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Cortisol enhances neural differentiation during fear acquisition and extinction in contingency aware young women

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ABSTRACT

Previously, we observed cortisol induced enhancement of neural fear acquisition in women. Yet, less is known about cortisol effects on neural fear extinction. Via differential fear conditioning, we explored cortisol effects on acquisition and extinction. Twenty contingency aware women taking monophasic oral contraceptives were included; 10 received placebo, 10 cortisol before conditioning. Group differences emerged in anterior cingulate cortex (ACC), hippocampus, and – as trend – in insula and thalamus during acquisition and in hippocampus, thalamus, and – as trend – in amygdala, insula, and ACC during extinction. During acquisition group differences were due to higher responses to the CS+ than to the CS− in the cortisol group. Notably, during extinction, group differences were due to higher responses to the CS− than to the CS+ in this group. Thus, cortisol induced a fear acquisition and extinction specific enhanced neural differentiation.

1. Introduction

Stress, stress-associated glucocorticoid (GC; cortisol in humans) release from the adrenal cortex, and exogenous GC administration have been demonstrated to influence affective learning and memory (e.g. Bangasser & Shors, 2010; de Kloet, Oitzl, & Joëls, 1999; Joëls, 2010; Sandi, 1998; Sandi & Pinelo-Nava, 2007; Wolf, 2009). Thus, many models of the pathogenesis of affective and anxiety disorders have incorporated stress as well changes in cortisol release and cortisol levels as vulnerability factors (Korte, 2001; Mineka & Zinbarg, 2006; Wolf, 2008).

During the last decade, increasing efforts were made in the attempt to identify the neural structures and processes responsible for these effects (Bangasser & Shors, 2010; van Stegeren, 2009). Altogether, animal and human research point to the amygdala, the hippocampus, and the prefrontal cortex as potential candidate regions, as these regions are rich in mineralocorticoid (MRs) and glucocorticoid receptors (GRs) that bind circulating GC and thus are potentially modulated by stress related hormonal responses (Bangasser & Shors, 2010; Rodrigues, LeDoux, & Sapolsky, 2009; van Stegeren, 2009; Wolf, 2008).

In order to study potential effects of stress and stress hormones on affective learning, classical conditioning is a promising and thoroughly validated approach that allows the exploration of effects on the acquisition as well as the extinction of fear. Animal studies provided first evidence for an influence of stress and stress hormones on fear acquisition via conditioning (Bohus & Lissák, 1968; Brinks, Berger, Gass, de Kloet, & Oitzl, 2009; Rodrigues et al., 2009; Wolf, 2008). However, to date the number of human studies on this important topic is still very limited. Interestingly, most of the conducted studies reported sex differences (e.g. Jackson, Payne, Nadel, & Jacobs, 2006; Stark et al., 2006; Wolf, 2008). Three studies showed a positive correlation between basal cortisol concentrations and fear acquisition or a facilitating effect of psychosocial stress on conditioned responses in male subjects (Jackson et al., 2006; Zorawski, Blanding, Kuhn, & LaBar, 2006; Zorawski, Cook, Kuhn, & LaBar, 2005). Yet, contrasting findings have also been reported, e.g. impaired eyeblink conditioning after psychosocial stress in men and women (Wolf, Minnebusch, & Daum, 2009)

Abbreviations: ACC, anterior cingulate cortex; CS, conditioned stimulus; CS+, conditioned stimulus predicting the electrical stimulation; CS−, conditioned stimulus predicting the absence of the electrical stimulation; FIR, first interval response; fMRI, functional magnetic resonance imaging; FWE, family-wise error; GC, glucocorticoid; GR, glucocorticoid receptor; HPA, hypothalamus–pituitary–adrenal; mPFC, medial prefrontal cortex; MR, mineralocorticoid receptor; OC, oral contraceptives; OFC, orbitofrontal cortex; ROI, region of interest; SCR, skin conductance response; SIR, second interval response; UCR, unconditioned response; UCS, unconditioned stimulus.

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and impaired electrodermal conditioning in men after exogenous cortisol treatment (Stark et al., 2006).

Similarly to fear acquisition, acute GC activity has been shown to influence extinction learning in animals, predominantly enhancing effects, but less is known about GC effects on extinction in humans (Barrett & Gonzalez-Lima, 2004; Yang, Chao, & Lu, 2006; for overviews see e.g. Bentz, Michael, de Quervain, & Wilhelm, 2010; Rodrigues et al., 2009; Wolf, 2008). Clinical studies found an attenuation of post-traumatic stress disorder and phobia symptoms in humans after GC treatment presumably via an impairment in traumatic memory retrieval and a facilitated extinction, however, no sex specific effects occurred (Aerni et al., 2004; de Quervain & Margraf, 2008; Schelling, Roozendaal, & de Quervain, 2004; Soravia et al., 2006). Yet, one study investigating electrodermal fear conditioning reported diverging stress effects in males and females during early extinction (Jackson et al., 2006).

Despite the merits of classical fear conditioning paradigms in studying stress and GC effects on the neural activations underlying fear acquisition in humans, only few imaging studies have been conducted so far. Further, to our best knowledge, no fMRI study has directly investigated GC effects on neural activations during extinction in healthy humans. In two previous fMRI studies, we observed impaired conditioned neural differentiation in men after cortisol as compared to placebo intake in prefrontal and subcortical structures as well as the insula, whereas women exhibited the opposite pattern of results (Merz et al., 2010; Stark et al., 2006). Yet, cortisol enhanced unconditioned responses (UCRs) in the anterior and posterior cingulate cortex, irrespective of sex (Stark et al., 2006; but see Merz et al., 2010). Thus, to complement and extend the knowledge about GC effects on neural activation during fear conditioning, we conducted a differential fear conditioning experiment with an acquisition and an adjacent extinction session in a sample of young healthy women. Thus, we investigated the acquisition of extinction, i.e., the initial learning that the UCS no longer follows the CS+, not extinction consolidation and recall or retrieval (Quirk & Mueller, 2008). Prior to the conditioning procedure, half of the participants received an oral dose of hydrocortisone, whereas the other half received placebo.

