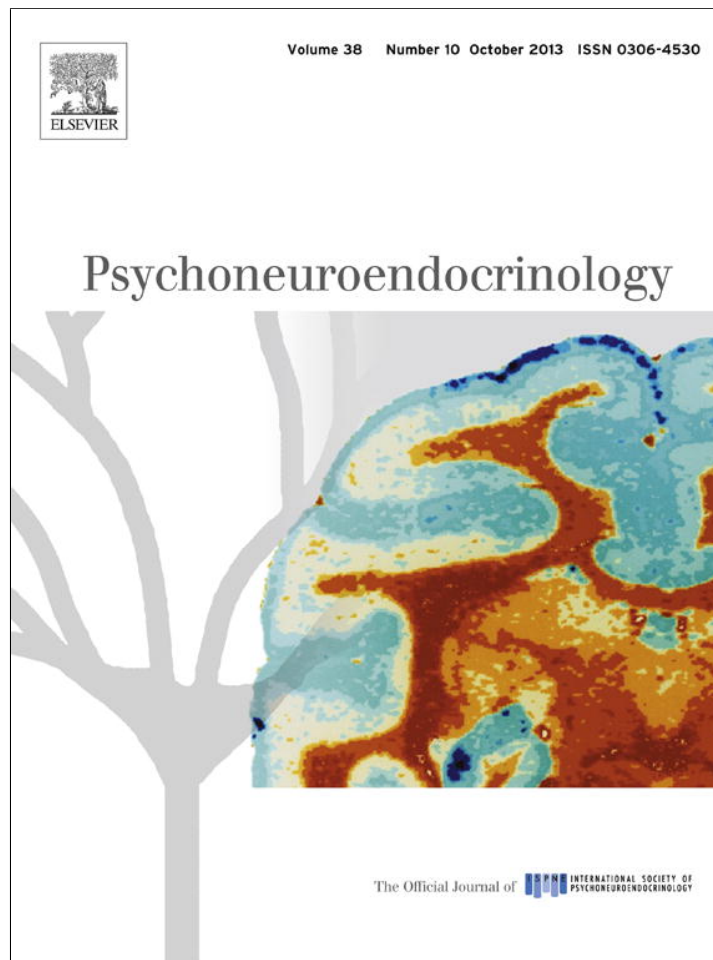


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Stress-induced enhancement of response inhibition depends on mineralocorticoid receptor activation

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Summary Stress is a well-known modulator of cognitive functions. These effects are, at least in part, mediated by glucocorticoid stress hormones which act via two receptor types in the brain, glucocorticoid receptors (GR) and mineralocorticoid receptors (MR). Here, we examined whether stress affects inhibitory control processes and, if so, whether these effects are mediated by the MR. To this end, healthy participants received 300 mg of the MR antagonist spironolactone or a placebo and underwent a stressor (socially evaluated cold pressor test) or a non-stressful control task 90 min later. Shortly after the stressor, participants performed a stop-signal task that required them to rapidly suppress a well-established response whenever a tone was presented. Results revealed that stress enhanced response inhibition in the stop-signal task and that this enhancement was abolished by spironolactone. Our results show that stress may facilitate inhibitory control and that these effects depend on MR functioning.

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1. Introduction

The ability to inhibit automatic or natural responses that are inappropriate in the current context is a hallmark of adaptive behavior. Lack of inhibitory control may lead to interpersonal conflicts and has also been suggested to play an important role in attention-deficit hyperactivity disorder (ADHD) or substance abuse (Ersche et al., 2012; Sergeant et al., 2003). At the neural level, response inhibition is subserved

by a fronto-thalamo-basal ganglia network that includes the inferior frontal cortex, the middle frontal gyrus, the medial frontal cortex, the insula, the pre-supplementary motor area, the basal ganglia and the thalamus (Aron and Poldrack, 2006; Chambers et al., 2009; Verbruggen and Logan, 2008; Wager et al., 2005).

