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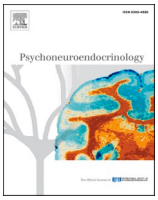

Social avoidance and testosterone enhanced exposure efficacy in women with social anxiety disorder: A pilot investigation

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ABSTRACT

Social avoidance has been associated with more persistent social anxiety disorder (SAD) symptoms and low testosterone levels in individuals with SAD. We tested whether pre-treatment avoidance tendencies moderate the efficacy of testosterone-augmented exposure therapy. Fifty-five females with SAD received two exposure sessions during which fear levels were assessed. Session 1 was augmented with testosterone (0.50 mg) or placebo. Avoidance tendencies and symptom severity were assessed pre- and post-exposure. Participants showed stronger avoidance for social versus non-social stimuli and this tendency remained stable over time. Stronger pretreatment avoidance tendencies were associated with larger fear reduction in the testosterone but not the placebo condition. This effect did not transfer to the second non-enhanced session or symptom severity. The findings support the hypothesis that individuals suffering from SAD with relatively stronger pretreatment avoidance tendencies benefit more from testosterone-augmentation, pointing to a potential behavioral marker for testosterone enhancement of exposure therapy.

1. Introduction

Social anxiety disorder (SAD) is the most common of all anxiety disorders with a lifetime prevalence of 13 % (Bandelow and Michaelis, 2015; Bruce et al., 2005; Hendriks et al., 2016). Social avoidance is a major factor that prevents fear to extinguish in individuals with SAD (Arnaudova et al., 2017) and is therefore a main target in exposure therapy (Clark and Wells, 1995). Based on the well-established social approach-promoting and avoidance-reducing effects of testosterone (Enter et al., 2016a; Hermans and Van Honk, 2006; Maner et al., 2008), researchers have started to study the use of testosterone interventions to boost the effects of exposure therapy in SAD (Hutschemaekers et al., 2021, 2020). Although initial findings are promising, it remains unclear whether social avoidance tendencies in individuals with SAD influence the efficacy of testosterone-enhanced exposure interventions. Identification of social avoidance tendencies as a behavioral marker for the efficacy of these interventions is relevant for the optimization of (personalized) treatments. In the present study, we tested social avoidance tendencies before and after an exposure-based treatment intervention in SAD. In half of the participants the exposure was augmented with testosterone, offering the unique opportunity to explore whether pretreatment social avoidance tendencies would moderate testosterone augmentation effects.

Cognitive models of SAD imply that attentional processes and social avoidance behaviors play an important role in the etiology and maintenance of SAD (Clark and Wells, 1995). In addition to more overt avoidance behaviors such as avoiding social situations or eye contact, individuals with SAD also show more implicit automatic avoidance (biased action tendencies). Those automatic social avoidance tendencies can be measured using Approach Avoidance Tasks (AAT: Rinck and Becker, 2007), which instruct participants to respond to visual stimuli by pushing or pulling a joystick. Socially anxious individuals typically show automatic avoidance of social stimuli - i.e., stronger avoidance tendencies compared to approach tendencies toward angry, but also happy faces (Heuer et al., 2007; Loijen et al., 2020; Roelofs et al., 2010, 2009) and even neutral faces, compared to non-social stimuli and

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healthy controls (Kuckertz et al., 2017). Cross-sectional studies show that these avoidance tendencies toward social threat relate to higher SAD symptom levels (Enter et al., 2016a), and to the onset and chronic course of social anxiety symptoms (Struijs et al., 2018). Although not all evidence points to such predictive value of symptom development (Kampmann et al., 2018a; Struijs et al., 2017), the observation of relative avoidance tendencies to threatening cues on AAT-tasks is robust in individuals with SAD (for review see Loijen et al., 2020).

Testosterone enhances social approach behavior in socially challenging situations where social status may be threatened (Maner et al., 2008; Mazur and Booth, 1998; Terburg and Van Honk, 2013). A recent study showed that pre-treatment rises in testosterone were predictive of better exposure outcomes in terms of larger symptom reduction for individuals with SAD (Hutschemaekers et al., 2020). Moreover, single-dose testosterone administration in individuals with SAD increases automatic approach behavior toward threatening (angry) faces on an AAT (Enter et al., 2016a) and reduces biased processing (van Peer et al., 2017) and gaze-avoidance toward angry faces (Enter et al., 2016b), together suggesting that testosterone can alleviate automatic avoidance behavior in individuals with SAD. Indeed neuroimaging studies have indicated that testosterone administration increases amygdala activation, specifically when one has to approach an angry face and not during threat avoidance (Radke et al., 2015). It does so presumably by enhancing (largely dopaminergic) projections from the amygdala to the ventral striatum, relevant for motivated action (Hermans et al., 2010). Together, these findings suggest that testosterone can stimulate approach behavior in healthy individuals and importantly in highly avoidant individuals with SAD. Translated to clinical application, testosterone administration may be a viable augmentation strategy for exposure therapy for SAD. Indeed, the increased engagement in an exposure session afforded by testosterone may facilitate corrective learning and thereby optimize outcomes (Hutschemaekers et al., 2021).

