NeuroImage 73 (2013) 1–7

Contents lists available at SciVerse ScienceDirect

NeuroImage

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

Opposite effects of noradrenergic arousal on amygdala processing of fearful faces in men and women

Lars Schwabe [a,*], Oliver Höffken [b], Martin Tegenthoff [b], Oliver T. Wolf [a]

[a] Institute of Cognitive Neuroscience, Department of Cognitive Psychology, Ruhr-University Bochum, Universitaetsstrasse 150, 44780 Bochum, Germany
[b] Department of Neurology, Ruhr-University Bochum, BG-Kliniken Bergmannsheil, Bürkle de la Camp-Platz 1, 44789 Bochum, Germany

ARTICLE INFO

Article history:
Accepted 25 January 2013
Available online 4 February 2013

Keywords:
Stress
Noradrenaline
Glucocorticoids
Amygdala
Fear
Sex differences

ABSTRACT

Fear-related disorders are significantly more prevalent in women than in men. Stress may modulate the neurocircuitry of fear and is a critical factor in the pathogenesis of fear-related disorders. Therefore, we tested in the present experiment the hypothesis that noradrenaline and glucocorticoids, two major stress mediators, have differential effects on fear processing in men and women. In a placebo-controlled, double-blind between-subject design, 80 healthy men and women were administered orally the α2-adrenoceptor antagonist yohimbine and/or the synthetic glucocorticoid hydrocortisone before they rated images of neutral and fearful faces with respect to the degree of fearfulness of the facial expression. During presentation of facial expressions, functional magnetic resonance images were collected. Yohimbine increased subjective ratings of the fearfulness of the faces in women but reduced fearfulness ratings in men. Neuroimaging data showed that yohimbine increased amygdala activity in response to fearful faces in women, whereas it attenuated amygdala responsivity to fearful faces in men. Moreover, yohimbine decreased orbitofrontal activity while viewing fearful faces in women. Hydrocortisone did not affect fear processing, neither in men nor in women. Our findings suggest that noradrenergic arousal may have opposite effects on fear processing in men and women. These sex differences may represent a biological mechanism that contributes to the differential prevalence of fear-related disorders in men and women.

Introduction

Aberrant fear is at the heart of many psychiatric disorders, including panic disorder, post-traumatic stress disorder (PTSD) and phobias. Across cultures and countries, women are at least twice as likely as men to suffer from such fear-related disorders (Kessler et al., 2005; Wittchen et al., 2011). Despite this striking sex difference and great interest in that area, neural mechanisms that contribute to the differential prevalence of fear-related disorders in men and women remain largely elusive.

The key structure in the processing of fear is the amygdala (LeDoux, 2000). Bilateral damage to the amygdala impairs the processing of fearful facial expressions and the acquisition of conditioned fear responses (Adolphs et al., 1994). Neuroimaging data from healthy subjects confirm the critical role of the amygdala in fear processing and learning (Büchel et al., 1998; Morris et al., 1998). In line with the view that altered fear processing is related to psychopathology, exaggerated amygdala activity during the processing of fearful information has been noted in PTSD, depression and social anxiety (Birbaumer et al., 1998; Rauch et al., 2000; Shin et al., 2005; Stein et al., 2002). Moreover, there is considerable evidence for sex differences in amygdala responding during fear-related activities (Cahill, 2006), with some studies reporting stronger amygdala activation in response to fearful information in women than in men (Williams et al., 2005).

Animal and human studies indicate that amygdala activity can be modulated by neurotransmitters and hormones, such as noradrenaline and glucocorticoids (mainly cortisol in humans), that are released in response to stress (Cahill and McGaugh, 1998; Henckens et al., 2010; Rasch et al., 2009; Roozendaal et al., 2009; Strange and Dolan, 2004; van Stegeren et al., 2005). Stressful experiences are also critically involved in the pathogenesis of PTSD and other fear-related disorders (Horowitz, 1997). It is therefore tempting to hypothesize that sex differences in the prevalence of fear-related disorders are (at least partly) related to sex differences in the impact of stress (hormones) on amygdala processing of fear.

The present experiment addressed this hypothesis in a large sample of men and women and examined potential sex differences in the influence of noradrenaline and glucocorticoids on neural processing of fear. We administered healthy men and women orally the α2-adrenoceptor antagonist yohimbine, which leads to increased noradrenergic stimulation, the synthetic glucocorticoid hydrocortisone, or a combination of both drugs in order to assess potential interaction effects of noradrenaline and glucocorticoids on fear processing. After drug intake, participants

* Corresponding author at: Ruhr-University Bochum, Department of Cognitive Psychology, 44780 Bochum, Germany. Fax: +49 234 3214308.
E-mail address: Lars.Schwabe@ruhr-uni-bochum.de (L. Schwabe).

1053-8119/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.01.057

saw, while lying in a 3 Tesla scanner, pictures of fearful (and neutral) facial expressions, which are known to reliably recruit the amygdala and other fear relevant structures such as the medial prefrontal cortex, the insula or the anterior cingulate cortex (Breiter et al., 1996; Stein et al., 2007; Vuilleumier et al., 2001). Given that stress- and fear-related disorders are significantly more prevalent in women than in men and that amygdala activity is often increased during fear processing in these disorders, we expected that yohimbine and glucocorticoids would result in stronger amygdala activation during viewing of fearful faces in women than in men.

