Psychoneuroendocrinology (2013) **38**, 1460—1465

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

SHORT COMMUNICATION

Stress disrupts response memory retrieval

Friederike M. Guenzel [a,b], **Oliver T. Wolf** [a,b], **Lars Schwabe** [a,*]

[a] *Institute of Cognitive Neuroscience, Department of Cognitive Psychology, Ruhr-University Bochum, Universitaetsstrasse 150, 44780 Bochum, Germany*

[b] *International Graduate School of Neuroscience (IGSN), Ruhr-University Bochum, Universitaetsstrasse 150, 44801 Bochum, Germany*

Received 31 October 2012; received in revised form 13 December 2012; accepted 14 December 2012

KEYWORDS
Stress;
Glucocorticoids;
Memory;
Memory retrieval;
Striatum

Summary Stress effects on memory are well-known. Most studies, however, focused on the impact of stress on hippocampus-dependent 'declarative' memory processes. Less is known about whether stress influences also striatum-based memory processes, such as stimulus—response (S—R) memory. First evidence from rodent experiments shows that glucocorticoid stress hormones may enhance the consolidation of S—R memories. Whether stress affects also S—R memory retrieval remains largely elusive. Therefore, we tested in the present experiment in humans the effect of stress on the retrieval of S—R memories. Healthy men and women were trained to locate three objects in an S—R version of a virtual eight-arm radial maze. One week later, participants underwent a stressor or a control condition before their memory of the S—R task was tested. Our results showed that participants ($n = 43$) who were exposed to the stressor before retention testing made significantly more errors in this test trial, suggesting that stress impaired S—R memory retrieval. Moreover, high cortisol concentrations were associated with reduced S—R memory. These findings indicate that stress may affect memory retrieval processes in humans beyond hippocampal 'declarative' memory.

1. Introduction

Stressful experiences trigger a cascade of physiological changes, including the release of glucocorticoids and catecholamines. These stress mediators may modulate cognitive processes. Particularly, stress (hormone) effects on hippocampus-dependent 'declarative' learning and memory are well documented (Roozendaal et al., 2009; Schwabe et al., 2012). These effects may depend on the intensity of the stressor (Taverniers et al., 2010). Moreover, it is generally assumed that these stress effects are time-dependent, and that stress enhances the consolidation but impairs the retrieval of 'declarative' memories (De Quervain et al., 1998; Smeets et al., 2008; Roozendaal et al., 2009).

Whether and how, stress affects memory processes beyond hippocampus-dependent 'declarative' memory remains largely elusive. For decades, the predominant view held that stress has a specific and particularly strong influence on the hippocampus (Lupien and Lepage, 2001). There is, however, by now accumulating evidence that stress may also alter non-hippocampal, in particular striatal memory processes (Schwabe et al., 2010b). For example, recent rodent studies demonstrated that glucocorticoid injections

* Corresponding author. Tel.: +49 234 3229324; fax: +49 234 3214308.
E-mail address: Lars.Schwabe@ruhr-uni-bochum.de (L. Schwabe).

0306-4530/$ — see front matter
http://dx.doi.org/10.1016/j.psyneuen.2012.12.010

into the dorsal striatum directly after learning of a stimulus—response (S—R) or inhibitory avoidance task enhanced the consolidation of these tasks (Medina et al., 2007; Quirarte et al., 2009; Sánchez-Resendis et al., 2012). Whether stress may also alter the retrieval of consolidated S—R memories and whether stress affects S—R memories in humans remains largely elusive.

Therefore, our study examined the influence of stress on the retrieval of S—R memories in humans. Healthy participants were trained in an S—R navigation task in a virtual environment. Previous fMRI studies that used a very similar task demonstrated that such S—R navigation memory depends on the striatum and not on the hippocampus (Iaria et al., 2003; Bohbot et al., 2007). One week after training in the S—R task, participants underwent a stressor or a non-stressful control task before S—R memory was tested. Because stress hormones enhanced the consolidation of S—R memories (Quirarte et al., 2009) in a similar manner as the consolidation of declarative memories, we expected that stress effects on S—R memory retrieval would also resemble those on declarative memory retrieval, i.e., we predicted that stress would impair the retrieval of S—R memories.

