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

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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.

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

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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.

anxiolytic 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

Table 2
First fixations (percentage ± SEM) toward the eye-region of angry, happy, and neutral facial expressions after administration of placebo and testosterone for Healthy Control participants ($n = 19$) and the combined group of participants with syndromal and sub-syndromal Social Anxiety Disorder ($n = 18$).

	Healthy Controls		Social Anxiety Disorder	
Emotion	Placebo	Testosterone	Placebo	Testosterone
Angry	43 (6)	36 (6)	30 (6)	37 (8)
Happy	49 (7)	42 (6)	36 (7)	37 (9)
Neutral	48 (7)	40 (6)	41 (8)	40 (9)

to gaze behavior, EEG and facial mimicry were recorded, results of which will be reported elsewhere.

2.5. Data acquisition and statistical analyses

Eye movements were recorded with a Tobii T120 binocular infrared eye tracker (Tobii Technology, Danderyd, Sweden), sampling at 120 Hz, with 0.5° accuracy. Oval Areas of Interest (AOIs) were created around each eye for each picture separately and excluded the inter-ocular space (Fig. 2c). Gaze fixations were defined as the average location of all subsequent gaze points within 1.5° visual angle, with a minimal duration of 100 ms excluding the initial gaze points on the central fixation cross (Tobii Technology, Danderyd, Sweden). Calculated parameters were percentage first fixations (i.e., 100 times the amount of first fixations in the eye AOI divided by the total amount of first fixations) and the duration of first fixations. In addition, percentage total fixations (i.e., 100 times the amount of fixations in the eye AOI divided by the total amount of fixations) and fixation duration were calculated for fixations during the total stimulus presentation time.

To account for data loss due to eventual motion and eye blink artifacts, we applied a cut-off of at least 150 data points per trial (25% of the possible 600 data points in each trial, 120 Hz sampling-rate and 5 s presentation) for trial inclusion in the analysis. Using this filter criterion 4.7% of the trials were discarded which was not different between groups, treatment condition or their interaction (all $ps > .23$).

Parameters were entered in a three-way repeated measures Analysis of Variance (rmANOVA) with Treatment (placebo, testosterone) and Emotion (angry, happy, neutral) as within-subject factors, and Group (HC, SAD) as between-subjects factor. Alpha was set at .05 (two-tailed) and effect sizes are reported in partial eta squared (η_p^2). Greenhouse-Geisser correction was used when appropriate (uncorrected degrees of freedom are reported together with the correction factor epsilon (ϵ)). The statistics will first be reported for the combined group of participants with syndromal and sub-syndromal SAD participants (SAD combined, $n = 18$), and will be subsequently repeated for the target group of participants who still fulfilled all criteria for SAD at the time of testing (SAD syndromal, $n = 13$).

3. Results

3.1. Percentage first fixations

The percentage first fixations to the eye region for each condition, emotion and group are presented in Table 2. First we conducted a three-way rmANOVA with all emotions in the analysis for the percentage first fixations, with Treatment (placebo, testosterone) and Emotion (angry, happy, neutral) as within-subject factors, and Group (HC, SAD) as between-subjects factor. There was no significant Treatment × Emotion × Group interaction; this counted both when including the SAD (combined) group, $F(2,70) = 1.04$, $p = .360$, and when including the SAD (syndromal) group, $F(2,60) = 1.13$, $p = .331$. However, a significant Treatment × Group interaction was present both when including the SAD (combined) group, $F(1,35) = 6.67$, $p = .014$, $\eta_p^2 = .16$, and when including the SAD (syndromal) group, $F(1,30) = 7.39$, $p = .011$, $\eta_p^2 = .20$, indicating that testosterone affects gaze behavior in the HC and SAD groups in a differential manner (Fig. 1). There were no significant post-hoc effects involving Group with all emotions in the analyses, all $Fs < 1.83$, $ps > .285$, but a main effect of Emotion (both with the SAD (combined) group, $F(2,70) = 7.32$, $p = .002$, $\eta_p^2 = .17$, and with the SAD (syndromal) group, $F(2,60) = 5.12$, $p = .009$, $\eta_p^2 = .15$), indicated relative avoidance of angry versus happy faces (both with SAD (combined), $F(1,35) = 10.52$, $p = .003$ $\eta_p^2 = .23$, and with SAD (syndromal), $F(1,30) = .8.41$, $p = .007$, $\eta_p^2 = .22$) and angry versus neutral faces (both with SAD (combined), $F(1,35) = 10.46$, $p = .003$ $\eta_p^2 = .23$, and with SAD (syndromal), $F(1,30) = 8.06$, $p = .008$, $\eta_p^2 = .21$) across groups.

