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Cortisol boosts risky decision-making behavior in men but not in women

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ABSTRACT

Acute stress may escalate risky decision-making in men, while there is no such effect in women. Although first evidence links these gender-specific effects of stress to stress-induced changes in cortisol, whether elevated cortisol is indeed sufficient to boost risk-taking, whether a potential cortisol effect depends on simultaneous noradrenergic activation, and whether cortisol and noradrenergic activation exert distinct effects on risk-taking in men and women is unknown. In this experiment, we therefore set out to elucidate the impact of cortisol and noradrenergic stimulation on risky decision-making in men and women. In a fully-crossed, placebo-controlled, double-blind design, male and female participants received orally either a placebo, hydrocortisone, yohimbine, an alpha-2-adrenoceptor-antagonist leading to increased noradrenergic stimulation, or both drugs before completing the balloon analogue risk task, a validated measure of risk-taking. Overall, participants' choice was risk-sensitive as reflected in reduced responding in high- compared to moderate- and low-risk conditions. Cortisol, however, led to a striking increase in risk-taking in men, whereas it had no effect on risk-taking behavior in women. Yohimbine had no such effect and the gender-specific effect of cortisol was not modulated by yohimbine. Our data show that cortisol boosts risk-taking behavior in men but not in women. This differential effect of cortisol on risk-taking may drive gender differences in risky decision-making under stress.

1. Introduction

Stressful events are common in our everyday life. These events trigger an orchestrated physiological response that involves numerous stress mediators with specific spatial and temporal niches (Joels and Baram, 2009; McEwen, 2007). Within seconds after a stressful event, monoamines, including noradrenaline, are released by neuronal circuits that are involved in the evaluation of the stressor or indirectly by the autonomic nervous system. With a delay of several minutes, stressful encounters trigger the secretion of glucocorticoid hormones (mainly cortisol in humans) through the activation of the hypothalamus-pituitary-adrenal (HPA) axis. The many neurotransmitters, hormones and neuropeptides that are released in response to stressors, and in particular noradrenaline and glucocorticoids, are known to modulate a broad range of cognitive functions (Joels et al., 2011; Roozendaal et al., 2009; Sandi and Haller, 2015; Schwabe et al., 2012a), including decision-making and risk-taking behavior (Bendahan et al., 2017; Porcelli and Delgado, 2009, 2017; Starcke and Brand, 2012, 2016; van den Bos and Flik, 2015; van den Bos et al., 2009; Vinkers et al., 2013). Effects of stress and stress mediators on risk-taking, i.e. actions that may have unpleasant or undesirable outcomes, are of particular interest since people are often forced to make important decisions while being stressed, whether at the stock market, in the emergency room, or in combat.

Acute stress has been repeatedly shown to boost risky decision-making, i.e. decision-making processes in which explicitly the outcome probabilities are specified (Buckert et al., 2014; Jamieson and Mendes, 2016; Starcke and Brand, 2012; Starcke et al., 2008), as well as financial risk preferences, reflected, for example, in the willingness to enter a competitive environment (Buser et al., 2016). This impact of stress on risk-taking as well as related behavior, however, appears to be different in men and women: whereas the majority of studies showed that stress increases risk-taking in men, stress has no effects or even decreases risk-taking in women (Lighthall et al., 2009; Lighthall et al., 2012; van den Bos et al., 2009). These gender differences may be owing to opposite effects of stress on brain areas critical for decision-making, including the striatum and insular cortex (Mather and Lighthall, 2012). Moreover, the stress-induced increase in risky decision-making has been associated with the cortisol response to the stressor (Buckert et al., 2014; van den Bos et al., 2014) and there is first evidence that stress-induced or pharmacological cortisol elevations may be differentially related to risk-taking in men and women (Buser et al., 2016; Cueva et al., 2015; Kandasamy et al., 2014; van den Bos et al., 2014). However, whether cortisol is indeed causally involved in risky decision-

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making, whether it acts alone or, as demonstrated for other cognitive processes (Roozendaal et al., 2004; Roozendaal et al., 2006; Schwabe et al., 2010), in interaction with noradrenaline, and whether the influence of cortisol and noradrenaline on risk-taking actually differs in men and women has not been systematically investigated so far.

In this experiment, we examined the impact of cortisol and noradrenergic stimulation on risk-taking behavior in men and women in a risky decision-making task, referred to as the balloon analogue risk task (BART; Lejuez et al., 2002). To this end and in order to determine potential interactions between cortisol and noradrenergic stimulation, in absence of a stress reaction, participants received orally either a placebo, hydrocortisone, the α2-adrenoceptor-antagonist yohimbine leading to increased noradrenergic stimulation, or both drugs, before they completed the BART. The BART has been shown to mirror real world risk-taking scenarios, as the willingness to take a risk is rewarded up to a certain point, after which participants are faced with an increased likelihood for negative outcomes, and each decision is worth more than the previous one (Lejuez et al., 2002). To validate the action of the drugs, salivary cortisol (to measure hydrocortisone administration) and autonomic parameters (systolic and diastolic blood pressure) were measured repeatedly across the experiment. Furthermore, we repeatedly measured subjective assessments (for which we expected no change in placebo and cortisol groups, while yohimbine intake may be associated with increased subjective arousal (Goldberg et al., 1983; Mattila et al., 1988). Based on previous evidence showing that acute stress increases risk-taking in men but not in women in the BART (Lighthall et al., 2009; Lighthall et al., 2012) and that this effect is related to the stress-induced cortisol response (Buckert et al., 2014; van den Bos et al., 2014), we predicted that hydrocortisone administration would boost risk-taking in men but not in women. Although the role of noradrenergic activation in risky decision-making is less well studied, there is first evidence that adrenergic activity may be linked to increased risk-taking in women but not in men (van den Bos et al., 2014). We therefore hypothesized that yohimbine might elevate risk-taking solely in women. If hydrocortisone and yohimbine have indeed such different effects in men and women, an interactive influence of the two substances was considered to be rather unlikely.

2. Methods

2.1. Participants and experimental design

One-hundred and three healthy, normal-weight volunteers participated in this experiment (52 female; age (M ± SEM): 24.79 ± 0.36 years; body-mass-index (BMI, M ± SEM):22.79 ± 0.19 kg/m^2). Exclusion criteria were checked in a standardized interview and comprised any current illness, lifetime history of any neurological or mental disorders, history of hydrocortisone intolerance, cardiovascular disorders, including low and high blood pressure, diabetes or any related disorders, medication intake within the four weeks prior to participation, a self-reported BMI below 19 or above 27 kg/m^2, tobacco- or drug use and, in women, intake of hormonal contraceptives. Female participants were not tested during their menses and menstrual phase was recorded. In retrospect, the number of women in the luteal and follicular phase was comparable in the different experimental groups ($x^2(6) = 6.26$, $P = .395$).

