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Influence of glucocorticoid and mineralocorticoid receptor stimulation on task switching

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ABSTRACT

The influence of stress on executive functions has been demonstrated in numerous studies and is potentially mediated by the stress-induced cortisol release. Yet, the impact of cortisol on cognitive flexibility and task switching in particular remains equivocal.

In this study, we investigated the influence of pharmacological glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) stimulation, two corticosteroid receptor types known to be responsible for cortisol effects on the brain. We conducted two experiments, each with 80 healthy participants (40 women and 40 men), and tested the effect of the unspecific MR/GR agonist hydrocortisone (Experiment I) and the more specific MR agonist fludrocortisone (Experiment II) on switch costs and task rule congruency in a bivalent, cued task switching paradigm.

The results did not confirm our hypotheses; we found no significant effects of our manipulations on task switching capacity, although general switching and congruency effects were observed. We discuss the absence of MR/GR-mediated effects and propose alternative mechanisms that could explain stress induced effects on task switching.

1. Introduction

Effects of stress and cortisol on cognitive functions such as learning and memory are well documented (Wingenfeld and Wolf, 2014; Wolf et al., 2016). Yet, research on stress effects on other cognitive domains such as task switching is rather limited. Task switching reflects the capacity to shift attentional and processing resources between distinct tasks that need to be operated in parallel (Monsell, 2003). Among other functions such as set shifting, task switching is a subcomponent of cognitive flexibility, which constitutes one core executive function and comprises abilities such as the change of perspective or flexible adjustments to new rules, requirements or circumstances (Diamond, 2013). Task switching can be considered as the most complex form of cognitive flexibility (Dajani and Uddin, 2015). Overall stress has rather dampening effects on executive processes (Shields et al., 2016). Findings with regard to task switching or cognitive flexibility in general are heterogeneous. Some studies report impairing effects on cognitive flexibility (Alexander et al., 2007; Hillier et al., 2006; Plessow et al., 2012; Shields et al., 2017), with others reporting no effects (Ishizuka et al., 2007; Steinhauser and Hubner, 2007) or effects in the opposite direction, with increased cognitive flexibility after stress (Kofman et al., 2006). These mixed results might reflect variations in experimental manipulations and timing between studies.

Depending on stressor type and delay between stress exposure and testing, different physiological stress systems might mediate the effects. Two distinct, but interacting stress response systems constitute the human physiological stress response: the sympathetic nervous system (SNS) with noradrenaline, and the hypothalamic-pituitary-adrenal (HPA-) axis with cortisol as the main downstream hormone. While the ANS gets activated immediately within seconds after stress exposure, effects of cortisol set in about 15 min after stress at the earliest and last up to several hours (Hermans et al., 2014). Cortisol easily crosses the blood–brain barrier and acts on two different receptor types in the brain: the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). These receptor types differ in their anatomical distribution, binding properties for cortisol and their specific time windows of activation (de Kloet, 2014; Maggio and Segal, 2012). MRs bind cortisol with high affinity, whereas GRs have approximately one tenth of the

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affinity. While GRs are widely distributed throughout the brain, MRs are predominantly present in the limbic system and the prefrontal cortex (de Kloet et al., 2018).

Stress-related cortisol effects have traditionally been attributed to GR activation. Unlike the almost permanently occupied nuclear MR, the membrane-bound MR serves an active role in the acute stress response (de de Kloet and Joëls, 2017; de Kloet et al., 2018; Joels, 2018). Recent studies could demonstrate the significance of the MR for various cognitive processes (de Kloet, 2014; Deuter et al., 2016; Groeneweg et al., 2011; Hinkelmann et al., 2015a; Hinkelmann et al., 2015b; Otte et al., 2015; Piber et al., 2016; Ter Horst et al., 2012), with both receptor types promoting different, and to some degree opposing functional processes (Hermans et al., 2014; Vogel et al., 2016). From what is known from previous research, the membrane-bound MR has an active role in the early stress response that is characterized by disruption of ongoing cognitive processes and a shift of attentional resources to the potential source of threat (de de Kloet and Joëls, 2017; Vogel et al., 2016). The MR is vastly distributed in the prefrontal cortex areas that are important for the execution of task switching (Sakai, 2008). The GR seems to be responsible for delayed effects of the stress response, presumably by altering genomic expression, that are related to normalization and recovery from the stress response and restoration of homeostasis (Hermans et al., 2014; Joels, 2018). During this stage, cortisol prevents the initial reaction from overshooting and facilitates recovery. The GR-mediated processes protect less against the source of stress itself, but against the normal defense reactions that are activated by stress (Munck et al., 1984), or as Marius Tausk put it metaphorically: “to limit the water damage caused by the fire brigade” (Tausk (1952), as cited in: de Kloet, 2008). In summary, it can be said that both receptor types perform different functions, some of them in opposite directions (de Kloet et al., 2018).

