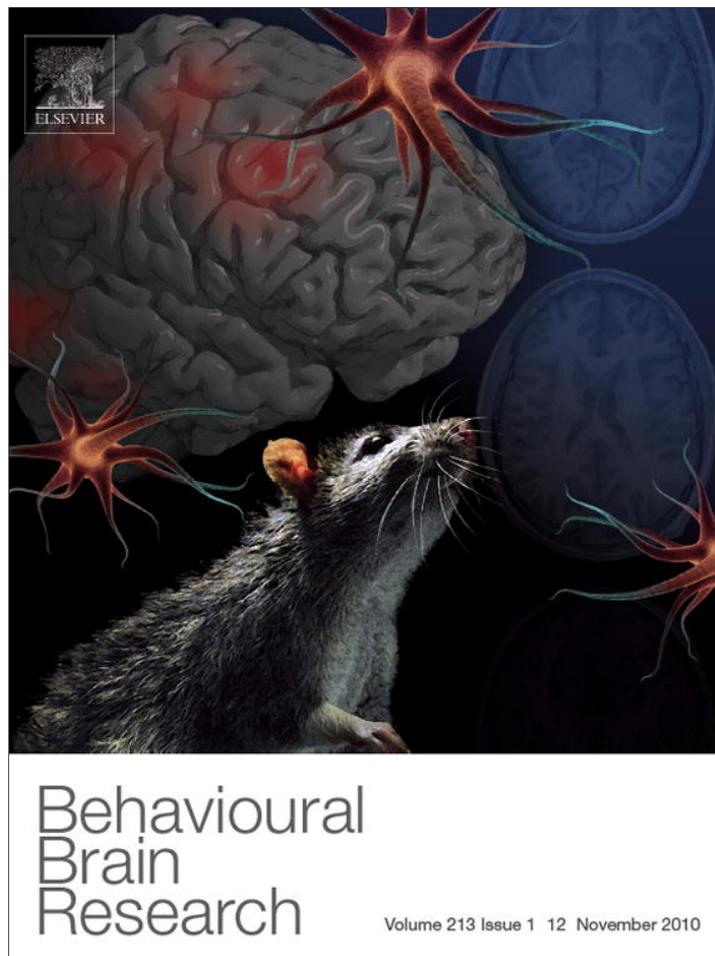


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Research report

Stress impairs spatial but not early stimulus–response learning

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ABSTRACT

Recent evidence indicates that stress modulates multiple memory systems, favoring caudate nucleus-based stimulus–response learning at the expense of hippocampus-based spatial learning. Whether this is due to a facilitating effect of stress on stimulus–response learning, an impairing effect on spatial learning, or both, is not known. To answer this question, mice were either subjected to restraint stress, injected with vehicle or corticosterone or left untreated before training in two circular hole board tasks that could discriminate spatial and stimulus–response strategies. Stress, vehicle and corticosterone injection all impaired learning performance in the spatial task. Conversely, performance in the stimulus–response task was not affected by stress or corticosterone injection, although performance was generally lower than in the spatial task. Irrespective of the treatment, mice had to overcome the preference to use their spatial memory system to achieve the stimulus–response task. These findings suggest that (i) the caudate nucleus-based memory system is less stress sensitive than the hippocampus-based system and may thus dominate behavior in situations of stress and (ii) that multiple memory systems may compete for control of behavior even in tasks that can solely be solved by one system.

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1. Introduction

Stress and glucocorticoid hormones (GCs; mainly cortisol in humans, corticosterone in rodents) that are secreted in response to stress, affect learning and memory processes [1–3]. The nature of the stress (hormone) effect depends critically on the timing of the stressor. Stress associated with the learning episode facilitates memory whereas stress out of the learning context predominantly impairs memory [4,5]. Most studies describe stress- or GC-induced changes in spatial/declarative memory, a memory system that is based on information processing in the hippocampus and adjacent cortices [6–10]. Less is known about stress effects on non-declarative memory processes which are not dependent on an intact hippocampus. Although it is commonly assumed that non-declarative memory is largely unaffected by stress [11–13], recent evidence suggests that stress and GCs may influence non-declarative memory [14,15].