Because of our specific hypothesis on the effects of testosterone on the first fixations toward the eyes of angry faces in SAD, we checked whether the Treatment x Group effect would hold for angry faces alone. Indeed, the significant Treatment × Group interaction remained for angry faces. This occurred both when including the SAD (combined) group, $F(1,35) = 8.41$, $p = .006$, $\eta_p^2 = .19$, and when including the SAD (syndromal) group, $F(1,30) = 9.53$, $p = .004$ $\eta_p^2 = .24$ (Fig. 2a). A similar rmANOVA did not reveal significant Treatment × Group effects for first fixations on the eyes of happy and neutral faces (again both when including the SAD (combined) group, happy: $F(1,35) = 3.22$, $p = .085$, neutral: $F(1,35) = 1.61$, $p = .213$; and when including the SAD (syndromal) group, happy: $F(1,30) = 3.40$, $p = .075$, neutral: $F(1,30) = 1.63$, $p = .211$). These findings confirm that testosterone increases the first fixations toward the eye region of angry faces in SAD versus HC.

To further explore the Treatment X Group effect of the omnibus analysis, we conducted analyses for each group separately. A two-way rmANOVA with Treatment (placebo, testosterone) and Emotion (angry, happy, neutral) for the percentage first fixations in the SAD group revealed a significant Treatment × Emotion interaction. This counted both for the SAD (combined) group, $F(2,32) = 4.43$, $p = .020$, $\eta_p^2 = 0.21$, and for the SAD (syndromal) group, $F(2,24) = 3.56$, $p = .044$, $\eta_p^2 = 0.23$. In addition, there was a significant main effect of Emotion in the SAD (combined) group, $F(1.5,25.8) = 5.54$, $p = .016$, $\epsilon = .759$, $\eta_p^2 = .25$, but not in the SAD (syndromal) group: $F(1.4,16.9) = 2.76$, $p = .105$, $\epsilon = .702$, $\eta_p^2 = .19$, nor did this analysis yield a significant main effect of Treatment in either group, all $Fs < 1.28$, all $ps > .280$. Subsequent one-way rmANOVA's for each emotion separately yielded a trend toward a main effect of Treatment for Angry faces, $F(1,17) = 4.09$, $p = .059$, $\eta_p^2 = .19$, in the SAD (combined) group. Critically, the Treatment effect of testosterone for angry faces was significant in the SAD (syndromal) group, $F(1,12) = 4.90$, $p = .047$, $\eta_p^2 = .29$, suggesting that testosterone increased first fixations to the eye-region of angry faces within the SAD patients (Fig. 2a). There was no such effect for Happy ($F(1,17) = 0.12$, $p = .729$ (SAD combined); $F(1,12) = 0.39$, $p = .543$ (SAD syndromal)), or Neutral faces ($F(1,17) = 0.15$, $p = .706$ (SAD combined); $F(1,12) = 0.02$, $p = .968$ (SAD syndromal)).

Separate analyses for the SAD participants per condition showed significant avoidance of the eyes of angry faces, when compared to neutral faces in the placebo condition. This Emotion effect was present both in the SAD (combined) group, $F(1,17) = 11.73$, $p = .003$, $\eta_p^2 = .41$, and in the SAD (syndromal) group, $F(1,12) = 7.01$, $p = .021$, $\eta_p^2 = .37$. There was also significant avoidance for angry faces when compared to happy faces, in the SAD (combined) group, $F(1,17) = 6.07$, $p = .025$, $\eta_p^2 = .26$, which was a trend in the SAD (syndromal) group, $F(1,12) = 3.95$, $p = .070$, $\eta_p^2 = .25$. There were no such effects for happy versus neutral faces, not in the SAD (combined) group, $F(1,17) = 4.08$, $p = .059$, nor in the SAD (syndromal) group, $F(1,12) = 2.02$, $p = .180$. These gaze avoidance effects for the eyes of angry faces in the SAD group were no longer present in the

