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Research paper

Intranasal oxytocin and the stress-buffering effects of social support during experimentally induced pain: The role of attachment security

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ABSTRACT

Background: This study examined whether intranasal oxytocin enhances the stress-buffering effects of social support during experimentally induced pain, taking into account the role of individual differences in attachment security.

Methods: Female participants (N = 193) were randomly assigned to oxytocin (24 IU intranasal) or placebo and to receive support or no support from a friend (2 × 2 factorial design with repeated measures)). Participants underwent the Cold Pressor Task (CPT) and were monitored for heart rate variability (HRV: RMSSD) and heart rate and reported pain levels. The Experiences in Close Relationships Questionnaire was used to measure attachment.

Results: Oxytocin reduced RMSSD (p = 0.003, partial η^2 = 0.03) and increased heart rate (p = 0.039, partial η^2 = 0.03) in individuals who received support, possibly reflecting an enhanced attentional state. Oxytocin did not enhance beneficial effects of social support on perceived pain, but increased pain intensity in avoidantly attached individuals who were supported by a friend (p = 0.009, partial η^2 = 0.06).

Limitations: Only female participants were examined. Future studies are needed to determine sex differences in how oxytocin shapes stress-buffering effects of support.

Conclusions: Oxytocin may enhance the salience of social proximity and may be a mechanism underlying previously reported social influences on cardiovascular and mental health. However, oxytocin effects depend on interpersonal insecurities and may trigger discomfort in avoidantly attached individuals. Caution about oxytocin's therapeutic promise is warranted.

1. Introduction

High-quality social relationships are associated with healthier, happier, and longer lives and serve important psychological functions across the lifespan (Fiori et al., 2006; Holt-Lunstad et al., 2010). Research indicates that individuals with a lack of a support network have higher mortality rates, especially from cardiovascular and infectious diseases (Barth et al., 2010), possibly because social support lowers reactivity to stress and promotes more adaptive immune system functioning (Uchino et al., 1996; Uchino, 2006; Kiecolt-Glaser et al., 2010). Social isolation even rivals the effects of well-established health risk factors, such as obesity and physical inactivity (Holt-Lunstad et al., 2010). In addition, social support has analgesic effects and reduces pain intensity ratings (Brown et al., 2003). However, the mechanisms by which social support influences these health-related outcomes are still unclear.

One biological pathway that potentially underlies the link between social support and health is oxytocin. The hormone oxytocin is well-known for its trust-enhancing effects and its role in social behavior (Baumgartner et al., 2008; Bartz, 2016; Shamay-Tsoory and Abu-Akel, 2016), although the effects are not always straightforward (e.g. see Shamay-Tsoory et al., 2009). In addition to the role in social affiliation, oxytocin has anxiolytic properties and is released from the pituitary gland in response to stress, which may in turn stimulate the tendency to seek support from others in conditions of adversity such as threat, high demand or pain (Cardoso et al., 2013; Cardoso et al., 2014). For example, intranasal administration of oxytocin enhances the buffering effects of social support and reduces cortisol and anxiety when participants receive support from a friend during experimentally induced psychosocial stress (Heinrichs et al., 2003; Riem et al., 2020). In

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line with Taylor's tend-and-befriend theory (Taylor, 2006), these findings point to oxytocin as a neurobiological means to attain social support and to establish comforting relationships under stressful circumstances.

Oxytocin's enhancing effects on social support have also been examined in the context of physical stress. More specifically, Kreuder et al. (2019) showed that intranasal oxytocin modulates the pain-relieving effect of social support in romantic couples, possibly by increasing trust toward close others. Moreover, oxytocin may also have analgesic properties (Louvel et al., 1996; Rash et al., 2014; Zunhammer et al., 2016, but see Kessner et al., 2013; Mameli et al., 2014; Tracy et al., 2017; Skvortsova et al., 2018) and affects autonomic nervous system (ANS) responses to aversive stimuli such as psychological or physical stressors (Kubansky et al., 2012; Tracy et al., 2018). Acute experimentally induced pain results in reduced parasympathetic activity (Koenig et al., 2014), but intranasal oxytocin administration attenuates autonomic response to stressors, including a flattened parasympathetic withdrawal and lower increases in sympathetic activation in response to stress (Kubansky et al., 2012). Notably, oxytocin effects on ANS responses have also been found during rest in the absence of external stimuli (Kemp et al., 2012; Schoormans et al., 2020). Together, findings point to oxytocin as a mechanism underlying previously reported social influences on psychophysiological measures relevant to cardiovascular and mental health (Norman et al., 2011).

