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2 **Stress disrupts context-dependent memory**

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Abstract

Memory is facilitated when the retrieval context resembles the learning context. The brain structures underlying contextual influences on memory are susceptible to stress. Whether stress interferes with context-dependent memory is still unknown. We exposed healthy adults to stress or a control procedure before they learned an object-location-task in a room scented with vanilla. Memory was tested 24h later, either in the same or in a different context (unfamiliar room without the odor). Stress administered prior to encoding abolished the context-dependent memory enhancement found in the control group. Thus, these findings represent the first demonstration of impaired context-dependent memory following stress.

Keywords: Context-dependent memory; stress; declarative memory; encoding

1 Information is better recalled when the retrieval environment resembles the previous
2 learning environment (Smith and Vela 2001, Tulving and Thompson 1973). In a classic
3 example for contextual effects on memory Godden and Baddeley (1975) asked divers to learn
4 lists of words either on dry land or underwater and tested the memory for these words
5 subsequently either in the same or the opposite environment. Those divers who had to recall
6 the words in the original environment remembered significantly more words than those
7 required to change environments. Recent studies suggest that the hippocampus and the
8 prefrontal cortex are likely candidates for context-dependent memory in the brain (Kalisch et
9 al. 2006, Rasch et al. 2007, Wagner et al. 1998). Interestingly, both of these structures express
10 a high density of receptors for glucocorticoids (cortisol in humans), the steroid hormones that
11 are released from the adrenal cortex in response to stress, and are highly sensitive to stress (de
12 Kloet et al. 2005, Wolf 2008). Memory functions that rely on the integrity of the hippocampus
13 or prefrontal cortex, such as spatial or working memory, are often impaired when stress or
14 cortisol was administered before learning (Lupien et al. 1999, Schoofs et al. 2008, Schwabe et
15 al. 2007; but see also Nater et al. 2007 and Schwabe et al. 2008 for reports of enhanced
16 memory following pre-learning stress). Moreover, stress and cortisol suppress memory-
17 related neuroplasticity processes, such as long-term potentiation, in both the hippocampus and
18 the prefrontal cortex (Diamond et al. 2007). In the same line, rodent studies argue that stress
19 before training impairs spatial memory due to a stress-induced suppression of hippocampal
20 spine plasticity (Diamond et al. 2006, Diamond et al. 1999). Thus, it could be predicted that
21 stress impairs the beneficial effect of congruent learning and retrieval environments on
22 memory performance. This prediction, however, has not been tested yet.

23 In the present study, we examined the influence of stress on context-dependent
24 memory in 72 young adults (36 women; age 18-35 yr, $M \pm SEM$: 25.0 ± 0.5 yr). Participation
25 was restricted to healthy non-smokers. Women that used oral contraceptives (OCs) were
26 excluded because OCs change the cortisol stress response (Kirschbaum et al. 1999).

1 Participants were asked to refrain from meals, drinking alcohol or caffeine, and severe
2 physical exercise within the 2 hours before the experiment. All subjects provided written
3 informed consent for their participation in the protocol as approved by the ethics committee of
4 the German Psychological Society (DGPs). Participants were exposed to a stress or control
5 procedure before they learned an object location task in a room scented with a vanilla odor.
6 On the following day, retention performance was tested either in the same room where
7 learning had taken place and again with the vanilla odor present (congruent context) or in a
8 different room without the odor (incongruent context), resulting in four experimental
9 conditions (9 men and 9 women per condition): stress/congruent context, stress/incongruent
10 context, control/congruent context, control/incongruent context.

11 In the stress condition, participants were exposed to the socially evaluated cold pressor
12 test (SECPT) as described elsewhere (Schwabe et al. 2008). Briefly, participants immersed
13 their hand up to and including the wrist for up to 3 minutes (or until they could no longer
14 tolerate it) in ice water (0-2°C). They were monitored by an unfamiliar person and videotaped
15 during hand immersion as social evaluation is critical for stress-induction (Dickerson and
16 Kemeny 2004). Participants in the control condition submerged their hand up to and including
17 the wrist for 3 minutes in warm water (35-37°C); they were neither monitored nor videotaped.
18 To assess the efficacy of the SECPT, saliva samples were collected by means of Salivette[®]
19 (Sarstedt, Germany) collection devices immediately before as well as 1 minute, 20 minutes
20 and 35 minutes after cessation of the SECPT or control condition. Free cortisol concentrations
21 were measured from saliva using an immunoassay (IBL, Hamburg). Moreover, blood pressure
22 measurements were taken immediately before, during and immediately after the SECPT or
23 control condition and subjects rated immediately after the SECPT or control condition on a
24 scale from 0 (“not at all”) to 100 (“very much”) how stressful, painful and unpleasant they
25 had experienced the previous situation.

