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# Sex differences in stress effects on response and spatial memory formation

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ABSTRACT

Stress and stress hormones are known to affect learning and memory processes. However, although effects of stress on hippocampus-dependent declarative learning and memory are well-documented, relatively little attention has been paid to the impact of stress on striatum-dependent stimulus–response (S–R) learning and memory. Recent evidence indicates that glucocorticoid stress hormones shortly after learning enhance S–R memory consolidation, whereas stress prior to retention testing impairs S–R memory retrieval. Whether stress affects also the acquisition of S–R memories in humans remains unclear. For this reason, we examined here the effects of acute stress on S–R memory formation and contrasted these stress effects with those on hippocampus-dependent spatial memory. Healthy men and women underwent a stressor (socially evaluated cold pressor test, SECPT) or a control manipulation before they completed an S–R task and two spatial learning tasks. Memory was assessed one week later. Our data showed that stress impaired S–R memory performance in men but not in women. Conversely, spatial memory was impaired by stress in women but not in men. These findings provide further evidence that stress may alter learning and memory processes beyond the hippocampus. Moreover, our data underline that participants' sex may play a critical role in the impact of stress on multiple memory systems.


## 1. Introduction

In response to stressful events, catecholamines are released from the adrenal medulla and, with a short delay, glucocorticoids (corticosterone in rodents, cortisol in humans) are released from the adrenal cortex. These hormones mediate stress effects on health, emotion, and cognition (De Kloet, Joëls, & Holsboer, 2005; McEwen, 2000; Roozendaal, McEwen, & Chattarji, 2009). In particular, hippocampus-dependent, 'declarative' learning and memory processes are known to be affected by stress and stress hormones. Extensive evidence shows that the direction of these stress (hormone) effects is influenced by many factors, one of them being the timing of the stressor (Roozendaal et al., 2009; Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012). Acute stress shortly after learning enhances the consolidation of episodic or spatial memory tasks (Cahill, Gorski, & Le, 2003; Roozendaal et al., 2009; Smeets, Otgaar, Candel, & Wolf, 2008) that are known to rely on the hippocampus (Burgess, Maguire, & O'Keefe, 2002; Maguire, Woollett, & Spiers, 2006; Morris, Garrud, Rawlins, & O'Keefe, 1982; Ryan et al., 2001). Stress before retention testing, however, impairs memory retrieval in these tasks (De Quervain, Roozendaal, & McGaugh, 1998; Kuhlmann, Piel, & Wolf, 2005; Roozendaal et al., 2009), which are also dependent on the hippocampus (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Maguire et al., 1998; Nyberg, McIntosh, Houle, Nilsson, & Tulving, 1996; Ryan et al., 2001). The effects of stress before learning are more controversial. Some studies suggested that stress before learning of a word list enhances subsequent memory (Schwabe, Bohringer, Chatterjee, & Schachinger, 2008; Smeets, Giesbrecht, Jelicic, & Merckelbach, 2007), whereas other studies reported that pre-learning stress impairs spatial or episodic memory (Elzinga, Bakker, & Bremner, 2005; Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996).

In addition to the timing of the stressor, participants' sex is another factor that can modulate the influence of stress on memory. Several studies indicated that men show stronger cortisol responses to stress than women (Kajantie & Phillips, 2006; Kudielka & Kirschbaum, 2005). Moreover, there is some evidence that stress may have different effects on declarative memory processes in men and women (Andreano & Cahill, 2006; Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum, 2001). These findings emphasize that participants' sex should be taken into account when investigating stress effects on memory.

In contrast to the well-documented effects of stress on hippocampus-dependent memory, the influence of stress on striatum-dependent learning and memory processes is less

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understood. First evidence provided by rodent studies indicated that stress affects striatum-dependent memory processes and that these effects were similar to those on hippocampus-dependent memory. It has been shown that a striatal injection of corticosterone immediately after learning of either a striatum-dependent inhibitory avoidance- or stimulus–response (S–R) learning task enhances the consolidation of these tasks (Medina et al., 2007; Quirarte, Ledesma de la Teja, & Casillas, 2009). Furthermore, the infusion of an $\alpha_2$-adrenoreceptor antagonist, which leads to increased noradrenergic stimulation, after training enhances the consolidation of an S–R task as well (Wingard & Packard, 2008). Thus, the effects of stress hormones on the consolidation of S–R memories resemble those on the consolidation of hippocampus-dependent memories (Cahill et al., 2003; Roozendaal et al., 2009). Moreover, a recent study in humans shows that acute stress may also hamper the retrieval of S–R memories (Guenzel, Wolf, & Schwabe, 2013), similar to what has been found for retrieval of hippocampus-dependent memories before (De Quervain et al., 1998; Kuhlmann et al., 2005). Together, these findings suggest that (i) stress may also affect striatum-dependent S–R memory processes and (ii) stress after learning or before retention testing affects striatum-dependent and hippocampus-dependent memory in a similar manner. Although it has been shown, that stress (hormones) may affect the consolidation and the retrieval of S–R memories, it remains unclear whether stress may also affect the formation of striatum-dependent S–R memories in humans and, if so, whether these stress effects are different in men and women. To address these questions, we examined the effect of acute stress before learning of a striatum-dependent S–R task in healthy men and women. We exposed our participants to a standardized laboratory stressor (socially evaluated cold pressor test, SECPT) before they learned three different learning tasks: (i) a computer-based S–R navigation learning task, (ii) a computer-based spatial navigation learning task, and (iii) a spatial learning task in a real environment. This allowed us to contrast stress effects on response learning with those on hippocampus-dependent spatial learning. We included a spatial navigation task in a real environment, in addition to the virtual spatial navigation task, because the role of the hippocampus in navigation in real environments is very well-documented (Maguire et al., 2000, 2006). Although previous studies showed that stress before learning may alter subsequent (hippocampus-dependent) memory, these studies yielded inconsistent findings (Elzinga et al., 2005; Kirschbaum et al., 1996; Schwabe, Bohringer et al., 2008; Smeets et al., 2007), thus making it difficult to predict the direction of potential stress effects. Possible differences between men and women were examined without specific hypotheses.

## 2. Methods and materials

### 2.1. Participants

Seventy healthy university students (35 men, 35 women) participated in this study (age: M = 24.20 years, SEM = 0.33 years; body-mass-index: M = 22.35 kg/m$^2$, SEM = 0.28 kg/m$^2$). Exclusion criteria were assessed in a standardized interview and comprised any physical and psychiatric diseases, medication intake, drug abuse, smoking, and in women the use of oral contraceptives. Moreover, women were not tested during their menstruation. Seven participants (3 men, 4 women), had to be excluded from further statistical analyses because of technical problems, thus leaving a sample of 63 participants. All participants provided written informed consent and received a compensation of 15 € for their participation. The study was approved by the ethics committee of the psychological faculty of the Ruhr-University Bochum.

