



Glucocorticoids mediate stress-induced impairment of retrieval of stimulus-response memory



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ABSTRACT

Acute stress and elevated glucocorticoid hormone levels are well known to impair the retrieval of hippocampus-dependent 'declarative' memory. Recent findings suggest that stress might also impair the retrieval of non-hippocampal memories. In particular, stress shortly before retention testing was shown to impair the retrieval of striatal stimulus-response associations in humans. However, the mechanism underlying this stress-induced retrieval impairment of non-hippocampal stimulus-response memory remains elusive. In the present study, we investigated whether an acute elevation in glucocorticoid levels mediates the impairing effects of stress on retrieval of stimulus-response memory. Male Sprague-Dawley rats were trained on a stimulus-response task in an eight-arm radial maze until they learned to associate a stimulus, i.e., cue, with a food reward in one of the arms. Twenty-four hours after successful acquisition, they received a systemic injection of vehicle, corticosterone (1 mg/kg), the corticosterone-synthesis inhibitor metyrapone (35 mg/kg) or were left untreated 1 h before retention testing. We found that the corticosterone injection impaired the retrieval of stimulus-response memory. We further found that the systemic injection procedure per se was stressful as the vehicle administration also increased plasma corticosterone levels and impaired the retrieval of stimulus-response memory. However, memory retrieval was not impaired when rats were tested 2 min after the systemic vehicle injection, before any stress-induced elevation in corticosterone levels had occurred. Moreover, metyrapone treatment blocked the effect of injection stress on both plasma corticosterone levels and memory retrieval impairment, indicating that the endogenous corticosterone response mediates the stress-induced memory retrieval impairment. None of the treatments affected rats' locomotor activity or motivation to search for the food reward within the maze. These findings show that stress may affect memory processes beyond the hippocampus and that these stress effects are due to the action of glucocorticoids.

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1. Introduction

Stress has profound effects on different learning and memory functions (Roozendaal, 2002; Schwabe et al., 2012). Extensive

evidence indicates that acute stress exposure shortly before retention testing impairs the retrieval of memories, such as of declarative memory in humans and spatial/contextual memory in rodents (de Quervain et al., 1998; Kuhlmann et al., 2005b; Park et al., 2008; Wolf, 2009). Activation of the hypothalamic-pituitary-adrenocortical (HPA) axis and high circulating levels of glucocorticoid hormones (corticosterone in rodents, cortisol in humans) are known to mediate these dampening effects of stress on memory retrieval (de Quervain et al., 1998; Roozendaal, 2002; Buss

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et al., 2004; Het et al., 2005; Kuhlmann et al., 2005a; Schwabe et al., 2012). For instance, pharmacological inhibition of HPA-axis activity or direct suppression of glucocorticoid synthesis in the adrenal glands prevents the impairing effect of stress exposure on memory retrieval of spatial information in rats (de Quervain et al., 1998; Barsegyan et al., 2015). In accordance, the administration of corticosterone or glucocorticoid receptor agonists to rats or mice shortly before retention testing is sufficient to mimic the impairing effect of stress on the retrieval of previously acquired spatial and contextual memory (de Quervain et al., 1998; Roozendaal et al., 2004b; Cai et al., 2006; Schutsky et al., 2011; Atsak et al., 2012a). Likewise, cortisol administration before retention testing impairs free or cued recall of declarative memory in humans (de Quervain et al., 2000; de Quervain et al., 2003; Buss et al., 2004; Het et al., 2005; Kuhlmann et al., 2005a).

As a large body of evidence indicates that free and cued recall of declarative information in humans as well as retrieval of spatial and contextual memory in rats depend heavily on the hippocampus (Squire, 1992; Moser and Moser, 1998), for decades the predominant view held that stress might have a particularly robust influence on the hippocampus whereas other memory systems are relatively spared (McEwen and Sapolsky, 1995; Lupien and McEwen, 1997). This view has also been supported by findings of studies investigating the modulatory effects of stress on the use of multiple memory systems: Stress exposure to both animals and humans prior to learning shifts the relative use of a declarative or spatial strategy toward a hippocampus-independent habit-like strategy (Kim et al., 2001; White and McDonald, 2002; Packard and Wingard, 2004). However, we recently reported that brief exposure to socially evaluated cold pressor stress in humans impaired the retrieval of stimulus-response (S-R) associations in a virtual radial maze, in which subjects use non-spatial, hippocampus-independent strategies to locate and collect objects in response to an intra-maze cue (Guenzel et al., 2013). Lesion or pharmacological inhibition studies indicated that the association between a stimulus and behavioral response is not dependent on the hippocampus (Packard et al., 1989; Packard and McGaugh, 1996) but heavily relies on the dorsal striatum (Packard and Knowlton, 2002; White and McDonald, 2002; Iaria et al., 2003; Bohbot et al., 2007). Taken together, these findings suggest that comparable to hippocampus-dependent memories, stress might also impair the retrieval of striatal-dependent memories. Moreover, we found that the stress-induced retrieval impairment of S-R memory correlated with the amount of cortisol released (Guenzel et al., 2013). However, whether glucocorticoids actually mediate the S-R memory retrieval impairment remained elusive.

In the present study, we investigated the involvement of glucocorticoids in regulating stress-induced impairment of retrieval of S-R memory. To test this, rats received a subcutaneous injection of vehicle, corticosterone or were left untreated 1 h before retention testing on an S-R task in an eight-arm radial maze. Based on previous evidence indicating that the injection procedure per se can induce mild stress and lead to an increase in plasma corticosterone (Schwabe et al., 2010), we predicted that the stress associated with the injection procedure (“injection stress”) would impair S-R memory retrieval. We hypothesized further that if corticosterone mediates the stress effect on memory retrieval, then exogenous glucocorticoid administration that induces plasma corticosterone levels comparable to those by stress exposure would be sufficient to mimic the stress-induced retrieval impairment of S-R memory, and that a suppression of endogenous corticosterone release with the 11β -hydroxylase inhibitor metyrapone would prevent the impairing effect of injection stress on the retrieval of S-R memory.

