task to ensure effortful encoding. However, we were also interested in a surprise delayed free recall test given to them 24 h later.[1] To reduce the likelihood that participants would rehearse the word lists, they were told that their physiological stress reactivity to the TSST would be discussed with them the next day. No mention of the upcoming delayed recall test was made. When they returned 24 h later, delayed free recall was assessed. None of the participants indicated that they had expected a delayed recall test.

Following the 24 h delayed free recall test participants were asked to rate the presented words for arousal on 9-point scales (anchors: 1 = *not at all arousing*; 9 = *extremely arousing*). Based on the arousal ratings thus obtained, for each participant individually, presented words were further categorized into (1) the 6 stressor-related words that received the highest arousal ratings (i.e., *stressor-related high arousing words*), (2) the 6 stressor-related words that received the lowest arousal ratings (i.e., *stressor-related low arousing words*), (3) the 6 stressor-unrelated words that received the highest arousal ratings (i.e., *stressor-unrelated high arousing words*), and (4) the 6 stressor-unrelated words that received the lowest arousal ratings (i.e., *stressor-unrelated low arousing words*). Hence, the words within each category differed between subjects as a function of how arousing they considered the words to be. This procedure allows for investigating the assumption that the effects of stress on learning and memory performance are modulated by the arousal elicited by the stimuli (e.g., Cahill et al., 2003).

[1] In order to eliminate the effects of acute stress and GC elevations on retrieval processes, the delayed recall test was administered 24 h after initial learning took place.

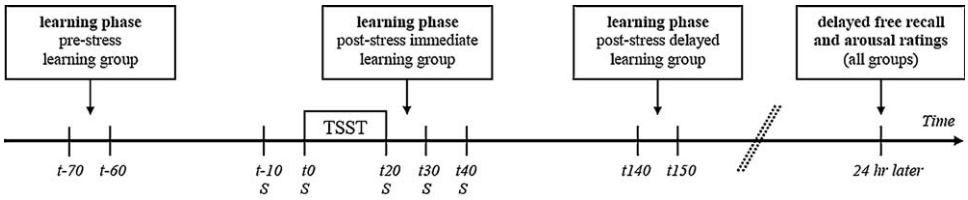
2.4. Saliva sampling and biochemical analyses

CORT and sAA was measured in response to the TSST as a measure of activity of the stress-responsive HPA- and SAM-axis, respectively. CORT and sAA data were obtained with cotton Salivette (Sarstedt®, Etten-Leur, the Netherlands) devices. The saliva samples were stored at $-40\,^{\circ}C$ 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; 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. Levels of sAA 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 3(Group: pre-stress learning vs. post-stress immediate learning vs. post-stress delayed learning) × 4(WordType: stressor-related high arousing words vs. stressor-related low arousing words vs. stressor-unrelated high arousing words vs. stressor-unrelated low arousing words) mixed-model was employed, with the latter factor being a repeated measure. Thus, participants were randomly allocated to one of three groups and tested in individual sessions run between 09:00 and 12:30 h. Preference was given to morning testing sessions as GCs yield stronger effects on learning/memory in the morning hours than in the afternoon (e.g., Het et al., 2005; Maheu et al., 2005). Participants were instructed to refrain from eating, drinking, and heavy exercise at least 1 h prior to the test phase. All participants reported to have adhered to these instructions. After arrival in the laboratory, they were informed about the TSST and learning phase 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.

Participants in the first group (i.e., the *pre-stress learning* group; $n = 16$) were then given a 15 min rest phase after which they engaged in the learning phase (cf. supra), followed by a 1 h rest phase and subsequent exposure to the modified TSST. After a 24 h interval had passed, participants returned to the lab for a surprise free recall test and finally were asked to rate the arousal of all 24 presented words. Participants in the second group (i.e., the *post-stress immediate learning* group; $n = 16$) were also given a 15 min rest phase upon arrival, yet afterwards were exposed to the modified TSST. Integrated at the end of the TSST, participants carried out the learning phase. Similar to the pre-stress learning group, participants returned to the lab 24 h later for the free recall test and arousal ratings. Participants in the third group (i.e., the *post-stress delayed learning* group; $n = 16$) followed the same procedure as those



Notes: S = Salivette device for measuring CORT and sAA at t-10, t0, t20, t30, and t40. Groups differed only with respect to timing of the TSST vs. learning phase.