### 2.2. Experimental procedure

Participants were tested between 1 pm and 6 pm on two testing days with a time-interval of one week. The testing time varied randomly across participants, so that systematic differences between men and women or the stress and control groups could be ruled out. Moreover, participants were not allowed to eat or drink anything except water within 1 h before the beginning of the experimental sessions.

#### 2.2.1. Training phase

After their arrival at the lab on the first testing day, participants were first trained how to navigate in a 3D virtual environment. More specifically, they were trained to collect four balls by using the left-, right-, and forward arrow keys of a keyboard. The training program was created using a commercially available computer game editor (Conitec, Gamestudio, Germany) and resembled the navigation tasks that were used in the learning session (see below).

#### 2.2.1. Stress and control manipulation

Immediately after the training session, participants were exposed to a stressor or a control manipulation. In the stress condition (16 men, 16 women), participants were exposed to the socially evaluated cold pressor test (SECPT). The SECPT is a standardized stress protocol which combines a physical stressor with social evaluative components, as described in detail elsewhere (Schwabe, Haddad, & Schachinger, 2008). In brief, participants were instructed to submerge their right hand including the wrist for as long as possible (maximum duration 3 min) into ice water (0–2 °C). During hand immersion, participants were observed by a rather cold, non-reinforcing experimenter and videotaped. Participants in the control condition (16 men, 15 women) were instructed to immerse their right hand up to and including the wrist for 3 min into warm water (35–37 °C). They were not monitored by the experimenter nor were they videotaped.

Subjective and physiological measurements were taken at several time points across the experiment to assess the effectiveness of the stress induction. After the SECPT/control manipulation, participants rated on a scale from 0 (“not at all”) to 100 (“very”) how unpleasant, stressful and painful they had experienced the previous situation. Moreover, blood pressure was measured with a Dinamap system (Critikon, Florida) immediately before, during, and immediately after the stress or control manipulation. To assess the activity of the hypothalamus-pituitary adrenal (HPA) axis, participants collected saliva samples with the help of Salivette collection devices (Sarstedt, Germany) shortly after their arrival at the lab (baseline) as well as 20 min, 35 min and 50 min after exposure to the SECPT/control manipulation. Another saliva sample was taken before retention testing on the second experimental day. Saliva samples were stored at −20 °C until the completion of the study. From saliva, we analyzed cortisol concentrations with an immunoassay (IBL, Hamburg); interassay and intra-assay coefficients of variance were below 10%.

#### 2.2.3. Learning tasks

Twenty-five minutes after the exposure to the SECPT/control manipulation, participants completed (i) a computer-based S–R learning task with a single cue for orientation, (ii) a computer-based spatial learning task with external landmarks for orientation and (iii) a spatial learning task in a real environment. The computer-based tasks were presented in counterbalanced order. The spatial navigation task in the real environment, however, took place always at the end of the first testing day. Participants were

not informed that their memory of the three learning tasks would be tested on the second experimental day.

*2.2.3.1. S–R navigation task in a virtual environment.* The S–R navigation task has been used in a previous study (Guenzel et al., 2013). It was designed as a 3D virtual maze consisting of a center platform, eight radiating arms and a single intra-maze cue (chair) which allowed orientation (see Fig. 1). The maze-arms were assembled identically and surrounded by high walls. Each maze-arm had a wooden hollow at the end and three of these wooden-hollows contained one of three distinct objects (book, cake or bag). Participants were instructed to collect these objects in a given order (book – cake – bag) as quickly as possible. Both, the location of the objects and the order in which the objects should be collected were constant across all trials. Participants could use the left-, right-, and forward arrow keys of a keyboard to move in the maze and to collect the objects. In all trials, the starting position of the participants was the center platform; the viewing direction of the participants, however, differed between trials. Extra-maze cues were not provided. Thus, in order to collect the objects, participants had to acquire a sequence of movements with respect to the single intra-maze cue. Neuroimaging studies which used a similar task design (Bohbot, Lerch, Thorndycraft, Iaria, & Zijdenbos, 2007; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003) showed that the caudate nucleus is associated with such 'response' learning.

A maximum of 6 trials was given, each with a maximum duration of 3 min (i.e., the maximum duration was 18 min). Each entry into an incorrect arm (i.e., an arm without an object or with the incorrect object) was counted as an error and taken, together with the time needed to complete a trial, as an indicator of learning performance. The learning session was finished if a participant solved two trials in a row errorless. However, participants who did not reach the learning criteria of two error free trials in a row were not excluded from the statistical analysis.

*2.2.3.2. Spatial navigation task in a virtual environment.* The spatial navigation task was very similar to the S–R navigation task. Again, three objects (book, cake, and bag) were placed in a 3D virtual radial maze with eight identical arms originating from a center platform. The only difference to the S–R task was that a spatial environment (mountains, grassland, desert, and forest) surrounded the radial maze (see Fig. 1). Intra-maze cues, however, were not provided. Therefore, participants could learn the locations of the objects solely in relation to these external landmarks. Previous neuroimaging studies demonstrated that such spatial learning is supported by the hippocampus (Bohbot et al., 2007; Iaria et al., 2003). Importantly, none of the extra-maze cues could individually predict the location of a certain object, thus ruling out the possibility of S–R learning.

The learning criteria in the spatial navigation task were exactly the same as in the S–R navigation task. Again, entries into incorrect arms (i.e., arms without an object or with the incorrect object) were counted as errors and, together with the time needed to solve a trial, taken as indicator of learning performance. Participants received a maximum of 6 trials, each with a maximum duration of 3 min (i.e., the maximum duration was 18 min), and the task was finished if a participant solved two trials in a row errorless. However, participants that did not reach this rather strict learning criterion were not excluded from analyses.

*2.2.3.3. Spatial learning task in the real environment.* At the end of the first testing day, participants were guided along a pre-defined route in the psychology building of the Ruhr-University Bochum; psychology students were excluded from participation, thus none of our participants was familiar with the building. The route was about 70 m long, and comprised 15 forks. Participants were not allowed to talk while walking this route and they were not informed that they would have to retrieve this route on the second experimental day.

