Psychoneuroendocrinology 96 (2018) 42–51

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

Effects of testosterone administration on threat and escape anticipation in the orbitofrontal cortex

Sarah J. Heany[a], Richard A.I. Bethlehem[b], Jack van Honk[a,c,d], Peter A. Bos[d], Dan J. Stein[a,e], David Terburg[a,d,*]

[a] Department of Psychiatry and Mental Health, University of Cape Town, South Africa
[b] Autism Research Centre, Department of Psychiatry, University of Cambridge, United Kingdom
[c] Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, South Africa
[d] Department of Experimental Psychology, Utrecht University, The Netherlands
[e] MRC Unit on Anxiety & Stress Disorders, University of Cape Town, South Africa

ARTICLE INFO

Keywords:
Fear
Avoidance
Aggression
Testosterone
Orbitofrontal cortex

ABSTRACT

Recent evidence suggests that the steroid hormone testosterone can decrease the functional coupling between orbitofrontal cortex (OFC) and amygdala. Theoretically this decoupling has been linked to a testosterone-driven increase of goal-directed behaviour in case of threat, but this has never been studied directly. Therefore, we placed twenty-two women in dynamically changing situations of escapable and inescapable threat after a within-subject placebo controlled testosterone administration. Using functional magnetic resonance imaging (fMRI) we provide evidence that testosterone activates the left lateral OFC (LOFC) in preparation of active goal-directed escape and decouples this OFC area from a subcortical threat system including the central-medial amygdala, hypothalamus and periaqueductal gray. This LOFC decoupling was specific to threatening situations, a point that was further emphasized by an absence of such decoupling in a second experiment focused on resting-state connectivity. These results not only confirm that testosterone administration decouples the LOFC from the subcortical threat system, but also show that this is specifically the case in response to acute threat, and ultimately leads to an increase in LOFC activity when the participant prepares a goal-directed action to escape. Together these results for the first time provide a detailed understanding of functional brain alterations induced by testosterone under threat conditions, and corroborate and extend the view that testosterone prepares the brain for goal-directed action in case of threat.

1. Introduction

The steroid hormone testosterone has a well-established role in the reduction of fear and the promotion of dominance motivation and aggression in many species (Mazur and Booth, 1998; Wingfield et al., 1990). In humans, the neural mechanisms underlying these effects are not yet clear, but it has been suggested that testosterone administration can decouple the orbitofrontal cortex (OFC) from subcortical threat reactivity, leading to an increase in impulse-driven and goal-directed behaviour in response to threat (Terburg and van Honk, 2013b; van Honk et al., 2011). Direct evidence for this hypothesis is however currently lacking as acute threat reactivity in the brain and associated goal-directed behaviour have not yet been studied in relation to testosterone administration.

We do know that testosterone can reduce physiological fear responses in humans (Hermans et al., 2007, 2006), and testosterone has repeatedly been linked to subcortical-cortical decoupling (Schutter and van Honk, 2004) and decoupling of the OFC from the amygdala in particular (Bos et al., 2012a; van Wingen et al., 2010; Volman et al., 2011, 2016). Although the specific functions ascribed to the OFC are highly diverse (Stalnaker et al., 2015), it is generally accepted that its coupling with the amygdala serves to adjust behaviour based on the integration of top-down goal-directed action tendencies and bottom-up emotional reactivity (Kringelbach and Rolls, 2004; Milad and Rauch, 2007; Murray and Izquierdo, 2007; Zald et al., 2014). We aimed to tap into this function by means of a functional magnetic resonance imaging (fMRI) experiment with dynamically changing situations of acute threat with goal-directed escape possibilities (Montoya et al., 2015). We applied this experiment in a double-blind placebo-controlled testosterone administration design along with a measurement of baseline resting-state fMRI (RS-fMRI) connectivity. Using this design, we were able to investigate the hypothesis that testosterone's decoupling of the OFC

* Corresponding author at: Utrecht University, Department of Psychology, Heidelberglaan 1, 3584 CS, Utrecht, The Netherlands.
E-mail address: d.terburg@uu.nl (D. Terburg).

https://doi.org/10.1016/j.psyneuen.2018.05.038
Received 24 November 2017; Received in revised form 7 May 2018; Accepted 29 May 2018