2. Materials and methods

2.1. Participants

Sixty healthy, non-smoking students (30 men, 30 women; age: $M = 23.88$ years, SEM = .34 years; body-mass-index: $M = 22.73\ kg/m^2$, SEM = .30 kg/m^2) without a history of any neurological or psychiatric diseases, drug abuse or medication intake provided written informed consent for their participation in this study. We tested only women that were not taking hormonal contraceptives and women were not tested during their menses.

2.2. Procedure

Participants were tested in a between-subject design on two experimental days with an interval of one week: day 1, learning; day 2, stress (or control condition) and retention testing. In order to control for diurnal variations of cortisol, all testing took place in the afternoon between 13:00 and 18:00 h.

After participants' arrival at the laboratory on day 1, blood pressure measurements were taken and a single saliva sample was collected (see below). Before the training in the S—R learning task, participants completed two practice trials, in order to become familiar with navigating in a virtual environment. In these practice trials, participants were instructed to collect four objects in a computer-based 3D virtual room. All objects were inserted into wooden hollows and could be collected by using the left-, right- and forward-arrow keys. Afterwards, training in the S—R task started. In this task, participants were presented a 3D virtual 8-arm radial maze on a computer screen (Fig. 1A). Both, the computer-based virtual room for practice and the computer-based radial maze for S—R learning, were designed using a commercially available video game editor (Gamestudio, Conitec, Germany).

We designed the radial maze task to parallel the key features of radial maze tasks that have been used in rodents to examine S—R memory (McDonald and White, 1993). The radial maze consisted of eight identical arms originating from a center platform. Each maze-arm was surrounded by high walls and contained a wooden hollow at the end. Different objects (book, cake, and bag) were placed in three of these hollows and participants were instructed to collect these objects in a given order (book, cake, bag) as quickly as possible. The location of the objects was constant in all trials. Three learning trials were given, each with a maximum duration of 3 min. If participants made one or more errors in the last trial, up to three extra trials were given. The time to complete a trial and the errors per trial were (automatically) recorded for statistical analysis. Importantly, the eight maze arms looked exactly the same and no extra-maze cues were provided. There was just a single intra-maze cue (a chair) that could be used for orientation. Thus, participants could learn the location of the objects solely by linking the single intra-maze cue with a sequence of movements. Previous neuroimaging studies that used a very similar task design demonstrated that such "response" learning is dependent on the caudate nucleus (Iaria et al., 2003; Bohbot et al., 2007). Participants were not informed that memory for the S—R task would be tested on the second day.

On the second day, seven days after experimental day 1, participants were randomly assigned to the stress or control condition. Participants in the stress condition were exposed to the socially evaluated cold pressor test (SECPT), as described in detail elsewhere (Schwabe et al., 2008). Briefly, participants immersed their right hand up to and including the wrist for as long as possible (maximum 3 min) into ice water (0—2°). They were videotaped and observed by a non-reinforcing, unsociable experimenter. In the control condition, participants immersed their right hand up to and including the wrist for 3 min into warm water (35—37°). They were neither videotaped nor monitored by the experimenter.

In order to verify the successful stress induction by the SECPT, subjective and physiological measurements were taken at several time points before and after the stress and control condition, respectively. Immediately after the SECPT/control condition, participants rated on a scale from 0 ("not at all") to 100 ("very") how unpleasant, stressful and painful they had experienced the stress/control condition. Moreover, we collected saliva samples immediately before the stress/control condition (baseline), 20 min after the SECPT/control condition, i.e., immediately before the retention test, as well as 40 min after the SECPT/control condition. Saliva samples were collected with Salivette collection devices (Sarstedt, Nümbrecht, Germany) and stored at about −20°. The free fraction of the stress hormone cortisol was analyzed from saliva by means of an immunoassay (IBL, Hamburg). Interassay and intra-assay coefficients of variance were below 10%. Furthermore, we measured blood pressure with the Dinamap system (Critikon, FL) shortly before, during and, shortly after the stress/control condition.

After a 25 min-break during which subjects were allowed to read, retrieval of S—R memory was tested. Participants completed another trial of the S—R task. The radial maze was exactly the same as during training on day 1. Again, participants were instructed to collect the three objects as quickly as possible and in the same order as on day 1.