Toward the goal of personalizing treatment, the present study sought to test the hypothesis that testosterone-enhancement of exposure-therapy would be most effective among individuals with SAD who present with high (as opposed to lower) levels of automatic social avoidance tendencies. We tested this hypothesis using data from a clinical trial involving 55 females with SAD who completed a session of exposure therapy and were randomized to receive either a single dose of testosterone (0.5 mg) or placebo prior to this session (Hutschemaekers et al., 2021). To assess the transfer of testosterone effects, the participants engaged in a second exposure session one week later that did not involve testosterone administration.

We predicted that social avoidance tendencies as measured at baseline would moderate testosterone augmentation effects, such that those showing stronger social avoidance tendencies at baseline and receive testosterone would profit more compared to those participants that receive placebo. Finally, we tested whether social avoidance tendencies changed over time with (testosterone enhanced) exposure therapy.

2. Materials and methods

2.1. Participants

A complete description of the sample and procedures has been provided elsewhere (Hutschemaekers et al., 2021) and in the supplementary materials section 1.1. In short, the sample included 55 females suffering from SAD (M_{age} = 23.31, SD = 5.63, range = 18–43). Participants were recruited at an outpatient clinic specialized in anxiety disorders, at the Radboud University Nijmegen, and from the community. We focused exclusively on females because the pharmacodynamics of the currently used testosterone administration methods have as yet been established in females only (Tuiten et al., 2000). Exclusion criteria were: A) Prior non-response to speech exposure therapy for SAD, B) other predominant emotional disorder(s) C) Psychosis or delusion disorders (current or lifetime), D) Significant suicidal ideations or behaviors within 6 months prior to screening, E) Intellectual developmental disorder, F) Substance or alcohol dependence, G) Somatic illness, H) Females unwilling to use an active form of birth control during the trial, I) pregnancy or lactation, J) Infertility, K) Antipsychotic medication, L) Unstable dose of Antidepressants or Benzodiazepines within 6 weeks prior to enrollment, M) Insufficient proficiency of Dutch language, N) Use of contraceptive containing cyproterone acetate. Ethical approval for this study was granted by the local Review Board (Arnhem-Nijmegen).

2.2. Medication and randomization

Participants were randomly assigned to testosterone (T) or placebo (P) treatment. T was suspended in a clear solution (0.5 ml) with 0.5 mg hydroxypropyl-beta-cyclodextrin, 0.005 ml ethanol 96 %, and distilled water. P contained the same ingredients, except the T. Participants held the liquid under their tongue for 60 s (4 h prior to the first exposure, see Section 2.7). Participants and researchers were blind to treatment condition until completion of the primary outcome analyses of the parent trial.

2.3. Exposure intervention

Participants received 2 public speaking exposure sessions of 90 min, at two separate days, based on the protocol developed by Rodebaugh, Levinson, and Lenze (2013). The second session, one week later, followed the same protocol as the first session without drug administration. Therapists were advanced Bachelor- or Master-level psychology students trained and supervised by authors M.H. and M.K. Adherence to the protocol was checked during supervisions and deviations from the protocol were reported by the therapists. Adherence was good as 96.3 % of the sessions was performed according to the protocol.

2.4. Outcome measures

2.4.1. Symptom severity

Social anxiety symptoms were assessed with the Social Phobia Scale (SPS; Mattick and Clarke, 1998), a self-report measure assessing the fear of being observed or watched during social or performance situations. The scale has shown good internal consistency; α = .94 (Mattick and Clarke, 1998); Dutch translation; α = .91 (De Beurs et al., 2014); current study α = .86. The SPS was completed at baseline, post-assessment (after the second exposure session) and at one month follow-up (online).

2.4.2. Fear levels

Participants rated their fear levels, using a Subjective Units of Distress (SUDs) scale ranging from 0: no fear to 100: extreme fear (Wolpe and Lazarus, 1966). SUDs were assessed after the psychoeducation (initial SUDs), at the beginning of each exposure session (baseline SUDs), immediately prior to the speech (start SUDs), every 2 min during and immediately after the speech (end SUDs).

