Hormones and Behavior 84 (2016) 75–83

Contents lists available at ScienceDirect

Hormones and Behavior

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

Cortisol alters reward processing in the human brain☆

Valerie L. Kinner, Oliver T. Wolf *, Christian J. Merz

Institute of Cognitive Neuroscience, Department of Cognitive Psychology, Ruhr-University Bochum, Germany

ARTICLE INFO

Article history:
Received 12 February 2016
Revised 22 April 2016
Accepted 5 May 2016
Available online 08 May 2016

Keywords:
Functional magnetic resonance imaging
Glucocorticoids
Reward anticipation
Sex differences
Oral contraceptives

ABSTRACT

Dysfunctional reward processing is known to play a central role for the development of psychiatric disorders. Glucocorticoids that are secreted in response to stress have been shown to attenuate reward sensitivity and thereby might promote the onset of psychopathology. However, the underlying neurobiological mechanisms mediating stress hormone effects on reward processing as well as potential sex differences remain elusive. In this neuroimaging study, we administered 30 mg cortisol or a placebo to 30 men and 30 women and subsequently tested them in the Monetary Incentive Delay Task. Cortisol attenuated anticipatory neural responses to a verbal and a monetary reward in the left pallidum and the right anterior parahippocampal gyrus. Furthermore, in men, activation in the amygdala, the precuneus, the anterior cingulate, and in hippocampal regions was reduced under cortisol, whereas in cortisol-treated women a signal increase was observed in these regions. Behavioral performance also indicated that reward learning in men is impaired under high cortisol concentrations, while it is augmented in women. These findings illustrate that the stress hormone cortisol substantially diminishes reward anticipation and provide first evidence that cortisol effects on the neural reward system are sensitive to sex differences, which might translate into different vulnerabilities for psychiatric disorders.

Introduction

Stress is one of the strongest predictors for the onset of psychiatric disorders (Grant et al., 2003). Besides, prevalence rates largely differ among men and women with a higher incidence for depression in women and men being more susceptible to substance use disorders (Cover et al., 2014; Kessler et al., 2005). However, unraveling the mechanisms that underlie the relationship between stress, sex and psychopathology continues to be a challenging endeavor. First imaging studies in humans suggest that acute stress attenuates reward sensitivity through the disruption of dopaminergic neural circuitry (Berghorst et al., 2013; Ossewaarde et al., 2011). However, as males were not included in these studies, it remains unclear how sex might modulate stress hormone effects on the reward network. Likewise, little is known about the specific impact of oral contraceptive (OC) usage on stress effects on reward anticipation in women.

Under stress two systems are activated: the fast reacting sympathetic nervous system initiating the release of (nor)adrenaline and the somewhat slower hypothalamus-pituitary-adrenocortical (HPA) axis leading to the release of glucocorticoids (GCs; Joels and Baram, 2009). The main human GC cortisol binds to mineralocorticoid-receptors (MRs) and glucocorticoid-receptors (GRs) in the brain (de Kloet, 2004) and thereby exerts manifold effects on cognition, learning and emotion (Schwabe et al., 2010).

MRs and GRs are expressed extensively in the dopaminergic reward system (de Kloet et al., 2005; Sinclair et al., 2014; Van Craenenbroeck et al., 2005) making it highly susceptible for glucocorticoid regulation. Important projection areas of dopaminergic neurons comprise prefrontal cortex (PFC) regions as well as subcortical limbic regions, including the amygdala, hippocampus and the striatum (Arias-Carrión et al., 2010). Accordingly, stress has been found to alter activation in prefrontal, limbic and striatal regions (Pruessner et al., 2008; Wang et al., 2005). However, results are rather mixed concerning the direction of the effects, with studies reporting decreased (Pruessner et al., 2008) or increased activation in these structures in response to stress (Wang et al., 2005). One possible explanation for the divergent results could be the timing of cortisol or stress induction relative to the scanning session. In line with this notion, Lovallo et al. (2010) reported reduced BOLD signals in the amygdala and in the hippocampus with a peak response minimum 25–30 min after an intravenous injection of 10 mg hydrocortisone, whereas immediately after hormone administration the opposite effect emerged.

Most laboratory studies suggest that both, stress induction and cortisol administration diminish reward responsiveness, in particular the ability to modulate behavior as a function of rewards (Bogdan and Pizzagalli, 2006; Lewis et al., 2014; Montoya et al., 2014). So far, neuroimaging studies focusing on acute stress effects used experimental paradigms which typically compare a monetary reward with a non-

☆ Funding for this study was provided by Project P5 (WO 733/13-2) of the German Research Foundation (DFG) Research Unit 1581 "Extinction Learning". We gratefully acknowledge the help of Nuria Mackes and Lina Reimers during data collection and recruitment of participants. Moreover, we thank Tobias Otto and PHILIPS Germany for technical support.

* Corresponding author at: Institute of Cognitive Neuroscience, Department of Cognitive Psychology, Ruhr-University Bochum, Universitätsstraße 150, 44780 Bochum, Germany.
E-mail address: oliver.t.wolf@rub.de (O.T. Wolf).

http://dx.doi.org/10.1016/j.yhbeh.2016.05.005
0018-506X/

reward or a punishment condition (Ossewaarde et al., 2011; Porcelli et al., 2012). Specifically, participants under stress showed a lack of differential neural responding to rewards and punishments which was mainly driven by decreased sensitivity to rewarding outcomes (Porcelli et al., 2012). But, the question arises whether stress or GC treatment affect neural responses differently when the magnitude or type of reward varies. For instance, receiving positive feedback is perceived as (socially) rewarding and thus may constitute a reward type that is more relevant to daily life. In line with this notion, data from human electroencephalography and functional magnetic resonance imaging (fMRI) demonstrated that positive feedback is reliably activating brain regions implicated in the reward circuitry (Becker et al., 2014; Diekhof and Ratnayake, 2015; Foerde and Shohamy, 2011; Kirsch et al., 2003). However, little is known about the neuroendocrine mechanisms underlying stress effects on neural responses to different reward types.

Importantly, the brain reward system is not only active during reward delivery but also during its anticipation (Kirsch et al., 2003, 2006; Knutson et al., 2001). Thus, already the expectancy of a positive outcome constitutes a reward value, which motivates an individual to behave in a manner that actually increases the probability of receiving the desired reward. Since alterations in reward-seeking and goal-directed behavior are common symptoms of depression and drug addiction (Everitt and Robbins, 2005), investigating anticipation processes might foster our understanding of the basic reward-related phenomena relevant for clinical applications. For instance, anhedonia, a core symptom of depression, has been associated with blunted responses to rewarding stimuli in striatal and prefrontal brain regions (Pizzagalli et al., 2009). However, anticipatory processes, especially with regard to different reward magnitudes were less considered in past reward research. Likewise, little is known about the potential modulatory role of the stress hormone cortisol on the neural underpinnings of anticipating different reward types.

In the present study, participants therefore received either an oral dose of cortisol or a placebo and were subsequently tested in the Monetary Incentive Delay Task including verbal as well as monetary rewards. Based on the acute stress-imaging literature (Berghorst et al., 2013; Bogdan and Pizzagalli, 2006; Ossewaarde et al., 2011; Porcelli et al., 2012), we expected cortisol to decrease reward-related striatal and prefrontal activity during the anticipation of both reward types. Since previous studies have reported sex-dependent effects of stress and cortisol on working memory (Schoofs et al., 2013), decision-making (Lighthall et al., 2009) and emotional processes (Kinner et al., 2014; Merz et al., 2012) we additionally sought to examine the potential interplay between cortisol and sex.

Methods

Participants

In total, 60 healthy male and female students were recruited for study participation. They were aged between 18 and 40 years (M = 24.0 years, SD = 3.4) and had a mean body mass index (BMI) of M = 22.9 kg/m^2 (SD = 1.9 kg/m^2). Exclusion criteria covered standard fMRI exclusion criteria, somatic diseases, history of psychiatric or neurological treatment, smoking and regular medication. All participants were right-handed, as assessed by the Edinburgh Inventory of Handedness (Oldfield, 1971), and had normal or corrected vision. Based on previous work from our laboratory (Merz and Wolf, 2015; Merz et al., 2012, 2013), we decided to only include women who have been taking OC (only monophasic preparations with an ethinylestradiol and a gestagenic component) for at least three months. They were tested during pill intake to reduce potential influences of circulating sex hormones across the normal menstrual cycle (Merz et al., 2012). All participants should refrain from exercise and consumption of food and drinks except water two hours prior to testing. Participants provided written informed consent and received a financial reimbursement of 40€. In addition, participants could gain additional money during the experiment. All procedures were in accordance to the Declaration of Helsinki and approved by the ethic committee of the Medical Faculty of the Ruhr-University Bochum.