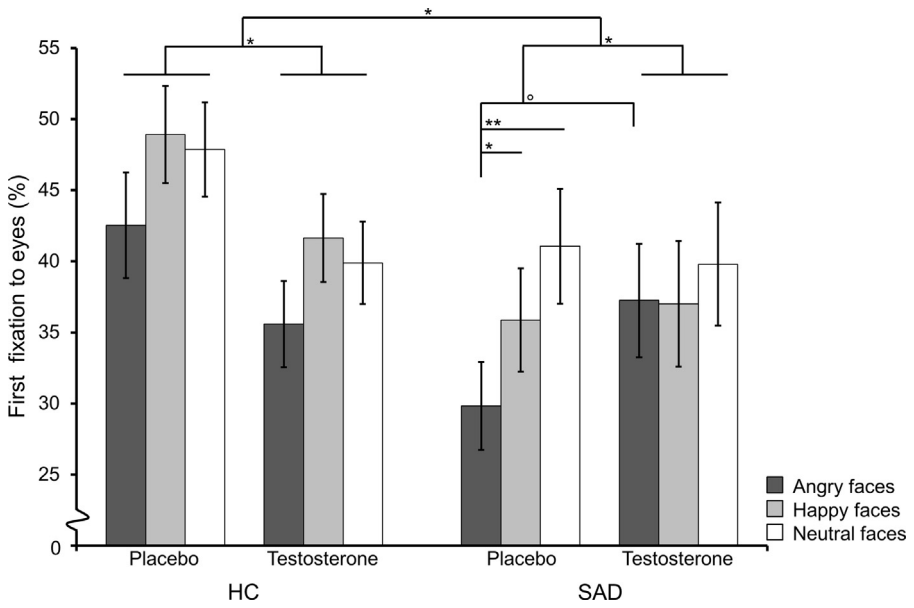

Fig. 1. First fixation data for angry, happy, and neutral facial expressions. Percentage (mean ± SEM) first fixations toward the eyes of angry, happy and neutral facial expressions after administration of placebo and testosterone for healthy control participants (HC, $n = 19$) and the combined group of participants with syndromal and sub-syndromal social anxiety disorder (SAD combined, $n = 18$). A significant Treatment × Group interaction indicates that testosterone differentially affects gaze behavior in SAD and HC groups. The Treatment × Group effect remains significant when tested for angry faces alone but not when tested for happy or neutral faces.$^{**}p < .01$, $^{*}p < .05$, $^{\circ}p < .06$.