2.5. Approach avoidance task

To assess approach-avoidance tendencies toward facial expressions we used the Approach Avoidance Task (AAT; Rinck and Becker, 2007). In the AAT participants responded to emotional stimuli: happy, angry, neutral facial expressions presented on a computer screen by either pulling a joystick toward themselves or pushing it away as quickly as possible with their dominant hand. Instructions were indirect based on the color of the picture (grey or sepia). By doing this, the size of the picture increased (pulling movement) or decreased (pushing movement). After making a complete correct movement, the picture disappeared from the screen. Participants then moved the joystick back to its central position and, by pressing the fire button of the joystick, they

initiated a new trial. The stimuli were selected from the Karolinska Directed Emotional Faces database based on quality of emotional expression (Goeleven et al., 2008; Lundqvist et al., 1998). The three types of emotions were taken from the same models (5 females and 5 males). The task also included 20 checkerboards as control stimuli, resulting in 80 different pictures presented in random order twice. Reaction times (RTs) were recorded in ms. Relative faster execution of the push response compared to the pull response reflects heightened behavioral avoidance of the specific type of stimulus. In general, response latencies for affect-congruent (e.g., happy-approach and angry-avoid) are shorter compared to affect incongruent responses (e.g., happy-avoid and angry-approach). The task consisted of 30 practice trials (with different models) and 160 experimental trials. The AAT was performed at baseline and at post-assessment (30 min post the second exposure session).

Before calculating mean reaction times for each picture type (happy, angry, neutral and control) and movement (push, pull), we removed all incorrect trials (on average 2 %) and outliers (fastest and slowest 1 %). We computed a combined AAT effect score from these RTs in which mean RTs for pulling were subtracted from pushing RTs (all facial combined) corrected for the control stimuli ([Push RTs – Pull RTs of all facial expressions combined]/3 – [checkerboards Push – checkerboards Pull]), resulting in a score that reflects the direction of the response tendency. For this AAT effect score negative values indicate stronger avoidance then approach (see also supplementary section 1.3, available online).

2.6. Saliva samples

To assess endogenous testosterone levels, saliva samples were collected (2 ml passive drool saliva by Salicap; Hamburg, Germany) at eight time points: (1) at baseline, (2) prior to T/P intake, (3) prior to exposure session 1, (4) immediately after speech delivery in session 1, (5) 30 min after speech delivery in session 1, (6) prior to exposure session 2, (7) immediately after speech delivery in session 2, and (8) 30 min after speech delivery in session 2.). These timepoints were similar for all participants to control for fluctuations of testosterone levels during the day, see also procedure Section 2.7. For the current study only the first three samples were relevant. Sample 1 (at baseline) and sample 2 (prior to drug intake) were used to assess endogenous baseline testosterone levels and sample 3 (prior to exposure session 1) was assessed as a manipulation check. Samples were stored at –20 °C until radio immune assays were performed by Dr. Kirschbaum's laboratory (Dresden, Germany), for descriptions of methodology, see Miller, Plessow, Kirschbaum, and Stalder (2013), Reardon, Herzhoff, and Tackett (2016).

2.7. Procedure

Participants first completed the baseline assessment (between 9 and 11 AM), including questionnaires, saliva collection and the pre-exposure AAT. The first exposure session was scheduled within the week of the baseline session. Participants began this session by taking a pregnancy test, followed by saliva collection, psychoeducation, a baseline SUDS rating, and administration of study drug commensurate with group assignment (always between 9 and 11 AM). Participants returned 4 h later for a salivary sample and the first exposure session. SUDs were collected during exposure and AEs were assessed at the end of the session. The second exposure session took place one week later (at the same time of the day as the first exposure session) and was, apart from the study medication administration, identical to the first exposure session. Participants completed the post-exposure assessment, which included the SPS and the post-exposure AAT, 30 min after the second session. One month later, participants completed an online follow-up assessment which included the SPS. The original parent trial was registered in the Dutch trial register (https://www.trialregister.nl/trial/6238) and at EudraCT (2014–004475–23).