Central cortisol effects are one active pathway of how stress effects on cognitive flexibility and task switching can be conceptualized. Goldfarb et al. (2017) found stress-induced impairments in task switching to be mediated by cortisol levels. While Wingenfeld et al. (2011) and Vaz et al. (2011) found no effects of acute administration of hydrocortisone, Dierolf et al. (2016) reported interacting effects of hydrocortisone administration and basal cortisol levels. Hydrocortisone, a synthetic equivalent of physiologically occurring cortisol, can be administered to mimic a stress-induced cortisol response in human in the absence of other stress-related processes, such as SNS activation. However, receptor-specific effects cannot be differentially assessed by hydrocortisone administration alone, because hydrocortisone acts on both: MR and GR.

To assess effects of specific MR and unspecific MR and GR activation, we used a bivalent, cued task switching paradigm (Monsell, 2003). In this paradigm, participants need to categorize target stimuli presented in alternating sequence on a computer screen. While the set of target stimuli as well as stimulus-response contingencies remain constant, the response rule varies between trials. Trials in which the rule or task is the same as in the preceding trial (so-called ‘repetition trial’) alternate with trials in which the task has changed (‘switch trial’). As a common finding, participants perform slower and make more mistakes on switch trials compared to repetitions; a ratio termed as ‘switch costs’. While switch costs are the primary outcome for task switching performance, task rule congruency is a distinct informative measure. The task rule congruency effect describes slower responding on incongruent compared to congruent trials. Congruent trials are those in which the correct response is the same for both tasks (e.g. if ‘lower than five’ and ‘even’ both require a left button press, trials with the target number ‘2’ are congruent while ‘3’ is incongruent). Whereas both measures require interference control, they depend on distinct underlying cognitive processes: while switch cost relates to intentional control processes (Kiesel et al., 2010), the task congruency effect presumably reflects the intrusion of irrelevant information from long term memory (Kessler and Meiran, 2010; Meiran and Kessler, 2008).

We therefore conducted two experiments to investigate the influence of MR and GR activation of task switching. In the first experiment, we administered hydrocortisone to assess effects of both GR and MR stimulation. In the second experiment, we tested for the specific effects of MR activation. For this purpose, we administered the selective MR agonist fludrocortisone, which specifically stimulates the MR without affecting the GR. We expected impairing effects of both, hydrocortisone and fludrocortisone, on our outcome measures. However, based on the functional properties of both receptors, these effects should be more pronounced for specific MR stimulation as compared to unspecific MR and GR stimulation.

2. Methods

2.1. Participants

In both studies, 80 healthy participants (40 women and 40 men) participated. All participants had a completed German-university entrance diploma (German Abitur), were currently enrolled at university, and between 18 and 30 years of age. The mean age of participants was 24.5 years (SD = 3.4) in Experiment I and 23.9 years (SD = 3.3) in Experiment II. The participants were recruited through local advertisements. Due to technical difficulties, we were not able to verify the group assignment in five participants in Experiment I. Those participants were excluded from further analysis. All participants in both studies were healthy, medication-free and had no psychiatric disorder. Demographic characteristics and exclusion criteria are described in previous studies: for Experiment I (Duesenberg et al., 2016b) and for Experiment II (Schultebraucks et al., 2016). Written informed consent was obtained from all participants. Both studies were approved by the Ethics Committee of the German Psychology Association and are in line with the latest version of the Declaration of Helsinki.

2.2. Procedure

Both studies were conducted using a double-blind, placebo-controlled, between-group design, with randomized assignment to groups. Due to the circadian rhythm of cortisol (Edwards et al., 2001; Kirschbaum and Hellhammer, 1989), experiments were conducted in the afternoon, starting at 1 p.m. All participants were instructed not to do sports, not to smoke, eat or drink alcoholic or caffeinated beverages within 1 h prior to testing. Both studies were performed in a quiet surrounding.