Despite the beneficial effects of social relationships on health outcomes and the buffering effects on the autonomic nervous system response to stress and pain, support from others is not a panacea. Rather, effects of support depend on the type and quality of the relationship and the perceived quality of the support (Krahe et al., 2013). In particular, adult attachment style has been shown to be an important factor moderating the effects of support (Girme et al., 2015). Attachment styles are individual differences in the way people approach close relationships and can be assessed in two dimensions of insecurity: attachment avoidance and anxiety (Feeney and Noller, 1990; Brennan and Shaver, 1995). Individuals with attachment anxiety report fear of abandonment and rejection and are more preoccupied with relationships. These individuals tend to show overdependence on others to regulate stress and only benefit from support when support givers are highly empathic (Sambo et al., 2010). Individuals who score high on avoidance also show aberrant support seeking. They are less inclined to seek social support as they feel uncomfortable in close relationships and prefer not to depend on others (Anders and Tucker, 2000; Mikulincer,1998; Collins and Feeney, 2000; Shaver and Mikulincer, 2007). More specifically related to coping with pain, Sambo et al. (2010) showed that individuals with higher attachment avoidance benefitted less from social presence during an experimental pain induction paradigm and even reported more pain compared to being alone, possibly because these individuals prefer not to rely upon others to regulate stress. In contrast, individuals who score low on attachment anxiety and avoidance are considered securely attached. These individuals cope well with stress by turning to trusted others as they are confident about the availability of others in times of need (Collins and Feeney, 2000).

The lack of social coping to down-regulate stress in avoidantly attached individuals may be explained by individual differences in oxytocinergic system functioning (see Ein-Dor et al., 2018). There is some evidence indicating that the pro-social effects of intranasal oxytocin are more pronounced or altered in insecure individuals, thus indicating that oxytocin interacts with adult attachment in predicting social cognition and behavior (Bartz et al., 2015). De Dreu (2012) showed that intranasal oxytocin reduced betrayal aversion and facilitates the development of trust and cooperation in particular in adults with high attachment avoidance. Similarly, another study showed that repeated oxytocin administration particularly decreased attachment avoidance and distrust in others (Bernaerts et al., 2017), indicating that oxytocin lowers reluctance to engage in closeness or intimacy with others. These findings are consistent with the previously proposed affiliative-motivation hypothesis (Bartz, 2016) suggesting that oxytocin may specifically act by increasing affiliative strivings and that individuals who are less inclined to affiliate, such as avoidantly attached individuals, benefit most from oxytocin treatment. In light of these findings, oxytocin may have a therapeutic promise. For example, an oxytocin adjunct to therapy may enhance patient-therapist alliance (Flanagan et al., 2018), which may be particularly beneficial for insecurely attached individuals who have weaker therapeutic alliance (Diener and Monroe, 2011).

In the current study, we test the affiliative-motivation hypothesis by examining whether oxytocin enhances stress-buffering effects of social support during experimentally induced pain. In addition, we examine whether oxytocin's stress-protective effects are related to attachment security. Although several studies have addressed the effects of oxytocin on autonomic nervous system regulation during psychosocial stress, little is known about the role of oxytocin in social coping with pain-provoking stimuli. Therefore, the aim of this study is to examine whether intranasally administered oxytocin enhances beneficial effects of support from a friend on perceived pain. Pain was induced in healthy women with the Cold Pressor Task (CPT). We examined: (1) whether oxytocin and social support affect parasympathetic autonomic nervous system activity (heart rate variability (HRV) (RMSSD) and lower heart rate (HR)) and self-reported pain responses to the CPT; and (2) whether the effects of oxytocin on ANS activity and perceived pain are dependent on attachment security. We hypothesized that oxytocin would enhance the buffering effect of social support. More specifically, we expected that, oxytocin would increase parasympathic activity and lower pain intensity ratings, particularly in individuals who are supported by a friend. In addition, consistent with the affiliative-motivation hypothesis, we predicted that these autonomic and pain attenuating effects of oxytocin and social support would be most pronounced in individuals who are less inclined to affiliate, that is, avoidantly attached individuals.