Concerning neural structures, we focused on brain regions which are crucially involved in the acquisition and the extinction of fear (e.g. Sehlmeyer et al., 2009) and potentially influenced by GC treatment (de Quervain, Aerni, Schelling, & Roozendaal, 2009; Merz et al., 2010; Rodrigues et al., 2009; Stark et al., 2006; van Stegeren, 2009). The underlying assumption is that cortisol may directly affect these structures altering fear learning processes (cf. Bangasser & Shors, 2010). Based on findings on human fear conditioning, the amygdala, the anterior cingulate cortex (ACC), the insula, the orbitofrontal cortex (OFC), and to a less specifical extend, the thalamus were chosen as regions of interest (ROI) for the acquisition (Büchel & Dolan, 2000; Knight, Cheng, Smith, Stein, & Helmstetter, 2004; Knight, Smith, Stein, & Helmstetter, 1999; LeDoux, 2000; Rolls, 1999; Sehlmeyer et al., 2009; Tabbert, Stark, Kirsch, & Vaitl, 2005; Öhman, 2005). Moreover, the amygdala, the hippocampus, and the medial prefrontal cortex (mPFC) including the ACC seem to play a crucial role during different phases of extinction and thus were selected as ROI for the extinction phase (Knight, Smith, Cheng, Stein, & Helmstetter, 2004; Phelps, Delgado, Nearing, & LeDoux, 2004; Quirk & Mueller, 2008). As with other forms of affective learning (see above), GCs might act in the different subcortical and cortical brain regions influencing fear conditioning (e.g. de Quervain et al., 2009; Rodrigues et al., 2009).

In our female sample, we expected cortisol to facilitate learning during acquisition (cf. Stark et al., 2006). Concerning extinction, facilitating effects of cortisol have been reported previously in animal studies (Rodrigues et al., 2009; Wolf, 2008). However, as we administered cortisol already prior to acquisition, other than in relevant previous studies, and due to little knowledge from human studies, analyses in this phase were explorative. Finally, we also expected enhancing effects of cortisol on UCRs on the neural level (cf. Merz et al., 2010; Stark et al., 2006).

2. Materials and methods

2.1. Subjects

A total of 20 female subjects taking oral contraceptives (placebo group: $n = 10$; cortisol group: $n = 10$) was included in the presented study, which was approved by the ethics committee of the German Psychological Society. The women were required to have been taking their birth control pill (only monophasic preparations including an ethinylestradiol component) at least during the last three months and were tested during the "on phase" of pill intake. All participants were university students who had been recruited via announcements at bulletin boards at the campus. None of them was taking regular medication except oral contraceptives (OC) or had a history of any psychiatric or neurological treatment. Exclusion criteria were somatic and in particular endocrine diseases, which can have an impact on hormonal concentrations (e.g. acute asthma, hypo- or hyperthyroidism). All participants were right-handed as assessed by the Edinburgh Inventory of Handedness (Oldfield, 1971) and had normal or corrected-to-normal vision. Inclusion criteria were age between 19 and 35 and a body mass index (BMI = kg/m2) between 18 and 26.

All subjects were instructed to refrain from any caffeine and food intake, as well as from smoking two hours before the experiment. Five women of the placebo group and eight women of the cortisol were non-smokers. Smoking behavior was not assessed in three placebo women. The remaining four women (two of each group) were smokers. At the beginning, participants received a detailed explanation of the procedure in general (the conditioning schedule was of course not explained until the experiment was finished). Written informed consent was obtained. The cover story concealing the conditioning procedure was the investigation of the impact of cortisol and several distractors (including an electrical stimulation) on memory performance. After finishing the experiment, participants were debriefed about the real purpose of the study and received 25 Euros for their participation.

The experiment is part of a larger study investigating the effects of cortisol on fear acquisition and extinction with respect to contingency awareness and sex differences. Neural activation during conditioning can be modified by contingency awareness (potentially in interaction with stress hormones), which refers to the explicit knowledge of the CS/UCS relationship (e.g. Klucken et al., 2009; Knight, Waters, & Bandettini, 2009; Tabbert, Stark, Kirsch, & Vaitl, 2006; Tabbert et al., 2010; Öhman, 2005). Due to subject selection procedures, distribution of male and free cycling female subjects was unequal between the placebo and the cortisol group (male subjects: placebo: $n = 4$; cortisol: $n = 11$; free cycling women: placebo: $n = 6$; cortisol: $n = 10$). This prevented proper testing of sex differences or differences due to hormonal status. The current manuscript thus only reports the findings of female participants taking OCs who learned the CS/UCS contingencies during the experiment (learned aware group).

Data of the 10 learned aware females who received placebo are also part of a previous publication (Tabbert et al., 2010) investigating the effects of contingency awareness (and the way it is achieved) on fear acquisition. However, this group has not been analyzed separately or in any other study (i.e., addressing cortisol or hormonal effects). The data of the 10 cortisol women have not been analyzed or published elsewhere.