In particular, prefrontal areas express receptors for glucocorticoid stress hormones (cortisol in humans) at a high density (McEwen et al., 1986; Reul and de Kloet, 1985) and stress and glucocorticoids are well-known modulators of prefrontal activity (Diamond et al., 2007; Qin et al., 2009; Schwabe et al., 2012b), thus suggesting that stress and stress hormones may alter prefrontal cortex-dependent behaviors. Indeed, there is ample evidence that stress affects working memory and executive functions that are supported by the

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prefrontal cortex. The direction of these effects, however, is not entirely clear as some studies showed impairing (Barsegyan et al., 2010; Plessow et al., 2011; Scholz et al., 2009) and others enhancing effects of stress (hormones) on working memory and executive functions (Henckens et al., 2011; Yuen et al., 2009). Because inhibitory control has been suggested to play a crucial role in substance abuse disorders (Ersche et al., 2012; Nigg et al., 2006) and the development of and relapse to substance abuse can be triggered by stress (Sinha, 2001), potential stress effects on inhibitory control would be of particular interest. There is already some evidence that cortisol, chronic or early life stress may affect inhibitory control (Lyons et al., 2001; Mika et al., 2012; Mueller et al., 2010; Tops and Boksem, 2011). However, whether and how acute stress affects response inhibition has not been systematically tested yet.

Glucocorticoids are a key modulator of stress effects on the brain (Roozendaal et al., 2009; Schwabe et al., 2012a). They exert their actions via two types of membrane-bound and intracellular receptors: glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs; de Kloet et al., 2005; Joëls and Baram, 2009). Evidence from rodent studies indicates that GRs are mainly involved in memory consolidation, whereas MRs are involved in the initial appraisal of a situation and the coordination of different cognitive processes (Barsegyan et al., 2010; Oitzl and de Kloet, 1992; Schwabe et al., 2010a). In other words, it is well-documented that MRs can have fast effects on cognitive processes. Based on these findings, one may hypothesize that if glucocorticoids are involved in potential stress effects on response inhibition, these effects should be mediated by MRs rather than by GRs. Accordingly, stress effects on response inhibition should disappear after MR blockade.

In the present experiment, we examined whether stress influences response inhibition and, if so, whether this effect is mediated by the MR. Healthy participants received first the MR antagonist spironolactone or a placebo and were later exposed to a stressor or a control manipulation. Shortly after the stressor, inhibitory control was tested with the well-known stop-signal task, which requires participants to rapidly suppress an ongoing, well-established response whenever an auditory signal is present (Logan et al., 1997).

2. Materials and methods

2.1. Participants and design

Seventy-two healthy, right-handed university students with normal or corrected-to-normal vision and without medication intake, any current medical condition, any substance abuse or lifetime history of any neurological or psychiatric disorder participated in this experiment (32 men, 40 women; mean age = 24.4 years, range 20–32 years). Smokers and women using (any type of) hormonal contraceptives were excluded from participation because smoking and hormonal contraceptives are known to change the endocrine stress response (Kirschbaum et al., 1999; Rohleder and Kirschbaum, 2006). Moreover, women were not tested during their menses. The study protocol was approved by the Review Board of the Medical Faculty of the Ruhr-University Bochum. All participants provided written informed consent.

We used a fully crossed, double-blind, placebo-controlled between-subjects design with the factors treatment (control vs. stress condition) and drug (placebo vs. spironolactone), thus resulting in four experimental groups ($n = 18$ per group): control condition/placebo (CON/PLAC), control condition/spironolactone (CON/aMR), stress condition/placebo (STRESS/PLAC), and stress condition/spironolactone (STRESS/aMR).

2.2. Experimental procedure

In order to control for the diurnal rhythm of the stress hormone cortisol, all testing took place between 1.30 and 6.30 pm. Upon their arrival at the lab, participants gave a first saliva sample (see below) and completed a German mood questionnaire (MDBF; Steyer et al., 1994) that assesses subjective mood on three scales: restlessness vs. calmness, depressed vs. elevated mood, and sleepiness vs. wakefulness. Moreover, we measured participants' blood pressure with a Dinamap system (Critikon, FL) on the left upper arm. Afterwards, participants were randomly assigned to one of the four experimental groups.

2.2.1. Drug administration

Depending on the experimental group, participants were administered orally either 300 mg of the MR antagonist spironolactone (Ratiopharm) or a placebo. This dosage of spironolactone seemed likely to result in effective MR blockade on the one hand (Cornelisse et al., 2011) and to minimize potential discomfort on the side of the participants on the other hand. Behavioral testing started 90 min after drug intake; until then, participants remained reading in a quiet room adjacent to the testing room.