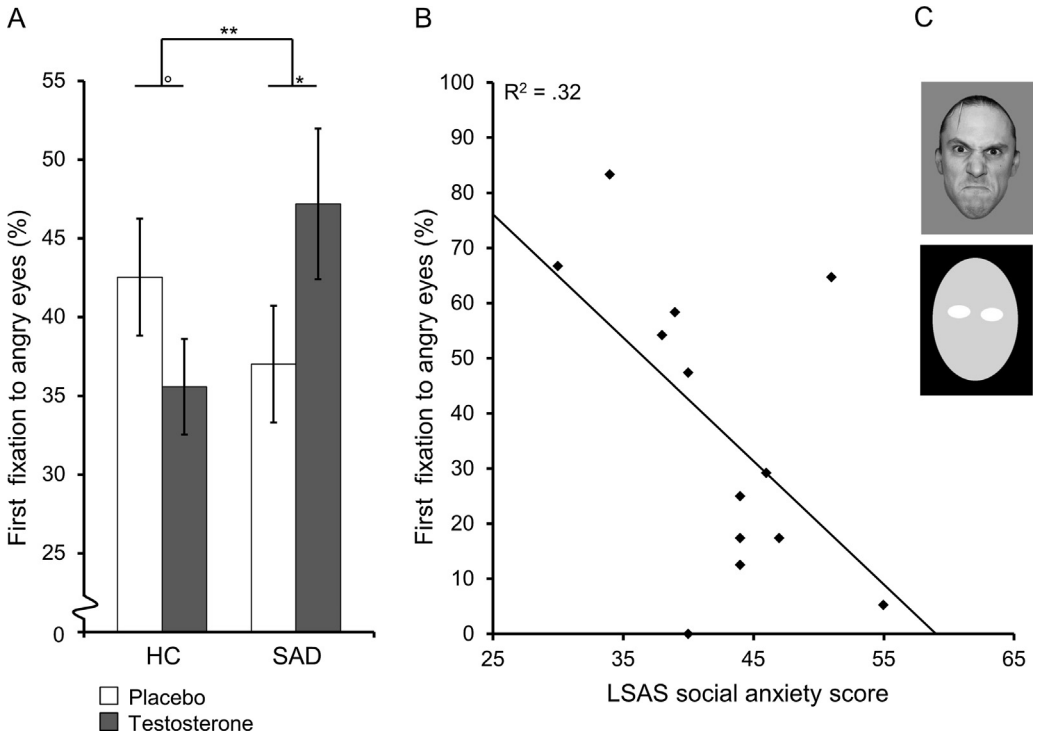

Fig. 2. First fixation data for angry facial expressions and correlation with social anxiety scores for the participants with syndromal SAD. (A) Percentage (mean ± SEM) first fixations toward the eyes of angry facial expressions after administration of placebo and testosterone for healthy control participants (HC, $n = 19$) and participants with generalized social anxiety disorder who met the full DSM-IV criteria on the day of testing (SAD syndromal, $n = 13$). In SAD participants testosterone enhanced the percentage of first fixations to the eyes of angry faces, whereas HCs showed the opposite pattern. $^{**}p < .01$, $^{*}p < .05$, $^{\circ}p < .06$. (B) A significant correlation between percentage first fixations on angry eyes and LSAS social anxiety scores in the placebo condition indicated that SAD participants ($n = 13$) with stronger anxiety symptomatology showed increased gaze avoidance of angry eye contact. (C) Example of an angry facial expression and corresponding Area of Interest (AOI) map, with the eye AOI depicted in white.

testosterone condition, all $Fs < 0.89$, $ps > .398$. To further explore the nature of the avoidance effects in the placebo condition in the subgroup of participants who met the full DSM-IV criteria for SAD, we tested whether gaze avoidance toward the eye-region was correlated to symptom severity. A significant correlation between percentage first fixations on angry eyes and LSAS social anxiety scores in the placebo condition, $r = -.561$, $p = .046$, indeed indicated that participants with stronger social anxiety symptomatology showed relatively greater gaze avoidance of angry eye contact (Fig. 2b). This effect was no longer present after testosterone admin-

istration, $r = -.384$, $p = .195$. A similar correlation existed for the first fixations toward the eyes of happy faces, $r = -.575$, $p = .040$, and neutral faces, $r = -.590$, $p = .034$, which became a trend after testosterone administration: happy, $r = -.498$, $p = .083$, and neutral, $r = -.502$, $p = .080$. Interestingly, none of these effects was significant in the SAD (combined) group, all $rs < -.404$, all $ps > .097$.

Together these analyses within the SAD group indicate that initial gaze avoidance of eye contact is related to the severity of social anxiety symptomatology in individuals with syndromal SAD, and that the avoidance of angry eyes in particular can be alleviated by single dose testosterone administration.

In contrast, in the HC group the two-way rmANOVA with Treatment (placebo, testosterone) and Emotion (angry, happy, neutral) showed no significant Treatment × Emotion interaction, $F(2,36) = 0.03$, $p = .974$. However, a main effect of Treatment, $F(1,18) = 9.06$, $p = .008$, $\eta_p^2 = .34$, indicated a relative decrease in the number of first fixations on the eyes of emotional faces after testosterone (Fig. 1). A main effect of Emotion, $F(2,36) = 3.60$, $p = .038$, $\eta_p^2 = .17$, showed that the HC, like the SAD group, showed relatively less first fixations to the eye-region of angry faces, relative to happy, $F(1,18) = 4.80$, $p = .042$, $\eta_p^2 = .21$, but not relative to neutral faces, $F(1,18) = 1.88$, $p = .187$. However, in the HC group avoidance of angry eye-contact in the placebo-condition was not related to the level of social anxiety (all $rs < .328$.; all $ps > .170$), as was observed for the syndromal SAD group

3.2. First fixation duration, percentage total fixations, and total fixation duration

Separate three-way rmANOVAs with Treatment (placebo, testosterone) and Emotion (angry, happy, neutral) as within-subject factors, and Group (HC, SAD) as between-subjects factor, revealed neither Treatment, nor Group effects for first fixation duration, percentage total fixations, or total fixation duration; not when including the SAD (combined) group, (all $Fs < 1.53$, $ps > .225$), nor when including the SAD (syndromal) group, all $Fs < 2.25$, $ps > .148$ (see Table S3 and S4). In addition, none of these measurements was significantly related to symptom severity in the SAD (combined) group (all $ps > .391$), nor in the SAD (syndromal) group (all $ps > .05$).