2. Materials and methods

2.1. Subjects

Male adult Sprague-Dawley rats (300–350 g at the start of the behavioral experiments) from Charles River Breeding Laboratories (Kisslegg, Germany) were housed individually in a temperature-controlled (22 °C) vivarium room and maintained on a 12 h:12 h light:dark cycle (lights on: 7:00–19:00 h) with water available *ad libitum*. Rats were fed a restricted diet of rat chow (19–21 g/rat per day), provided immediately after the daily training session. Training and testing were performed during the light phase of the cycle between 10:00 and 16:00 h. Food rewards during behavioral testing were highly palatable chocolate pellets, thus minimizing the need for dietary regulation. As a consequence, the rats kept gaining weight during the course of the experiment: animals of the first experiment gained on average 32.4 ± 3.6 g (starting weight: 341.0 ± 2.8 g, end weight: 373.4 ± 3.3 g) and the animals of the second experiment gained on average 33.3 ± 2.2 g (starting weight: 347.0 ± 2.4 g, end weight: 381.2 ± 2.4 g). Moreover, evidence indicates that feeding rats in the late afternoon reduces a disruption of the circadian rhythm of the HPA axis and the release of endogenous corticosterone caused by the food restriction (Gallo and Weinberg, 1981). All experimental procedures were in compliance with the European Communities Council Directive of 24 November 1986 (86/609/EEC) and approved by the Institutional Animal Care and Use Committee of the Radboud University Nijmegen, The Netherlands.

2.2. Experimental design and groups

The rats were assigned to two separate experiments. The first experiment consisted of four treatment groups: animals were injected with vehicle ($n=14$), 1 mg/kg corticosterone (CORT 1) ($n=11$) or were left untreated ($n=11$) and tested 1 h later for retention. The fourth group ($n=9$) was injected with vehicle but tested 2 min later (vehicle 2'). The second experiment also consisted of four groups: animals were injected with vehicle ($n=14$), metyrapone ($n=13$) or metyrapone together with two doses of corticosterone (0.3 or 1 mg/kg) ($n=12$ and 13, respectively) 1 h before retention testing. For determination of plasma corticosterone levels, separate groups of trained animals received the same drug treatments and were killed 30 min later without retention testing, except for one vehicle group that was killed 2 min after the systemic injection.

2.3. Stimulus-response task

S-R training and testing were performed in a radial-arm maze, in which rats learned the association between an intra-maze cue and a reward (McDonald et al., 2002). Previous studies confirmed that performance in this task relies on the striatum but not on the hippocampus (White and McDonald, 2002). As shown in Fig. 1, the radial-arm maze was made of grey perspex and consisted of eight equal arms (in cm: $501 \times 15 \text{ w} \times 15 \text{ h}$) that were connected with a central area (40×40 cm). The maze was elevated 60 cm above the floor. Before initiation of any training, the rats were habituated to the maze for 10 min per day for two consecutive days, which was sufficient to accustom them to eating chocolate pellets placed in food wells at the end of each arm. Rats were trained daily and each training day consisted of five trials. On each trial, one arm was equipped with three cues (bright orange colored balls—4 cm diameter) that were positioned above the arm (13 cm height) at the entrance, the middle and at the end. Only this cued arm was baited with a chocolate pellet placed in the food well at the end of the arm. At the start of each trial, the rat was placed in the middle of

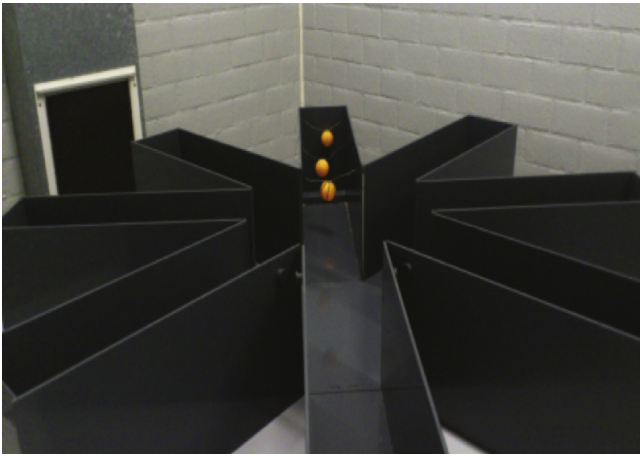


Fig. 1. The radial-arm maze was made of grey perspex and consisted of eight equal arms that were connected with a central area. Three bright orange colored balls (4 cm diameter) were positioned in one random arm and used as the stimulus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

a random starting arm (-45 – 45° angle to the cued arm) facing the center of the maze. The cued arm and the starting arm were selected randomly and were different on each trial. The number of errors per trial (i.e., entrances into non-cued arms) and the latency to make a first arm entry (as a measure of the rat's motivation to search for the food reward) were recorded on each trial and the number of error-free trials was calculated per day. An animal was considered to have entered an arm only if all four paws crossed the border of that arm. The maximum duration of each trial was 90 s and rats were allowed to make a maximum of three errors. In case of reaching the maximum number of errors, the rat was removed from the maze without collecting the reward. The maze was cleaned with 10% ethanol between each trial to remove olfactory traces. Regardless of the success at the trial, the rats were returned to their home cage for 90 s until the start of the next trial. Training trials continued until the rats reached a criterion of at least three error-free trials out of the five daily trials for two consecutive days. Animals (10%) that did not reach this criterion within 20 days were excluded from further analysis.