Experiment I: All participants received either 10 mg hydrocortisone or placebo, both given orally (at 1 pm). A dose of 10 mg hydrocortisone was used in several other studies in different laboratories, reliably increasing salivary cortisol concentration (Entringer et al., 2009; Henckens et al., 2012; Terfehr et al., 2011; van Ast et al., 2013; Wingenfeld et al., 2013a; Wingenfeld et al., 2013b). The task switching paradigm started 60 min after intake of hydrocortisone/placebo. Salivary cortisol was collected immediately prior to drug intake (0 min) and after 45, 75 and 105 min. Systolic and diastolic blood pressure as well as heart rate were measured at the same time points. During this study, participants also performed other behavioral tasks that are reported elsewhere (Duesenberg et al., 2016a; Duesenberg et al., 2016b).

Experiment II: All participants received either 0.4 mg fludrocortisone (Florinef, E.R. Squibb & Sons Ltd.) or placebo, both given orally (at 1 pm). The task switching paradigm started 135 min after drug intake at maximum plasma concentrations of fludrocortisone (Ribot et al., 2013). Between drug intake and testing, the participants were sitting in a quiet room and were allowed to read. Salivary cortisol was collected five times using Salivettes (blue cap, Sarstedt, Germany): 0 (baseline—immediately before fludrocortisone or placebo intake), 90, 120, 180, and 210 min. Systolic and diastolic blood pressure as well as heart rate were measured at the same time points. During this study, participants also performed other behavioral tasks that are reported

elsewhere (Deuter et al., 2017; Piber et al., 2016; Schultebraucks et al., 2016).

2.3. Hormonal assessment

Salivary cortisol samples were collected at room temperature and kept at −80 °C until biochemical analysis.

Cortisol concentration was determined in the Neurobiology Laboratory of the Department of Psychiatry, Charité - Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany. Cortisol levels were analyzed using an adapted homogenous time-resolved fluorescence resonance energy transfer (HTRFRET)-based competitive immunoassay. Intra-assay coefficients of variation were below 8%; inter-assay coefficients of variation were below 10%. All samples and standards were measured twice, and the limit of detection was 0.2 nmol/L. For a detailed description of the method that was used for hormonal assessment, see Duesenberg et al. (2016a, 2016b).

2.4. Task switching paradigm

In order to measure cognitive control processes, a task switching paradigm was used. At the beginning of each trial, a fixation cross appeared at the center of the computer screen. The required response rule was indicated by a cue presented in unpredictable order briefly before the target. One of two possible cues (either a circle or a triangle) was presented and lasted for 500 ms until the target stimulus appeared.

Participants had to respond to one-digit numbers as target stimuli (excluding 5, i.e. 1, 2, 3, 4, 6, 7, 8, 9) by left or right button press. The presentation of target stimuli was randomized so that the same number must not occur on two consecutive trials. The task of the participant was to categorize the target number as correctly and as quickly as possible with respect to two different rules: (1) lower than 5 vs. higher than 5, or (2) even vs. odd, respectively. Which of these two attributes of the target the subjects had to pay attention to was signalized by the cue: a circle indicated the discrimination of lower vs. higher than 5, whereas the triangle indicated the distinction even and odd, or vice versa. The association between cue and categorization rule was quasi-randomized and counterbalanced between participants. The participants responded via pressing the left (lower or even number, respectively) or right (higher or odd number) marked key, depending on the task. The target was presented with a duration of 4000 ms, a non-response within this time window was considered an error. The inter-trial interval randomly varied between 600 and 1000 ms (see Fig. 1). The task consisted of 128 trials, which took an average of 7.5 min (without instructions and practice trials).

Similar to a study of Kieffaber and Hetrick (2005), the switch of the two tasks was varied as follows: In 26 cases of each task, subjects had to switch to the other task after one trial (X - Y). In 13 cases of each task, subjects had to switch to the other task after two trials of the same task, i.e., after one repeat trial (X - X - Y). Also, in 13 cases of each task, subjects had to switch to the other task after four trials of the same task, which is after three repeat trials (X - X - X - X - Y). The order of these different switch rules between tasks was completely randomized. The first trial was always discarded from analysis.