### 2.3. Memory testing

The second (testing) day took place seven days after experimental day 1. Here, participants' memory of all three learning tasks was tested. Participants were presented the two computer-based learning tasks in exactly the same way as on day 1. This time, however, participants completed only a single test trial for each of the two virtual navigation tasks. Finally, participants retrieved the route through the psychology building. Incorrect turns were counted as errors and, together with the time needed to retrieve the route, taken as indicators of retention performance.

### 2.4. Statistical analysis

Physiological and subjective measurements as well as learning performance were analyzed by means of mixed-design ANOVAs,

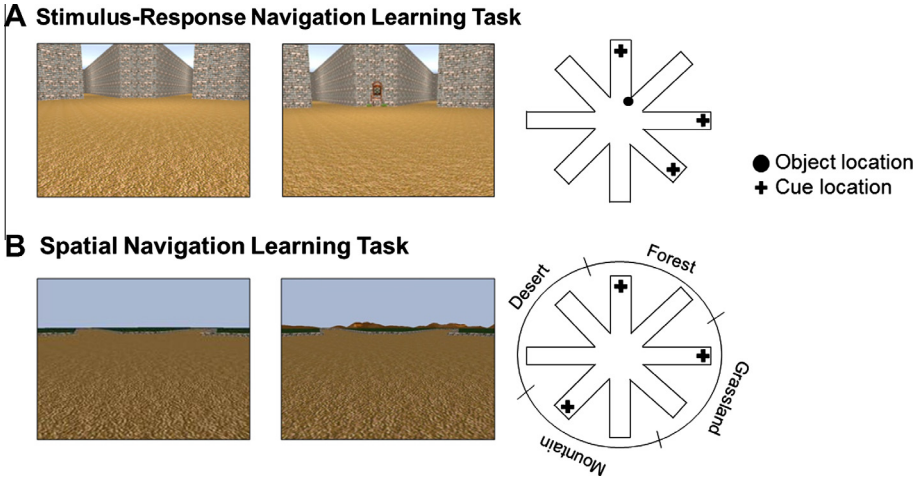


**Fig. 1.** Learning Tasks. (A) Stimulus–response (S–R) navigation learning task: center platform with four out of the eight radiating arms and scheme of the radial maze including the intra-maze cue (circle) and the object locations (cross); (B) Spatial navigation learning task: center platform with four out of the eight radiating arms and two surrounding environments (grassland and desert) and scheme of the radial maze with the location of the cues (circle) as well as the position of the four different environments (mountains, grassland, desert and forest). Parts of Fig. 1A have been reproduced from Guenzel et al., 2013, with permission from Elsevier.

follow-up ANCOVAs and *t*-tests. All analyses were performed with SPSS (version 20, IBM); all reported *p*-values are two-tailed.

## 3. Results

### 3.1. Effectiveness of stress induction

The subjective and physiological measurements confirmed that the stress induction by the SECPT was successful

#### 3.1.1. Subjective measurements

Group × sex ANOVAs indicated that the exposure to the SECPT was experienced as more unpleasant, stressful, and painful than the exposure to the control condition (main effects group: all $F > 45.84$; all $p < .01$; all $\eta^2 > .43$; Table 1). Moreover, the evaluation of the stressfulness and unpleasantness of the stressor differed between men and women (sex × group interaction effects: both $F > 4.18$; both $p \leqslant .05$; both $\eta^2 < .12$): women experienced the stress manipulation as significantly more stressful ($t_{(25.13)} = -2.53$; $p = .02$) and unpleasant ($t_{(30)} = -2.91$; $p = .01$) than men.

#### 3.1.2. Systolic and diastolic blood pressure

Systolic and diastolic blood pressure were significantly increased during the SECPT but not during the control manipulation (group × time point of measurement interaction for systolic and diastolic blood pressure: both $F > 13.77$; both $p < .01$; both $\eta^2 > .18$; Table 1). Although men had overall a higher systolic blood pressure than women (main effect sex for the systolic blood pressure: $F_{(1,59)} = 18.72$; $p < .01$; $\eta^2 = .24$; main effect sex for the diastolic blood pressure: $F_{(1,59)} = 0.45$; $p = .51$; $\eta^2 = .01$), there were no sex differences in the blood pressure response to the stressor (interaction effect time × group × sex for the systolic and diastolic blood pressure: both $F < 0.73$; both $p > .45$; both $\eta^2 < .02$).

#### 3.1.3. Salivary cortisol concentrations

Salivary cortisol was significantly increased in response to the stressor but not in response to the control manipulation (time point of measurement × group interaction effect: $F_{(2.12,125.27)} = 5.92$; $p < .01$; $\eta^2 = .09$; Fig. 2). Peak cortisol levels were reached 20 min after the stressor exposure, when the learning session started. Men and women did not differ in their cortisol responses to the stressor (main effect sex and all interaction effects including the factor sex: all $F < 1.36$; all $p > .24$; all $\eta^2 < .03$).

Post-hoc tests for the different time points of measurement indicated a significant difference in salivary cortisol concentration between the stress and control groups 20 min after stressor exposure for men ($t_{(20.84)} = 2.05$; $p = .05$) and at trend-level for women ($t_{(29)} = 1.69$; $p = .10$). Thirty-five and fifty minutes after the stressor, cortisol concentrations were not significantly elevated any more (all $p > .20$).

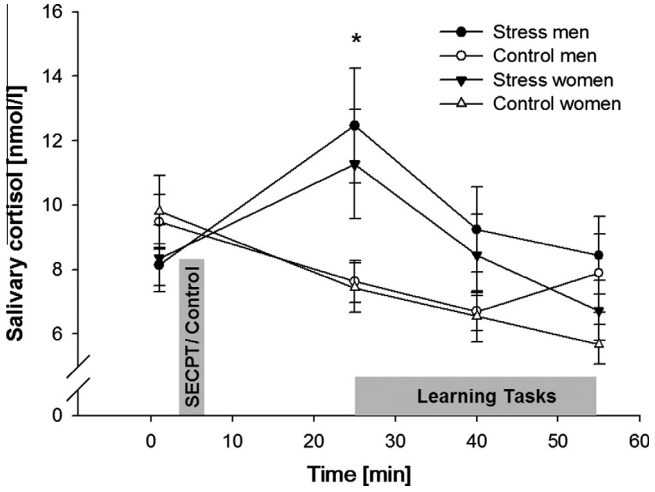


**Fig. 2.** Salivary cortisol concentrations across the experiment in men and women of the stress and control groups, respectively. The grey bars indicate the beginning and duration of the SECPT/control condition and the learning tasks, respectively. *$p = .05$ for men.

