Stress eliminates retrieval-induced forgetting—Does the oral application of cortisol?

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Summary It is well established that stress and glucocorticoids can affect memory. Psychosocial stress has been reported to eliminate retrieval-induced forgetting (RIF), the phenomenon that repeated retrieval of a subset of previously learned material impairs later recall of related, but non-retrieved information. The stress-related reduction of RIF has been found correlated with an increase in salivary cortisol levels. Based on these findings, the current placebo-controlled study examined the effect of an oral dose of 25 mg hydrocortisone on the RIF effect in 37 healthy men. Even though participants in the hydrocortisone group showed a marked increase in salivary cortisol, retrieval-induced forgetting was not affected by the pharmacological treatment. Thus, cortisol administration alone in contrast to stress experience does not impair the RIF effect. However, participants with high state anxiety during retrieval practice did not show RIF, whereas participants with low state anxiety did. This finding suggests a role for state anxiety in stress-related elimination of retrieval-induced forgetting, perhaps indicative of a memory-modulating sympathetic nervous system effect.

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1. Introduction

Psychosocial stress affects episodic memory (Schwabe et al., 2010 for review). Common findings are improved consolidation by post-learning stress (Cahill et al., 2003; Smeets et al., 2008) and impaired recall by pre-retrieval stress (Kuhlmann et al., 2005a; Buchanan et al., 2006). These effects have been attributed to the memory modulating effects of glucocorticoid release from the hypothalamic–pituitary–adrenal (HPA) axis. Consequently, many memory modulating effects of stress can be mimicked pharmacologically by hydrocortisone intake (Kirschbaum et al., 1996; de Quervain et al., 2000, 2003). Here, we investigate whether retrieval-induced forgetting (RIF) which was previously shown to be eliminated by psychosocial stress (Koessler et al., 2009), is affected by hydrocortisone intake. RIF refers to the seemingly paradoxical phenomenon that the act of remembering can be a cause of forgetting (Brown, 1981; Roediger and Neely, 1982).
Successful retrieval of a specific memory requires that irrelevant, potentially interfering, memories are at least temporarily inhibited. Such inhibition in episodic memory can be studied using the retrieval practice paradigm (Anderson et al., 1994). Participants learn a study list consisting of a series of category—exemplar pairs (e.g. fruit — strawberry, spice — ginger, fruit — apricot, etc.). In a subsequent retrieval practice phase they have to retrieve half of the exemplars from some of the categories. Not very surprisingly, retrieval practice leads to enhanced recall of the practiced compared to unpracticed items. Crucially, however, recall of the unpracticed portion of items from practiced categories is poorer than recall of items from totally unpracticed categories. This occurs even though both item types are presented equally often during the experiment (i.e. in the study phase and the final test phase). This effect is referred to as RIF. During retrieval, not only the to-be-retrieved items, but also related items are activated. These related items interfere and therefore need to be inhibited (e.g. Anderson et al., 1994; Anderson and Spellman, 1995).

Generally, RIF is viewed as an adaptive mechanism of active interference resolution during retrieval guaranteeing enhanced access to target material. Larger RIF effects are related to fewer everyday cognitive failures (Groome and Grant, 2005) and superior working memory capacity (Aslan and Bäuml, 2011). Also, carriers of a genetic variant that leads to higher prefrontal dopamine availability have larger RIF effects (Wimber et al., 2011). Neuroimaging studies indicate specific prefrontal activation that predicts the magnitude of the RIF effect and is suggested to reflect inhibition that reduces access to interfering memories (Wimber et al., 2008).

On the other hand, RIF is reduced in individuals who experience stress, anxiety, and negative emotions. Negative mood (Bäuml and Kuhbandner, 2007), high state anxiety (Law et al., 2011) or anxiety disorder (Amir et al., 2001), exposure to traumatic life stress (Amir et al., 2009; Koessler et al., 2010), or experimental stress all reduce the RIF effect, although these factors probably operate on different time scales. The mechanisms mediating these reductions are so far largely unexplored. On a cognitive level, item-specific processing in negative affective states has been proposed to account for the elimination of RIF, since RIF crucially depends on the binding of an item to its category cue (Bäuml and Kuhbandner, 2007). Regarding experimental stress, an earlier study (Koessler et al., 2009) demonstrated that psychosocial stress experienced immediately before the retrieval practice phase eliminates RIF and leads to a concomitant rise in salivary cortisol inversely correlated with the magnitude of the RIF effect. This finding may appear counterintuitive, because stress is usually thought to impair memory retrieval, whereas in RIF it apparently aids retrieval by releasing items from inhibition. This release from inhibition may at least transiently serve an adaptive role in allowing access to a wider range of information in potentially dangerous or stressful situations regardless of its typical contextual embedding. Arguably, an undesirable long-term effect may be facilitated and de-contextualized access to disturbing information in disorders of chronic stress such as PTSD.

Biologically, stress-hormone induced impairment of hippocampal contextual binding and/or prefrontally mediated inhibition of competing memories may play a key role (Oei et al., 2007; Schwabe et al., 2009a). Based upon theoretical considerations as well as previous correlational evidence (Koessler et al., 2009), cortisol may act as a crucial mediator in the elimination of RIF under stress. 