We used a fully-crossed, placebo-controlled, double-blind, between-subjects design, with the factors cortisol (placebo vs. hydrocortisone) and noradrenergic stimulation (placebo vs. yohimbine), thus resulting in four experimental groups. Participants were randomly assigned to these four groups (placebo:13 men and 14 women, cortisol: 12 men and 13 women, yohimbine: 13 men and 12 women and combined cortisol and yohimbine: 13 men and 13 women per group). To control for the diurnal rhythm of cortisol, all testing took place between 12:30 and 19:00. Participants were advised to abstain from food and caffeine intake, as well as excessive exercise 2 h before testing. All participants gave written informed consent before participation in the study. After completion of the experiment, participants received a compensation of 36.50€. The sample tested was part of a larger study on stress mediators and cognition (Kluen et al., 2017; Kluen et al., 2016), which was approved by the ethics committee of the Hamburg Medical Association.

2.2. Experimental procedure

2.2.1. Physiological and subjective measures

After their arrival at the lab, participants completed the Beck Depression Inventory (BDI; Beck et al., 1961), the Trier Inventory for Chronic Stress (TICS; Schulz and Schlotz, 1999) and the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1994), to control for depressive mood, chronic stress as well as state and trait anxiety, respectively. Further, participants completed the Barratt Impulsiveness Scale (Patton et al., 1995) as well as the BIS/BAS Scales (Carver and White, 1994) to control for impulsive behavior as well as behavioral inhibition and activation. Subjective mood (German Mood Scale, MDBF; Steyer et al., 1994) and blood pressure (Omron Healthcare Europe B.V) were measured before pill intake (baseline), as well as 45 min, 70 min, 85 min (i.e. before the task) and 100 min after pill intake (i.e. when the task was completed). Saliva samples were also taken at these times, using Salivette® collection devices (Sarstedt, Germany). After collection, saliva samples were frozen at −18 °C and later analyzed for concentrations of cortisol using a luminescence assay (IBL, Germany; intra- and inter assay coefficients of variance were below 10 percent).

2.2.2. Pharmacological manipulation

After completing the questionnaires and baseline measurements of the subjective and physiological parameters, participants received orally either a placebo, 20 mg hydrocortisone, 20 mg yohimbine, an α2-adrenoceptor-antagonist leading to increased noradrenergic stimulation, or both drugs. Pills could not be differentiated in size or color and neither the experimenter nor the participant knew about the contents (double-blind). Drug dosages and timing of administration were chosen in accordance with previous studies (Buchanan and Lovallo, 2001; Henckens et al., 2011; Margittai et al., 2016; Schwabe et al., 2010, 2012b, 2013).

2.2.3. Balloon analogue risk task (BART)

About 85 min after pill intake, when the drug actions were assumed to be fully developed, participants completed a modified version of the Balloon Analogue Risk Task (BART), which was previously introduced as a measure of risky decision-making (Lejuez et al., 2002; Lighthall et al., 2009; Lighthall et al., 2012). In this task, participants saw one balloon at a time on a computer screen (60 balloons in total) and were instructed that the goal of the task was to win money by pumping up the balloons without exploding. They were also told that at the end of the task they would receive a monetary bonus, which would be calculated from 20 randomly picked trials. After task completion, the bonus amount was displayed on the computer screen.

Balloons could be inflated by pressing a ‘Pump up balloon’ button (Fig. 1). Each balloon belonged to one of three categories, ‘high risk’, ‘moderate risk’, and ‘low risk’, with a total of 20 balloons per category. Categories were defined according to the probability of exploding. More specifically, the risky balloon was assigned integers from 1 to 16, the moderately risky balloon from 1 to 32 and the low risky balloon from 1 to 64. The computer program chose integers randomly one after the other when the participant pumped up the balloon (i.e., one integer per button press). When a 1 was chosen, the balloon exploded. Thus, fewer integers available to choose from implicates a higher probability of an explosion. Each risk category had a specific color (yellow, green, or blue), which was counterbalanced across participants and experimental groups. For each button press, participants heard a sound of a balloon blowing up and saw the image of the balloon expanding in size. Participants were told that balloons could explode at any time, however

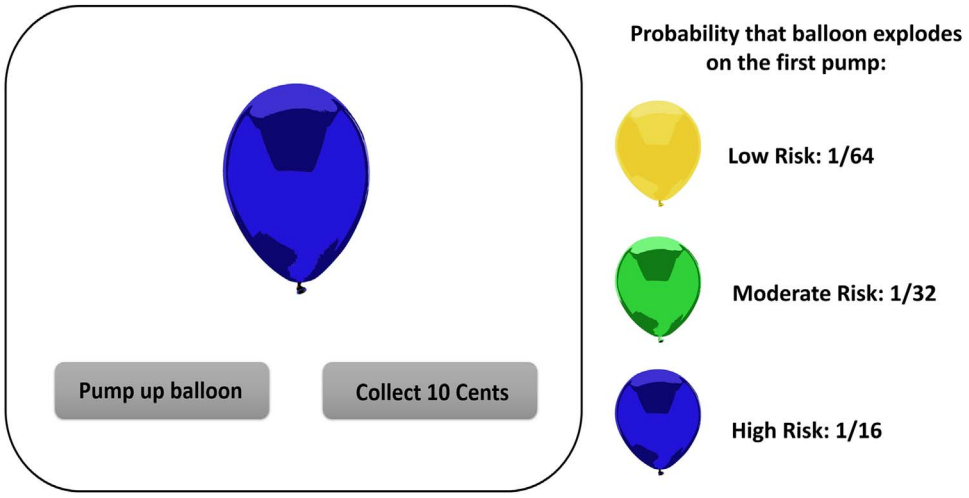

Fig. 1. Balloon Analogue Risk Task used to probe risky decision-making. Participants were presented with one balloon at a time and were instructed that their goal was to win money by pumping up each balloon without exploding. Balloons were inflated by pressing the 'Pump Up Balloon' button. Balloons belonged to one of three categories, high risk, moderate risk and low risk, which were shown in different colors. These colors were counterbalanced across participants and groups. Risk categories corresponded to the probability of exploding. High risk balloons had a chance of 1/16 of exploding, while moderately risky balloons exploded with a chance of 1/32 and low risk balloons with a probability of 1/64. For each pump, the balloon grew in size, while participants received one cent in a temporary bank, which was displayed on a second button. Participants could decide to cash out and press the temporary bank button, after which a new balloon appeared and the money was transferred to a permanent bank, while the temporary bank started again with zero, or to continue pumping the current balloon. Cashing out was only possible when the balloon did not explode. If however the balloon exploded, participants lost all money, which they collected in the temporary bank up to this point.