1 Twenty-five minutes after the SECPT or control condition, participants went to
2 another room where they were presented a computer version of the well known card game
3 “memory” (also known as “concentration”). This interval between stress and learning has
4 been chosen because cortisol reaches peak levels at about 20 to 30 minutes after stress
5 (Schoofs et al. 2008, Schwabe et al. 2008). Subjects saw a configuration of 15 card-pairs (5
6 pictures \times 6 rows) showing colored pictures. First, all cards were shown as grey squares (“laid
7 face down”). Next, participants could choose two cards and turn them face up. If the two
8 cards showed the same picture, subjects could turn the next two cards. If they were not the
9 same, the second card was turned face down again and subjects had to continue their search
10 for the matching card. Participants were requested to turn over all pairs of matching picture
11 cards as fast as possible. Pictures were taken from the International Affective Picture System
12 (Lang et al. 1997) and varied in emotional valence from neutral to positive and negative.
13 Negative pictures (arousal ratings taken from Lang et al. (1997), $M \pm SEM$: 6.8 ± 0.3) were
14 associated with significantly higher emotional arousal than positive pictures (4.5 ± 0.1), which
15 were more arousing than neutral pictures (2.9 ± 0.1 ; $P_s < .001$). Participants completed four
16 trials of the memory task. They were asked to memorize the picture locations as these would
17 be tested later. The spatial arrangement of the cards was randomized across subjects but
18 constant for each subject. During learning we presented a vanilla odor as earlier studies
19 showed that odors are very potent context cues facilitating memory (Rasch et al. 2007).

20 Twenty-four hours later, participants returned to the laboratory and completed one
21 further trial of the memory task. Importantly, retention testing took either place in the same,
22 *congruent* context (same room and same odor) or in a different, *incongruent* context (new
23 room in a different part of the university building without the odor). Memory performance
24 was expressed as (i) the number of hits (correct card-pair locations without error) in the test
25 trial on day 2 relative to the number of hits in the last training trial on the previous day and (ii)
26 the time needed to complete the memory game on day 2 minus the time needed to complete

1 the memory game in the last training trial 24 hours before. All testing took place between
2 1:00 pm and 5:30 pm to control for the diurnal rhythm of cortisol (Kirschbaum and
3 Hellhammer 1994).

4 Significant increases in salivary cortisol (stress \times time points of measurement
5 interaction: $F_{(3,189)} = 21.23$, $P < .001$; see Figure 1), systolic and diastolic blood pressure (both
6 $F_{(2,128)} > 30$, both P s $< .001$; see Table 1) as well as the subjective ratings of stressfulness,
7 painfulness and unpleasantness (all $F_{(1,64)} > 120$, P s $< .001$; see Table 1) indicated the success
8 of the stress induction by the SECPT. The physiological and subjective stress responses were
9 comparable in the congruent and incongruent context groups and not influenced by
10 participants' sex (all P s $> .15$). All subjects except four women and two men (mean duration:
11 70 seconds) underwent the SECPT for the full 3 minutes. The subjective ratings, blood
12 pressure and cortisol levels of these 6 participants were, however, not significantly different
13 from the other subjects in the stress group.

14 All participants improved over the four learning trials (for both hits and time to
15 complete the task both $F_{(3,198)} > 80$, both P s $< .001$); irrespective of sex, stress and context
16 condition (all P s $> .12$). On average, participants scored 11 hits (SEM: 0.3) and needed 50
17 seconds for task completion (SEM: 2.5 seconds) in the last learning trial. Performance for
18 neutral, positive and negative pictures was comparable in the final learning trial (between 70
19 and 75 percent; $F_{(2,128)} = 0.93$, $P = 0.40$).

20 In the retention test 24h later, participants of the control group showed significantly
21 better memory performance, expressed as percentage of hits, if the retrieval context matched
22 the learning context ($t_{(34)} = 2.53$, $P < .02$). This memory enhancing effect of congruent
23 learning and testing contexts disappeared when subjects were stressed before learning ($t_{(34)} =$
24 0.19 , $P = .85$; context \times stress interaction: $F_{(1,65)} = 4.34$, $P = .04$; see Figure 2). Interestingly,
25 the effects of stress and context depended significantly on the emotionality of the presented
26 pictures (stress \times context \times picture emotionality interaction: $F_{(2,128)} = 3.80$, $P < .03$). Stress

1 abolished the context effect on memory most clearly for neutral pictures ($F_{(1,64)} = 8.85$, $P <$
2 $.01$). A comparable trend was found for positive pictures ($F_{(1,64)} = 2.93$, $P = .09$), whereas
3 memory for negative pictures remained virtually unaffected by stress and context ($P > .90$;
4 see Figure 2). The main effects of stress, context and picture emotionality did not reach
5 statistical significance (all P s $> .13$).