The hippocampus (McEwen et al., 1969) as well as the anterior cingulate (Gos et al., 2008; Treadway et al., 2009) and the prefrontal cortex (PFC; Webster et al., 2002; Perlman et al., 2007), whose coordinated activity gives rise to the RIF effect (Conway and Fthenaki, 2003; Johannson et al., 2007; Kuhl et al., 2007, 2008; Wimber et al., 2008, 2009) are densely populated with glucocorticoid receptors and their function can be impaired by stress or application of glucocorticoids (Arnsten, 2000; McEwen and Magarinos, 2001; Oei et al., 2007).

If indeed cortisol secretion caused the abolition of RIF in our previous study, then oral (PO) application of hydrocortisone should also eliminate the effect. Several studies so far show analogous effects of stress and hydrocortisone application, indicating that glucocorticoids can be causative in stress effects on memory. de Quervain et al. (1998) found that both stress and systemic corticosterone administration led to impaired retention performance in rodents’ spatial memory. Similarly, in humans, episodic memory retrieval was found to be impaired by stress (Kuhlmann et al., 2005a) or cortisol alone (Kuhlmann et al., 2005b). Working memory processes involving frontal brain areas are likewise affected by stress (Oei et al., 2006) or cortisol application (Lupien et al., 1999).

Thus, the primary goal of this study was to elucidate the role of glucocorticoids in the elimination of RIF. We replaced the Trier Social Stress Test (TSST; Kirschbaum et al., 1993; Kudielka et al., 2007) that was used for stress-induction in our previous study by administration of hydrocortisone (cortisol) 25 mg PO. In previous studies this amount of hydrocortisone has been successfully used to simulate the cortisol increase induced by a laboratory stressor (Deinzer et al., 1997; de Quervain et al., 2000, 2003). Based upon the previously reported negative correlation between the RIF effect and cortisol increase and other findings concerning the effects of cortisol on memory, the administration of hydrocortisone was expected to mimic the influence of stress on the forgetting effect. However, a recent study demonstrated reduced RIF in people with high state anxiety (Law et al., 2011). State anxiety as measured by the State Trait Anxiety Inventory (STAI; Laux et al., 1981) is defined as consisting of “subjective feelings of tension, apprehension, nervousness and worry, with associated activation (arousal) of the autonomic nervous system” (Spieberger and Reheiser, 2009) and states of emotional arousal have been shown to affect memory in animals (Okuda et al., 2004) and humans, either alone (e.g. Bradley et al., 1996) or in interaction with cortisol (Kuhlmann and Wolf, 2006a,b). Therefore, effects of state anxiety alone and in interaction with hydrocortisone on RIF are also explored in psychometrically defined sub-groups with high versus low state anxiety. If present, such effects may point to a role of autonomic nervous system (ANS) activation, possibly primarily involving its adrenergic sympathetic arm, or an interaction between sympathetic activation and glucocorticoid effects in the elimination of RIF as has been reported for some other phenomena in episodic memory (for reviews, see McGaugh and Roozendaal, 2008; Wolf, 2009).
2. Methods

2.1. Participants

Forty-five healthy male participants (mean age 25.03 years, \(SE = 0.54\)) were recruited by advertisements at the University of Konstanz, Germany. All participants were non-smoking native Germans free from neurological or psychiatric disorder as determined by a specifically developed screening questionnaire. Beck Depression Inventory (BDI; Hautzinger et al., 1994) did not reveal clinically relevant scores in any of the participants (mean BDI score = 3.41, \(SE = 0.53\)).

None of them was taking medications known to influence cortisol levels. Eight participants had to be excluded from the sample due to noncompliance with instructions (e.g. not getting enough sleep the night before the experiment or getting up too late on the day of the experiment), leaving 37 data sets for analysis. In line with other previous studies we confined hydrocortisone administration to males (e.g. Kirschbaum et al., 1996; Abercrombie et al., 2003; Kuhlmann and Wolf, 2006a,b), since there is evidence that cortisol can have different effects on memory in females and males (Wolf et al., 2001). Prior to the experiment, all participants were informed that they were taking part in a double-blind pharmacological memory study and that half of the participants would receive hydrocortisone 25 mg PO during the experiment, whereas the other half would receive a placebo. Using a self-report questionnaire, participants were extensively screened for acute and chronic health problems in order to prevent unwanted side effects of the drug.

Participants were instructed to refrain from eating and drinking caloric beverages or caffeine for 1 h before the experiment and were informed they could only take part if they had a regular sleep pattern (no night shifts, rising between 0700 h and 0900 h in the morning) and slept at least 6.5 h the night before the experiment. They were also asked about their body-weight and height because body-mass index (BMI) may influence cortisol metabolism (Weiner et al., 1987). Participants were randomly assigned to the cortisol condition (\(n = 19\)) or the placebo condition (\(n = 18\)). Groups did not differ significantly in age \(F(1, 35) = 3.74, p > .05\) or body mass index (BMI): \(F(1, 35) = 2.27, p > .10\).