We used *E*-Prime 2.0 presentation software for stimulus presentation and data acquisition, randomization of task lists was accomplished with RQube (Seifert and Britz, 2007).

2.5. Statistical analysis

SPSS version 22.0 was used for all statistical analyses. Differences between the treatment groups (hydrocortisone vs. placebo; fludrocortisone vs. placebo) in demographic characteristics and plasma cortisol levels were compared using Student's *t*-tests for continuous variables and $\chi 2$-tests for categorical variables.

In order to analyze the influence of gluco- and mineralocorticoid stimulation, respectively, as well as the influence of gender on cognitive control processes during the task switching paradigm, an mixed-measures analysis of variance (rmANOVA) was conducted, including 'transition" (switch vs. repeat) and 'congruency" (congruent vs. incongruent) as within-subject factors and 'treatment" (placebo vs. hydrocortisone (Experiment I) or fludrocortisone (Experiment II)) and 'sex" (male vs. female) as between-subject factors, with reaction times and accuracy (percentage of correct responses) of as the dependent variables.

To assess how cortisol levels relate to task switching performance, we calculated bivariate correlations (Pearson's *r*) between absolute cortisol levels at the time of testing, baseline-corrected cortisol levels (difference between levels at time of testing and baseline) and our dependent measures 'transition' and 'congruency' and report and *p*-values.

Given an error probability of 1-β = 0.8, statistical power in both experiments was sufficient to detect effects of d = 0.6 or higher. A *p*-value smaller than 0.05 was considered to indicate statistical significance.

3. Results

3.1. Demographic characteristics

Experiment I: We found no significant differences between treatment groups (hydrocortisone vs. placebo) with regard to age, BMI and smoking. All but two women were tested in luteal phase or while taking oral contraceptives. For more details, see Duesenberg et al. (2016b).

Experiment II: We found no significant differences between treatment groups (fludrocortisone vs. placebo) regarding age, body mass index, smoking, and psychological state immediately prior to testing. Female participants in the fludrocortisone group and female participants in the placebo group did not differ with respect to the intake of oral contraceptives. For more details, see Schultebraucks et al. (2016).

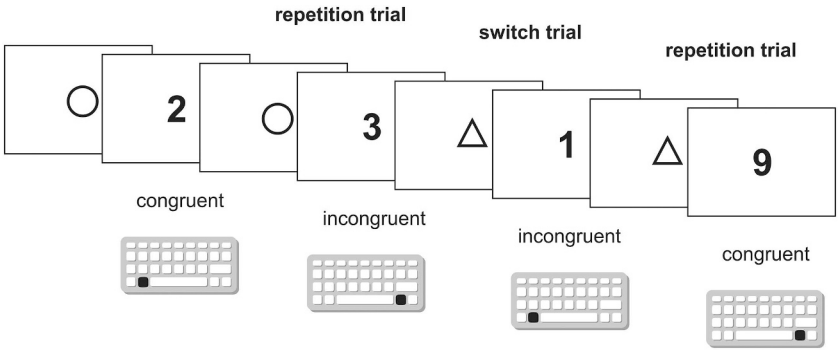

Fig. 1. Potential sequence of trials in the bivalent, cued task switch paradigm (with required responses: left or right button press). In this example, 'circle' indicates an 'odd vs. even', 'triangle' indicated a 'lower vs. higher than five' classification; both 'even' and 'lower than five' require a left button press, while 'odd' and 'higher than five' require a right button press. The task rule is indicated by a cue (circle or triangle), followed by the target stimulus: a one-digit number. The number needs to be categorized, either by odd/even or by lower/higher than five. Trials are considered as congruent if the same response is required for both tasks (left vs. right press). In between trials, a fixation cross was displayed (omitted in the figure).

