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Remembering under stress: Different roles of autonomic arousal and glucocorticoids in memory retrieval

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Abstract It is commonly assumed that stress impairs memory retrieval. Glucocorticoids, released with a delay of several minutes in response to stressful experiences, are thought to play a key role in the stress-induced retrieval impairment. Accordingly, most studies on the impact of stress on retrieval tested memory a considerable time after stressor exposure, when glucocorticoid levels were elevated. Here, we asked how stress affects memory when retrieval takes place under stress, that is, when stress is part of the retrieval situation and glucocorticoids are not yet increased at the time of testing. To contrast stress effects on ongoing and delayed memory retrieval, 72 participants learned first neutral and emotional material. Twenty-four hours later, half of the learned material was tested either in a stressful, oral examination-like testing situation or in a standard, non-stressful free recall test. Memory for the other half of the learned material was assessed 25 min after the first, stressful or non-stressful retention test. Significant increases in blood pressure and salivary cortisol confirmed the stress induction by the first, examination-like testing situation. Retrieval performance under stress was positively correlated with the blood pressure response to the stressor but unaffected by cortisol. Conversely, retrieval performance 25 min post stress was negatively correlated with the cortisol response to the stressor, particularly for emotional items. These results suggest that the same stressor may have opposite effects on ongoing and delayed memory retrieval, depending on the presence of autonomic arousal and glucocorticoids.

1. Introduction

When we perceive an actual or potential threat to our well-being (i.e., a stressor), our body initiates a cascade of physiological events. Within seconds after stressor exposure,

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the autonomic nervous system triggers the release of adrenaline and noradrenaline from the adrenal medulla, which in turn stimulate noradrenergic nuclei in the brain by activating vagal afferents to the nucleus of the solitary tract. In parallel to the activation of the autonomic nervous system, the hypothalamus-pituitary-adrenal axis leads via intermediate steps and with a delay of several minutes to the secretion of glucocorticoids (cortisol in humans) from the adrenal cortex. In concert with numerous other hormones, peptides, and neurotransmitters that are released during stressful experiences, adrenaline, noradrenaline, and glucocorticoids help us cope with ongoing challenges and, at the same time, prepare us for similar situations in the future. An integral part of how these stress mediators prepare us for future stress situations is by shaping learning and memory processes (Diamond et al., 2007; Joëls et al., 2011; Schwabe et al., 2012). Stress hormones promote lasting memories; in particular the formation of memories for events that are related to the stressor is enhanced by stress hormones (Cahill et al., 2003; McGaugh and Roozendaal, 2002; Sandi et al., 1997; Smeets et al., 2007; Zoladz et al., 2011).

Although stress may facilitate memory formation and consolidation, it is commonly assumed that stress impairs memory retrieval (de Quervain et al., 1998; Guenzel et al., 2013; Kuhlmann et al., 2005; Roozendaal et al., 2004; Schwabe and Wolf, 2009; Smeets et al., 2008; but see also Schilling et al., 2013; Schwabe et al., 2009). These disruptive effects of stress on retrieval are mainly mediated by glucocorticoids (Buchanan et al., 2006; de Quervain et al., 1998, 2000), in interaction with noradrenergic arousal (de Quervain et al., 2007; Roozendaal et al., 2004, 2006a). The stress-induced impairment of memory retrieval might be beneficial for coping with stress in the sense that it reduces distraction by stressor-unrelated information and allows well-established habits and routines to control behavior (Schwabe and Wolf, 2010, 2013).

A general retrieval impairment in stressful situations, both for stressor-related and stressor-unrelated information, however, would be clearly disadvantageous. According to a popular model (Joëls et al., 2006), rapid noradrenaline and glucocorticoid actions facilitate specifically the processing of information relevant to the ongoing stressor. Although this model focusses primarily on memory formation, there is some evidence that rapid actions of stress mediators might also facilitate, within a relatively short time window, memory retrieval processes. In particular, noradrenergic arousal has been associated with enhanced memory retrieval (Sara, 2009). For instance, stimulation of the locus coeruleus, the origin of noradrenergic forebrain projections, enhances retrieval in rats (Devauges and Sara, 1991). Similarly, the locus coeruleus is active during successful memory retrieval in humans (Sterpenich et al., 2006). Moreover, noradrenergic blockade impairs memory retrieval, both in humans and rats (Devauges and Sara, 1991; Kroes et al., 2010; Murchison et al., 2004). Based on these data, it can be hypothesized that, whereas stress-induced cortisol impairs retrieval, noradrenergic arousal may facilitate memory retrieval, particularly for information related to the stressful situation.