they were not informed that there were three pre-defined categories, which determined the approximate number of pumps until explosion of a balloon. It was, however, possible for participants to learn across trials which balloon had a higher chance of exploding. For each time participants pressed the 'Pump up balloon' button, they received one cent in a temporary bank, which was displayed on a second button (Fig. 1). Initially the button displayed 'collect €€€', but once the participant pumped up the balloon the Euro symbols were replaced by the amount of money that corresponded to the number of times the button was pressed. When participants pressed the 'Collect' button they could transfer their money to a permanent bank, which terminated the trial and a new balloon was displayed. While participants could see the amount of money they accumulated in the temporary bank when blowing up the balloon, once they transferred the money to the permanent bank, the temporary bank started again from zero. The money saved in the permanent bank was not shown to the participant. Participants could only transfer the money to the permanent bank when the balloon did not explode, otherwise all money in the temporary bank was lost. When the balloon exploded, participants saw an exploding balloon and heard a popping noise. Participants did not have to adhere to a specific timing, but completed the task in ten minutes on average. Before and after each trial, participants saw a black fixation cross on a white background for 1 s.

Our primary measure of participants' risk taking behavior was the mean adjusted number of button clicks that was calculated for each balloon condition (Lejuez et al., 2002; Lighthall et al., 2009). Specifically, the mean adjusted button presses across one balloon condition were taken only for the trials in which the balloon did not explode. Additionally, we used the total number of balloons that exploded for each risk category as a measure of learning and risk-taking.

2.3. Statistical analyses

Physiological and subjective measures were analyzed using mixed-design ANOVAs, with time-point of measurement as within-subjects factor and noradrenergic stimulation (placebo vs. yohimbine), cortisol (placebo vs hydrocortisone) and gender (male vs female) as between-subjects factors. Task performance was analyzed using two different performance indices, the mean adjusted button clicks and the total number of balloons that exploded. These parameters were analyzed by means of mixed-design ANOVAs with the within-subjects factor risk category (low vs. moderate vs. high risk of exploding), and block (5 trials per block) and the between-subjects factors noradrenergic stimulation, cortisol and gender. Significant main or interaction effects were pursued with appropriate follow-up tests, including univariate ANOVAs or mixed-design ANOVAs. In case of violations of sphericity, Greenhouse-Geisser correction was used. All reported *P*-values are two-tailed.

3. Results

3.1. Manipulation check

At baseline, i.e. before pill intake, there was no significant difference between groups in systolic blood pressure, salivary cortisol levels or subjective mood (all $F \leq 3.32$, all $P \geq .071$, all $\eta^2 < .034$, see Table 1). Yohimbine groups showed slightly elevated diastolic blood pressure at baseline ($F(1, 95) = 4.00$, $P = .048$, $\eta^2 = .040$). Over time, however, we observed a significant increase in both systolic and diastolic blood pressure in participants that had received yohimbine alone or in combination with hydrocortisone, compared to those groups that had not received yohimbine (time point of measurement × noradrenergic stimulation: both $F \geq 4.23$, both $P \leq .005$, all $\eta^2 > .043$). At 45 minutes, 70 minutes, 85 minutes (i.e. before the start of the task), and 100 minutes (i.e. after completion of the task) after pill intake, participants in the yohimbine groups showed significantly elevated systolic and diastolic blood pressure, compared to participants that did not receive yohimbine (all $F \geq 11.72$, all $P \leq .001$, all $\eta^2 > .110$). Increases in systolic and diastolic blood pressure were not influenced by hydrocortisone administration (time point of measurement × cortisol and time point of measurement × cortisol × noradrenergic stimulation, all $F < 2.10$, all $P > .091$, all $\eta^2 < .022$).

Intake of hydrocortisone, however, led, as expected, to a significant increase in salivary cortisol (time point of measurement × cortisol: $F(1.55, 146.74) = 39.03$, $P < .001$, $\eta^2 = .291$), compared to the intake of placebo and/or yohimbine. Forty-five, 70, 85 and 100 minutes after pill intake, salivary cortisol concentrations were significantly increased in participants that had received hydrocortisone alone or in combination with yohimbine, compared to those who had not received hydrocortisone (all $F \geq 72.13$, all $P < .001$, all $\eta^2 > .432$). The increase in salivary cortisol after hydrocortisone intake was not affected by yohimbine intake ($F(1.55, 146.74) = 2.28$, $P = .119$, $\eta^2 = .023$) and intake of yohimbine alone had no impact on salivary cortisol concentrations ($F(1.55, 146.73) = 1.90$, $P = .162$, $\eta^2 = .020$).

Although hydrocortisone did not influence subjective mood, neither alone nor in combination with yohimbine (all $F < 1.25$, all $P > .29$, all $\eta^2 < .013$, see Table 3), yohimbine intake increased subjective restlessness (time point of measurement × noradrenergic stimulation: *F*

Table 1
Physiological measures for all groups.

