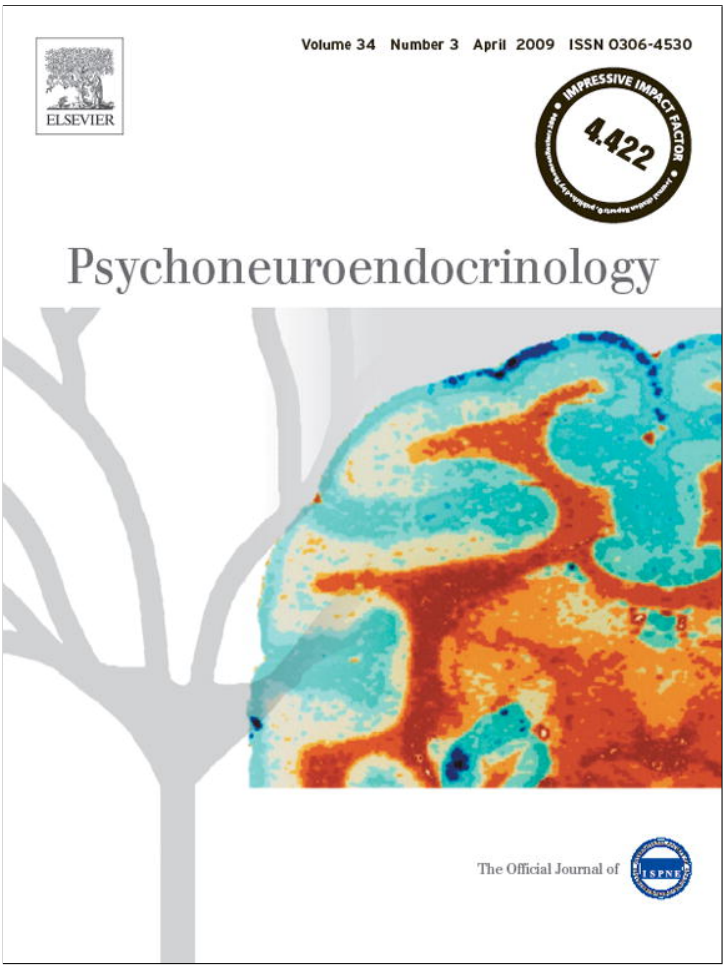

Psychoneuroendocrinology (2009) **34**, 358—366

available at www.sciencedirect.com

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

Modulation of spatial and stimulus—response learning strategies by exogenous cortisol in healthy young women

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Received 31 May 2008; received in revised form 24 September 2008; accepted 24 September 2008

KEYWORDS
Glucocorticoids;
Cortisol;
Multiple memory systems;
Spatial learning;
Stimulus—response learning

Summary Glucocorticoids (GCs) are known to influence learning and memory processes. While most studies focus on the effects of GCs on the performance *within* a single memory system, we asked whether GCs modulate also the transition *between* hippocampus-dependent spatial and caudate nucleus-dependent stimulus—response memory systems. Eighty-four young healthy women received a placebo, 5 or 30 mg hydrocortisone orally. One hour later, participants were asked to locate a win-card in a 3D model of a room. The card could be located via two strategies: spatial (multiple distal cues) and stimulus—response (a single proximal cue). Relocation of the proximal cue after 12 trials revealed the strategy, number of trials to learning criterion the performance. As expected, more trials were needed to acquire the task with hydrocortisone. Remarkably, hydrocortisone switched the use of learning strategies towards more spatial learning (dose-dependently: placebo 4% < 5 mg 21% < 30 mg 32%), independent of autonomic and subjective arousal. The learning curves of spatial and stimulus—response learners were comparable. Our results demonstrate that exogenous GCs prior to learning affect the performance within a memory system and also coordinate the use of multiple memory systems. Taking into account this dual action of GCs will contribute to a better understanding of stress (hormone) effects on learning and memory.

1. Introduction

Glucocorticoids (GCs; cortisol in humans) secreted by the adrenal cortex regulate metabolic, immunological and cardiovascular homeostasis as well as cognitive functions, such as memory (Lupien and McEwen, 1997; Sapolsky et al., 2000; de Kloet et al., 2005). Effects of stress- or pharmacologically induced GC elevations on memory depend critically on the

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doi:10.1016/j.psyneuen.2008.09.018

timing of GC activity. While GCs released around the time of learning enhance memory, memory performance is impaired when GCs are experienced out of the learning context (for a review: Joels et al., 2006).