2.2.2. Stress induction

Ninety minutes after drug intake, participants underwent a stressor or a control manipulation. In the stress condition, participants were exposed to the socially evaluated cold pressor test (SECPT) as described in detail elsewhere (Schwabe et al., 2008). In brief, participants immersed their right hand up to and including the wrist for 3 min (or until they could not stand it any longer) into ice water (0–2 °C). During hand immersion, they were videotaped and monitored by a non-reinforcing, rather cold and unsociable experimenter. In the control condition, participants submerged their right hand up to and including the wrist for 3 min into warm water (35–37 °C). They were neither videotaped nor monitored by an unsociable experimenter.

In order to assess the efficacy of the SECPT, we measured subjective and physiological stress responses at several time points across the experiment. Participants completed a subjective mood questionnaire (MDBF) after their arrival at the lab, immediately before and immediately after the stress/control manipulation. In addition, participants rated immediately after the stress/control manipulation on a scale from 0 ("not at all") to 100 ("very") how stressful, painful, and unpleasant they had experienced the previous treatment. We measured participants' blood pressure after their arrival as well as before, during and immediately after the stress/control manipulation. Moreover, participants collected saliva samples with the help of salivette collection devices

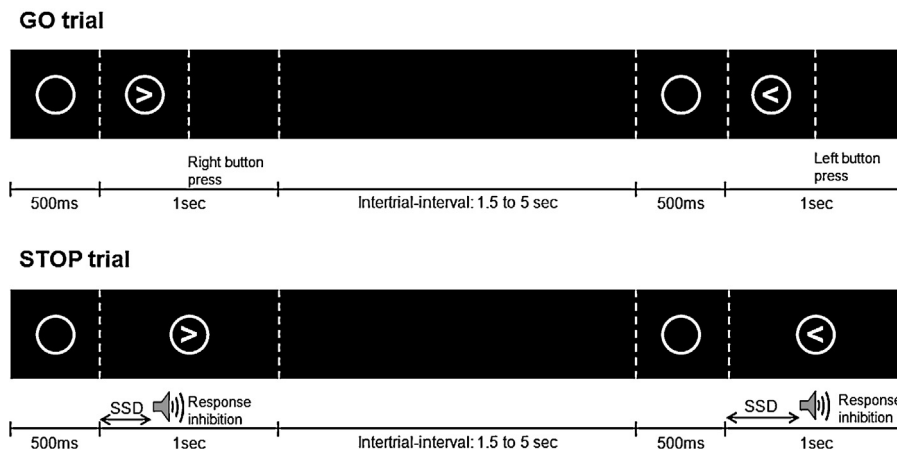


Figure 1 Stop-signal task structure and timing. Participants were presented Go trials and Stop trials. On each trial, participants were shown a left-pointing or a right-pointing arrow. On Go trials, participants were instructed to respond as fast as possible by pressing the left key (for left warded arrows) and the right key (for right warded arrows), respectively, on a response box. The arrow disappeared when participants pressed a key. On Stop trials, which were signaled by a tone shortly after arrow stimulus onset, participants were asked to withhold responding. Response inhibition was made difficult by the preponderance of Go trials (75%) and by varying the timing of the tone (stop signal delay, SSD) by means of a tracking algorithm.

(Sarstedt, Germany) after the arrival at the lab, immediately before and after the stress/control manipulation as well as immediately before and about 30 min after the stop-signal task. Saliva samples were stored at -20°C until analysis. From saliva we analyzed cortisol concentrations using an immunoassay (IBL International). Inter- and intraassay coefficients of variance were below 10%.

2.2.3. Stop-signal task

Thirty minutes after the stress/control manipulation and 120 min after drug intake, participants completed a stop-signal task (Aron and Poldrack, 2006; Logan et al., 1997; Fig. 1). This interval between the stress induction and the stop-signal task was chosen because it is known that cortisol concentrations reach peak levels at about 30 min after stressor onset (Schwabe et al., 2008). The stop-signal task consists of two trial types: Go trials and Stop trials. On Go trials, a white circular ring appeared at the center of a computer screen. After 500 ms, an arrow appeared within the fixation circle. The arrow pointed to the left or to the right; the number of leftward and rightward arrows was equal. Participants were instructed to respond to the arrows as fast as possible by pressing the left and the right key on a response box, respectively. An arrow was presented for a maximum of 1 s and disappeared after the participant had responded. The inter-trial interval varied between 1.5 and 5 s. Stop trials were identical to Go trials with the critical exception that a tone (500 ms; 900 Hz) was presented shortly after the arrow stimulus. This tone signaled participants NOT to press any key on the response box, i.e., it required participants to inhibit a response.