Although it has been known for many years that stress can influence the performance within a single (mainly hippocampal) memory system, it was only recently discovered that stress may also operate as switch between multiple memory systems

(for a review see [16]). In particular, stress, whether acute or chronic, favors caudate nucleus-based stimulus–response (S–R) learning at the expense of hippocampus-based spatial learning [17–20]. Corticosteroids mediate this stress-induced switch from spatial to S–R learning [21]. In a previous study, mice were trained in a six-trial circular hole board (CHB) task that could be learned by hippocampus-based spatial and caudate nucleus-based S–R strategies. A test trial revealed the employed strategy in this dual-solution task. All naïve mice used a spatial strategy. Restraint stress, injection stress (injection with vehicle) and corticosterone administered 30 min before the learning task resulted in a significant bias towards more S–R learning. This switch in learning strategies disappeared when mice were pretreated with an antagonist of the mineralocorticoid receptor, demonstrating the critical role of this receptor in the stress-induced switch between memory systems [21]. What we also showed was the intriguing relationship between strategy and performance in the group of injection-stressed mice: switching to the S–R strategy enhanced performance. Being stressed without switching learning strategy resulted in deterioration of performance. While these findings demonstrate the critical role of GCs in the stress-induced switch between memory systems, it still remains unknown *how* stress modulates the use of hippocampus-based spatial and caudate nucleus-based S–R learning. Does stress primarily affect spatial memory, S–R memory or both memory systems?

In the present experiment, we tested the effects of stress and GCs on spatial and S–R learning separately. We used a similar experi-

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mental set up as in our previous study [21] and designed spatial and S–R versions of the CHB task, anticipating that both tasks could be solely solved by either spatial or S–R strategies, respectively. Mice were either left untreated or received one of 3 different treatments 30 min before the first training trial in the learning tasks: (1) restraint stress, (2) injection with vehicle (injection stress) or (3) injection with corticosterone. Based on earlier reports [22,17], we assumed that stress and corticosterone would impair spatial learning. Given the lack of studies on the effect of stress and GCs on subsequent S–R learning, we could not predict the direction of the effects of stress and GCs on S–R learning.

2. Materials and methods

2.1. Animals

Male C57BL/6J mice ($n=64$; 12 weeks old; purchased from Janvier, France) were single housed with free access to food and water. A 12:12 h light/dark cycle (lights on at 0730 h; 120 lux) was maintained, with all testing carried out between 0830 and 1230 h. The mean bodyweight of the mice at the time of testing was 27.0 g (SEM=0.26). Mice were housed in the testing room (same light-dark cycle; temperature $21 \pm 1^\circ\text{C}$) one week before behavioral experiments started. Each second day before training started, mice were weighed. 'Pretraining' consisted of climbing through the tunnel, which was part of the test-equipment (see Section 2.2), after weighing. All experiments were approved by the Local Committee for Animal Health, Ethics and Research at the University of Leiden. Animal care was conducted in accordance with the EC Council Directive of November 1986 (86/609/EEC).

2.2. Learning tasks

2.2.1. Apparatus

The circular hole board (CHB) is a revolvable white round plate (plexiglass, 110 cm in diameter, situated 1 m above the floor) with 12 holes at equal distances from each other, located 10 cm from the rim of the board. Holes are 5 cm in diameter and can be closed by a lid at a depth of 5 cm. Whether a hole is open or not can only be recognized if the mouse puts its head over the edge of the hole. If open, the hole is the exit to the animals' home cage via an s-shaped tunnel (diameter: 5 cm; 15 cm long). Numerous cues in the room allow spatial orientation.