2.8. Data analytic strategy

The research questions, hypotheses and data analytic procedures were pre-registered at Open Science Framework (OSF): see https://osf.io/3cxsv. At two minor points the analyses we performed deviated from the pre-registration (https://osf.io/3cxsv), which are discussed in the supplementary section 1.2. For the parent trial a sample size of 52 participants was deemed necessary to detect group differences with at least a moderate effect size and a power of 80 %. Consistent with pre-registration, we ran preparatory analyses to further specify our AAT predictors in our analyses. Specifically, we first tested if participants showed an avoidance bias toward facial expressions and if this bias was affected by picture type with a Repeated Measures ANOVA with factor picture type (happy, angry, neutral, control) and response direction (push, pull) on the AAT reaction times. Based on the results of this analysis (e.g., all facial stimuli showed faster push than pull RTs, see supplementary materials for details) we decided to analyze AAT reaction times for social stimuli (i.e., all facial expressions) versus non-social stimuli (i.e., the checkerboards).

To test the moderator hypothesis, we conducted mixed model analyses for the first (enhanced, with testosterone (T) or placebo (P)) and second (unenhanced) session separately. More specifically, to determine whether avoidance tendencies toward facial expressions moderated (testosterone enhanced) exposure efficacy in terms of self-reported fear (SUDs) during the exposure sessions, AAT combined effect score, group (T/P) and time (start, 2 min, 4 min, 6 min, 8 min, end) were included as predictors. Because we found that SUD scores did not follow a linear pattern (Hutschemaekers et al., 2021), we included linear and quadratic time terms. Participant was included as random intercept. Initial SUD scores were included as a fixed factor to control for variance in fear levels unrelated to time or group. To test the relation between social avoidance tendencies and symptom severity, we modeled SPS scores, with AAT combined effect score, group (T/P) and time (pre/post/FU) as predictors and participant as the random intercept.

To test the effects of treatment condition on pre- to post changes in avoidance tendencies toward facial expressions, we modelled AAT RTs with Time (pre-post exposure), Group (T/P), Response direction (Push/Pull) and Picture type (Social/Non-social) as predictors. Participant and Stimulus model (e.g., the model presented on the stimulus) were included as random intercepts. Response direction and time (and their interaction) were included as random slopes for participant. Response direction, Time and Group (and their interactions) as random slopes for Stimulus model.[1]

Per registration, see also parent trial Hutschemaekers et al. (2021), we included endogenous baseline testosterone as an additional control variable (mean saliva sample 1 and 2) in all models. We used the Lme4 package in R (Bates et al., 2013) and *p*-values were calculated using the likelihood ratio tests in the Afex package (Singmann, 2013). The confidence intervals were determined using Lme4's confint function using Bootstrapping (1000 simulations). Continuous predictor variables were centered, and sum-to-zero contrasts used. Consistent with the recommendations for mixed models (Pek and Flora, 2018), we report

[1] We aimed to test a maximum random effect structure (picture type, response direction and time and their interactions as random slopes for the random intercept of participant and random slopes of response direction, time and group for the random intercept of stimulus model) but this model did not converge due to model estimation problems. Therefore, we ran simpler random effects models by dropping random slopes step by step and comparing the AIC after each step. As is common with mixed models, some of the simplified models also resulted in convergence warnings, but these warnings are more often false positives. In line with the recommendations by Bolker (2022), we used different optimizers (allFit function) and compared the estimates which all showed the same results and highly similar estimates. As such we decided to report the results of the model with the best fit (i.e. lowest AIC) and most extended random effect structure that was modeled.

Table 1
Mean AAT reaction times in ms and Standard deviations depending on group (placebo/testosterone), picture type, response direction and measurement time.

Measure	Picture type Angry Pre	Post	Neutral Pre	Post	Happy Pre	Post	Control Pre	Post
Testosterone group ($n = 27$)								
Push	643.66 (86.21)	622.75 (88.58)	641.77 (74.74)	626.89 (81.85)	647.98 (77.14)	638.59 (76.87)	679.08 (82.13)	651.08 (91.03)
Pull	659.13 (83.1)	648.98 (94.70)	672.50 (81.16)	651.27 (92.98)	647.03 (64.73)	639.89 (83.62)	664.48 (81.51)	635.99 (70.52)
Placebo group ($n = 27$)								
Push	631.59 (81.38)	605.80 (60.95)	627.23 (56.52)	609.30 (63.20)	632.80 (65.04)	611.23 (48.77)	688.10 (81.65)	639.62 (62.45)
Pull	649.67 (58.09)	628.39 (73.79)	649.56 (65.02)	618.41 (57.40)	652.93 (79.96)	627.70 (68.86)	658.52 (81.26)	626.67 (61.09)

N = 54

Table 2
Multiple linear regression predicting exposure success (SUD reductions), without and with baseline testosterone included.