All participants gave written informed consent. After the experiment they were extensively debriefed and received a financial compensation of 15€. The study conformed to the Declaration of Helsinki and was approved by the local ethics committee.

2.2. Procedure

The experiment took place in the afternoon between 1400 h and 1800 h, when cortisol levels are relatively low and stable (Kirschbaum and Hellhammer, 2000). The phases of the retrieval practice paradigm and the materials were similar to the psychosocial stress study of Koessler et al. (2009) with the exception that the time interval between study and retrieval practice phase was extended to 60 min to assure sufficient resorption of the hydrocortisone (e.g. Abercrombie et al., 2003; de Quervain et al., 2003). During the intermission between the study and the retrieval practice phase participants filled in questionnaires for 30 min and then solved Sudoku puzzles. Fig. 1 illustrates the experimental procedure.

2.2.1. Drug treatment

Immediately after the study phase participants received either hydrocortisone PO or placebo. The hard capsules containing either hydrocortisone (25 mg; Hoechst) or lactose in powder form had been manufactured by a pharmacist and the participants took them with water.

2.2.2. Retrieval-induced forgetting paradigm

2.2.2.1. Materials. Eleven categories with six items each were chosen from different published norms (Battig and Montague, 1969; Mannhaupt, 1983; Scheithe and Bäuml, 1995) typically used in RIF research (e.g. Bäuml et al., 2005; Koessler et al., 2009; Hanslmayr et al., 2011). The norms contain data on how often (relative frequency) and at which position (mean rank) an item is generated by participants given a particular category cue for free association. Each category consisted of six emotionally neutral exemplars. Within each category three of these exemplars were high frequency members of that category with a mean relative item frequency of 37.2% (SD = 16.45%) and a mean rank of 7.15 (SD = 1.85) and the other three exemplars had a moderate relative item frequency of 10.24% (SD = 4.16%) and a mean rank of 19.78 (SD = 2.74). The three items with the highest rank per category were excluded to avoid guessing. During retrieval practice only the moderate category members had to be retrieved, because there is evidence that the RIF effect is more pronounced when the non-practiced competitors are high frequency members of the category (Anderson et al., 1994). Within each category no two exemplars began with the same initial letters. Two categories served as filler categories to control for primacy and recency effects. All experimental stimuli were presented on a laptop computer (Fujitsu Siemens Amilo M 7400) using Presentation software (Neurobehavioral Systems, Inc., Albany, NY).

2.2.2.2. Study phase. Sixty-six category—exemplar pairs (e.g. fruit — strawberry; spice — ginger; fruit — apricot) were presented to the participants in a blocked randomized order with the instruction to learn these stimuli. Each block consisted of 11 items and comprised one exemplar from each of the 11 categories. Each category—exemplar pair was presented for 5 s with an inter stimulus interval (ISI) of 200 ms. The study phase started and ended with two examples from the two filler categories.

2.2.2.3. Retrieval practice phase. In the retrieval practice phase, participants had to retrieve half of the exemplars from six of the nine experimental categories and one of the two filler categories. The filler category was included to control for primacy and recency effects. Category names were presented together with the two-letter word stem of the exemplar (e.g. fruit — ap__) and participants were instructed to name the corresponding exemplar from the study phase. This procedure results in three different item types: the retrieval-practiced items (Rp+ items, e.g. fruit — apricot), the non-practiced items from practiced categories (Rp- items, e.g. fruit — strawberry) and the exemplars from non-practiced categories (Nrp items, e.g. spice — ginger) that were only presented...
Figure 1  Experimental procedure. Participants filled in questionnaires and provided a baseline saliva sample. Then they performed the study phase of the retrieval-practice paradigm, followed by the oral administration of either 25 mg hydrocortisone or placebo and a 60 min time interval, during which participants completed questionnaires and solved Sudoku puzzles. One hour after drug application a second saliva sample was collected and participants completed the retrieval-practice phase of the retrieval-practice paradigm, followed by another questionnaire session, a final recall test of the studied items and a third saliva sample.
during the study phase. Every category—exemplar stem pair was presented for 2.5 s with an ISI of 200 ms. We counterbalanced across participants and conditions which of the nine exemplar categories received retrieval practice (constituting the Rp+ and Rp− items) and which served as control categories (constituting the Nrp items). All category—exemplar stem pairs were presented three times during the retrieval practice phase. Exemplar stems of the same category were never presented in immediate succession. Participants performed the retrieval practice phase in the presence of the investigator who wrote down their responses.

2.2.2.4. Final test phase. In the final test phase that followed 8 min after retrieval practice, memory for the items in the study list was assessed using a cued-recall test. Recall of the exemplars was tested in a category-blocked order. The category name and the one-letter word stem of the exemplar (e.g. fruit – a____) were presented for 2.5 s on the screen and like in the retrieval practice phase participants were required to respond orally. The ISI was 200 ms. In order to acquaint the participants with the procedure, the test phase started with six items from one of the two filler categories. The remaining categories and the items within a given category were tested in a random order to control for output interference. Again, this experimental phase was performed in the presence of the investigator who wrote down the participants’ responses.