2.2.2. General procedure

Each trial started by placing the mouse in a grey cylinder (Plexiglas; 25 cm high; 10 cm diameter) which was located at the centre of the CHB. After 5 s, the cylinder was lifted and the animal could explore the board and exit through the tunnel. If a mouse did not enter the exit hole within 120 s, it was guided there by the experimenter along a grid (20 cm \times 6 cm). The board was cleaned after each trial with 1% acetic acid solution and turned clockwise until another hole was at the location of the exit. The home cage was placed hereunder so that it could not be seen by the mouse on the board. Same as in our previous study [21], mice were given six training trials with an intertrial interval of 15 min.

2.2.3. Free exploration trial

One week before the first training trial, general activity and exploratory behavior of mice were assessed on the CHB (5 min). All holes were covered with a lid. In the S–R task condition but not in the spatial task condition, a customary transparent 0.5 L bottle (22 cm high, 5 cm diameter) filled with water was placed next to the hole which was opened at the end of the exploration trial (proximal cue). The mouse was gently guided by the experimenter towards the exit hole by means of a grid (20 cm \times 6 cm). This initial exploration trial served to estimate differences in mouse exploratory behavior before treatment. In retrospect, we did not find behavioral differences between the groups with respect to velocity, distance moved and number of holes visited (all $F < 1$, all $P > 0.45$).

2.2.4. The spatial task

In the spatial task, the position of the exit hole remained constant across the six training trials. There were no proximal cues on the CHB. Thus, the position of the exit hole could be learned solely via extramaze room cues. Earlier studies that had used similar tasks to examine spatial learning showed that learning in such tasks is mediated by the hippocampus [23,24].

2.2.5. The stimulus–response (S–R) task

In the S–R task, a transparent 0.5 L bottle could serve as a proximal cue to locate the exit hole. The position of the bottle was always next to the exit hole and changed from trial to trial using the same sequence for all animals. Thus, mice had to use a stimulus-based strategy to locate the exit hole. This procedure is very similar to the procedure used in other studies to investigate S–R learning [25,23]. These studies provided convincing evidence that behavior in such tasks is dependent on the caudate nucleus. As we were primarily interested in

the contribution of S–R learning to performance in the dual-solution task following stress or corticosterone, the distal cues remained the same as in the dual-solution task.

2.2.6. Analysis of behavior

Behavior was recorded on videotape and analyzed by EthoVision 1.95 (Noldus Information and Technology BV, Wageningen, The Netherlands). This image analysis system sampled the position of the mouse 12.5 times per second. To calculate the distance walked, we chose a minimal distance between samples of 3 cm. The following parameters were measured for all trials: latency to exit hole (s), velocity (cm/s), distance moved (cm) as well as the holes visited (a hole visit was counted, when the animal at least put its nose in the hole). Latency measures were cross-checked with manual protocols.

2.2.7. Corticosterone and restraint stress

Corticosterone (250 $\mu\text{g}/\text{kg}$ bw in 200 $\mu\text{l}/25$ g bodyweight HBC complex dissolved in physiological saline) and vehicle were administered subcutaneously (s.c.) 30 min before training. This corticosterone dose and the timing of drug injection are based on our previous studies [26,21] and served to parallel the experimental set up of our recent study on memory systems [21]: (i) a corticosterone injection 30 min prior to training results in significantly increased corticosterone concentrations at the start of the learning task (mean \pm SEM ng/ml 197 ± 16); (ii) 250 $\mu\text{g}/\text{kg}$ bw corticosterone is sufficient to switch the learning strategy towards more S–R learning in the dual-solution task. (iii) This dose results in physiological levels of corticosterone in blood plasma comparable to the corticosterone secretion induced by 1-min swimming in the water maze and (iv) had been used to rescue the impaired spatial performance of mice in the Morris water maze [26]. Solutions were prepared freshly the day before injection. It is important to note that the subcutaneous vehicle injection is a stressor itself that leads to increased corticosterone concentrations and may change behavior [27,21]. After the injection animals were placed back in their home cage. At the start of behavioral testing, plasma corticosterone concentrations of vehicle injected mice were 66 ± 4 (mean \pm SEM ng/ml [21]).