In the present experiment, we tested the hypothesis that stress may not necessarily impair memory retrieval and that stress-induced elevations in autonomic arousal and cortisol may have opposite effects on remembering. To this end, participants first learned neutral and emotional material. Twenty-four hours later, memory was tested either in a common free recall test (control condition) or in a stressful retrieval situation that resembled the well-known Trier Social Stress Test (TSST; Kirschbaum et al., 1993). Thus, in the 'retrieval-stress' condition, participants retrieved the learned material under stress, when autonomic arousal was high but cortisol concentrations not yet increased. Moreover, retrieval was a pivotal part of this stress situation and hence stressor-related. We predicted that autonomic arousal would enhance retrieval performance under stress. In order to contrast the hypothesized effects of autonomic arousal on retrieval with those of stress-induced cortisol, participants recalled part of the learned material after the stressor (or control condition), when cortisol concentrations were elevated. We expected that cortisol would impair memory retrieval, based on previous evidence (Buchanan et al., 2006; de Quervain et al., 1998, 2000). Moreover, because it has been shown that stress and glucocorticoid effects on memory are more pronounced for emotional than for neutral material (Buchanan et al., 2006; Cahill et al., 2003), we included both neutral and emotionally arousing stimuli and predicted that the effects of autonomic arousal and, in particular, those of cortisol would be stronger for emotional than for neutral stimuli.

2. Methods

2.1. Participants

Seventy-two non-smoking university students (36 men, 36 women; age: $M = 23.2$ years, SEM = 0.4 years) participated in this experiment. Exclusion criteria were checked in a standardized interview and comprised current illness or medication intake, current or life-time history of any psychiatric or neurological disorder, drug abuse, smoking, and in women the use of hormonal contraceptives. In addition, women were not tested during their menses. All participants provided written informed consent before participating in this study, which was approved by the local ethics committee.

2.2. Stimulus material

Stimulus materials consisted of 50 German nouns (25 neutral, 25 negative) and 50 pictures (25 neutral, 25 negative). Neutral and negative nouns were taken from a German database (Hager and Hasselhorn, 1994), based on their valence (neutral: $M = 4.17$, SEM = 0.03; negative: $M = 2.59$, SEM = 0.04, $p < 0.0001$) and arousal scores (neutral: $M = 3.78$, SEM = 0.07; negative: $M = 4.65$, SEM = 0.12, $p < 0.0001$), and matched with respect to word length ($p = 0.72$). Neutral and negative pictures were chosen from the International Affective Picture System (IAPS; Lang et al., 1997), according to their normative scores for valence (neutral: $M = 5.18$, SEM = 0.44; negative: $M = 2.45$, SEM = 0.66, $p < 0.0001$) and arousal (neutral: $M = 3.43$, SEM = 0.72; negative: $M = 5.88$, SEM = 0.73, $p < 0.0001$), and matched for their semantic categories (e.g. animals, humans). The pictures and words were not conceptually related.

2.3. Experimental procedure

Testing took place between 1300 h and 1830 h on two consecutive days. On the first experimental day, participants collected first a saliva sample before their blood pressure was measured. Saliva samples were collected with Salivette collection devices (Sarstedt, Germany) and stored at −18 °C until analyses. From saliva, we analyzed concentrations of the stress hormone cortisol by means of an immunoassay (IBL, Hamburg). Interassay and intra-assay coefficients of variance were below 10%. Blood pressure was measured with a Dinamap system (Critikon, USA) on the left upper arm. After the blood pressure measurements, participants were presented two lists of items, one after another, on a computer screen: a list of 50 German nouns and a list of 50 IAPS pictures (see above). Participants were instructed to memorize these items because they would be tested later on. The order of presentation of the word list and the picture list was counterbalanced across participants and experimental groups. Each word and picture was presented for 3 s and both the word and the picture list were presented twice. We presented the stimulus material twice to ensure sufficient encoding and prevent a possible floor effect during memory testing. Following the repeated presentation of the word and picture list, respectively, participants completed an immediate free recall test for the words and pictures, respectively. The words that were recalled by the participants were checked by the experimenter on a check list. For the recall of the pictures, participants were instructed to describe the pictures they recalled in as much detail as possible. If the experimenter was not sure to which picture the participant was referring to, he/she was asked to provide more details. There was no time limit for the free recall test.