Experimental paradigm

An adapted version of the Monetary Incentive Delay Task (Kirsch et al., 2003) was applied to investigate reward anticipation. The MID-task is known to robustly engage striatal and medial prefrontal regions (Lutz and Widmer, 2014). Prior to scanning, participants were informed about the different stimulus types used in the experiment and their association with potential rewards. During scanning, participants underwent three different conditions, which were indicated by distinct visual cues (Fig. 1).

In the "monetary reward" (mS+) condition, a vertical arrow pointing upward was presented for 6 s and immediately followed by a bright flashlight (100 ms) to which participants had to respond as fast as possible by pressing a button. Subsequently, verbal feedback was given whether they had responded fast enough to earn 50ct or not. The "verbal reward" (vS+) condition was introduced by a vertical double-sided arrow (6 s) which was also followed by the bright flashlight (100 ms). Verbal feedback was given on response speed, but no monetary gains were possible. In both conditions the feedback screen was displayed for 1.5 s and followed by the actual account balance for another 1.5 s. The reaction time window distinguishing fast and slow responses was set to 300 ms for the first trial but varied for each of the following trials depending on the individual reaction time. The adaptive algorithm consisted of a 5%-increase of the threshold after a slow response and a 5%-decrease after a fast response in the preceding

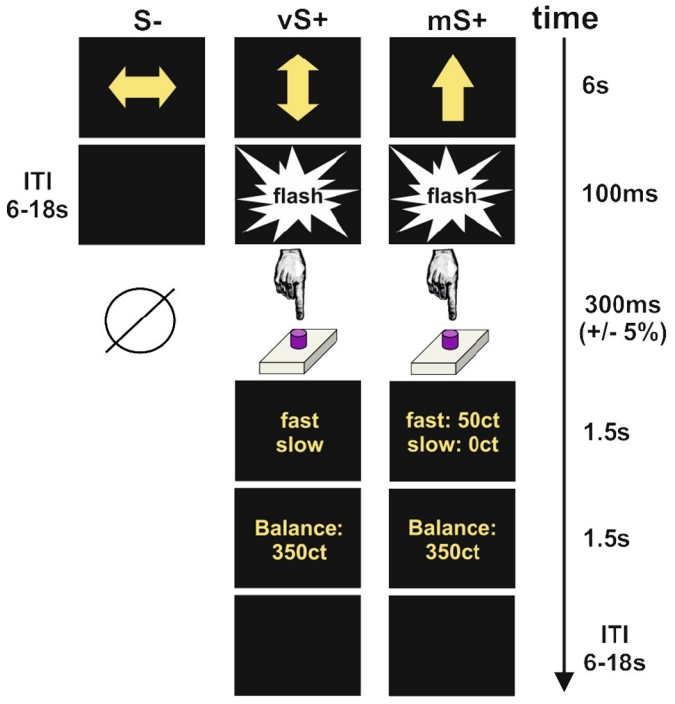

Fig. 1. MID-task with the three experimental conditions: S− (control), vS+ (verbal reward) and mS+ (monetary reward). Participants had to respond as fast as possible to a bright flashlight following the presentation of the vS+ and the mS+ by pressing a response button. The threshold for the response time window was adapted on an overall trial-by-trial basis with a 5% increase after a slow response and a 5% decrease after a fast response (independent from reward type). The following verbal feedback was given in both, the vS+ and the mS+ condition: "fast response" in case of a fast response, "unfortunately, too slow response" in case of a slow response, and "unfortunately, no response" in case of a missing response. In mS+ trials, additional information on the amount of gained money was given at the same time ("gain: 50ct" or gain: "0ct"). For illustration purpose, abbreviations are used in the figure.

trial (independent from reward type). Thus, it was ensured that all participants were able to win some money. In a third "control" (S−) condition, a horizontal double-sided arrow (6 s) was followed by the inter-trial interval depicting a black screen. In order to include a condition without any anticipation of a consequence, no response was required in the control condition.

Each of the three conditions was presented 15 times in a pseudo-randomized trial order with no more than two equal conditions in succession. The inter-trial interval was randomly jittered between 6 and 18 s. In total, participants underwent 45 trials, with an entire duration of approximately 13 min. The experiment was realized with the Presentation software package (Neurobehavioral Systems, Albany, CA) and presented via fMRI-ready goggles (VisuaStim Digital; Resonance Technology Inc., Northridge, CA, USA). Responses were given on an fMRI-ready keyboard (LUMItouch™ response pad; Photon Control Inc., BC, Canada).

Experimental procedure

Experimental sessions were scheduled between 1 and 6 pm to test participants under low and relatively stable endogenous cortisol concentrations. At the beginning, participants received an explanation of the procedure, the pharmacological agents and the fMRI protocol. After signing the informed consent form participants filled out a demographic questionnaire and were provided with the instructions for the MID-task.

In a double-blind, randomized, and placebo-controlled design 15 men and 15 women received three 10 mg tablets of cortisol (hydrocortisone; Hoechst) 60 min before the start of the functional scans for the MID-task. The dosage of 30 mg hydrocortisone was chosen based on previous studies from our laboratory and other groups demonstrating clear effects of similar dosages on behavioral and brain functions (Kuhlmann and Wolf, 2005; Merz et al., 2012; Montoya et al., 2014; Oei et al., 2009; Stark et al., 2006). Visually identical placebos (magnesium and tablettose) were given to the remaining 15 men and 15 women.

To assess cortisol concentrations we collected saliva samples at three different times; directly before tablet intake (baseline) as well as 30 min (before the fMRI run) and 85 min (after the fMRI run) after tablet intake. We used Salivette sampling devices (Sarstedt, Nümbrecht, Germany) which were stored at −20 °C until biochemical analysis. Commercially available chemiluminescence immunoassays (CLIA; IBL International, Hamburg, Germany) were used. Inter- and intra-assay variations were below 10%. Due to problems with saliva sampling and analyses, the data from two participants had to be excluded from cortisol analyses.

To verify a change in subjective motivational value towards the three stimuli arousal ratings (from 1 "quiet and relaxed" to 9 "very excited") were assessed prior and after completion of the MID-task.

The present study was part of a larger project investigating cortisol effects on cognitive processes. Experimental scan sessions thus, included a second neutral learning task which will be reported elsewhere.

Statistics

Statistical analyses were performed using IBM SPSS 22 Statistics for Windows with Greenhouse–Geisser correction when needed and the significance level set to $\alpha = 0.05$. For cortisol as well as for the arousal ratings, we conducted analyses of variance (ANOVA) with the repeated measurement factor time (cortisol: baseline, + 30 min, + 85 min; ratings: pre- and post-MID) and the between subject factors treatment (cortisol vs. placebo) and sex (men vs. women). To assess behavioral performance in the MID-task, we calculated mean reaction times and hit rates for both reward conditions. Hits were defined as responses given within the actual reaction time window. ANOVA with the between subject factors treatment and sex were conducted for reaction times, hit rates and the amount of gained money. For ANOVAs, partial η^2 were reported as estimations of effect sizes. Significant interactions were resolved by two-tailed t-tests and Cohen's *d* was reported as estimation of effect sizes. Since we were exclusively interested in cortisol effects and their modulation by sex main effects of sex were not analyzed.

fMRI data acquisition and analyses

Functional and structural brain scans were acquired using a whole-body 3 T scanner (Philips Achieva 3.0 T X-Series, Philips, Netherlands) with a 32-channel SENSE head coil. Structural images were obtained with an isotropic T1 TFE sequence (field of view = 240×240 mm^2; slice thickness = 1 mm; voxel size = $1 \times 1 \times 1$ mm^3) and comprised 220 transversally orientated slices covering the whole brain. For functional imaging, 272 volumes were registered using a T2*-weighted gradient echoplanar imaging sequence with 40 transaxial slices parallel to the orbitofrontal cortex-bone transition which covered the whole brain (TR = 2.5 s; TE = 30 ms; flip angle = 67°; field of view = 192×192 mm^2; slice thickness = 3 mm; gap = 0.75 mm; ascending slice order; voxel size = $2 \times 2 \times 2$ mm^3).

For preprocessing and statistical analyses of imaging data we used the software Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London, UK), implemented in MatLab R2012a (Mathworks Inc., Sherborn, MA). Three dummy scans, during which magnetization reached steady state, preceded data acquisition. Preprocessing on the first level comprised the following steps: unwarping and realignment, slice time correction, co-registration of functional data to each participant's anatomical image, segmentation into gray and white matter, normalization to the standard space of the Montreal Neurological Institute (MNI) brain, and spatial smoothing with a 6 mm full-width half-maximum (FWHM) kernel. The statistical model for each participant included the following experimental conditions: mS+, vS+, and S−. The bright flashes, button presses, feedback and balance screens as well as the black screens following the control condition were introduced as additional regressors. All regressors were modeled by a stick function convolved with the canonical hemodynamic response function in the general linear model, without specifically modeling the duration of the different events (i.e. event-related design). In order to account for movement related variance, the six movement parameters from the realignment step were included as covariates in the analysis. A high pass filter (time constant = 128 s) was implemented by using cosine functions in the design matrix.