	Men				Women			
	Plac	Yoh	Cort	Cort + Yoh	Plac	Yoh	Cort	Cort + Yoh
Systolic Blood Pressure								
Before pill intake	132.88 (2.71)	131.81 (3.32)	136.08 (3.20)	133.46 (3.54)	114.79 (2.34)	114.42 (2.12)	115.85 (2.01)	119.69 (3.15)
45 min after Pill Intake	**127.62* (2.37)**	133.23 (4.54)	**126.29 (2.99)**	**139.96* (3.94)**	115.54* (2.29)	**122.04# (2.90)**	112.27# (2.76)	**125.00* (3.10)**
70 min after pill intake	**126.08* (2.05)**	136.46* (3.60)	**127.1 (3.00)**	**140.38* (3.16)**	113.79* (2.42)	**121.96* (3.16)**	116.00 (1.85)	124.31* (2.79)
85 min after pill intake	130.69* (2.14)	**140.92*# (4.10)**	**124.50*# (2.05)**	**141.58* (3.16)**	120.07* (3.97)	**124.08 (2.72)**	117.27 (2.66)	**126.81 (2.68)**
100 min after pill intake	129.27* (1.71)	**138.81* (3.87)**	131.33 (2.33)	**144.35* (3.69)**	118.86* (2.00)	**126.79*# (2.50)**	119.46# (1.89)	**128.92* (2.47)**
Diastolic Blood Pressure								
Before pill intake	82.31 (2.12)	84.62 (2.38)	80.88 (2.30)	82.04 (1.87)	75.18 (2.16)	80.50 (2.08)	78.00 (2.05)	81.35 (2.14)
45 min after pill intake	79.42* (1.80)	85.12*# (1.84)	**76.79# (2.37)**	**86.92* (1.53)**	**78.18* (2.09)**	**85.21*# (2.27)**	75.81# (1.99)	83.46 (2.22)
70 min after pill intake	80.04 (1.89)	85.65# (1.97)	**76.96# (2.22)**	**86.50* (1.66)**	76.14* (1.92)	**85.17*# (2.28)**	78.15# (1.60)	82.31* (1.94)
85 min after pill intake	82.77 (1.90)	**87.81 (2.63)**	**75.46 (2.20)**	**85.81* (1.64)**	77.75* (1.92)	**84.13* (2.80)**	77.62 (2.33)	83.58* (1.85)
100 min after pill intake	82.62 (2.26)	86.85 (2.74)	79.67 (3.03)	**88.92 (3.06)**	**81.57* (2.38)**	**87.04# (3.19)**	79.05# (2.06)	**85.12 (1.75)**
Cortisol								
Before pill intake	5.39 (0.80)	4.94 (0.50)	5.32 (0.84)	5.93 (0.99)	3.67 (0.60)	2.87 (0.57)	4.38 (0.88)	4.18 (0.86)
45 min after pill intake	**2.95* (0.58)**	**3.23# (0.69)**	**48.15*# (10.70)**	**58.25*# (8.70)**	**2.27* (0.30)**	2.34# (0.39)	**46.79*# (15.82)**	**85.84*# (16.81)**
70 min after pill intake	**2.55* (0.42)**	4.15# (1.47)	**37.23*# (4.43)**	**50.91*# (5.38)**	**2.14* (0.29)**	2.06# (0.35)	**60.06*# (8.03)**	**64.79*# (8.24)**
85 min after pill intake	**2.36* (0.41)**	5.93# (1.68)	**35.81*# (3.53)**	**44.60*# (5.36)**	**1.40* (0.18)**	1.99# (0.42)	**66.37*# (9.12)**	**61.10*# (6.45)**
100 min after pill intake	**2.47* (0.43)**	6.74# (2.15)	**38.73*# (3.86)**	**37.54*# (4.00)**	**1.43* (0.16)**	2.07# (0.45)	**62.34*# (8.45)**	**63.25*# (8.33)**

Data represent means (standard error). Plac - placebo, Yoh - yohimbine', Cort - hydrocortisone. Bold represents significant differences from the respective baseline measure of the group ($P < .05$), * $P < .05$ vs. placebo and # $P < .05$ vs. groups that did not receive hydrocortisone and yohimbine, respectively.

(2.83, 268.60) = 6.51, $P < .001$, $\eta^2 = .064$) and tended to decrease mood ($F(2.98, 283.33) = 2.62$, $P = .052$, $\eta^2 = .027$) and wakefulness ($F(2.99, 283.55) = 2.35$, $P = .073$, $\eta^2 = .024$).

Overall, systolic blood pressure and wakefulness were higher in men than in women, whereas overall cortisol concentrations were higher in women than in men (all $F > 8.28$ all $P < .005$, $\eta^2 > .08$). However, both men and women showed a marked increase in blood pressure and salivary cortisol over time after yohimbine and hydrocortisone intake, respectively (all $F \geq 3.22$ all $P \leq .025$, all $\eta^2 > .063$; see Table 1).

3.2. Elevated cortisol increases risk-taking behavior in men but not in women

3.2.1. Mean adjusted button clicks

As in previous studies using the BART (Lejuez et al., 2002; Lighthall et al., 2009; Lighthall et al., 2012), we used the mean adjusted button clicks for each balloon risk condition as a primary measure of participants' risk taking behavior. First of all, participants pressed the 'pump'-button significantly less often for the high risk vs. moderately risky balloons ($P < .001$) and for the moderately risky vs. low risk balloons ($P < .001$; main effect risk condition: ($F(1.45, 137.90) = 153.02$, $P < .001$, $\eta^2 = .617$), indicating that participants learned the different risk levels well. Furthermore, we did obtain a significant main effect of block ($F(2.74, 259.74) = 6.69$, $P < .001$, $\eta^2 = .066$) as well as a significant block × risk condition interaction $F(4.68, 444.41) = 5.33$, $P < .001$, $\eta^2 = .053$), although there was no clear-cut pattern of variation of button presses in the different risk conditions across blocks (see supplemental Fig. S1). This effect of block was, however, not dependent on participants' gender *(all $F \leq 1.710$. all $P \geq .136$,* all $\eta^2 > .018$*)*. Critically, while there was no overall gender effect (*$F(1, 95) = .57$, $P = .454$,* $\eta^2 = .006$) the data showed a differential effect of cortisol on the mean adjusted button clicks in men and women (cortisol × gender interaction ($F(1,95) = 5.77$, $P = .018$, $\eta^2 = .057$) and this differential effect depended on the risk condition (risk condition × cortisol × gender: $F(1.45, 137.90) = 3.62$, $P = .043$, $\eta^2 = .037$). Follow-up tests showed that, while there was no effect of cortisol or gender on the mean adjusted button clicks in the high risk condition (all $F \leq .211$, all $P \geq .647$, $\eta^2 = .002$), we obtained significant gender × cortisol interactions for the moderate risk condition ($F(1, 95) = 7.98$, $P = .006$, $\eta^2 = .078$) as well as for the low risk

Table 2
Control variables in all groups.

	Men				Women			
	Plac	Yoh	Cort	Cort + Yoh	Plac	Yoh	Cort	Cort + Yoh
Chronic Stress								
TICS Screening Score	13.15 (2.86)	12.23 (2.68)	15.92 (2.22)	13.00 (1.66)	15.71 (2.12)	18.17 (2.52)	15.38 (2.10)	16.54 (1.99)
Depression Index								
BDI Score	5.15 (1.27)	4.62 (0.96)	4.42 (0.69)	4.08 (1.12)	6.14 (1.53)	5.92 (1.31)	8.08 (1.11)	6.00 (0.96)
State and Trait Anxiety								
State	36.08 (2.00)	33.08 (1.15)	36.90 (1.84)	32.75 (1.71)	34.62 (2.60)	35.55 (2.09)	33.92 (1.06)	35.54 (2.41)
Trait	37.23 (2.62)	33.62 (2.32)	38.92 (2.59)	32.85 (1.55)	36.64 (2.75)	36.64 (2.39)	39.77# (2.04)	33.38# (2.10)
Impulsivity								
Barrat Impulsivity Scale	33.77 (0.92)	34.46 (0.84)	36.17 (1.28)	35.69 (0.94)	35.64 (0.90)	37.50 (1.56)	35.85 (1.14)	35.92 (1.35)
Behavioral Activation and Inhibition								
BIS	17.38 (0.84)	16.31 (0.72)	16.25 (0.60)	16.54 (1.50)	15.71 (0.70)	15.50 (0.65)	16.77 (0.80)	15.08 (0.67)
BAS	24.31 (1.42)	23.46 (1.80)	23.00 (1.25)	23.08 (2.21)	19.93 (0.68)	23.17* (1.30)	21.77 (0.79)	20.85 (0.96)

Data represent means (standard error). Plac - placebo, Yoh - yohimbine', Cort - hydrocortisone. Bold represents significant differences from the respective baseline measure of the group ($P < .05$), * $P < .05$ vs. placebo and # $P < .05$ vs. groups that did not receive hydrocortisone and yohimbine, respectively.