On the second experimental day, participants collected another saliva sample and the blood pressure was measured again. Afterwards, participants were randomly assigned to the retrieval-stress or control condition (n = 36 per group). In the retrieval-stress group, participants were asked to verbally recall either the words or the pictures they had seen the day before in front of a rather cold and non-reinforcing panel consisting of a man and a woman, both dressed in a white coat. Participants were told that this panel would not only note the items they recall but also assess the participants' non-verbal behavior. Moreover, participants were videotaped while recalling the learned items. Thus, this retrieval situation, which resembled an (unpleasant) oral examination, contained core elements of the TSST (Kirschbaum et al., 1993), one of the most frequently used and most effective laboratory stressors (Dickerson and Kemeny, 2004). In the control condition, participants recalled either the words or the pictures in the presence of a single experimenter and no video recordings were taken. The retention test took 4 min in both conditions and in both conditions blood pressure was measured once during the retention test, again with a Dinamap system (Critikon, USA) on the left upper arm. After this first retention test, another saliva sample was collected and blood pressure was measured once again. Twenty-five minutes after the beginning of the first, stressful or non-stressful, retention test, participants collected another saliva sample and their blood pressure was measured once again. Next, they completed another retention test for the material that had not been tested in the first retrieval session (i.e., if participants recalled the words in the first retention test, they were asked to recall the pictures in the second retention test and vice versa). This second retention test was the same as the first retrieval session in the control condition and the same for all participants. Whether words or pictures were tested in the first and second retention test, respectively, was counterbalanced across participants and groups. The timing of the two retention tests was chosen to ensure that autonomic arousal was high and cortisol concentrations were low during the first retention test. Conversely, during the second retention test autonomic arousal should be low again whereas cortisol concentrations should have reached a peak at the time of the second retention test (Kirschbaum et al., 1993). During the 25-min-interval between the two retention tests, participants were allowed to read.

2.4. Statistical analyses

Salivary cortisol and blood pressure responses to the first (stressful or non-stressful) retention test were analyzed by separate group (stress vs. control) × time point of measurement ANOVAs. Participants' memory performance was analyzed by group × emotion (neutral vs. negative) ANOVAs. In order to assess the influence of stress-induced autonomic arousal and cortisol elevations on memory, we calculated correlations between the increases in blood pressure and cortisol (expressed as difference between peak and baseline levels), on the one hand, and memory performance on the other hand. In addition, we classified stressed participants by means of a median split into those showing high vs. low increases in cortisol or blood pressure after the first retention test and subjected the memory data to an ANOVA with the factors emotion and stress response (control vs. low-responder vs. high-responder). All reported p-values are two-tailed.

3. Results

3.1. Day 1: Cortisol and blood pressure at encoding

Before the learning session on day 1, participants in the control and stress groups did not differ in their salivary cortisol concentrations (control vs. stress group ($M \pm$ SEM): 8.22 ± 0.87 nmol/l vs. 8.37 ± 0.71 nmol/l), in systolic (127.83 ± 2.24 mmHg vs. 133.60 ± 2.61 mmHg) or diastolic blood pressure (74.74 ± 1.12 mmHg vs. 76.38 ± 1.48 mmHg; all ts < 1.69, all ps > 0.10).

3.2. Day 1: Learning performance

In the immediate free recall test on day 1, participants recalled on average 9.4 neutral and 11.1 negative words as well as 13.8 neutral and 16.8 negative pictures. Memory was significantly better for negative than for neutral stimuli (F (1, 70) = 55.73, $p < 0.0001$, $\eta^2 = 0.44$) and for pictures compared to words (F (1, 70) = 143.75, $p < 0.0001$, $\eta^2 = 0.67$). The influence of stimulus emotionality was stronger for pictures than for words (F (1, 70) = 4.46, $p < 0.05$, $\eta^2 = 0.06$), although both emotional pictures and emotional words were better remembered than their neutral counterparts (both ts (72) > 4, both ps < 0.001). Most importantly,

the stress and control groups did not differ in their immediate free recall performance (main effect group and all interaction effects including the factor group: all Fs < 1.45, all ps > 0.23), thus ruling out group differences in memory encoding.