3.3. Checks for confounding factors

No significant relationship between depression symptoms (Beck Depression Inventory score, Luteijn and Bouman, 1988) and percentage first fixations emerged in the SAD (combined) group, all $rs < -.230$, $ps > .358$, nor in the SAD (syndromal) group, all $rs < -.454$, $ps > .119$. Finally, the effects of testosterone on the percentage first fixations remained after controlling for testing order and other possibly confounding variables such as time of testing and use of contraceptives (see Supplementary material).

4. Discussion

This study shows that a single dose testosterone administration can alleviate gaze avoidance, which is one of the core communicative features of social anxiety and Social Anxiety Disorder (SAD) in particular (Weeks et al., 2013). In accordance with previous research, avoidance of eye contact was correlated to severity of social anxiety symptoms. Critically, we showed that administration of testosterone leads to an increase of initial fixations to the eyes of facial stimuli in SAD compared to healthy control (HC) participants. This finding supports theories on the anxiolytic and social dominance enhancing properties of testosterone and extends those models by indicating that the avoidance-reducing effect of testosterone is context dependent and only present in individuals featured by clinical avoidance behavior.

The first eye movement or first fixation has previously been used as a reliable measure of overt attention toward or away from a social threat stimulus (Becker and Detweiler-Bedell, 2009; Gamer et al., 2010; Garner et al., 2006). The latter authors argued that initial orienting to the eyes is relevant for not only adequate social information processing, but also for preparation of approach and avoidance behavior (Bradley, 2009). In our study, participants showed significant avoidance of the eyes of angry faces when compared to happy and neutral facial expressions. It is probable that they quickly detected the threatening eyes of angry faces preceding their first avoiding eye movement upon stimulus onset (Armstrong and Olatunji, 2012; Becker and Detweiler-Bedell, 2009; Garner et al., 2006). This behavior can be defined as gaze avoidance (i.e., the prevention of threatening eye contact by avoiding to directly gaze at the dominant threat), and is in concurrence with the hypervigilance-avoidance theory (Bogels and Mansell, 2004). Most importantly, in our sample we see the clinical relevance of first fixations on the eye-region for patients with SAD confirmed by the correlation between this measure and the severity of anxiety symptoms in the placebo condition: increased social anxiety scores were associated with reduced initial fixations on the eyes of the facial stimuli in patients with SAD and not in HC. This finding concurs with literature which shows that gaze avoidance of eye contact is a typical feature of SAD, and is related to symptom severity (Clark and Wells, 1995; Moukheiber et al., 2012, 2010; Stein and Stein, 2008). Our finding that testosterone specifically affects the first fixation, and decreases the amount of eye-area avoiding eye movements (by enhancing the amount of first fixations toward the eyes), is in agreement with literature that suggests that testosterone biases the brain toward social dominance by influencing early automatic mechanisms (Bos et al., 2012; Radke et al., 2015; Terburg and van Honk, 2013). Moreover, this finding is in line with earlier findings showing that testosterone influences actual social motivational behavior. In healthy females testosterone promotes relative increase of threat approach action tendencies (Enter et al., 2014) and increases social dominant gaze behavior by prolonging stares into the eyes of angry faces (Terburg et al., 2012a). We extend these findings by showing that testosterone administration also leads to a reduction of submissive gaze avoidance of angry eye contact in participants who suffer from SAD.