Table 3
Subjective measures of stress in all groups.

	Men				Women			
	Plac	Yoh	Cort	Cort + Yoh	Plac	Yoh	Cort	Cort + Yoh
Mood Questionnaire								
Subjective mood								
Before pill intake	34.15 (1.31)	35.08 (0.76)	32.83# (1.04)	36.15# (0.85)	34.93 (0.87)	34.92 (1.13)	33.62 (1.28)	34.00 (1.94)
45 min after pill intake	34.08 (1.21)	35.31 (1.02)	33.25 (1.02)	34.08 (1.53)	35.36 (0.67)	31.42 (1.91)	33.62 (1.35)	32.92 (1.96)
70 min after pill intake	33.54 (1.35)	34.92 (0.91)	32.92 (1.09)	**33.00 (1.67)**	32.93 (1.38)	**31.50 (1.64)**	33.31 (1.36)	32.00 (2.10)
85 min after pill intake	**33.15 (1.55)**	34.23 (0.91)	33.08 (1.24)	**33.62 (1.30)**	33.00 (1.70)	32.42 (1.87)	33.46 (1.10)	32.15 (2.41)
100 min after pill intake	33.85 (1.36)	33.62 (1.05)	33.33 (1.43)	33.77 (1.46)	34.14 (1.37)	32.67 (1.75)	34.08 (1.29)	33.00 (2.40)
Wakefulness								
Before pill intake	32.15 (1.74)	31.92 (1.22)	30.00 (1.35)	32.85 (1.63)	30.07 (1.29)	32.50 (1.32)	28.62 (1.67)	31.15 (1.41)
45 min after pill intake	32.69 (1.74)	30.69 (1.21)	28.50 (1.66)	30.69 (1.32)	28.50 (0.96)	**28.00 (1.71)**	26.85 (1.81)	29.77 (1.82)
70 min after pill intake	32.46 (2.07)	29.77 (1.71)	29.75 (1.69)	30.92 (1.50)	**25.21 (1.22)**	**27.58 (1.59)**	26.08 (1.86)	**25.92 (2.03)**
85 min after pill intake	33.38 (1.69)	**28.77 (1.70)**	29.00 (1.58)	30.62 (1.62)	**26.57 (1.11)**	**27.83 (1.47)**	27.46 (1.65)	**27.62 (2.32)**
100 min after pill intake	**33.46 (1.72)**	**28.92 (1.65)**	29.67 (1.76)	31.00 (1.40)	**26.29 (1.34)**	**27.67 (1.75)**	27.38 (1.34)	28.08 (2.29)
Restlessness								
Before pill intake	33.08* (0.96)	35.08# (0.72)	29.33*# (1.34)	34.92# (1.03)	32.71 (1.16)	31.67 (1.47)	31.69 (1.04)	31.46 (1.90)
45 min after pill intake	34.00 (1.08)	34.15 (1.80)	32.75 (0.95)	32.08 (2.06)	32.71* (1.02)	28.08 (2.63)	31.69 (1.29)	26.85* (2.55)
70 min after pill intake	33.69 (1.18)	33.38 (1.21)	**31.58 (1.20)**	32.08 (1.97)	31.71 (1.72)	28.75 (2.29)	32.00 (1.03)	28.69 (2.36)
85 min after pill intake	33.08 (1.25)	32.85 (1.42)	30.25 (1.39)	33.31 (1.38)	30.93 (1.47)	29.75 (2.73)	31.00 (0.93)	29.38 (2.05)
100 min after pill intake	34.38 (1.02)	32.62 (1.25)	31.75 (1.41)	32.31 (1.95)	32.50 (1.36)	29.83 (2.53)	31.15 (0.96)	30.62 (1.91)

Data represent means (standard error). Plac - placebo, Yoh - yohimbine', Cort - hydrocortisone. Bold represents significant differences from the respective baseline measure of the group ($P < .05$), * $P < .05$ vs. placebo and # $P < .05$ vs. groups that did not receive hydrocortisone and yohimbine, respectively.

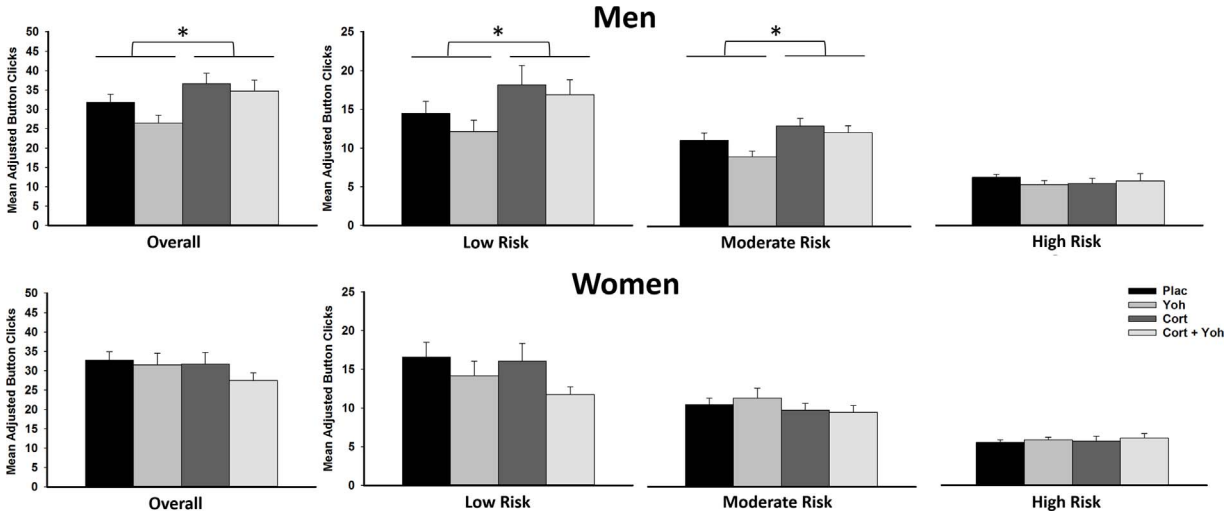

Fig. 2. Impact of cortisol on the mean adjusted button clicks in men and women. Risk-taking was expressed as mean adjusted button presses for trials in which the balloon did not explode. Overall, participants showed decreasing mean adjusted button clicks from the low to the moderate and high risk condition, illustrating an understanding of the different risk categories. More importantly, however, cortisol increased the mean adjusted button presses in men, in particular for low and moderately risky trials, indicating increased risk-taking behavior. In women, there was no such effect of cortisol. Yohimbine had no such effect and did also not modulate the impact of cortisol on risk-taking behavior. Plac − placebo, Yoh − yohimbine, Cort − cortisol. Error bars represent standard error of the mean. * $P < .05$.