	Exposure success SUDs session 1 Estimate (95 % CI)	P-value	SUDs session 2 Estimate (95 % CI)	P-value
Model step 1				
AAT effect score	.004 (–.08,.08)	.911	.05(–.03,.14)	.223
AAT effect score * time (linear)	.21 (–.20,.65)	.346	.21(–.17,.58)	.278
AAT effect score * time (quadratic)	–.01 (–.42,.43)	.963	–.08(–.43,.28)	.683
AAT effect score * group	.05 (–.02,.12)	.205	.08(.001,.17)	.065
AAT effect score * group * time (l)	–.44 (–.89,.02)	.051	–.08(–.44,.31)	.680
AAT effect score * group * time(q)	–.35 (–.81,.07)	.099	–.02(–.39,.30)	.924
Model step 2 (with baseline testosterone)				
AAT effect score	.01 (–.06,.08)	.862	.06(–.02,.14)	.153
AAT effect score * time (linear)	.19 (–.28,.63)	.399	.18(–.19,.55)	.338
AAT effect score * time (quadratic)	–.06 (–.05,.03)	.794	–.10(–.45,.26)	.582
AAT effect score * group	.05 (–.02,.12)	.135	.09(.003,.18)	.041
AAT effect score * group * time (l)	–.41 (–.87,.001)	.067	–.07(–.44,.31)	.727
AAT effect score * group * time(q)	–.34 (–.74,.04)	.108	–.01(–.36,.34)	.937

Note. there was no correlation between baseline testosterone and AAT effect scores prior to exposure: $r = .029$, $p = .837$ or post exposure: $r = –.079$, $p = .580$.

unstandardized effect sizes (estimates).

3. Results

3.1. Sample characteristics

The data of 54 participants were analyzed ($M_{age} = 23.31$, SD = 5.64, range = 18–43) since one participant receiving placebo dropped out before the first exposure due to illness. Another participant in the same group dropped out during the first session (3.6 %). All other participants completed both sessions and the follow-up. A full overview of the sample characteristics have been described elsewhere (Hutschemaekers et al., 2021). There were no baseline differences between the placebo and testosterone group on any of the AAT reaction times, all p-values >.257 (see Table 1).

3.2. Predictive effects of automatic avoidance tendencies on exposure success

Only effects relevant for the current research questions are reported. For a full overview of the results of the exposure and testosterone administration, we refer the reader to the report of the parent trial (Hutschemaekers et al., 2021).

3.2.1. Fear levels

3.2.1.1. Session 1 (enhanced session). The three-way interaction of AAT effect score x Time (linear) x Group approached statistical significance, *Estimate*(linear) = –.44(.23), 95 % CI [–.89, –.02]; F(1, 213) = 3.85, p = .051 (see step 1, Table 2, also for the quadratic time term). To further test our hypothesis that those who show greater social avoidance tendencies at baseline and receive testosterone would profit better compared to those participants that receive placebo, we post-hoc decomposed this result. This follow-up analyses revealed a significant two-way interaction of AAT effect score X Time (linear) for the testosterone group: *Estimate* = .66(.33), 95 % CI [– .01, 1.27]; F(1106) = 4.04, p = .047, but not for the placebo group, *Estimate* = –.23(.31), 95 % CI [–.82,.39]; F(1, 107) = .538, p = .465. Simple slope analyses further showed that, among those assigned to the testosterone condition, participants with lower AAT effect scores (- 1 SD, relative avoidance) reported greater reductions of fear (*Estimate* = –126.72(27.58), 95 % CI [–187.13, – 71.55]; $t(106) = –4.60$, $p < .001$) relative to those with higher AAT effect scores (mean + 1 SD, relative approach; *Estimate* = –53.46 (23.84), 95 % CI [– 103.61, – 7.16], $t(106) = –2.24$, p = .03). These differential effects were not observed for the placebo group (see Fig. 1). The inclusion of baseline testosterone as a control variable did not change the results (step 2, see Table 2).

3.2.1.2. Session 2 (non-enhanced). There was no significant three-way interaction effect between AAT effect score, time and group (see Table 2)[2] or two-way interaction between AAT effect score and time. Inclusion of baseline testosterone in the model showed a significant interaction of AAT effect score with Group: *Estimate* = .09(.04), 95 % CI [.001,.17]; F(1,45) = 4.44, p = .041. For the testosterone group, avoidance scores were not associated with fear levels while for the placebo group, stronger avoidance scores were associated with lower overall fear levels. All other main effects and interaction with AAT effect scores remained non-significant (see step 2, Table 2).