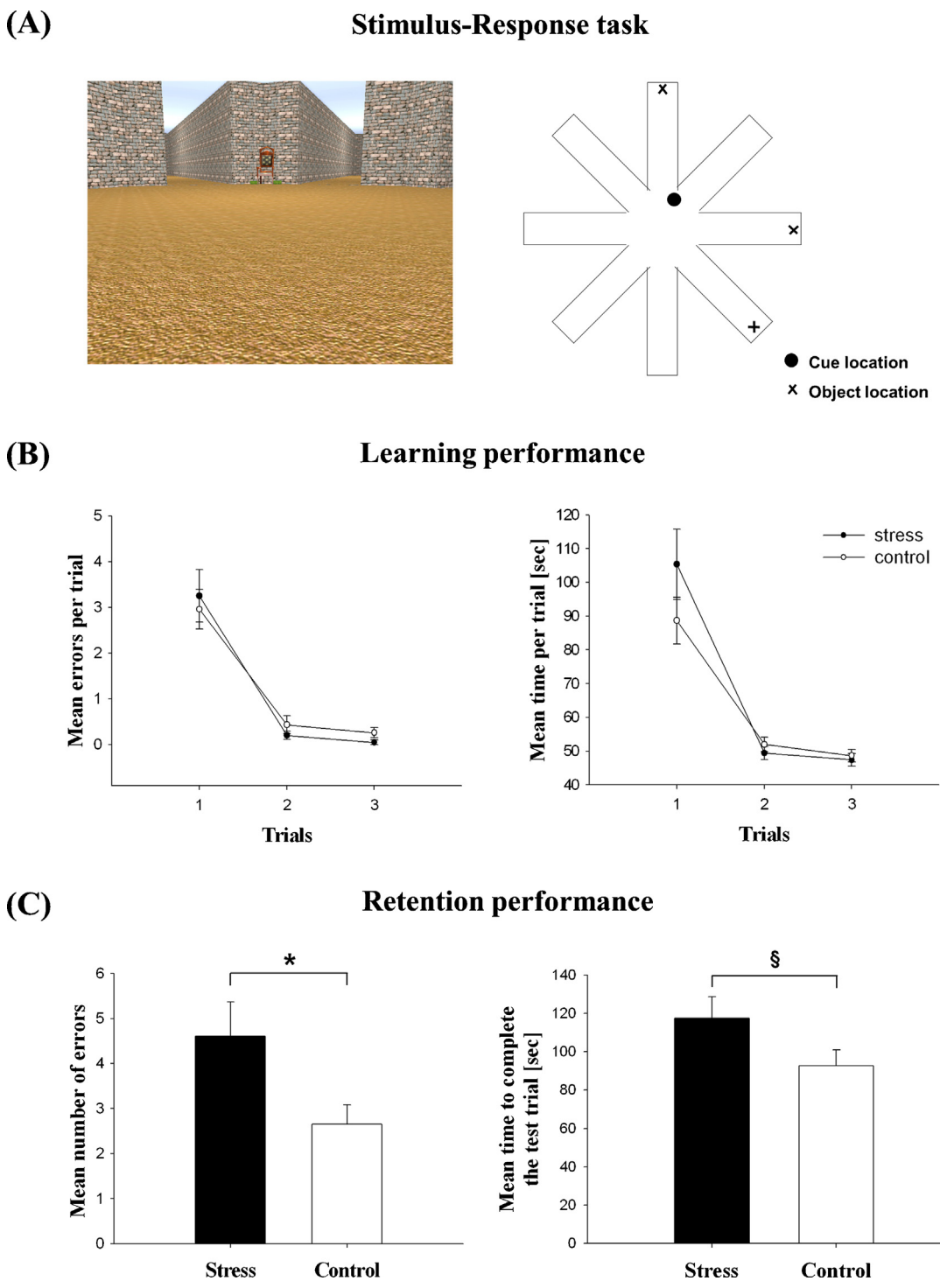

Figure 1 Stimulus—response (S—R) task, learning and retrieval performance. (A) Left: center platform with two maze-arms and the single intra-maze cue (chair) that could be used for orientation. Right: scheme of the 8-arm radial maze, including the single intra-maze cue (indicated by the filled circle) and the locations of the three objects that the participants should collect (indicated by the crosses). The starting position was at the center of the platform in all trials; the viewing direction however varied randomly. (B) Errors and the time needed to complete a trial decreased in both groups ($n = 43$; shown are the last 3 learning trials), indicating successful S—R learning. (C) Seven days after training, stressed participants made more errors ($^{*}p < .05$) and needed longer to complete the test trial ($^{\S}p = .12$) than participants in the control group. Data represent mean ± SEM.