Response inhibition was made difficult by the preponderance of Go trials: 75% (153 trials) of the presented 204 trials were Go trials and only 25% (51 trials) were Stop trials. Moreover, we varied the stop signal delay (SSD), i.e., the time between arrow presentation and onset of the tone, by a tracking algorithm. The initial SSD was 250 ms. If participants inhibited the response successfully in one trial, the SSD was

increased by 50 ms, thus making response inhibition more difficult in the next Stop trial. If participants, however, failed to inhibit a response, the SSD was decreased by 50 ms, making it easier to withdraw from responding on the subsequent Stop trial. This method led to a successful inhibition rate of about 50%. Response inhibition was expressed as stop signal reaction time (SSRT), which was calculated according to the *integration method*: Go reaction times were rank-ordered, then the n th reaction time was selected, where n is obtained by multiplying the number of Go reaction times in the distribution by the probability of responding at a SSD ($p(\text{respond}|\text{signal})$). Finally, the SSRT is calculated by subtracting the SSD from the n th reaction time (see Verbruggen and Logan, 2009). After the stop-signal task, participants performed another cognitive task, which will be reported elsewhere.

2.3. Data analysis

Subjective mood data, blood pressure and salivary cortisol data were analyzed by mixed-design ANOVAs with the between-subject factors treatment (control vs. stress condition) and drug (placebo vs. spironolactone) and the within-subject factor time point of measurement. SSRTs were subjected to a treatment \times drug ANOVA. Significant interaction effects were pursued by appropriate follow-up tests (simple effects analyses). Greenhouse–Geisser correction was used to correct for violations of sphericity. All reported p values are two-tailed.

3. Results

3.1. Subjective and physiological stress responses

The subjective and physiological responses to the SECPT verified the successful stress induction. Exposure to the

Table 1 Subjective and blood pressure changes in the four groups across the experiment.

	CON/PLAC	STRESS/PLAC	CON/aMR	STRESS/aMR
<i>Depressed vs. elevated mood</i>				
Baseline	32.5 ± 1.6	34.1 ± 1.0	33.0 ± 0.9	34.6 ± 1.7
Before stress/control	33.2 ± 1.1	33.5 ± 1.1	32.7 ± 1.0	32.8 ± 1.2
After stress/control	33.1 ± 1.2	31.9 ± 1.1	33.6 ± 0.9	31.2 ± 1.3
<i>Restlessness vs. calmness</i>				
Baseline	31.8 ± 1.4	32.8 ± 1.1	31.1 ± 1.1	33.4 ± 0.9
Before stress/control	32.6 ± 1.1	33.0 ± 1.3	31.7 ± 1.1	33.4 ± 1.1
After stress/control	35.2 ± 0.8	30.1 ± 1.1*	33.9 ± 1.0	31.2 ± 1.3*
<i>Sleepiness vs. wakefulness</i>				
Baseline	31.0 ± 1.2	29.1 ± 1.2	30.7 ± 1.0	33.5 ± 2.2
Before stress/control	29.8 ± 1.3	29.5 ± 1.5	30.2 ± 1.3	30.4 ± 1.3
After stress/control	30.8 ± 1.2	29.4 ± 1.2	31.6 ± 1.1	31.8 ± 0.9
<i>Ratings after stress/control</i>				
Stressfulness	1.0 ± 1.0	62.4 ± 5.4**	3.1 ± 2.1	50.6 ± 7.2**
Painfulness	0.5 ± 0.5	70.5 ± 4.9**	2.1 ± 2.1	68.7 ± 4.5**
Unpleasantness	5.2 ± 3.9	72.4 ± 5.3**	3.2 ± 2.3	68.0 ± 5.0**
<i>Systolic blood pressure</i>				
Baseline	122.0 ± 2.2	119.9 ± 3.5	127.3 ± 3.2	127.7 ± 3.5
Before stress/control	117.3 ± 2.5	115.4 ± 3.7	117.7 ± 2.9	121.3 ± 3.8
During stress/control	117.0 ± 2.4	135.4 ± 4.1**	117.5 ± 2.9	144.1 ± 3.4**
After stress/control	116.0 ± 2.4	116.5 ± 3.5	116.2 ± 2.8	122.6 ± 3.4
<i>Diastolic blood pressure</i>				
Baseline	68.7 ± 1.6	68.3 ± 1.8	70.7 ± 1.7	69.2 ± 2.3
Before stress/control	67.8 ± 1.8	65.5 ± 1.8	65.9 ± 1.5	68.6 ± 2.0
During stress/control	70.1 ± 1.5	83.5 ± 2.9**	66.8 ± 1.6	86.6 ± 2.6**
After stress/control	69.0 ± 1.8	66.9 ± 1.9	67.5 ± 1.7	70.8 ± 2.0

Data represent mean ± s.e.m.