3.3. Day 2: Physiological responses to the stressor

Significant changes in blood pressure and salivary cortisol suggest that the first, TSST-like retention test was indeed experienced as stressful. Diastolic blood pressure increased in the retrieval-stress group but not in the control group (group × time point of measurement: F (3, 207) = 9.76, $p < 0.001$, $\eta^2 = 0.12$; Fig. 1A). Follow-up tests showed significant group differences in diastolic blood pressure during the first retention test ($p < 0.01$) but not at baseline or 25 min after the first retention test, when the second retention test started (both ps > 0.85). Similarly, systolic blood pressure was significantly increased during and shortly after the first retention test in the retrieval-stress group relative to the control group (both ps < 0.05), whereas groups did not differ at baseline or before the second retention test (both ps > 0.15; group × time point of measurement: F (3, 207) = 14.02, $p < 0.001$, $\eta^2 = 0.17$; Fig. 1B). In addition to blood pressure, salivary cortisol increased also in the retrieval-stress group but not in the control group (group × time point of measurement: F (2, 136) = 14.51, $p < 0.001$, $\eta^2 = 0.18$), with significant group differences at the time of the second retention test ($p < 0.05$) but not before or shortly after the first retention test (both ps > 0.12; Fig. 1C). There was a strong trend for a correlation between the stress-induced cortisol elevation and the increase in systolic blood pressure in response to the stressor ($r = 0.32$, $p = 0.06$); the increase in diastolic blood pressure, however, was not correlated with the cortisol increase ($r = 0.04$, $p = 0.81$). Although men had generally higher systolic blood pressure than women (F (1, 71) = 22.40, $p < 0.001$, $\eta^2 = 0.25$), the increase in (systolic and diastolic) blood pressure and salivary cortisol in response to the stressor was similar in men and women (all main or interaction effects including participants' sex: all Fs < 1.10, all ps > 0.30).

3.3.1. Identification of high vs. low responders

In order to directly test the hypothesis that autonomic arousal enhances and cortisol impairs memory retrieval, we classified the stressed participants into high- and low-responders based on their stress-induced increases in cortisol, systolic and diastolic blood pressure, respectively. Cortisol low-responders had lower cortisol responses to the stressor than high responders (t (34) = 7.48, $p < 0.001$) but did not differ in their cortisol response from controls (t (51) = 0.62, $p = 54$). Similarly, participants classified as low-responders based on their increase in diastolic blood pressure had a lower diastolic blood pressure response than diastolic blood pressure high responders (t (34) = 8.49, $p < 0.001$) but were similar to controls (t (51) = 0.01, $p = 99$). For systolic blood pressure, however, participants identified as low-responders showed a lower increase in systolic blood pressure than systolic blood pressure high-responders (t (34) = 6.45, $p < 0.001$) but a higher increase than participants in the control group (t (51) = 2.65, $p = 0.01$).

In line with the obtained correlation between the stress-induced cortisol increase and the increase in systolic blood pressure, participants that were classified as cortisol high-responders were significantly more often also classified as high-responders with respect to systolic blood pressure than cortisol low-responders (χ^2 (1) = 4.86, $p = 0.03$). There was, however, no significant association between the classification as cortisol high- and low-responder and the classification as high- and low-responder with respect to diastolic blood pressure (χ^2 (1) = 0.72, $p = 0.40$).

3.4. Day 2: Stress effects on ongoing and delayed memory retrieval

In the retention tests on day 2, participants recalled on average 6.4 neutral and 7.0 negative words as well as 12.6 neutral and 15.9 negative pictures. Overall, participants recalled in the retention tests on day 2 significantly more negative than neutral items (F (1, 70) = 48.92, $p < 0.001$, $\eta^2 = 0.42$) and more pictures than words (F (1, 70) = 339.33, $p < 0.001$, $\eta^2 = 0.83$). Stress per se did not affect retrieval performance (main effect group, group × emotion × time of