Table 1 Subjective ratings, salivary cortisol as well as systolic and diastolic blood pressure measurements in the control and stress groups across the experiment.

	Control group	Stress group
Subjective ratings		
Unpleasentness	6.96 ± 3.35	51.50 ± 4.94**
Stressfullness	2.61 ± 1.44	43.00 ± 4.98**
Painfulness	1.30 ± 0.95	54.00 ± 5.59**
Salivary cortisol [nnmol/l]		
Day 1	11.08 ± 0.93	9.68 ± 1.38
Day 2, prestress	8.66 ± 0.76	9.38 ± 1.14
Day 2, 20 min post stress	7.34 ± 0.81	14.38 ± 1.97**
Day 2, 40 min post stress	6.59 ± 0.67	11.09 ± 1.17**
Systolic blood pressure [mmHg]		
Pre treatment	119.80 ± 2.84	116.67 ± 3.10
During treatment	115.96 ± 3.00	134.09 ± 3.64**
Post treatment	113.35 ± 2.61	117.73 ± 2.96
Diastolic blood pressure [mmHg]		
Pre treatment	66.38 ± 2.04	66.73 ± 1.74
During treatment	64.50 ± 1.83	81.93 ± 2.09**
Post treatment	64.39 ± 1.85	68.93 ± 1.92

Data represent mean ± SEM.
** $p < .01$.

3. Results

3.1. Day1: learning performance in the S–R task

Group × trial × sex mixed-design ANOVAs showed significant decreases in the number of errors (main effect trial: $F_{(1.58, 88.34)} = 12.33$, $p < .01$) and the time to complete a trial ($F_{(1.35, 75.85)} = 16.70$; $p < .01$) across trials, without any differences between groups (main effect group and group × trial interaction for errors and time to complete the task: all $F < 1.98$, all $p > .15$), thus suggesting successful learning in both groups. Irrespective of the experimental group, women needed longer to complete a trial than men (main effect sex: $F_{(1, 56)} = 12.46$; $p < .01$; all interaction effects with the factor sex: all $p > .17$).

Inspection of the individual data, however, revealed a subgroup of 17 participants who did not show any improvement across the learning session (main effect trial for errors and time to complete the task: both $F < .50$, both $p > .50$). These 17 "non-learners" made on average 5.88 errors in the last learning trial and needed almost 3 min to finish the last learning trial. The number of "non-learners" did not differ between the two experimental groups (stress: $n = 10$; control: $n = 7$; $\chi^2(1) = .74$, $p = .39$). However, there were more women ($n = 12$) than men ($n = 5$) who did not successfully acquire the task ($\chi^2(1) = 4.02$, $p < .05$). Because the present study examined stress effects on memory retrieval and an examination of retrieval performance requires robust learning, the "non-learners" were excluded from further statistical analysis.

The remaining 43 participants (stress group: 12 men, 8 women; control group: 13 men, 10 women) needed on average five trials (SEM = 0.16) to solve the task without errors. A group × trial × sex ANOVA for these "learners" indicated a significant improvement of performance across trials (main effect trials for number of errors: $F_{(1.13, 44.04)} = 57.84$; $p < .01$; main effect trials for time to complete a trial: $F_{(1.08, 42.17)} = 60.15$; $p < .01$), without any differences between groups (group and group × trial effects for number of errors and time to complete a trial: all $F < 2.66$, all $p > .10$; Fig. 1B). Male and female "learners" did not differ in their learning performance (main effect sex and all interaction effects with the factor sex: all $p > .09$).

3.2. Day2: subjective and physiological responses to the SECPT

Subjective and physiological measurements verified the successful stress induction by the SECPT. As shown in Table 1, participants in the stress group experienced the treatment as significantly more unpleasant, stressful, and painful than participants of the control condition (all $t > 7.62$, all $p < .01$). Similarly, a group × time point of measurement × sex ANOVA showed that salivary cortisol concentrations increased in response to the SECPT but not in response to the control condition (group × time point of measurement interaction: $F_{(1.23, 45.47)} = 10.14$, $p < .01$; Table 1). Peak cortisol levels were reached 20 min after the SECPT, when retention testing started. Participants' sex did not affect the cortisol response to the SECPT (all main or interaction effects: all $p > .36$).