6 All participants completed the memory task faster when the learning and retrieval
7 contexts were congruent ($F_{(1,64)} = 7.58$, $P < .01$; Δ time for task completion ($M \pm SEM$; in sec):
8 13.9 ± 3.1 in congruent vs. 29.3 ± 4.4 in incongruent context), while there were no effects of
9 stress or picture emotionality on the time needed to complete the memory task (all P s $> .17$).
10 Overall, memory performance was unaffected by participants' sex (all P s $> .15$).

11 To summarize, our findings support the hypothesis that stress administered prior to
12 encoding impairs context-dependent memory. Memory performance in the control group was
13 overall enhanced by about 30 percent when the retrieval context resembled the learning
14 context. This beneficial context effect disappeared when participants were stressed before
15 learning. Importantly, since the stress-induced elevations in cortisol, sympathetic and
16 subjective arousal were over at the time of retention testing 24h after learning, the observed
17 effect is most likely due to stress effects on the integration of context cues in the memory
18 trace rather than on the retrieval of the context. A theoretical context for our findings can be
19 found in Easterbrook's (1959) cue utilization hypothesis, which assumes that increasing levels
20 of emotional arousal result in a restriction of the range of cues that are attended to. In our
21 study, stressed subjects might have focused primarily on information related to the memory
22 task and less to context cues. This interpretation fits well to recent studies showing that stress
23 modulates multiple memory systems in favor of rather simple, caudate nucleus-dependent
24 stimulus-response learning and at the expense of hippocampus-dependent "cognitive"
25 learning which requires the integration of multiple cues (Kim et al. 2001, Schwabe et al.
26 2007).

1 Specific learning episodes are automatically embedded within a temporal, spatial and
2 sensorimotor context. This integration of contextual information into the memory trace is
3 known to rely on the hippocampus (Moscovitch et al., 2005). Thus, our findings suggest that
4 participants stressed before learning do not benefit from the contextual cues when tested for
5 their memory one day later because of reduced hippocampal functioning. This interpretation
6 is in line with electrophysiological evidence showing a reduced neuronal plasticity 20-30
7 minutes after stress exposure (Diamond et al. 2007, Joels et al. 2006). It is also in agreement
8 with human fMRI evidence of reduced hippocampal activity following stress (Pruessner et al.
9 2008) or pharmacological administration of the stress hormone cortisol (Oei et al. 2007).

10 Importantly, while stress disrupted the context-dependent memory enhancement, the
11 memory for the object-location task per se, which is thought to rely on medial temporal lobe
12 (MTL) structures, was not affected by stress. At first glance, this might appear to be in
13 conflict with previous reports suggesting that stress prior to learning influences on MTL-
14 based memory performance. However, the literature on the effects of pre-learning stress is
15 very heterogeneous with some studies showing impairing effects (Kirschbaum et al. 1996,
16 Lupien et al. 1997), while others found enhancing effects (Nater et al. 2007, Schwabe et al.
17 2008) or no effects at all (Domes et al. 2002). Moreover, these studies tested participants in
18 the same context where learning had taken place, thus they did not take the influence of the
19 learning/testing environment into account. The fact that stress impaired the use of the context
20 as a cue for memory whereas memory per se remained unaffected by stress suggests that both
21 functions rely on medial temporal lobe structures differing in their sensitivity to stress.

22 Interestingly, the effects of context and stress on memory depended on the valence and
23 arousal of the presented pictures. Context effects were strongest for low arousal (neutral) and
24 weakest for high arousal (negative) pictures. Usually, memory is better for high arousal than
25 for low arousal stimuli (Buchanan and Tranel 2008, Payne et al. 2006, Schwabe et al. 2008).
26 In line with this view, memory tended to be better for negative than for positive and neutral

1 pictures in the incongruent context/control condition. Surprisingly, the congruency between
2 learning and retrieval contexts made memory for low arousing pictures not only similar to but
3 even better than memory for high arousing pictures. A possible explanation for this could be
4 the fact that the processing of high arousing information relies on different brain structures
5 than the processing of low arousing information (e.g. amygdalar-hippocampal vs. prefrontal
6 cortex-hippocampal networks; Kensinger and Corkin 2004, LaBar and Phelps 2002). These
7 structures make memories more stable on the one hand but prevent beneficial influences, e.g.
8 of context congruency, on the other hand.