Twenty-four hours after reaching the learning criterion, the rats were randomly assigned to a treatment group and left either untreated or given a subcutaneous injection of vehicle, corticosterone, metyrapone or a combination of these drugs and tested for retention on the S-R task 1 h later. In addition, one group was exposed to the injection stress (i.e., vehicle injection) 2 min prior to retention testing, before corticosterone levels were elevated. Retention testing consisted of five additional trials and was performed identical to the training sessions. Retention performance was calculated as the number of error-free trials at retention as percentage of each rat's performance on the last training day. Retention response time, as a measure of rat's locomotion or incentive to explore the maze, was expressed as the mean latency to the first arm entry, irrespective of whether this was the correct or wrong arm, as percentage of that on the last training day.

2.4. Systemic drug manipulations

For the first experiment, corticosterone (1 mg/kg; Sigma–Aldrich) was dissolved in 5% ethanol and 95% saline and injected subcutaneously 1 h before the retention test. The vehicle contained 5% ethanol and 95% saline only (de Quervain et al., 1998; Cai et al., 2006). Another group of animals was tested 2 min after the vehicle injection. For the second experiment,

the 11 β -hydroxylase inhibitor metyrapone (2-methyl-1,2-di-3-pyridyl-1-propanone; 35 mg/kg; Sigma–Aldrich) alone or together with corticosterone (0.3 or 1 mg/kg) was dissolved in a vehicle containing 5% ethanol, 40% polyethylene glycol 200 and 55% saline and administered subcutaneously 1 h before retention testing. Drug doses for corticosterone, metyrapone and their respective vehicle solutions were selected on the basis of previous findings (de Quervain et al., 1998). These doses of corticosterone result in an increase in circulating corticosterone levels within the physiological range and are known to impair spatial memory retrieval (de Quervain et al., 1998; Cai et al., 2006) and this dose of metyrapone is sufficient to block stress-induced corticosterone synthesis (Rooszendaal et al., 2001). All drugs were injected in a volume of 2 ml/kg and were freshly prepared before each experiment.

2.5. Blood collection and corticosterone radioimmunoassay

Since retention testing lasted approximately 10 min, which is long enough to influence corticosterone levels by itself, the effect of the different drug treatments on plasma corticosterone levels was assessed in parallel groups of rats that were trained on the S-R task but not tested for retention. As mild and short-lasting stress stimulation, like a systemic injection, triggers an HPA-axis response that leads to a corticosterone plasma peak at 15–30 min and returns to baseline by 60–90 min (Grota et al., 1997) in order to capture this corticosterone response in plasma, rats were sacrificed 30 min after the injection. Corticosterone levels in brain, which are considered responsible for regulating stress effects on memory retrieval, are known to peak at a slightly later time point (Droste et al., 2008). Thus, although stress-induced increases in plasma corticosterone levels were expected to be visible at 30 min after the injection, it is plausible that the behavioral effects were observed at a later time point, once corticosterone levels reached to their peak in the brain. Other rats were sacrificed 2 min after the vehicle injection. Non-injected control rats were sacrificed at matching times. All rats were anesthetized with an overdose of sodium pentobarbital (100 mg/kg, ip) and sacrificed within 120 s following the pentobarbital injection. After decapitation, trunk blood was collected in tubes containing 0.5 M EDTA. Samples were placed on ice until centrifugation ($2900 \times g$ for 15 min at 4°C) and the supernatant was stored at -80°C until the corticosterone assay. Corticosterone plasma levels were determined by radioimmunoassay using a ^{125}I kit (MP Biomedicals Inc., CA, USA) according to the manufacturer's instructions. Concentrations were determined in duplicate from a standard curve (0, 12.5, 25, 50, 100, 250, 500 and 1000 ng corticosterone per ml).

2.6. Statistical analysis

The number of error-free trials and the latency to make a first arm entry during the last S-R training day and plasma corticosterone levels are expressed as mean \pm SEM. Retention performance was calculated as the number of error-free trials during the retention test as percentage of each rat's performance on the last training day. Retention response time (mean \pm SEM) was calculated as the mean latency to make the first arm entry relative to each rat's response on the last training day. Planned paired t-tests were used to make within group comparisons between the performance on the retention test day and the last training day. Further, one-way ANOVAs with treatment (4 levels for both experiment 1 and 2) as between-subject factor were used to analyze the number of error-free trials, entrance latencies, retention performance as well as response time and plasma corticosterone levels between groups. Retention performance of experiment 2 was analyzed with a one-way ANCOVA with treatment (4 levels) as between-subject factor in order to control for a pre-existing difference in entrance latency