Moreover, a group × time point of measurement × sex ANOVA for the blood pressure data revealed that systolic and diastolic blood pressure were elevated during the SECPT but not during the control condition (group × time point interaction for systolic and diastolic blood pressure: both $F > 45.01$, both $p < .01$; Table 1). Irrespective of the experimental group, men showed higher systolic blood pressure values during and after SECPT exposure than women (main effect sex: $F_{(1, 39)} = 4.90$, $p = .03$).

3.3. Day 2: retrieval of S–R memories after stress

Exposure to the SECPT 25 min before retention testing impaired the retrieval of S–R memories. As shown in

Fig. 1C, participants that were exposed to the SECPT made more errors ($F_{(1,\ 39)} = 4.16$; $p < .05$) and tended to need longer for the completion of the test trial ($F_{(1,\ 39)} = 2.56$; $p = .12$) compared to participants in the control condition.

Finally, peak salivary cortisol levels that were measured immediately before memory retrieval correlated significantly with the number of errors made in the test trial ($r = .32$; $p < .05$) as well as with the time needed to complete the test trial ($r = .31$; $p = .05$).

Stress effects on memory retrieval were not modulated by participants' sex (all main or interaction effects with the factor sex: all $p > .14$).

4. Discussion

Most previous research on the impact of stress on memory focused on hippocampus-dependent 'declarative' memory processes (Schwabe et al., 2012). Based on rodent data suggesting that glucocorticoids enhance striatal memory consolidation (Medina et al., 2007; Quirarte et al., 2009; Sánchez-Resendis et al., 2012), we asked in this experiment whether stress may influence S—R memory processes in humans as well. We exposed participants to a stressor before they retrieved an S—R memory task that is known to rely on the striatum (Iaria et al., 2003; Bohbot et al., 2007) and found that stress impaired the retrieval of S—R memories.

These findings extend recent rodent studies (Quirarte et al., 2009) in that they show that stress may not only affect the consolidation but also the retrieval of S—R memories. Moreover, this is, to the best of our knowledge, the first study demonstrating an effect of stress on S—R memory in humans. Glucocorticoids seem to play a critical role in the stress effects on S—R memory processes. In rodents, an injection of glucocorticoids into the dorsal striatum enhanced S—R memory consolidation. Here, we found a significant correlation between peak cortisol concentrations and S—R memory impairment. However, whether glucocorticoids alone are indeed sufficient to modulate S—R memory processes or whether simultaneous noradrenergic activity is required, as is the case for hippocampus-dependent memory (Roozendaal et al., 2006), needs to be addressed in future studies.

At first glance, the present finding that stress impairs S—R memory retrieval might appear to be in conflict with recent data showing that stress promotes a shift from hippocampus-dependent spatial to striatum-dependent S—R learning strategies (Kim et al., 2001; Schwabe et al., 2010a) and that this shift is not accompanied by impaired performance (Schwabe et al., 2007; Schwabe and Wolf, 2012). It is to be noted, however, that 'qualitative' changes in learning strategies after stress reflect most likely changes in the strength of two (or more) memory systems relative to one another and therefore do not necessarily implicate specific enhancements or impairments within a single memory system (Schwabe et al., 2010b). Moreover, in previous studies on the engagement of multiple memory systems stress was administered before learning whereas participants were exposed to stress before retention testing in the present study. These differences in stressor timing may explain these seemingly discrepant findings on striatal memory and further suggest that stress effects on striatum-dependent memory are, comparable to those on hippocampus-dependent memory (Roozendaal et al., 2009; Schwabe et al., 2010b), time-dependent.

In sum, we show here that stress before retention testing may impair the retrieval of S—R memories in healthy humans. Our findings provide further evidence that stress may affect memory processes beyond the hippocampus. Understanding the underlying neuroendocrine mechanisms and the temporal dynamics of these effects is a challenge for future research.

Role of funding sources

Funding for this study was provided by grants from the German Research Foundation (DFG, grant SCHW1357/2-2 and project B4 of Collaborative Research Center (SFB) 874 ''Integration and Representation of Sensory Processes''); the DFG had no further role in study design in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest

The authors report no conflict of interest.