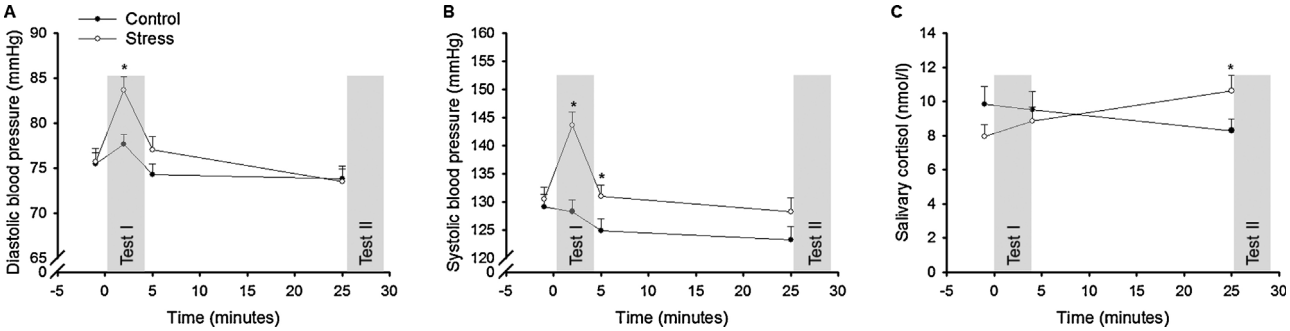

Figure 1 Physiological responses to the first retention test. Participants of the 'retrieval-stress' condition showed significant increases in (A) diastolic and (B) systolic blood pressure during the first retention test; no such increases were seen in participants of the control condition. (C) Moreover, salivary cortisol increased after the first retention test in the 'retrieval-stress' group but not in the control group. Note that autonomic arousal (indicated by diastolic and systolic blood pressure) was elevated during the first retention test but not before the second retention test, whereas cortisol was elevated before the second retention test but not before or shortly after the first retention test. Error bars represent SEM. *$p < 0.05$.