Most studies that examined stress or GC effects on memory focused on changes in performance within a single memory system, mainly the hippocampus (Newcomer et al., 1994; Buchanan and Lovallo, 2001; Lupien et al., 2002; Abercrombie et al., 2003; Kuhlmann et al., 2005a; Roozendaal et al., 2006). However, it is important to note that memory is no unitary entity but consists of multiple anatomically and functionally distinct systems (White and McDonald, 2002; Squire, 2004). Two of these systems have been in the spotlight of the multiple memory systems literature: a hippocampus-dependent "cognitive" memory which has been associated with spatial learning and memory and a caudate nucleus-dependent "habit" memory that was related to stimulus–response (S–R) learning and memory (Packard and McGaugh, 1992; Kim et al., 2001; White and McDonald, 2002; Iaria et al., 2003; Bohbot et al., 2004). Though, both systems make distinct contributions to the optimization of behavior, they can interact both in a cooperative or competitive fashion (Poldrack and Packard, 2003; Voermans et al., 2004). This raises the question which factors determine in case of competition between memory systems the nature of interactions and the dominance of either system. Kim et al. (2001) suggested that stress plays a critical role in the modulation of multiple memory systems. They showed that stress prior to training in a water maze task led to a shift from predominant spatial to more S–R learning in rats. Similarly, Packard and Wingard (2004) reported that rats that were injected anxiogenic drugs predominantly displayed caudate nucleus-based S–R learning in a plus maze task, whereas vehicle-treated rats predominantly displayed hippocampus-based spatial learning. We translated these findings recently to humans and found that psychosocial stress modulated multiple memory systems in favor of caudate nucleus-dependent S–R learning and at the expense of hippocampus-dependent spatial learning in healthy men and women (Schwabe et al., 2007a). Moreover, we showed that S–R learning was most likely in the face of large cortisol increases. However, these increases in cortisol were confounded with other stress effects, such as autonomic and subjective arousal. Thus, this study allowed – same as the rodent studies cited above – no clear conclusion about the involvement of GCs in the modulation of spatial and S–R learning.

In the present study we examined whether the increase in cortisol is the mechanism underlying the stress-induced modulation of multiple memory systems. Therefore, 84 healthy young women were administered either a placebo or a low or high dose of hydrocortisone. Different doses of hydrocortisone were given because previous studies suggested that GC effects on memory are dose-dependent (Lupien and McEwen, 1997; Abercrombie et al., 2003). We hypothesized that hydrocortisone would shift learning strategies towards more S–R learning and that this effect would be most pronounced in the high hydrocortisone group. One hour after drug intake, participants completed a non-arousing learning task that was designed to differentiate spatial from S–R learning strategies in humans (Schwabe et al., 2007a). Subjects were presented a 3D model of a room and had to identify a "win-card" out of four that could be located with the help of a single proximal cue (S–R strategy) or the relation between multiple distal cues (spatial strategy). The applied strategy was inferred from the participants' performance in a test trial in which the proximal cue was relocated as well as from their verbal report. To control for effects of autonomic and psychological arousal, heart rate and subjective feeling were measured at several time points across the experiment.

2. Materials and methods

2.1. Participants

Eighty-four healthy women (University of Trier, Germany) participated in this study (mean age: 22.8 years, SD = 2.7 years; placebo group: 22.8 years, SD = 2.2 years; 5 mg hydrocortisone group: 22.5 years, SD = 3.2 years; 30 mg hydrocortisone group: 23.2 years, SD = 2.8 years; criteria: non-smoking, use of oral contraceptives (except use of Yasmin® and PettiBelle® which contain a moderate mineralocorticoid receptor antagonist), no reported history of psychiatric disorders or drug abuse). Participation was restricted to women taking oral contraceptives which allows homogeneity of our sample with respect to sex hormones. Subjects had to refrain from physical exercise, large meals, coffee and alcohol for at least 2 h before the start of the experiment. All participants provided written consent in accordance with procedures approved by the local ethics committee.

2.2. Experimental design

A double-blind, placebo-controlled, between-subject design was used. Participants were randomly assigned to one of three treatments: placebo, 5 mg hydrocortisone or 30 mg hydrocortisone given 1 h before the learning trials ($n = 28$ per group). The precise time line of the experiment is shown in Fig. 1. All testing took place between 14.00 and 18.00 h.

2.3. Drug administration

Each participant (body mass index (BMI) 20–25 kg/m^2) received three pills containing either 5 or 10 mg hydrocortisone or placebo (Jenapharm, Germany). Mild and severe memory effects, respectively, were reported after 5 and 30 mg hydrocortisone (e.g. Beckwith et al., 1986; Kuhlmann et al., 2005b). Drugs were administered 60 min prior to the beginning of the learning task. Until the behavioral testing, participants remained reading in a quiet room adjacent to the testing room.

