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Research Paper

Exogenous testosterone affects early threat processing in socially anxious and healthy women

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ABSTRACT

Testosterone plays an important role in social threat processing. Recent evidence suggests that testosterone administration has socially anxiolytic effects, but it remains unknown whether this involves early vigilance or later, more sustained, processing-stages. We investigated the acute effects of testosterone administration on social threat processing in 19 female patients with Social Anxiety Disorder (SAD) and 19 healthy controls. Event-related potentials (ERPs) were recorded during an emotional Stroop task with subliminally presented faces. Testosterone induced qualitative changes in early ERPs (< 200 ms after stimulus onset) in both groups. An initial testosterone-induced spatial shift reflected a change in the basic processing (N170/VPP) of neutral faces, which was followed by a shift for angry faces suggesting a decrease in early threat bias. These findings suggest that testosterone specifically affects early automatic social information processing. The decreased attentional bias for angry faces explains how testosterone can decrease threat avoidance, which is particularly relevant for SAD.

1. Introduction

Testosterone has an important role in the regulation of social motivational behavior. A surge in testosterone has anxiolytic effects and facilitates social dominance and approach behavior in socially challenging situations (Archer, 2006; Bos, Panksepp, Bluthe, & van Honk, 2012; Terburg & Van Honk, 2013). Especially an angry looking face with direct gaze is perceived as a signal of social threat, as it can signal an impending aggressive encounter (Öhman, 1986). In line with this notion, recent single dose administration studies showed that testosterone promotes approach action tendencies to angry faces on a social approach-avoidance task (Enter, Spinhoven, & Roelofs, 2014; Enter, Terburg, Harrewijn, Spinhoven, & Roelofs, 2016). In addition, it facilitated socially dominant gaze behavior as indicated by increased fixation to the eyes of angry faces (Enter, Terburg et al., 2016; Terburg et al., 2016; Terburg, Aarts, & van Honk, 2012).

At the neural level, testosterone has been found to enhance the reactivity of the amygdala towards angry facial expressions (Goetz et al., 2014; Hermans et al., 2008), and to reduce its connectivity with circuits involving the orbitofrontal or prefrontal cortex, thalamus, brainstem, and striatum (van Wingen, Mattern, Verkes, Buitelaar, & Fernandez, 2010; Volman, Toni, Verhagen, & Roelofs, 2011). Furthermore, using a social approach-avoidance task, in which angry and happy faces have to be approached or avoided by pulling or pushing a joystick, Radke et al. (2015) showed that testosterone *increased* amygdala responses specifically during *approach* of angry faces, but *decreased* amygdala responses during angry face *avoidance*, suggesting that testosterone modulates social threat processing in a motivation-specific manner. However, little is known about the temporal dynamics of these effects, and it remains unknown whether they involve early vigilance or later, more sustained, stages of social threat processing. Gaining insight into these processes would be of particular interest for Social Anxiety Disorder (SAD), as this frequent and persistent disorder is characterized by increased early automatic vigilance and biased goal-directed processing of social threat (for reviews see Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; Gilboa-Schechtman & Shachar-

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Lavie, 2013; Staugaard, 2010) as well as by decreased salivary levels of basal testosterone (Giltay et al., 2012).

In the current study we therefore investigate the effects of testosterone on social threat processing in participants with SAD and healthy participants, using temporally fine-grained recordings of the event-related brain potentials (ERPs) during an emotional Stroop task with subliminally presented (i.e., backward masked) angry, happy and neutral faces. We used the masked version of this paradigm, as previous studies suggested that effects of social anxiety (Putman, Hermans, & van Honk, 2004) and hormonal manipulations (cortisol: Van Honk et al., 1998; van Peer, Spinhoven, & Roelofs, 2010, and testosterone: Van Honk et al., 2000; Wirth & Schultheiss, 2007) are stronger in this version than in the unmasked version. We performed a spatiotemporal clustering analysis (Brunet, Murray, & Michel, 2011; Murray, Brunet, & Michel, 2008) on the ERPs, as this method has several advantages compared to conventional ERP amplitude analyses. Most importantly, it can tease apart the following two ERP effects: 1) topographic modulations, which reflect a change in neural sources, indicating the activation of different cognitive processes (a *qualitative* change in processing), and 2) amplitude modulations, which, in absence of a concurrent topographic modulation, reflect increases or decreases in response strength of a common cognitive process (a *quantitative* change in processing) (see e.g., Murray et al., 2008; Pourtois, Delplanque, Michel, & Vuilleumier, 2008). Furthermore, this method may be more sensitive in detecting differences between groups or task conditions (Murray et al., 2008), as it includes the full range (instead of only a limited number) of channels and time windows, and it can detect topographic changes even when amplitude is low. Particularly for pharmacological interventions like testosterone, which modulates multiple parts of the emotion circuitry (see e.g., Bos et al., 2012; van Wingen et al., 2010), effects are unlikely to be bound to single ERP peaks.

