The effect of intranasally administered oxytocin on observed social behavior in social anxiety disorder

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Abstract
Research has shown that patients with a social anxiety disorder (SAD) show social performance deficits. These deficits are a maintaining factor in SAD, as mending social behavior improves interpersonal judgments and reduces social anxiety. Thus finding ways to enhance social behavior is evidently of importance in the treatment of SAD. This double-blind, placebo-controlled study investigated the effect of an intranasal administration of the hormone oxytocin (24 IU) on social behavior and anxious appearance in SAD patients (N = 40) and healthy controls (N = 39). Forty minutes after oxytocin administration participants were submitted to two live social situations (i.e., a waiting room situation and a getting acquainted task). The participants (‘self-rated’) and observers (‘observer-rated’) scored participants’ social behavior and anxious appearance. Participants also rated their positive and negative affect. Confirming the social performance deficits in SAD, observers regarded SAD patients as more anxious and less socially skilled than healthy controls. Results indicated oxytocin-induced improvement of observer-rated social behavior in SAD patients compared to placebo but only in the getting acquainted task. This effect
1. Introduction

Social anxiety disorder (SAD) is the most prevalent anxiety disorder (12% lifetime). SAD is characterized by persistent, excessive anxiety during social interactions, and it negatively affects the quality of life (Kessler et al., 2005; Simon et al., 2002). SAD patients feel socially isolated and have difficulties developing friendships and intimate relationships (Lipsitz and Schneier, 2000). Subjectively they fear that they appear anxious and behave socially inadequate (Clark, 2005; Hofmann, 2007). Sadly, research shows that SAD patients not only subjectively experience that they perform worse in social interactions but also observer-ratings by independent observers confirm diminished social performance compared to healthy controls (see overview (Schneider and Turk, 2014)). This diminished social performance is seen as an important factor that feeds the social anxiety of SAD patients as it elicits negative responses from their social environment (Alden and Taylor, 2010). Recent CBT focusing on increasing social performance in SAD has shown to improve their social relations and decrease anxiety (Alden et al., 2018). Nevertheless, many patients do not show a symptom decrease after first-line Cognitive Behavioral Therapy (CBT) (Loerinc et al., 2015; Norton and Price, 2007; Stein and Stein, 2008). Finding other ways to enhance their social performance is evidently of importance.

The hormone and neuropeptide oxytocin is conventionally considered to enhance social behavior and reduce social fear (Bartz and Hollander, 2006; Campbell, 2010; Gaustella and MacLeod, 2012). However, recent reviews suggest that oxytocin can also enhance the salience of negative interaction (Steinman et al., 2019) and modulate non-social cognition and behavior (Quintana and Gaustella, 2020). Despite these new insights in the more complex function of oxytocin in human, it is still frequently suggested to help psychiatric patients (Insel, 2016), in particular, patients with social deficits (Leppanen et al., 2018; Quintana and Gaustella, 2020) such as SAD (Bartz et al., 2011; Dos Santos et al., 2019; Heinrichs et al., 2009). While animal studies support this therapeutic potential of oxytocin, clinical research is less convincing (Leppanen et al., 2018; Tabak et al., 2019). A recent meta-analysis of the effects of oxytocin (De Cagna et al., 2019) included seven studies on SAD and showed no improvement of symptomatology after oxytocin administration (24 IU). The largest shortcoming, however, is that clinical studies to date have not addressed the effects of oxytocin on social behavior in face-to-face social interaction. Three studies in the meta-analysis came nearest to assessing social behavior (Fang et al., 2014, 2017; Gaustella et al., 2009) utilizing computer tasks (Fang et al., 2014, 2017) and a public speaking task (Guastella et al., 2009). Although of interest, computer tasks do not embody the day-to-day social interactions that are the core fear in SAD, and the public speaking does not exemplify everyday social interaction (Schneider and Turk, 2014). In addition, only self-report social performance and affect was assessed in the latter. Regarding the oxytocin effect on affect in SAD, the conclusion in the meta-analysis (De Cagna et al., 2019) was straightforward, as none of the seven evaluated studies showed an improvement of affect by oxytocin. Still, this conclusion cannot be translated to ecologically valid social interaction situations as a day-to-day social interactive setting was not used in these studies. Concluding, it remains undetermined whether oxytocin can effectively enhance self- and observer-rated social performance and valence of affect in ecologically valid social situations in SAD.