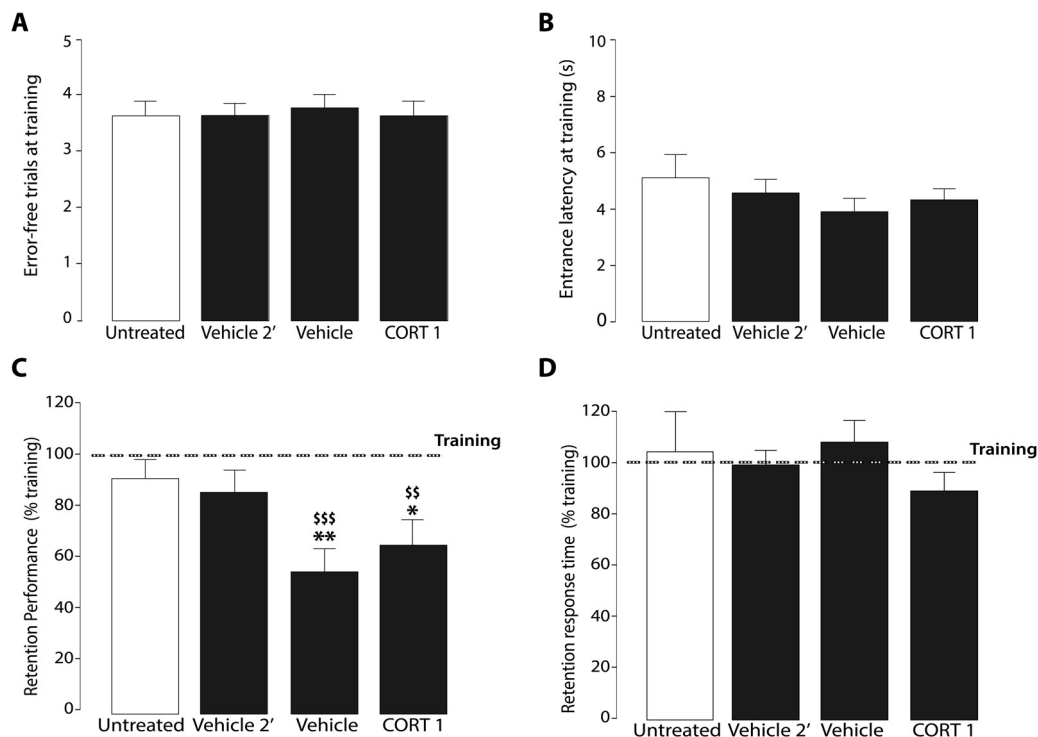


Fig. 2. Stress and corticosterone impair retention of S-R memory. Rats were trained on the S-R task in a radial-arm maze until they reached the criterion of at least three error-free trials for two consecutive days. Twenty-four hours later, injection stress (vehicle, $n = 14$) or corticosterone (1 mg/kg, CORT 1, $n = 11$) was administered subcutaneously 1 h before retention testing. Other rats were administered vehicle but tested 2 min later (Vehicle 2', $n = 9$) or were tested without any systemic injection (untreated, $n = 11$). (A) The number of error-free trials on the last training day before any drug treatment. No significant group differences were found. (B) Mean latency to first arm entry(s) on the last training day. No significant group differences were found. (C) Retention performance was calculated as the number of error-free trials on the retention test as percentage of each rat's performance on the last training day. Rats injected with either corticosterone or vehicle 1 h before retention testing showed significantly impaired retention performance relative to that of the untreated group. Moreover, retention performance of rats administered corticosterone or vehicle was significantly impaired in comparison to their performance on the last training day (dashed line). (D) Retention response time was calculated as the mean latency to first arm entry on the retention test as percentage of each rat's performance on the last training day. No significant treatment effect was found. * $P < 0.05$; ** $P < 0.01$ compared to the untreated group. \$\$ $P < 0.01$; \$\$\$ $P < 0.001$ compared to their performance on the last training day (dashed line). Data are presented as mean \pm SEM.

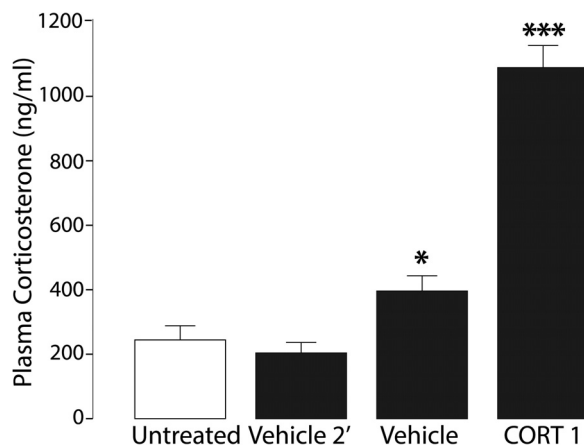


Fig. 3. Subcutaneous administration of vehicle or corticosterone increases plasma corticosterone levels. Rats were administered injection stress (vehicle, $n = 10$) or corticosterone (1 mg/kg, CORT 1, $n = 7$) and sacrificed 30 min after the treatment without retention testing. Other rats were administered vehicle and sacrificed 2 min later (Vehicle 2', $n = 11$) or were sacrificed without any systemic injection (untreated, $n = 11$). The vehicle injection significantly increased plasma corticosterone levels 30 min, but not 2 min, after the injection. Corticosterone administration significantly elevated plasma corticosterone levels with respect to all other treatment groups. * $P < 0.05$; *** $P < 0.001$ compared to the untreated group. Data are presented as mean \pm SEM.

at training between groups. Further analyses used Fisher's post-hoc comparison tests to determine the source of the detected significance, when appropriate. A probability level of <0.05 was accepted as statistical significance for all tests. The number of rats per group is indicated in the figure legends.

3. Results

3.1. Experiment 1: stress and corticosterone impair the retrieval of stimulus-response memory

The first experiment investigated the effect of corticosterone administration on the retrieval of S-R memory. To this end, rats