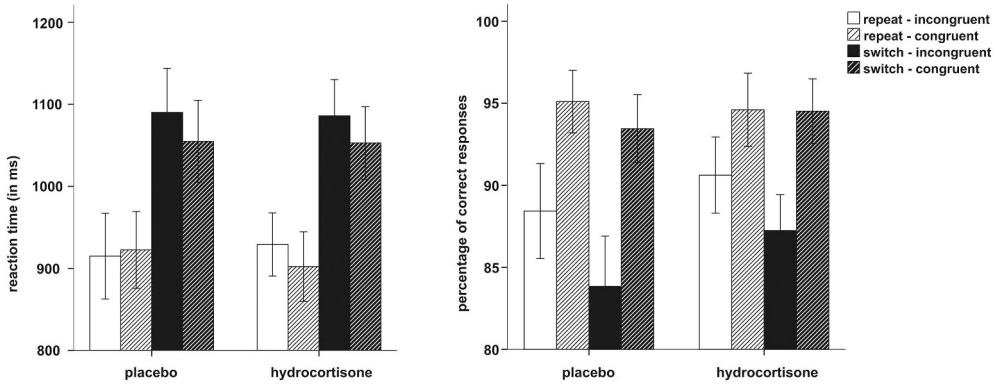

Fig. 2. Experiment I – left: reaction times (in milliseconds), right: accuracy (percentage of correct responses), Error bars represent ± 1SE.

3.2. Task switching capacity

Experiment I – Reaction times: We found a significant effect of 'transition" ($F_{1,71} = 112.66$, $p < .001$, $\eta^2 = 0.606$) indicating longer reaction times in the 'switch' condition compared to the 'repeat' condition (see Fig. 2).

There were no significant main effects of 'treatment' ($F_{1,71} = 0.001$, $p = .97$, $\eta^2 = .000$) or 'sex' ($F_{1,71} = 0.48$, $p = .49$, $\eta^2 = 0.000$) and no significant interactions of 'treatment × sex'($F_{1,71} = 0.09$, $p = .77$, $\eta^2 = 0.000$), 'transition × treatment' ($F_{1,71} = 0.00$, $p = .99$, $\eta^2 = 0.000$), 'transition × sex' ($F_{1,71} = 1.85$, $p = .18$, $\eta^2 = 0.010$), 'transition × treatment × sex' ($F_{1,71} = 0.44$, $p = .51$, $\eta^2 = 0.002$) and 'congruency × treatment' ($F_{1,71} = 0.44$, $p = .51$, $\eta^2 = 0.006$), 'congruency × sex' ($F_{1,71} = 0.83$, $p = .36$, $\eta^2 = 0.011$), 'congruency × treatment × sex' ($F_{1,71} = 0.01$, $p = .94$, $\eta^2 = 0.000$) or 'transition × congruency' ($F_{1,71} = 1.04$, $p = .31$, $\eta^2 = 0.014$), 'transition × congruency × treatment' ($F_{1,71} = 0.57$, $p = .45$, $\eta^2 = 0.008$), 'transition × congruency × sex' ($F_{1,71} = 0.00$, $p = .99$, $\eta^2 = 0.000$), 'transition × congruency × treatment × sex' ($F_{1,71} = 0.34$, $p = .56$, $\eta^2 = 0.005$).

Experiment I – Accuracy: With regard to accuracy (percentage of correct answers), we found an effect of 'transition' ($F_{1,71} = 25.73$, $p < .001$, $\eta^2 = 0.257$) indicating more correct answers in the 'repeat' condition compared to the 'switch' condition. Furthermore, we found an effect of 'congruency' ($F_{1,71} = 26.12$, $p < .001$, $\eta^2 = 0.265$) indicating more correct answers in the 'congruent' condition compared to the 'incongruent' condition and an interaction 'transition × congruency' ($F_{1,71} = 10.22$, $p < .001$, $\eta^2 = 0.125$), indicating higher switch costs for incongruent trials (see Fig. 2).

There were no significant main effects of 'treatment' ($F_{1,71} = 0.25$, $p = .62$, $\eta^2 = .000$) or 'sex' ($F_{1,71} = 0.33$, $p = .57$, $\eta^2 = 0.000$) and no significant interactions of 'treatment × sex' ($F_{1,71} = 0.30$, $p = .58$, $\eta^2 = 0.000$), 'transition × treatment' ($F_{1,71} = 2.11$, $p = .15$, $\eta^2 = 0.021$), 'transition × sex' ($F_{1,71} = 0.78$, $p = .38$, $\eta^2 = 0.008$), 'transition × treatment × sex' ($F_{1,71} = 0.65$, $p = .42$, $\eta^2 = 0.006$) and 'congruency × treatment' ($F_{1,71} = 0.88$, $p = .35$, $\eta^2 = 0.009$), 'congruency × sex' ($F_{1,71} = 0.19$, $p = .66$, $\eta^2 = 0.002$), 'congruency × treatment × sex' ($F_{1,71} = 0.54$, $p = .46$, $\eta^2 = 0.006$) or 'transition × congruency × treatment' ($F_{1,71} = 0.03$, $p = .86$, $\eta^2 = 0.000$), 'transition × congruency × sex' ($F_{1,71} = 0.04$, $p = .84$, $\eta^2 = 0.001$), 'transition × congruency × treatment × sex' ($F_{1,71} = 0.17$, $p = .68$, $\eta^2 = 0.002$).