This double-blind, placebo-controlled experimental study in real-life social interactions (a waiting room and a getting-acquainted setting) aimed to test whether a single intranasal application of oxytocin (24 IU) could improve observer- and self-rated social performance and valence of affect of SAD patients and healthy controls. To gain insight into the potential effect of oxytocin on social performance, this was split into two core components: anxious appearance and social behavior (Voncken and Bögels, 2008). It was hypothesized that people with SAD would show improvement on both social performance measures after administration, compared to the SAD placebo group and the healthy controls.

2. Patients and methods

2.1. Design and treatments

The study was conducted according to a double-blind, placebo-controlled, two by two design, including Group and Treatment as between-subject factors. Treatment consisted of oxytocin (Syntocinon®) (OXT) or a placebo (PLA) in a nasal spray. Total supervised self-administration consisted of 24 IU of OXT, three times 4 IU into each nostril, with a time-interval of 45 s in between each dosing. This dose falls in the range (18-40 IU) that is usually used in OXT research (see review by (MacDonald and MacDonald, 2010)). The PLA nasal spray was identical in appearance and formulation, apart from the active ingredient (OXT). In this study, two groups were included, patients diagnosed with a Social Anxiety Disorder (SAD) and an age- and sex-matched healthy control group (HC). Participants were randomized over the OXT and PLA conditions based on the stratification of sex and Group. For the randomization a computer program was used. The randomization procedure was done by a person who was not directly involved in the study. Blinded OXT and PLA inhalators were used.

was not perceived as such by patients themselves and did not improve their affect ratings. In conclusion, this study found support for the idea that oxytocin helps SAD patients to perform better in social interactions, although this improvement seemed context-dependent (i.e., only present in the getting-acquainted task) and ‘not perceived by the patient.

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The study was approved by the institutional review board of the Academic Hospital Maastricht and Maastricht University (NL38026.068.12), and it was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008. The study was registered in the Netherlands Trial Register (https://www.trialregister.nl/; Identifier: NTR3672). The present data is part of a larger project testing the effects of intranasally administered OXT in people with SAD and healthy controls on social performance (this paper), social mimicry and bonding (manuscript in preparation), and social cooperation (Hurlemann et al., 2019).

2.2. Participants

The recruitment and testing took place in Maastricht between July 2013 and July 2016. It was initially planned to include a second patient group with other anxiety disorders as a control group, but this arm was discarded due to a lack of eligible patients.

Male and female participants were recruited by advertisements in local and national newspapers and via two local outpatient mental health clinics. The central inclusion criterion for the SAD group was having a primary diagnosis of SAD according to the SCID-I (First et al., 1996; Groenestijn et al., 1997) or Mini-International Neuropsychiatric Interview (MINI) (Overbeek et al., 1999; Sheehan et al., 1998). According to the SCID-I, healthy volunteers had to be free of a current or past diagnosis of any anxiety or depressive disorder, including SAD. Women had to be free from contraceptives and they were assessed in the mid-luteal phase of their menstrual cycle. Exclusion criteria were actual or chronic nasal disease, major medical condition, use of anxiolytic medication, acute psychotic complaints, risk for suicide or auto mutilation, and dependency on alcohol or drugs. and for women, pregnancy or breastfeeding. In total, 79 participants were recruited for this study. The final study population consisted of patients with a SAD (N = 40) and HCs (N = 39) (Figure 1; Table 1), all fluent Dutch speakers. All participants completed the Dutch version of the Social Phobia and Anxiety Inventory (SPAI) (Turner et al., 1989), validated by (Bögels and Reith, 1999), and the Dutch translation of the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). STAI scores range 0-192 with a score ≥88 indicating a SAD diagnosis, the CES-D scores range 0-60, with a score ≥16 indicating mild to moderate depressive symptoms and ≥21 major depressive symptoms. Characteristics of the participants are depicted in Table 1.