Figure 1 Timeline depicting the saliva sampling procedure, the phases in which the three groups received the stressor (TSST), engaged in the learning phase, performed the delayed free recall test and provided the arousal ratings.

in the post-stress immediate learning group, except that the learning phase was delayed so that there was a 2 h interval between the end of the TSST and the start of the learning phase. Fig. 1 shows the time line of the experimental procedure. During the rest phases, participants engaged in unrelated and undemanding filler tasks (e.g., reading a neutral text).

To collect the samples needed for sAA and CORT analysis, participants were asked to provide a saliva sample via the Salivette devices 10 min before (*t-10*), immediately before (*t0*), immediately following (*t20*), as well as 10 and 20 min after cessation of the TSST (*t30* and *t40*, respectively). After all measures were completed, participants were debriefed, paid, and thanked for their participation.

2.6. Data analysis

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 3(Group: pre-stress learning group vs. post-stress immediate learning group vs. post-stress delayed learning group) $\times$ 5(Time: *t-10* vs. *t0* vs. *t20* vs. *t30* vs. *t40*) Analysis of Variance (ANOVA), with Time being a repeated measure. Individual arousal ratings were analyzed using a 3(Group: pre-stress learning group vs. post-stress immediate learning group vs. post-stress delayed learning group) $\times$ 4(WordType: stressor-related high arousing vs. stressor-related low arousing vs. stressor-unrelated high arousing vs. stressor-unrelated low arousing) ANOVA, with the latter factor being a repeated measure. Learning performance was analyzed using a 3(Group: pre-stress learning group vs. post-stress immediate learning group vs. post-stress delayed learning group) $\times$ 3(Trial: learning trial 1 vs. learning trial 2 vs. learning trial 3) $\times$ 4(WordType: stressor-related high arousing vs. stressor-related low arousing vs. stressor-unrelated high arousing vs. stressor-unrelated low arousing) ANOVA. Delayed free recall performance was evaluated using 3(Group: pre-stress learning group vs. post-stress immediate learning group vs. post-stress delayed learning group) $\times$ 4(WordType: stressor-related high arousing vs. stressor-related low arousing vs. stressor-unrelated high arousing vs. stressor-unrelated low arousing) ANOVA. Finally, Spearman's *Rho* correlations were computed between delayed recall and the Area Under the Curve with respect to increase (AUCi; see Pruessner et al., 2003) for both CORT and sAA responses to the TSST. 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. In case of (borderline) significant results, ANOVAs are supplemented with Partial Eta Squared (η_p^2) values as a measure of effect size.

3. Results

3.1. CORT and sAA stress levels

Mean CORT and sAA levels prior to and following the TSST for all groups are shown in Table 1. As expected, for CORT the ANOVA yielded a significant main effect of Time [$F(4,180) = 44.21$; $p < 0.001$; $\eta_p^2 = 0.50$], in the absence of a main effect of Group [$F(1,45) = 1.33$; $p = 0.28$] or a Group $\times$ Time interaction [$F(8,180) = 2.12$; $p = 0.11$]. Similarly, for sAA there was a significant main effect of Time [$F(4,180) = 62.27$; $p < 0.001$; $\eta_p^2 = 0.58$], but no main effect of Group [$F(2,45) = 0.36$; $p = 0.70$] or Group $\times$ Time interaction [$F(8,180) = 0.72$; $p = 0.65$]. Follow-up tests showed that all three TSST groups displayed CORT increases from immediately before stress onset (i.e., *t0*) to the first post-stress measurement (*t20*), and that compared with baseline the CORT levels remained high at *t30* and *t40* (all $ps < 0.05$).[2] Correspondingly, sAA levels increased from *t0* to *t20* (all $ps < 0.05$), but immediately afterwards dropped back to around baseline levels at *t30* (all $ps < 0.05$ for *t20* to *t30* comparison; all $ps > 0.05$ for *t30* compared with *t0*) in all groups.