2.2.3. Salivary cortisol

Ten minutes before as well as 60 and 90 min after (−10 min, +60 min and +90 min, respectively) the intake of hydrocortisone or placebo, salivary cortisol concentration was assessed. Measurement of baseline cortisol levels was preceded by an acclimatization period of 25 min during which participants filled in questionnaires. To standardize blood glucose levels, participants drank 300 ml of grape juice, 15 min prior to the baseline saliva sampling (Kudielka et al., 2007). Ten minutes after the baseline cortisol measurement participants received 25 mg of hydrocortisone or a placebo.

Saliva samples were obtained with commercial collection devices (Salivette®; Sarstedt, Nümbrecht, Germany). They were stored at −20 °C until assayed. Cortisol levels were measured using a competitive bead-based assay as previously described (Koessler et al., 2009). Antibody cross-reactivity with other relevant steroids was 4.0% (testosterone) and 0.9% (progesterone). Intra- and inter-assay variance was 5.4% and 10.7%, respectively.

2.2.4. Self-rating questionnaires

Participants filled in questionnaires three times during the experiment: (a) during the 25-min acclimatization period prior to the baseline saliva sampling, (b) during the first half of the 60-min interval between study and retrieval practice phase, and (c) during the 8-min time period between retrieval practice and final recall. In the first questionnaire session the BDI (Hautzinger et al., 1994), a German version of the State Trait Anxiety Inventory (STAI; Laux et al., 1981), and three mood assessment instruments, the Basler Befindlichkeits-Skala (BBS; Hobi, 1985), the Mehrdimensionaler Befindlichkeitsfragebogen (MDBF; Steyer et al., 1997) and the Self Assessment Manikin (SAM; Bradley and Lang, 1994) were applied.

Thirty minutes of the delay between the study and the retrieval practice phase were also spent filling in various questionnaires. Participants completed a German version of the Positive and Negative Affect Schedule (PANAS; Krohne et al., 1996); a German stress-coping questionnaire, the Stressverarbeitungsfragebogen (SVF 120; Janke et al., 1997); a German questionnaire on competence and control beliefs, the Fragebogen zu Kompetenz- und Kontrollüberzeugungen (FKK; Krampen, 1991); and two personality tests, the Freiburger Persönlichkeitsinventar (FPI-R; Fahrenberg et al., 2001); and a German version of the 16 Personality Factor Questionnaire, the 16-Persönlichkeits-Faktoren-Test Revidierte Fassung (16 PF-R; Schneewind and Graf, 1998). In this phase, questionnaires served as a means to keep participants occupied in a standardized manner and were not further analyzed and interpreted. After retrieval practice and before the final test, participants were re-presented some of the initial questionnaires to assess treatment-induced changes in affective state. Using the STAI-State (Laux et al., 1981), the BBS (Hobi, 1985), the MDBF (Steyer et al., 1997) and the SAM (Bradley and Lang, 1994), participants retrospectively assessed, how they had felt before (during the Sudoku phase) and during retrieval practice. Additionally, seven visual analog scales were applied, consisting of a horizontal line, whose endpoints were labeled not at all and extremely, respectively. On these scales, participants were asked to indicate their personal involvement in the Sudoku and retrieval practice task; how new, unpredictable, difficult, personally challenging and stressful the task was; and if they had expected that poor task performance would yield negative consequences.

3. Results

3.1. Manipulation check: hydrocortisone versus placebo

3.1.1. Salivary cortisol levels

Mean salivary cortisol levels in the two treatment groups over the course of the experiment are shown in Fig. 2. As expected, participants in the hydrocortisone group showed a significant increase in salivary cortisol after ingestion of 25 mg hydrocortisone. A repeated-measures analysis of variance (ANOVA) with the factors treatment (hydrocortisone versus placebo) and time (−10 min, +60 min, +90 min) revealed a significant treatment × time interaction (F(2, 68) = 3.44, p < .05). Post hoc t-tests showed a significant increase in salivary cortisol 60 min after hydrocortisone ingestion compared to baseline (t(17) = 3.09, p < .01) and cortisol levels remained on a similarly high level for the following 30 min. Ninety minutes after hydrocortisone intake, salivary cortisol levels were still significantly elevated from baseline (t(17) = 4.16, p < .001). In the placebo group, no significant increase in cortisol relative to baseline was found (all ps > .20). Treatment groups did not significantly differ in baseline cortisol (t(34) = .15, p > .80). However, salivary cortisol levels in the hydrocortisone group were elevated at +60 min (t(35) = 1.96, p = .057) and significantly higher at +90 min (t(35) = 2.23, p < .05) compared to placebo controls. There was also a significant main effect of treatment (F(1, 34) = 2.91, p > .09).
3.1.2. Self-rating questionnaires
For the state anxiety version of the STAI, the BBS, the MDBF and the SAM repeated-measures analyses of variance with the factors time (before and after treatment) and treatment (hydrocortisone versus placebo) were conducted. Results are detailed in Table 1. Significant main effects of time were found on the STAI, the BBS and both the valence and arousal dimensions of the SAM, indicating a significant increase in state anxiety and arousal and a significant decrease in subjective well-being from the beginning of the experiment to the second questionnaire session that retrospectively assessed psychological state during the Sudoku and retrieval practice phases. Neither a significant main effect of treatment nor a significant interaction effect of treatment and time of questionnaire administration was found on any of the self-rating questionnaire scores. No significant effects were found on the MDBF. For the visual analog scales, independent samples t-tests showed that there was no significant group difference in participants’ retrospective ratings of the Sudoku and retrieval practice phase on any of the seven VAS.