2.3. Questionnaires

2.3.1. Social behavior and anxious appearance rating scale
An abbreviated version of the Social Behavior and Anxious Appearance Rating Scale (SBA)-rating scale (Voncken and Bögels, 2008) was used, consisting of 16 nine-point Likert scale items. The SBA comprises of two subscales, Anxious Appearance, reflected by four items (fidgeting, faltering of the voice, laughing nervously, and being nervous) and Social Behavior reflected by 12 items (e.g., making eye contact, ability to keep the conversation going and silences). Ratings for the Anxious Appearance subscale were reverse-coded, after which means for each subscale were calculated (Min-max: 1–9). As a result, a higher score indicated better evaluations: a lower anxious appearance on the Anxious Appearance subscale and better social behavior on the Social Behavior subscale. The SBA was rated by observers (see below) after the subsequent social tasks and by the participants as a self-report measure after the getting-acquainted task only.

2.3.2. Positive and negative affect scale
The 11-item Positive and Negative Affect Scale (PANAS) (Engelen et al., 2006; Watson et al., 1988) included five positive (attentive, interested, enthusiastic, inspired, strong) and six negative items (ashamed, anxious, nervous, tense, insecure, and one extra Dutch word for nervous), assessing respectively positive and negative affect. Participants rated each item on a 5-point scale (1= not at all, 5= very much). Mean scores were calculated for the subscales (Min-max: 1–5), with higher scores indicating higher positive and negative affect.

2.4. Social tasks

2.4.1. Waiting room
This 5-minute Waiting Room task has been used in prior studies (Thompson and Rapee, 2002; Voncken and Dijkstra, 2012) to assess social behavior in a natural setting as participants are unaware of the assessment of their social behavior. Participants interact for 5 min with a confederate, supposedly waiting for the real experiment to begin. Confederates were instructed to initiate social interaction and leave further initiatives to the participant and behave according to a trained protocol (see below). Video recordings were taken with a hidden camera.

2.4.2. Getting acquainted
The 5-minute Getting Acquainted task is widely used to assess SAD’s social performance behavior (see overview (Voncken and Bögels, 2008)). The participant and confederate are placed in front of a camera and informed that the confederate and the video observers will rate their social performance. Participants then receive clear instructions that they are responsible for initiating the conversation and keeping the conversation going. Confederates were instructed to let the participant start the conversation and behave according to a trained protocol (see below).
2.5. Observers and confederates

Video observers (N = 3, one male, two females) were trained for six hours and rated the Anxious Appearance and Social Behavior of the participants using the SBA. All were blind to Group and Treatment. Confederates (N = 13, females) received an 8-hour training to act according to a protocol based on (Voncken and Bogels, 2008; Voncken and Dijk, 2012) in each of the social tasks. Rules included being friendly, showing an open attitude towards the participant, leaving the conversation’s burden with the participant, and constraining their answers to three pieces of information per response.

2.6. Procedure

After participants were informed about the study procedure and gave consent, they were asked about their medication, caffeine, and alcohol use on the night before and on the assessment day. Participants were not allowed to use any kind of medication. However, in case participants used anxiolytic medicines, they were asked to abstain from intake the night before and on the actual test day. Female participants of childbearing age were submitted to a urine pregnancy test, which had to be negative before proceeding. Subsequently, participants filled out a set of questionnaires assessing their social anxiety (SPAI) and depressive symptoms (CES-D), and their affect state (PANAS-D). Hereafter, participants, under the supervision of a research assistant, self-administered OXT or PLA via a nasal spray (i.e., Treatment administration), followed by a supposedly 45-minute break in a waiting room equipped with a hidden video camera. After 40-minutes, the participant filled out PANAS-1, followed by the confederate entering the room to engage with the unaware participant in the Waiting Room task. After the 5-minute Waiting Room task, the confederate left the room, and the participant filled out the PANAS-2. The Getting Acquainted task took place 45 min after Treatment administration in another room equipped with two chairs and a visible video camera. Participants received instructions, filled out the PANAS-3, engaged in the Getting Acquainted task, and filled out the PANAS-4 together with the SBA self-rating. Afterward, participants were carefully debriefed and asked for their permission to use the video material. Participants were reimbursed for their invested time.