3.2. Individual arousal ratings

Mean arousal ratings for the 4 word categories did not differ between groups, with ANOVA showing no main effect of Group [$F(2,45) = 0.32$; $p = 0.73$] or Group $\times$ WordType interaction [$F(6,135) = 1.22$; $p = 0.31$]. As anticipated, ANOVA did reveal a significant main effect of WordType [$F(3,135) = 214.57$; $p < 0.001$; $\eta_p^2 = 0.83$]. Post hoc comparisons confirmed that the high arousing words were rated as more arousing than their low arousing counterparts ($ps < 0.001$) and that this was true for both stressor-related and stressor-unrelated words. Averaged ratings for high arousing words within the stressor-related as well as stressor-unrelated category were comparable between the three treatment

[2] In the current sample, 3 non-responders (i.e., participants who did not show a CORT elevation in response to the TSST) were identified. The CORT and sAA analyses reported here, as well as all subsequent analyses (e.g., learning performance and delayed recall) pertain to the full sample of 48 participants. Importantly, when analyses were restricted to data from the CORT responders ($n = 45$), the same conclusions were reached.

Table 1 CORT and sAA levels (mean ± SEM) in response to the TSST.

	Pre-stress learning group	Post-stress immediate learning group	Post-stress delayed learning group
sAA (U/ml)			
t-10	72.13 ± 11.31	63.39 ± 10.29	90.64 ± 16.93
t0	73.37 ± 10.25	63.13 ± 10.54	75.51 ± 12.28
t20	140.58 ± 17.54	141.71 ± 15.23	150.70 ± 19.40
t30	99.13 ± 13.04	79.23 ± 11.12	99.43 ± 13.79
t40	84.86 ± 14.43	71.14 ± 11.27	84.44 ± 14.24
CORT (nmol/l)			
t-10	8.00 ± 1.51	9.94 ± 1.53	9.43 ± 0.88
t0	6.21 ± 1.1	10.27 ± 1.34	9.81 ± 0.93
t20	13.50 ± 1.55	17.97 ± 2.30	18.00 ± 2.09
t30	18.33 ± 2.35	20.02 ± 2.50	18.28 ± 2.35
t40	17.70 ± 2.56	17.57 ± 2.33	15.34 ± 2.15

groups; the same was true for low arousing words. Also, when comparing stressor-related and stressor-unrelated high arousing words or stressor-related and stressor-unrelated low arousing words, no differences in mean arousal were found (all $ps > 0.35$).

3.3. Learning performance

Learning performance was evaluated by inspecting the data from the immediate free recall tests that followed each learning trial (see Fig. 2). ANOVA showed significant main effects of Trial [$F(2,90) = 232.71$; $p < 0.001$; $\eta_p^2 = 0.84$] and WordType [$F(3,135) = 14.95$; $p < 0.001$; $\eta_p^2 = 0.25$], and a significant Group × WordType interaction [$F(6,135) = 6.24$; $p < 0.001$; $\eta_p^2 = 0.22$]. No other main or interactive effects were found. Further analyses indicated that at all three learning trials, both post-stress learning groups (but not the pre-stress learning group) demonstrated superior recall of stressor-related high arousing words compared with stressor-related low arousing, stressor-unrelated high arousing, and stressor-unrelated low arousing words (all $ps < 0.05$).

3.4. Delayed recall performance

Delayed free recall of stressor-related high arousing, stressor-related low arousing, stressor-unrelated high arousing, and stressor-unrelated low arousing words is shown in Fig. 3. The ANOVA yielded a significant main effect of WordType [$F(3,135) = 11.88$; $p < 0.001$; $\eta_p^2 = 0.21$] and Group × WordType interaction [$F(6,135) = 4.64$; $p < 0.001$; $\eta_p^2 = 0.17$], but no main effect of Group [$F(2,45) = 1.34$; $p = 0.27$]. Further exploring this interaction, univariate ANOVAs with WordType as repeated measure were run for each of the 3 groups separately. In the pre-stress learning group no differences between the 4 word categories were observed [$F(3,45) = 0.37$; $p = 0.77$]. In contrast, a significant WordType effect was found in the post-stress immediate learning [$F(3,45) = 10.37$; $p < 0.001$; $\eta_p^2 = 0.41$] as well as the post-stress delayed learning [$F(3,45) = 10.64$; $p < 0.001$; $\eta_p^2 = 0.42$] group. Bonferroni-corrected follow-up *t*-tests showed that in both post-stress learning groups the proportion delayed recall of stressor-related high arousing words was higher than delayed recall of stressor-related low arousing, stressor-unrelated high arousing, and stressor-unrelated low arousing words ($ps < 0.001$; also see Fig. 3). Specific contrast analyses were used to evaluate whether delayed recall of stressor-related high arousing words was enhanced at the cost of delayed recall of stressor-related low-arousing words. Results showed that stressor-related high arousing words were recalled more often in the post-stress immediate learning as well as the post-stress delayed learning group (both $ps < 0.05$). Lower levels of delayed recall of stressor-related low arousing words, on the other hand, were characteristic of the post-stress immediate learning ($p < 0.05$), but not the pre-stress learning or the post-stress delayed learning group.