condition ($F(1, 95) = 4.66$, $P = .033$, $\eta^2 = .047$). Both in moderate and low risk trials, men that had received hydrocortisone showed significantly more mean adjusted button clicks, compared to men that had not received hydrocortisone (all $F \geq 5.11$, all $P \leq .028$, $\eta^2 \geq .098$), while this was not the case in women (all $F \leq 1.73$, all $P \geq .195$, $\eta^2 \leq .035$; see Fig. 2).

Beyond these effects of hydrocortisone intake, we obtained a significant interaction of risk condition × block × noradrenergic stimulation ($F(4.68, 444.41) = 2.87$, $P = .017$, $\eta^2 = .029$; all other main or interaction effects including the factor noradrenergic stimulation: all $F > 2.8$, all $P > .079$, all $\eta^2 > .029$). Follow-up tests revealed a significant interaction of block and risk condition both in participants that had received yohimbine ($F(4.55, 213.84) = 2.37$, $P = .046$, $\eta^2 = .048$) and in those that did not receive yohimbine ($F(4.27, 205.02) = 5.40$, $P < .001$, $\eta^2 = .101$), yet this effect was much stronger in the latter groups. Participants in the yohimbine groups appeared to act more carefully and their choice behavior did not vary as much across blocks and risk conditions as the choice behavior of individuals that did not receive yohimbine (see supplemental Fig. S1).

3.2.2. Total number of balloons exploded

As a second indicator of risk taking we calculated the total number of balloons that exploded for each risk condition. Overall, balloons exploded in about 42 percent of all trials, with critical differences between risk conditions: while about 24 percent of the balloons exploded in the low risk condition and 42 percent in the moderately risky condition, about 60 percent of the balloons exploded in the high risk condition. Accordingly, we obtained a significant main effect for risk condition ($F(1.81, 171.78) = 241.62$, $P < .001$, $\eta^2 = .718$), indicating that participants learned which balloons were the risky ones (both $P < .001$), as well as a main effect for block ($F(2.49, 236.75) = 7.14$, $P < .001$, $\eta^2 = .070$), and a significant interaction between risk

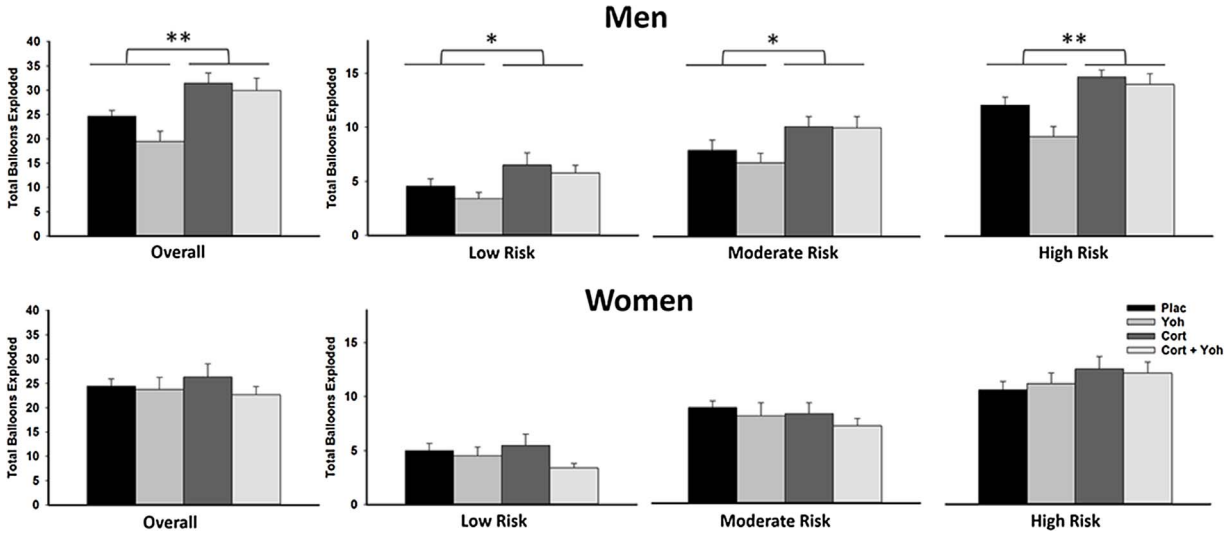

Fig. 3. Cortisol administration increases the total number of balloons exploded in men. Overall, the total number of balloons exploded increased from the low to the moderate and high risk condition. Furthermore, cortisol administration led to an increased number of balloons exploded in men. In women, there was no such effect. Increased noradrenergic stimulation after yohimbine intake tended to decrease the total number of balloons exploded in both men and women, however these differences did not reach statistical significance. For each risk condition, participants completed a total of 20 trials. Error bars represent standard error to the mean. * P < .05, ** P < .001

condition × block: $F(6, 570) = 6.22$, $P < .001$, $\eta^2 = .061$). In the high risk condition, there was no main effect of block ($F(3, 285) = 1.59$, $P = .192$, $\eta^2 = .016$), which may be due to less variance as a high number of balloons exploded. In the moderately risky and low risk condition, however, we did observe a slight increase in the number of balloons exploded across blocks (both $F > 2.95$, both $P < .033$, $\eta^2 > .030$, see supplemental Fig. S2). There was however no significant effect of block and risk condition in interaction with cortisol and/or yohimbine, neither with nor without gender (all $F < 1.68$, all $P \geq .129$, all $\eta^2 \leq .017$) (Fig. 3).