Experiment II – Reaction times: We found a significant effect of 'transition' ($F_{1,71} = 74.79$, $p < .001$, $\eta^2 = 0.493$) indicating longer reaction times in the 'switch' condition compared to the 'repeat'condition (see Fig. 3).

There were no significant main effects of 'treatment' ($F_{1,71} = 0.01$, $p = .91$, $\eta^2 = .000$) or 'sex' ($F_{1,71} = 0.96$, $p = .33$, $\eta^2 = 0.001$) and no significant interactions of 'treatment × sex'($F_{1,71} = 0.15$, $p = .70$, $\eta^2 = 0.000$), 'transition × treatment' ($F_{1,71} = 0.03$, $p = .87$, $\eta^2 = 0.000$), 'transition × sex' ($F_{1,71} = 0.70$, $p = .41$, $\eta^2 = 0.005$), 'transition × treatment × sex' ($F_{1,71} = 0.05$, $p = .83$, $\eta^2 = 0.000$) and 'congruency × treatment' ($F_{1,71} = 0.25$, $p = .62$, $\eta^2 = 0.003$), 'congruency × sex' ($F_{1,71} = 0.34$, $p = .56$, $\eta^2 = 0.004$), 'congruency × treatment × sex' ($F_{1,71} = 0.84$, $p = .36$, $\eta^2 = 0.010$) or 'transition × congruency' ($F_{1,71} = 0.67$, $p = .41$, $\eta^2 = 0.009$), 'transition × congruency × treatment' ($F_{1,71} = 0.09$, $p = .76$, $\eta^2 = 0.001$), 'transition × congruency × sex' ($F_{1,71} = 0.81$, $p = .37$, $\eta^2 = 0.010$), 'transition × congruency × treatment × sex' ($F_{1,71} = 1.19$, $p = .28$, $\eta^2 = 0.015$).

Experiment II – Accuracy: With regard to accuracy (percentage of correct answers), we found an effect of 'transition' ($F_{1,71} = 7.17$, $p = .01$, $\eta^2 = 0.084$) indicating more correct answers in the 'repeat' condition compared to the 'switch" condition. Furthermore, we found an effect of 'congruency' ($F_{1,71} = 35.69$, $p < .001$, $\eta^2 = 0.316$) indicating more correct answers in the 'congruent" condition compared to the 'incongruent" condition (see Fig. 3).

There were no significant main effects of 'treatment' ($F_{1,71} = 0.05$, $p = .83$, $\eta^2 = .000$) or 'sex' ($F_{1,71} = 0.23$, $p = .63$, $\eta^2 = 0.000$) and no significant interactions of 'treatment × sex'($F_{1,71} = 0.03$, $p = .86$, $\eta^2 = 0.000$), 'transition × treatment'($F_{1,71} = 0.10$, $p = .75$, $\eta^2 = 0.001$), 'transition × sex'($F_{1,71} = 0.80$, $p = .37$, $\eta^2 = 0.009$), 'transition × treatment × sex'($F_{1,71} = 1.34$, $p = .25$, $\eta^2 = 0.016$) and 'congruency × treatment' ($F_{1,71} = 0.01$, $p = .93$, $\eta^2 = 0.000$), 'congruency × sex' ($F_{1,71} = 0.57$, $p = .45$, $\eta^2 = 0.005$), 'congruency × treatment × sex' ($F_{1,71} = 0.70$, $p = .41$, $\eta^2 = 0.006$) or 'transition × congruency' ($F_{1,71} = 2.65$, $p = .11$, $\eta^2 = 0.033$), 'transition × congruency × treatment' ($F_{1,71} = 1.18$, $p = .28$, $\eta^2 = 0.015$), 'transition × congruency × sex' ($F_{1,71} = 0.02$, $p = .90$, $\eta^2 = 0.001$), 'transition × congruency × treatment × sex' ($F_{1,71} = 0.03$, $p = .85$, $\eta^2 = 0.000$).