This behavior is likely caused by the influence of testosterone on the neural pathways that mediate automatic motivational tendencies. Testosterone affects the amygdala and connected frontal-striatal circuits (Hermans et al., 2008; Radke et al., 2015), which typically show altered functioning in SAD (Fouche et al., 2013). Interestingly, reduced striatal dopamine (D2) receptor binding is related to subordinate social status in female Cynomolgus monkeys (Grant et al., 1998) and similarly, deviating striatal functioning has also been found in SAD (Freitas-Ferrari et al., 2010). It is known that testosterone enhances dopamine levels in the ventral striatum (de Souza Silva et al., 2009), which in turn can lead to increased reward sensitivity and augmented motivational behavior (Cools, 2008; Enter et al., 2012). In line with the current findings in SAD, effects of testosterone administration on striatal functioning have previously been found to be particularly pronounced in individuals who are scoring low on reward-seeking behavior (Hermans et al., 2010). This could suggest that the dominance enhancing effect of testosterone in the current study is related to increased reward sensitivity. An increase in eye-contact may lead to an encounter with a possibly rewarding outcome, such as increased social status and its benefits. Indeed, it has been shown that the reward value of a stimulus has an effect on eye-movements: humans automatically orient their eyes toward potentially rewarding stimuli (Hickey et al., 2010; Hickey and van Zoest, 2012). Hence, it could be

that testosterone increases the reward-sensitivity of the socially submissive individual, which leads to augmented behavioral responses toward a potentially rewarding stimulus; in this case in increased first fixations to the eyes of facial stimuli (Bos et al., 2012; van Honk et al., 2004). In addition, the behavioral effects of testosterone may also be influenced by anxiolytic processes via glucocorticoid pathways, steroid receptors, and gamma-aminobutyric acid (GABA) receptors (e.g., Terburg and van Honk, 2013). Future studies combining testosterone administration, eye tracking and neuroimaging techniques should elucidate the neuroendocrine mechanisms underlying the gaze enhancing effect of testosterone in SAD and the extent to which such effects could reflect or are mediated by anxiolytic processes.

In contrast to the SAD group, the healthy controls showed a tendency toward diminished first fixations on the eyes of facial expressions. This finding is consistent with earlier studies showing a testosterone-induced reduction in social cognition: after testosterone administration healthy female participants showed less facial mimicry—which is a measure of empathy—of angry and happy facial expressions (Hermans et al., 2006), reduced conscious recognition of angry faces (van Honk and Schutter, 2007), and decreased performance on the Reading the Mind in the Eye Task (RMET), which assesses the ability to infer the mental state of another by reading subtle cues expressed by the eyes (van Honk et al., 2011a). In addition, reduced eye-contact has been associated with a decline in empathy (Cowan et al., 2014). Together, these findings concur with the notion that testosterone promotes approach motivation in order to facilitate self-oriented dominance seeking behavior (Bos et al., 2012).

The differential findings for patients and controls are in line with literature that suggests that social context determines how testosterone affects social status (i.e., social reward) promoting behavior (Eisenegger et al., 2011; Terburg and van Honk, 2013; van Honk et al., 2011b). Both the social environment and individual differences have been shown to influence the modulatory effects of testosterone (Mehta and Josephs, 2010). Concerning the latter, van Honk et al. (2011a) found that the quantity of prenatal testosterone exposure predicted the effects of administered testosterone on cognitive empathic ability in adult participants. Similarly, social anxiety seemed to modulate the effects of both endogenous and exogenous testosterone on behavioral responses toward social dominance threat (Enter et al., 2014; Maner et al., 2008). Therefore, it is not curious that our study, which entails two disparate groups of participants, finds differential effects of testosterone on gaze behavior toward the eye-region of emotional faces. Future research should address the mechanisms underlying the differential effects of testosterone on gaze behavior in healthy controls and participants with SAD.

A few interpretational issues should be discussed with regard to the present findings. First, one might perceive the result in the healthy controls (i.e., a tendency toward diminished first fixations toward angry eyes) to be in conflict with a study by Terburg et al. (2012a), who showed that testosterone administration in healthy females prolongs dominant staring into the eyes of angry faces. However, the two studies probably captured two different types of subordinate gaze behavior (Terburg et al., 2012b), namely gaze aversion (i.e., rapid breaking of eye-contact with a more dominant conspecific, and thus signaling submission and ending the threatening encounter), versus gaze avoidance (i.e., the prevention of threatening eye contact by avoiding to directly gaze at the dominant threat in the first place) in the present study. Crucially, we show that this type of subordinate gaze behavior is also affected by testosterone administration; hence presenting the first evidence that testosterone diminishes not only submissive gaze aversion in healthy participants (Terburg et al., 2012a), but also submissive gaze avoidance in socially anxious individuals. In addition, we show that the effect of testosterone on gaze avoidance is context dependent and only present in individuals featured by clinical avoidance behavior.