2.7. Statistical analyses

Data were analyzed with the statistical program SPSS (version 24.0). Intra-class Correlation Coefficients (ICC) and their 95% confidence intervals (CI) were calculated to assess inter-rater reliability between the three observers. The ICC was based on a mean-rating (k = 3), consistency, 2-way random-effects model for the SBA subscales Anxious Appearance and Social Behavior. ICC values less than 0.5 suggest low reliability, values between 0.5 and 0.75 of moderate reliability, values between 0.75 and 0.9 of good reliability, and values greater than 0.90 of excellent reliability (Koo and Li, 2016). Statistical significance was assumed at p < .05 for all Analysis of Variance (ANOVA).

Data of the two SBA subscales were analyzed separately for the Waiting Room and the Getting Acquainted task with a two-by-two ANOVA with Group (2 levels) and Treatment (2 levels) as between-subject factors. In the case of a Group by Treatment interaction, post-hoc analyses were conducted. This procedure was followed for both observer- and self-ratings of the SBA scales. Data of the positive and negative PANAS subscales were entered separately in two
mixed General Linear Model Repeated Measures (GLM RM) ANOVAs with Time (5 levels) as within-subject factor and Group (2 levels) and Treatment (2 levels) as between-subject factors. In the case of Time by Treatment interactions, post-hoc analyses were performed. In casephericity was violated, Greenhouse-Geisser corrections were applied.

Partial eta squared (partial $\eta^2$) is reported to demonstrate the effect's magnitude, and it is based on Cohen's $f$, which defines small, medium, and large as respectively 0.10, 0.25, and 0.50, which corresponds to partial $\eta^2$ values of 0.01, 0.06, and 0.14 (Richardson, 2011), and an approximate overlap between distributions of respectively 85, 67, and 53% (Sullivan & Feinn, 2012).

Before the study start, a power calculation was conducted around the primary outcome measure (reciprocity of self-disclosure) of the larger study; the effect size ($d = 0.64$) was based on the study of (Meleshko and Alden, 1993). The power analysis (power 80%, $\alpha = 0.05$, two-tailed) indicated that 39 participants were required in each group (patients and controls). To understand whether the study presented in this paper was powered enough to detect changes in the behavior of socially anxious patients when they received OXT compared to PLA and a healthy control group, a post-hoc power calculation was performed based on previous study in a similar patient group, using the Getting Acquainted task with observer-rated and self-rated scales (Voncken and Bogels, 2008). Based on this, a sample size between 44 and 53 would be needed for the observer-rated behavior and anxiety, respectively, and 17-24 participants to detect effects between socially anxious participants treated with OXT and PLA.

3. Results

Due to technical issues, video recordings in the Waiting Room (SAD, $N = 5$; HC, $N = 4$) and Getting-Acquainted Task (SAD, $N = 3$; HC, $N = 5$) were lost.

3.1. Observer-rated anxious appearance and social behavior

3.1.1. Waiting room (WR) task

3.1.1.1. Reliability. The ICC including the three observers for Anxious Appearance was 0.69 (95% CI [.57, .78], $F_{68,136} = 7.52, p < .001$), whereas the ICC for Social Behavior was 0.89 (95% CI [.84, .92], $F_{67,134} = 24.13, p < .001$). These values indicate that the inter-rater reliability was moderate to excellent. Means (SEM) for observer-rated Anxious Appearance and Social Behavior are depicted in Table 2.

