



Intranasal oxytocin enhances stress-protective effects of social support in women with negative childhood experiences during a virtual Trier Social Stress Test



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ABSTRACT

Oxytocin is considered a biological mechanism underlying stress-protective effects of positive social interactions. It is assumed to underlie the women-specific tend-and-befriend response to stress, although few studies have tested this assertion with female samples. The aim of the present study was, therefore, to test whether oxytocin enhances stress-protective effects of social support during stress in women, taking into account the moderating role of childhood adversity. The sample consisted of 180 female undergraduate students who had reported on experiences of childhood abuse and how often their mother used love withdrawal as an insensitive disciplinary strategy. Women participated in a virtual version of the Trier Social Stress Test (TSST) and were randomly assigned to receive 24 IU oxytocin or a placebo and to receive support or no support from a female friend (subgroups $N = 45$). Results showed that oxytocin reduced heart rate variability during the TSST in participants who received support, possibly indicating that oxytocin increases attention and stimulates a challenge motivational state in the presence of a friend. In addition, we found that, in the presence of a friend, oxytocin reduced state anxiety levels and cortisol levels after the TSST, but only in women with higher levels of adverse childhood experiences. Our findings may indicate that oxytocin is a neurobiological means to attain and benefit from social support under stressful circumstances, which may be particularly adaptive for women with a history of adversity. Thus, oxytocin may function as motivator for affiliative disposition during stress exposure in women with a history of childhood adversity. Results should be replicated in clinical samples.

1. Introduction

The hormone oxytocin is well-known for its role in social affiliation and stress regulation. It is released into the bloodstream by the posterior pituitary gland, for example in response to stress (Donadon et al., 2018; Pierrehumbert et al., 2012). Oxytocin administration experiments have highlighted oxytocin as an anti-stress hormone and show increases in parasympathetic control (Kubzansky et al., 2012) and attenuated anxiety and cortisol reactivity after intranasal administration, in particular when confronted with social stressors (Cardoso et al., 2013a, 2013b; Kubzansky et al., 2012; Linnen et al., 2012). For example, Heinrichs et al. (2003) showed that intranasal oxytocin administration lowers cortisol responses to stress induced by the Trier Social Stress Test. More specifically, this study showed that oxytocin enhanced the buffering effect of social support from a friend on stress

responsiveness in men, suggesting a crucial role of oxytocin as a biological mechanism underlying stress-protective effects of positive social interactions.

The majority of oxytocin administration experiments examining oxytocin's stress-protective effects have been conducted in men. However, stress-reducing effects of oxytocin may be different in women (Steinman et al., 2016). Taylor et al. (2000) theorized that oxytocin may be the neurobiological mechanism underlying the tend-and-befriend response, a women specific bio-behavioural response to stress. Specifically, women are suggested to use social coping and support seeking in response to stress, because the fight-or-flight may be maladaptive for women who provide childcare and are smaller in stature than men. Given this assumed role of oxytocin in women's specific stress responses, it is surprising that Heinrichs' study (2003) on oxytocin's enhancing effects of social support during stress has never been

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replicated in women. Although women have been greatly under-represented in oxytocin and stress research for a long time (Cardoso et al., 2014), some recent studies including both men and women point to sex differences in the effects of oxytocin on stress and social functioning. Cardoso et al. (2016) showed that, in women, oxytocin induced motivation to affiliate with an experimenter and increased feelings of being emotionally supported when disclosing negative memories. This effect was, however, absent in men, suggesting that in the presence of desired social relationships, oxytocin promotes receptiveness to social support particularly in distressed women.

Oxytocin effects may not only differ by sex (Cardoso et al., 2016; Kubzansky et al., 2012; Steinman et al., 2016). A vast amount of literature shows that intranasal oxytocin effects are shaped by childhood caregiving experiences. More specifically, multiple studies point to attenuated or hindered effects of oxytocin in individuals with adverse childhood experiences (Bakermans-Kranenburg and Van IJzendoorn, 2013). For example, Meinschmidt and Heim (2007) found that intranasal oxytocin has stress-reducing effects, as reflected by cortisol decreases, but these effects were impeded in individuals with a history of early parental separation, suggesting altered central sensitivity to the effects of oxytocin after childhood adversity. In a similar vein, we found that oxytocin reduced interpersonal distance, a measure of emotional closeness, but only in individuals without experiences of maternal disciplinary use of love withdrawal (Riem et al., in press), which is an insensitive caregiving strategy that is considered emotional maltreatment when used excessively (Euser et al., 2010). One explanation for this reduced sensitivity to oxytocin is that adversity results in reductions in oxytocin receptor expression, via epigenetic changes (Bakermans-Kranenburg and Van IJzendoorn, 2017), which may in turn lead to a dysregulated oxytocin system and an impeded response to intranasal administration.

Interestingly, while the majority of extant studies indicate that intranasal oxytocin effects are hindered in individuals with a history of childhood adversity (Bakermans-Kranenburg and Van IJzendoorn, 2013), some studies show opposite patterns, with more prosocial effects of oxytocin in individuals with a history of childhood adversity. For example, oxytocin improved emotion recognition particularly for individuals with a history of adversity (Riem et al., 2014; Schwaiger et al., 2019), possibly because these individuals generally have lower socio-cognitive functioning skills (Cicchetti et al., 2003; Font and Berger, 2015), and may therefore benefit more from oxytocin. Oxytocin is considered a self-regulatory mechanism motivating social approach or support seeking (Carter, 2014), and is released during isolation or other stressful conditions when the need for social proximity is high (Pierrehumbert et al., 2010; Taylor et al., 2006). This may be particularly important for individuals with a history of adversity who often lack supportive relationships (Horan and Widom, 2015). An interesting question is, therefore, whether oxytocin motivates support seeking behaviors in case of childhood adversity and can enhance stress-protective effects of positive social interactions in individuals with a history of adversity.