9 While stress disrupted the context effect for memory expressed as correctly recalled
10 card-pair locations (hits), the context effect for the time needed to complete the memory task
11 remained unaffected by stress. Similar to other authors who used the same object-location
12 task (Benedict et al. 2008, Rasch et al. 2007), we suggest that accuracy parameters are more
13 sensitive to the influence of memory modulators, such as stress, than speed parameters.

14 In the present study, the learning context was made up of an odor and a spatial
15 environment. It is important to note that we did not aim to separate the contributions of these
16 context components but to create a distinct context that may support memory. Nevertheless,
17 previous research suggested that both the memory for odors and the memory for spatial
18 arrangements rely on the hippocampus and adjacent cortices (Burgess et al. 2002, Fortin et al.
19 2004, Levy et al. 2004, O'Keefe and Nadel 1978). Thus, it is tempting to speculate that there
20 is a common mechanism underlying the impact of stress on odor context-dependent and
21 spatial context-dependent memory enhancement, namely the effect of stress (hormones) on
22 the integrative function of the hippocampus.

23 Finally, our findings could also be interpreted in light of studies on mood- or state-
24 dependent memory (Lewis and Critchley 2003). According to this view, the presence or
25 absence of stress could be construed as an internal, biological context. As no stress was
26 induced on the test-day, this internal context was different for the stress group resulting in

1 incongruent learning and testing contexts in stressed participants tested in congruent spatial
2 and odor environments. Though, this interpretation cannot fully account for our findings
3 future studies are required to include subjects that are re-exposed to stress before retrieval
4 testing to dissect the potential interactions between internal and external context elements.

5 To conclude, our results suggest that stress can interfere with our ability to integrate
6 context information into a memory trace. These findings might improve our understanding of
7 the pathogenesis of psychiatric disorders, such as the posttraumatic stress disorder (PTSD) in
8 which the failure to connect the traumatic event with the appropriate (temporal and spatial)
9 contextual information is a common pathological hallmark (Rauch et al. 2006).

10

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1 **Table 1.** Participants' ratings of stressfulness, painfulness and unpleasantness as well as
 2 systolic and diastolic blood pressure responses indicated the success of the stress
 3 manipulation.

	Stress		Control	
	M	SEM	M	SEM
<i>Subjective assessment</i>				
Unpleasant	67.57	4.62	1.67	1.02
Stressful	51.35	4.95	3.33	1.05
Painful	70.00	4.50	0.56	0.39
<i>Systolic blood pressure</i>				
Pre	116.62	2.45	119.83	2.64
During	133.14*	3.62	114.31	3.82
Post	112.25	2.29	113.05	2.26
<i>Diastolic blood pressure</i>				
Pre	65.55	1.43	67.08	1.38
During	81.19*	2.13	65.55	1.15
Post	64.83	1.31	65.00	1.17

Bold – significantly higher in the stress than in the control group ($P < .001$);

* Significant difference within the stress group ($P < .01$).

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1 **Figure legends**

2

3 **Figure 1:**

4 Salivary cortisol concentrations immediately before as well as 1, 20 and 35 minutes after the
5 socially evaluated cold pressor test (SECPT) or control condition. The grey bars denote the
6 timing and duration of the treatment (SECPT vs. control condition) and the learning phase,
7 respectively. Error bars indicate standard errors of the means. ** $P < .01$.

8

9 **Figure 2:**

10 Percent of hits (correct card-pair locations) in the retention test on day 2 relative to the
11 number of hits in the last training trial 24h before as a function of stress (socially evaluated
12 cold pressor test vs. control condition) and context condition (incongruent vs. congruent
13 context). Note that this measure can yield values > 100 percent if more card-pair locations are
14 recalled in the retention test than in the last training trial. Error bars indicate standard errors of
15 the means. * $P < .05$.