3.1.1.2. Observer-rated anxious appearance WR task. GLM ANOVA revealed a main effect of Group ($F(1, 65) = 10.20, p = .002, \eta^2_p = .136$) on observer-rated Anxious Appearance ratings; SAD were rated 0.69 points more anxious than HC (95% CI [0.257, 1.116]). Analysis did not reveal a main effect of Treatment ($F(1, 65) = 0.003, p = .958, \eta^2_p = 0.000$) or a Group by Treatment interaction ($F(1, 65) = 0.14, p = .715, \eta^2_p = 0.002$).

3.1.1.3. Observer-rated social behavior WR task. For Social Behavior, a main effect of Group was demonstrated ($F(1, 65) = 4.09, p = .047, \eta^2_p = 0.059$); SAD were rated to perform 0.86 (95% CI [-1.714, -0.011]) points lower than HC. Analysis did not show a main effect of Treatment ($F(1, 65) = 0.22, p = .638, \eta^2_p = 0.003$) or a significant Group by Treatment interaction ($F(1, 65) = 3.62, p = .062, \eta^2_p = 0.053$).

3.1.2. Getting acquainted (GA) task

3.1.2.1. Reliability. The ICC for Anxious Appearance was 0.77 (95% CI [.68, .84], $F_{69,138} = 10.88, p < .001$) with Cronbach’s $\alpha = 0.91$. For Social Behavior, the ICC was 0.80 (95% CI [.72, .86], $F_{68,136} = 12.94, p < .001$) with Cronbach’s $\alpha = 0.92$. These values indicate that the inter-rater reliability was moderate to excellent. Means (SEM) for observer-rated Anxious Appearance and Social Behavior are depicted in Table 2.

3.1.2.2. Observer-rated anxious appearance GA task. GLM ANOVA revealed a significant Group effect on Anxious Appearance showing that, independent of treatment, raters perceived SAD as 1.22 (95% CI [.532, 1.898]) points more anxious than HC ($F(1, 66) = 12.61, p = .001, \eta^2_p = 0.160$). Analysis did not reveal a main Treatment effect ($F(1, 66) = 0.10, p = .756, \eta^2_p = 0.001$) or a Treatment by Group interaction effect ($F(1, 66) = 0.87, p = .353, \eta^2_p = 0.013$).

3.1.2.3. Observer-rated social behavior GA task. Analysis demonstrated a Group by Treatment interaction effect on Social Behavior ($F(1, 66) = 4.39, p = .040, \eta^2_p = 0.062$). In the PLA condition, the SAD group was rated 1.71 points (95% CI [−2.623, −0.801]) lower than the HC.

| Table 2 | Mean scores (SEM) for SAD patients and HC of observer and self-ratings of anxious appearance and social behavior of the waiting room and getting acquainted task. |
|---------|---------------------------------------------------------------|
|         | SAD Mean (SEM)                                               | HC Mean (SEM) |
|         | PLAs                                                          | OXTs           | PLAs                                                          | OXTs |
| Waiting Room Task | Observer-Rated Anxious appearance                              | 1.85 (0.22)\(^a\) | 2.00 (0.21)\(^a\) | 1.24 (0.20)\(^b\) | 1.15 (0.22)\(^b\) |
|         | Observer-Rated Social behavior                                | 5.27 (0.44)\(^a\) | 5.88 (0.42)\(^a\) | 6.94 (0.41)\(^b\) | 5.93 (0.44)\(^b\) |
| Getting Acquainted Task | Observer-Rated Anxious Appearance                              | 3.00 (0.34)\(^a\) | 2.78 (0.34)\(^a\) | 1.46 (0.35)\(^b\) | 1.89 (0.35)\(^b\) |
|         | Observer-Rated Social behavior                                | 6.25 (0.32)\(^a\) | 7.23 (0.32)\(^b\) | 7.96 (0.33)\(^b\) | 7.59 (0.33)\(^b\) |
|         | Self-Rated Anxious Appearance                                 | 6.11 (0.35)\(^a\) | 5.59 (0.33)\(^a\) | 2.66 (0.27)\(^b\) | 3.09 (0.23)\(^b\) |
|         | Self-Rated Social Behavior                                   | 4.28 (0.30)\(^a\) | 4.89 (0.23)\(^b\) | 7.02 (0.15)\(^b\) | 6.64 (0.23)\(^b\) |