In the present study, we examine whether oxytocin enhances beneficial effects of social support during stress in women, taking into account the moderating role of childhood adversity. We examined 1) whether oxytocin and social support from a friend affect self-reported anxiety, neuroendocrine (cortisol), and cardiac (heart period (i.e., inter-beat interval (IBI)) and parasympathetic activity induced heart rate variability (RMSSD)) responses to psychosocial stress, and 2) whether effects of oxytocin are dependent on childhood adversity. Psychosocial stress was induced by means of an innovative Virtual paradigm of the Trier Social Stress Test (TSST). This virtual TSST has been shown to elicit significant acute stress responses (Fallon et al., 2016). It offers experimental advantage, such as more confederate standardization, and enables the study of oxytocin effects in an optimally controlled, but real life setting. We hypothesized that oxytocin would amplify beneficial effects of social support during stress. More specifically, we predicted

that, in particular in participants who received social support from a friend, intranasal oxytocin would lower anxiety and cortisol reactivity to stress, would increase parasympathetic control as reflected by increased RMSSD reactivity, and would reduce arousal as reflected by increased IBI reactivity. However, we predicted oxytocin effects would depend on negative childhood experiences.

2. Materials and methods

2.1. Participants

A sample of 200 female undergraduate students from Tilburg University was recruited and invited to participate in the study. Three participants cancelled participation or did not show up, and 17 participants had no data or incomplete data on primary outcomes because they were not able to participate in the lab session because of sickness ($N = 1$), because they did not bring a friend with them to the lab session ($N = 3$), and because of missing primary outcomes because of technical problems with the TSST and/or ECG equipment failure ($N = 13$), resulting in a final sample consisting of 180 participants. See supplemental material for a power analysis. The target sample was 180, but we anticipated a 10% drop-out rate (e.g., due to equipment malfunctioning) because multiple physiological measures were used. The ages ranged from 18 to 27 years old ($M = 20.15$, $SD = 1.77$). The majority of participants used hormonal contraceptives. Exclusion criteria involved drug or alcohol abuse, nasal problems, use of prescribed medication (except contraception), psychiatric and neurological disorders, cardiovascular diseases, and high blood pressure. Further, participants who were pregnant, breastfed or had children were excluded from this study. Participants were randomly assigned to four different conditions: 1) oxytocin with support of a friend ($N = 45$), 2) oxytocin alone ($N = 45$), 3) placebo with support of a friend ($N = 45$), 4) placebo alone ($N = 45$). Participants received a monetary reward or study credits for participation. Permission for this study was obtained from the Medical Ethics Committee Brabant (NL60593.028.17) and all participants gave informed consent. The study was registered in the Dutch Trial Registry (NTR6513).

2.2. Procedure

Participants were asked to complete questionnaires on childhood experiences approximately one week before a lab session. Participants who were assigned to the friend condition were asked to bring a female friend with them to the lab session. They were invited preferably in the luteal phase of their (self-reported) menstrual cycle in order to control for influences of menstrual cycle. During the luteal phase, plasma oxytocin levels are lower (Salonia et al., 2005). Women were asked about the date of their last menstruation and this information was used to schedule the lab session. Menstrual phase and hormonal contraceptives were balanced across the placebo and oxytocin group: 16.7% of participants in the oxytocin group and 12.2% of participants in the placebo group were in the follicular phase, whereas 83.3% of participants in the oxytocin group and 86.7% of participants in the placebo group were in the luteal phase. In the placebo group, 65.6% of participants used hormonal contraceptives, and in the oxytocin group, 50% of participants used hormonal contraceptives. They were instructed to abstain from alcohol during the 24 h before the start of study, and from caffeine and smoking on the data collection day.

Lab sessions were scheduled in the afternoon in the Behavioral Physiology Lab of Tilburg University (GO Lab). At the start of the lab session, participants read and signed the consent form, and started with reporting on their state anxiety levels. In addition, a saliva sample was collected to measure cortisol levels before nasal spray administration. Afterwards, participants took 6 puffs of nasal spray containing oxytocin (24 IU total) or 6 puffs of a placebo spray under supervision of the experimenter. Drug administration was double-blind. After intranasal

administration, a task measuring interpersonal distance was administered for another purpose in the overall project. Approximately 10–15 minutes after this task, ECG electrodes were attached and a resting measurement of heart rate and heart rate variability was performed during a 5-minute rest baseline measure, while watching a landscape photograph. The rest measure started approximately one hour after intranasal administration. Afterwards, a baseline state anxiety measurement was conducted and a saliva sample for cortisol analysis was collected, followed by the virtual TSST. State anxiety and cortisol were measured immediately after the virtual TSST, 30 min after speech onset, and 45 min after speech onset. At the end of the session participants were thanked for their participation and properly debriefed.

2.3. Measurements

2.3.1. The virtual trier social stress test

The experimenter instructed (see supplemental material) participants to imagine applying for an internship position through the *Second Life* platform. They were asked to prepare a 5-minute speech to convince two professors that they would be the ideal candidate for the position. After the speech, an additional math task would provide information about the applicant's working memory capacity. Participants prepared their speech during a 5-minute preparatory period.

The TSST took place in a large auditorium with a stage (see Fig. 1). This virtual space has also been used by Fallon et al. (2016). The experimenter told the participant that (s)he would briefly contact the professors, to verify that they had logged in to *Second Life* successfully. Afterwards, the experimenter moved to the observation room and announced through an intercom that the professors would be in contact shortly. Participants remained seated throughout the entire procedure.

The experimenter controlled the gestures and messages of the two virtual professors in *Second Life*. During the paradigm, we presented pre-recorded audio messages that followed the TSST protocol of Kupper

et al. (submitted) using the Sounds function in *Second Life*. A total number of 36 messages were recorded to have a variety of options in case participants behaved unexpectedly (e.g., 'I cannot comment on that'). The first recordings included a brief introduction of the female professor ('Hi, can you hear me?', 'Ok, we will begin the task shortly'). The male professor then instructed participants to start their speech. The following prompts were presented when participants were silent for 3 s: female: 'You still have some time, please continue', male: 'You still have time, go on', male: 'Can you tell us something about your strengths?', female: 'How would other students describe your social skills?', and male: 'Can you tell me something about your weaknesses?'. In line with Fallon et al. (2016), the virtual professors used the gestures 'bored' twice and 'shrug' once, at 1, 3 and 4 min into the speech respectively.