3.5. Associations between CORT/sAA levels and delayed recall performance

To determine whether CORT and sAA were implicated in the increased memorability of stressor-related high arousing words in the post-stress learning groups, Spearman's *Rho* correlational analyses were run between delayed recall performance and the AUCi for CORT, sAA, and the CORT × sAA interaction. In the post-stress immediate learning group, delayed recall of stressor-related high arousing words was strongly associated with AUCi for the CORT × sAA interaction ($r = .79$; $p < 0.01$), but not with the AUCi for CORT or sAA alone ($rs < .28$). Likewise, delayed recall of stressor-related high arousing words was correlated with AUCi for the CORT × sAA interaction ($r = .54$; $p < 0.01$) but not with the AUCi for CORT or sAA alone ($rs < .23$) in the post-stress delayed learning group. No other meaningful correlations emerged.

3.6. Learning and memory under non-stressful conditions

To exclude the possibility that the enhanced learning effect for stressor-related words in both post-stress learning groups was due to mere priming effects unrelated to stress, a no-stress control group was tested on a post hoc basis. This group ($N = 20$) followed the exact same procedure as either the post-stress immediate learning or the post-stress delayed learning group, but was not exposed to the TSST. Instead, this group had to critically describe their personality characteristics during a free speech held in an empty room. This procedure allows the priming of stressor-related words to