[2] The residuals of the model did show some deviations from normality. However, log or square root transformations did not improve the distribution of the data.

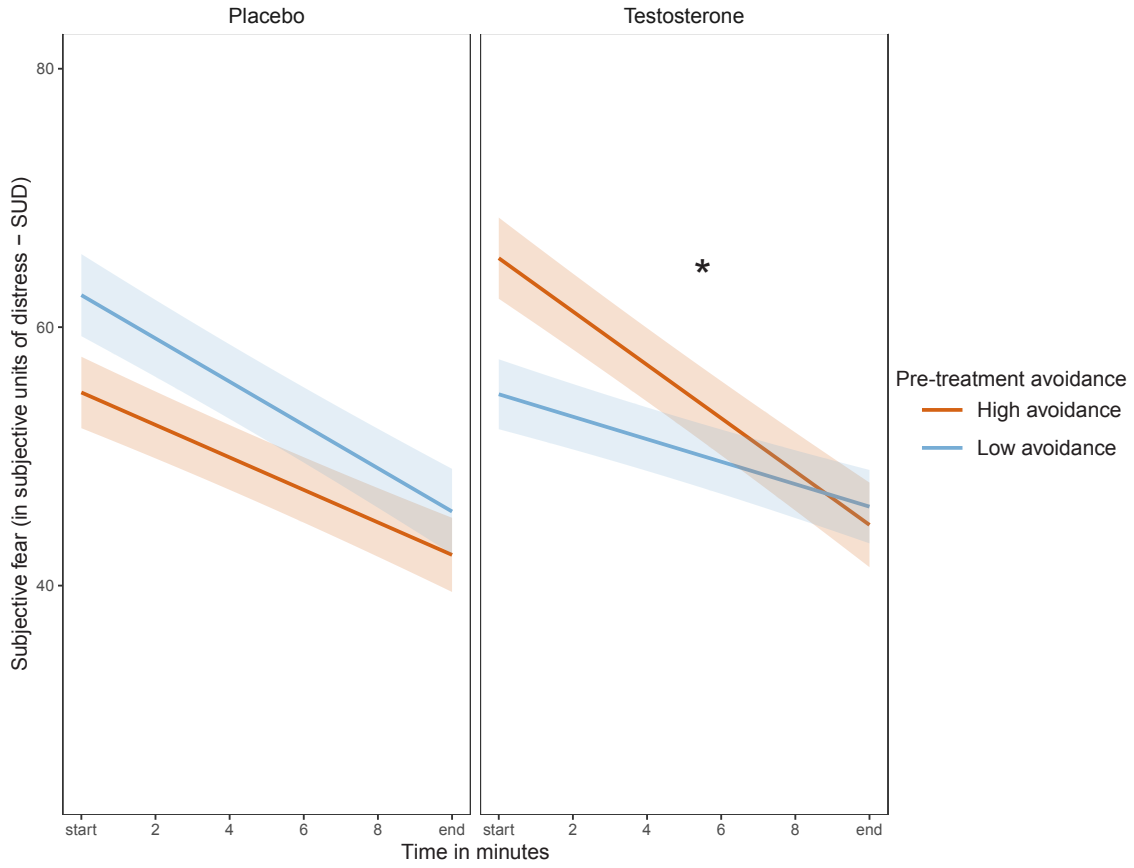

Fig. 1. Illustration of the interaction effect between pre-treatment avoidance and testosterone (vs placebo) enhanced fear-reduction in session 1. The panels show the model based predicted values of the AAT-effect score x Time x Group (testosterone, placebo). The left panel shows the simple slopes of time for the placebo group and the right panel for the testosterone group. The separate lines reflect high (orange) and low (blue) levels of automatic avoidance (note that high and low avoidance groups were only created for display purposes). In the testosterone group we see a significant interaction of automatic avoidance and time (p=.047). Specifically, we see steeper reduction in fear levels for high levels of automatic avoidance of facial expressions compared to lower levels of avoidance. In contrast, in the placebo group relatively low and high avoidance levels are associated with similar patterns of fear reduction (p=.466). Note that there was no relation between avoidance level and the start SUD, not for the placebo group (r = .30, p=.17); nor for the testosterone group (r = .–13, p=.51).

3.2.2. *Social anxiety symptoms*

We did not observe a three-way interaction effect of AAT effect score x Time (Pre/Post/Follow-up) x Group, on social anxiety symptoms (pre-post-follow-up) or two-way interaction between AAT effect score and time (all p > .084). The inclusion of baseline testosterone as a control variable did not change the results (see supplementary section 1.4 for details of analysis, available online).