Previous ERP studies have shown increased amplitudes for subliminally presented angry (compared to neutral) faces especially on early components such as the frontocentral P2 or VPP (van Peer et al., 2010), the N2 (Balconi & Lucchiari, 2005, 2007), and the EPN (Mühlberger et al., 2009). Some studies with supraliminal stimuli suggest that this effect may be amplified in socially anxious compared to non-anxious participants (e.g., P1 amplitude: Mueller et al., 2009; Hagemann, Straube, & Schulz, 2016; N170 amplitude: Kolassa & Miltner, 2006; Wieser, Pauli, Reicherts, & Mühlberger, 2010; see also P3/LPP amplitude: Moser, Huppert, Duval, & Simons, 2008; Hagemann et al., 2016). Other studies, however, reported increased early amplitudes in high socially anxious participants irrespective of emotion (e.g., P1: Kolassa et al., 2009; Peschard, Philippot, Joassin, & Rossignol, 2013; Rossignol, Campanella, Bissot, & Philippot, 2013; Rossignol, Philippot, Bissot, Rigoulot, & Campanella, 2012), suggesting a general early hypervigilance to face stimuli. Overall electrophysiological evidence for hypervigilance to social threat in social anxiety is still inconsistent (cf., Kanai, Nittono, Kubo, Sasaki-Aoki, & Iwanaga, 2012; Mühlberger et al., 2009; Wangelin, Bradley, Kastner, & Lang, 2012) and findings may depend on task conditions and choice of specific ERPs (see Schulz, Mothes-Lasch, & Straube, 2013 for a review).

Based on these ERP studies, we expected to find increased processing of angry faces mainly in the early (< 250 ms) time window. Most importantly, based on the social-anxiolytic and approach-promoting effects of testosterone (Archer, 2006; Terburg & Van Honk, 2013) we expected that testosterone administration compared to placebo would reduce processing of angry versus neutral and happy faces, particularly in SAD patients who are characterized by a social threat bias as well as lower endogenous testosterone levels. Finally, based on behavioral findings suggesting that effects of testosterone are most pronounced for preconscious processing of threat (Van Honk et al., 2000) we hypothesized that these effects may be predominantly manifested in the early processing stages.

Table 1
Group Characteristics.

Variable	HC (n = 19)	SAD (n = 19)	p
Order (testosterone first)	n = 8	n = 11	0.330
Age	25.3 (4.1)	23.0 (4.5)	0.104
LSAS social anxiety	9.4 (7.1)	43.2 (6.7)	< 0.001
LSAS avoidance	7.7 (6.2)	37.0 (7.8)	< 0.001
LSAS total	17.1 (12.8)	80.2 (13.5)	< 0.001
SPAI social phobia	47.6 (26.6)	122.6 (23.4)	< 0.001
SPAI agoraphobia	10.9 (10.1)	23.5 (10.2)	0.001
SPAI difference	36.7 (22.2)	99.2 (21.5)	< 0.001
BDI	2.5 (2.2)	14.7 (11.9)	< 0.001

Note. Data are presented in mean and standard deviation. Abbreviations: HC, Healthy Controls; SAD, Social Anxiety Disorder; LSAS, Liebowitz Social Anxiety Scale; SPAI, Social Phobia and Anxiety Inventory; BDI, Beck Depression Inventory. *P*-values indicate group differences.

2. Materials and methods

2.1. Participants

Participant characteristics are presented in Table 1. Participants for the Social Anxiety Disorder (SAD) group were recruited from outpatient anxiety departments of mental health centers, through advertisements on the internet, and in local newspapers. Inclusion criterion was a total score of > 60 on the Liebowitz Social Anxiety Scale (Liebowitz, 1987; Rytwinski et al., 2009). In addition these participants were screened with the Mini International Neuropsychiatric Interview script (M.I.N.I.; Lecubier et al., 1997) to verify the DSM-IV diagnosis of generalized Social Anxiety Disorder. One participant (LSAS score 56) scored just below the LSAS cutoff but was included as she did fulfill the DSM-IV diagnostic criteria. Healthy control (HC) participants were recruited via advertisements in community centers, on the internet, and in local newspapers. Only female participants were included, because the parameters (e.g., dose and time course) for inducing neurophysiological effects in men with a single dose administration of testosterone are as yet unknown (Tuiten et al., 2000). Both women using single-phase contraceptives and

normally cycling women participated in the study. All participants had normal or corrected-to-normal vision. Exclusion criteria were age < 18 and > 50, use of (psychotropic) medication, somatic illnesses, neurological conditions, recent or past psychiatric problems (HC group only), psychotic disorder, current comorbid diagnosis of mood or anxiety disorders other than SAD (SAD group only), history of head injury, left-handedness, *peri-* or postmenopause, and pregnancy or breast feeding. Initially, 24 participants were included in each group. However, as these groups differed significantly in age ($F(1,46) = 12.59$, $p = 0.001$, $\eta^2 = 0.21$), and there is no appropriate method to statistically control for such an effect in the analyses (Miller & Chapman, 2001), a subset of 19 SAD and 19 HC participants (age $F(1,36) = 2.78$, $p = 0.104$, $\eta^2 = 0.07$, see Table 1) was selected on basis of matching for age (Field, 2009; see also Enter, Terburg et al., 2016). Thirteen of the 19 SAD participants met full DSM-IV criteria for generalized SAD at the time of testing; the other five had subsyndromal SAD (i.e., they fulfilled all criteria at the telephone screening but the symptoms did no longer lead to significant burden in social or occupational functioning [DSM-IV criterion IV] at time of testing). All participants provided written informed consent, and received financial compensation. The study was approved by the Medical Ethics Committee of the Leiden University Medical Centre, and was in accordance with the declaration of Helsinki.

2.2. Testosterone administration

In a double-blind, randomized, placebo-controlled, cross-over design participants received a single dose of 0.5 mg testosterone