The individual contrasts were analyzed in random effects group analyses. To check whether both reward conditions provoked activation in the reward system we first focused on the contrasts [mS+ minus S−] and [vS+ minus S−] separately. For a direct comparison of the two reward conditions a third contrast [vS+ minus mS+] was generated. Since we were exclusively interested in the anticipatory neural responses to the respective reward types, all trials (correct and incorrect) were included into the analyses. ANOVA was conducted for the three contrasts with the group factors treatment and sex in the full factorial model in SPM8. In particular, we aimed to explore the main effect of cortisol as well as potential interactions between cortisol and sex (main effects of sex were not analyzed separately).

For all statistical analyses, we used region of interest (ROI) analyses including brain regions known to be part of the reward network and which were reported in previous studies using the MID-task (Kirsch et al., 2003, 2006) amygdala, anterior cingulate gyrus, nucleus accumbens, nucleus caudatus, putamen, pallidum, orbitofrontal cortex, ventromedial prefrontal cortex (vmPFC), hippocampus, and anterior parahippocampal gyrus. The required masks were maximum probability masks with the probability threshold set to 0.25 taken from the Harvard-Oxford Cortical and Subcortical Structural Atlases provided by the Harvard Center for Morphometric Analysis (http://www.cma.mgh.harvard.edu/fsl_atlas.html). The vmPFC mask consisted of a 5 mm sphere surrounding the peak voxel for reward-related neural responses in the vmPFC (MNI coordinates $x = 4$, $y = 42$, $z = -16$), as indicated in a meta-analysis on the

Table 1
(**A**) Mean (SE) salivary cortisol concentrations before, 30 min and 85 min after the administration of 30 mg cortisol or placebo in men and women. (**B**) Mean (SE) hit rates and response times to the verbal feedback cue (vS+) and to the monetary reward cue (mS+) as well as self-reported arousal ratings to the vS+, mS+ and the control cue (S−) before (pre) and after (post) the Monetary Incentive Delay Task. Data is shown separately for men and women in the cortisol and placebo group, respectively. The statistics are described in detail in the text.

	Cortisol		Placebo	
	Men	Women	Men	Women
(*A*) *Salivary cortisol* (*nmol/l*)				
Before treatment	11.64 ± 1.21	12.07 ± 1.56	10.23 ± 0.78	11.54 ± 1.16
30 min after treatment	385.88 ± 67.85	258.74 ± 42.43	13.61 ± 1.71	11.36 ± 1.09
85 min after treatment	225.47 ± 61.12	244.97 ± 17.86	9.80 ± 1.07	10.31 ± 1.60
(*B*) *Behavioral data* (*MID-task*)				
Hit rates (*%*)				
vS+	53.33 ± 2.91	56.89 ± 3.04	59.11 ± 2.75	56.89 ± 3.67
mS+	76.44 ± 2.90	68.89 ± 1.92	70.22 ± 3.04	67.11 ± 3.08
Response times (*ms*)				
vS+	253.91 ± 0.02	242.57 ± 0.01	228.41 ± 0.01	274.48 ± 0.02
mS+	219.74 ± 0.00	231.58 ± 0.01	217.37 ± 0.01	239.16 ± 0.01
Arousal ratings (*1 = quiet and relaxed – 9 = very excited*)				
Pre: S−	3.47 ± 0.58	4.93 ± 0.50	4.13 ± 0.53	4.53 ± 0.45
Post: S−	2.80 ± 0.44	4.93 ± 0.39	2.93 ± 0.52	3.20 ± 0.38
Pre: vS+	3.40 ± 0.47	4.33 ± 0.52	4.47 ± 0.52	4.67 ± 0.44
Post: vS+	4.07 ± 0.50	5.53 ± 0.34	4.93 ± 0.46	5.07 ± 0.36
Pre: mS+	4.07 ± 0.60	5.73 ± 0.56	3.87 ± 0.57	4.47 ± 0.57
Post: mS+	5.20 ± 0.72	5.67 ± 0.41	6.60 ± 0.47	6.27 ± 0.56

neural correlates of personal reward (Morelli et al., 2015). The intensity threshold was set to $\alpha < 0.05$ uncorrected, the minimal cluster size was 5 voxels, and the significance threshold was set to $\alpha < 0.05$ on voxel-level, family-wise error (FWE) corrected (using small volume correction options of SPM8). In addition, we conducted exploratory whole brain analyses (k = 10 voxels; significance threshold: $\alpha < 0.05$ on voxel-level, FWE-corrected).

Results

Salivary cortisol

ANOVA revealed a significant main effect of time ($F_{(1.5, 80.5)} = 48.36$; $p < 0.001$, $\eta^2 = 0.48$), treatment ($F_{(1, 53)} = 62.03$; $p < 0.001$, $\eta^2 = 0.54$), and a time × treatment interaction ($F_{(1.5, 80.5)} = 47.69$; $p < 0.001$, $\eta^2 = 0.47$). Whereas groups did not differ at baseline ($p = 0.40$), cortisol concentrations were elevated 30 and 85 min after hydrocortisone but not placebo administration (both $p < 0.001$, both $d > 1.93$, Table 1). No significant interaction effects with sex were found. Groups neither differed with respect to the time of baseline cortisol sampling nor the time between waking and baseline measure (all Fs < 2.16; all ps > 0.15).

Behavioral data

Participants won 5.33€ on average (range: 3–7€; SD = 0.83). There was neither a difference between the cortisol and placebo group, nor an interaction with the factor sex (all ps > 0.10).

Participants made significantly more hits in the monetary (M = 70.67%, SD = 11.06) than in the verbal reward condition (M = 56.56%, SD = 11.93; main effect reward type: $F_{(1, 56)} = 26.82$, $p < 0.001$, $\eta^2 = 0.32$). No main effect of treatment or interaction effects with treatment or sex were found (all ps > 0.1).

Overall, response times were significantly longer for the vS+ than for the mS+ trials (main effect reward type: $F_{(1, 56)} = 12.02$; $p = 0.001$, $\eta^2 = 0.18$). Additionally, a trend towards a three-way interaction between reward type, treatment and sex ($F_{(1, 56)} = 3.23$; $p = 0.08$, $\eta^2 = 0.06$) occurred. Separate ANOVAs for mS+ and vS+ further indicated a trend towards a treatment × sex interaction in vS+ trials ($F_{(1, 56)} = 3.76$; $p = 0.058$, $\eta^2 = 0.06$). As follow-up t-tests revealed, men were significantly faster than women ($t_{(28)} = 2.07$; $p < 0.05$, $d = 0.87$) after placebo administration in vS+ trials, however this difference disappeared after cortisol administration since men got slower and women faster under cortisol ($t_{(28)} = 1.16$; $p = 0.26$). For the mS+, no main effect of treatment or interaction effects with treatment or sex emerged.

For *arousal ratings*, ANOVA revealed a main effect of reward type ($F_{(2, 86)} = 40.74$; $p < 0.001$, $\eta^2 = 0.42$), time ($F_{(1, 56)} = 6.43$; $p = 0.014$, $\eta^2 = 0.10$), a reward type × time interaction ($F_{(2, 97)} = 34.34$; $p < 0.001$, $\eta^2 = 0.38$) and a trend towards a three-way interaction between reward type, time and treatment ($F_{(2, 97)} = 3.11$; $p = 0.056$, $\eta^2 = 0.05$). Separate ANOVAs for pre- and post-MID ratings indicated that prior to the MID-task arousal ratings did not differ between mS+, vS+ and S− (main effect of reward type: $p = 0.55$). However, after completion of the MID-task participants reported higher

Table 2
Localization and statistics of the peak voxel for the main effect of condition as well as for the comparison between the cortisol and placebo group and for the treatment × sex interaction in the contrast [vS+ minus S-].