3.3. *Avoidance tendencies over time*[3]

Results revealed a main effect of Time, *Estimate* = 13.19(3.25), 95 % CI [6.10, 19.65]; $t(37) = 4.06$, $p < .001$, suggesting that reaction times on the AAT reduced from pre- to post-exposure. A significant interaction effect for picture type (social, non-social) and response direction (push, pull), *Estimate* = 8.84(3.66), 95 % CI [1.30, 15.81]; $t(6) = 2.42$, $p = .050$, showed that participants were faster in pushing compared to pulling social faces (e.g. an avoidance bias), whereas they were faster in pulling compared to pushing non-social stimuli (e.g., an approach bias). This effect was present for both groups and did not change over time (pre- to post treatment). All other main effects and interactions were not significant (see Fig. 2). The inclusion of baseline testosterone as a control variable did not change the results (see supplementary section 1.4.2 for details analysis, available online).

4. Discussion

This study provides preliminary findings to suggest that augmenting exposure therapy for SAD with testosterone administration may be most effective when targeted to individuals who present with strong avoidance tendencies. These results are consistent with theory and replicate and extend the findings of earlier experiments (Enter et al., 2016a, 2016b) and a clinical trial (Hutschemaekers et al., 2021).

It is important to note that the moderating effect of social avoidance tendencies were only observed for one outcome, namely acute changes in fear. We are left speculating as to the reasons why the observed moderator effects did not emerge for the other outcomes – fear at the second session and changes social anxiety symptom severity. The latter may not be surprising as the parent trial did not show any effects of testosterone on social anxiety symptoms either (Hutschemaekers et al., 2021). One possibility is that single-session enhancement is not sufficient to yield longer-term effects or changes in social anxiety symptom severity. These observations call for follow-up parametric studies.

In line with previous work, individuals with SAD showed avoidance tendencies not only for angry but also neutral and (to a lesser extend)

[3] The residuals of this model showed that the assumption of normality was violated. Therefore, a log transformation was performed. This improved the distribution of the residuals and yielded similar results compared to the model without this transformation. To improve interpretation of the estimates we reported the results of the non-transformed data. Moreover, mixed model analyses are fairly robust against violations of normality (Knief and Forstmeier, 2021; Schielzeth et al., 2020).

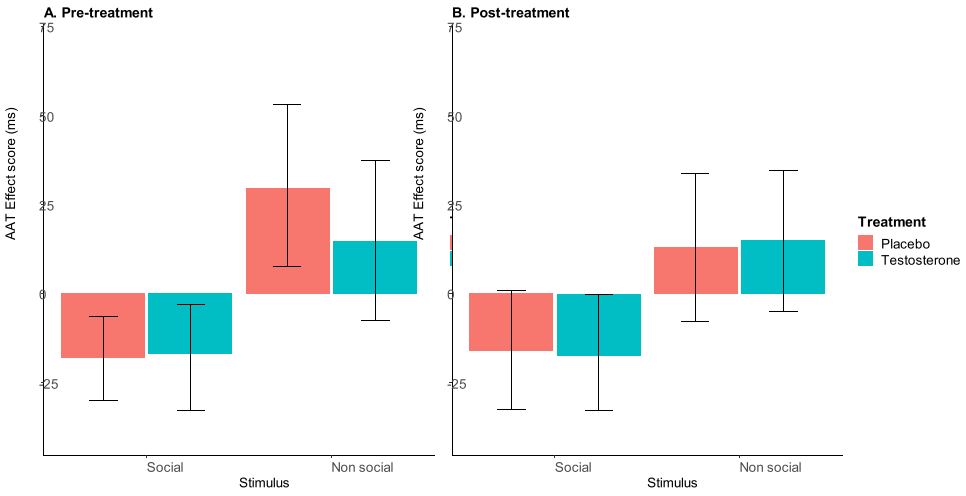

Fig. 2. *Automatic avoidance tendencies displayed in mean AAT effect scores (in ms) per picture type (social/non-social) over time separated per group (Testosterone/Placebo).* The AAT effect scores are calculated (for display purposes only), by subtracting the individual reaction times for pull movements from the individual reaction times for push movements. Negative AAT effect scores indicate stronger avoidance and positive AAT effect scores reflect stronger approach. As shown in the left panel (A) a pre-treatment avoidance bias towards social stimuli is shown while for non-social stimuli an approach bias is shown, for both the placebo and testosterone group. This pattern stays stable over time (right panel, B).