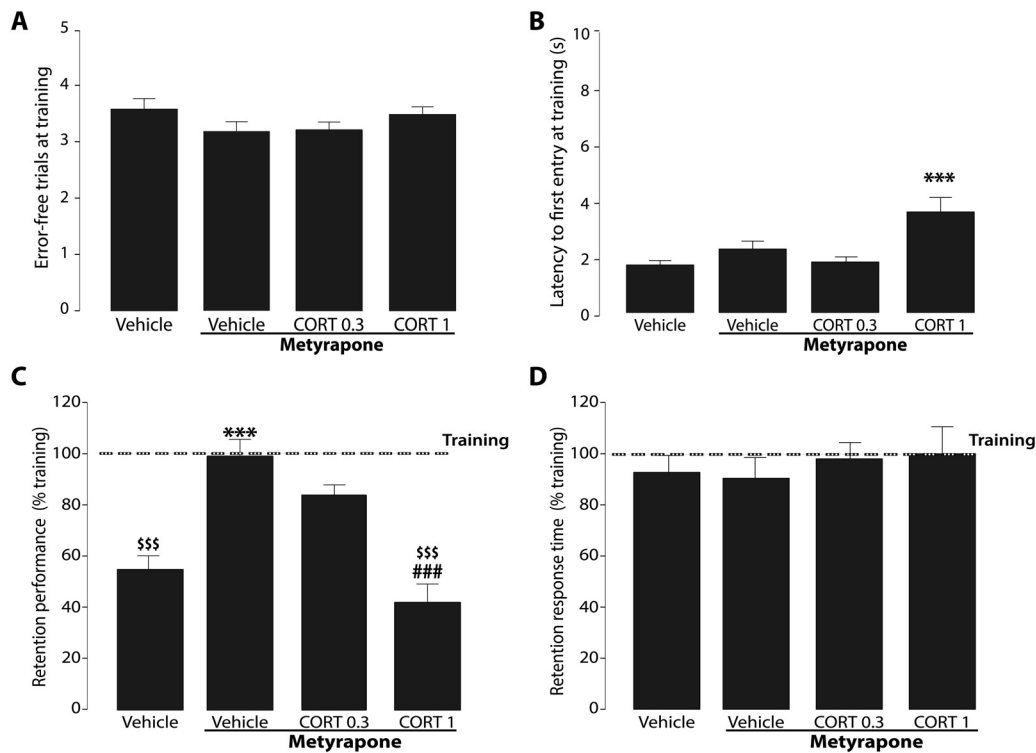


Fig. 4. Corticosterone mediates the stress effect on retention of S-R memory. Rats were trained on the S-R task in a radial-arm maze until they reached the criterion of at least three error-free trials for two consecutive days. Twenty-four hours later, injection stress (vehicle, $n = 14$), metyrapone (35 mg/kg, $n = 14$) or the combination of metyrapone and corticosterone at a dose of 0.3 mg/kg (CORT 0.3, $n = 12$) or 1 mg/kg (CORT 1, $n = 13$) was administered subcutaneously 1 h before retention testing. (A) The number of error-free trials on the last training day. No significant group differences were found. (B) Mean latency to first arm entry (s) on the last training day. The metyrapone-CORT 1 group had significantly longer entrance latencies than all other treatment groups. (C) Retention performance was calculated as the number of error-free trials on the retention test as percentage of each rat's performance on the last training day. Retention performance of rats administered vehicle 1 h before the test session was significantly impaired relative to their performance on the last training day. Retention performance of rats administered metyrapone alone was significantly better than that of rats administered vehicle and did not differ from their performance on the last training day. Co-administration of the higher (1 mg/kg), but not lower (0.3 mg/kg), dose of corticosterone significantly impaired retention relative to that of the metyrapone alone group. (D) Retention response time was calculated as the mean latency to first arm entry on the retention test as percentage of each rat's performance on the last training day. No significant treatment effect was found. *** $P < 0.001$ compared to vehicle; ### $P < 0.001$ relative to metyrapone alone; \$\$\$ $P < 0.001$ compared to their performance on the last training day (dashed line). Data are presented as mean \pm SEM.

were trained on the S-R task until they performed a minimum of three error-free trials for two consecutive days. On the next day, S-R retention was assessed 1 h after a subcutaneous injection of either vehicle or corticosterone (1 mg/kg) or without any treatment. As we found that the stress resulting from the systemic injection procedure (injection stress) alone was sufficient to impair memory retrieval, some animals were tested 2 min after the vehicle injection, before any stress-induced corticosterone release could occur (vehicle 2'). In parallel groups of rats, we examined whether the injection stress is sufficient to elevate plasma corticosterone levels.

3.1.1. Stimulus-response training

The number of error-free trials (as a measure of learning) and the latency to the first arm entry (as a measure of motivation and/or locomotor activity) were recorded on each trial. The rats reached the S-R learning criterion of at least three error-free trials (out of five daily trials) for two consecutive days within an average of 14.7 ± 0.6 days. One-way ANOVA for the number of error-free trials ($F_{3,41} = 0.03$; N.S., Fig. 2A) and latency to first arm entry ($F_{3,41} = 0.69$; N.S., Fig. 2B) on the last training day revealed no differences between later treatment groups.

3.1.2. Stimulus-response retention test

Retention performance is shown as the number of error-free trials on the retention test day as percentage of each rat's performance on the last training day. One-way ANOVA for retention performance revealed a significant treatment effect ($F_{3,41} = 3.83$; $P = 0.01$; Fig. 2C).

Post-hoc comparison tests indicated that retention performance of rats treated with corticosterone was significantly impaired in comparison to that of non-injected control rats ($65.3 \pm 9.8\%$ versus $91.0 \pm 9.8\%$, $P = 0.04$, Fig. 2C). Moreover, the vehicle injection alone was sufficient to impair retention performance 1 h ($55.0 \pm 8.9\%$, $P = 0.005$), but not 2 min ($85.7 \pm 8.5\%$, $P = 0.69$), after the injection. Consistent with these findings, paired t -tests indicated that retention performance of rats injected with either vehicle ($55.0 \pm 8.9\%$, $t_{13} = 4.80$; $P = 0.0003$) or corticosterone ($65.3 \pm 9.8\%$, $t_{10} = 3.99$; $P = 0.003$) was significantly impaired in comparison to their respective performance on the last training day. None of the other groups showed retention impairment in comparison to their performance on the last training day. To examine the effect of the different treatments on rats' motivation to seek reward, the retention response time (i.e., mean latency to the first arm entry on the retention test relative to that on the last training day) was calculated. For none of the groups, entrance latencies on the retention test differed from those on the last training day. Moreover, one-way ANOVA for retention response time revealed no treatment effect ($F_{3,41} = 0.67$; N.S., Fig. 2D), indicating that the retention impairment was not caused by any non-mnemonic effects of the mild stress procedure or corticosterone injection on the motivation or exploratory behavior of the animals.