Note. Means with different superscript differ significantly ($p < .05$) from each other.
Fig. 2 Observer- and self-rated mean (SEM) social behavior in the Getting Acquainted task of SAD patients and HC per Treatment Condition. Analysis revealed a Group by Treatment interaction which was due to the higher observed-rated social behavior in the SAD patients after having received oxytocin, compared to PLA, while there was no difference in behavior in the two HC groups.* signifies statistical significance at \( p < .05 \).

The difference between the two HC groups was not significant. However, SAD patients in the oxytocin condition were rated 0.98 points higher than SAD patients receiving PLA (95% CI [.079, 1.875]) \((F(1, 66) = 4.72, p = .033, \eta_p^2 = 0.067)\). Differences for Treatment in the HC group were not significant \((F(1, 66) = 0.66, p = .420, \eta_p^2 = 0.010)\). There was a main effect of Group \((F(1, 66) = 10.31, p = .002, \eta_p^2 = 0.135)\) but not of Treatment \((F(1, 66) = 0.87, p = .36, \eta_p^2 = 0.013)\) on observer-rated social behavior in the GA task. See Figure 2.

3.2. Self-rated anxious appearance and social behavior

3.2.1. Getting acquainted (GA) task

3.2.1.1. Reliability. Participants provided self-reports on their Anxious Appearance and Social Behavior during the Getting Acquainted task using the SBA (Table 2). Cronbach’s \( \alpha \) was 0.88 for Anxious Appearance and 0.95 for Social Behavior which indicated that the internal consistency was good to very good.

3.2.1.2. Self-rated anxious appearance GA task. Analysis revealed a main effect of Group \((F(1, 75) = 96.71, p < .001, \eta_p^2 = 0.563)\) demonstrating that SAD patients rated themselves as more anxious than HC (difference: 2.97; 95% CI [2.37; 3.57]). There was no Treatment effect \((F(1, 75) = 0.02, p = .87, \eta_p^2 = 0.000)\) or Group by Treatment interaction \((F(1, 75) = 2.49, p = .12, \eta_p^2 = 0.03)\).

3.2.1.3. Self-rated social behavior GA task. Analysis revealed a Group by Treatment interaction \((F(1, 75) = 4.41, p = .04, \eta_p^2 = 0.05)\). Further analyses showed that the SAD patients rated themselves less in social behavior compared to HC, however, this difference between groups was smaller for the persons treated with OXT (mean difference: 1.75; \( p < .001; \) 95% CI [−2.42; −1.08]) compared to PLA (mean difference: −2.74; \( p < .001; \) 95% CI [3.40; 2.08]). Means suggested that this effect was driven by lower self-ratings of HC in the OXT condition and higher in the SAD compared to the PLA conditions. There was a main effect of Group \((F(1, 75) = 91.08, p < .001, \eta_p^2 = 0.55)\) demonstrating that SAD patients rated themselves as behaving less socially adequate than HC (mean difference: −2.97, 95% CI [−3.57; −2.37]). There was no main effect of Treatment \((F(1, 75) = 0.23, p = .63, \eta_p^2 = 0.003)\) on self-rated Social Behavior. See Figure 2.

3.2.1.4. Self-rated affect.

3.2.1.4.1. Reliability. Cronbach’s alpha for each time point, and for both positive and negative affect was between 0.66 and 0.71, indicating an internal consistency that is in the acceptable range.