2.4. Learning task

2.4.1. Apparatus

Participants were presented a wooden 3D model of a room (box 50 cm × 50 cm × 50 cm; Fig. 2; see also Schwabe et al., 2007a). In the centre of this room is a square table on which four identical cards (white side up) are placed, exactly in the middle of one of the four quadrants. There is a small plant in one of the corners of the table. Each wall contains one cue: door, window, picture, or clock. These cues are exactly in the middle of the walls. Therefore, a direct association of one of

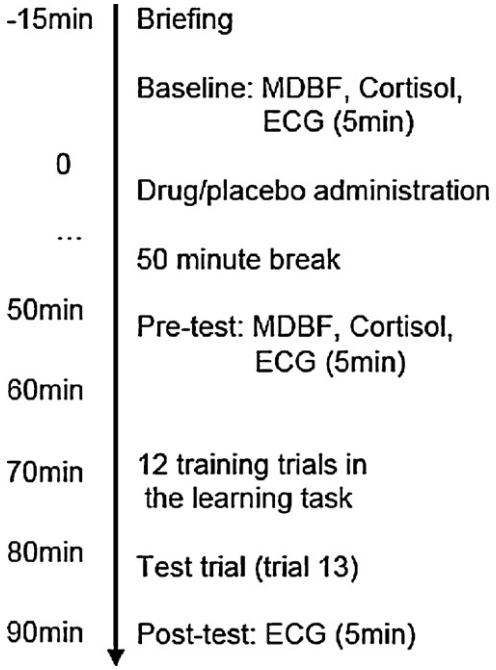

Fig. 1 Time line of the experiment.

these cues to one of the four cards is excluded. All these symbols should allow spatial orientation. The box is revolvable; the walls can be removed.

2.4.2. Procedure

Sixty minutes after the drug/placebo administration subjects were told that they will see a 3D model of a room, containing amongst other things four white cards on a table. One of the four cards would be a ''win-card'' (word ''win'' written on the card); while the other three cards would be ''no-win'' cards (word ''blank'' written on the card). One wall of the box was removed. The participant sat in front of the model and was asked to point with the finger at the card which she guessed to be the ''win-card''. The experimenter presented the card, thus the participant received an immediate positive or negative feedback. Thirteen trials were given. Eyes had to be closed between the trials. The experimenter turned the box, replaced one and removed another wall after each trial (same sequence for all participants). In this way, each trial provided a different view into the same room, with all objects in a fixed position. The participants were not told that the ''win-card'' was at the same position in relation to room cues in all trials.

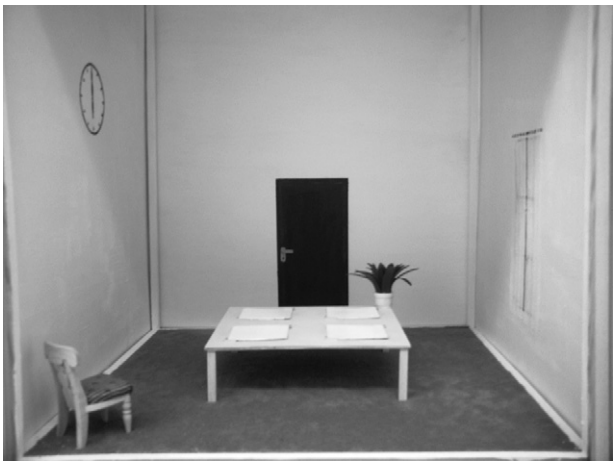

Fig. 2 Three-dimensional model of the room. Participants were asked to identify the win-card out of four. Pictures at the walls allowed spatial orientation. The plant was next to the win-card during all training trials and relocated in the test trial.

In the course of 12 trials, the subject could acquire the position of the ''win-card'' either by learning that the ''win-card'' was always next to the plant (S—R strategy) or by learning the position of the ''win-card'' relative to other room cues (spatial strategy). Since the probability is 25% to locate the correct card by chance, we used a strict criterion to define learning: the ''win-card'' had to be chosen in three consecutive trials without change in the following trials. The learning (acquisition) speed was set to this same trial. Performance in trial 13, the last trial, revealed the learning strategy. In this trial, the plant (stimulus) had been moved to another corner of the table. The use of a spatial strategy was accepted, if a participant pointed at the card in the quadrant in which the ''win-card'' had been located in all other trials. Choosing the card next to the plant was considered as an S—R strategy. We showed previously, that the performance in the win-card task is unaffected by the participants' sex (Schwabe et al., 2007a). To exclude the possibility that the decision in trial 13 might be influenced by the side from which subjects look into the room, the latter was varied between subjects.

2.5. Verbal report

After participants chose the location of the ''win-card'' in the test trial, but before receiving feedback, they were asked (i) to describe the used strategy, (ii) if there might be a reasonable alternative and (iii) to estimate the certainty of the decision on a scale from 0 to 100, where 0 stands for ''absolutely uncertain'' and 100 for ''absolutely certain''.

2.6. Subjective and autonomic arousal

The psychological arousal of the participants was assessed by MDBF, a German multidimensional mood scale (Steyer et al., 1994), prior to drug administration and before the beginning of behavioral testing (duration: 5 min). This questionnaire measures three dimensions of subjective feeling (''elevated vs. depressed mood'', ''wakefulness vs. sleepiness'', ''calmness vs. restlessness'') on a 5-point rating scale ranging from ''not at all'' (=1) to ''very much'' (=5).