Although groups did not differ in their baseline cortisol concentrations on day 1 ($F_{(1,61)} = 1.59$; $p = .21$; $\eta^2 = .03$), before retention testing on day 2, participants of the stress group had lower cortisol concentrations (6.67 ± 0.46 nmol/l) than those in the control group (9.40 ± 1.07 nmol/l; $F_{(1,61)} = 5.63$; $p = .02$; $\eta^2 = .09$).

### 3.2. Spatial and S–R learning on day 1

#### 3.2.1. Virtual S–R navigation learning task

On average, participants needed 5.16 trials to reach the learning criterion of two error free trials in a row. Men and women did not differ in the number of learning trials that was required ($p = .33$). Stressed participants, however, tended to need more trials to reach the criterion than control participants (stress group: 5.41 trials; control group: 4.90 trials; $p = .07$).

Twenty-eight participants (stress group: 17, control group: 11) failed to reach the learning criterion of two error free trials in a

**Table 1**
Subjective and physiological data of the stress and control group.

| | Stress group | | | Control group | | |
|---|---|---|---|---|---|---|
| | Total | Men | Women | Total | Men | Women |
| *Subjective ratings* | | | | | | |
| Unpleasentness | 64.06 ± 4.66** | 51.88 ± 6.21** | 76.25 ± 5.62** | 13.23 ± 4.18 | 16.88 ± 6.31 | 9.33 ± 5.47 |
| Stressfulness | 45.00 ± 4.28** | 35.00 ± 4.18** | 55.00 ± 6.71** | 10.97 ± 3.02 | 11.25 ± 3.75 | 10.67 ± 4.92 |
| Painfulness | 64.69 ± 3.91** | 56.88 ± 4.98** | 72.50 ± 5.52** | 7.42 ± 2.78 | 6.25 ± 2.87 | 8.67 ± 4.96 |
| *Systolic blood pressure [mmHg]* | | | | | | |
| Pre treatment | 122.43 ± 3.77 | 135.83 ± 5.24 | 109.02 ± 2.73 | 127.49 ± 2.63 | 131.04 ± 2.14 | 123.71 ± 4.83 |
| During treatment | **136.73 ± 3.80**** | **149.06 ± 4.87*** | **124.40 ± 3.95** | 127.25 ± 2.91 | 132.17 ± 2.53 | 122.00 ± 5.15 |
| Post treatment | 121.60 ± 3.11 | 132.54 ± 4.33 | 110.67 ± 2.29 | 123.92 ± 2.54 | 124.17 ± 2.58 | 123.67 ± 4.57 |
| *Diastolic blood pressure [mmHg]* | | | | | | |
| Pre treatment | 75.91 ± 2.63 | 81.73 ± 4.17 | 70.08 ± 2.57 | 80.62 ± 2.42 | 78.58 ± 2.59 | 82.80 ± 4.19 |
| During treatment | **90.56 ± 2.96**** | **94.92 ± 3.75**** | **86.21 ± 4.43** | 82.01 ± 2.65 | 80.52 ± 2.56 | 83.60 ± 4.81 |
| Post treatment | 76.68 ± 1.91 | 80.52 ± 2.48 | 72.83 ± 2.64 | 79.46 ± 2.71 | 75.77 ± 2.78 | 83.40 ± 4.64 |

Data represent mean ± SEM.
**Bold** – Significant change compared to pre- and post-measurements ($p < .05$).
* $p < .05$ Compared to the control group.
** $p < .01$ Compared to the control group.

row. However, groups did not significantly differ in the number of 'learners' and 'non-learners' ($p = .27$). In order to compare the learning performance between experimental groups, the last three learning trials of each participant were used for further statistical analysis. A trial × group × sex ANOVA showed that the time needed to complete a trial (main effect trial: $F_{(2,\ 18)} = 24.48$; $p < .01$; $\eta^2 = .29$) as well as the number of errors made per trial ($F_{(1.80,106.39)} = 25.88$; $p < .01$; $\eta^2 = .31$) decreased significantly across trials and for both experimental groups in a comparable way (main effect group and trial × group interaction for both the time needed and the errors: all $F > .26$; all $p > .52$; all $\eta^2 < .02$; Fig. 3).

Irrespective of the experimental group, men outperformed women both with respect to the time needed to complete a trial and the number of errors made (main effects sex: both $F > 9.84$; both $p < .01$, both $\eta^2 < .31$; all interaction effects with the factor sex: all $F < 1.28$; all $p > .27$; all; $\eta^2 < .03$).

### 3.2.2. Spatial navigation learning task in the virtual environment

Similar as in the S–R navigation learning task, participants needed on average 5.13 trials to complete the spatial navigation learning task. The number of trials needed to learn the task did not differ between the experimental groups ($p = 1.00$), nor between men and women ($p = .73$). However, 37 participants (stress group: 18; control group: 19) did not reach the learning criterion of two error-free trials in a row. The number of 'learners' and 'non-learners' did not differ between the experimental groups ($p = .61$). A trial × group × sex ANOVA, conducted for the last 3 learning trials of the participants, showed that the time needed to complete a trial ($F_{(1.79,105.50)} = 12.86$; $p < .01$; $\eta^2 = .18$) as well as the number of errors per trial ($F_{(1.76,103.87)} = 13.38$; $p < .01$; $\eta^2 = .19$) decreased across these trials without any differences between the experimental groups (main effect group and trial × group interaction for the time needed and the number of errors: all $F < 1.02$; all $p > .35$; all $\eta^2 < .03$; Fig. 4), indicating that the learning performance in the spatial navigation task was not influenced by the SECPT.

Moreover, although men completed the learning trials faster than women (main effect sex for the time needed: $F_{(1,59)} = 8.12$; $p = .01$; $\eta^2 = .12$; all interaction effects with the factor sex for the time needed: all $F < 1.24$; all $p > .28$; all $\eta^2 < .03$), stress did not affect the learning performance of men and women differently (interaction effect sex × group: $F_{(1,59)} = .03$; $p = .87$; $\eta^2 < .01$).