In the restraint stress condition, mice were immobilized for 10 min in a cylinder (transparent plexiglas; diameter: 2.5 cm, 8 cm long) in a room adjacent to the testing room. After immobilization, mice returned to their home cage in the testing room, followed by the first training trial 20 min later. At this time point, corticosterone concentrations in the blood ranged around 95 ± 19 (mean \pm SEM ng/ml [21]).

2.2.8. Statistical analyses

Statistical analyses used mainly mixed-design ANOVAs with the between-subject factor group (untreated vs. vehicle injection stress vs. restraint stress vs. corticosterone) and the within-subject factor trial (training trials 1–6). ANOVA was followed by post hoc Tukey tests to correct for Type-I error accumulation, if required. All reported P -values are two-tailed.

3. Results

3.1. Spatial learning

To examine the effects of stress and corticosterone when only distal spatial stimuli are available, mice (untreated, vehicle injection stress, restraint stress, corticosterone; $n=8$ per group) received six training trials in a spatial version of the CHB task. Previous studies suggested that stress prior to learning impairs hippocampus-dependent learning and memory [22,17]. Corroborating these findings a mixed-design ANOVA over trials 1–6 revealed that vehicle injection-stressed, restraint-stressed and corticosterone-treated mice had longer latencies to exit hole compared to untreated controls ($F(3,29)=5.46$, $P < .005$; vs. untreated: all $P < .05$; Fig. 1A). Latencies changed over trials ($F(5,145)=11.48$, $P < .001$). Untreated mice showed a continuous decrease of latencies over trials, while the performance of the other groups varied over trials. Similar results were derived from the number of holes visited ($F(3,29)=5.29$, $P = .005$; Fig. 1B) and the distance moved ($F(3,29)=3.66$, $P = .02$; not shown), indicating that corticosterone and stress impair this hippocampus-dependent behavior. Conversely, the injection stress, restraint stress and corticosterone groups did not differ in latencies or number of holes visited (all $P > .27$). Vehicle injection-stressed and corticosterone-injected mice moved even faster than untreated mice ($F(3,29)=3.35$, $P = .03$; vehicle injection

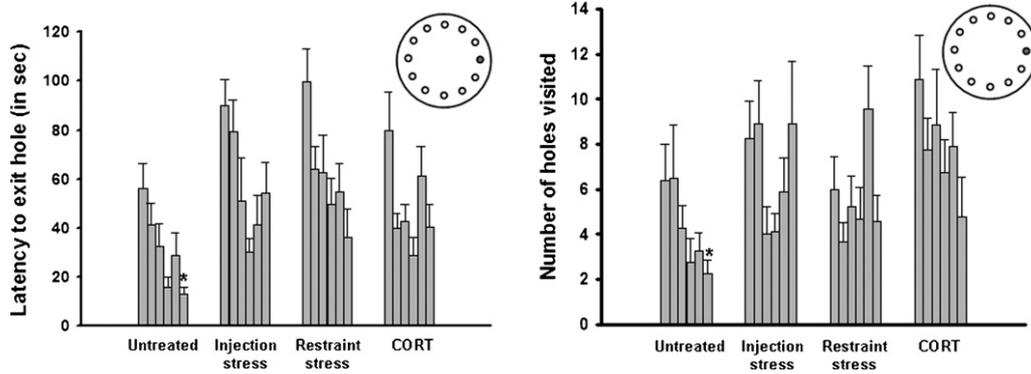


Fig. 1. (A) Latencies to the exit hole and (B) number of holes visited as measure of performance in untreated, vehicle-injected (injection stress), restraint-stressed and corticosterone (CORT)-injected mice in the six trials of the spatial task. Decreasing latencies and numbers of holes visited over trials indicate improvement of performance. Untreated mice had superior performance compared to all other groups. Insert: circular hole board with exit hole in fixed location (gray circle) * $P < 0.05$ vs. all other groups. Data represent mean \pm SEM.

stress/corticosterone vs. untreated: both $P \leq .05$; restraint stress vs. untreated: $P = .17$).