* $p < .05$ ** $p < .01$ (vs. CON/PLAC and CON/aMR).

SECPT led to significant decreases in positive mood and calmness, whereas we observed no such changes after the control manipulation (treatment × time point of measurement interactions: both $F > 4.30$, both $p < .05$, both $\eta^2 > .06$); wakefulness was not affected by the SECPT ($F(1, 68) = 0.20$, $p = .66$; Table 1). In addition, participants that underwent the SECPT rated the treatment as significantly more stressful, painful, and unpleasant than participants that underwent the control condition (main effect treatment: all $F(1, 68) > 120$, all $p < .001$, all $\eta^2 > .64$; Table 1). Importantly, the MR antagonist spironolactone did not affect subjective mood, nor did it modulate the subjective experience of the SECPT (main effect drug and all possible interaction effects: all $F < 1.85$, all $p > .18$).

Systolic and diastolic blood pressure increased significantly in response to the SECPT but not in response to the control manipulation (treatment × time point of measurement interactions: both $F > 66$, both $p < .001$, both $\eta^2 > .49$). As displayed in Table 1, systolic and diastolic blood pressure were higher in the stress than in the control groups during the treatment (both $p < .001$) but not before or after the SECPT/control condition (all $p > .47$). Blood pressure was not affected by spironolactone (main effect drug and all possible interaction effects: all $F < 1.50$, all $p > .23$).

As expected, salivary cortisol was modulated by both the SECPT and MR blockade (Fig. 2). The exposure to the SECPT resulted in significantly increased cortisol concentrations 25 min after the treatment, shortly before the stop-signal task started ($p < .01$; treatment × time point of measurement interaction: $F(2.90, 182.80) = 9.11$, $p < .001$, $\eta^2 = .13$). In addition to the influence of the SECPT, cortisol concentrations were significantly elevated by the MR antagonist spironolactone (immediately before, immediately after, and 25 min after the stress/control manipulation: all $p < .04$; drug × time point of measurement interaction: $F(2.90, 81.27) = 2.41$, $p = .05$, $\eta^2 = .04$). Because the MR is critically involved in the negative feedback control of the hypothalamus-pituitary-adrenal axis (de Kloet et al., 2005), increased cortisol concentrations after spironolactone intake were expected and verify the action of the drug (see also Cornelisse et al., 2011; Otte et al., 2007). It is, however, important to note that spironolactone did not prevent the cortisol increase in response to the SECPT (treatment × drug and treatment × drug × time point of measurement interactions: both $F < 1.5$, both $p > .23$). Men and women did not differ in their cortisol responses to the SECPT or spironolactone (main effect gender and all interaction effects with treatment or drug: all $F < 1$, all $p > .44$).

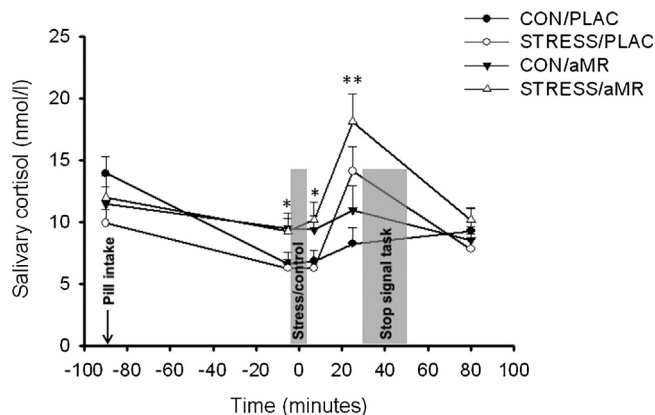


Figure 2 Salivary cortisol concentrations across the experiment. The intake of the mineralocorticoid receptor antagonist (aMR) spironolacton led to a significant increase in cortisol before and after the stress/control condition ($*p < .05$ compared to the placebo groups). The exposure to the socially evaluated cold pressor test resulted in significantly elevated cortisol concentrations before the beginning of the stop-signal task, both in the placebo and in the spironolactone groups ($**p < .01$ compared to the respective control groups). Data represent mean \pm s.e.m.

