



Single dose testosterone administration alleviates gaze avoidance in women with Social Anxiety Disorder



Dorien Enter^{a,b,c,*}, David Terburg^{d,e}, Anita Harrewijn^{c,f}, Philip Spinhoven^{c,g}, Karin Roelofs^{a,b}

^a Radboud University Nijmegen, Behavioural Science Institute (BSI), 6500 HE, Nijmegen, The Netherlands

^b Donders Institute for Brain, Cognition and Behaviour, 6525 EN, Nijmegen, The Netherlands

^c Leiden University, Institute of Psychology, 2300 RB, Leiden, The Netherlands

^d Utrecht University, Department of Psychology, 3584 CS, Utrecht, The Netherlands

^e University of Cape Town, Department of Psychiatry & Mental Health, Cape Town 7925, South Africa

^f Leiden Institute for Brain and Cognition, 2300 RC, Leiden, The Netherlands

^g Leiden University Medical Center, Department of Psychiatry, 2300 RC, Leiden, The Netherlands

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ABSTRACT

Gaze avoidance is one of the most characteristic and persistent social features in people with Social Anxiety Disorder (SAD). It signals social submissiveness and hampers adequate social interactions. Patients with SAD typically show reduced testosterone levels, a hormone that facilitates socially dominant gaze behavior. Therefore we tested as a proof of principle whether single dose testosterone administration can reduce gaze avoidance in SAD. In a double-blind, within-subject design, 18 medication-free female participants with SAD and 19 female healthy control participants received a single dose of 0.5 mg testosterone and a matched placebo, at two separate days. On each day, their spontaneous gaze behavior was recorded using eye-tracking, while they looked at angry, happy, and neutral facial expressions. Testosterone enhanced the percentage of first fixations to the eye-region in participants with SAD compared to healthy controls. In addition, SAD patients' initial gaze avoidance in the placebo condition was associated with more severe social anxiety symptoms and this relation was no longer present after testosterone administration. These findings indicate that single dose testosterone administration can alleviate gaze avoidance in SAD. They support theories on the dominance enhancing effects of testosterone and extend those by showing that effects are particularly strong in individuals featured by socially submissive behavior. The finding that this core characteristic of SAD can be directly influenced by single dose testosterone administration calls for future inquiry into the clinical utility of testosterone in the treatment of SAD.

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1. Introduction

Social Anxiety Disorder (SAD) is a common anxiety disorder, characterized by persistent fear and avoidance of social situations (American Psychiatric Association, 2013). SAD has been related to a ubiquitous social hierarchy system, in which individuals with SAD display socially submissive as opposed to socially dominant behavior (Hermans and van Honk, 2006; Maner et al., 2008; Weisman et al., 2011). Typical submissive behavior, such as avoidance of eye contact plays a crucial role in the persistence of this disorder by hindering extinction of fear in social situations (Clark and Wells, 1995;

Stein and Stein, 2008). Especially angry facial expressions with direct gaze signal social scrutiny or a potential dominance challenge and elicit avoidance tendencies in highly socially anxious individuals (Öhman, 1986; Roelofs et al., 2010). Indeed, eye-tracking studies investigating gaze behavior in SAD, have demonstrated avoidance of the eye-region of angry faces (Horley et al., 2004; Moukheiber et al., 2012, 2010). Because avoidance behavior is the major maintaining factor in SAD, it is relevant to develop interventions that directly target this behavior (Clark and Wells, 1995; Gamer and Büchel, 2012; Hofmann et al., 2014; Roelofs et al., 2010).

SAD is associated with reduced endogenous testosterone levels (Giltay et al., 2012), and because testosterone is known to reduce social avoidance (Enter et al., 2014; Terburg et al., 2012a), it is striking that so far no studies have tested the direct effects of testosterone administration in SAD. Testosterone has an important role in the regulation of social motivational behavior: It has socially anxi-

* Corresponding author at: Radboud University Nijmegen, Behavioural Science Institute (BSI), Montessorilaan 3, P.O. Box 9104, 6500 HE Nijmegen, The Netherlands.
E-mail address: d.enter@psych.ru.nl (D. Enter).

Table 1
Group characteristics for the healthy control (HC) group and the combined group of participants with syndromal and sub-syndromal social anxiety disorder (SAD).

	HC (n = 19)	SAD (n = 18)	t(35)	p-Value
Age (years)	25.2 (4.0)	23.1 (4.6)	1.49	.145
LSAS anxiety	9.5 (7.2)	41.5 (6.2)	−14.49	<.001
LSAS avoidance	7.8 (6.3)	35.4 (7.4)	−12.21	<.001
LSAS total	17.3 (12.9)	76.8 (12.5)	−14.25	<.001
BDI	2.5 (2.2)	13.5 (11.9)	−3.86	.001

Data are presented in mean and standard deviation. Abbreviations: LSAS, Liebowitz Social Anxiety Scale; BDI, Beck Depression Inventory.

olytic effects, and is associated with social dominance and approach behavior (Bos et al., 2012; Enter et al., 2014; Terburg and van Honk, 2013). Based on recent findings indicating that testosterone administration in healthy females promotes social dominant gaze behavior to angry faces (Terburg et al., 2012a, 2011), we predicted that testosterone administration would alleviate submissive gaze avoidance to angry faces in individuals with SAD.