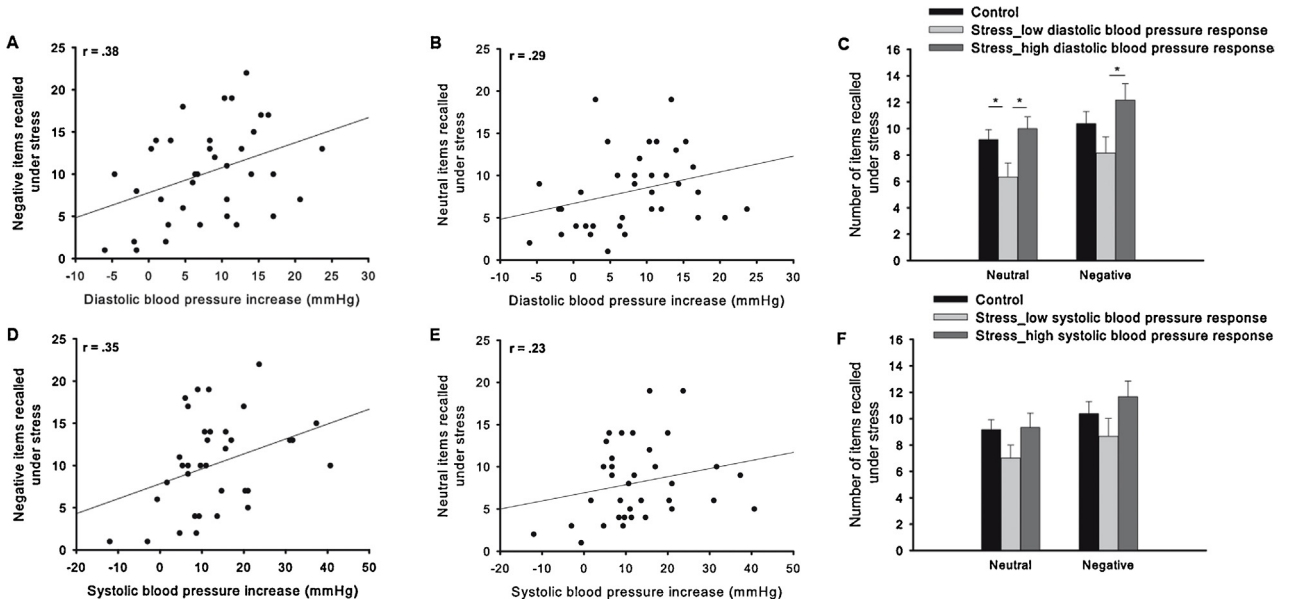

Figure 2 Influence of autonomic arousal (expressed as increases in blood pressure) on memory in the first (stressful or non-stressful) retention test, that is, retrieval under stress. (A) Increases in diastolic blood pressure were positively correlated with memory for negative not items during the first retention test, (B) whereas there was only a trend for a correlation with neutral items. (C) Participants showing a large diastolic blood pressure increase recalled more items in the first retention test than participants showing a small diastolic blood pressure increase; the latter were also impaired relative to participants in the control group. (D) Increases in systolic blood pressure were also positively correlated with memory for negative items and (E) again this correlation was not significant for neutral words. (F) The differences between control participants, participants showing a large systolic blood pressure increase and participants showing a small systolic blood pressure increase, however, did not reach statistical significance. Error bars represent SEM. *$p < 0.05$.

testing interaction, group × emotion interaction, and group × time of testing interaction: all Fs < 2.6, all ps > 0.12), neither during the stressor (i.e., in the first retention test; $p = 0.59$) nor 25 min after the stressor (i.e., in the second retention test; $p = 0.51$), and there were no group differences in memory for pictures vs. words or neutral vs. negative stimuli (both Fs < 0.20, both ps > 0.68).

3.4.1. Autonomic arousal enhances memory retrieval under stress

Although the 'stress-retrieval' did not affect memory at the group level, retrieval performance was significantly influenced by the individual stress response. Memory for negative items in the first retention test was positively correlated with the increases in diastolic ($r = 0.38$, $p = 0.02$) and systolic blood pressure ($r = 0.35$, $p = 0.04$) during the first (stressful) retention test (Fig. 2A and D). For neutral items, these correlations did not reach statistical significance (diastolic blood pressure: $r = 0.29$, $p = 0.08$; systolic blood pressure: $r = 0.23$, $p = 0.18$; Fig. 2B and E), although they were similar to those observed between blood pressure and memory for negative items (both ts < 1.05, both ps > 0.10). When we classified participants as controls, stressed participants that showed a low diastolic blood pressure increase, and stressed participants that showed a high diastolic blood pressure increase during the first retention test, we obtained a significant difference between these groups (F (2, 69) = 3.42, $p = 0.04$, $\eta^2 = 0.09$): low diastolic blood pressure responders were impaired both relative to high diastolic blood pressure responders ($p = 0.01$) and relative to participants in the control group ($p = 0.058$; Fig. 2C), irrespective of the emotionality of the stimuli (group × emotion interaction: $p = 0.65$). High diastolic blood pressure responders and control participants did not differ significantly (t (52) = 1.13, $p = 0.26$). When participants were subdivided according to their increases in systolic blood pressure, no significant group differences occurred ($p = 0.20$; Fig. 2F). The cortisol increase in response to the first retention test was not associated with memory performance during this retention test ($p > 0.75$).

3.4.2. Cortisol impairs memory retrieval 25 min after stress

Memory performance 25 min after the stressful or non-stressful first retrieval session was not affected by changes in systolic or diastolic blood pressure (all ps > 0.17). The increase in salivary cortisol in response to the first (stressful) retrieval session (defined as peak minus baseline cortisol concentration), however, was negatively correlated with memory for negative items 25 min later ($r = -0.44$, $p = 0.008$, Fig. 3A); whereas memory for neutral items was not significantly affected by the cortisol increase ($r = -0.30$, $p = 0.07$; Fig. 3B; correlation for neutral vs. negative items: t (33) = 1.87, $p < 0.05$). Based on these correlations, we subdivided our sample into controls, stressed participants that showed a low cortisol response and stressed participants that showed a high cortisol response and subjected the memory performance 25 min post stress to an emotion (neutral vs. negative) × cortisol response (control vs. low response vs. high response) ANOVA. This analysis yielded a significant emotion × cortisol response interaction (F (2, 69) = 3.79, $p = 0.03$, $\eta^2 = 0.10$), indicating that cortisol high responders