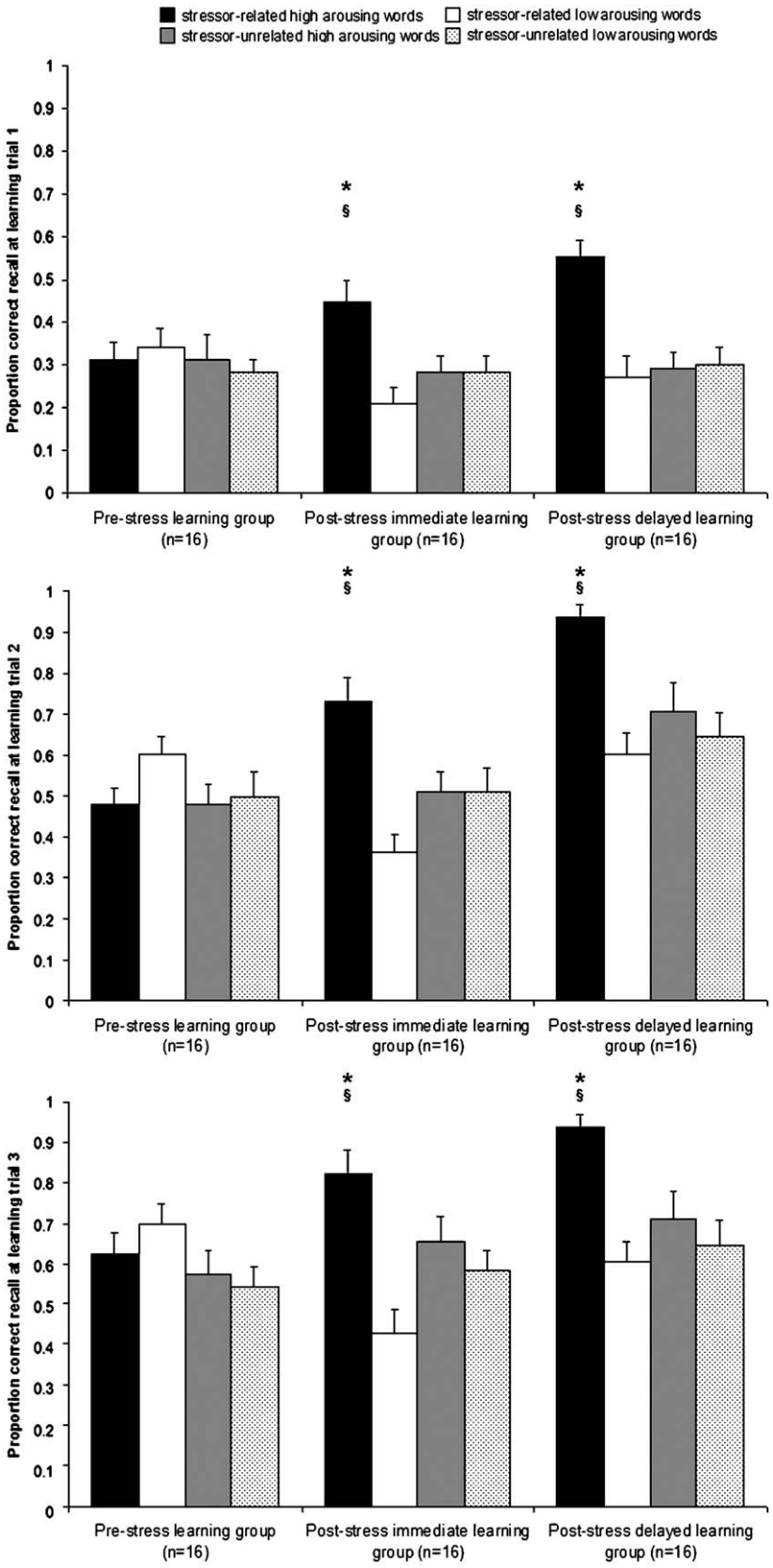


Figure 2 Proportion correct recall of stressor-related and stressor-unrelated high and low arousing words at learning trials 1–3. Error bars represent standard error of mean (SEM). $^{*}p < 0.05$ when compared with stressor-related high arousing words in the pre-stress learning group. $^{\S}p < 0.05$ when compared within-group with stressor-related low arousing, stressor-unrelated high arousing, and stressor-unrelated low arousing words.

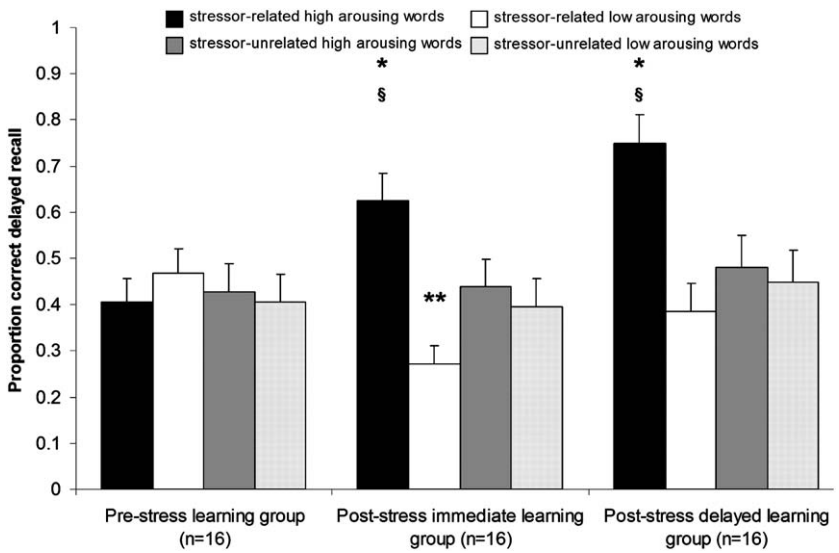


Figure 3 Proportion delayed free recall of stressor-related and stressor-unrelated high and low arousing words. Error bars represent standard error of mean (SEM). $^{*}p < 0.05$ when compared with stressor-related high arousing words in the pre-stress learning group. $^{**}p < 0.05$ when compared with stressor-related low arousing words in the pre-stress learning group. $^{\S}p < 0.001$ when compared within-group with stressor-related low arousing, stressor-unrelated high arousing, and stressor-unrelated low arousing words.

occur similar as to how it occurred in both post-stress learning groups, but under non-stressful conditions (i.e., without the social evaluative stress of the TSST). Thus, after a 15 min rest phase upon arrival at the laboratory, participants were asked to give a free speech about their personality characteristics under non-stressful conditions and then either carried out the learning phase immediately ($n = 10$) or 2 h ($n = 10$) following the end of the free speech. Twenty-four hours later, they returned to the lab for the free recall test and arousal ratings.