2. Method

2.1. Participants

A total sample of 200 female undergraduate students from Tilburg University was recruited. Sample size was based on a priori power analysis using G Power (see Riem et al., 2020). Power analysis (repeated measures anova, between-within interactions) showed that, with α set to .05, $(1-\beta) = 0.95$, a medium effect size 0.15, 4 measurements and 4 groups, the required sample size amounted to 136. The target sample size of the study was 180 participants, which was larger than the required sample size resulting from the power analysis because we aimed to examine moderating effects. Because multiple physiological measures were used, we anticipated a 10% drop-out rate, e.g., due to equipment malfunctioning. Oversampling was done to compensate for this drop-out. Participants were invited for a lab session. Participants were randomly assigned to four different conditions: (1) oxytocin with support, (2) oxytocin alone, (3) placebo with support, (4) placebo alone. Participants received study credits or a monetary reward for participation. All participants gave informed consent. Permission for this study was obtained from the Medical Ethics Committee Brabant (NL60593.028.17). The study was registered in the Dutch Trial Registry (NTR6513).

Exclusion criteria were drug/alcohol abuse, nasal problems, use of prescribed medication (except contraception), psychiatric and neurological disorders, cardiovascular diseases, and high blood pressure. Participants who reported being pregnant, breastfeeding or who had children were also excluded from this study. A total of 7 participants (3.5%) dropped out before or during participation because of sickness or procedural mistakes, resulting in a final sample consisting of 193 participants for the current study.

2.2. Procedure

Participants were asked to complete questionnaires regarding demographic details and attachment approximately one week before the lab session. Details of the procedures of the overall project have been published previously (Riem et al., 2020). Participants who were assigned to the friend condition were asked to bring a female friend with them to the lab session, which was scheduled preferably in the luteal phase of their (self-reported) menstrual cycle in order to control for menstrual cycle influences, similar to previous studies (Riem et al.,2013; Riem et al., 2019) (see supplemental material S1). Menstrual phase and hormonal contraceptives were balanced across the placebo and oxytocin group. Participants were instructed to abstain from alcohol during the 24 h before the lab session, and from caffeine and smoking on the data collection day.

Laboratory sessions were scheduled in the afternoon in the Behavioral Physiology Lab of Tilburg University (GO-Lab). At the start of the session, participants signed the consent form and reported on their current state anxiety levels and were asked to indicate whether they had adhered to instructions regarding alcohol, nicotine, and coffee. In addition, participants rated their baseline pain level on a visual analogue scale (VAS) and participants who brought a friend with them to the lab session were asked to rate the quality of their friendship (see supplemental material). 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. After this task, ECG electrodes were attached and HR and RMSSD were assessed throughout the remainder of the protocol. The pre-CPT rest measure started approximately 40 min after intranasal oxytocin administration. Pain was measured four times (baseline before intranasal administration, second baseline, during CPT, post-CPT).

2.3. Tasks and measurements

Cold pressor test. The CPT has been used extensively to study pain and stress reactivity (Lovallo, 1975; Campbell et al., 2004; Campbell et al., 2006). Participants were instructed to keep their dominant hand and wrist under water during a 1-min immersion period and were examined in a sitting position. The water temperature was carefully maintained with ± 3 × 3 cm ice cubes (mix of water and ice) between 4–8 °C. The temperature of the water was measured with a digital water thermometer during the entire experimental protocol. Participants were instructed to keep their hand open and relaxed and to move their hand slightly to prevent the development of local warming around the hand (Mitchell et al., 2004). In addition, they were asked to alert the experimenter when they started feeling pain by saying “now”. Data on time starting feeling pain was missing for 30 participants due to procedural mistakes. The experimenter stayed in the room to observe the compliance, but did not speak to the participants and did not make eye contact. Participants were allowed to remove their hand when they experienced severe pain. Eight participants removed their hand from the water before the end of the 1-min immersion period (minimum duration = 30 s).

*Social support condition.*Participants who brought a friend with them to the lab session were asked to hold the hand of their friend with their non-dominant hand. Friends were asked to sit next to the participant and to support the participant by handholding. Participants and friends were not allowed to speak during the immersion period.

Experiences in close relationships questionnaire (ECR). The ECR questionnaire is a well validated questionnaire for measuring the underlying dimensions of attachment in adult relationships (Brennan et al., 1998; Sibley et al., 2005). The ECR is designed to assess individual differences with respect to attachment anxiety and attachment avoidance, as measured with two subscales (each 18 items). Higher scores on the ECR denote an insecurely attached person, whereas lower scores represent a securely attached person. All items are measured on a 7-point numerical scale ranging from 1 (strongly disagree) to 7 (strongly agree). The internal consistencies of the subscales were excellent in this sample (Cronbach's alpha: Anxiety = 0.89; Avoidance = 0.93). Two example items are ‘I worry about being alone’ (anxiety) and ‘I prefer not to be too close to romantic partners’ (avoidance).