After 5 min, the professors instructed the participant to start with the math task, which entailed subtracting 13 from a number, and then repeatedly subtracting 13 from the remainder during a 5-minute period. A new starting number was given upon each mistake (e.g., 'That's incorrect, please start again, and this time start from 1072'). Post virtual TSST state anxiety levels were measured and cortisol saliva samples were collected, followed by the debriefing procedure. During the debriefing procedure, participants were asked whether they believed the experimental set-up. Of all participants, 33.7% believed the entire experimental set-up, 36.6% reported doubts (e.g. questioned whether she was talking to real people, whether the audience members were actual professors), and 29.7% did not believe the set-up. Participants were additionally asked to indicate how certain they were that they were talking to 'real' people during the task (0 to 100%). Mean certainty was 47.46%. Certainty and ratio believers/doubts/non-believers did not differ between the four groups ($ps > .46$). Data on believing in the set-up was missing for eight participants due to procedural mistakes. There was no significant effect of believing in the set-up on state anxiety ($F(1, 165) = 0.85, p = .36$) or cortisol ($F(1, 165) = 2.36, p = .13$). However, there was an effect on RMSSD ($F(1, 165) = 6.19, p = .01$). Duration of the entire TSST procedure was approximately 15–20 minutes.

2.3.2. Social support

Participants who brought a friend to the lab session received support during the preparatory period. The friend was instructed to help the participant with the preparation: "You are going to help your friend with the preparation of the presentation as best as you can." The friend was also instructed to provide emotional support: "You should also offer emotional support, for example by wishing her good luck." (see supplemental material for detailed instructions). The friend was asked to leave the room after the preparatory period. Immediately after the math task, the friend was instructed to return to the participant in the lab room and was allowed to talk to the participant. After 2 min, the friend was again asked to leave the lab room.

2.3.3. Childhood experiences

Childhood rearing experiences were measured with two questionnaires in order to increase accurateness of the early rearing environment. First, we assessed an insensitive disciplinary parenting strategy; maternal use of love withdrawal. This strategy involves withholding love and affection when a child misbehaves. Maternal use of love withdrawal was measured by an 11-item questionnaire which combines seven items of the Withdrawal of Relations subscale of the Children's Report of Parental Behavior Inventory (Beyers and Goossens, 2003) and four items from the Parental Discipline Questionnaire (Hoffman and Saltzstein, 1967). Participants rated how well each statement described their mother (e.g., "My mother is a person who, when I disappoint her, tells me how sad I make her") on a 5-point scale. This 11-item questionnaire has been used in previous studies showing that love withdrawal moderates oxytocin effects (Huffmeijer et al., 2012; Riem et al., 2013a, 2013b). Internal consistency was good



Fig. 1. The virtual TSST paradigm.

(Cronbach's $\alpha = .83$). Mean love withdrawal was 2.28 ($SD = 0.80$). There were no significant group differences in mean love withdrawal ($F(1,176) = .51, p = .48$).

In addition, childhood adversity was measured with the Childhood Trauma Questionnaire Short Form (CTQ-SF, Bernstein et al., 2003). CTQ-SF is a measure of self-reported experiences of childhood abuse. Twenty-eight items were used to assess experiences of physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect. Each item (e.g., "During my childhood I felt hated by family") was rated on a 5-point Likert scale ranging from never true to very often true. Internal consistency was good (Cronbach's $\alpha = .73$). The sum total score was 33.34 ($SD = 7.67$). A log transformation was applied to approach a normal distribution because the distribution was skewed (see Fig. S1). There were no significant group differences in mean childhood trauma ($F(1,176) = .36, p = .55$). See supplemental material for the CTQ and maternal love withdrawal scores for participants in the four groups.

2.3.4. State anxiety

State anxiety was measured at 5 time points during the lab session: before intranasal administration, before the virtual TSST (baseline), right after the math task, and 30 and 45 min after speech onset. We used the Spielberger Trait-State Anxiety Inventory, State version (STAI), which includes 6 items that are scored on a 5-point Likert scale (Marteau and Bekker, 1992). At each measurement occasion, participants were asked to indicate how they were feeling at that moment. There were no significant group differences (oxytocin-friend, oxytocin-alone, placebo-friend, placebo-alone) in mean state anxiety before intranasal administration ($F(1,174) = 1.51, p = 0.22$).

2.3.5. Perceived support

Perceived support received during the preparation phase was measured with the Social Support List (subscale emotional support, 12 items, Cronbach's $\alpha = 0.84$ (Van Sonderen, 2012)), 45 min after speech onset. Participants in the friend condition were asked to evaluate the support received by their friend during the experimental procedure.

2.3.6. Heart rate variability

In the virtual TSST study, heart rate variability was derived from continuous ECG recordings using the Biopac MP150 system with ECG100C module and three hydrogel ECG electrodes. Data were recorded at a sampling frequency of 2000 Hz. Data processing was conducted in AcqKnowledge, version 4.4. Human ECG complex boundaries were identified automatically and artefacts and missed QRS peaks were identified and corrected manually. We calculated period averages for heart period (IBI) and the average root mean square of successive differences (RMSSD), a measure of cardiac parasympathetic activation. These measures were collected for each phase of the virtual TSST, that is, during baseline, preparation, speech, and the math task. ECG was not recorded during the recovery period. RMSSD was log transformed because the distribution was skewed. ECG data of thirteen participants was missing due to poor data quality or premature ventricular contractions.