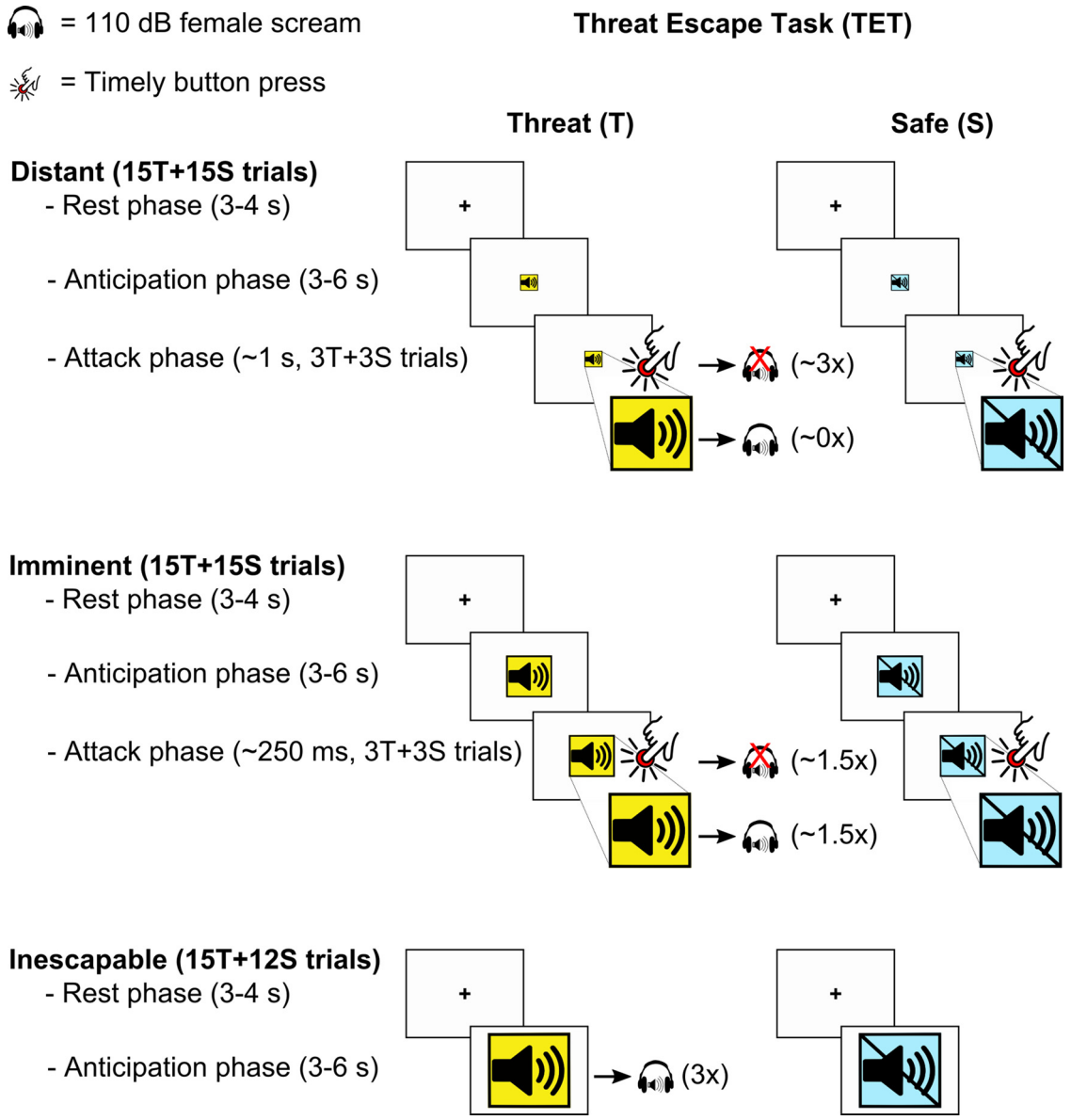

Fig. 1. Outline of the threat escape task. Participants are repeatedly attacked by rapidly approaching pictures. Participants can escape by pressing a button, but when they fail to do so they will be presented with a highly aversive noise (AN). The pictures are manipulated to be distant-escapable, imminent (escapable at chance-level) or inescapable, and all conditions are compared with an equivalent safe-context control condition involving the same procedure but without the threat of AN exposure.

from the amygdala is directly involved in threat and escape anticipation.

2. Methods

2.1. Participants

Thirty healthy young women were recruited to participate in the experiment. Ethical approval was granted by the Human Research Ethics Committee of the University of Cape Town (UCT). Before being invited to participate, all women were screened with self-report questionnaires for present or previous psychiatric conditions. Additional exclusion criteria, also assessed by self-report questionnaire, were: Current or recent use of psychotropic medications, use of hormonal contraceptives, pregnancy, abnormal menstrual cycle, any endocrine disorders, any other serious medical condition, left-handedness, habitual smoking, hearing problems, and colour blindness. Upon their arrival at the laboratory, all participants provided written informed consent before testing began. After recruitment, four participants were unable to complete their scans: One did not fit in the head coil, and three could not complete scans due to electricity failure at the scan facility. This left 26 participants who were included in the resting state analyses. A further four were excluded from the task-based statistical analyses: One due to excessive head movement in the scanner (40 mm) during the task, one due to coil signal failure, and two due to headphone failure. After these 8 exclusions, the total sample consisted of 22 participants (age range 18–37, mean age 21.3, $SD = 4.4$), with 11 in each administration order (placebo in first session, or testosterone in first session). Only women were considered as participants because the parameters (quantity and time course) for inducing neurophysiological effects after a single sublingual administration of 0.5 mg of testosterone are known in women, whereas these parameters are not known in men (Tuiten et al., 2000). Each participant was paid ZAR250 for their participation.