Heart rate was derived from a single standard lead II ECG configuration employing telemetric HP 78100A transmitter and HP 78101A receiver system (Hewlett Packard Corp.). ECG was sampled by 1 kHz with 12bit resolution. Beat detection was performed offline by WinCPRS (Absolute Aliens Oy, Turku, Finland) as was artifact control. The following parameters, which have been used successfully in stress research (Schwabe et al., 2007b), were used: mean heart rate and the root mean square successive differences of the interbeat interval (RMSSDibi), the latter being a sensitive index of stress-induced vagal withdrawal (van den Berg et al., 1997).

Heart rate measurements were taken prior to drug administration (baseline), immediately before and after the learning task (pre- and post-test, respectively).

2.7. Collection of saliva and biochemical analyses

Saliva samples were taken at baseline and before the learning task, put directly into standard Eppendorf tubes (1.5 ml, Eppendorf, Hamburg, Germany), stored at room temperature until completion of the session, and then kept at −20 °C until analysis. After thawing for biochemical analysis, the fraction of free cortisol in saliva was determined using a time-resolved immunoassay with fluorometric detection, as described in detail elsewhere (Dressendorfer and Kirschbaum, 1992). Inter- and intra-assay coefficients of variance were below 9%.

2.8. Statistical analyses

Chi-square tests were used to assess the effect of the hydrocortisone treatment on the used learning strategy and the reported alternatives. Furthermore, a multiple regression model was used to dissect the effects of autonomic and subjective arousal from effects of cortisol on learning strategy. Effects of hydrocortisone administration on salivary cortisol concentration, heart rate, RMSSDibi, and subjective feeling (i.e. the MDBF scales) were analyzed by ANOVA. Learning gradients of spatial and S–R learners were compared by means of Kaplan–Meier survival analysis. Cortisol data were logarithmized (log) for follow-up analyses as they did not meet the assumption of normal distribution. All calculations were done with SPSS software (Version 15.0). Reported *P*-values are two-tailed. $P < 0.05$ was accepted as statistical significance.

3. Results

3.1. Manipulation check

As expected, saliva cortisol concentrations differed significantly just prior to behavioral testing (all $P < 0.001$), while there were no significant baseline differences. Significant elevations in saliva cortisol concentrations were found in the 30 and 5 mg hydrocortisone groups (both P's < 0.001) but not in the placebo group ($P = 0.39$; Table 1).

3.2. Cortisol effects on strategy use and learning performance

3.2.1. Strategy use

Cortisol treatment exerted a significant effect on the strategy used in the test trial ($\chi^2(2) = 7.02$, $P < 0.03$). While the spatial

Table 1 Cortisol, cardiovascular (heart rate, root mean square successive difference of the interbeat interval; RMSSDibi) and subjective data (multidimensional mood questionnaire, MDBF) of the placebo, 5 and 30 mg hydrocortisone group at baseline and before (pre-test)/after (post-test) the spatial task. Saliva cortisol concentrations were increased after hydrocortisone administration, as expected. Neither cardiovascular nor subjective responses were influenced by the experimental treatment. Reduced heart rate and increases in RMSSDibi, sleepiness and calmness were observed in all groups and are most likely due to the 60 min waiting period between drug intake and behavioral testing. Data represent $M \pm$ S.E.M.

	Placebo	5 mg	30 mg	Group effect		Time effect		Time × group	
				F	*P*	*F*	*P*	*F*	*P*
Saliva cortisol (in nmol/l)						130.81	0.001	93.16	0.001
Baseline	13.71 ± 1.98	13.91 ± 1.63	16.98 ± 2.19	1.45	0.25				
Pre-test	20.10 ± 6.62	50.10 ± 6.10	343.71 ± 25.40	138.57	0.001				
Heart rate (in bpm)						64.87	0.001	0.25	0.71
Baseline	76.09 ± 2.17	75.25 ± 1.43	73.02 ± 1.51	0.84	0.44				
Pre-test	68.29 ± 1.76	68.72 ± 1.59	66.27 ± 1.05	0.77	0.47				
Post-test	70.12 ± 2.25	70.55 ± 1.72	68.82 ± 1.19	0.69	0.51				
RMSSDibi (in ms)						35.53	0.001	0.54	0.89
Baseline	56.29 ± 9.85	51.29 ± 5.41	44.00 ± 2.39	0.83	0.44				
Pre-test	75.36 ± 11.30	70.60 ± 3.41	61.37 ± 4.66	0.64	0.53				
Post-test	68.64 ± 8.37	64.10 ± 5.54	51.78 ± 4.28	0.30	0.74				
MDBF scales									
Elevated vs. depressed mood						0.02	0.88	0.49	0.62
Baseline	32.59 ± 0.78	33.32 ± 0.99	33.21 ± 0.68	0.22	0.80				
Pre-test	33.07 ± 0.86	33.11 ± 0.96	33.11 ± 0.75	0.00	1.00				
Sleepiness vs. wakefulness						20.27	0.001	0.94	0.39
Baseline	28.70 ± 1.09	31.29 ± 1.11	27.64 ± 1.22	2.72	0.07				
Pre-test	26.63 ± 1.30	26.36 ± 1.14	24.64 ± 1.36	0.92	0.40				
Calmness vs. restlessness						5.24	0.03	0.26	0.77
Baseline	29.67 ± 0.89	30.82 ± 1.04	31.46 ± 1.02	0.84	0.44				
Pre-test	31.15 ± 0.86	31.54 ± 0.88	32.36 ± 0.84	0.51	0.60				