2.3.7. Cortisol

Five saliva samples for cortisol analysis were collected: before intranasal administration, before the virtual TSST (baseline), right after the math task, and 30 and 45 min after speech onset. The saliva samples collected with cortisol salivettes (Sarstedt, Rommelsdorf, Germany) and were stored at -20°C until analysis. After thawing, saliva samples were centrifuged at 2000 g for 10 min, which resulted in a clear supernatant of low viscosity. 100ul of saliva were used for duplicate analysis. Cortisol levels were determined employing a competitive solid phase time-resolved fluorescence immunoassay with fluorometric end point detection (DELFI). Mean intra-assay coefficient of variation was 4.3%. Cortisol levels were ln transformed because of a skewed

distribution. Cortisol levels before oxytocin/placebo administration did not differ between the four groups ($F(1, 174) = .35, p = .55$). According to the criteria of a 1.5-nM rise (Miller et al., 2013), we found that 66.7% of participants in the placebo-alone group were classified as responders. This is somewhat lower than the response elicited by a real TSST (e.g. see Shibani et al., 2016) but similar to a previously reported ratio of responders (62%) in a study using the same virtual TSST paradigm (Fallon et al., 2016). The number of responders was lower in the oxytocin and friend conditions (placebo – friend: 11.1%, oxytocin-alone: 20.0%, oxytocin-friend: 13.3%).

2.4. Statistical analyses

First, as a manipulation check, we performed a repeated measures analysis of variance with participants in the placebo alone condition only in order to examine whether the virtual TSST was effective in elevating cortisol and anxiety. Time (baseline, immediately post virtual TSST, 30 min post speech onset, and 45 min post speech onset) was included as a within-subject factor. Data on effects of social support in the placebo group will be presented elsewhere (Kunst et al., in preparation). In order to examine effects of oxytocin on self-reported and neuroendocrine stress reactivity, repeated measures analyses of variance (RM-ANCOVAs) were conducted with state anxiety and cortisol as dependent variables, treatment group (oxytocin/placebo) as between subject factor, and time (baseline, immediately post virtual TSST, 30 min post speech onset, and 45 min post speech onset) as a within-subject factor. In addition, RM-ANCOVAs were conducted with heart rate variability and IBI as dependent variables, treatment group (oxytocin/placebo) as a between subject factor, and time (baseline, preparation, speech, math) as a within-subject factor. Furthermore, an ANCOVA was conducted to test the effect of oxytocin on perceived support received from their friend. Hormonal contraceptives, and menstrual phase were included as covariates in all analyses.

In a second step, childhood trauma sum scores and maternal use of love withdrawal scores (both continuous) were entered separately as additional covariates in the analyses with anxiety, perceived support, RMSSD, and cortisol. Previous research points to differential effects of oxytocin on stress reactivity versus recovery (recovery-boosting effects rather than reactivity-buffering) (Engert et al., 2017). We therefore examined influences of childhood experiences on reactivity to stress (post virtual TSST measurement versus baseline) and recovery separately. Planned contrasts were used to interpret interactions. Greenhouse-Geisser correction was used when Mauchly's test indicates that the assumption of sphericity was violated. The Benjamini Hochberg procedure (McDonald, 2014) was applied to p values resulting from main effects in the analyses with autonomic arousal (2 repeated tests: IBI and HRV) in order to correct significance levels for Type I error.

3. Results

3.1. Stress induction

There was a significant effect of time on anxiety ($F(2.24, 98.48) = 62.19, p < .001$, partial $\eta^2 = .59$), cortisol ($F(2.31, 101.75) = 45.19, p < .001$, partial $\eta^2 = .51$), IBI ($F(2.35, 103.19) = 76.14, p < .001$, partial $\eta^2 = .64$), and RMSSD ($F(2.02, 88.89) = 14.97, p < .001$, partial $\eta^2 = .25$), indicating that the virtual TSST effectively induced stress.

3.2. Anxiety

The RM-ANCOVA with state anxiety as dependent variable showed a significant effect of time ($F(2.43, 422.27) = 15.38, p < .001$, partial $\eta^2 = .08$). In addition, we found significant interactions between time and social support ($F(2.43, 422.27) = 5.07, p = .004$, partial $\eta^2 = .03$) and between time and treatment ($F(2.43, 422.27) = 3.02, p = .040$,

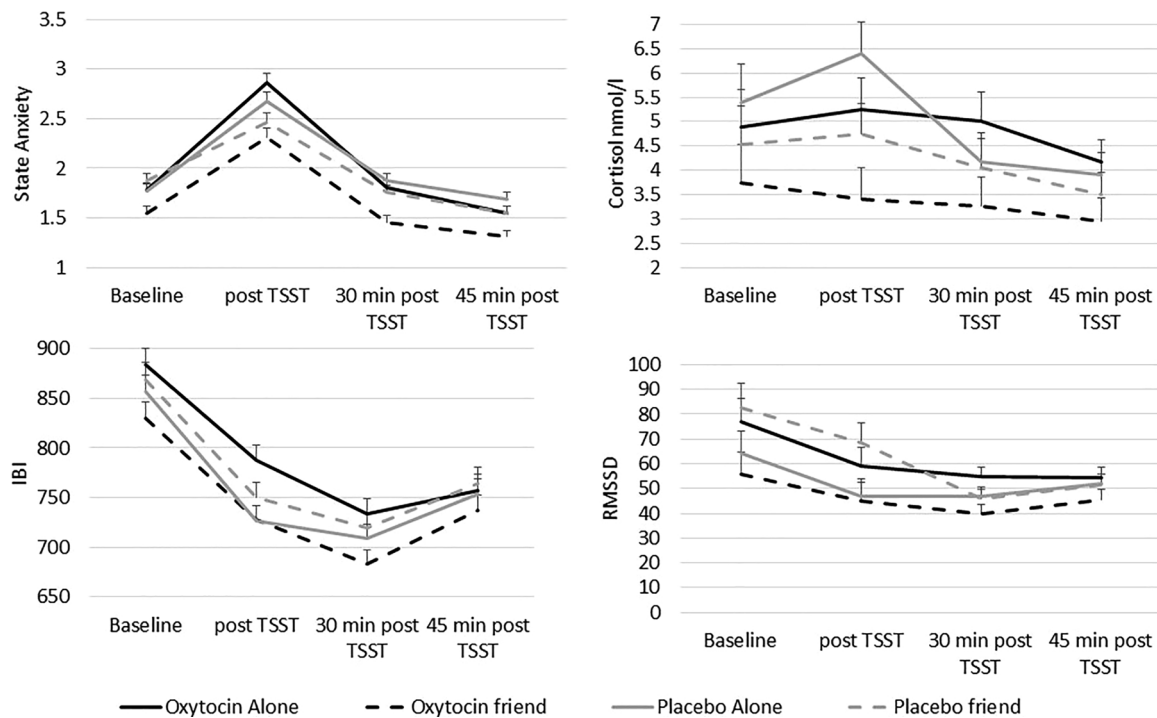


Fig. 2. Mean state (SE) anxiety and raw cortisol levels at baseline, immediately after virtual TSST, and 30 min, and 45 min after speech onset, and RMSSD and IBI at baseline, during the preparation, speech, and math part of the virtual TSST.