happy faces (Heuer et al., 2007; Kuckertz et al., 2017; Loijen et al., 2020; Roelofs et al., 2010, 2009). Angry faces explicitly communicate threat to the individual and may therefore automatically activate avoidance mechanisms, especially in socially anxious individuals (Heuer et al., 2007; Roelofs et al., 2010). The same can be true for neutral faces. Indeed, neutral faces are ambiguous, activate negative bias, and have been labeled as threatening by socially anxious individuals (Heuer et al., 2007; Lange et al., 2012). Relative avoidance tendencies to happy faces (Heuer et al., 2007; Lange et al., 2012; Roelofs et al., 2010) are also common, pointing perhaps to tendencies among individuals with SAD to avoid any potential social interaction partner (Roelofs et al., 2010).

We did not observe any changes in social avoidance tendencies over time with exposure therapy. It is possible that such changes require testing social avoidance tendencies during the testosterone treatment window (Enter et al., 2016a, 2014). The fact that social avoidance tendencies did not change from pre to post exposure may in fact suggest that avoidance tendencies in individuals with SAD are stable over time. Interestingly, (Kampmann et al., 2018b) found no change in social avoidance tendencies in individuals with SAD even after 10 sessions of (successful) exposure therapy. Collectively, these observations point to the possibility that targeting social avoidance tendencies during the course of established interventions for SAD as a way to boost their efficacy and reduce relapse may require more intensive (e.g., frequency, duration) treatment with testosterone or other augmentation strategies that can directly engage this therapeutic target.

Several strengths and limitations of this study deserve comment. As far as the strengths, we only included individuals who met the diagnostic criteria of SAD (American Psychiatric Association, 2013) and we used well-established tasks and protocols. Second, the hypotheses were preregistered and were grounded in a long standing research line testing prosocial properties of testosterone and their boundary conditions in individuals with SAD (Enter et al., 2016a, 2016b; Hutschemaekers et al., 2021). As far as the limitations, first, the study was underpowered to detect small effects. Second, we only included females because the administration method we used has been validated only in females (Bos et al., 2012; Enter et al., 2016b; Tuiten et al., 2000). Building upon recent single-dose testosterone administration studies in men that have documented changes in social approach and avoidance behaviors (see Carré and Robinson, 2020; Geniole and Carré, 2018), future work may focus on generalizing the findings observed here to men. Third, we did not include an additional CBT control condition and therefore cannot assess specificity. Lastly, our study was not optimized to test subtle changes in avoidance behavior *during* exposure. Therefore, we can only speculate about the effects of testosterone on avoidance behaviors, and other mechanisms of action regarding the effects of testosterone cannot be ruled out. However, the fact that testosterone facilitated in-session exposure-effects in participants with stronger automatic avoidance potentially suggests that it reduces avoidance and facilitates engagement in exposure therapy. In order to test this hypothesis, we recommend future studies to include more specific in-session approach-avoidance measures, for example body posture-, eye movement- or personal distance measures, which may help to disentangle different types of avoidance such as Pavlovian flight behaviors and more instrumental or goal directed avoidance (Cain, 2019; Lu et al., 2023; Wagels et al., 2017).

4.1. Conclusion

In sum, the current study adds to a growing body of literature indicating that individuals with SAD who enter exposure treatment with strong social avoidance tendencies may benefit from additional treatment with testosterone. Specifically, probing the data from a proof-of-principle clinical trial of this augmentation strategy that included females with SAD regardless of their levels of social avoidance tendencies yielded initial evidence to support a more targeted application of this clinical strategy. We hope that these pilot findings encourage follow-up studies of testosterone-augmented exposure therapy that can aid the goal to optimize its application and efficacy.

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CRediT authorship contribution statement

Moniek Hutschemaekers: Conceptualization, Methodology, Validation, Investigation, Formal Analysis, Data curation, Writing – original draft, Project administration. **Rianne de Kleine:** Conceptualization, Methodology, Supervision over investigation and analyses, Writing and Editing. **Mirjam Kampman:** Conceptualization, Methodology, Supervision over investigation, Writing and Editing. **Jasper Smits:** Methodological design of the parent trial and assisted with the analyses and write-up of the manuscript. **Karin Roelofs:** Conceptualization, Methodology, Supervision over investigation and analyses, Writing and Editing. All authors approved the final version of the paper for submission.

Declaration of Competing Interest

The other authors declared no conflicts of interest with respect to the authorship or the publication of this article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106372.

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