Contrast	Brain structure	*x*	*y*	*z*	T_{max}	p_{corr}
[vS+ minus S-]	L supplementary motor area (WB)	−8	8	50	9.20	<0.001
	R supplementary motor area	2	6	58	8.68	<0.001
	Anterior cingulate gyrus	8	12	42	4.89	0.010
	L orbitofrontal cortex	−32	28	−4	4.71	0.011
	R orbitofrontal cortex	32	30	0	4.53	0.016
	R ventromedial prefrontal cortex	*2*	*46*	*−14*	*2.84*	*0.078*
	L nucleus accumbens	−12	6	−8	3.63	0.019
	L nucleus caudatus	−16	16	2	5.91	<0.001
	R nucleus caudatus	16	18	−2	5.63	<0.001
	L putamen	−20	14	2	7.42	<0.001
	R putamen	26	10	2	7.12	<0.001
Placebo – Cortisol	L pallidum	−18	0	−6	3.72	0.034
Cortisol – Placebo	No significant activations					
Treatment × Sex	L precuneus	−2	−48	70	5.97	0.018
	Anterior cingulate gyrus	−2	−2	42	4.59	0.024
	L anterior parahippocampal gyrus	−28	−14	−30	4.08	0.027

The significance threshold was $p_{corr} \leq 0.05$ (FWE-corrected; small volume correction in SPM8). All coordinates (x, y, z) are given in MNI space. L = left, R = right, WB = whole brain. Trends up to a threshold of $P_{corr} < 0.10$ are written in italics. The peak voxel from the WB analysis was labeled based on the Harvard-Oxford Cortical and Subcortical Structural Atlas.

subjective arousal to the vS+ as well as to the mS+, whereas subjective arousal for the control stimulus (S−) was attenuated when compared to pre-MID-ratings (main effect of time: *all Fs* > 6.16; all *ps* < 0.05, all $\eta^2 > 0.10$). No other main or interaction effects with treatment or sex were found. Table 1 contains all the descriptive results for the behavioral data.

Functional imaging data

To identify brain regions activated during the presentation of a motivating stimulus we first compared the effects of verbal and monetary reward anticipation separately with the control condition. In order to track activation differences caused by the anticipation of different reward types, the verbal reward was then directly compared with the monetary reward. For the contrast [vS+ minus S−] exploratory whole brain analyses revealed enhanced neural activation in the supplementary motor area. ROI analyses further indicated that the anterior cingulate, nucleus accumbens, nucleus caudatus, putamen, and OFC were significantly activated during verbal reward anticipation compared to the control condition (Table 2). For the contrast [mS+ minus S−] we found significant activations in the right supplementary motor area, left midcingulate cortex, and right insula (whole brain analyses) as well as in all pre-selected ROI (Table 3). When comparing the verbal to the monetary reward [vS+ minus mS+], no significant differences were found. However, for the reversed contrast [mS+ minus vS+] enhanced neural activation to the monetary reward was detected in the anterior cingulate gyrus, the left precentral gyrus and the left superior frontal gyrus (whole brain analyses) and in all ROI (Table 4).

Cortisol significantly attenuated anticipatory neural responses to the verbal reward in the left pallidum when compared to placebo treatment (vS+ minus S−; Fig. 2A). Analogous, this decrease in the BOLD response in the left pallidum under cortisol was also evident as a trend during anticipation of the monetary reward (mS+ minus S−; Fig. 2B). Interestingly, when comparing both reward types directly, a cortisol-induced disruption of anticipatory responses was observed in the right anterior parahippocampal gyrus specifically for the verbal reward (vS+ minus mS+; Fig. 2C). Exploratory whole brain analyses did not reveal any significant effects.

In order to explore the potential interplay between cortisol and sex in neural reward anticipation, interaction effects were tested separately for all contrasts. In the whole brain analyses, the contrast [vS+ minus S−] revealed a significant treatment × sex interaction in the left precuneus. As illustrated in Fig. 3A, cortisol attenuated neural activation during verbal reward anticipation in men but enhanced it in women. ROI analyses substantiated this sex-specific cortisol effect by revealing further interactions in the anterior cingulate and left anterior parahippocampal gyrus. Again, cortisol treated men showed decreased neural responses when anticipating the vS+ while activation patterns in women were reversed, with enhanced activation in the cortisol group (Fig. 3B and C). When considering the monetary reward condition, ROI analyses indicated the same sex-dependent cortisol effect on neural activation in the right amygdala but this time only as a trend (Fig. 3D). Exploratory whole brain analyses did not reveal any significant effect in this contrast. For the direct comparison of the two reward types [vS+ minus mS+] ROI analyses revealed that left hippocampus signaling was diminished after cortisol administration in men, whereas it was enhanced in women during anticipation of the verbal reward (Fig. 3E).

Table 3
Localization and statistics of the peak voxel for the main effect of condition as well as for the comparison between the cortisol and placebo group and for the treatment × sex interaction in the contrast [mS+ minus S-].

Contrast	Brain structure	*x*	*y*	*z*	T_{max}	p_{corr}
[mS+ minus S-]	R supplementary motor area (WB)	2	6	58	15.09	<0.001
	L midcingulate cortex (WB)	−8	10	44	14.55	<0.001
	R insula (WB)	32	26	10	13.95	<0.001
	L amygdala	−20	−2	−14	5.91	<0.001
	R amygdala	26	0	−12	6.42	<0.001
	Anterior cingulate gyrus	8	12	42	11.45	<0.001
	L nucleus accumbens	−14	14	−6	9.28	<0.001
	R nucleus accumbens	12	18	−4	9.68	<0.001
	L nucleus caudatus	−14	14	2	12.17	<0.001
	R nucleus caudatus	16	18	−2	11.30	<0.001
	L pallidum	−20	0	4	9.02	<0.001
	R pallidum	18	4	4	8.53	<0.001
	L putamen	−22	14	2	13.62	<0.001
	R putamen	24	8	6	13.44	<0.001
	L orbitofrontal cortex	−30	30	−2	10.34	<0.001
	R orbitofrontal cortex	34	30	2	9.73	<0.001
	R ventromedial prefrontal cortex	8	44	−16	3.63	0.008
	R hippocampus	24	−30	−8	4.68	0.005
	L anterior parahippocampal gyrus	−18	−10	−30	4.20	0.018
Placebo – Cortisol	*L pallidum*	*−16*	*−6*	*−4*	*3.38*	*0.070*
Cortisol – Placebo	No significant activations					
Treatment × Sex	*R amygdala*	*28*	*−6*	*−22*	*3.34*	*0.094*

The significance threshold was $p_{corr} \leq 0.05$ (FWE-corrected; small volume correction in SPM8). All coordinates (*x*, *y*, *z*) are given in MNI space. L = left, R = right, WB = whole-brain. Trends up to a threshold of $P_{corr} < 0.10$ are written in italics. The peak voxel from the WB analysis was labeled based on the Harvard-Oxford Cortical and Subcortical Structural Atlas.

Table 4
Localization and statistics of the peak voxel for the main effect of condition as well as for the comparison between the cortisol and placebo group in the contrast [vS+ minus mS+].

Contrast	Brain structure	*x*	*y*	*z*	T_{max}	p_{corr}
[vS+ minus mS+]	No significant activations					
[vS+] [mS+ minus vS+]	Anterior cingulate gyrus (WB)	2	2	52	13.03	<0.001
	L precentral gyrus (WB)	−42	−14	48	12.12	<0.001
	R superior frontal gyrus (WB)	−22	2	68	11.98	<0.001
	L amygdala	−20	−2	−14	5.85	<0.001
	R amygdala	22	0	−14	5.78	<0.001
	Anterior cingulate gyrus	2	4	46	11.11	<0.001
	L nucleus accumbens	−14	16	−6	9.51	<0.001
	R nucleus accumbens	14	18	−6	7.96	<0.001
	L nucleus caudatus	−16	16	−4	10.88	<0.001
	R nucleus caudatus	10	6	8	10.54	<0.001
	L pallidum	−22	−8	4	7.70	<0.001
	R pallidum	20	4	2	7.84	<0.001
	L putamen	−18	18	−6	10.99	<0.001
	R putamen	22	18	−4	9.46	<0.001
	L orbitofrontal cortex	−36	30	6	8.96	<0.001
	R orbitofrontal cortex	40	26	−2	10.21	<0.001
	L hippocampus	−28	−14	−22	4.78	0.004
	R hippocampus	30	−32	−8	6.96	<0.001
	L anterior parahippocampal gyrus	−20	−12	−32	4.83	0.003
	R anterior parahippocampal gyrus	22	−4	−28	3.89	0.046
Placebo – Cortisol	R anterior parahippocampal gyrus	30	−18	−32	5.20	0.001
Cortisol – Placebo	No significant activations					
Treatment × Sex	*L hippocampus*	*−32*	*−36*	*−8*	*3.76*	*0.070*

The significance threshold was $p_{corr} \leq 0.05$ (FWE-corrected; small volume correction in SPM8). All coordinates (*x*, *y*, *z*) are given in MNI space. L = left, R = right, WB = whole-brain. Trends up to a threshold of $P_{corr} < 0.10$ are written in italics. The peak voxel from the WB analysis was labeled based on the Harvard-Oxford Cortical and Subcortical Structural Atlas.