3.2. Memory performance

3.2.1. Retrieval practice
In the placebo group, 66.26% (SE = 2.02%) of the items were successfully retrieved in the retrieval practice phase. After hydrocortisone ingestion, participants retrieved 69.88% (SE = 2.53%) of the items correctly. There was no significant difference in memory performance between the two groups ($F(1, 35) = 1.24, p > .20$).

3.2.2. Final test
3.2.2.1. Overall effect of item types. The different item-types (Rp+, Nrp, Rp−) were associated with very different overall recall performance on the final test ($F(2, 70) = 93.82, p < .001$). The placebo and the hydrocortisone group had similar overall recall performance ($F(1, 35) = 2.5, p > .10$) and overall the effects of placebo and hydrocortisone treatment did not vary between item types ($F(1, 35) = 61, p = .55$).

In retrieval-induced forgetting experiments two separate effects of different magnitudes are found, the retrieval practice effect where retrieval practice improves retrieval on the final recall by about 20% compared to non-practice and the retrieval-induced forgetting effect, where an additional impairment of about 10% for non-retrieval practiced items from retrieval-practiced categories compared to non-retrieval practiced items from non-practiced categories is observed. Here, treatment-dependent modulation was hypothesized only for the latter, the retrieval-induced forgetting effect itself. Therefore, and in line with previous reports (Anderson et al., 1994; Bäuml and Kuhbandner, 2007; Koessler et al., 2009), the two effects are further analyzed separately in a next step.

Practice effect. For the assessment of the practice effect, a repeated-measures ANOVA with item type (Rp+, Nrp) as within-subjects factor and treatment (hydrocortisone versus placebo) as between-subjects factor was calculated. It revealed a clear practice effect in both groups ($F(1, 35) = 79.21, p < .001$), meaning that words, that were practiced during the retrieval practice phase (Rp+), were recalled better than control items (Nrp). There was neither a significant main effect of treatment ($F(1, 35) = 2.03, p > .10$), nor a significant treatment × item type interaction ($F(1, 35) < 1$).

Retrieval-induced forgetting (RIF). To examine the effect of cortisol on RIF, another ANOVA with item type (Rp+, Nrp) as repeated measures factor and treatment (hydrocortisone versus placebo) as between-subjects factor was calculated. The analysis yielded a significant main effect of item type ($F(1, 35) = 8.12, p = .007$), indicating that retrieval practice impaired the recall of the unpracticed items from practiced categories (Rp−) relative to unpracticed items from unpracticed categories (Nrp). No significant main effect of treatment ($F(1, 35) = 2.36, p > .10$) and no significant treatment × item type interaction ($F(1, 35) < 1$) were observed, indicating that the two groups did not differ significantly in their amount of RIF. Memory performance as a function of item type and treatment is depicted in Fig. 3.

3.2.2.2. State anxiety and RIF. To investigate the effect of anxiety alone or in interaction with cortisol on RIF effect, we analyzed STAI State scores from the second questionnaire session (t2 in the following), during which participants retrospectively rated their psychological state shortly before and during retrieval practice. Participants were divided by median split into high and low scorers on the state scale of the STAI at t2 yielding a group of 18 low and 19 high state-anxious participants. High and low state anxiety was evenly distributed across the hydrocortisone and placebo group (hydrocortisone: 9 low scorers and 10 high scorers; Placebo: 9 low scorers and 9 high scorers). A repeated-measures ANOVA with within-subjects factor item type (Rp+, Nrp, Rp−) and the
Table 1  Self-rating questionnaire scores from the beginning of the experiment (T1) and from the questionnaire session that retrospectively assessed psychological state during the Sudoku and retrieval-practice phases (T2) as well as significant effects in the repeated-measures ANOVA. The reported effects are main effects of time. Data represent M ± SEM. STAI: State Trait Anxiety Inventory (Laux et al., 1981); BBS: Basler Befindlichkeits-Skala (Hobi, 1985); MDBF: Mehrdimensionaler Befindlichkeitsfragebogen (Steyer et al., 1997); SAM: Self Assessment Manikin (Bradley and Lang, 1994).