partial $\eta^2 = .02$). Within-subject contrasts showed that participants in the oxytocin condition showed a larger increase in anxiety from baseline to immediately after the virtual TSST ($F(1, 174) = 3.85, p = .051$, partial $\eta^2 = .02$; Baseline: oxytocin $M = 1.66 \pm 0.46$, placebo $M = 1.83 \pm 0.48$, Post virtual TSST: oxytocin $M = 2.59 \pm 0.71$, placebo: $M = 2.57 \pm 0.60$). Fig. 2 shows that in particular participants in the oxytocin-alone condition showed a strong increase from pre to post virtual TSST. However, there was not a significant three-way interaction between treatment, social support, and time ($F(2.43, 422.27) = 1.02, p = .371$, partial $\eta^2 = .01$). Furthermore, there was a significant treatment by social support interaction ($F(1, 174) = 5.10, p = .025$, partial $\eta^2 = .03$). Fig. 2 shows that state anxiety levels were lowest for the group of participants who received oxytocin and who brought a friend, regardless of time. Planned contrasts with averaged anxiety showed that oxytocin reduced anxiety relative to placebo in the friend condition ($t(176) = -3.22, p = .002$), but there was no effect in the alone condition ($t(176) = 0.02, p = .981$). Thus, oxytocin overall enhanced anxiety-reducing effects in the presence of friend. It should be noted that the interaction effect between treatment group and support condition was already present at baseline (before virtual TSST but after intranasal administration) ($F(1, 174) = 6.48, p = .012$, partial $\eta^2 = .04$).

3.3. Perceived Support

There was a significant effect of oxytocin on perceived support received during the experimental procedure. Participants in the oxytocin group ($M = 3.05, SD = 0.61$) reported higher levels of perceived support than the participants in the placebo condition ($M = 2.75, SD = 0.58$) ($F(1, 85) = 4.26, p = .042$, partial $\eta^2 = .05$).

3.4. Autonomic arousal

The RM-ANCOVA with RMSSD as dependent variable did not show a significant effect of time ($F(2.18, 351.41) = 0.68, p = .564$, partial $\eta^2 = .00$) and no significant interaction between time and treatment (F

(2.18, 351.41) = 0.48, $p = .637$, partial $\eta^2 = .00$) or time and social support ($F(2.18, 351.41) = 2.21, p = .107$, partial $\eta^2 = .01$). However, we found a significant interaction between treatment and social support ($F(1, 161) = 3.98, p = .048$, partial $\eta^2 = .02$). This interaction was, however, only marginally significant after controlling for the effect of believing in the experimental set-up ($F(1, 153) = 3.30, p = .071$). Fig. 2 shows that RMSSD was lowest for participants who received oxytocin and brought a friend, regardless of time. Planned contrasts with averaged RMSSD showed that oxytocin tended to reduce RMSSD relative to placebo in the friend condition ($t(163) = -1.84, p = .068$), but there was no effect in the alone condition ($t(163) = -0.89, p = .371$). There was a marginally significant three-way interaction between treatment, social support, and time ($F(2.18, 351.41) = 2.51, p = .08$, partial $\eta^2 = .02$), although within-subject contrasts did not show a significantly different reactivity in the four groups during preparation, speech, and math compared to baseline ($ps > .10$). Analyses with IBI showed a significant effect of time ($F(2.32, 372.90) = 6.12, p < .001$, partial $\eta^2 = .04$), which remained significant after BH correction. There was a significant interaction between treatment and social support ($F(1, 161) = 4.75, p = .031$, partial $\eta^2 = .03$) (see Fig. 3), but no significant three-way interaction between treatment, social support, and time ($F(2.32, 372.90) = 1.82, p = .156$, partial $\eta^2 = .01$).

3.5. Cortisol

The RM-ANCOVA with cortisol as dependent variable did not show a significant effect of time ($F(2.27, 395.27) = 0.29, p = .779$, partial $\eta^2 = .00$). However, the interactions between time and treatment ($F(2.27, 395.27) = 10.51, p < .001$, partial $\eta^2 = .06$) and time and social support ($F(2.27, 395.27) = 9.61, p < .001$, partial $\eta^2 = .05$) were significant, as well as the interaction between treatment and social support ($F(1, 174) = 4.66, p = .032$, partial $\eta^2 = .03$). Fig. 2 shows that cortisol levels were lowest for participants who received oxytocin and brought a friend, regardless of time. Planned contrasts with averaged cortisol showed that oxytocin reduced cortisol relative to placebo in the friend condition ($t(176) = -2.45, p = .015$), but there was no

