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Cortisol alters reward processing in the human brain☆

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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-

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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

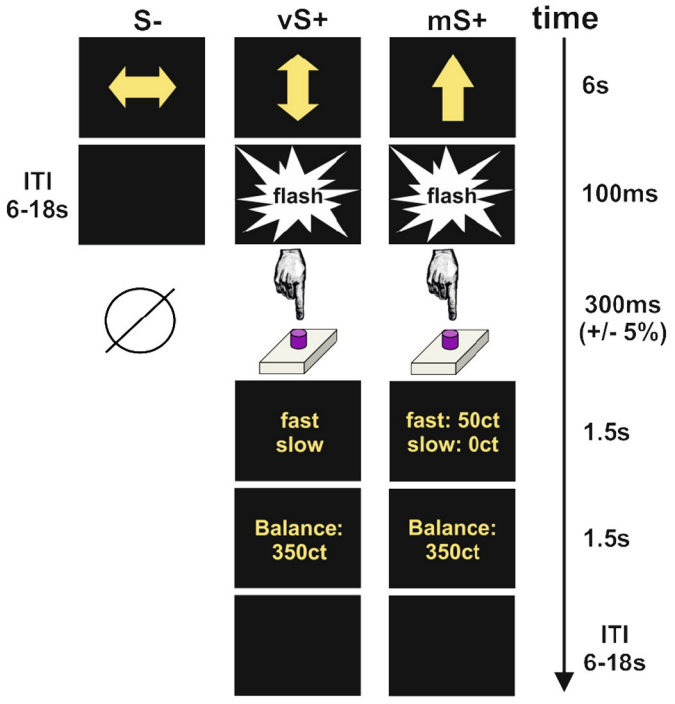

Fig. 1. MID-task with the three experimental conditions: S− (control), vS+ (verbal reward) and mS+ (monetary reward). Participants had to respond as fast as possible to a bright flashlight following the presentation of the vS+ and the mS+ by pressing a response button. The threshold for the response 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.