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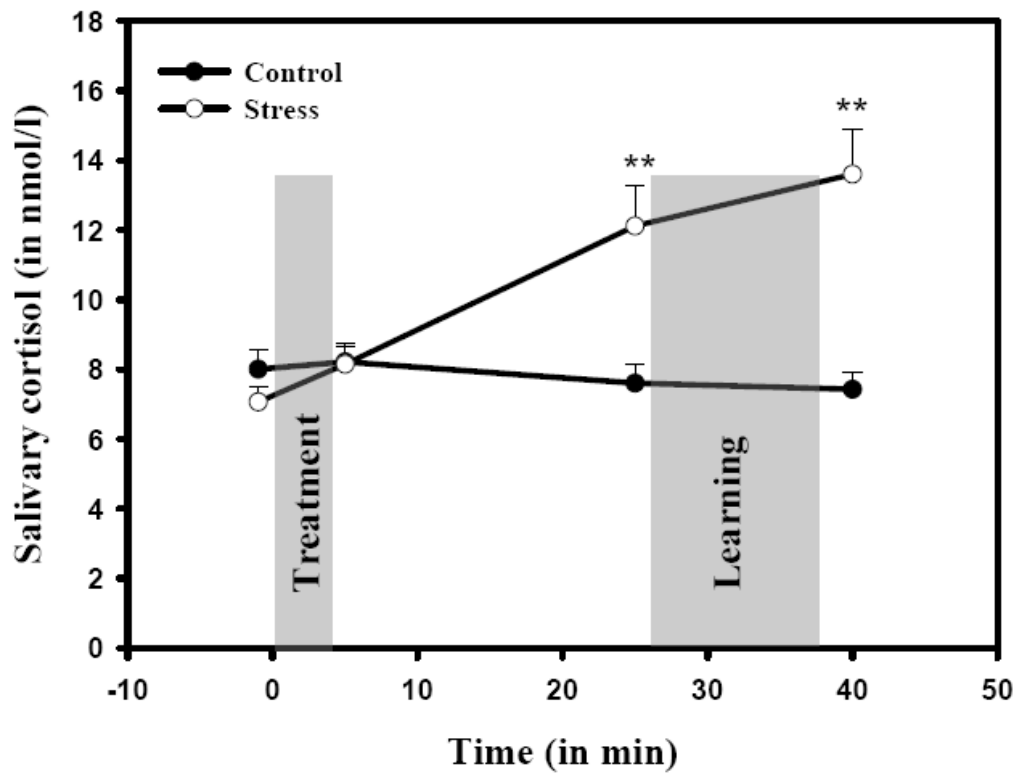
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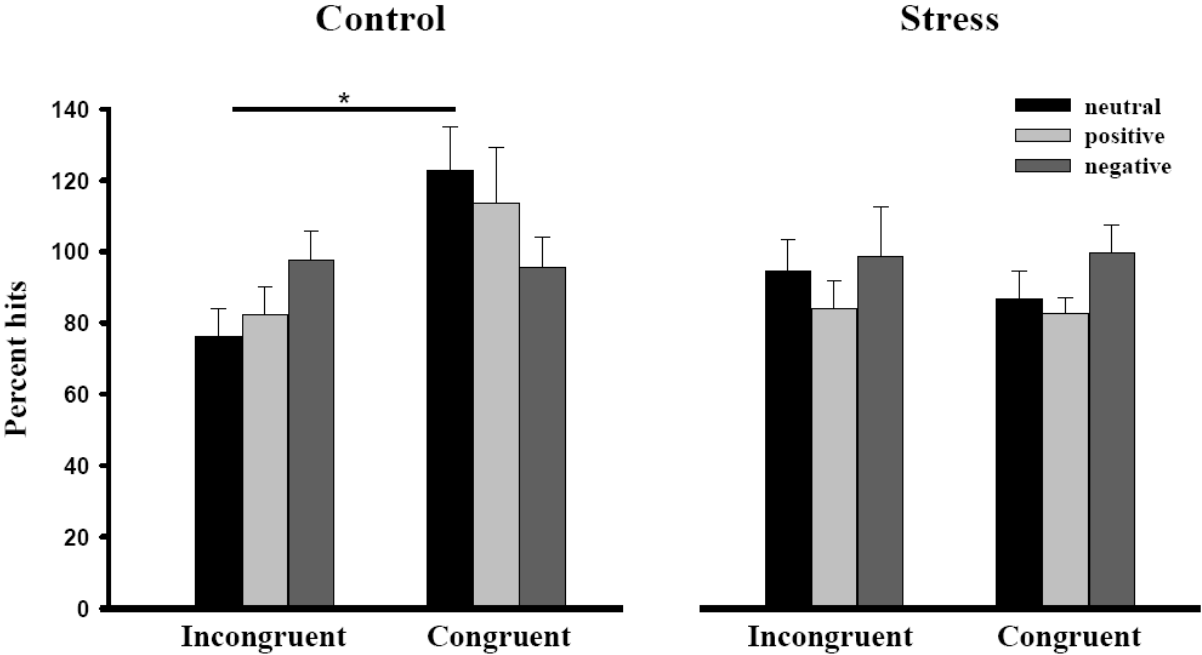
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1 **Figure 1**
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1 **Figure 2**
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