3.3. Salivary cortisol levels during testing

Experiment I: Cortisol levels in the hydrocortisone and placebo groups differed significantly at +45 min ($t_{df72} = 9.13$, $p < .001$, $d = 2.11$), +75 min ($t_{df73} = 9.92$, $p < .001$, $d = 2.29$), and +105 min ($t_{df73} = 9.99$, $p < .001$, $d = 2.31$), with higher cortisol levels in the hydrocortisone group. The results of the salivary cortisol secretion during testing are described in details in Duesenberg et al. (2016b).

Experiment II: Baseline corrected cortisol levels in the fludrocortisone and placebo groups differed significantly at +180 min ($t_{df71} = 2.03$, $p < .05$, $d = 0.47$) and + 210 min ($t_{df71} = 2.95$, $p < .05$), with lower cortisol levels in the fludrocortisone group. There was no significant between-groups difference at the time immediately before the task switching paradigm (+120 min). The results of the salivary cortisol secretion during testing are described in details in Schultebraucks et al. (2016).

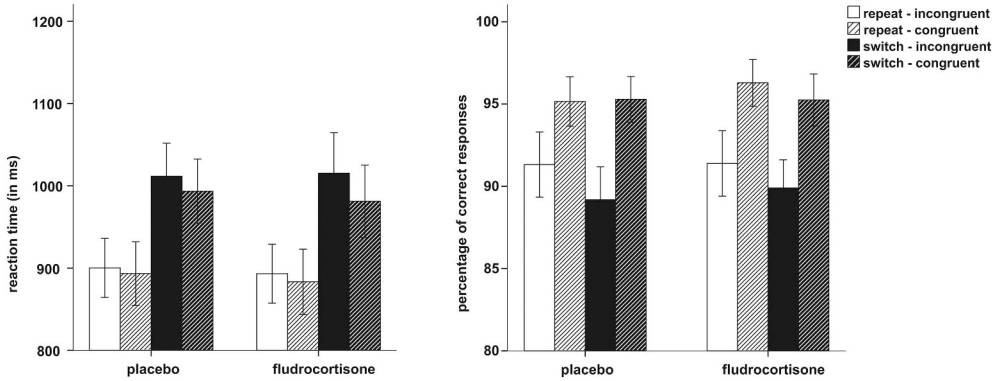

Fig. 3. Experiment II – left: reaction times (in milliseconds), right: accuracy (percentage of correct responses), Error bars represent ± 1SE.

3.4. Correlation between salivary cortisol and task switching

Experiment I: There were no significant correlations between absolute cortisol levels at the time of testing (+45 min) and 'transition' (reaction times: $r = -0.01$, $p = .92$, accuracy: $r = -0.70$, $p = .56$) or 'congruency' (reaction times: $r = -0.12$, $p = .30$, accuracy: $r = -0.01$, $p = .90$) nor between baseline corrected levels) and 'transition' (reaction times: $r = 0.03$, $p = .78$, accuracy: $r = -0.03$, $p = .78$) or 'congruency' (reaction times: $r = -0.13$, $p = .26$, accuracy: $r = -0.01$, $p = .98$).

Experiment II: There were no significant correlations between absolute cortisol levels at the time of testing (+120 min) and 'transition' (reaction times: $r = 0.04$, $p = .75$, accuracy: $r = 0.04$, $p = .71$) or 'congruency' (reaction times: $r = 0.08$, $p = .49$, accuracy: $r = 0.05$, $p = .68$) nor between baseline corrected levels) and 'transition' (reaction times: $r = -0.19$, $p = .10$, accuracy: $r = 0.19$, $p = .11$) or 'congruency' (reaction times: $r = -0.01$, $p = .93$, accuracy: $r = -0.01$, $p = .98$).

4. Discussion

In contrast to our hypotheses, we did not find an effect of hydrocortisone or fludrocortisone on our outcome measures. The implication of our findings is that stress-induced effects on those processes are not mediated by cortisol, or at least not by cortisol alone. This raises the question of how the effects of stress on task switching as described in the literature can be explained – if cortisol in isolation is not sufficient.