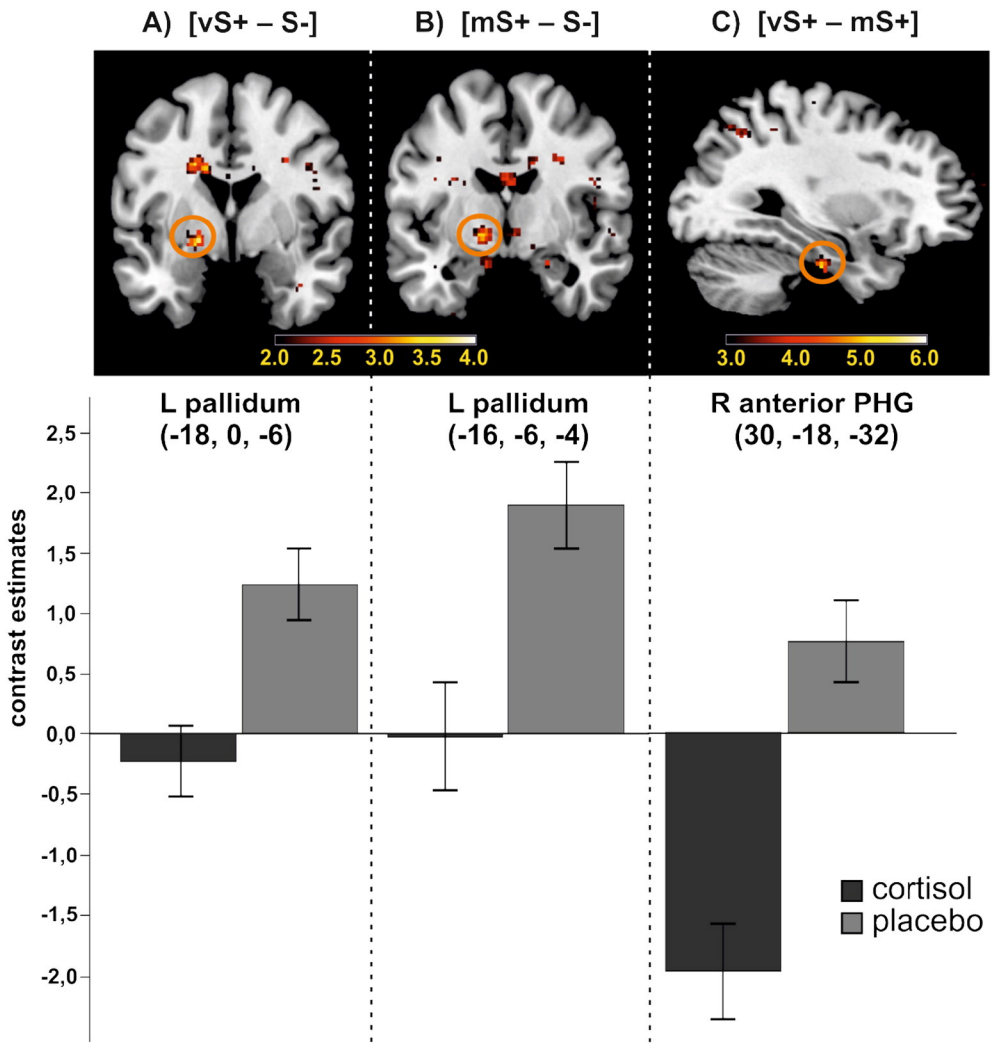

Fig. 2. Neural activations for the main effect of treatment are shown separately for the contrast **A**) [vS + minus S −], **B**) [mS + minus S −] and **C**) [vS + minus mS + −]. The depicted coronal slices were selected according to the reported activation in the left pallidum and right anterior parahippocampal gyrus (PHG). For demonstration purposes, data were thresholded with $T \geq 2.0$ **A**), **B**) and $T \geq 3.0$ **C**) (see color bar for exact *T*-values) and displayed on the standard MNI brain template. In the bar graphs, mean differential contrast estimates for [vS + minus S −], [mS + minus S −] and [vS + minus mS+] are additionally given for the cortisol and placebo group in the respective peak voxel. Error bars are standard errors of the mean. Cortisol significantly reduced activation to the verbal reward cue (vS +) **A**) and to the monetary reward cue (mS +) **B**) when compared to the control stimulus (S −). This decrease in BOLD-responses was also detectable when the verbal reward cue was directly compared to the monetary reward cue **C**).

Discussion

The aim of the current study was to investigate the effects of the stress hormone cortisol on the neural correlates of reward anticipation. Results revealed that cortisol substantially diminishes anticipatory responses of the neural reward system, specifically to the verbal reward. Moreover, sex-dependent cortisol effects were observed indicating reduced reward-related activation under cortisol in men but enhanced reward signaling in cortisol-treated women.

Consistent with prior fMRI studies using the MID-task (Dillon et al., 2008; Kirsch et al., 2003; Knutson et al., 2001) we found reward anticipation to be associated with activations in striatal and prefrontal regions. As expected, the increase in reward-related BOLD signal was more pronounced in response to the monetary reward than to the verbal reward (Kirsch et al., 2003). This motivational difference was further supported by faster reaction times and higher arousal ratings to the cue predicting monetary rewards.

Cortisol reduced anticipatory responses in the pallidum to both, the verbal and the monetary reward. Moreover, these cortisol-induced reductions in activation during reward anticipation were also apparent in the parahippocampal gyrus when the verbal reward was directly compared to the monetary reward. In line with the present data, human stress studies have previously shown that elevated cortisol concentrations are associated with a decrease in reward-related neural activity (Ossewaarde et al., 2011). For instance, Porcelli et al. (2012) found stress-induced reductions in dorsal striatal and orbitofrontal responses to monetary outcomes during a card-guessing task. This converges with behavioral evidence indicating a reduction in reward responsiveness under acute stress (Bogdan and Pizzagalli, 2006). Moreover, stress exposure has been found to decrease risky decisions, in particular when monetary gains were considered, whereas risk taking with regard to financial losses increased under stressful conditions (Porcelli and Delgado, 2009). In contrast, Maier et al. (2015) found that stress increased the impact of immediate food rewards on participants' choice behavior.

However, in the present study we used an exogenous administration of cortisol which cannot be directly translated to stress-induced cortisol elevations. As far as emotional learning and memory is concerned, studies from our laboratory repeatedly showed that the effects of a 30 mg cortisol dose on task-related brain responses as well as on behavioral measures mainly correspond with those obtained after exposure to acute stress (Kuhlmann et al., 2005; Kuhlmann and Wolf, 2005; Merz et al., 2012, 2013). Nevertheless, it is important to note that a stress response always entails both, noradrenergic activity and glucocorticoid