3.3. Positive affect

Analysis revealed a significant main effect of Time \((F(3, 01, 225.93) = 19.12, p < .001, \eta_p^2 = 0.20)\). Pairwise comparisons demonstrated that positive affect did not change significantly from pre- to post-WR the other consecutive assessments did differ significantly from each other \((p < .001)\). Analysis also revealed a significant main effect of Group \((F(1, 75) = 40.75, p < .001, \eta_p^2 = 0.35)\). That is, independent of Time and Treatment, SAD patients rated themselves 0.74 points lower on positive affect than HC (95% CI [−0.975, −0.515], \( p < .001 \)). Analysis did not reveal a significant Treatment by Group by Time interaction effect \((F(3, 01, 225.93) = 0.17, p = .95, \eta_p^2 = 0.002)\), Treatment by Group interaction effect \((F(1, 75) = 0.72, p = .40, \eta_p^2 = 0.01)\), Treatment by Time interaction effect \((F(3, 01, 225.93) = 0.56, p = .69, \eta_p^2 = 0.007)\), Group by Time interaction effect \((F(3, 01, 225.93) = 1.01, p = .40, \eta_p^2 = 0.01)\), or Treatment effect \((F(1, 75) = 0.09, p = .76, \eta_p^2 = 0.001)\) (See Figure 3, Panel A).

3.4. Negative affect

Analysis revealed a significant Group by Time interaction \((F(3, 05, 228.77) = 32.543, p < .001, \eta_p^2 = 0.30)\). While the self-rated negative affect of the healthy controls was lower than the SAD patients and followed a relatively stable pattern, the affect of the SAD had a more erratic pattern. The self-rated negative affect of SAD patients dropped at pre-waiting room compared to baseline, where after it rose considerably (post waiting room) and it did not drop anymore until the end of the study (See Fig. 3, Panel B). Analysis did not reveal a significant Treatment by Group effect \((F(1, 75) = 2.76, p = .10, \eta_p^2 = 0.03)\), Treatment by Time effect \((F(3, 05, 228.77) = 0.90, p = .44, \eta_p^2 = 0.01)\), Treatment by Group by Time interaction effect \((F(3, 05, 228.77) = 0.68, p = .57, \eta_p^2 = 0.009)\) or Treatment effect \((F(1, 75) = 0.001, p = .98, \eta_p^2 = 0.00)\).

4. Discussion

The present study examined the effect of a single dose of intranasal oxytocin (24 IU) on social performance (i.e., social behavior and anxious appearance) in patients with social anxiety disorder (SAD) compared to healthy controls (HC). SAD patients in the oxytocin condition were rated higher on social behavior in the getting-acquainted task by trained
observers compared to SAD patients in the PLA condition. This effect was not present in the waiting room task. Furthermore, in contrast to social behavior, there was no effect of oxytocin on anxious appearance. Also, participants’ self-ratings did not show an overall effect of oxytocin. Independent of treatment condition, SAD patients rated themselves as more anxious than healthy controls and less socially skilled than HC. Finally, SAD patients scored lower on positive affect and higher on negative affect compared to HC, and these ratings were not affected by oxytocin.

Findings supported the hypothesis that a single administration (24 IU) of oxytocin could enhance SAD patients’ social performance. Of note, oxytocin did not affect SAD patients’ anxious appearance, whereas it did improve their social behavior. Interestingly in this light, previous research has shown that the treatment of social behavior seems to be of greater value than of anxious appearance. For instance, displaying anxious symptoms while behaving socially adequately does not negatively affect interpersonal processes, whereas the opposite does (Papsdorf and Alden, 1998). The finding that oxytocin improved SAD patients’ social behavior in the getting-acquainted task and not in the waiting room is in line with previous studies (Bartz et al., 2011; Steinman et al., 2019) that have demonstrated oxytocin’s context-dependence. In a negative social setting, for example, oxytocin can promote avoidance behavior, whereas in a positive social setting, it can enhance approaching behavior.

In the current study, the social context of the tasks differed as, in the second (getting-acquainted) task, the participants were already familiar with the confederate and were instructed to interact with the other, while this was not the case in the first (waiting room) task. The more positive context created in the second task due to familiarity with the interaction person (Bartz et al., 2011) might have promoted social behavior in this task a greater extent.