Moreover, there was a significant main effect of cortisol ($F(1,95) = 9.32$, $P = .003$, $\eta^2 = .089$), indicating that in the cortisol groups a higher number of balloons exploded overall. Further analyses revealed a significant interaction between gender and cortisol ($F(1, 95) = 7.7$, $P = .007$, $\eta^2 = .075$). Follow up tests showed a significant cortisol effect in men ($F(1, 47) = 17.74$, $P < .001$, $\eta^2 = .274$), indicating that significantly more balloons exploded in men that received hydrocortisone (~ 50 percent), than in men that received yohimbine only or a placebo (~ 37 percent). In women, we did not obtain a significant cortisol effect ($F(1, 48) = .04$, $P = .848$, $\eta^2 = .001$), with the balloon exploding in about 40 percent of all trials in all groups.

Moreover, we obtained, independent of participants' sex, a significant influence of cortisol on participants behavior in the individual risk conditions (risk condition × cortisol: $F(1.81, 171.78) = 4.15$, $P = .021$, $\eta^2 = .042$). Univariate ANOVAs for each risk condition revealed that especially in the high risk condition participants in the cortisol groups had a significantly higher number of balloons exploding (67 vs. 54 percent exploded in the cortisol vs- no-cortisol groups; $F(1, 95) = 15.96$, $P < .001$, $\eta^2 = .022$). In the moderate and low risk conditions, we did not obtain a significant cortisol effect (all $F \leq 2.76$, all $P \geq .100$).

In contrast to hydrocortisone, yohimbine administration tended to reduce the number of balloons exploded (trend for a main effect of noradrenergic stimulation ($F(1, 95) = 3.49$, $P = .065$, $\eta^2 = .035$). We did, however, not obtain a significant interaction of noradrenergic stimulation with risk condition, neither in combination with cortisol nor dependent on participants' gender (all $F \leq 1.93$, all $P \geq 0.153$).

Additionally, there was no difference between groups in the winnings obtained, neither between men and women ($F(1, 95) = 0.00$, $P = 0.991$, $\eta^2 = .00$), nor in interaction with cortisol and/or yohimbine (all $F < 2.28$, all $P > .13$, all $\eta^2 < .023$).

3.3. Control Variables

We did not obtain any significant group differences in state anxiety, chronic stress, impulsiveness or behavioral inhibition (all $F \leq 3.13$, all $P \geq .080$, all $\eta^2 < .033$; Table 2). Trait anxiety, however, was higher in the groups that had received yohimbine than in those who did not receive yohimbine ($F(1, 94) = 5.92$, $P = .017$, $\eta^2 = .059$) and women showed, overall, greater behavioral activation ($F(1, 95) = 4.33$, $P = .040$, $\eta^2 = .044$) as well as increased depressive mood ($F(1, 95) = 5.75$, $P = .018$, $\eta^2 = .057$). To rule out that the gender specific effects of hydrocortisone on risk-taking behavior were owing to these differences in trait anxiety, behavioral activation or mood, we ran all our analyses again with the respective measures as covariates. Importantly, our main findings remained virtually unchanged when including BDI score, BAS score, or trait anxiety as covariates in the analyses of the mean adjusted button clicks (risk condition × gender × cortisol interactions: all $F > 3.34$, all $P \leq .053$, $\eta^2 > .034$; and noradrenergic stimulation × block risk condition: all $F > 2.19$, all $P \leq .058$, $\eta^2 > .023$). Likewise, in the analyses of the number of balloons exploded the interaction of risk condition and cortisol remained significant after controlling for BDI, BAS and trait anxiety scores (all $F > 3.8$, all $P < .03$, $\eta^2 > .039$). Furthermore, to control for the individual measures in impulsivity and behavioral inhibition we ran our analyses again, taking the BIS and Barratt Impulsivity Score as covariates in the analyses of the mean adjusted button clicks and total balloons exploded. The main interactions for the mean adjusted button clicks (gender × cortisol × risk condition and noradrenergic stimulation × risk condition × block) as well as for the total balloons exploded (risk condition × cortisol) remained significant (all $F > 2.94$, all $P \leq .04$, all $\eta^2 > .03$).

To further control for the blood pressure and cortisol differences observed overall between men and women, we performed further analyses of covariance including cortisol and systolic blood pressure as covariates. Again, including these covariates left our findings for the mean adjusted button clicks essentially unchanged (risk condition × gender x cortisol: both $F > 3.5$, both $P < .05$, $\eta^2 > .036$). The noradrenergic stimulation × block × risk condition interaction remained virtually unchanged when including mean cortisol as a covariate ($F(4.66, 437.86) = 3.03$, $P = .013$, $\eta^2 = .031$), however, factoring in systolic blood pressure the interaction dropped to trend level ($F(4.66, 437.58) = 1.99$, $P = .083$, $\eta^2 = .021$). The same was true for

the total number of balloons exploded (risk condition × cortisol when controlling for systolic blood pressure ($F(1.81, 170.42) = 4.39$, $P = .017$ $\eta^2 = .045$). Only when the mean cortisol level was included as a covariate, the risk condition × cortisol interaction dropped to trend level ($F(1.80, 169.33) = 2.55$, $P = .087$, $\eta^2 = .026$). Decomposing for the risk condition, however, showed a significant cortisol effect in high risk trials only ($F(1, 94) = 5.11$, $P = .026$, $\eta^2 = .052$), while there was again no cortisol effect for the moderate and low risk conditions (both $F \leq 1.11$, both $P \geq .295$, $\eta^2 < .012$).

4. Discussion

Stress has been repeatedly shown to boost risk-taking in men but not in women (Lighthall et al., 2009; Lighthall et al., 2012; Mather and Lighthall, 2012). In the present experiment, we aimed to shed light on the neuroendocrine mechanism underlying this gender-specific impact of stress on risky decision-making. Specifically, we investigated whether the activity of major stress mediators, i.e. cortisol and noradrenaline, is sufficient to increase risk-taking behavior in men, without affecting it in women. Our results showed that cortisol administration resulted indeed in an increase in risk-taking specifically in men. This increase in risk-taking was reflected in more risky decision-making both in low and moderately risky conditions and a significantly higher number of balloons exploded. In women, however, cortisol did not alter risk-taking. Moreover and in contrast to cortisol, increased noradrenergic stimulation after intake of the α2-adrenoceptor antagonist yohimbine tended to attenuate risk taking, both in men and in women.

Cortisol is well known to modulate decision-making processes. For instance, cortisol may increase more intuitive decisions (Margittai et al., 2016) and motivated decision-making (Putman et al., 2010), presumably through the down-regulation of the brain's reward circuitry (Lighthall et al., 2012; Montoya et al., 2014). Furthermore, stress-induced cortisol has been shown to correlate with risk-taking behavior (Buckert et al., 2014; van den Bos et al., 2014), particularly in men (van den Bos et al., 2014). While these previous findings were correlational, our data demonstrate a causal influence of cortisol on risk-taking in men. In women, however, cortisol administration did not alter risk-taking behavior. Together with the previous correlational data, the current data thus suggest that cortisol is the driving force in the gender-specific impact of acute stress on risky decision-making; most likely in interaction with sex hormones (see below). Since previous neuroimaging data suggest that acute stress increases the activity in the brain's reward circuitry during the BART (e.g. the insula and striatum) in men, whereas activity in these regions was decreased in women after stress (Lighthall et al., 2012), we propose that the present gender-dependent effects of cortisol might also be due to altered reward processing.