## 3.3. Memory of the spatial and S–R tasks on day 2

### 3.3.1. S–R navigation learning task in the virtual environment

As shown in Fig. 3, the retention performance in the single test trial of the S–R navigation learning task was similar in the two

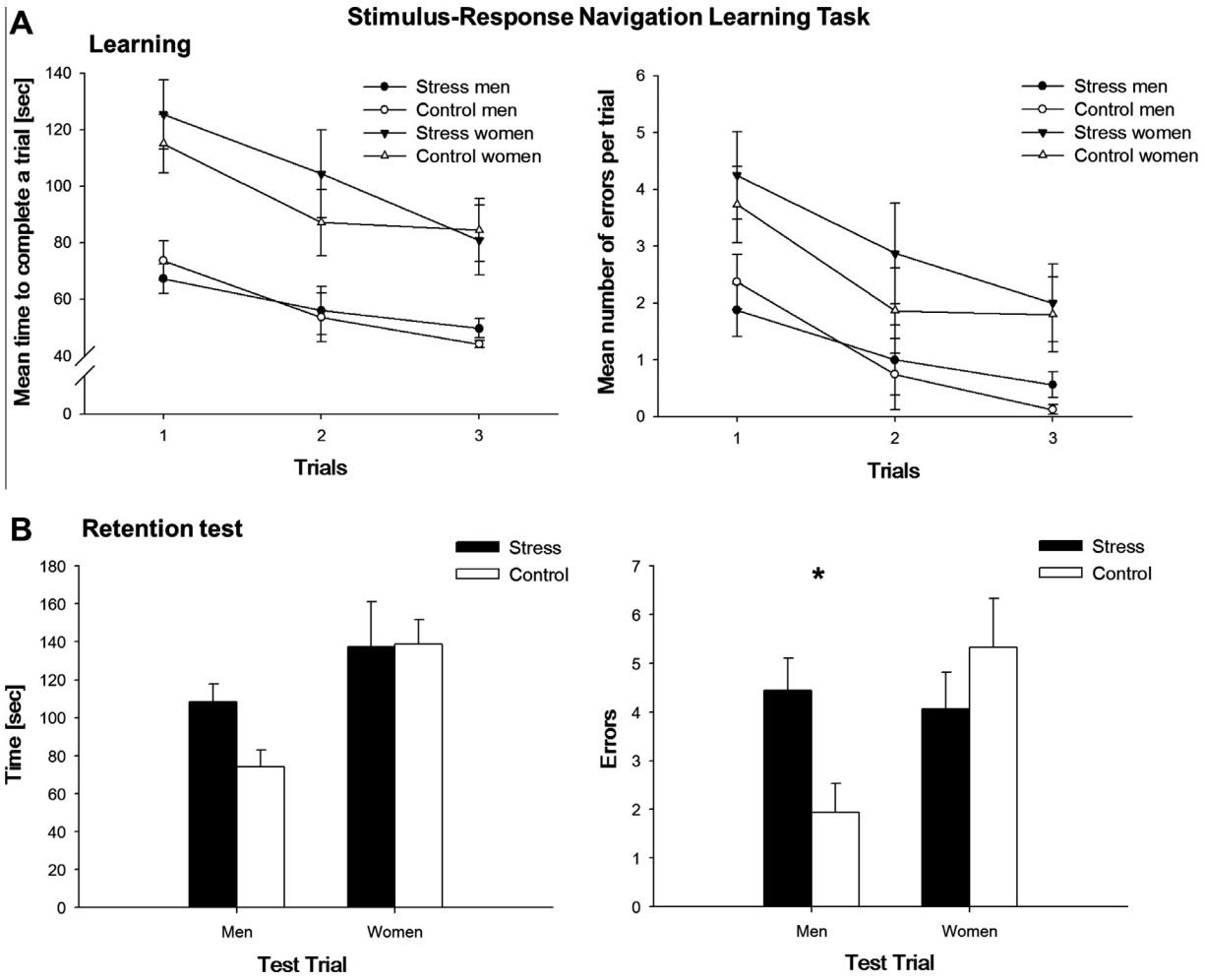


**Fig. 3.** Performance in the S–R navigation task. (A) The time needed (left) and the errors made (right) decreased across the learning trials of the S–R task similarly in men and women of the experimental groups (shown are the last three learning trials of the S–R task). (B) The time needed (left) and the errors made (right) in the test trial of the second experimental day. The time needed (left) was comparable between men and women of the experimental groups. The errors made, however, differed between men and women of the experimental groups: stress impaired retention performance in men, but not in women. Data represent the mean ± SEM.*$p = .01$.