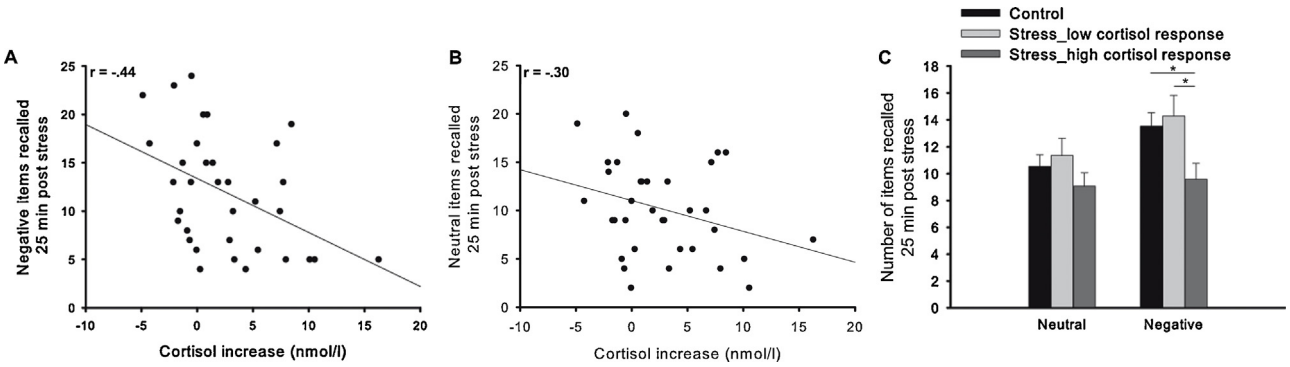

Figure 3 Influence of cortisol on memory in the second retention test, that is, retrieval 25 min post stress. (A) The increase in salivary cortisol after the first, stressful retention test was negatively correlated with memory for negative items in the second retention test but (B) not with memory for neutral items. (C) Accordingly, participants showing a large increase in cortisol in response to the stressor were significantly impaired in their retrieval performance for negative items relative to participants in the control group and stressed participants showing no or only a small cortisol response to the stressor. Error bars represent SEM. $^{*}p < 0.05$.

were impaired in their memory for negative items both compared to control participants ($p = 0.02$) and compared to low cortisol responders ($p = 0.02$; main effect group for negative items: F (2, 70) = 3.50, $p = 0.04$, $\eta^2 = 0.10$), whereas there were no differences between these groups for neutral items ($p = 0.38$; Fig. 3C).

Men and women did not differ in their memory performance and participants' sex did not affect the influence of stress on memory in the two retention tests (main effects sex and all interaction effects including the factor sex: all Fs < 1.58, all ps > 0.21). Finally, it is important to note that the effects of stress or stress mediators on memory during and after the stressor was not influenced by the order in which pictures and words were tested, that is, whether words or pictures were tested during or after the stressor, respectively (all Fs < 0.20, all ps > 0.70).

4. Discussion

It is commonly accepted that stress interferes with memory retrieval (Roozendaal et al., 2006a; Schwabe et al., 2012). Most studies supporting this view, however, tested retrieval 20—30 min after stress, when cortisol concentrations reach peak levels (Buchanan et al., 2006; Kuhlmann et al., 2005; Schwabe and Wolf, 2009; Smeets et al., 2008). Here, we asked whether stress does indeed universally impair memory retrieval and tested participants' memory for previously learned material during a stressful experience and 25 min thereafter. Although we obtained no overall effect of stress on retrieval, our data show that individual differences in autonomic and cortisol responses to the stressor were differentially related to memory performance during and after stress. Autonomic arousal, expressed as change in blood pressure, was positively correlated with memory retrieval under stress but unrelated to retrieval 25 min post stress. The cortisol response to the stressor, however, was negatively correlated with retrieval performance 25 min after stress but unrelated to retrieval under stress.

In the first retention test, memory retrieval was an integral part of the stressful situation. For instance, if participants did very well in the memory test, this could have reduced the unpleasantness of the testing situation. Stress during this first retention test did not disrupt retrieval performance. The activity of the fast acting autonomic nervous system, one of the major stress response systems, was even associated with enhanced memory performance under stress. This finding corroborates previous data showing that noradrenaline facilitates retrieval (Devauges and Sara, 1991; Murchison et al., 2004). Moreover, the positive correlation between autonomic activity and memory is also in line with the idea that rapidly acting stress mediators improve the processing capacities of areas such as the hippocampus or prefrontal cortex (Joëls et al., 2011, 2006), which are critically involved in successful memory retrieval (Buckner and Wheeler, 2001). It is, however, important to note that although participants who showed a strong autonomic response to the stressor tended to perform slightly better than non-stressed control participants, the more striking effect was that participants showing a weak autonomic stress response recalled significantly fewer items during the stress situation than control participants and participants who showed a strong autonomic stress response. Thus, this pattern of results suggests that autonomic arousal is required to maintain memory performance under stress. Lacking autonomic arousal during a stressful experience, however, is accompanied by impaired retrieval, even in the absence of glucocorticoids which had not yet been increased during the first retention test. The panel or the video camera may have distracted the participants during the (stressful) memory test and noradrenaline may have helped them to (re)focus attention (Coull et al., 2004; Smith et al., 1992).