<table>
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<tr>
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<th>T1</th>
<th>T2</th>
<th>Effects</th>
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<tr>
<td><strong>STAI State</strong></td>
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<tr>
<td>Placebo</td>
<td>33.44 ± 1.31</td>
<td>36.44 ± 2.08</td>
<td>State anxiety significantly increased in both groups</td>
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<tr>
<td>Hydrocortisone</td>
<td>33.47 ± 1.27</td>
<td>35.74 ± 2.02</td>
<td>(F(1, 35) = 5.94, p &lt; .05)</td>
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<td><strong>BBS</strong></td>
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<tr>
<td>Placebo</td>
<td>87.61 ± 2.43</td>
<td>74.94 ± 2.74</td>
<td>Subjective well-being significantly decreased in both groups</td>
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<tr>
<td>Hydrocortisone</td>
<td>88.47 ± 2.36</td>
<td>79.37 ± 2.66</td>
<td>(F(1, 35) = 40.70, p &lt; .001)</td>
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<td><strong>Vitality subscale</strong></td>
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<td>Placebo</td>
<td>22.22 ± .75</td>
<td>19.44 ± .95</td>
<td>Ratings of vitality significantly decreased in both groups</td>
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<tr>
<td>Hydrocortisone</td>
<td>22.37 ± .73</td>
<td>20.79 ± .92</td>
<td>(F(1,35) = 15.84, p &lt; .001)</td>
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<td><strong>Intrapsychic equilibrium subscale</strong></td>
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<td>Placebo</td>
<td>23.61 ± .77</td>
<td>21.50 ± 1.00</td>
<td>Intrapsychic equilibrium significantly decreased in both groups</td>
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<tr>
<td>Hydrocortisone</td>
<td>23.10 ± .75</td>
<td>21.68 ± .97</td>
<td>(F(1, 35) = 6.12, p &lt; .05)</td>
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<td><strong>Social extraversion subscale</strong></td>
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<td>Placebo</td>
<td>20.61 ± .83</td>
<td>13.39 ± 1.18</td>
<td>Ratings of social extraversion significantly decreased in both groups</td>
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<td>Hydrocortisone</td>
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<td>13.68 ± 1.15</td>
<td>(F(1, 35) = 63.44, p &lt; .001)</td>
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<td><strong>Vigilance subscale</strong></td>
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<td>Placebo</td>
<td>21.17 ± .90</td>
<td>20.61 ± 1.44</td>
<td>n.s.</td>
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<tr>
<td>Hydrocortisone</td>
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<td>23.21 ± 1.40</td>
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<td><strong>MDBF</strong></td>
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<td>Good versus bad mood</td>
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<td>Placebo</td>
<td>34.29 ± .84</td>
<td>32.35 ± 1.23</td>
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<td>Alertness versus tiredness</td>
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<td>28.18 ± 1.50</td>
<td>n.s.</td>
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<td>Calmness versus nervousness</td>
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<tr>
<td>Placebo</td>
<td>33.71 ± .97</td>
<td>30.23 ± 1.50</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>33.58 ± .92</td>
<td>29.42 ± 1.42</td>
<td></td>
</tr>
<tr>
<td><strong>SAM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>7.56 ± .27</td>
<td>6.44 ± .45</td>
<td>Subjective ratings of valence significantly decreased in both groups</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>7.21 ± .26</td>
<td>7.10 ± .44</td>
<td>(F(1, 35) = 5.59, p &lt; .05)</td>
</tr>
<tr>
<td>Arousal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>2.39 ± .27</td>
<td>3.67 ± .52</td>
<td>Arousal ratings significantly increased in both groups</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>2.63 ± .26</td>
<td>3.53 ± .51</td>
<td>(F(1, 35) = 10.95, p &lt; .01)</td>
</tr>
</tbody>
</table>

n.s., non significant
between-subjects factors treatment (placebo, hydrocortisone) and STAI subgroup (high versus low anxiety) was computed. The analysis revealed that the three item-types differed in their overall recall ($F(2,66) = 94.89$, $p < .001$) with no major overall difference in effect between groups ($F$s < 2).

Because out of the two effects present in typical RIF experiments only the comparison between Nrp and Rp–items was expected to be modulated by anxiety and/or stress the retrieval practice and the retrieval impairment effects were further analyzed separately in two targeted analyses.

**Practice effect.** For the assessment of the practice effect, a repeated-measures ANOVA with item type (Rp+ , Nrp) as within-subjects factors and state anxiety (STAI high versus STAI low) and treatment (hydrocortisone versus placebo) as between-subjects factors was calculated. As in the original analysis without the STAI, the main effect of item type was significant ($F(1,33) = 76.34$, $p < .001$), Rp+ items were recalled better than control items (Nrp). As hypothesized, this effect did not vary with treatment ($p = .35$), state anxiety ($p = .59$) or an interaction of any of these (all $ps > .35$).