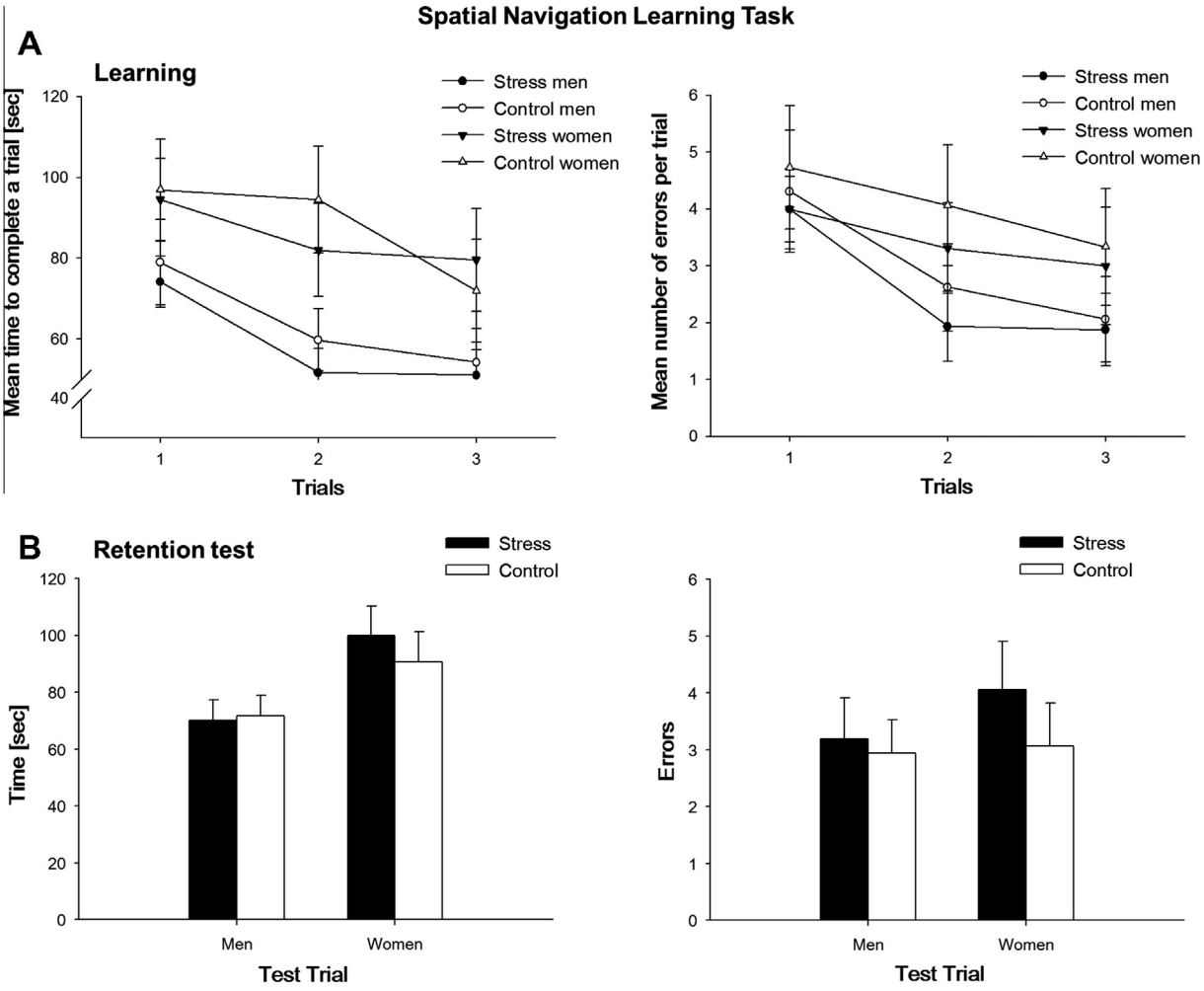


**Fig. 4.** Performance in the virtual spatial navigation learning task (A) The time needed (left) and the errors made (right) decreased across the learning trials of the computer-based spatial navigation learning task similarly in men and women of the experimental groups (shown are the last three learning trials). (B) The time needed (left) and the errors made (right) during the retention test trial were comparable between men and women of the experimental groups. Data represent the mean ± SEM.

experimental groups (main effect group for the time needed and the errors: both $F > .65$; both $p > .27$; both $\eta^2 < .03$). However, a significant sex × group interaction effect showed that stress before learning affected the retention performance of men and women in the test trial differently (for errors made: $F_{(1,59)} = 6.17$; $p = .02$; $\eta^2 = .10$), with stress impairing S–R memory in men ($t_{(30)} = 2.82$; $p = .01$) but not in women ($t_{(29)} = -1.02$; $p = .32$; sex × group interaction for the time needed to complete a trial $F_{(1,59)} = 1.40$; $p = .24$; $\eta^2 = .02$). Post-hoc tests indicated that men outperformed women in the control condition (for the time needed and the errors made: both $p \leqslant .01$), whereas there were no sex differences after stress, indicating that stress equalized S–R memory performance in men and women. A sex × group ANCOVA with baseline cortisol levels of the second day as covariate showed that the lower cortisol levels in the stress compared to the control group before testing did not influence the differential effect of stress in men and women for the errors made (interaction effect sex × group for the errors: $F_{(1,58)} = 5.79$; $p = .02$; $\eta^2 = .09$), nor did it affect the performance of men and women for the time needed to solve the test trial (interaction effect sex × group for the time: $F_{(1,58)} = 1.26$; $p = .27$; $\eta^2 = .02$).

Because men outperformed women on day 1 with respect to the number of errors made, we analyzed in a next step the impact of stress on retention performance in men and women relative to the performance in the last learning trial on day 1. To this end, we performed an ANOVA with the factors group, sex and testing day (last learning trial vs. single retention test trial). This analysis showed that the performance decreased from the last learning trial to the testing day, across groups and sexes (main effect testing day for the errors made: $p < .01$). More importantly, however, this analysis yielded also a significant testing day × sex × group interaction (for the errors: $F_{(1,59)} = 5.32$; $p = .03$; $\eta^2 = .08$), indicating that men of the stress group made more errors than men of the control condition during the retention test but not at the end of the learning session (main effect group and testing day × group interaction effect for men: both $F > 4.94$; $p \leqslant .03$; $\eta^2 > .13$), whereas the retention performance of women was not influenced by stress, neither on day 1 nor on day 2 (main effect group and testing day × group interaction effect for women: both $F < 1.44$; both $p > .23$; both $\eta^2 < .06$).

Because men and women differed also in their subjective experience of the SECPT and in their blood pressure response to the stressor, we tested in further analyses whether the differential effect of stress before learning on subsequent memory in men and women for the errors made was due to the differences in the subjective and physiological stress response. Separate sex × group ANCOVAs with either the subjective ratings, cortisol measurements of the first testing day or systolic and diastolic blood pressure as covariates, showed similar results after controlling for the subjective ratings (interaction effect sex × group for the errors: $F_{(1,56)} = 4.08$; $p = .05$; $\eta^2 = .07$), the cortisol measurements (interaction effect sex × group for the errors: $F_{(1,55)} = 5.18$; $p = .03$; $\eta^2 = .09$)

and the blood pressure measurements (interaction effect sex × group for the errors: $F_{(1,53)} = 3.13$; $p = .08$; $\eta^2 = .06$). However, after including all covariates (the subjective, blood pressure and cortisol measurements) in one ANCOVA the results changed (interaction effect sex × group for the errors: $F_{(1,46)} = 0.96$; $p = .33$; $\eta^2 = .02$), suggesting that the different effects of stress on S–R memory in men and women were at least partly owing to sex differences in the sympathetic nervous system and hypothalamus-pituitary adrenal axis responses to the stressor.

*3.3.2. Spatial navigation learning task in the virtual environment*

A sex × group ANOVA showed that the retention performance in the spatial navigation task was not significantly affected by stress (main effect group for the time needed and the errors: all $F > .17$; all $p > .39$; all $\eta^2 < .02$; Fig. 4), nor did stress affect the performance of men and women differently (interaction effect sex × group for both the time needed and the errors: $F > .25$; $p > .54$; $\eta^2 < .02$). However, overall men completed the test trial faster than women (main effect sex: $F_{(1,59)} = 7.36$; $p = .01$; $\eta^2 = .11$).

*3.3.3. Spatial learning task in the real environment*

A sex × group ANOVA revealed that participants who were stressed before learning made significantly more mistakes (main effect group: $F_{(1,59)} = 6.37$; $p = .01$; $\eta^2 = .10$) and tended to need longer to retrieve the correct route through the real-life environment (main effect group: $F_{(1,59)} = 3.28$; $p = .08$; $\eta^2 = .05$) than participants of the control condition (Fig. 5).