strategy was used by 32% of the 30 mg hydrocortisone and 21% of the 5 mg hydrocortisone group, only 4% of the placebo group used the spatial strategy (placebo vs. 5 mg: $\chi^2(1) = 4.08$, $P < 0.05$, placebo vs. 30 mg: $\chi^2(1) = 7.79$, $P < 0.01$; Fig. 3A). To exclude the possibility that these effects of cortisol treatment were mediated by autonomic and subjective arousal, we performed a stepwise regression analysis with age and BMI included in a first step, the pre-test heart rate and RMSSDibi values as well as the pre-test scores of the three MDBF scales included in a second step, and cortisol prior to training included in a third step. Importantly, neither subjective nor autonomic arousal predicted the used strategy; the only significant predictor was cortisol ($P < 0.04$; Table 2).

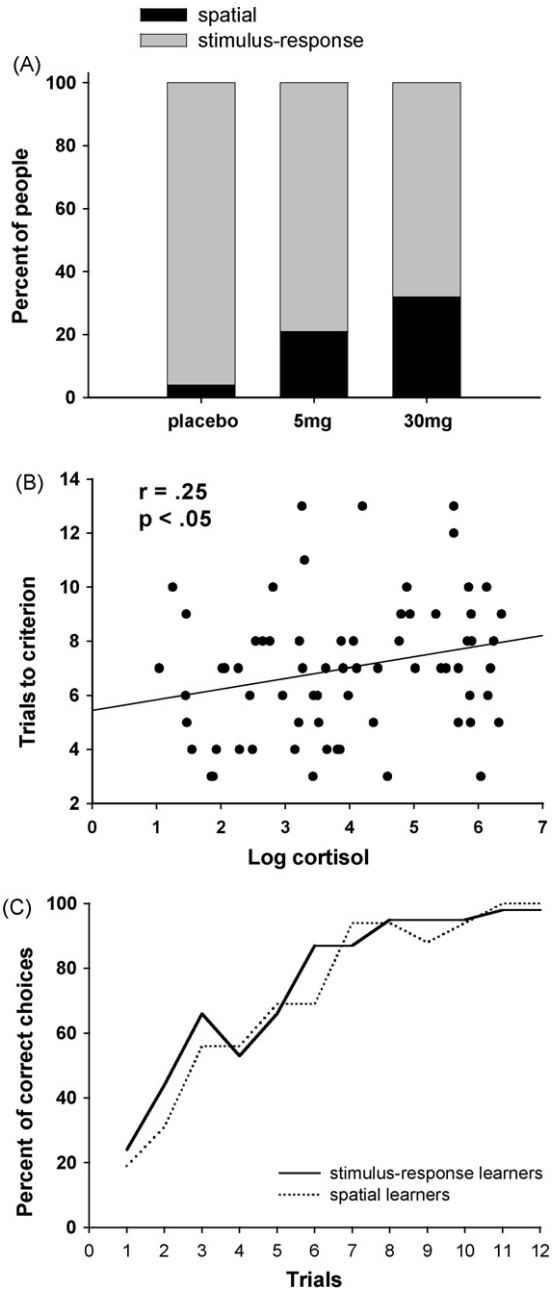

Fig. 3 (A) Percent of spatial and stimulus–response learners in the test trial. Hydrocortisone shifted learning strategies towards more spatial learning in a dose-dependent manner. (B) Correlation between log cortisol and the number of trials to reach the learning criterion (three hits in a row). (C) Learning curves of spatial and stimulus–response learners were comparable.

3.2.2. Learning performance

Interestingly, log cortisol prior to training (i.e. 60 min after drug intake) correlated significantly positive with the number of trials needed to reach the learning criterion (three hits in a row without changing in the following trials; $r = 0.25$, $P < 0.05$). The higher the cortisol concentrations prior to training were, the more trials were needed to reach the learning criterion (placebo: 6.6 trials; 5 mg: 6.9 trials; 30 mg: 7.9 trials; Fig. 3B). Groups were similar with respect to the number of non-learners (placebo: 2; 5 mg: 3; 30 mg: 2). The learning curves of spatial and S–R learners were comparable (Kaplan-Meier log-rank $\chi^2(1) = 0.28$, $P = 0.60$; Fig. 3C). Both, spatial and S–R learners needed on average about seven trials to reach the learning criterion.