**Retrieval-induced forgetting (RIF).** To examine the effect of state anxiety and hydrocortisone on RIF, another ANOVA with item type (Rp—, Nrp) as repeated measures factor and treatment (hydrocortisone versus placebo) and state anxiety (STAI high versus STAI low) as between-subjects factors was calculated. Again the main effect of item type ($F(1,33) = 10.08$, $p < .003$) indicated a significant RIF effect. Furthermore, a significant interaction between item type and STAI group ($F(1,33) = 4.78$, $p = .036$) with significant RIF in the low ($p = .001$), but not in the high STAI group ($p = .53$) was found. Hydrocortisone treatment did not interact with RIF ($F(1,33) = .99$, $p = .33$) and no significant main effect of hydrocortisone treatment ($F(1,33) = 2.23$, $p = .15$) or STAI ($F(1,33) = .26$, $p = .62$), and no significant three-way interaction between item-type, treatment and STAI were observed ($F(1,33) = 2.83$, $p = .10$). Retrieval-induced forgetting as a function of state anxiety is depicted in Fig. 4.

### 4. Discussion

The present study examined the effect of a pharmacologically induced rise in cortisol on retrieval-induced forgetting (RIF). A previous study had demonstrated that stress can eliminate RIF and that stress-induced increases in salivary cortisol levels correlate negatively with RIF, experimental participants with higher cortisol levels showing less RIF (Koessler et al., 2009). Other studies have reported a reduction in RIF in individuals with clinical disorders of stress and anxiety (Amir et al., 2001; Koessler et al., 2010) or high in state anxiety (Law et al., 2011) which led us to include an analysis of the effect of state anxiety.

Overall, we found no evidence that elevated cortisol levels per se had any major effect on RIF, even though the pharmacological treatment with 25 mg hydrocortisone PO was effective and led to a significant rise in salivary cortisol levels, whereas no such change was observed in the placebo group. The magnitude of the present cortisol increase was comparable to cortisol changes observed in response to moderate to strong physiological or psychological stressors (Deinzer et al., 1997; de Quervain et al., 2000, 2003; Buchanan and Lovallo, 2001; Abercrombie et al., 2003; Koessler et al., 2009; Weerda et al., 2010) and several reports of cortisol effects on memory retrieval 1 h after cortisol application exist in the literature (for example see de Quervain et al., 2000; Wolf et al., 2004; Kuhlmann et al., 2005b). Therefore, the current treatment should have been effective in revealing a cortisol influence on RIF similar to that observed after psychosocial stress (Koessler et al., 2009). Nevertheless, hydrocortisone did not reduce RIF.
Figure 4  Percentage of items recalled in the final recall test as a function of state anxiety (high versus low STAI State score at t2) and item type. T2 refers to the time point, where participants retrospectively rated how they had felt before and during the retrieval practice phase. Item types are the retrieval-practiced items (Rp+), the non-practiced items from practiced categories (Rp−) and the non-practiced items from non-practiced categories (Nrp). Asterisks mark the significant retrieval-induced forgetting effect in the low anxiety group (**p < 0.001). Results are shown as mean ± SEM.

An important point to consider is that within the present as well as a previous implementation of the paradigm (Koessler et al., 2009), cortisol was elevated during retrieval practice, which is regarded as the crucial phase of the paradigm that changes an item's processing status, but remained high into the final recall phase. In both studies, performance in the retrieval practice phase did not differ between the treatment and the control group facilitating interpretation of effects in the final recall phase. This lack of a difference in retrieval practice performance between the treatment and the placebo group may be due to the relative ease of the word-stem completion test and the fact that initial learning and retrieval practice are separated by about 1 h, whereas stress-induced retrieval impairment is typically observed more with longer delays (Elzinga et al., 2005). In contrast to the often-reported stress-induced retrieval impairment, in our study hydrocortisone may, if anything, have somewhat, although not significantly, improved retention. However, there is the possibility that, although not evident in recall performance on either test, glucocorticoid secretion differentially affected both retrieval practice and the final recall, resulting in a complex interaction that generated a net null effect. While the present as well as our previous study adhere to the typical timing of events in RIF experiments, efforts should be made to separate the phases substantially to be able to more clearly assign stress or stress hormone effects to either the retrieval practice or the final recall phase and to avoid the possibility of covert interactions between different phases. For retrieval-induced forgetting this endeavor is complicated by the fact that the magnitude of RIF generally decreases as the interval between retrieval practice and final recall increases (MacLeod and Macrae, 2001), resulting in sub-optimal experimental power for detecting treatment-dependent differences. Nevertheless, future studies should attempt to better target stress effects in the different experimental phases. At any rate, in the present experiment no effects of hydrocortisone treatment alone were found, either during retrieval practice or at final recall. Whether this could have been also due to a complex interaction of effects during different experimental phases, is open to further experimentation. Also, timing of the stressor or pharmacological treatment in relation to the original learning event might be critical, since stress, hydrocortisone, anxiety, or adrenaline effects on retrieval-induced forgetting may differ between very recent and better-consolidated memories. It is important to note that in Bäuml and Kuhbandner (2007), negative mood effects on RIF were induced within less than 5 min after initial learning, in Koessler et al. (2009) stress modulation occurred on memories that were about 25 min old, and the present study, due to hydrocortisone resorption times, addressed RIF modulations for memories that were about 45 min old.