We tested this hypothesis in a double-blind and placebo controlled within-subject study. A total of 18 medication-free participants with SAD and 19 healthy control participants received a single dose of 0.5 mg testosterone and a matched placebo in two sessions. In each session, their spontaneous gaze behavior was recorded while they looked at angry, happy, and neutral facial expressions. Gaze avoidance of eye contact was reliably indexed as relative reduction of initial gaze fixations on the eye-region (Becker and Detweiler-Bedell, 2009; Gamer et al., 2010; Gamer and Büchel, 2012; Garner et al., 2006). We predicted that testosterone administration in contrast to placebo would reduce gaze avoidance and increase the number of first fixations to the eyes of angry faces in particular in SAD.

2. Method

2.1. Participants

Characteristics of the participant groups are presented in Table 1 (see also Table S1 and S2). Participants with Social Anxiety Disorder (SAD) 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 (LSAS; Liebowitz, 1987; Rytwinski et al., 2009). In addition participants were screened with the Mini International Neuropsychiatric Interview script (Lecubier et al., 1997) to determine the presence of a DSM-IV diagnosis of generalized Social Anxiety Disorder. Healthy control (HC) participants were recruited via advertisements in community centers, on the internet, and in local newspapers. Only female participants were included, because there are as yet no known parameters (e.g., dose and time course) for inducing neurophysiological effects in men after administration of a single dose of testosterone (Tuiten et al., 2000). Both women using single-phase contraceptives (11 HC, 15 SAD), and normally cycling women (8 HC, 3 SAD) participated in the study (e.g., Hermans et al., 2010). Exclusion criteria were age <18 and >50, use of (psychotropic) medication, somatic illnesses, neurological conditions, psychotic disorder, history of head injury, left-handedness, peri- or postmenopause, and pregnancy or breast feeding (for both HC and SAD groups), recent or past psychiatric problems (only HC group), and current comorbid diagnosis of mood or anxiety disorders other than SAD (only SAD group). After initial screening of 24 subjects for both groups, 19 HC and 19 SAD participants were selected on basis of matching for age and level of education (all participants were following or completed higher education). Data of one SAD participant was lost due to technical failure, leaving 18 SAD participants for analyses. Thirteen of

the 18 SAD participants met full DSM-IV criteria for gSAD at the time of testing; the other five had sub-syndromal SAD (i.e., they did no longer fulfill DSM-IV criterion E ‘the fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning’ at time of testing). See Table S2 for the demographic characteristics of this group of 13 participants with syndromal SAD. Our primary aim was to test effects in participants who fulfill all DSM-IV criteria for generalized SAD (SAD syndromal group) but for transparency reasons we will also report analyses for all participants, including the five who were in remission (SAD combined). All participants had normal or corrected-to-normal vision, were unaware of the aim of the study, 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 (0.5 ml) of 0.5 mg testosterone suspended in a clear solution with 0.5 mg hydroxypropyl-beta-cyclodextrin, 0.005 ml ethanol 96%, and distilled water. The matched placebo contained the same ingredients, except the testosterone. Participants were asked to hold the liquid under their tongue for 60 s. During sublingual administration of 0.5 mg testosterone cyclodextrin, testosterone is directly absorbed into the bloodstream. In females, such a dose yields a sharp increase of 20–25 nmol/l in plasma testosterone levels within 15 min, which declines to baseline levels within the next 90 min (van Rooij et al., 2012). Previous research applying this method has convincingly shown consistent psychophysiological and behavioral effects approximately 4–6 h after administration, therefore this time interval was also applied in the current study (Bos et al., 2012; Enter et al., 2014; Tuiten et al., 2000).

2.3. Passive viewing task

Face stimuli were selected from the NimStim set of facial expressions (Tottenham et al., 2009). Happy, Angry, and Neutral facial expressions were taken from the same model (four male and four female models), cut out in an oval shape (368 × 515 pixels) to remove distracting features, and presented with a grayish filter on an equiluminant gray background. One face at the time was shown on the middle of the screen (9.3° × 12.9° visual angle; screen resolution 1280 × 1024 pixels), in such a way that the pre-trial fixation cross was situated on the nasal bridge below the eyes. Stimuli were repeated three times, resulting in 72 randomized trials in total. Trials started when the participant maintained a fixation on the central fixation cross for 1000 ms. Stimulus presentation time was 5000 ms, followed by an intertrial interval (blank gray screen) of 4000–7000 ms. Three breaks were offered throughout the task, and could be terminated by a button press. Participants sat at a distance of 60–65 cm from the screen and were instructed to look at the fixation cross, and then look at the pictures without further instructions except for not moving their head.

2.4. Procedure

Participants were tested individually at two identical testing sessions with two days in between. Testing sessions started at either 0930 or 1330, and participants were tested on the same time of day on both sessions. Four hours after administration of testosterone or placebo participants were seated in a dimly lit and sound attenuated room, where they performed a standard nine-point calibration procedure, followed by the passive viewing task. In addition

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