Results of the delayed free recall test for the no-stress control group can be summarized as follows.[3] First, a 2(ControlGroup: no-stress immediate learning group vs. no-stress delayed learning group) $\times$ 4(WordType: stressor-related high arousing vs. stressor-related low arousing vs. stressor-unrelated high arousing vs. stressor-unrelated low arousing) ANOVA showed no main effect of ControlGroup [$F(1,18) = 2.32$; $p = 0.15$] or WordType [$F(3,54) = 0.28$; $p = 0.84$], nor a ControlGroup $\times$ WordType interaction [$F(3,54) = 1.53$; $p = 0.22$]. Therefore, data from these 2 post-stress control groups were collapsed. A separate univariate ANOVA confirmed that there were no differences between the 4 word categories in this overall no-stress control group [$F(3,57) = 0.27$; $p = 0.85$]. Second, when delayed free recall data from the no-stress control group were compared with those of the 3 experimental groups (cf. supra), the following results were obtained. As expected, the 4(Group: pre-stress learning group vs. post-stress immediate learning group vs. post-stress delayed learning group vs. no-stress control group) $\times$ 4(WordType: stressor-related high arousing vs. stressor-related low arousing vs. stressor-unrelated high arousing vs. stressor-unrelated low arousing) ANOVA yielded a significant main effect of WordType [$F(3,192) = 9.48$; $p < 0.001$; $\eta_p^2 = 0.13$] and a Group $\times$ WordType interaction [$F(9,192) = 4.36$; $p < 0.001$; $\eta_p^2 = 0.17$], but no main effect of Group [$F(3,64) = 0.99$; $p = 0.40$]. Follow-up tests confirmed our earlier analyses showing higher levels of delayed recall of stressor-related high arousing words in both post-stress learning groups compared with the pre-stress learning and no-stress control groups, as well as impaired delayed recall of stressor-related low arousing words in the post-stress immediate learning group. The pre-stress learning and the no-stress control groups did not differ in delayed recall for any of the 4 word categories. To specifically test whether the post-stress learning groups differed from the no-stress control group, we ran a 3(Group: post-stress immediate learning group vs. post-stress delayed learning group vs. no-stress control group) $\times$ 4(Word-4(WordType: stressor-related high arousing vs. stressor-related low arousing vs. stressor-unrelated high arousing vs. stressor-unrelated low arousing) ANOVA. A significant main effect of WordType [$F(3,147) = 14.70$; $p < 0.001$; $\eta_p^2 = 0.23$] and a significant Group $\times$ WordType interaction [$F(6,147) = 4.36$; $p < 0.001$; $\eta_p^2 = 0.15$], but no main effect of Group [$F(2,49) = 1.21$; $p = 0.31$] emerged.

4. Discussion

The current study investigated whether stress-induced modulation of learning and memory performance depends on (i) the conceptual relatedness between to-be-learned material and stressor and (ii) the timing of stress exposure versus learning phase. In line with our hypotheses, results of this study show that when learning coincides with stress exposure, immediate and delayed recall of stressor-related high arousing words is enhanced relative to stressor-unrelated words, at the expense of delayed recall of stressor-related low arousing words. Delayed recall was proportional to data derived from the learning (i.e., immediate recall) trials,

[3] Importantly, individual arousal ratings for the 4 word categories of the no-stress control group did not differ from those of the other 3 groups, with all Fs < 1 (all ps > 0.45). Moreover, memory acquisition data for the no-stress control group closely paralleled those of the pre-stress learning group in showing the anticipated learning effect over time, but no main or interactive effects involving WordType.