The finding that oxytocin did not improve affect is in line with previous research (De Cagna et al., 2019). However, the observation that oxytocin did not affect SAD patients’ self-ratings of social performance contrasts with previous research that has shown that SAD patients report subjective improvements in social behavior after oxytocin administration (Guastella et al., 2009). An explanation for this discrepancy may lie in the type of social task performed (i.e., public speech versus a conversation in the current study) and potential differential effects of repeated oxytocin administration versus the single administration used in the present study.

That SAD patients, independent of oxytocin, performed worse on social behavior tasks compared to HC is in line with previous findings (Schneider and Turk, 2014). This stresses the importance of enhancing SAD patients’ social functioning again. While refraining from over-interpreting current findings, a cautious outlook on clinical implications is provided here. For instance, oxytocin could play a role as an add-on in CBT treatment (Heinrichs et al., 2009) as findings suggest that oxytocin could disrupt the negative self-perpetuating cycle in SAD. By improving social behavior, oxytocin might reduce negative responses that SAD patients elicit in others. In turn, this would diminish the negative influence that feeds social anxiety in SAD. The CBT regimen may help patients to adjust their perception of their performance. Together these changes might help to reduce patients’ negative affect in social interactions. Again, as the current findings are considered preliminary, more robust evidence is needed to support such a clinical program.

While no study comes without limitations, so does the current. First and foremost, the present study assessed the acute effects of a single oxytocin administration while single-dose administration has been criticized in the past years. It is argued that a single dose is unlikely to affect core symptomatology (Dos Santos et al., 2019). Randomized clinical trials (RCT) testing repeated administrations for a prolonged period are needed to examine oxytocin’s full potential as a social enhancer in psychiatric disorders like SAD (De Cagna et al., 2019; Dos Santos et al., 2019). The findings of the current study can serve as input for those RCTs. Second, increasing evidence shows that oxytocin has differential effect in women and men (Lieberz et al., 2020; Rilling et al., 2014). However, our sample size did not allow us to run separate analyses. Additionally, whereas the sample was large enough to detect changes in observed social behavior, it cannot be excluded that we have missed effects on other parameters. Future research will benefit from increasing the sample size to allow the testing of sex-differences and to replicate the data of the present study. Third, although effort was put into translating the natural social interaction into an experimental context, the social tasks were still artificial to a certain extent. Arguably the effect of oxytocin becomes more apparent in more in-
timate social interaction (Bartz et al., 2011). Related to social context, individual differences are also of importance (Bartz et al., 2011). It is known that some SAD patients show relatively good social performance, others exhibit severe social dysfunction (Schneider and Turk, 2014). The benefits of oxytocin might be more pronounced in SAD patient with more severe social difficulties; future studies might incorporate assessment of baseline social performance to investigate the moderating effect of this on the oxytocin’s effects.

Taken together, the findings of the present study do support the hypothesis that a single administration of intranasal oxytocin enhances observer-rated social behavior, but this seems context-dependent. No indications were found that it affects subjective experiences in SAD patients. Future studies need to determine whether moderating variables influence oxytocin effects on social behavior, including individual differences and contextual variables, to understand oxytocin treatment’s optimal therapeutic conditions. Future clinical trials in SAD might combine oxytocin treatment with performance feedback to change self-perceived performance.

Author contribution

MJ Voncken C Dijk, K Schruers, KPC Kuypers: Conceptualization; M Voncken, F Stöhr, IJM Niesten, K Schruers, KPC Kuypers: Screening and data collection; MJ Voncken, C Dijk, F Stöhr, KPC Kuypers: Data curation; MJ Voncken, IJM Niesten, F Stöhr, KPC Kuypers: Formal analysis; MJ Voncken: Funding acquisition; MJ Voncken: Investigation; MJ Voncken, C Dijk, K Schruers, KPC Kuypers: Methodology; MJ Voncken, KPC Kuypers: Project administration; MJ Voncken, F Stöhr, IJM Niesten, KPC Kuypers: Original draft; MJ Voncken, C Dijk, F Stöhr, IJM Niesten, K Schruers, KPC Kuypers: Writing - review & editing.

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Declaration of Competing Interest

All authors state to have no conflict of interest.

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