3.1.3. Corticosterone levels

We examined the effect of the different treatments on plasma corticosterone levels in separate groups of trained animals. One-

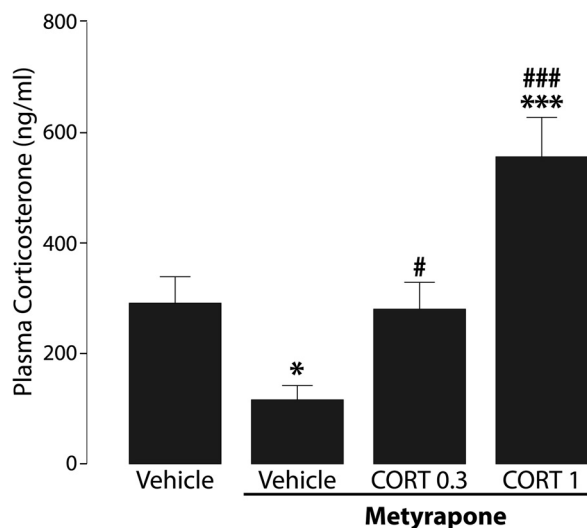


Fig. 5. Subcutaneous administration of metyrapone blocks the effect of injection stress on plasma corticosterone levels. Rats were administered injection stress (vehicle, $n=9$), metyrapone (35 mg/kg, $n=9$) or the combination of metyrapone and corticosterone at a dose of 0.3 mg/kg (CORT 0.3, $n=8$) or 1 mg/kg (CORT 1, $n=9$) and sacrificed 30 min after the treatment without retention testing. Rats administered metyrapone alone had lower plasma corticosterone levels than those administered vehicle. Co-administration of either dose of corticosterone elevated plasma corticosterone levels with respect to the metyrapone alone group. Moreover, rats given metyrapone and the higher dose of corticosterone had significantly higher plasma corticosterone levels than those administered vehicle. * $P<0.05$; *** $P<0.001$ compared to vehicle group; # $P<0.05$; ### $P<0.001$ relative to metyrapone alone. Data are presented as mean \pm SEM.

way ANOVA for plasma corticosterone levels indicated a significant treatment effect ($F_{3,35} = 64.29$; $P<0.0001$). As shown in Fig. 3, post-hoc comparison tests indicated that rats injected with vehicle had significantly higher plasma corticosterone levels 30 min ($P=0.02$), but not 2 min ($P=0.51$), after the injection compared to the non-injected control group, confirming that the handling and injection procedure per se was mildly stressful. As expected, rats administered corticosterone (1 mg/kg) had significantly elevated plasma corticosterone levels with respect to all other treatment groups (for all comparisons, $P<0.0001$).

3.2. Experiment 2: corticosterone mediates the stress effect on retrieval of stimulus-response memory

In the first experiment, we found that exogenous corticosterone administration impaired S-R retention performance. Moreover, the subcutaneous injection procedure per se was stressful and also impaired retention when tested 1 h, but not 2 min, later. In agreement with these findings, the injection stress induced an elevation in plasma corticosterone levels at 30 min, but not 2 min, after stress. To test whether the stress-induced S-R retention impairment is mediated by corticosterone, in the second experiment rats were injected subcutaneously with metyrapone (35 mg/kg), which reduces the corticosterone production by inhibiting the 11 β -hydroxylase enzymatic activity in the adrenal cortex, 1 h before the retention test. Additionally, we investigated whether exogenous corticosterone (0.3 or 1.0 mg/kg) administration would reverse the metyrapone effect on retrieval of S-R memory.

3.2.1. Stimulus-response training

Rats reached the S-R learning criterion of a minimum of three error-free trials (out of five daily trials) for two consecutive days within an average of 11.9 ± 0.6 training days. One-way ANOVA for the number of error-free trials on the last training day indicated no difference between the prospective treatment groups ($F_{3,48} = 1.50$;

N.S.; Fig. 4A). However, one-way ANOVA for the latency to the first arm entry yielded a significant group effect on the last training session ($F_{3,48} = 7.60$, $P=0.0002$) (Fig. 4B). Post-hoc comparisons indicated that rats treated later with the combination of corticosterone 1 mg/kg and metyrapone had longer entrance latencies than the prospective vehicle group ($P<0.001$). Therefore, we included the latency to the first arm entry during training as a covariate in the analyses of retention performance.

3.2.2. Stimulus-response retention test

In the first experiment, we demonstrated that the vehicle injection 1 h before the retention test impaired the retention performance in comparison to their respective performance on the last training day. In the second experiment, we reproduced these findings; paired t-test indicated that the vehicle injection 1 h before the test session significantly impaired retention performance relative to the last training day ($54.8 \pm 7.2\%$, $t_{13} = 5.68$; $P<0.0001$). Because we found a pre-existing difference in training latencies between groups, in order to exclude any possible confound that can derive from this priori difference, we analysed differences in retention performance between the treatment groups with one-way ANCOVA by using training latencies as covariate. Even after controlling for this, we found a significant treatment effect on retention performance ($F_{3,48} = 5.37$; $P=0.03$; Fig. 4C). Post-hoc comparisons indicated that retention performance of rats injected with metyrapone was significantly better than that of rats injected with vehicle (“injection stress”; $99.1 \pm 9.9\%$ versus $54.8 \pm 7.2\%$, $P=0.0002$). Moreover, retention performance of rats treated with metyrapone also did not differ from the performance on the last training day ($99.1 \pm 9.9\%$, $t_{12} = 0.24$, $P=0.80$). Exogenous corticosterone supplementation dose-dependently reversed the metyrapone effect. Rats treated with metyrapone in combination with the higher (1 mg/kg), but not lower (0.3 mg/kg), dose of corticosterone had significantly impaired retention performance relative to those treated with metyrapone alone ($P<0.0001$) or in comparison to their respective performance in the last training day ($54.8 \pm 7.2\%$, $t_{12} = 6.39$, $P<0.0001$) and did not differ from rats treated with vehicle. One-way ANOVA for retention response time revealed no treatment effect ($F_{3,48} = 0.30$; N.S.), indicating again that the retention impairment was not the result of any treatment effect on rats’ locomotor activity or motivation to search for the food reward (Fig. 4D).