MR stimulation relates to fast cortisol effects of the stress response, while the concurrent MR and GR stimulation rather corresponds to delayed cortisol effects. However, even "fast" non-genomic cortisol effects manifest 15 min post stressor at the earliest, and last up to one hour. As mentioned above, the stress reaction is initiated by the SNS and the initial cortisol reaction is accompanied by SNS activation as well. While the SNS response normalizes soon within this first hour after stress exposure, there is evidence for a moderating effect of SNS activation on the impact of cortisol. So far, only a few studies investigated the combined influence of SNS and HNA activation on psychological processes. Although some studies found interaction of combined cortisol administration and noradrenergic stimulation on domains such as risk taking (Kluen et al., 2017) or social discounting (Margittai et al., 2018b), cortisol effects on other domains such as declarative memory (Roozendaal et al., 2004; Roozendaal et al., 2009; Roozendaal et al., 2006), decision making (Margittai et al., 2018a) or shifting from goal-directed to habitual behavioral control seem to require concurrent SNS activation (Schwabe et al., 2010).

In a recent study, cognitive flexibility as measured with a delayed match-to-sample task was impaired after acute stress induction, the performance decrease was correlated with increased cortisol levels (Goldfarb et al., 2017). Plessow et al. (2012) reported decreased dual task performance at interval of 20 and 40 min after stress onset. Since comparable effects were found for both intervals and salivary cortisol levels (but not salivary α-amylase as a marker for SNS activation) inversely correlated with task switching performance, the authors attributed the effects to the action of cortisol. To our best knowledge, no study so far investigated concurrent pharmacological SNS and HNA activation in such a design. However, Alexander et al. (2007) studied effects of acute stress on set shifting with and without pharmacological SNS blockade. The impairing effects of stress were not observed in the group that received the nonspecific beta-adrenergic, antagonist propranolol, which was interpreted as a mediating role of the SNS. Marko and Riecansky (2018) found cognitive flexibility, assessed by the Remote Associates Test, to be reduced after acute stress. Again, this effect could be associated with increased SNS activation.

Taken together, the effects of stress on task switching most likely require an activation of SNS. The mechanisms of interaction between both stress systems are intricate and are further complicated by the fact that cortisol is not the sole active hormone of the HPA axis. Corticotropin-releasing hormone (CRH), which is secreted from the paraventricular nucleus of the hypothalamus in response to stress and which triggers downstream release of cortisol, also excites neurons of the locus coeruleus (LC) region. Again, the LC is the main source of noradrenaline and central for SNS-mediated processes in the brain. Accordingly, Snyder et al. (2012) showed that CRH injection in the brain of rats has an influence on set shifting by influencing LC activity.

Irrespective of MR or GR activation, we did find the task switch effect (Kiesel et al., 2010; Monsell, 2003), i.e. increased reaction times and reduced accuracy in switch trials as compared to repetition trials. With respect to task rule congruency, we found an effect for accuracy in both experiments, with more correct responses in congruent trials. With this finding, we could replicate previous studies (Kessler and Meiran, 2010; Meiran and Kessler, 2008).

As a limitation, statistical power was sufficient to detect medium size effects. This assumed effect size was in accordance with reported effects of stress on task switching and cognitive flexibility (Alexander et al., 2007; Hillier et al., 2006; Ishizuka et al., 2007; Marko and Riecansky, 2018; Plessow et al., 2012). With our design, we cannot rule out that smaller effects of cortisol exist. Furthermore, higher dosages of both drugs might have had different effects. However, with both interventions, we used dosages that correspond to activation levels in the natural human stress response and proved to have effects on other psychological domains (Deuter et al., 2016; Piber et al., 2016; Schlosser et al., 2013; Schultebraucks et al., 2016).

Another possibility, which cannot be investigated with our design, is an alteration in response strategies after GR or MR activation. Some studies have observed stress or cortisol induced changes in the distribution of processing resources for other psychological domains (Schwabe et al., 2010a, 2010b; Vogel et al., 2015). These are not necessarily accompanied by changes in error rates or reaction times. Thus,

the same reactions at a behavioral level could potentially be based on different neurophysiological implementations.

We conclude that stimulation of the MR or GR in isolation, is not sufficient to explain impairing effects of stress on task switching. As stated above, a simultaneous or preceding activation of the SNS and/or the release of CRH seems to be required. The role of these components of the stress response needs to be explored in future studies.

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