Material and methods

Participants

In a placebo-controlled, double-blind between-subject design, 80 healthy, normal weight, right-handed nonsmokers (40 men, 40 women; age: 23.53 ± 0.34 years; body-mass-index (kg/m^2): 23.29 ± 0.33) with normal or corrected-to-normal vision were randomly assigned to one of four experimental groups (n = 20/group): placebo/placebo (PLAC), yohimbine/placebo (YOH), hydrocortisone/placebo (CORT), or yohimbine/hydrocortisone (YOH + CORT). Exclusion criteria for participation were checked by a psychologist (LS) in a standardized interview and included medication intake, hormonal contraceptive use, any current or chronic medical condition, current or lifetime history of any psychiatric or neurological disorder, and any contraindications for MRI. Women were tested only during the late follicular and luteal phase of their menstrual cycle when estrogen and progesterone levels were relatively high in order to reduce variability in sex hormone variations; menstrual cycle phase was determined based on participants' reports. The study protocol was approved by the Review Board of the Medical Faculty of the Ruhr-University Bochum. All participants provided written informed consent.

Drug administration and manipulation check

Participants were administered 20 mg Yohimbine (Desma) and/or 20 mg Hydrocortisone (JenaPharm) orally about 45 min before the MRI session. Drug dosage and timing of drug administration were chosen according to previous studies using these drugs (Buchanan and Lovallo, 2001; Schwabe et al., 2010; van Stegeren et al., 2010). In order to verify the action of the drugs, we collected saliva samples at several time points before and after drug administration. From saliva, we analyzed the biologically active, free fraction of the stress hormone cortisol, the major glucocorticoid in humans, and the enzyme alpha-amylase, an indicator of adrenergic activity (Chatterton et al., 1996). Cortisol concentrations were determined by a luminescence immunoassay (IBL, Hamburg, Germany; Westermann et al., 2004). Mean intra- and inter-assay coefficients of variation are less than 8% and 12%, respectively. Levels of salivary alpha-amylase were determined from the saliva samples using a commercially available kinetic reaction assay (Salimetrics, Penn State, PA; Granger et al., 2007). Mean intra- and interassay coefficients of variation of the salivary alpha-amylase analyses are less than 8% and 6%, respectively.

Stimuli

Stimuli consisted of frontal view images of 36 neutral and 36 fearful faces (18 male and 18 female faces per category) taken from the Radboud Faces Database, a validated set of pictures of models displaying different emotional expressions (Langner et al., 2010). Examples of the face stimuli are shown in Fig. 1.

Procedure

Because of the diurnal rhythm of the stress hormone cortisol, all testing took place in the afternoon between 1.00 and 6.30 pm. After their arrival at the laboratory, all participants completed the State-Trait-Anxiety Inventory (STAI; Spielberger, 2010) to control for potential group differences in state or trait anxiety. Moreover, participants gave a first saliva sample before they received placebo, yohimbine (20 mg) or hydrocortisone (20 mg) pills, depending on the experimental group. After a 30-minute break during which they remained in a quiet room, participants gave another saliva sample and were prepared for the MRI session. About 45 min after pill intake, participants gave another saliva sample immediately before the MRI session started. After a short anatomical scan, participants saw images of 36 fearful and 36 neutral faces that were presented in randomized order at the center of a computer screen (Fig. 1). Each picture was presented for 4 s. Participants were instructed to rate on a scale from 1 ("not at all fearful") to 4 ("very fearful") the degree of fearfulness of the facial expressions by pressing the corresponding button on a four-button response box. Between trials, participants were presented a fixation cross for 5 to 7 s (random jitter: 0–2 s). In total, the face rating task took about 13 min. After scanning, participants gave a final saliva sample out of the scanner.

Image acquisition

Imaging was conducted on a 3.0 Tesla Philips Achieva scanner equipped with a 32-channel head coil. For each participant, one high-resolution T1-weighted anatomical scan was acquired with the following parameters: 220 slices, slice thickness 1 mm, repetition time (TR) = 8.2 ms, echo time (TE) = 3.8 ms. During the face rating task, functional scans (370 volumes) were acquired parallel to the AC–PC plane (30 slices, slice thickness 3 mm, TR = 2.0 s, TE = 30 ms, flip angle = 90°, 64 × 64 matrix, 2 mm × 2 mm pixel size, field of view = 200 × 200 mm). The first 3 images were discarded to allow T1 equilibration.

Data analysis

Cortisol and alpha-amylase data were analyzed by sex × yohimbine (placebo vs. yohimbine) × hydrocortisone (placebo vs. hydrocortisone) × time point of measurement analyses of variance (ANOVAs). The face rating data were subjected to a mixed-design ANOVA with the factors sex, yohimbine, hydrocortisone and facial expression (neutral vs. fearful). Significant main or interaction effects were followed by appropriate post-hoc tests. All reported p-values are two-tailed.

Preprocessing and analysis of the event-related fMRI data were performed using SPM8 (Wellcome Trust Center for Neuroimaging, University College London). Functional imaging data were corrected for slice-timing and head motion. Structural images were segmented into gray matter, white matter, and cerebrospinal fluid. Gray matter images were normalized to the MNI template image. Functional images were co-registered with the structural image and combined with normalization parameters of the gray matter image in the final warp. Finally, data were spatially smoothed using an 8 mm full width half-maximum Gaussian kernel and filtered in the temporal domain using a nonlinear high-pass filter with a 128 s cut-off.

Functional data were analyzed using a general linear model with the regressors neutral face and fearful face. In addition, we included button presses and the six movement regressors counting information about motion correction into our model. Regressors of interest were constructed by a stick function convolved by a hemodynamic response function (HRF). The data were filtered in the temporal domain using a nonlinear high-pass filter with a 128 s cut-off. Contrast estimates were calculated for fearful face–neutral face and neutral face–fearful face.