3.2. Stimulus–response (S–R) learning

To address the impact of stress and corticosterone on S–R learning, mice (untreated, vehicle injection stress, restraint stress, corticosterone; $n = 8$ per group) were given six trials to find an exit hole in an S–R version of the CHB task. Treatment did not affect performance: latencies, number of holes visited, distance moved and velocity were comparable between groups. None of the groups showed decreasing latencies over the six training trials which would be indicative for forming an association between the bottle and the exit hole (Fig. 2). Inspection of individual data revealed that some mice moved directly towards the bottle and exit in trial 6 which is indicative of S–R learning. We regrouped the mice, independent of their treatment into “S–R learners” ($n = 12$) and “S–R non-learners” ($n = 24$). S–R learners significantly decreased their latencies and the number of holes visited over trials (latency: $F(5,140) = 3.16, P = .01$; holes visited: $F(5,140) = 4.13, P < .01$; Fig. 3A and B). Importantly, no treatment effect was obtained on the performance of “S–R learners” in the S–R task, neither for latencies nor for the number of holes visited (both P s $> .25$).

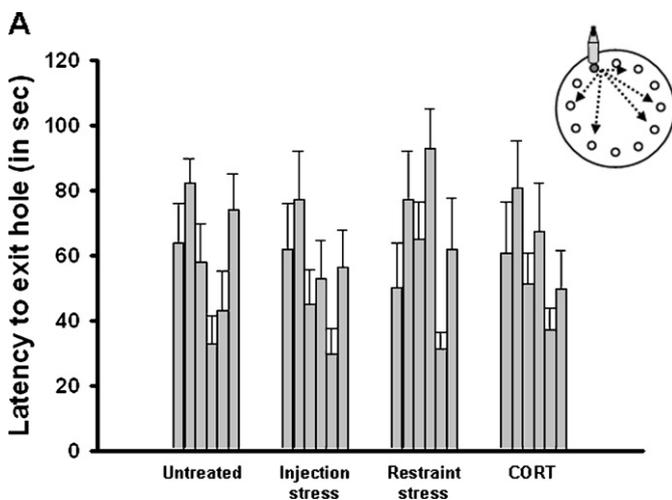


Fig. 2. Performance of untreated, vehicle-injected (injection stress), restraint-stressed and corticosterone (CORT)-injected mice in the six trials of the stimulus–response (S–R) task. Overall, mice did not show a decrease in latencies to the exit hole which would indicate learning.

3.3. Stimulus–response learning: interference with spatial memory?

Earlier findings suggested that (non-stressed) rodents prefer spatial over S–R learning [17]. We therefore hypothesized that the “natural” use of a spatial strategy might have interfered with learning in the S–R task. To address this, we calculated a “spatial tendency” score: i.e., the number of holes between the first hole visited in the current trial and the exit hole–bottle location in the previous trial (for trial 1 the exploration trial was considered as previous trial). A repeated measurements ANOVA revealed a significant time effect ($F(5,130) = 5.21, P < .01$). The first hole visit of mice in training trials 1 and 2 was to a hole close to the location of the exit hole–bottle in the previous trial, indicating spatial memory. Interestingly, mice that were classified as “S–R learners” based on their latencies to the exit hole showed the same “spatial tendency” as “S–R non-learners” in trials 1 and 2, but responded more directly to the stimulus in trials 4–6 ($F(1,29) = 5.16, P = .03$). The “S–R non-learners” kept their “spatial tendency” ($P < 0.05$; Fig. 3C).