3.2.3. Verbal report

Subsequent to their choice in the test trial, but before they received feedback, participants were interviewed about their chosen strategy, possible alternatives and their decision certainty. Reports of spatial and S–R learners about the possible strategies differed significantly but were independent of treatment ($\chi^2(3) = 41.38$, $P < 0.001$). All spatial and all S–R learners were aware of their strategy. Interestingly, 69% of the spatial learners reported also the S–R strategy, while only 10% of the S–R learners were also aware of the spatial strategy. Certainty of choice was not influenced by strategy or treatment ($F(2, 83) = 0.44$, $P = 0.64$).

3.3. Physiological and subjective arousal

Administration of 5 or 30 mg hydrocortisone had no effect on heart rate, RMSSDibi and subjective feeling (all F's < 1, all

Table 2 Stepwise multiple regression on the strategy applied in the test trial as a function of age, body–mass–index (BMI), heart rate and root mean square successive difference of the interbeat interval (RMSSD), scores on the MDBF scales "restlessness vs. calmness", "elevated vs. depressive mood" and "wakefulness vs. sleepiness" and cortisol prior to the start of the learning task.

Variable	β	Adjusted R^2
Step I		0.01
Age	0.10	
BMI	0.14	
Step II		0.03
Heart rate	0.19	
RMSSD	0.08	
Calmness vs. restlessness	0.15	
Elevated vs. depressed mood	0.07	
Wakefulness vs. sleepiness	0.10	
Step III		0.09*
Cortisol	0.27*	

The cortisol concentration prior to training was the only significant predictor of the applied strategy.
* $P < 0.05$.

P's > 0.39; see Table 1). However, significant time effects for heart rate ($P < 0.001$) and RMSSDibi ($P < 0.001$) indicated that participants were more aroused at the beginning of the experiment than immediately before training in the learning task. These time-dependent differences were reflected in the changes in the MDBF scales "sleepiness vs. wakefulness" ($P < 0.01$) and "calmness vs. restlessness" ($P = 0.03$) and are most likely due to the 60 min waiting period between drug intake and behavioral testing.

4. Discussion

The present study asked whether exogenous glucocorticoids in the absence of subjective and autonomic arousal are sufficient to modulate the use of spatial and S–R learning strategies. Indeed, participants that were administered hydrocortisone prior to training in a 3D spatial task changed their learning strategy and used – contrary to our expectation – significantly more often a spatial strategy than placebo-treated controls. This effect was dose-dependent. It is important, that the change of learning strategies occurred in a non-stressful context, independent of autonomic or subjective arousal. Hierarchical regression revealed no effect of heart rate, RMSSDibi or subjective feeling on the used learning strategy, but a significant influence of cortisol.

Our findings provide a novel view of GC effects on learning and memory processes. The majority of studies focus on GC functions in a single memory system expressed by changes in quantitative memory parameters such as the number of words or slides recalled (Abercrombie et al., 2003; Kuhlmann et al., 2005a; Buchanan and Tranel, 2008). Here, we also obtained evidence for GC effects on the quantitative learning performance: the higher the saliva cortisol concentration, the more trials were needed to reach the learning criterion. However, since we created the conditions for solving the task in two ways, we were able to capture another aspect of GC action. We show that GCs also affect the quality of learning, i.e. which memory system is used to acquire the task. We thus propose two modes of GC action: GCs modulate performance (a) *within* a memory system but also (ii) due to a switch *between* memory systems.

In line with earlier studies (Kim et al., 2001; Schwabe et al., 2007a), spatial and S–R learners were comparable in their learning performance (learning curves, learning speed). Thus, differences in the quality of learning can come without changes in quantitative parameters, indicating that the switch in strategies might rescue performance. The advantage of human studies (present study, Schwabe et al., 2007a) is the verbal report. Spatial and S–R learners differed significantly in their awareness of the possible strategies. While more than 90% of spatial learners were aware of the used spatial and an S–R option, the majority of the S–R learners was only aware of the employed S–R strategy. This underlines the cognitive rigidity and inflexibility of "habit" learning. However, as we have argued elsewhere "habit" learning makes decisions fast and frugal and thus appears to be an adaptive response to stress (Schwabe et al., 2007a).

It is of relevance to separately address the issue of the "control" group. Our previous study (Schwabe et al., 2007a) and the present study were performed at the same time of the day. In the present study, we used a placebo group as control for drug treatment. According to German law, all participants of the study had to be informed about cortisol and its possible side effects prior to participation. Unexpectedly, participants started the experiment with rather high baseline cortisol concentrations of 13–17 nmol/l. These are considered as "stress levels" which supposedly are due to expectations of later drug treatment. Thus, participants of the placebo control group cannot be considered as naïve, untreated subjects like we tested in the previous study. In our previous study (Schwabe et al., 2007a), the initial cortisol values were in the range of 1–3 nmol/l, which are generally accepted as basal cortisol secretion values. Cortisol concentrations prior to the beginning of the learning task were even higher in the current placebo group than in the stressed group of the previous study (Schwabe et al., 2007a). This might account for the rather low number of spatial learners in the placebo group (4% compared to 40% in the non-stressed controls of the previous study). Future pharmacological studies should include an untreated control group. While this argument focuses on baseline differences in cortisol, it cannot be completely excluded that there is some baseline variation in the use of spatial vs. S–R strategies. This would imply that stress or pharmacologically elevated cortisol levels cause a shift in ongoing behavior, i.e. a shift in the learning strategy one "normally" would have used.