However, a significant sex × group interaction indicated that this impairing effect of stress was mainly due to impaired performance after stress in women (for the errors: $F_{(1,59)} = 5.68$; $p = .02$; $\eta^2 = .09$; and for the time needed: $F_{(1,59)} = 3.18$; $p = .08$; $\eta^2 = .05$): women of the stress group made more errors than women of the control group ($t_{(27.05)} = 3.70$; $p < .01$), whereas stress did not affect the retention performance of men ($t_{(24.41)} = .09$; $p = .93$). A similar pattern of results was found for the time needed to retrieve the correct route: women of the stress group needed longer to retrieve the way than women of the control group ($t_{(29)} = 2.21$; $p = .04$), whereas the retention performance of men ($t_{(25.70)} = .02$; $p = .98$) was not affected.

In addition, a sex × group ANCOVA with baseline cortisol levels of day 2 as covariate showed that controlling for group differences in cortisol levels of the second day did not affect the differential effects of stress in men and women (interaction effect sex × group for the errors: $F_{(1,58)} = 5.62$; $p = .02$; $\eta^2 = .09$; interaction effect sex × group for the time needed: $F_{(1,58)} = 3.21$; $p = .08$; $\eta^2 = .05$).

Again, we pursued the differential stress effect in men and women by ANCOVA analyses including the subjective ratings, cortisol measurements of day 1 and the systolic and diastolic blood pressure as covariates, in order to assess whether the sex differences in the impact of stress were owing to differences between men and women in the subjective and autonomic stress response. The previously reported results remained after including the subjective, blood pressure, and cortisol measurements as covariates in one ANCOVA (interaction effect sex × group for the errors: $F_{(1,46)} = 4.98$; $p = .03$; $\eta^2 = .10$).

## 4. Discussion

The present experiment addressed two questions: (i) whether stress before learning affects S–R memory formation in humans, and (ii) whether the potential stress effects on S–R learning and memory differ between men and women. In order to contrast the impact of stress on S–R learning with those on hippocampus-dependent spatial learning, we exposed participants to a stressor before they completed an S–R and two spatial learning tasks, which are known to rely on the striatum and hippocampus, respectively (Bohbot et al., 2007; Iaria et al., 2003). Our data showed sex-dependent effects of stress on the retention performance in the virtual S–R learning task and the spatial navigation task in the real environment. For the S–R learning task, stress before learning impaired the subsequent memory in men but not in women. Because men outperformed women under control conditions, stress thus equalized S–R memory performance in men and women. In the spatial task, however, stress before learning reduced subsequent retention in women but not in men.

To date, studies on the effects of stress on memory focused mainly on hippocampus-dependent memory processes. Recent evidence, however, showed that stress alters also striatum-dependent S–R memory processes. Post-learning injection of glucocorticoids enhanced the consolidation of an S–R task in rats (Quirarte et al., 2009), whereas stress prior to retention testing impaired the retrieval of S–R memories in humans (Guenzel et al., 2013). Our present data extend these previous findings by showing that stress may affect S–R memory also when induced shortly before learning. Based on the present data, it remains unclear whether stress affected mainly the encoding or the consolidation of S–R memories because stress effects on these processes can hardly be disentangled if participants are stressed before learning. Rodent data, however, showed that glucocorticoids after learning, affecting consolidation but not encoding, enhance S–R memory (Quirarte et al., 2009). Thus, even though species differences or an influence of other stress mediators cannot be ruled out, the present finding that pre-learning stress disrupted subsequent S–R memory might suggest that the observed effects of stress were at least partly

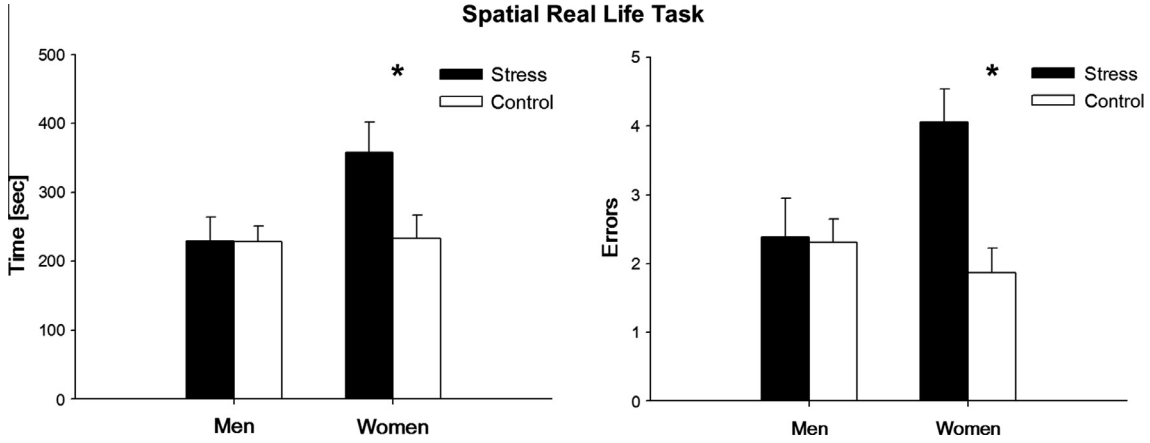


**Fig. 5.** Performance in the spatial task in the real environment. Stress impaired spatial retention performance in women both with respect to the time needed and the number of errors made. Performance of men, however, was unaffected by stress. Data represent mean ± SEM. $^*p \leqslant .05$.

due to altered memory encoding, as is also suggested by the increased number of learning trials in the S–R task after stress.