4. Discussion

It has now been repeatedly shown that stress and stress hormones favor S–R over spatial strategies in dual-solution tasks that can be solved by hippocampus-based spatial and nucleus caudate-based S–R strategies [17–21]. Here, we examined the potential contributions of the spatial and S–R memory systems to performance in a six-trial dual-solution task. We used two modified versions of a previously used dual-solution task [21] that were designed to assess the effect of stress on spatial and S–R learning separately. We show that stress and the injection of corticosterone impair spatial learning whereas the early form of S–R learning that was developed after six trials remained unaffected by these treatments. Thus, we suggest that the stress-induced modulation of spatial and S–R learning strategies in dual-solution tasks is mainly due to a detrimental effect of stress on spatial learning. Moreover, we show that a spatial memory bias affects the acquisition of the S–R task, pointing to competitive interactions between memory systems even in a task that can solely be solved by one of the systems.

Our findings are in line with previous evidence showing that hippocampal functions such as spatial learning are highly stress sensitive. Numerous studies have demonstrated the time-dependent effects of stress and GCs on hippocampal neuroplasticity and hippocampus-dependent behavior [22,17,28,12,10]. Stress associated with the learning episode facilitates memory whereas stress out of the learning context predominantly impairs memory

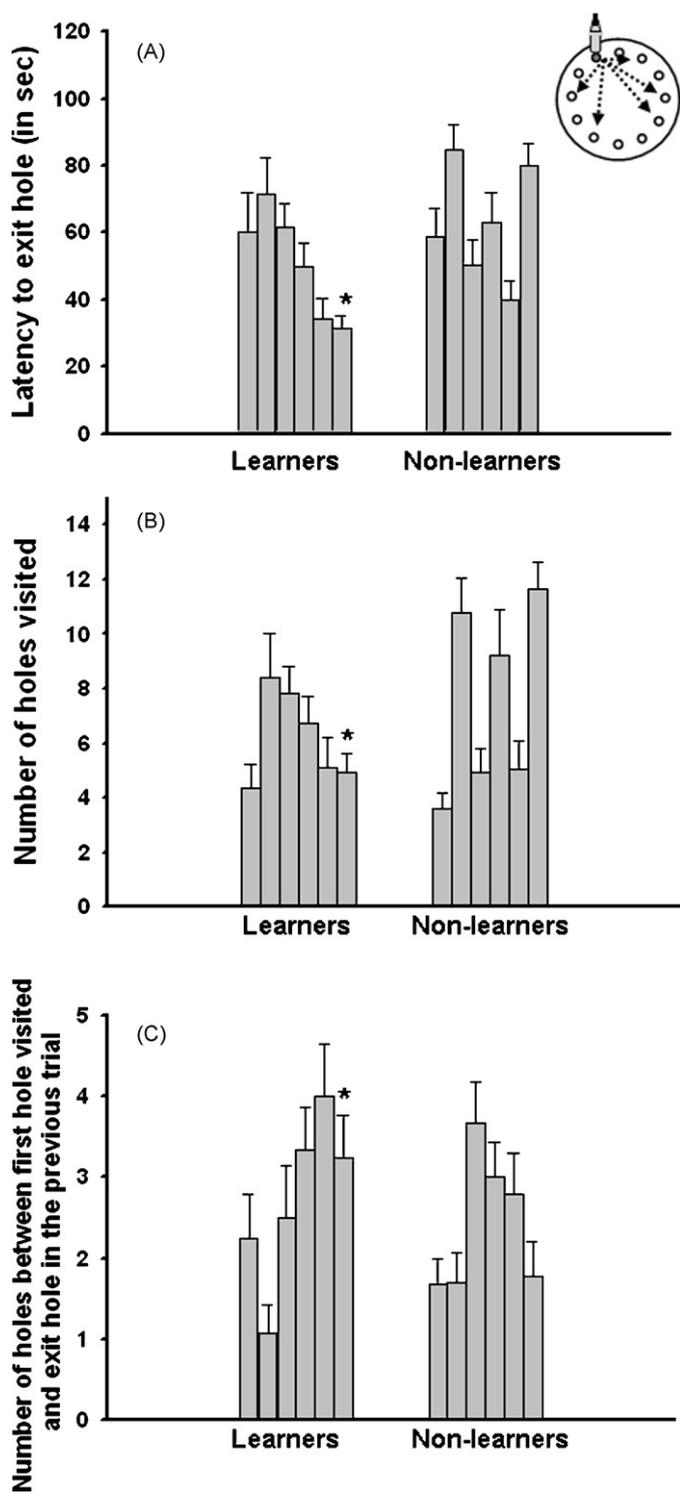


Fig. 3. “Learners” and “non-learners” in the stimulus–response (S–R) task. A subgroup of mice that were classified as “S–R learners” showed decreasing latencies (A) and decreasing number of holes visited (B) across the six training trials while non-learners did not. (C) The spatial learning tendency in the stimulus–response (S–R) task was expressed as number of holes between the first hole visited in the current trial and the position of the exit hole in the previous trial. Note that a low number reflects a spatial learning tendency. A higher number means a reduced spatial learning tendency and more of a S–R response. In contrast to “S–R non-learners”, those mice classified as “S–R learners” were able to overcome the spatial learning tendency in the last training trials. * $P < .05$. Data represent mean \pm SEM.

[4,5]. In the current study the stress procedures and/or stress hormone administration occurred 30 min prior to the learning trials, out-of-context of the learning task. Hence, impairment of spatial learning was predicted, which indeed was observed. Such impairment may occur via emotional influences relayed via the amygdala [2]. Interestingly, stressed and corticosterone-injected mice needed significantly longer to find the exit hole in the spatial learning task despite they were moving faster than untreated controls. Although the room cues were the same in the two tasks, no such treatment effects on velocity occurred in the SR task.