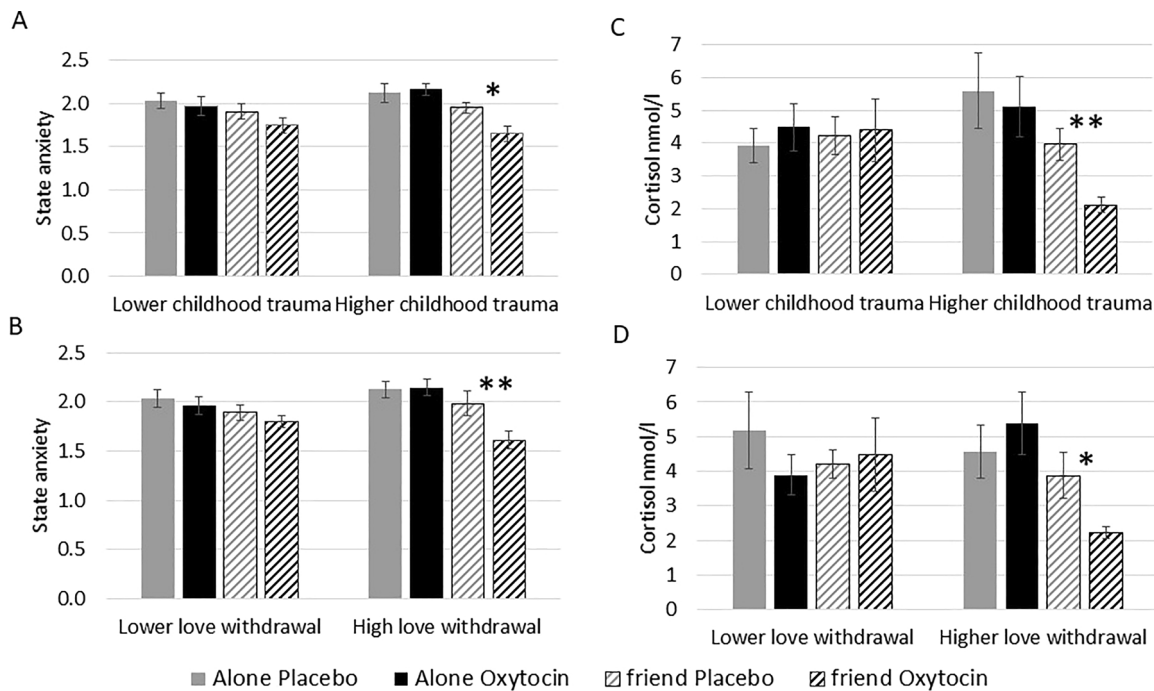


Fig. 3. Mean (SE) state anxiety and cortisol levels (log transformed) after virtual TSST for participants in the alone-placebo, alone-oxytocin, friend-placebo, friend-oxytocin condition, stratified for individuals with higher or lower levels of childhood trauma. Subsamples with lower versus higher childhood trauma and love withdrawal ranged from $N = 19$ to $N = 26$ and partly overlapped because these experiences were correlated ($r = .36$, $p < .001$). * $p < .05$, ** $p < .01$.

effect in the alone condition ($t(176) = -1.22$, $p = .224$). The three-way interaction between time, support, and treatment was not significant ($F(2.27, 395.27) = 2.15$, $p = .110$, partial $\eta^2 = .01$).

3.6. Childhood trauma

The RM-ANOVA with state anxiety was repeated with childhood trauma sum score as an additional covariate. We found a significant three-way interaction between childhood trauma, social support, and treatment ($F(1, 171) = 4.71$, $p = .031$, partial $\eta^2 = .03$). Childhood trauma was dichotomized using a median split (median = 31) in order to interpret the interaction. Anxiety levels during recovery (30 min post speech onset and 45 min post speech onset) were averaged because there were no significant interactions with time ($ps > .12$). Fig. 3 shows mean anxiety levels during recovery for participants in the oxytocin-friend, oxytocin-alone, placebo-friend, and placebo-alone condition, stratified for individuals with lower or higher levels of childhood trauma. Planned contrasts showed that oxytocin significantly reduced state anxiety levels during recovery relative to placebo only for participants with higher levels of childhood trauma who brought a friend ($t(171) = 3.07$, $p = .002$). Thus, oxytocin enhanced stress-reducing effects of social support and this effect tended to be more pronounced for participants with more negative childhood experiences. Planned contrasts with anxiety reactivity level (post virtual TSST anxiety level – baseline anxiety) did not show any significant group differences ($ps > .315$).

The RM-ANCOVA with RMSSD and childhood trauma as an additional covariate did not show a significant three-way interaction between childhood trauma, social support, and treatment ($F(1, 158) = 2.23$, $p = .137$, partial $\eta^2 = .01$). Additionally, there was no significant interaction between childhood trauma and treatment in the analysis with perceived support ($F(1, 83) = 0.59$, $p = .444$, partial $\eta^2 = .01$).

The RM-ANCOVA with cortisol as dependent variable and childhood trauma as an additional covariate showed a significant three-way interaction between childhood trauma, social support, and treatment ($F(1, 171) = 5.18$, $p = .024$, partial $\eta^2 = .03$). Planned contrasts with

cortisol reactivity levels did not show significant oxytocin effects ($ps > .412$). However, planned contrasts with averaged cortisol levels during recovery showed that oxytocin reduced cortisol only for participants with higher levels of childhood trauma who brought a friend ($t(171) = 3.28$, $p = .001$).

3.7. Maternal use of love withdrawal

The RM-ANOVA with state anxiety was repeated with maternal use of love withdrawal as an additional covariate. We found a significant three-way interaction between love withdrawal, social support, and treatment ($F(1, 171) = 5.22$, $p = .024$, partial $\eta^2 = .03$). Again, there were no interactions with time ($ps > .22$). Love withdrawal was dichotomized using a median split (median = 2.18) in order to interpret the interaction. Planned contrasts showed that oxytocin (relative to placebo) significantly reduced mean state anxiety levels during recovery only for participants with higher levels of love withdrawal who brought a friend ($t(171) = 3.40$, $p = .001$; see Fig. 3). Thus, oxytocin enhanced stress-reducing effects of social support and this effect was more pronounced for participants with more experiences of maternal love withdrawal. Again, planned contrasts with anxiety reactivity levels (post virtual TSST anxiety level – baseline anxiety) did not show any significant group differences ($ps > .315$).

The repeated measures ANOVA with RMSSD and love withdrawal as an additional covariate did not show a significant three-way interaction between love withdrawal, social support, and treatment ($F(1, 158) = 2.44$, $p = .120$, partial $\eta^2 = .02$). No interaction was found between treatment and love withdrawal in the analysis with perceived support ($F(1, 83) = 2.51$, $p = .117$, partial $\eta^2 = .03$).

