



## 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.

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### 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<sup>2</sup>,  $SEM = 0.28$  kg/m<sup>2</sup>). 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

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