The molecular mechanisms of glucocorticoid action are mediated by two receptor types: the mineralocorticoid and glucocorticoid receptors, of which the hippocampus contains the highest density [29,30]. Most recently, we have identified the mineralocorticoid receptors to be crucial for the transition between learning strategies, as well as for the performance itself [21]. The caudate nucleus predominantly expresses glucocorticoid receptors, but at a relatively low density [29] suggesting a rather low sensitivity to stress. In the present study we found no effect of acute stress or corticosterone on S–R learning. The effects of chronic stress might differ. Recent evidence indicates that chronic stress causes a hypertrophy of parts of the caudate nucleus, accompanied by increased S–R learning [31].

Although our data shed some light on the stress-induced switch between spatial and S–R learning strategies in a six-trial dual-solution task [21] they do not rule out an effect of stress and stress hormones on S–R learning and memory in general. More pharmacological doses of corticosterone might have different effects. We have to consider that stress and corticosterone effects might occur during a later phase of S–R learning. In fact, injections of GCs into the caudate nucleus after extensive training in a cue-dependent water maze task enhanced the consolidation of S–R memories [15]. This is in line with the well-known memory facilitating effects of glucocorticoids. Furthermore, emotional arousal-inducing anxiogenic drugs enhanced S–R memories when administered before learning, after learning or before retrieval ([32,33]; but see [34] for a negative effect of pre-learning anxiogenic drugs on SR-learning).

Comparing the performance of untreated mice in the spatial vs. the S–R task, revealed that mice perfectly learn the spatial task within six trials which is not the case in the S–R task. There is evidence that caudate-based S–R learning needs much more training to develop than hippocampus-based spatial learning [35–37]. Indeed, most studies focusing on S–R learning applied significantly more trials than we did in the present study, often more than 100 trials [35,38,15,34]. Even after categorizing the mice in our study in “S–R learners” and “S–R non-learners”, performance in the S–R task was still relatively poor when compared to the spatial task. However, about one third of the mice showed a significant improvement of performance across training which indicates that they were starting to develop S–R learning. Interestingly, S–R learning even at this early stage (i.e., after six trials) may control behavior [19,21]. The finding that stress and corticosterone do not influence this early stage of S–R learning improves our understanding of the stress-induced shift in learning strategies in a six-trial dual-solution task [21].