3.2.3. Corticosterone levels

The effect of metyrapone administration and corticosterone supplementation on plasma corticosterone levels was examined in separate groups of animals that underwent the same S-R training procedure but were sacrificed 30 min after the drug manipulations without retention testing. One-way ANOVA for plasma corticosterone levels indicated a significant treatment effect ($F_{1,48} = 12.92$; $P<0.0001$). As shown in Fig. 5, rats given metyrapone had significantly lower plasma corticosterone levels than those given vehicle ($P=0.02$). Both doses of corticosterone increased plasma corticosterone levels with respect to metyrapone treatment alone (0.3 mg/kg: $P=0.03$; 1.0 mg/kg: $P<0.0001$). Rats treated with metyrapone in combination with the higher dose of corticosterone had significantly higher plasma corticosterone levels than those injected with vehicle ($P=0.0008$).

4. Discussion

This study investigated whether stress and an acute elevation in glucocorticoid levels impair the retrieval of S-R memory. The origin of this question stems from recent evidence indicating that acute stress exposure might not only impair the retrieval of hippocampus-dependent memories but also influence retrieval

processes that depend on other memory systems (Schwabe et al., 2012). A recent study reported that acute stress impairs the retrieval of S-R associations in humans (Guenzel et al., 2013). However, the underlying mechanism and, in particular, the role of glucocorticoid hormones in the impairing effects of stress on S-R memory remained elusive. Here, we demonstrate that a single injection of corticosterone administered to rats 1 h before testing impaired retention of S-R memory in a radial-arm maze. Moreover, in two independent experiments, we found that the injection procedure per se was mildly stressful, as it elevated circulating corticosterone levels and impaired retention when tested 1 h later. This retention impairment was apparent when comparing retention performance of individual rats to their own performance on the last training session (both in experiment 1 and 2) as well as by comparing retention performance of the vehicle-treated rats to that of an untreated group of rats (only in experiment 1). Our finding that retention was not impaired when rats were tested 2 min after the vehicle injection, when plasma corticosterone levels were still at baseline, suggests that the influence of injection stress on retention impairment was directly related to increased adrenocortical function. Importantly, pharmacological attenuation of the stress-induced rise in endogenous corticosterone levels with the 11β -hydroxylase inhibitor metyrapone blocked the stress-induced retention impairment. This impairing stress and glucocorticoid effect on S-R retention performance was still present after we controlled for a pre-existing difference in entrance latencies during training (experiment 2). Moreover, the injection stress and pharmacological manipulation of glucocorticoid levels did not influence rats' retention response times. Thus these findings indicate that stress and glucocorticoids did not impair retention performance on the S-R task by altering rats' incentive to search for the food reward nor produced any other non-specific behavioral effects. Rather, our findings suggest that stress and the associated elevated glucocorticoid levels specifically impaired the retrieval of S-R memory.

Studies that investigated the effect of stress on the relative use of multiple memory systems indicated that striatal memory functions appear rather insensitive to stress (Schwabe et al., 2012). These studies generally used dual-solution tasks in which rats could perform a task by either using a hippocampus- or striatum-dependent strategy. Findings of these studies show that stress exposure before learning prompts a shift from using a hippocampal spatial strategy toward a dorsal striatal S-R or habit-like learning strategy (de Quervain et al., 1998; de Quervain et al., 2000; de Quervain et al., 2003; Roozendaal et al., 2004b; Het et al., 2005; Kuhlmann et al., 2005b; Atsak et al., 2012a). Moreover, glucocorticoids have been shown to underlie this relative promotion of S-R memory processes under stress (Guenzel et al., 2014). However, here we show that if a task can be solved solely by an S-R strategy then stress also impairs the retrieval of striatal-dependent memory, indicating that striatal-dependent mnemonic processes are also sensitive to the effects of stress. In accordance with these findings, a previous study performed in healthy human subjects showed that acute socially evaluated cold-pressor stress impaired the subsequent retrieval of S-R memory in a virtual radial-arm maze (Guenzel et al., 2013). Moreover, salivary glucocorticoid levels were positively correlated with the magnitude of the retrieval impairment (Guenzel et al., 2013). Here we directly investigated the role of glucocorticoids in S-R memory retrieval impairment and found that a glucocorticoid injection per se is sufficient to mimic the stress-induced impairment of retrieval of S-R memory and that a blockade of glucocorticoid synthesis prevented the stress-induced impairment of S-R memory retrieval. These current findings are consistent with prior evidence that stress-induced high circulating levels of glucocorticoids impair memory retrieval in both humans and animals (de Quervain et al., 1998; de Quervain et al., 2000; Roozendaal et al., 2001; Kuhlmann et al., 2005a; Atsak

et al., 2012a) and that metyrapone pre-treatment blocks the stress-induced rise in glucocorticoid levels and thereby prevents the stress effect on memory retrieval (de Quervain et al., 1998; Roozendaal et al., 2001). However, some evidence in humans indicates that metyrapone administration under particular circumstances such as during the morning rise of glucocorticoids might also impair memory retrieval, most likely by also affecting mineralocorticoid receptor function (Rimmele et al., 2010; Marin et al., 2011; Rimmele et al., 2015).