The stress-induced S–R memory impairment, however, was found only in men, not in women. Given that stress before retention testing affected memory in men and women in a similar manner (Guenzel et al., 2013), the sex-dependent effects on S–R memory seem to be specific for memory formation. In contrast to S–R memory, spatial memory formation was affected by stress in women but not in men. The observed impairment of spatial memory after stress (in women), is in line with studies reporting that stress impairs hippocampus-dependent memories (Elzinga et al., 2005; Kirschbaum et al., 1996; but see Schwabe, Bohringer et al., 2008; Smeets et al., 2007 for enhancing effects of pre-learning stress). Sex-dependent effects of stress on memory have been reported before, particularly for hippocampus-dependent memory (Andreano & Cahill, 2006; Cahill, 2005; Conrad et al., 2004; Luine, 2002). Some of these studies yielded findings that might seem to be in conflict with the present findings. For example, it has been shown that stress may enhance hippocampus-dependent memory in men but not in women (Andreano & Cahill, 2006; Cahill, 2005) or that acute stress may impair memory in male but not in female rats (Conrad et al., 2004). Part of these discrepancies may be explained by different tasks that were used or by species differences. More importantly, however, some of the studies that yielded different findings exposed subjects to stress after learning (Andreano & Cahill, 2006) or to chronic stress (Luine, 2002) and it is well-known that stressor timing and stressor duration have a critical impact on the nature of stress effects on memory (Schwabe, Wolf, & Oitzl, 2010). The present study is, to the best of our knowledge, the first that contrasted the effects of acute stress before learning on spatial and S–R memory in men and women. Together with these previous studies, our findings indicate that the impact of stress on learning and memory may be different in men and women, although not all studies found such sex differences (Payne et al., 2007; Schwabe, Bohringer et al., 2008; Schwabe & Wolf, 2009; Smeets et al., 2008).

Moreover, it is generally assumed, that such sex differences in the impact of stress on hippocampus-dependent learning and memory are related to different concentrations of sex hormones (Andreano, Arjomandi, & Cahill, 2008). Sex hormones are known to affect the (endocrine) response to stress (Kajantie & Phillips, 2006; Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Kudielka & Kirschbaum, 2005). Indeed, men tended also in the present study to show stronger physiological responses to the stressor than women and these differences could explain, at least for the S–R task, partly the different effects of stress in men and women. In addition, sex hormones may also contribute to a differential development and functioning of brain structures that are critical for learning and memory such as the hippocampus and the amygdala (Cahill, 2006). For example, it has been shown that males and females differ in hippocampal long-term potentiation (LTP) (long-lasting LTP in males, short-term potentiation in females) and that these sex-dependent LTP differences influence contextual learning (Maren, De Oca, & Fanselow, 1994). Sex hormones are critically involved in these sex differences. For instance, hippocampal LTP patterns vary across the estrous cycle (Warren, Humphreys, Juraska, & Greenough, 1995) and estradiol enhances hippocampal LTP in males (Foy, Baudry, & Thompson, 2004). Furthermore, estradiol was also shown to influence (chronic) stress effects on spatial memory processes (Bowman, Ferguson, & Luine, 2002). Moreover, the structure of the dentate gyrus and the CA3 region differs between males and females (Roof & Havens, 1992) and these differences have been related to the action of testosterone (Roof & Havens, 1992). Together, these findings emphasize that future studies are required to measure or experimentally manipulate sex hormone concentrations in order to assess their role in sex-dependent effects of acute stress on hippocampal and non-hippocampal forms of memory.

It is important to note that the spatial memory impairment in women was observed in the spatial task in the real environment but not in the virtual spatial navigation task. Although both tasks required spatial learning, they differed in several aspects, for example, with respect to their motor and sensory characteristics. The computer-based navigation learning task was rather simple and provided an overview of the whole virtual environment. The real life task, however, was more complex and provided no overview of the environment. Moreover, real life and virtual environments differ in their complexity and in the way participants are able to combine distances with external landmarks (Andreano & Cahill, 2009; Cahill, 2005). In addition, movements of the whole body were required in the real but not in the virtual environment and hence the real life navigation task was associated with higher locomotor activity. Interestingly, locomotion has been associated with hippocampal activity (Ghaem et al., 1997; Jahn et al., 2004). Thus, it is tempting to speculate that we obtained an effect of stress in the real life navigation task (and not in the virtual spatial navigation task) because this task was associated with higher involvement of the hippocampus, which is particularly sensitive to stress (hormone) effects (Joëls, Pu, Wiegert, Oitzl, & Krugers, 2006; Lupien & Lepage, 2001).

The present data on the influence of stress on spatial and S–R memory may also have some implications for the reported impact of stress on the relative engagement of multiple memory systems (for reviews see Packard & Goodman, 2012; Schwabe, 2013; Schwabe & Wolf, 2013). More specifically, it has been shown in humans and rodents that stress may promote a shift from hippocampus-dependent to dorsal striatum-dependent memory (Kim, Lee, Han, & Packard, 2001; Schwabe, Schächinger, de Kloet, & Oitzl, 2010; Schwabe et al., 2007). This shift is supposed to be due to differential stress effects on the hippocampus and dorsal striatum, which allows the latter to dominate learning and memory (Schwabe, 2013). If stress impairs spatial but not S–R memory in women, whereas the opposite pattern of results is found in men, this might suggest that women are more susceptible to the shift from hippocampal to striatal memory after stress. Rodent studies on stress and multiple memory systems included only male animals and in human studies sex differences were not explicitly tested. Examining potential sex differences in the modulatory effect of stress on the engagement of multiple memory systems is a challenge for future studies, particularly because the stress-shift from hippocampal to striatal memory has been related to psychiatric disorders that have a different prevalence in men and women (Goodman, Leong, & Packard, 2012; Schwabe, Wolf et al., 2010).

Finally, two potential limitations of the present study have to be addressed. First, although we did not test women during their menses and excluded women taking hormonal contraceptives, we did not assess the menstrual cycle phase. For stress effects on memory consolidation, there is some evidence that the phase of the menstrual cycle is crucial for stress effects on memory (Andreano & Cahill, 2006; Andreano et al., 2008) and future studies on potential sex differences in stress effects on memory should also control for the cycle phase.

Second, although we counterbalanced the order of the virtual S–R and spatial navigation tasks, for reasons of practicality, the spatial navigation task in the real environment was always presented at the end. Thus, cortisol concentrations have most likely been lower during the spatial navigation task in the real environment than during the other two tasks. It is, however, important to note that we obtained a significant stress effect in this task (at least in women) and that the direction of this effect was in line with previous findings on the effect of stress or glucocorticoids on spatial memory (Diamond et al., 2006; Kirschbaum et al., 1996).

To conclude, we observed here sex-dependent effects of stress before learning on striatum-dependent S–R and hippocampus-dependent spatial memory processes. These results underline that participants' sex should be taken into account when investigating stress effects on both memory systems. Moreover, these findings may be relevant within the context of psychiatric disorders, such as phobia, addiction or post-traumatic stress disorder (PTSD), which have been related to abnormal S–R memory processes (Goodman et al., 2012; Schwabe, Wolf et al., 2010). Given that these disorders are often accompanied by a dysfunction of the body's major stress response systems, unraveling how exactly stress may alter striatum-based S–R learning, may have important clinical implications.

## Conflict of interest

None of the authors has any conflicts of interest.

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