Presently, evidence for an effect of state anxiety on RIF was obtained. A previous study by Bäuml and Kuhbandner (2007) suggested that experimentally induced negative affect during the retrieval practice phase eliminates the RIF effect at least when tested within 2 min after retrieval practice. Furthermore, reduced RIF has been found in individuals with high state anxiety (Law et al., 2011). In line with these two studies, also in our present study RIF was eliminated in participants with high state anxiety. This reduction was driven somewhat more by the cortisol group.

Memory strength can be modulated by emotionally arousing conditions. Noradrenergic projections from the locus coeruleus to higher brain areas play a major role in the mediation of emotional arousal states, like anxiety and stress, and the modulation of cognitive processes by such states (for reviews see Berridge and Waterhouse, 2003; Chamberlain et al., 2006). In a stressful situation the first step in the physiological stress reaction is the activation of
the ANS and primarily its sympathetic arm, which leads to the release of epinephrine and, to a lesser extent, norepinephrine from the adrenal medulla (e.g. Ulrich-Lai and Herman). Circulating epinephrine in turn stimulates central release of norepinephrine via the vagal nerve and the locus coeruleus (Gold and van Buskirk, 1978; McIntyre et al., 2002). There is evidence that noradrenergic activation of the basolateral amygdala plays a key role in arousal- and stress-induced memory modulation (see Roøzendaal et al., 2009). State anxiety as assessed by the STA-I-State is accompanied by feelings of tension and heightened autonomic nervous system activity (Buck and Spielberger, 1972; see also Kantor et al., 2001; Noto et al., 2005; Takahashi et al., 2005). The score on the STA-I-State at t2 should therefore reflect to a certain extent the participant’s individual degree of sympathetic activation at this time point.

The present results are compatible with our previous data, in that unlike the pharmacological application of cortisol, a real stress experience as induced for example by the Trier Social Stress Test activates the sympathetic-adrenal system (e.g. Ulrich-Lai and Herman, 2009). Moreover, the TSST not only induces elevated secretion of ACTH and cortisol, indicative of HPA axis activation, but also an increase in emotional arousal and state anxiety and in the release of epinephrine and norepinephrine (e.g. Federenko et al., 2004; Rohleder et al., 2004; de Kloet et al., 2005; Kudielka et al., 2007; Schoofs et al., 2008). So in a real stress situation both cortisol and norepinephrine are centrally acting. When only cortisol is administered and the subject is not emotionally aroused by external factors, the sympathetic-adrenal system is not activated and there is no increase in the release of norepinephrine (see for example Kuhlmann and Wolf, 2006a,b; Schwabe et al., 2009).

Several studies report that some glucocorticoid effects on memory require concomitant emotional arousal, possibly reflecting (nor)adrenergic activation (e.g. Okuda et al., 2004; Kuhlmann and Wolf, 2006b; for reviews see McGaugh and Roøzendaal, 2008; Wolf, 2009). However effects of anxiety (e.g. Darke, 1988) and emotional arousal alone, putatively indicative of noradrenergic activation, have also been reported (e.g. Cahill and McGaugh, 1998). In our present study we did not manipulate participants’ emotional arousal state. Nevertheless, an effect of state anxiety on RIF was found, with high anxiety eliminating RIF and this effect was mainly, although not significantly (p = .102), driven by the hydrocortisone group. To further test the individual and/or interactive effects of cortisol, sympathetic activation, and individual appraisal of the situation, future studies may combine experimental emotional activation and hydrocortisone application and additionally use salivary alpha-amylase, heart rate and heart rate variability as more direct physiological measures to examine the relative roles of the sympathetic-adrenal and HPA systems in influencing RIF. Also, it remains to be determined whether specifically anxiety contributes to an elimination of RIF, or the same would be true for a broad range of sufficiently emotionally arousing states. The present study found an effect specifically for state anxiety and not arousal in general and state anxiety was also critical in Law et al. (2011). However, given that Bäuml and Kuhbandner, albeit not controlling for anxiety levels or cortisol secretion, found similar effects for negative mood, the issue deserves further examination. Finally, the present study tested only males. As cortisol appears to differentially affect memory in males and females (Wolf et al., 2001), future studies are needed to determine whether state anxiety and/or cortisol application in females has similar or different effects on RIF.

Overall, this study demonstrates that cortisol alone, in contrast to a real-life stress experience, does not cause a release from RIF. Remembering can therefore cause forgetting even when cortisol levels are high. The present study produced evidence that state anxiety contributes to a reduction in RIF more than elevated cortisol levels alone implying that subjective appraisal may mediate stress effects on cognition more than hormone levels per se and/or that sympathetic activation might play an important role in modulating RIF. Further studies are needed to specify the effects of sympathetic arousal and activation of the HPA axis on retrieval-induced forgetting. These should use more direct physiological measures of adrenergic activation as covariates, or beta-adrenergic receptor blockers together with a laboratory stressor to experimentally manipulate the presently suggested effects. Moreover, the effects of stressor-timing relative to the different RIF-phases should be scrutinized.

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The Deutsche Forschungsgemeinschaft had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report and in the decision to submit the paper for publication.

Conflict of interest

All authors declare that they have no conflicts of interest.

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