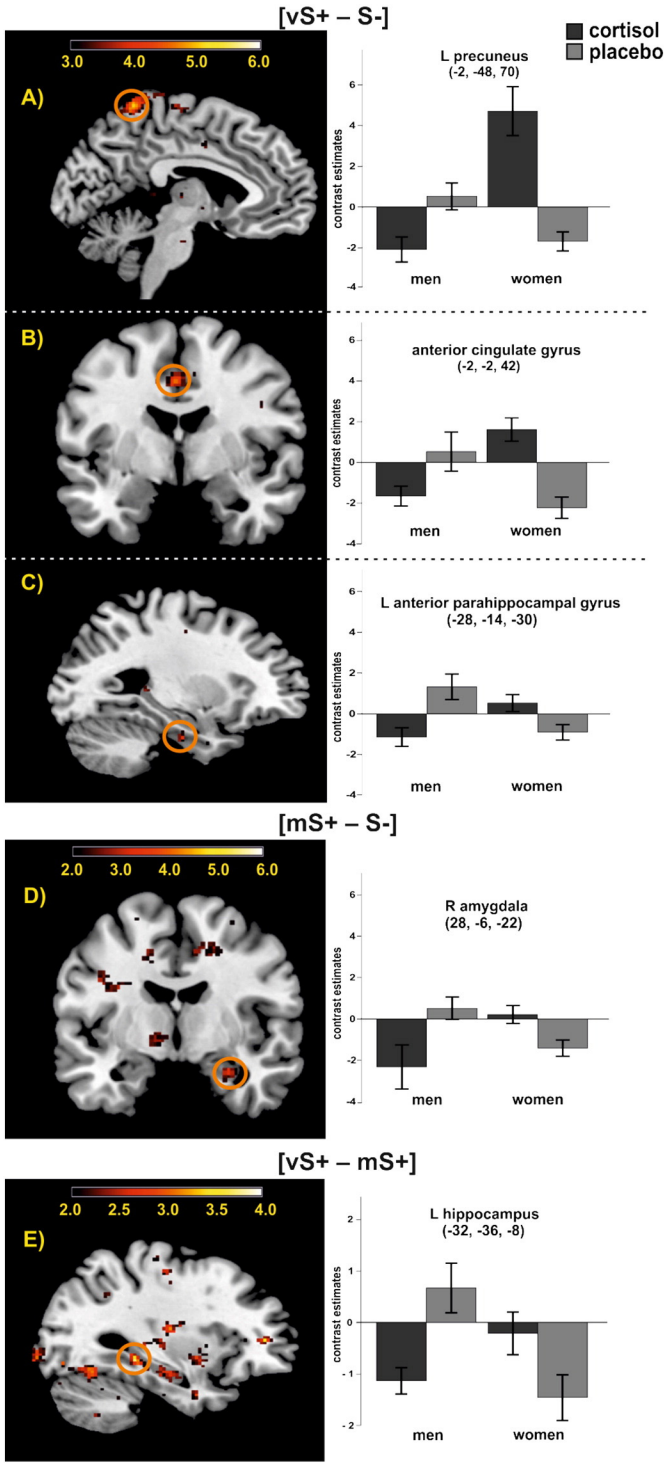

Fig. 3. Neural activations for the treatment × sex interaction are shown separately for the contrast [vS+ minus S−] **A**), **B**), **C**), [mS+ minus S−] **D**) and [vS+ minus mS+] **E**). The depicted coronal and sagittal slices were selected according to the reported activation in the left precuneus, anterior cingulate, left anterior parahippocampal gyrus, right amygdala and left hippocampus. For demonstration purposes, data were thresholded with $T \geq 3.0$ **A**), **B**), **C**) and $T \geq 2.0$ **D**), **E**) (see color bar for exact *T*-values) and displayed on the standard MNI brain template. In the bar graphs, mean differential contrast estimates for [vS+ minus S−], [mS+ minus S−] and [vS+ minus mS+] are additionally given for the cortisol and placebo group, separately for men and women in the respective peak voxel. Error bars are standard errors of the mean. In men, cortisol significantly attenuated activation to the verbal feedback cue (vS+) in the left precuneus **A**), anterior cingulate **B**), left anterior parahippocampal gyrus **C**) and left hippocampus **E**), whereas in women activation in these brain regions was enhanced in the cortisol compared to the placebo group. Accordingly, in the right amygdala **D**) reduced activation to the monetary reward cue (mS+) was found again in cortisol-treated men but not in women.

release. Moreover, dose-dependent response functions of cortisol on behavioral and psychophysiological measures have been reported (Buchanan et al., 2001; Lupien et al., 1999; Lupien et al., 2007) that might result from the different occupation of GRs and MRs when high or low cortisol concentrations are available (Lupien and McEwen, 1997). For instance, Buchanan et al. (2001) found that the acoustic startle reflex was increased after administration of 5 mg hydrocortisone, whereas a 20 mg dose had quite the opposite effect. Thus, we cannot exclude that different results would have been obtained with a lower dose of hydrocortisone or with an induction of psychosocial stress. Importantly, due to the mechanistic approach used in the present study, we provide evidence that the stress hormone cortisol is directly related to diminished reward anticipation. Consistent with that, a recent fMRI-study revealed that pharmacological administration of cortisol leads to blunted activation to monetary gains in the basolateral amygdala and the striatum (Montoya et al., 2014). In addition, they found cortisol to decrease subjective preference ratings for cues signaling reward. Together with these findings our data indicate that cortisol is critically involved in the neural regulation of motivational processing and thereby extend the existing stress-imaging literature to pharmacologically elevated cortisol concentrations.

Another important issue that has to be considered is the fact that fMRI scanning itself might have been potentially stressful for some participants. Accordingly, HPA-axis activation in response to fMRI sessions has been reported in a number of studies (Lueken et al., 2012; Muehlhan et al., 2011; Peters et al., 2011; Tessner et al., 2006), especially in individuals who were naïve to the scanner environment. Cortisol data in the present study, however, revealed that stress hormone concentrations in the placebo group significantly decreased from pre-scanning to post-scanning indicating that the fMRI session did not constitute an additional stressor that was superimposed on the pharmacological treatment. Nevertheless, we cannot rule out whether anticipatory anxiety may have led to increased baseline cortisol concentrations. To address this issue, an additional baseline cortisol sample which participants collect at home on a separate control day could have provided important information.

Interestingly, our results demonstrate that cortisol influences reward processing in some brain areas in a sex-specific manner. In men, cortisol attenuated anticipatory neural responses to the verbal reward in the precuneus, anterior cingulate, anterior parahippocampal gyrus, and left hippocampus, whereas it enhanced neural activation in these regions in women. For the monetary reward, a trend for the same sex-dependent cortisol effect was observed in the amygdala. Congruently, these structures host a high density of MRs and GRs (Joels, 2011) and are involved in the regulation of reward processes (Arias-Carrión et al., 2010). Furthermore, studies on human working memory and declarative memory retrieval have documented glucocorticoid-induced alterations in prefrontal and hippocampal activation (de Quervain et al., 2003; Oei et al., 2007; Weerda et al., 2010). Although the precuneus is not regarded as a key structure of the reward system, increased activation in this region has been previously linked to reward outcome, in particular to the experience of being liked (Davey et al., 2010). In line with that, we found cortisol-mediated changes of precuneus activation only in response to the verbal reward.

Importantly, using cortisol administration, our results parallel evidence from previous stress studies (Lighthall et al., 2009; Porcelli et al., 2012) showing similar cortisol-related sex differences in the neural correlates of reward processing. Notably, in the current study, the sex-specific cortisol effect was further substantiated on the behavioral level since men showed prolonged reaction times to the verbal reward after cortisol administration whereas women got faster in the cortisol compared to the placebo group. Albeit evidence from pharmacological studies is still lacking in reward literature, the present data are well in line with the cortisol-induced decrease in reward-related neural activation recently observed in men (Montoya et al., 2014). Furthermore, it

has been shown that cortisol which is released in response to psychological stress differently affects brain activation in men and women. For instance, in males, cortisol is associated with stronger activations of prefrontal areas and deactivation of the orbitofrontal cortex, whereas in females limbic structures, such as the ventral striatum, insula and putamen are activated by stress-induced cortisol concentrations (Wang et al., 2007). Similarly, in the current study, cortisol administration increased reward signaling of limbic structures in women but attenuated it in men. Supporting this line of argumentation, recent fear conditioning studies indicate that cortisol differentially influences fear learning in men and women which is accompanied by reduced nucleus accumbens, anterior cingulate, amygdala and hippocampus signaling in men but enhanced activation in these brain regions in women (Merz et al., 2012, 2013). Notably, although using an appetitive learning paradigm in the current study, we found the same brain regions to be targeted by this sex-specific cortisol effect. Together, these results suggest that cortisol modulates the neural correlates of emotional learning independent from valence.

It is important to note that we exclusively tested OC women. In contrast, most of the work that has been previously done on stress and reward did not provide information about sex hormone status or OC usage in women (Berghorst et al., 2013; Bogdan and Pizzagalli, 2006; Porcelli et al., 2012; but see Ossewaarde et al., 2011). Whether our results apply to free-cycling women as well therefore remains an issue of future research. At least with regard to fear learning, it has been shown that the effects of cortisol on brain activation are quite similar in free-cycling women and men (Merz et al., 2012). Thus, OC usage or rather sex hormone status and not sex per se appears to interfere with stress hormone actions. Consistently, the impact of menstrual cycle phase and OCs on emotional learning has been repeatedly demonstrated in animals (Dalla and Shors, 2009) as well as in humans (Merz and Wolf, 2015). Moreover, sex hormones are known to modulate how stress influences frontal and medial temporal lobe functioning (Andreano and Cahill, 2010; Toffoletto et al., 2014). For instance, cortisol has been found to impair memory retrieval in free-cycling women but not in OC women (Kuhlmann and Wolf, 2005). Likewise, a study by Nielsen et al. (2013) reported a differential impact of stress exposure on memory consolidation in free-cycling and OC women. A possible mechanism that could account for the diverse stress hormone effects on brain functions in OC women might be alterations in hypothalamus-pituitary-gonadal (HPG) axis activity. The HPG axis controlling the release of estradiol, progesterone and testosterone is influenced by acute stress and in turn the HPA axis response is modulated by sex hormones (Green and McCormick, 2016; Kajantie and Phillips, 2006; Kudielka and Kirschbaum, 2005). Moreover, estrogen and progesterone receptors colocalize with GC-receptors in brain regions involved in emotional and cognitive regulation (Brinton et al., 2008; Wharton et al., 2012) indicating a particular susceptibility to stress-sex interactions. For the present study, the differing neural reward patterns in men and women might therefore reflect a distinct responsivity of the brain to the complex interplay of circulating exogenous and endogenous hormones released by both axes. Since a considerable percentage of women are using OCs (United Nations, 2007) future studies are warranted comparing the impact of cortisol on reward processing in OC and free-cycling women.