Analyzing the behavior of the mice in more detail revealed an unexpected result. We discovered an intriguing interaction of proximal and distal cues for memory formation. All mice had a “spatial tendency” during the initial training trials, i.e., a tendency to visit first the location of the exit hole of the previous trial. Two thirds of the mice preserved in this approach until the last trial, while one third of the mice responded more directly to the proximal stimulus. This latter group of mice was characterized as “S–R learners” due to their more stimulus-oriented approach in the last training trial. We may conclude that (i) the preferentially used memory system in mice is spatial and (ii) there is a transition between memory

systems, extending the findings of our previous study [21]. If spatial cues had been removed, the spatial tendency would have most likely disappeared. Although, removing the spatial cues might have slightly facilitated S–R learning, previous evidence suggests that even without spatial cues S–R learning would not fully develop within six trials [35,38].

The caudate-based memory system may contribute to early stages of learning, but appears to be less stress sensitive than the hippocampal memory system. Therefore, if stressed and confronted with a task that allows the use of more than one memory system (as it is given in the dual-solution task) the caudate system may complement and even override the behavioral control associated with hippocampal function. This has been observed in several previous studies [17,18,20,21]. Thus, while memory systems compete for control of behavior in dual-solution tasks [39], there is also some cooperation between hippocampal and nucleus caudate memory systems. One system seems to be able to compensate the gradual dysfunction of the other (see also [40]). However, as discussed above, there was also some indication for competition between memory systems in the present study: we found that the “natural” preference of mice for hippocampus-dependent spatial learning [17,18] did not exclude S–R learning.

The finding that some animals started to learn the S–R task within the six trials while others did not is interesting with respect to previous studies, in which a certain percentage of rodents (and humans) did not shift to the S–R strategy following stress [17,20,21]. Our findings suggest that there are considerable interindividual differences in the speed of S–R learning. Some mice showed some evidence for early S–R learning (“S–R learners”), even within six trials. In these animals S–R learning might contribute to behavior in a six-trial dual-solution task and the S–R system might (at least partly) assume the role of the spatial system. Other mice, however, simply had not acquired the S–R strategy within six trials (“S–R non-learners”). Thus, they had to rely on the hippocampal system even when this is impaired by stress. Assessing potential factors contributing to these interindividual differences is a challenge for future research.

Finally, two caveats of the present study need to be addressed. First, as mentioned before, S–R learning was developed at a rather early stage in some mice (“S–R learners”) and not at all in other mice (“S–R non-learners”) after six trials. We had decided for only six S–R learning trials because we aimed to assess the potential contribution of S–R learning to performance in the previously used six-trial dual-solution task [21]. The present data suggest that S–R learning might contribute to performance after six trials in at least some mice and that this early stage of S–R learning is not modulated by stress or glucocorticoids. However, as S–R learning is clearly not fully developed after six trials, we cannot conclude that S–R learning is generally unaffected by these treatments. Although we had designed our tasks to parallel those for which it has been shown that they depend on the hippocampus and caudate nucleus, respectively, a second caveat of the present study is that we have no own data supporting the involvement of the hippocampus and the caudate nucleus in the spatial and S–R task, respectively. Thus, conclusions about the possible interaction of multiple memory systems in these tasks can only cautiously be made.

In summary, the present study is one of the few that examined stress effects on hippocampus-dependent spatial learning as well as on caudate-nucleus dependent S–R learning. In agreement with previous studies, our results suggest that the spatial memory system is already engaged in the initial stages of learning, whereas the S–R system contributes at a later stage [35–37]. Since (early) S–R learning appears to be less vulnerable to the influence of stress than hippocampus-dependent spatial learning this may enable the caudate nucleus to control behavior in dual-solution tasks during stress.

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