Previous studies showed that acute stress favors caudate-dependent "habit" (S–R) learning over hippocampus-dependent "cognitive" (spatial) learning (Kim et al., 2001; Packard and Wingard, 2004; Schwabe et al., 2007a). Here, we report an opposite effect in response to GC administration: the spatial strategy became more likely at the higher hydrocortisone dose. We will discuss this apparent discrepancy in relation to (1) the well-known u-shaped dose response effects of GCs, (2) the effects of stress and GC administration on endocrine and autonomic systems and (3) the context-dependent action of GCs on learning and memory.

First, in our previous study we used the same learning task but preceded by a psychosocial stressor raising GC levels (Trier Social Stress Test, TSST; Schwabe et al., 2007a). Cortisol concentrations induced in the present study were much higher. Addressing the findings of the present and the previous study (Schwabe et al., 2007a) separately, indicates a linear relationship between cortisol and learning strategy, albeit in opposite directions. Combining the findings of both studies suggests a u-shaped effect of GCs on the used learning strategy with (i) spatial learning being most likely in the face of either very low or very high GC (i.e. control group in the TSST and the 30 mg group in the present study, respectively) and (ii) S–R learning being most likely in the face of moderate, still physiological GC elevations (i.e. in the TSST and placebo groups). That more participants use the spatial strategy in the face of high cortisol concentrations appears to be contradictory to studies reporting impaired hippocampus-dependent memory following high cortisol treatment (Lupien and McEwen, 1997; Mateo, 2008). These studies indeed show a *quantitative* decline in the performance of a single memory system, whereas we refer to the *quality* of learning which is primarily determined by the relation of multiple, here hippocampus-based vs. caudate-based memory systems.

For quantitative memory parameters, u-shaped effects of GCs are often reported. The molecular mechanisms discussed are a differential involvement of mineralocorticoid (MR) and

glucocorticoid receptors (GR), the two receptor types that mediate GC effects in the brain (de Kloet et al., 1999; Diamond et al., 2007). Most likely, the distinct and brain-site dependent distribution of MR and GR underlies the use of learning strategies. For example, co-localization and density of MR and GR in the hippocampus dominates any other brain area, with a lack of MR in the caudate nucleus (de Kloet et al., 1998). Differential activation of the two receptors in distinct brain areas might determine the system that will guide behavior. In line with previous rodent studies (Packard and McGaugh, 1996; Kim et al., 2001) we assume that the hippocampus dominates behavior when GC levels are low and both, hippocampal and caudate systems are fully functional. Although at present rather speculative, we suggest that in the face of moderate GC levels, hippocampal functioning might start to decline, while the caudate nucleus is taking over, expressed as more S–R learning. High GC levels dampen the functionality of both systems (as reflected in a reduced overall performance) but restore the balance between the two systems allowing the use of hippocampus-based learning strategies. Contribution of cortical prefrontal regions could be considered as well. Comparative studies in animals will allow addressing this proposed shift of a differential contribution of brain areas to learning strategies.

Second, stress and exogenous GC administration have clearly different effects on central markers of autonomic and endocrine stress systems. While the TSST as a psychological stressor activates the sympathetic and glucocorticoid stress system, exogenous cortisol inhibits the activity of the autonomic nervous system, CRF and ACTH release via negative feedback processes. Thus, the opposite effects of stress and GC administration on the modulation of spatial and S–R learning may also be due to effects on these factors. CRF is known to be involved in the regulation of emotions and cognitive functions (Contarino et al., 1999; Radulovic et al., 1999). The interaction of GCs and adrenergic arousal on memory have been reported decades ago (Bohus and de Kloet, 1981) and were lately extended by elegant approaches demonstrating brain-site and task dependent interactions of GC and concurrent noradrenergic activity in the basolateral amygdala (Kim et al., 2001; Roozendaal et al., 2004; Roozendaal et al., 2006). Rodent studies ascribed a critical role in the modulation of memory systems to the amygdala. Intraamygdala infusions of anxiogenic drugs were sufficient to switch learning strategies from predominant spatial to more S–R learning (Packard and Wingard, 2004). Memory for non-arousing material, however, is unrelated to amygdala functioning (Kensinger, 2004). It is important to underline that our 3D learning task *per se* has neither activated the sympathetic nor the glucocorticoid stress axis (present study and participants of the non-TSST group in Schwabe et al., 2007a). Thus, the lack of a task-related negative emotional component that is so central to rodent studies might be another explanation for the opposite effects of psychosocial stress and exogenous GCs on the modulation of learning strategies.