Whereas autonomic arousal played an important part in memory retrieval under stress, it did not influence retrieval performance 25 min later. During this second retention test, cortisol concentrations were significantly increased. In contrast to autonomic arousal (in the first retention test), cortisol was negatively correlated with retrieval performance and cortisol high responders recalled fewer items 25 min post stress compared to control participants and cortisol low responders. These findings are in line with other reports pointing to the critical role of glucocorticoids in stress-induced retrieval impairments. For example, in rats stress impaired spatial memory retrieval only when

glucocorticoids were active, the glucocorticoid synthesis inhibitor metyrapone prevented this stress effect and the injection of hydrocortisone reinstated the retrieval impairment (de Quervain et al., 1998). Similarly, in humans retrieval can be impaired by hydrocortisone administration (de Quervain et al., 2000) and after stress retrieval is most strongly impaired in participants showing a strong cortisol response to the stressor (Buchanan et al., 2006). Moreover, our finding that the impairing effect of stress-induced cortisol was most pronounced for negative items corresponds to previous data indicating that endogenous or exogenous glucocorticoids interfere particularly with the retrieval of emotionally arousing material (Buchanan et al., 2006; de Quervain et al., 2007; Kuhlmann et al., 2005). Emotionally arousing material is associated with noradrenergic activity in the amygdala (Strange and Dolan, 2004) and there is compelling evidence that such arousal-induced noradrenergic activation of the amygdala is required for glucocorticoid effects on memory (Roozendaal et al., 2004, 2006a,b).

Differential effects of different stress mediators (in particular, glucocorticoids and noradrenaline) on memory processes were also reported in previous studies. For example, stress may have opposite effects on memory formation depending on the temporal proximity of stress and encoding, with stress shortly before encoding enhancing subsequent memory and stress 30 min before encoding impairing later recall (Zoladz et al., 2011). Interestingly, the enhancing effect of stress shortly before encoding was correlated with the activity of the autonomic nervous system, whereas the impairing effect of stress 30 min prior to encoding was associated with the cortisol response to the stressor. In addition to the differential effects of autonomic arousal and glucocorticoids on memory formation, there is also first evidence for opposite effects of autonomic arousal and cortisol on memory retrieval. Whereas the stress-induced retrieval impairment was dependent on a substantial cortisol response (Buchanan and Tranel, 2008; Buchanan et al., 2006), stress in the absence of an increase in cortisol tended even to enhance delayed retrieval (in men; Buchanan and Tranel, 2008). Together with the present results, these findings underline that stress is not universally good or bad for cognitive processes, such as memory retrieval. Many different systems and modulators are engaged in the response to a stressor, with some acting immediately after stressor exposure and others with a short delay (Joëls and Baram, 2009). The mode of action of these stress mediators is critical for the nature of the stress effect on memory (Joëls et al., 2011). Recent data point to the importance of temporal action profiles of different stress mediators for stress effects on memory encoding (Henckens et al., 2012, 2010; Zoladz et al., 2011). The present findings suggest that stress effects on memory retrieval processes are also time-dependent, that is, dependent on which stress mediators are active at the time of retrieval.

Alterations in memory processes are part of a generally adaptive response to a stressor. In order to cope with a stressful situation and similar situations in the future, it is important to process information in an efficient manner, to have access to information that are relevant to the current stressor, and to form lasting memories of the stressful encounter. Although it is widely accepted that stress mediators facilitate memory formation (McGaugh and Roozendaal, 2002), it is also commonly assumed that stress disrupts memory retrieval. Here, we challenge the view that stress results in a general retrieval impairment. Instead, our findings suggest that the same stressor may have different effects on ongoing and delayed retrieval processes, depending on the presence of autonomic arousal and glucocorticoids.

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Conflict of interest

The authors report no conflict of interest.

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