For cortisol, a three-way interaction between maternal use of love withdrawal, social support, and treatment was found ($F(1, 171) = 5.66$, $p = .019$, partial $\eta^2 = .32$). Planned contrasts with cortisol reactivity levels did not show significant oxytocin effects ($ps > .692$). However, planned contrasts with averaged cortisol levels during recovery showed that oxytocin reduced cortisol relative to placebo only for participants with higher levels of love withdrawal who brought a friend ($t(171) = 2.38$, $p = .019$, see Fig. 3)

4. Discussion

The present study aimed to investigate whether intranasal oxytocin enhances the effect of social support during stress in women, taking into account the role of negative childhood experiences. Psychosocial stress was induced by means of an innovative virtual paradigm of the Trier Social Stress Test (Fallon et al., 2016), enabling the study of oxytocin in a real life but optimally controlled setting. We found that women who were administered oxytocin and received support from a friend showed the lowest anxiety and cortisol levels before and after the virtual TSST, indicating that oxytocin enhanced stress-reducing effects of social support. Moreover, participants in the oxytocin condition reported higher levels of perceived support during the virtual TSST compared to participants in the placebo condition. Our findings add to the previously reported role of oxytocin in stress-protective effects of positive social interactions in men (Heinrichs et al., 2003) and demonstrate that, consistent with the tend-and-befriend hypothesis, similar results can be found in women. Our findings are also in line with research showing that oxytocin increases affiliative disposition after stress exposure in women (Cardoso et al., 2013a, 2013b) and point to oxytocin as a neurobiological means to attain and benefit from social support under stressful circumstances.

Interestingly, we found that stress-protective effects of oxytocin were more pronounced in women with negative childhood experiences. More specifically, oxytocin boosted recovery, as indicated by lower cortisol and anxiety levels after the virtual TSST, but only in participants with adverse caregiving experiences who received support from a friend. This seems contradictory to several previous studies showing that intranasal oxytocin effects on social behavior are attenuated in individuals with experiences of adversity (Bakermans-Kranenburg et al., 2012; Huffmeijer et al., 2012; Riem et al., 2013a, 2013b). In addition, it contrasts with a study showing attenuated cortisol levels reductions after oxytocin administration in a small sample of men with a history of parental separation (Meinlschmidt and Heim, 2007). Endogenous oxytocin has also been shown to be affected by adversity, although findings are paradoxical with reports indicating either reduced central oxytocin (Heim et al., 2009), or comparatively higher oxytocin levels in individuals with adverse childhood experiences (Bhandari et al., 2014; Pierrehumbert et al., 2010). Although multiple studies point to oxytocinergic dysregulations after childhood adversity, it is still unclear how such changes emerge and the effect may be sex-specific. For example, Seltzer et al. (2014) showed that girls with histories of physical abuse have higher levels of urinary oxytocin and lower levels of salivary cortisol following psychosocial stress induced by the TSST compared with controls, whereas maltreated boys did not show a differential neuroendocrine response. The authors reason that this pattern of blunted cortisol and high oxytocin responsivity may reflect a proximate mechanism through which social motivation takes place. Oxytocin may be a critical neurobiological means to attain social support under stressful circumstances and may stimulate females in an adverse rearing environment to seek out alternative forms of social support outside the family. An interesting hypothesis is, therefore, that oxytocinergic changes in individuals with adverse experiences may reflect an adaptive phenotypic plasticity rather than a neurobiological dysregulation (Seltzer et al., 2014).

Early adverse experiences may not only shape the plasticity and responsiveness of the oxytocin system. A recent study showed that childhood adversity may also shape oxytocin's function. Perry-Paldi et al. (2019) found that oxytocin enhanced affiliation tendencies among individuals with a history of adversity to the point of overlooking other people's flaws. More specifically, in individuals without childhood adversity, endogenous oxytocin levels were positively related to sensitivity to detect social threats, whereas in individuals with childhood adversity, oxytocin levels were linked to a lower sensitivity to detect social threats. This indicates that oxytocin promotes non-selective proximity seeking to others after childhood adversity, possibly because

under conditions of stress, the need for proximity to others may override a tendency for interpersonal selectivity (Perry-Paldi et al., 2019). Early adverse experiences may therefore shape the core function of oxytocin in an evolutionary predictable way, for example through epigenetic changes and altering the expression of genes regulating the oxytocinergic system (Carter, 2014; Toepfer et al., 2017).

Contrary to our expectations, we found that oxytocin reduced overall levels of RMSSD and IBI in participants who brought a friend. Thus, reflecting parasympathetic withdrawal and increased arousal respectively. Reactivity to stress remained unaffected. Our results are in congruence with a previous study in patients with chronic pain indeed showing decreases in HRV during mild mental stress after intranasal oxytocin (Tracy et al., 2018). As for an explanation, an enhanced attentional state during the experiment may explain reduced parasympathetic tone (Luft et al., 2009). Whereas research points to HRV-reducing effects of oxytocin during mild stress, other studies have shown that it increases HRV reactivity to more severe stress, indicating that the direction of the effect may depend on the level of distress. For example, Kubzansky et al. (2012) showed that oxytocin increased HRV reactivity to social stress induced by the in vivo TSST. Although the virtual procedure of the TSST that was used in the current study is effective in eliciting a physiological acute stress response (Fallon et al., 2016), the response is less strong compared to an in vivo TSST (Fallon et al., in preparation). Moreover, participants in the current study were in a lower state of distress due to the stress-protective presence of their friend. The general HRV-lowering effects of oxytocin in our study may therefore reflect enhanced vigilance and attention devoted to the task, consistent with the previously proposed Social Salience Hypothesis of oxytocin (Shamay-Tsoory and Abu-Akel, 2016). It may also indicate that oxytocin stimulates a challenge motivational state in the presence of a friend.