suggesting that stress selectively enhanced *encoding* of context-related high arousing words rather than improving memory consolidation processes for this type of information. In contrast to what we had expected, stress exposure 2 h prior to learning also results in enhanced recall of stressor-related high arousing words and does not suppress the encoding of stressor-unrelated words. Interestingly, in both of these groups the enhanced learning and memory effect of post-stress learning correlated with stress-induced CORT elevations in conjunction with high sympathetic activity as measured by sAA, but not with changes in either of the hormones alone. In the pre-stress learning group, stress applied 1 h after learning did not affect recall of stressor-related or stressor-unrelated material, regardless of arousal. The latter non-significant findings to some extent disagree with previous work showing enhanced consolidation following stress (e.g., Cahill et al., 2003; Smeets et al., 2008). Yet it must be noted that a much longer interval between learning and stress exposure was used in the current study compared to typical consolidation stress studies (but see Flood et al., 1978; Sandi and Rose, 1994, for examples of GC-related memory enhancement up to 150 min after learning). The results of the no-stress control group were well in line with those of the pre-stress learning group, with no differences between the word categories for delayed recall. Note that as there was no random assignment in the post hoc no-stress control group, the comparison with the stress groups may be considered sub-optimal.

4.1. Context dependency

Based on earlier animal work, it has been proposed that rapidly acting stress mediators, e.g. noradrenaline and corticosterone acting via membrane located mineralocorticoid receptors, promote the encoding of information that is processed in the areas targeted by these hormones (Joëls et al., 2006). In the current study, we show that acute stress selectively enhanced learning and delayed recall of context-related high arousing words at the cost of memory for context-related low arousing words. No effect was observed on context-unrelated information, which partially disagrees with some animal (e.g., Shors, 2006) and human (e.g., Schwabe et al., 2008) studies showing enhanced memory for stress-unrelated material. The current differentiation in effect on context-related versus-unrelated information is very relevant. We cannot fully exclude a putative role of stress-induced non-cognitive influences (e.g., in attention or motivation) on learning and delayed recall performance in the post-stress learning groups; however, if such stress-induced non-cognitive influences were present, one would expect them to indiscriminately affect all to-be-learned information and not exclusively the context-related information.

Human studies reported that consolidation of high arousing material is enhanced by stress-induced CORT and/or sAA activity (e.g., Buchanan and Lovallo, 2001; Cahill et al., 2003; Kuhlmann and Wolf, 2006; Smeets et al., 2008). From animal studies it is known that these hormonal systems do not act independently, but rather that memory-enhancing effects of GCs depend on arousal-induced noradrenergic activation (Roozendaal et al., 2006). At the network level it was indeed observed that GCs and β-adrenoceptor agonists act synergistically on LTP induction (Pu et al., 2007). Support for this crucial aspect of interaction was lent by the current study. Improved delayed recall of stressor-related high arousing words strongly correlated with the CORT × sAA interaction, while no meaningful correlations were observed with any of the hormone levels separately (N.B. Note that recent studies (e.g., Ehlert et al., 2006; Nater et al., 2006) have argued that sAA activity reflects central sympathetic activity). Thus, the observed link between modulation of learning and memory processes and concomitant increases in CORT *and* sAA (i.e., the CORT × sAA interaction) most likely mirrors learning and memory-enhancing effects of GCs that occur in the presence of central adrenergic activity (e.g., Roozendaal, 2002; Roozendaal et al., 2006). It should also be noted, though, that CORT and sAA were sampled at 5 time points around the time of stress exposure; no biochemical data was collected either at the time of the learning phase (pre-stress learning group; post-stress delayed learning group) or at delayed retrieval. Although it seems unlikely (based on data from no-stress control or placebo groups obtained in earlier studies in humans (e.g., Kuhlmann et al., 2005; Kuhlmann and Wolf, 2006; Smeets et al., 2008; also see Gore et al., 2006) that CORT levels were altered merely by the learning task, we cannot fully exclude that fluctuations in hormones at these time points influenced the overall performance. This, however, does not invalidate the clear correlation between the CORT × sAA interaction and delayed recall of stressor-related high arousing words. We conclude that the rapid joint effects GCs and catecholamines may help to encode important information related to the context of a stressful event.