2.4. Physiological reactivity

Continuous ECG recordings were obtained using the Biopac MP150 system with the ECG100C module and three hydrogel electrodes. Data were recorded at a sampling frequency of 2000 Hz. Data processing was conducted in AcqKnowledge 4.4. The ECG complex boundaries were identified automatically and artefacts and missed QRS peaks were identified and corrected manually. We calculated the average root mean square of successive differences (RMSSD, in m.s), a measure of cardiac parasympathetic activation, and heart rate (HR) in beats per minute. These measures were collected during the 5-minutes pre-CPT rest period, during the CPT, and during the second 5-minutes post-CPT recovery period. RMSSD was log-transformed because the distribution was skewed. Data of 13 participants were missing due to procedural or technical errors during ECG recording.

2.5. Pain responses

Pain was measured using the 10 cm VAS from the Dutch short-form McGill pain questionnaire (Vanderiet et al., 1987). Ends were defined as “no pain” and “worst possible pain” and expressed in mm (range 0–100). Assessments were made, prior to CPT, during CPT (assessed immediately after participants withdrew their hand out of the ice water), and approximately 30 s post-CPT.

2.6. Statistical analyses

Repeated Measures Analysis of Covariance (RM-ANCOVA) was performed with RMSSD, HR, or pain intensity ratings as repeated dependent variables in order to examine the effects of treatment group (oxytocin, placebo) and support group (friend, alone) on responses to the CPT. For the analyses for pain, time (pre-CPT, during CPT, and post-CPT) was the within-subject factor and treatment group (oxytocin, placebo) and support group (friend, alone) the between-subject factors. Similar RM-ANCOVAs were performed with RMSSD and HR as dependent variables. Repeated contrasts were used to identify significant differences between measurements. Greenhouse-Geisser correction was used when the sphericity assumption was violated. The Benjamini Hochberg (BH) procedure was applied to *p*-values resulting from the analyses with autonomic arousal (2 tests: RMSSD, HR) in order to correct for Type I error.

In order to examine influences of attachment on oxytocin effects, factorial 2 × 2 ANCOVAs were performed. Oxytocin effects on pain were tested with ANCOVA with treatment group and support group as between-subject factors and pain ratings during CPT as dependent variable. In addition, attachment anxiety and attachment avoidance were entered separately as covariates. Similar 2 × 2 ANCOVAs were conducted with RMSSD and HR as dependent variables. Age, menstrual cycle, water temperature, and use of hormonal contraceptives were included as covariates in all analyses, see (Riem et al., 2019, 2020; Schoormans et al., 2020). In addition, in the analyses with pain intensity, baseline pain ratings (before CPT, but after nasal spray administration) were added as additional covariate. Analyses were repeated without participants who removed their hand from the water before task completion, but this did not change the results. Group differences in pre-nasal spray pain scores, state anxiety, attachment anxiety and avoidance, and quality of relationship with friend were examined with one-way ANOVA, but there were no significant differences

Table 1
Results from the 2 × 2 × 3 RM-ANCOVA with RMSSD and HR as dependent variables.

Predictor	RMSSD					HR				
	Df_{Num}	Df_{Den}	F	p	partial η^2	Df_{Num}	Df_{Den}	F	p	partial η^2
Time	1.90	327.13	1.97	0.144	0.01	1.90	274.33	0.83	0.413	0.01
Treatment group	1	172	2.11	0.149	0.01	1	172	1.33	0.251	0.01
Support group	1	172	3.84	0.052	0.02	1	172	0.72	0.399	<.01
Time × treatment group	1.90	327.13	1.80	0.169	0.01	1.90	274.33	0.15	0.817	<.01
Time × support group	1.90	327.13	0.25	0.767	<.01	1.90	274.33	0.73	0.455	<.01
Treatment × support group	1	172	5.00	0.027	0.03	1	172	4.23	0.039	0.03
Time × treatment × support group	1.90	327.13	5.95	0.003	0.03	1.90	274.33	0.02	0.968	<.01

(see Table S1). All analyses were performed using SPSS 24.

3. Results

Table S1 presents participant characteristics for the oxytocin alone (N = 48), oxytocin friend (N = 50), placebo alone (N = 50), and placebo friend group (N = 45). The ages ranged from 18 to 27 years old (M = 20.10, SD = 1.78). The majority of participants used hormonal contraceptives (59.1%).

