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

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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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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