4.2. Time-dependency

While a number of recent electrophysiological studies in rodents have confirmed the rapid non-genomic pathway through which GCs can enhance memory formation shortly after stress exposure (e.g., Karst et al., 2005; Wiegert et al., 2006; Pu et al., 2007; Groc et al., 2008; Olijslagers et al., 2008), there is also abundant evidence that several hours after stress exposure GCs continue to affect learning and memory processes via gene-mediated pathways (for review, see Joëls et al., 2007; de Kloet et al., 2008). It was postulated that these slow GC actions serve to normalize the excitability of the hippocampal pathways (Joëls et al., 2006) and even introduce a refractory period during which encoding of new stressor-unrelated information is hampered (Diamond et al., 2007), thus allowing efficient consolidation of the earlier encoded memory traces. Hence, one would have expected the post-stress delayed learning group, in which learning occurred 2 h after stress exposure, to be characterized by impairments in learning and delayed recall performance, especially for stressor-unrelated and/or low arousing memory material. Our data plainly disagree with this, as we observed *enhanced* learning and delayed recall of stressor-related high arousing words in the post-stress delayed learning group, but no impairment in stressor-unrelated words.

How, then, can we account for these unexpected findings? One could argue that the positive effects of being exposed to a conceptually related stressor on delayed recall of stressor-related high arousing material merely reflect priming processes unrelated to stress exposure. To be precise, the fact that stress selectively enhanced delayed recall of stressor-related high arousing words suggests that learning is enhanced

only when the to-be-remembered material has been primed by prior exposure to a conceptually related stressor and the material was important to the learning individual (e.g., because it was highly associated with the topic that provoked the stress reaction). By this rationale, priming occurred not only when learning immediately followed stress exposure (i.e., in the post-stress immediate learning group), but even lasted up to 2 h after stress exposure in the post-stress delayed learning group. Indeed, there is good evidence from neuropsychological studies that priming can be relatively long-lasting and affects long-term semantic transfer (e.g., Becker et al., 1997; Joordens and Becker, 1997; Hughes and Whittlesea, 2003). However, data from the no-stress control group in which no enhanced learning effects were found despite the opportunity for priming effects to materialize, argue against a marked priming influence. This, of course, is also backed up by the strong associations between delayed recall of stressor-related high arousing words and alterations in adrenal stress hormone-related activity (i.e., the CORT $\times$ sAA interaction) observed in the post-stress learning groups. Collectively, this suggests that the enhanced learning effects occurred within the context of stress and stress-induced hormonal changes.

The fact that encoding of stressor-unrelated words was not impaired indicates that the delayed LTP-impairing action of GCs in the CA1 hippocampal area cannot be simply extrapolated to the current learning task. Importantly, the high-arousing words (both stressor-related and stressor-unrelated) are expected to substantially activate amygdalar circuits. Recently, it was shown that GCs do not suppress the activity of basolateral amygdala neurons in a delayed fashion, but rather enhance activity (Duvarci and Paré, 2007). There is also recent evidence from studies in rodents that the effects of a single stressor may yield long-lasting effects on brain areas involved in learning and memory, e.g., in the BLA (see Mitra and Sapolsky, 2008; Waddell et al., 2008). This leaves open the possibility that emotionally distressing situations introduce a longer time-window during which encoding of other information is not hampered.

In sum, this study for the first time shows that post-stress, but not pre-stress, learning, selectively and lastingly enhances encoding of stressor-related high arousing information in male subjects. Both animal (e.g., Wood and Shors, 1998; Luine, 2002; Conrad et al., 2004) as well as human (e.g., Wolf et al., 2001; Andreano and Cahill, 2006; Jackson et al., 2006; Stark et al., 2006; Zorawski et al., 2006) studies have indicated sex-specific differences in the link between stress-induced GC effects and memory performance. Given that the present study relied on an entirely male sample, future studies would need to consider sex differences when investigating the effects of adrenal stress hormones on learning and memory.

Our data suggest an important role for concurrent stress-induced GC and sympathetic activity in improving the learning of material that is stressor-related and highly arousing to the learning individual. These findings may have important ramifications for theories on how learning under stress operates. Specifically, they imply that when to-be-learned information is conceptually related to the stressor and considered important (i.e., arousing) by the learning individual, hormonal activation under stressful circumstances can enhance memory formation.

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Conflict of interest

No conflicts of interest are declared.

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