3.2. Mineralocorticoid receptor blockade prevents stress-induced facilitation of response inhibition

Mean reaction times in correct Go trials were similar as in previous studies with healthy young adults (Turner et al., 2002; Aron and Poldrack, 2006) and the inhibition rate was close to 50% in Stop trials (Table 2). In line with the assumptions of the race model of stop-signal task performance (Logan and Cowan, 1984), the inhibition rate decreased with increasing SSDs ($r = -.87$, $p < .001$), reaction times were significantly faster on Stop trials in which participants responded than in Go trials (mean \pm s.e.m.: 399.8 ± 8.2 ms vs. 460.9 ± 11.3 ms; $t(71) = 12.83$, $p < .001$), and reaction times on Stop trials in which participants responded increased with increasing SSDs ($r = .87$, $p < .001$).

Most relevant for the present study, inhibitory control was influenced by stress and MR blockade. An ANOVA with the factors treatment (control vs. stress) and drug (placebo vs. spironolactone) revealed a marginally significant interaction between treatment and drug ($F(1, 68) = 3.71$, $p = .058$, $\eta^2 = .05$) showing that stress facilitated response inhibition under placebo ($t(34) = 2.61$, $p = .01$) whereas this effect of stress disappeared when participants had received the MR antagonist spironolactone before ($t(34) = 0.02$, $p = .99$; Fig. 3). In addition, we obtained a trend for a main effect of treatment ($F(1, 68) = 3.79$, $p = .056$, $\eta^2 = .05$), which,

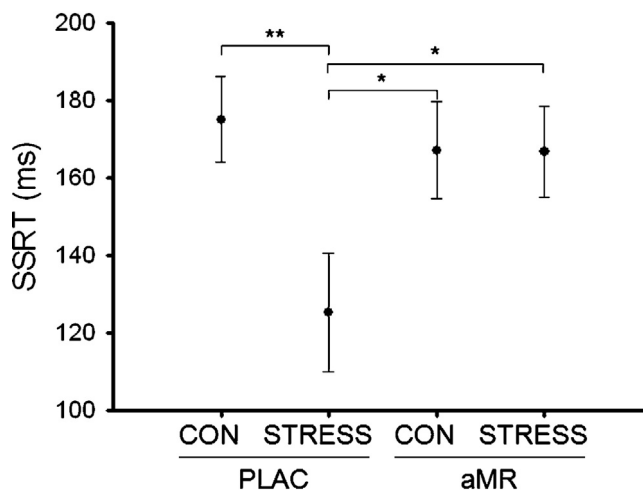


Figure 3 Mineralocorticoid receptor blockade prevents stress-induced facilitation of response inhibition. Stop signal reaction times (SSRTs) were lower (i.e., response inhibition was improved) in stressed participants that were administered a placebo (PLAC) compared to control participants that had received a placebo. After mineralocorticoid receptor blockade (aMR) by spironolactone, this stress-induced enhancement of inhibitory control disappeared. Data represent mean \pm s.e.m. $**p < .01$, $*p < .05$.

Table 2 Performance in the stop-signal task.

	CON/PLAC	STRESS/PLAC	CON/aMR	STRESS/aMR
Errors in Go trials	3.6 \pm 0.7	2.3 \pm 0.6	2.6 \pm 1.1	5.5 \pm 1.7
RT correct Go trials (ms)	457.0 \pm 21.9	481.9 \pm 21.1	443.8 \pm 23.13	458.9 \pm 25.3
RT responses in Stop trials (ms)	403.1 \pm 17.5	406.2 \pm 20.4	382.0 \pm 16.8	406.7 \pm 23.2
Inhibition rate	50.4 \pm 1.0	52.4 \pm 0.81	51.2 \pm 0.9	51.3 \pm 0.8
Stop signal delay (SSD; ms)	270.2 \pm 28.6	347.7 \pm 28.4	271.4 \pm 31.6	287.4 \pm 32.0

Data represent mean \pm s.e.m. RT, reaction time; ms, milliseconds.

however, was mainly due to the performance of the stress/placebo group. Moreover, the cortisol increase in response to the SECPT (cortisol concentration 25 min post-stress minus cortisol concentration before the treatment) correlated negatively with SSRTs, i.e., positively with inhibitory control, in the placebo groups ($r = -.37$, $p = .027$), whereas there was no significant correlation in the spironolactone groups ($r = .03$, $p = .89$; Fig. 4). When we calculated the area under the curve with respect to the increase and with respect to the ground and (AUC_i and AUC_g, respectively, see Pruessner et al., 2003), we obtained a trend for a negative correlation between SSRTs and AUC_i in the placebo groups ($r = -.27$, $p = .11$) but not in the spironolactone groups ($r = .20$, $p = .24$). For the AUC_g, we did not find any correlations, neither in the placebo nor in the spironolactone groups (both $p > .45$).