Acknowledgements

We thank Patrick Friedrich and Florian Watzlawik for assistance during data collection and Tobias Otto for his technical assistance.

References

Bohbot, V.D., Lerch, J., Thorndycraft, B., Iaria, G., Zijdenbos, A.P., 2007. Gray matter differences correlate with spontaneous strategies in a human virtual navigation task. J. Neurosci. 38, 10078—10083.

De Quervain, D.J.-F., Roozendaal, B., McGaugh, J.L., 1998. Stress and glucocorticoids impair retrieval of long-term spatial memory. Nature 394, 787—790.

Iaria, G., Petrides, M., Dagher, A., Pike, B., Bohbot, V.D., 2003. Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: variability and change with practice. J. Neurosci. 23, 5945—5952.

Kim, J.J., Lee, H.J., Han, J.-S., Packard, M.G., 2001. Amygdala is critical for stress-induced modulation of hippocampal long-term potentiation and learning. J. Neurosci. 21, 5222—5228.

Lupien, S.J., Lepage, M., 2001. Stress, memory and the hippocampus: can't live with it, can't live without it. Behav. Brain Res. 127, 137—158.

McDonald, R.J., White, N.M., 1993. A triple dissociation of memory systems: hippocampus, amygdala, and dorsal striatum. Behav. Neurosci. 107, 3—22.

Medina, A.C., Charles, J.R., Espinoza-González, V., Sánchez-Resendis, O., Prado-Alcalá, R.A., Roozendaal, B., Quirarte, G.L., 2007. Glucocorticoid administration into the dorsal striatum facilitates memory consolidation of inhibitory avoidance training but not of the context or footshock components. Learn. Mem. 14, 673—677.

Quirarte, G.L., Ledesma de la Teja, I.S., Casillas, M., Serafín, N., Prado-Alcalá, R.A., Roozendaal, B., 2009. Corticosterone infused

into the dorsal striatum selectively enhances memory consolidation of cued water-maze training. Learn. Mem. 16, 586—589.

Roozendaal, B., Okuda, S., De Quervain, D.J.-F., McGaugh, J.L., 2006. Glucocorticoids interact with emotion-induced noradrenergic activation in influencing different memory functions. Neuroscience 138, 901—910.

Roozendaal, B., McEwen, B.S., Chattarji, S., 2009. Stress, memory and the amygdala. Nat. Rev. Neurosci. 10, 423—433.

Sánchez-Resendis, O., Medina, A.C., Serafín, N., Prado-Alcalá, R.A., Roozendaal, B., Quirarte, G.L., 2012. Glucocorticoid—cholinergic interactions in the dorsal striatum in memory consolidation of inhibitory avoidance training. Front Behav. Neurosci. 6, 1—8.

Schwabe, L., Wolf, O.T., 2012. Stress modulates the engagement of multiple memory systems in classification learning. J. Neurosci. 32, 11042—11049.

Schwabe, L., Oitzl, M.S., Philippsen, C., Richter, S., Bohringer, A., Wippich, W., Schachinger, H., 2007. Stress modulates the use of spatial versus stimulus—response learning strategies in humans. Learn. Mem. 14, 109—116.

Schwabe, L., Haddad, L., Schächinger, H., 2008. HPA axis activation by a socially evaluated cold-pressor test. Psychoneuroendocrinology 33, 890—895.

Schwabe, L., Schächinger, H., de Kloet, E.R., Oitzl, M.S., 2010a. Corticosteroids operate as switch between memory systems. J. Cogn. Neurosci. 22, 1362—1372.

Schwabe, L., Wolf, O.T., Oitzl, M.S., 2010b. Memory formation under stress: quantity and quality. Neurosci. Biobehav. Rev. 34, 584—591.

Schwabe, L., Joëls, M., Roozendaal, B., Wolf, O.T., Oitzl, M.S., 2012. Stress effects on memory: an update and integration. Neurosci. Biobehav. Rev. 36, 1740—1749.

Smeets, T., Otgaar, H., Candel, I., Wolf, O.T., 2008. True or false? Memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval. Psychoneuroendocrinology 33, 1378—1386.

Taverniers, J., Van Ruysseveldt, J., Smeets, T., von Grumbkow, J., 2010. High-intensity stress elicits robust cortisol increases, and impairs working memory and visuo-spatial declarative memory in special forces candidates: a field experiment. Stress 13, 323—333.