We could rule out that this differential influence of cortisol in men and women was owing to gender differences in anxiety, depressive mood, impulsivity or in the physiological response to hydrocortisone intake. However, although we did not assess the role of sex hormones, such as estrogen and testosterone, in the present study, there is compelling evidence suggesting that these sex hormones may modulate the impact of stress and glucocorticoids on cognition and behavior. For instance, estrogen is thought to reduce the effectiveness of glucocorticoids by stimulating the synthesis of corticosteroid-binding globulin (Moore et al., 1978), which in turn reduces the biologically active fraction of cortisol and its impact on cognition. Furthermore, estrogen may affect the expression of receptors for glucocorticoids (Quinkler et al., 2002). For testosterone, there is even direct evidence suggesting an interactive effect with cortisol on decision-making and risk taking (Mehta et al., 2015). While there is ample evidence indicating that testosterone may affect decision-making (Apicella et al., 2015; Nave et al., 2017), testosterone has also been shown to modulate the impact of cortisol on risk behaviors (Cueva et al., 2015; Kandasamy et al., 2014). The findings on the interactive influence of cortisol and testosterone, however, is not consistent and several studies failed to find such an interaction (Apicella et al., 2015; Apicella et al., 2011; Schipper, 2015a; Schipper, 2015b). Thus, although the exact mechanisms underlying the interactive influence of glucocorticoids and sex hormones are not very well understood, especially in humans, sex hormones appear to be a likely source of the differential effect of cortisol in men and women.

While cortisol was traditionally thought to act via intra-cellular mineralocorticoid and glucocorticoid receptors (MRs and GRs, respectively) mediating relatively slow genomic effects that take 60–90 min to develop, more recent research showed that, at least for the MR, there is also a membrane-associated receptor type allowing rapid, non-genomic actions of glucocorticoids (Joels et al., 2012; Karst et al., 2005). As we administered hydrocortisone about 85 min before testing, we assume that rapid glucocorticoid actions still prevailed (see also: Henckens et al., 2012). However, it cannot be fully ruled out that genomic glucocorticoid actions had already developed while participants performed the task. Nevertheless, we assume that the present effects were mainly due to rapid glucocorticoid actions via the MR. First, because a very recent study that varied the time interval between stressor and a decision-making task to unravel time-dependent changes in stress (hormone) effects on risky decision-making (Bendahan et al., 2017) showed an increase in risk-taking, similar to the one we observed (in men) shortly after the stressor, whereas this effect reversed at later time points with risk averse behavior at longer delays when genomic glucocorticoid actions should have developed. Moreover, another recent study using the same task we used here showed that pharmacological stimulation of the MR led to the same increase in risk-taking that we obtained in the present study (Deuter et al., 2017). In addition, rapid MR actions were recently linked to more automatized, impulsive and less reflective behavior (Schwabe, 2013; Vogel et al., 2016) and the tendency to reflect less about the potential negative outcomes of ones actions might contribute to more risky behavior.

The impact of cortisol on risky decision-making was not modulated by parallel noradrenergic stimulation as has been previously demonstrated for other cognitive domains (Roozendaal et al., 2004; Roozendaal et al., 2006; Schwabe et al., 2010). The absence of such an interactive effect of cortisol and noradrenergic stimulation might be owing to the underlying neural processes. In particular, the interaction of cortisol and noradrenaline is thought to take place in the basolateral amygdala, which may then modulate cognitive processes in other areas (Roozendaal et al., 2009; Roozendaal et al., 2006). Such amygdala modulation, however, might be less relevant for risk-taking behavior which can be altered by direct cortisol effects on reward related areas (Lighthall et al., 2012; Mather and Lighthall, 2012). Although noradrenaline did not modulate the influence of cortisol, noradrenaline seemed, in sharp contrast to cortisol, to even attenuate risk-taking, irrespective of participants' sex. There is some first evidence linking noradrenaline to proper decision-making (Rogers et al., 2004), that may support the current findings. The effects observed in the current study, indicate a decline in risk-taking behavior in the high and moderately risky conditions, suggesting opposite effects of cortisol and noradrenergic arousal on risk-taking behavior, which should be explicitly tested in future studies including larger samples. These studies should also include different dosages of yohimbine to exclude a ceiling effect or possibly opposite effects at lower or higher dosages. The issue of dose-dependencies, however, is not limited to yohimbine but may also be relevant for cortisol. For instance, if the absence of a cortisol effect in women is indeed owing to a buffering effect of female sex hormones, higher dosages of hydrocortisone may affect risk-taking also in women. Moreover, beyond testing does-dependencies, future studies could also include baseline measures of risk-aversion in order to test whether the impact of hydrocortisone or yohimbine depends on the inherent risk-aversion. In order to gain mechanistic insights beyond the involvement of different hormone or neurotransmitter systems, future studies could combine neuroimaging with computational modelling (van Ravenzwaaij et al., 2011; Wallsten et al., 2005).

Increased risk-taking behavior after acute stress is not at all limited to laboratory settings but can be observed in many contexts, often with far-reaching consequences. Stress-induced increases in risky driving behavior, sexual risk-taking or other health-related risks are just a few of many examples (Halpern et al., 2002; Reidy et al., 2016; Reisner et al., 2009). For several of these risk behaviors, the impact of stress is more pronounced in men than in women. In the present experiment, we show that the stress hormone cortisol may boost risk-taking in men but not in women, suggesting that this gender-specific effect of cortisol may be the basis of the differential impact of acute stress on risk-taking in men and women, although it is important to note that we did not induce stress in this study. Identifying the causal role of cortisol in risk-taking may be a first step on the way to develop strategies to prevent or at least reduce risk-taking behavior and the detrimental consequences associated with it, in particular in men.

Disclosure

No of the authors has any biomedical conflicts of interest.

Contributors

L. S. conceived the study. L.S. and L.M.K. contributed to the study design. Testing and data acquisition was performed by L.M.K. A.A. and K.W. provided medical supervision during data collection. L. S. and L. M. K. analyzed and interpreted the data. L. M. K. drafted the manuscript, L. S. provided critical revisions. All authors contributed to and have approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2017.07.240.

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