Second, our findings were specific for the first fixations, whereas the gaze variables during the total stimulus presentation time were not affected by testosterone. This finding concurs with literature that suggests that testosterone biases the brain toward social dominance by influencing automatic processes (e.g., Terburg and van Honk, 2013). In addition, this early automatic measure is probably less vulnerable to other influences, such as effects of top-down control, fatigue, and repetition than the later measures. More research is required to test the specificity of the effects of testosterone for initial gaze behavior.

Third, in contrast to our hypothesis the gaze avoidance alleviating effect of testosterone was not specific for angry faces. Nevertheless, although the Treatment x Group effect did not interact with Emotion, separate analyses revealed that the Treatment x Group effect was only significant for angry faces and did not hold when testing this effect for happy or neutral faces in isolation. These results show that the alleviating effect of testosterone on gaze avoidance in SAD patients compared to healthy controls also holds for angry faces, although this effect is not specific for angry faces.

Fourth, we found no group-effect in initial gaze-avoidance in the placebo condition (see also Moukheiber et al., 2012, 2010). However, avoidance for angry versus neutral and happy faces was found across groups and replicated within the SAD group. Most interestingly, gaze-avoidance in the placebo condition was significantly associated with social anxiety levels in participants with syndromal SAD but not in healthy participants. These findings suggest that gaze avoidance was uniquely related to symptom severity in syndromal SAD, and future research using larger groups is needed to determine whether initial gaze avoidance is a specific trait for SAD.

Finally, only female participants were tested in this study, which was a consequence of the testosterone administration method (Tuiten et al., 2000). Future research should not only replicate these results in larger female samples, but also should investigate whether testosterone administration to men has similar effects, as suggested by similarities in social behavior related to endogenous and exogenous testosterone across sexes (Goetz et al., 2014; Hermans et al., 2008). In addition, as is customary with this testosterone administration paradigm, we aimed to control for steroid hormone level fluctuations associated with the menstrual cycle by including women on single-phase contraceptives, and naturally cycling women who were tested in the preovulatory phase (e.g., Hermans et al., 2010; van Honk et al., 2011a). Although the effects of testosterone on first fixations remained while statistically controlling for contraceptive use, future studies ideally control for hormone fluctuations by only testing participants who are on single-phase contraceptives, or by directly assessing estradiol levels, especially given evidence that this hormone possibly mediates testosterone-effects on social dominance (Terburg and van Honk, 2013; Ziomkiewicz et al., 2015).

In terms of clinical implications, the present results may encourage further investigation of whether testosterone could have clinical utility in the treatment of SAD. Forty to 50% of patients does not benefit from current evidence based psychological and pharmacological treatments (Hofmann and Bögels, 2006; Stein and Stein, 2008), and improving therapy efficacy by pharmacological enhancement seems a promising new venue (Hofmann et al., 2014; Singewald et al., 2015). Testosterone acts on the social motivational system and enhances social approach motivation while reducing social fear and avoidance in a socially challenging environment (Enter et al., 2014). Thus, it may be worthwhile to further explore whether testosterone can act as an adjunct in exposure thera-

pies, where boosting prosocial behavior in the first few sessions is essential for therapy outcome. Nevertheless, it should be noted that there is still much unclear about the working mechanisms of testosterone and of pharmacological add-ons for exposure-based therapy. It is possible that, besides the potentially beneficial effects of testosterone on dopamine transmission, its effects on the GABA system might not only work anxiolytic but could also potentially interfere with extinction learning, something worth investigating in future research (Singewald et al., 2015).

In conclusion, a single dose administration of testosterone alleviates gaze avoidance by increasing initial gaze toward the eyes of angry facial expressions in participants with syndromal Social Anxiety Disorder. These findings support the role of testosterone in dominance-enhancing behavior and suggest need for study of testosterone administration as a means to enhance therapy efficacy in Social Anxiety Disorder.

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The funding sources were not involved in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Conflict of interest

The authors declare no conflicts of interest.

Contributors

Authors DE, KR. and PhS designed the study. Authors DE and AH conducted the study. Authors DE and DT undertook the analysis of the data. Author DE wrote the first draft. All authors contributed to and have approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2015.09.008.

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