Stress and sex hormones have been implicated in the pathogenesis of several psychiatric disorders (Grant et al., 2003). Our data provides evidence that anticipation of rewards is diminished by cortisol particularly in men. It is therefore reasonable that a cortisol-induced mechanism might pave the way to aberrant reward processing in men experiencing stress, and therefore translate into a higher vulnerability for pathological behavior. In line with this, stress-associated alterations in striatal function have been implicated in the anhedonia observed in depressed patients (Pizzagalli et al., 2009) as well as in the relapse of drug and alcohol addiction (Sinha and Li, 2007). Stress hormones do not only modify the mere consumption of a reward but rather change its incentive salience in the first place, suggesting altered anticipation processes to play a critical role in the development of these disorders (Schwabe et al., 2011).

For the current findings, it is worth emphasizing that the observed cortisol effects on reward anticipation were mainly restricted to the verbal reward condition. In the monetary reward condition in which participants received both, verbal feedback and a financial reward, effects might have lacked significance due to ceiling effects in task performance. Consistent with this proposition, participants exhibited a remarkably high number of hits towards the monetary reward cue (71% compared to 57% in the verbal reward condition). Importantly, we could show that anticipating the monetary reward was most effective in activating our predefined reward network. It is, therefore, reasonable that the chance to receive high incentives has evoked a steep increase of dopaminergic activity in the respective brain regions which in turn might have left them more resilient to the effects of cortisol. In line with this notion, Porcelli and colleagues (2012) found striatal responses to high magnitude rewards to be unaffected by acute stress.

The experimental paradigm implemented in this study was specifically designed to investigate neural responses to reward anticipation, but not to reward outcome (Kirsch et al., 2003). Although the adaptive algorithm assured that all participants were able to win some money, hit rates and thus number of rewarding trials differed between individuals as well as between the two reward types. Therefore, analysis of brain activation to reward outcome would be confounded by reward frequency and is thus not applicable for the current data. However, when exploring anticipatory reward processes an asset of the adaptive mechanism is that it maximizes the participants' uncertainty concerning reward delivery and therefore continuously activates the reward system. Future studies dissecting the impact of stress hormones on the neural correlates of anticipatory and consummatory reward processes could provide further insights into which extent cortisol is involved in motivational as well as hedonic aspects of reward.

Conclusion

In sum, our data demonstrate that administration of cortisol diminishes the neural correlates of verbal and monetary reward anticipation. We provide direct evidence for cortisol to be critically involved in the regulation of motivating behavior which might constitute a potential risk factor for developing psychiatric disorders. Furthermore, results indicate that in some brain regions cortisol has opposing effects in men and women using OCs. These findings emphasize that the differential influence of stress hormones on individuals with varying sex hormones status needs to be explored in more detail, both in clinical as well as in basic research (Merz and Wolf, 2015).

References

Andreano, J.M., Cahill, L., 2010. Menstrual cycle modulation of medial temporal activity evoked by negative emotion. NeuroImage 53, 1286–1293.
Arias-Carrión, O., Stamelou, M., Murillo-Rodríguez, E., Menéndez-González, M., Pöppel, E., 2010. Dopaminergic reward system: a short integrative review. Int. Arch. Med. 3, 1–6.
Becker, M.P., Nitsch, A.M., Miltner, W.H., Straube, T., 2014. A single-trial estimation of the feedback-related negativity and its relation to BOLD responses in a time-estimation task. J. Neurosci. 34, 3005–3012.
Berghorst, L.H., Bogdan, R., Frank, M.J., Pizzagalli, D.A., 2013. Acute stress selectively reduces reward sensitivity. Front. Hum. Neurosci. 7, 1–15.
Bogdan, R., Pizzagalli, D.A., 2006. Acute stress reduces reward responsiveness: implications for depression. Biol. Psychiatry 60, 1147–1154.
Brinton, R.D., Thompson, R.F., Foy, M.R., Baudry, M., Wang, J., Finch, C.E., Morgan, T.E., Pike, C.J., Mack, W.J., Stanczyk, F.Z., Nilsen, J., 2008. Progesterone receptors: form and function in brain. Front. Neuroendocrinol. 29, 313–339.
Buchanan, T.W., Brechtel, A., Sollers, J.J., Lovallo, W.R., 2001. Exogenous cortisol exerts effects on the startle reflex independent of emotional modulation. Pharmacol. Biochem. Behav. 68, 203–210.
Cover, K.K., Maeng, L.Y., Lebron-Milad, K., Milad, M.R., 2014. Mechanisms of estradiol in fear circuitry: implications for sex differences in psychopathology. Transl. Psychiatry 4, e422.
Dalla, C., Shors, T.J., 2009. Sex differences in learning processes of classical and operant conditioning. Physiol. Behav. 97, 229–238.