To the best of our knowledge, this is the first study that demonstrates a role for glucocorticoids in mediating stress-induced retrieval impairment of S-R memory. It is well established that the dorsal striatum is involved in memory of procedural or implicit forms of learning (Packard and Knowlton, 2002) and expresses a moderate density of glucocorticoid, but not mineralocorticoid, receptors (Ahima and Harlan, 1990). Only a few studies examined the effect of glucocorticoids within the dorsal striatum on memory processes, but these studies exclusively investigated glucocorticoid actions on the consolidation of memory. Direct infusions of glucocorticoids into the dorsal striatum immediately after a training experience enhanced the consolidation of procedural memory on a cued water-maze task (Quirarte et al., 2009). A functional heterogeneity of the dorsal striatum in regulating different aspects of learning and memory has previously been described (Packard and Knowlton, 2002). In rodents, somatosensory and motor cortical areas innervate the dorsolateral division of the striatum, and lesions of this region impair the acquisition of S-R associations that rapidly become habitual (Packard and McGaugh, 1992; McDonald and White, 1993; Featherstone and McDonald, 2005). In contrast, the dorsomedial division of the striatum is involved in allocentric spatial navigation and place-response shifting tasks (Whishaw et al., 1987; Devan et al., 1999; Featherstone and McDonald, 2005; Holahan et al., 2005). Consistent with this evidence, we recently reported that glucocorticoid administration into the dorsomedial striatum after training enhances the consolidation for spatial place memory (Lozano et al., 2013) whereas infusions into the dorsolateral striatum promote memory consolidation for a cued version of water-maze learning without affecting the spatial or contextual components (Medina et al., 2007; Quirarte et al., 2009). Although these prior studies solely focused on glucocorticoid effects on memory consolidation processes, they still provide critical evidence for the existence of glucocorticoid effects on memory through direct actions within the dorsal striatum. Therefore, it is likely that stress and glucocorticoids impair the retrieval of S-R memory also by influences in the dorsolateral division of the striatum.

Previous studies investigating the underlying mechanism of how glucocorticoids impair retrieval of information indicated that activation of glucocorticoid, but not mineralocorticoid, receptors within the dorsal hippocampus 1 h before testing impairs retrieval on spatial memory, whereas a blunting of GR activation in the dorsal hippocampus prevents the impairing effects of glucocorticoid administration on memory retrieval (Roozendaal et al., 2004b; Ferguson and Sapolsky, 2008). Since a selective activation of membrane-associated GRs is sufficient to induce memory retrieval impairment (Chauveau et al., 2010), moreover a protein synthesis inhibitor does not prevent glucocorticoid effects on memory retrieval impairment (Sajadi et al., 2006), these findings suggest that glucocorticoids impair memory retrieval, at least in part, via an activation of GRs and nongenomic signaling pathways. Other studies reported that glucocorticoids do not impair the retrieval of all memories, but rather selective for emotionally arousing information or arousing test situations (Roozendaal et al., 2004b; de Quervain et al., 2009). Studies investigating the neurobiological mechanisms underlying this selectivity have indicated that glucocorticoids impair memory retrieval via critical interactions with arousal-associated noradrenergic activity (Roozendaal et al.,

2004b). For instance, a β -adrenoceptor antagonist administered concurrently was shown to block glucocorticoid-induced memory retrieval impairment of emotionally arousing declarative or spatial information in both animals and humans (Roosendaal et al., 2004a; de Quervain et al., 2007). Moreover, we showed that the endocannabinoid system plays an essential role in regulating such interactions between glucocorticoids and the noradrenergic system on memory retrieval (Atsak et al., 2012a; Atsak et al., 2012b). Future studies are needed to investigate whether glucocorticoid effects within the dorsal striatum on the retrieval of S-R memory are also restricted to emotionally arousing information or arousing test situations as well as whether these glucocorticoid effects depend on interactions with the noradrenergic and endocannabinoid arousal systems.

The present findings indicating that stress and elevated glucocorticoid levels impair the retrieval of S-R associations might also have important clinical implications. Several studies have indicated that exogenous glucocorticoid administration can reduce the exaggerated recall of trauma-related memories, and expression of fear responses in patients with post-traumatic stress disorder (PTSD) and other anxiety disorders (Aerni et al., 2004; Schelling et al., 2006; Soravia et al., 2006). In fact, a recent meta-analysis study comparing the effects of five different pharmacological interventions concluded that hydrocortisone is the most effective pharmacotherapy for the prevention of PTSD currently available (Amos et al., 2014). Although the exact neurobiological mechanism underlying these beneficial effects are not understood, the effects are likely mediated by a combination of glucocorticoid effects on both the impairment of memory retrieval as well as the promotion of memory extinction of traumatic experiences (de Quervain et al., 2009). Based on the available evidence, one legitimate concern has been that glucocorticoids might have a selective impact on the recall or extinction of hippocampus-dependent episodic aspects of traumatic experiences, whereas it is well established that traumatic memories and fear responses over time become more habitual and thus less dependent on the hippocampus (Goodman et al., 2012). Our present findings indicating that stress and glucocorticoids also impair the retrieval of striatal-dependent S-R memory suggest that glucocorticoids might also have beneficial effects on these more habitual or procedural aspects of trauma-related memory in patients.

Taken together, our current findings indicate that systemic corticosterone administration or injection stress alone shortly before retention testing impairs the retrieval of S-R memory in rats. A blockade of corticosterone synthesis is sufficient to reverse this stress-induced retrieval impairment, indicating an essential role for glucocorticoid hormones in the underlying mechanism. These findings extend the well-characterized impairing effects of glucocorticoids on the retrieval of hippocampus-dependent forms of memory to other types of memory and support the view that stress and glucocorticoids might have broad effects on the brain in influencing retrieval of different forms of memory.

Conflict of interests

The authors declare no conflict of interest.

Contributors

P.A., F.M.G., D.K and I.O. acquired and analyzed the data. P.A., F.M.G., P.Y., O.C.M., G.L.Q., O.T.W., L.S., and B.R. designed the study and interpreted the data. P.A. and B.R. wrote the paper with comments from all authors. All authors revised the paper, the intellectual content and approved the final submitted version.

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