Interestingly, oxytocin seemed to enhance anxiety-reducing effects of the presence of friend at baseline, that is, before the start of the virtual TSST. This is consistent with a previous study showing that social support increased overall HRV levels in individuals with a specific genetic variant of the oxytocin receptor even before psychosocial stress was induced by the TSST (Kanthak et al., 2016). Hence, stress-protective effects of oxytocin seem centrally mediated and may not show specificity to situations of threat. This finding may be explained from Social Baseline Theory, which suggests that proximity to social resources reduces the predicted cost of the environment through load sharing (Coan and Sbarra, 2015). For example, it has been shown that the brain is more threat vigilant when alone, even in the absence of external stimuli (Zhang et al., 2014), but looks more 'at rest' when social resources are available, possibly indicating that proximity to a familiar other represents a true 'baseline' state (Coan and Sbarra, 2015). Future studies should examine whether oxytocin plays a role in this social baseline state. For example, oxytocin may enhance the salience of the presence of a close other and, as a result, may strengthen feelings of security, even in the absence of external stimuli signalling potential threat.

Another unexpected finding was that oxytocin tended to result in a greater increase in state anxiety from pre to post virtual TSST. This effect seemed to be driven by a stronger increase in anxiety reported by participants who were given oxytocin in the absence of support from a friend (see Fig. 2). This finding is in line with research showing paradoxical oxytocin effects, with beneficial effects in safe and supportive settings, but defensive responding and anxiety-enhancing effects in the context of threat (De Dreu, 2012; Grillon et al., 2012).

It should be noted that a growing number of studies show inconsistent findings with respect to the moderating influence of caregiving experiences on the effects of oxytocin. Beneficial oxytocin effects on prosocial behaviour seem attenuated (Bakermans-Kranenburg et al., 2012; Meinlschmidt and Heim, 2007; Riem, Bakermans-Kranenburg, et al., 2013; Riem et al., 2013b), but at the same time, it increases emotion recognition in individuals with a history of adversity (Riem

et al., 2014; Schwaiger et al., 2019). Perhaps, early caregiving experiences shape both the sensitivity to and the core function of oxytocin, leading to either attenuated or more pronounced intranasal oxytocin effects, depending on the outcome that is at stake. Moreover, oxytocinergic system changes after adversity may be sex-specific (Seltzer et al., 2014). Future studies with large samples sizes are, therefore, needed to clarify under which conditions and for whom intranasal oxytocin effects are preserved, and which neurobiological mechanism may underlie reduced sensitivity to intranasal oxytocin after adversity (e.g. reduced receptor expression (Carter, 2014)). Furthermore, future research should examine the role of dosage as there is some evidence suggesting that lower dosages may be more effective in healthy (Cardoso et al., 2013a) and clinical samples (Quintana et al., 2017), and possibly also in individuals with a history of adversity. Intranasal oxytocin has been shown to enter the central nervous system and results in elevated central levels of oxytocin (Lee et al., 2018; Striepens et al., 2013). However, at present, it is generally acknowledged that we do not know how much intranasal oxytocin must reach the brain for a behavioral effect. With respect to dosage, it has been suggested that 'less is more' (Bakermans-Kranenburg and Van IJzendoorn, 2013; Quintana et al., 2017) as oxytocin may partially occupy vasopressin receptors at higher doses (Cardoso et al., 2013a, 2013b), thereby resulting in reduced effectiveness. It should be noted that previous studies on the role of dosage were conducted with male samples and it is still elusive whether dosage also matters for female samples.

Our findings also have clinical implications. A meta-analysis showed that intranasal oxytocin resulted in a greater dampening of the cortisol response to laboratory induced stress in samples characterized by stress-related psychiatric illness relative to studies of healthy participants (Cardoso et al., 2014). This highlights a role and a potential therapeutic promise for oxytocin in HPA dysfunction associated with stress-related psychopathology. However, other meta-analytic evidence suggests that intranasal oxytocin effects seem less effective in individuals with psychopathology rooted in adverse childhood experiences (Bakermans-Kranenburg and Van IJzendoorn, 2013). Future clinical studies examining oxytocin's therapeutic promise should therefore take into account the role of childhood trauma.

A few limitations should be noted. First, we included only female participants. Our study indicates that oxytocin enhances beneficial effects of social support, quite similar to the male sample in the study by Heinrichs et al. (2003). However, future studies should include both sexes in order to test whether oxytocin indeed stimulates tend-and-befriend behaviors similarly in men and women. Second, the use of a between-subject design implies the risk of pre-existing differences between the oxytocin and placebo group. However, randomization reduced this risk and we did not find group differences in childhood experiences, or in cortisol and state anxiety levels before intranasal administration. In addition, our sample consisted of female undergraduate students with only mild experiences of maltreatment. Results cannot be generalized to male samples, more diverse female samples or clinical samples with more severe maltreatment. Moreover, effect sizes were small. A meta-analysis showed that oxytocin effects on cortisol levels are more robust in clinical samples (Cardoso et al., 2014), possibly because of higher anxiety levels at baseline. Replication with clinical samples would therefore be an interesting direction for future studies. Furthermore, childhood experiences were measured with retrospective self-report questionnaires. Although we used two questionnaires in order to accurately assess the quality of the early rearing environment, interviews may yield more valid data. A recent meta-analysis showed poor agreement between retrospective and prospective measures of childhood trauma (Baldwin et al., 2019). Longitudinal studies are therefore needed in order to examine whether childhood experiences indeed causally shape the responsiveness and function of the oxytocin system.

To conclude, the present study shows that intranasal oxytocin enhances the stress-protective effect of social support during psychosocial

stress. Our findings point to oxytocin as a neurobiological means to attain social support under stressful circumstances, particularly in women with negative childhood experiences. Oxytocin may be a proximate mechanism through which social motivation takes place and, reasoning from an evolutionary perspective, this may be particularly adaptive for women with a history of adversity for whom the perceived need for proximity is high. Thus, oxytocin may function as a motivator for affiliative disposition during stress exposure in women with a history of childhood adversity. Future research should examine whether oxytocinergic system changes in the context of adversity indeed reflect an evolutionary adaptive plasticity rather than a maladaptive neurobiological dysregulation.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.psyneuen.2019.104482>.

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