There was no main effect of spironolactone on SSRTs ($F(1, 68) = 1.69$, $p = .20$). Mean Go reaction times varied between 332 and 775 ms and were not affected by stress or MR blockade (all $F < 0.80$, all $p > .40$). Men and women did not differ in their SSRTs, nor was there any effect of participants' sex on the influence of stress or spironolactone on SSRTs (all $F < 1.20$, all $p > .28$).

4. Discussion

Our results show enhanced response inhibition after stress. Glucocorticoids played a critical role in this effect of stress on inhibitory control. SSRTs correlated with stress-induced cortisol elevations in the placebo groups. Moreover, both the stress-induced enhancement of inhibitory control and the correlation between stress-induced cortisol and SSRTs disappeared after MR blockade by spironolactone, thus demonstrating the importance of glucocorticoids and the MR in particular for the observed effects of stress on response inhibition.

Although the MR is well characterized by rodent studies (Joëls et al., 2008; Karst et al., 2005; Schwabe et al., 2010a),

there are only relatively few studies that addressed MR functioning directly in humans. These studies showed that pharmacological MR blockade results in increased basal cortisol concentrations and increased cortisol response to stress, pointing to impaired negative feedback control of the HPA axis (e.g. Cornelisse et al., 2011; Heuser et al., 2000; Otte et al., 2007). Moreover, these studies suggested that MR blockade in combination with stress may impair working memory (Cornelisse et al., 2011) and that spironolactone alone may impair selective attention (Cornelisse et al., 2011; Otte et al., 2007). Such disruptive effects of MR blockade on attention processes, however, are for several reasons unlikely to account for the findings observed here. First, the control group that had received spironolactone performed similarly as the control/placebo group. Second, the stress/spironolactone group was not impaired in their performance but performed also comparable to the control/placebo group. Finally, if attention was affected in the spironolactone groups, one would expect more errors or slower reaction times on GO trials, which were, however, both not found.

The present study is to the best of our knowledge the first that could show that stress effects on human cognition can be prevented by the MR antagonist spironolactone. Over the past decade, it has been convincingly shown that there is, in addition to the intracellular MR that mediates slow, non-genomic glucocorticoid actions, also a membrane-bound MR that mediates rapid, non-genomic glucocorticoid effects (Joëls et al., 2008). Because participants underwent stress only 30 min before the stop-signal task in this study, it is unlikely that genomic glucocorticoid effects had already developed at the time of behavioral testing. Thus, we assume that the effects of stress on response inhibition were mediated by the membrane-bound MR.

Whereas previous studies suggested that chronic or early-life stress impairs response inhibition (Mika et al., 2012; Mueller et al., 2010), our findings show that acute stress may enhance inhibitory control. The enhanced ability to withhold responses that are inappropriate (e.g., potentially