Third, whether GCs facilitate or impair memory depends on the context and convergence of stress hormone action (de Kloet et al., 1999; Joels et al., 2006). Facilitation of memory takes place (i) when stress or GCs are experienced in the context and around the time of the event that needs to be remembered, and (ii) when the hormones and transmitters released in response to stress exert their actions on the same circuits as those activated by the situation. This theory is predominantly related to the effects of GCs on memory consolidation, involving the coordination of autonomous nervous system and hypothalamic-pituitary–adrenal axis activity, as well as the concerted and balanced activation of brain glucocorticoid receptors. Support is received from a variety of studies using declarative (humans) as well as spatial and fear-conditioning tasks (human and animals). Brain structures involved in these tasks cover amygdala, hippocampus and frontal cortex circuits. A rather usual situation in daily life is an elevation of GCs due to stress (or drug-treatment) prior to memory retrieval or the acquisition of novel information. This is predominantly out-of-context with the task. Consequently, the reported effects are mainly interrupting ongoing performance and considered as impairing for memory retrieval. Dealing with strategies addresses the acquisition phase. Here, the activity of brain systems can be shifted and thus, depending on the timing, concentration and localization of GC action modulate the behavioral response. A change in strategies may occur in conditions of moderate and high GCs (i.e. after stress and GC administration), albeit in different directions.

Each of the three hypotheses receives some support from the literature. We suggest that animal studies focusing on the molecular mechanisms will help to understand, which of the three hypotheses explains the discrepancy between stress and exogenous cortisol effects on the use of spatial and S–R strategies best. Very recently, we showed that the use of spatial and S–R strategies is not only modulated by acute but also by chronic stress (Schwabe et al., 2008). Both chronically stressed mice with an increased activation of the glucocorticoid system and healthy humans with a history of chronic stress used significantly more often an S–R strategy than controls in a task that allowed spatial as well as S–R learning strategies. It is tempting to speculate that chronic hydrocortisone intake might also affect the use of spatial vs. S–R learning strategies. Given the frequent prescription of cortisol-related treatments, this could have important clinical implications.

The use of a task which dissociates spatial from S–R learning strategies, demands that we address the issue of sex-effect. Using the same task under psychosocial stress, men and women implemented spatial and S–R strategies similarly (Schwabe et al., 2007a). In the present study we tested only young women taking oral contraceptives to allow a sample that is rather homogenous with respect to sex hormone levels. We cannot exclude that exogenous GCs might act differently in men or naturally cycling women. Contrary to the most general believe, more and more studies report that the use of spatial and S–R learning strategies is rather a matter of practice than of the participants' sex (Iaria et al., 2003; Bohbot et al., 2004). Nevertheless, some authors suggested that the use of oral contraceptives is associated with a reduced sensitivity of memory to acute GC elevations (Kuhlmann and Wolf, 2005); others indicated that women in the mid-luteal phase are particularly sensitive to effects of stress on memory (Andreano et al., 2008). Yet, the interaction between sex hormones and glucocorticoids in memory remains complex and is not well understood. Further studies are needed to corroborate our findings in men as well as in women tested at different times of their estrous cycle. Also

here, animal studies will contribute to our understanding of the underlying mechanisms.

Finally, our finding that the majority of the spatial learners were also aware of the S—R strategy might be interpreted as evidence that there is considerable overlap between "habit" and "cognitive" systems. Indeed, memory systems work in parallel and may interact in a cooperative manner (Kim and Baxter, 2001). Nevertheless, it has to be emphasized that predominantly spatial learners were aware of both strategies as the minority of the S—R learners reported both potential strategies. This highlights the differences between "habit" and "cognitive" systems with respect to cognitive flexibility vs. rigidity and thus supports the notion of functionally and anatomically distinct systems.

Taken together, GCs modulate the use of hippocampus-dependent "cognitive" and caudate nucleus-dependent "habit" learning, independent of subjective and autonomic arousal. GCs affect not only *how much* but also *how* individuals learn. This dual mode most likely emerges from differential GC action on memory-relevant brain regions. We expect that this distinction of GC action will have impact on the understanding of stress-related psychiatric disorders that are characterized by a hyper- or hypoactive HPA axis and reduced cognitive flexibility.

Role of funding sources

Funding for this study was provided by the German Research Foundation (DFG, grant GRK 1389/1) the Netherlands Organisation for Scientific Research (NOW, grant NWO DN 95-420); the DFG and the NWO 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

All authors report no conflict of interest.

Acknowledgements

This work was part of the Trier-Leiden IRTG program, supported by grants DFG GRK 1389/1, NWO DN 95-420. We thank Nina Mariel Knapp and Linn Kühl for their assistance during data collection.

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