Davey, C.G., Allen, N.B., Harrison, B.J., Dwyer, D.B., Yucel, M., 2010. Being liked activates primary reward and midline self-related brain regions. Hum. Brain Mapp. 31, 660–668.
de Kloet, E.R., 2004. Hormones and the stressed brain. Ann. N. Y. Acad. Sci. 1018, 1–15.
de Kloet, E.R., Joels, M., Holsboer, F., 2005. Stress and the brain: from adaptation to disease. Nat. Rev. Neurosci. 6, 463–475.
de Quervain, D.J.-F., Henke, K., Aerni, A., Treyer, V., McGaugh, J.L., Berthold, T., Nitsch, R.M., Buck, A., Roozendaal, B., Hock, C., 2003. Glucocorticoid-induced impairment of declarative memory retrieval is associated with reduced blood flow in the medial temporal lobe. Eur. J. Neurosci. 17, 1296–1302.
Diekhof, E.K., Ratnayake, M., 2015. Menstrual cycle phase modulates reward sensitivity and performance monitoring in young women: preliminary fMRI evidence. Neuropsychologia.
Dillon, D.G., Holmes, A.J., Jahn, A.L., Bogdan, R., Wald, L.L., Pizzagalli, D.A., 2008. Dissociation of neural regions associated with anticipatory versus consummatory phases of incentive processing. Psychophysiology 45, 36–49.
Everitt, B.J., Robbins, T.W., 2005. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat. Neurosci. 8, 1481–1489.
Foerde, K., Shohamy, D., 2011. The role of the basal ganglia in learning and memory: insight from Parkinson's disease. Neurobiol. Learn. Mem. 96, 624–636.
Grant, K.E., Compas, B.E., Stuhlmacher, A.F., Thurm, A.E., McMahon, S.D., Halpert, J.A., 2003. Stressors and child and adolescent psychopathology: moving from markers to mechanisms of risk. Psychol. Bull. 129, 447–466.
Green, M.R., McCormick, C.M., 2016. Sex and stress steroids in adolescence: gonadal regulation of the hypothalamic-pituitary-adrenal axis in the rat. Gen. Comp. Endocrinol.
Joels, M., 2011. Impact of glucocorticoids on brain function: relevance for mood disorders. Psychoneuroendocrinology 36, 406–414.
Joels, M., Baram, T.Z., 2009. The neuro-symphony of stress. Nat. Rev. Neurosci. 10, 459–466.
Kajantie, E., Phillips, D.I.W., 2006. The effects of sex and hormonal status on the physiological response to acute psychosocial stress. Psychoneuroendocrinology 31, 151–178.
Kessler, R.C., Chiu, W.T., Demler, O., Walters, E.E., 2005. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. Arch. Gen. Psychiatry 62, 617–627.
Kinner, V.L., Het, S., Wolf, O.T., 2014. Emotion regulation: exploring the impact of stress and sex. Front. Behav. Neurosci. 8, 397.
Kirsch, P., Schienle, A., Stark, R., Sammer, G., Blecker, C., Walter, B., Ott, U., Burkart, J., Vaitl, D., 2003. Anticipation of reward in a nonaversive differential conditioning paradigm and the brain reward system. NeuroImage 20, 1086–1095.
Kirsch, P., Reuter, M., Mier, D., Lonsdorf, T., Stark, R., Gallhofer, B., Vaitl, D., Hennig, J., 2006. Imaging gene-substance interactions: the effect of the DRD2 TaqIA polymorphism and the dopamine agonist bromocriptine on the brain activation during the anticipation of reward. Neurosci. Lett. 405, 196–201.
Knutson, B., Adams, C.M., Fong, G.W., Hommer, D., 2001. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J. Neurosci. 21, 1–5.
Kudielka, B.M., Kirschbaum, C., 2005. Sex differences in HPA axis responses to stress: a review. Biol. Psychol. 69, 113–132.
Kuhlmann, S., Wolf, O.T., 2005. Cortisol and memory retrieval in women: influence of menstrual cycle and oral contraceptives. Psychopharmacology 183, 65–71.
Kuhlmann, S., Piel, M., Wolf, O.T., 2005. Impaired memory retrieval after psychosocial stress in healthy young men. J. Neurosci. 25, 2977–2982.
Lewis, A.H., Porcelli, A.J., Delgado, M.R., 2014. The effects of acute stress exposure on striatal activity during Pavlovian conditioning with monetary gains and losses. Front. Behav. Neurosci. 8, 179.
Lighthall, N.R., Mather, M., Gorlick, M.A., 2009. Acute stress increases sex differences in risk seeking in the balloon analogue risk task. PLoS One 4, e6002.
Lovallo, W.R., Robinson, J.L., Glahn, D.C., Fox, P.T., 2010. Acute effects of hydrocortisone on the human brain: an fMRI study. Psychoneuroendocrinology 35, 15–20.
Lueken, U., Muehlhan, M., Evens, R., Wittchen, H.U., Kirschbaum, C., 2012. Within and between session changes in subjective and neuroendocrine stress parameters during magnetic resonance imaging: a controlled scanner training study. Psychoneuroendocrinology 37, 1299–1308.
Lupien, S.J., McEwen, B.S., 1997. The acute effects of corticosteroids on cognition: integration of animal and human model studies. Brain Res. Rev. 24, 1–27.
Lupien, S.J., Gillin, C.J., R.L., H., 1999. Working memory is more sensitive than declarative memory to the acute effects of corticosteroids: a dose-response study in humans. Behav. Neurosci. 113, 420–430.
Lupien, S.J., Maheu, F., Tu, M., Fiocco, A., Schramek, T.E., 2007. The effects of stress and stress hormones on human cognition: implications for the field of brain and cognition. Brain Cogn. 65, 209–237.
Lutz, K., Widmer, M., 2014. What can the monetary incentive delay task tell us about the neural processing of reward and punishment? Neurosci. Neuroeconomics 33.
Maier, S.U., Makwana, A.B., Hare, T.A., 2015. Acute stress impairs self-control in goal-directed choice by atering multiple functional connections within the brain's decision circuits. Neuron 87, 621–631.
Merz, C.J., Wolf, O.T., 2015. Stress and emotional learning in humans: evidence for sex differences. In: Shansky, R.M. (Ed.), Sex Differences in the Central Nervous System. Haley, M. Academic Press, Boston, pp. 149–169.
Merz, C.J., Tabbert, K., Schweckendiek, J., Klucken, T., Vaitl, D., Stark, R., Wolf, O.T., 2012. Oral contraceptive usage alters the effects of cortisol on implicit fear learning. Horm. Behav. 62, 531–538.
Merz, C.J., Wolf, O.T., Schweckendiek, J., Klucken, T., Vaitl, D., Stark, R., 2013. Stress differentially affects fear conditioning in men and women. Psychoneuroendocrinology 38, 2529–2541.
Montoya, E.R., Bos, P.A., Terburg, D., Rosenberger, L.A., van Honk, J., 2014. Cortisol administration induces global down-regulation of the brain's reward circuitry. Psychoneuroendocrinology 47, 31–42.
Morelli, S.A., Sacchet, M.D., Zaki, J., 2015. Common and distinct neural correlates of personal and vicarious reward: a quantitative meta-analysis. NeuroImage 112, 244–253.
Muehlhan, M., Lueken, U., Wittchen, H.U., Kirschbaum, C., 2011. The scanner as a stressor: evidence from subjective and neuroendocrine stress parameters in the time course of a functional magnetic resonance imaging session. Int. J. Psychophysiol. 79, 118–126.
Nielsen, S.E., Segal, S.K., Worden, I.V., Yim, I.S., Cahill, L., 2013. Hormonal contraception use alters stress responses and emotional memory. Biol. Psychol. 92, 257–266.
Oei, N.Y., Elzinga, B.M., Wolf, O.T., de Ruiter, M.B., Damoiseaux, J.S., Kuijer, J.P., Veltman, D.J., Scheltens, P., Rombouts, S.A., 2007. Glucocorticoids decrease hippocampal and prefrontal activation during declarative memory retrieval in young men. Brain Imaging Behav. 1, 31–41.
Oei, N.Y., Tollenaar, M.S., Spinhoven, P., Elzinga, B.M., 2009. Hydrocortisone reduces emotional distracter interference in working memory. Psychoneuroendocrinology 34, 1284–1293.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.
Ossewaarde, L., Qin, S., Van Marle, H.J., van Wingen, G.A., Fernandez, G., Hermans, E.J., 2011. Stress-induced reduction in reward-related prefrontal cortex function. NeuroImage 55, 345–352.
Peters, S., Cleare, A.J., Papadopoulos, A., Fu, C.H., 2011. Cortisol responses to serial MRI scans in healthy adults and in depression. Psychoneuroendocrinology 36, 737–741.
Pizzagalli, D.A., Holmes, A.J., Dillon, D.G., Goetz, E.L., Birk, J.L., Bogdan, R., Dougherty, D.D., Iosifescu, D.V., Rauch, S.L., Fava, M., 2009. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am. J. Psychiatry 166, 702–710.
Porcelli, A.J., Delgado, M.R., 2009. Acute stress modulates risk taking in financial decision making. Psychol. Sci. 20, 278–283.
Porcelli, A.J., Lewis, A.H., Delgado, M.R., 2012. Acute stress influences neural circuits of reward processing. Front. Neurosci. 6, 157.
Pruessner, J.C., Dedovic, K., Khalili-Mahani, N., Engert, V., Pruessner, M., Buss, C., Renwick, R., Dagher, A., Meaney, M.J., Lupien, S., 2008. Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance imaging studies. Biol. Psychiatry 63, 234–240.
Schoofs, D., Pabst, S., Brand, M., Wolf, O.T., 2013. Working memory is differentially affected by stress in men and women. Behav. Brain Res. 241, 144–153.
Schwabe, L., Wolf, O.T., Oitzl, M.S., 2010. Memory formation under stress: quantity and quality. Neurosci. Biobehav. Rev. 34, 584–591.
Schwabe, L., Dickinson, A., Wolf, O.T., 2011. Stress, habits, and drug addiction: a psychoneuroendocrinological perspective. Exp. Clin. Psychopharmacol. 19, 53–63.
Sinclair, D., Purves-Tyson, T.D., Allen, K.M., Weickert, C.S., 2014. Impacts of stress and sex hormones on dopamine neurotransmission in the adolescent brain. Psychopharmacology 231, 1581–1599.
Sinha, R., Li, C.S., 2007. Imaging stress- and cue-induced drug and alcohol craving: association with relapse and clinical implications. Drug Alcohol Rev. 26, 25–31.
Stark, R., Wolf, O.T., Tabbert, K., Kagerer, S., Zimmermann, M., Kirsch, P., Schienle, A., Vaitl, D., 2006. Influence of the stress hormone cortisol on fear conditioning in humans: evidence for sex differences in the response of the prefrontal cortex. NeuroImage 32, 1290–1298.
Tessner, K.D., Walker, E.F., Hochman, K., Hamann, S., 2006. Cortisol responses of healthy volunteers undergoing magnetic resonance imaging. Hum. Brain Mapp. 27, 889–895.
Toffoletto, S., Lanzenberger, R., Gingnell, M., Sundström-Poromaa, I., Comasco, E., 2014. Emotional and cognitive functional imaging of estrogen and progesterone effects in the female human brain: a systematic review. Psychoneuroendocrinology 50, 28–52.
United Nations, 2007. http://www.un.org/esa/population/publications/contraceptive2007/contraceptive2007.htm.
Van Craenenbroeck, K., De Bosscher, K., Vanden Berghe, W., Vanhoenacker, P., Haegeman, G., 2005. Role of glucocorticoids in dopamine-related neuropsychiatric disorders. Mol. Cell. Endocrinol. 245, 10–22.
Wang, J., Rao, H., Wetmore, G.S., Furlan, P.M., Korczykowski, M., Dinges, D.F., Detre, J.A., 2005. Perfusion functional MRI reveals cerebral blood flow pattern under psychological stress. Proc. Natl. Acad. Sci. U. S. A. 102, 17804–17809.
Wang, J., Korczykowski, M., Rao, H., Fan, Y., Pluta, J., Gur, R.C., McEwen, B.S., Detre, J.A., 2007. Gender difference in neural response to psychological stress. Soc. Cogn. Affect. Neurosci. 2, 227–239.
Weerda, R., Muehlhan, M., Wolf, O.T., Thiel, C.M., 2010. Effects of acute psychosocial stress on working memory related brain activity in men. Hum. Brain Mapp. 31, 1418–1429.
Wharton, W., Gleason, C.E., Olson, S.R., Carlsson, C.M., Asthana, S., 2012. Neurobiological underpinnings of the estrogen-mood relationship. Curr. Psychiatr. Rev. 8, 247–256.