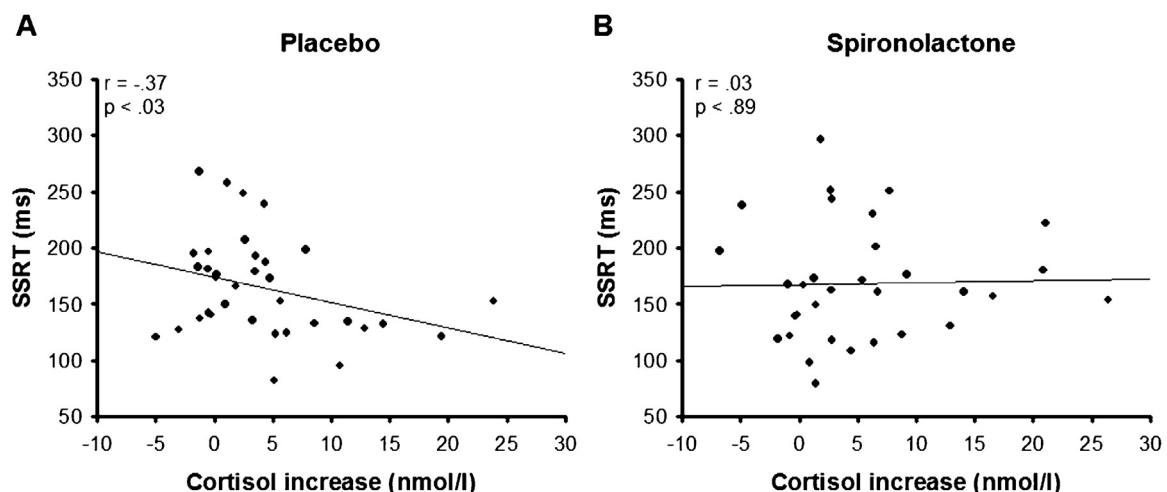


Figure 4 Correlation between increases in salivary cortisol increases from baseline to the beginning of the stop-signal task and the stop-signal reaction time (SSRT) in participants that received a placebo and those that received the mineralocorticoid receptor antagonist spironolactone. (A) In the placebo group, cortisol increases correlated negatively with SSRTs, indicating a facilitatory influence of cortisol on inhibitory control. (B) After spironolactone intake, there was no correlation between cortisol elevations and SSRTs.

dangerous) in the current environment may contribute to coping with the ongoing stressor. Previous studies on the impact of stress and stress hormones on related executive and working memory functions, however, yielded inconsistent results, with some studies showing, same as this study, enhancements (Henckens et al., 2011; Porcelli et al., 2008; Yuen et al., 2009) and others impairments (Plessow et al., 2011; Scholz et al., 2009) of frontal cortex-dependent behaviors. It has been argued that these discrepancies may be related to the stressor intensity and that low as well as high stressor intensities impair cognitive functioning, whereas moderate stress levels have beneficial effects (Joëls, 2006). Significant increases in blood pressure and salivary cortisol verified the successful stress induction by the SECPT in the present study, yet the obtained stress levels were clearly below those that are observed in stressful or even traumatic 'real-life' events (Deinzer et al., 1997). Thus, one might argue that our stressor was moderately stressful and hence beneficial for cognitive performance. However, such interpretations that are based on the assumption of an inverted U relationship of stress and cognitive function remain relatively vague. Another explanation for the discrepant findings on the influence of stress on executive functions takes differences between tasks into account that are associated with the recruitment of different brain areas. For instance, stress-induced impairments were found repeatedly in tasks that rely on the dorso-lateral prefrontal cortex (Barsegyan et al., 2010; Qin et al., 2009), whereas successful response inhibition in the stop-signal task is mainly associated with inferior and medial frontal areas (Aron and Poldrack, 2006; Verbruggen and Logan, 2008; Wager et al., 2005).

The present findings could have some implications for current research on the impact of stress on the control of instrumental action. Accumulating evidence suggests that stress may promote a shift from goal-directed to habitual action (Dias-Ferreira et al., 2009; Gourley et al., 2012; Schwabe et al., 2010b, 2011; Schwabe and Wolf, 2009). This shift toward habit behavior has also been related to increased impulsivity as assessed by the Barrett Impulsiveness Scale (Hogarth et al., 2012). Thus, the present finding that stress enhanced inhibitory control might be viewed as in conflict with data showing that stress facilitates habit behavior which in turn is related to increased impulsivity. It is, however, important to note that the personality trait impulsivity as measured by the Barrett Impulsiveness Scale is clearly distinct from the kind of inhibitory control that was assessed in the stop-signal task here. Our findings provide therefore (indirect) evidence that whereas the personality trait impulsivity appears to be linked to habit behavior, changes in inhibitory motor control are rather unlikely to play a major role in the shift toward habit action after stress.

In conclusion, the present study shows that stress may facilitate response inhibition in a stop-signal task. The enhancement of inhibitory control after stress may be part of the amazing plasticity that facilitates adaptation to stressful situations. Understanding, exactly *how* stress may enhance inhibitory control, that is, which pathways and systems are involved in these effects remains a challenge for future research. Here, we show for the first time that the stress-induced changes in response inhibition are critically dependent on the activation of the MR.

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Conflict of interest

The authors report no conflict of interest.

Contributors

L.S. designed the experiment, conducted the experiment, and analyzed the data. O.H. and M.T. provided pharmacological advice regarding the dosage and administration of the drug and the screening of the participants. All authors contributed to writing the manuscript.

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