3.1. Autonomic responses

Table 1 presents the statistics resulting from the 2 × 2 × 3 RM-ANCOVA with RMSSD as dependent variable with 3 repeated measures. There was a significant three-way interaction between treatment group, support group and time (p = 0.003, partial η^2 = 0.03). Analysis of simple effects showed that all subsequent time points significantly differed from each other (p < 0.05). Fig. 1 shows that participants who were administered a placebo showed a stress-induced reduction in RMSSD as well as participants who were administered oxytocin and who were tested with a friend. In contrast, participants who received oxytocin and who were tested alone showed a reduced drop in RMSSD. Analyses of the main effect and two-way interactions revealed a significant interaction between support group and treatment group, see Table 1. Fig. 1 also shows that participants who received oxytocin and were supported by a friend showed overall lower RMSSD compared to the other groups. No other significant main or interaction effects were found for RMSSD, see Table 1.

The 2 × 2 × 3 RM-ANCOVA with HR showed no significant three-way interaction between time, treatment group, and support group, see Table 1. However, the interaction between treatment group and support group was significant (p = 0.039, partial η^2 = 0.03), which is consistent with the observations for RMSSD. Fig. 1 shows that participants who were administered oxytocin and were supported by a friend had overall higher HR compared to the other groups. There were no significant of main effects or two-way interactions with time, see Table 1.

Table 2
Results from the 2 × 2 × 3 RM-ANCOVA with pain intensity as dependent variable.

Predictor	Pain				
	Df_{Num}	Df_{Den}	F	p	partial η^2
Time	2	370	4.08	0.018	0.02
Treatment group	1	185	2.22	0.140	0.01
Support group	1	185	0.83	0.364	<.01
Time × treatment group	2	370	0.99	0.373	0.01
Time × support group	2	370	0.46	0.626	<.01
Treatment × support group	1	185	1.59	0.210	0.01
Time × treatment × support group	2	370	1.99	0.138	0.01

3.2. Pain intensity

Table 2 presents the statistics resulting from the 2 × 2 × 3 RM-ANCOVA with pain intensity as a dependent variable. There was no significant three-way interaction between time, treatment group, and support group, see Table 2. There was a significant effect of time, indicating that the cold-pressor stress procedure produced a significant pain response that was similar for the four conditions. Repeated contrasts showed a significant increase in pain intensity from pre-CPT to during CPT (F(1,185) = 6.74, p = 0.01, partial η^2 = 0.04), but no change between pain reported during CPT compared to post-CPT (F (1,185) = 0.21, p = 0.652, partial η^2 < .001), see Table 2. Table 3 presents the mean ratings of pain during CPT for the four groups.

3.3. Attachment and autonomic reactivity

The 2 × 2 ANCOVA with attachment avoidance as an additional covariate was also used to examine associations of attachment with

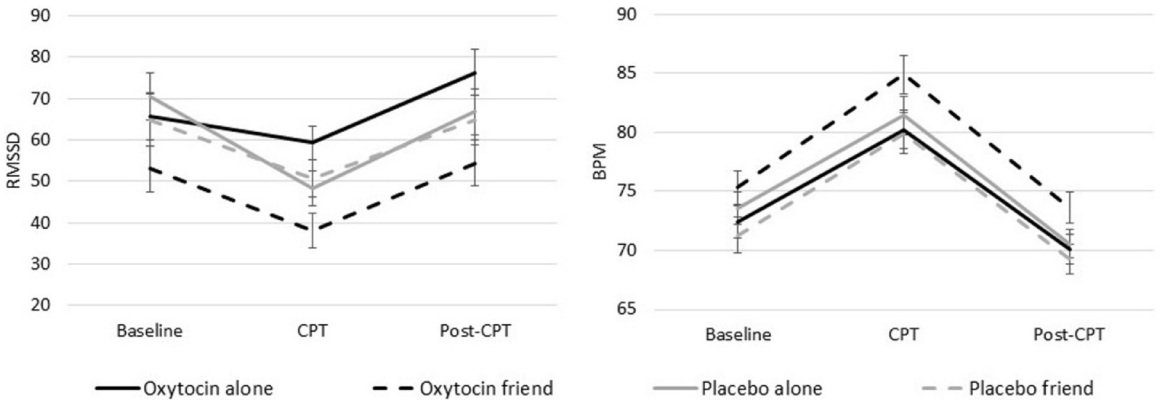

Fig. 1. Mean (SE) RMSSD (log m s^2) and mean (SE) HR (bpm) at rest 1 (baseline), during CPT and during rest 2 (post-CPT).

Table 3
Adjusted means and SE pain intensity for participants in the oxytocin alone (N = 48), oxytocin friend (N = 50), placebo alone (N = 50), and placebo friend group (N = 45).

	Oxytocin alone		Oxytocin friend		Placebo alone		Placebo friend	
	M	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*
Pre-CPT	3.79	0.82	3.94	0.81	3.67	0.82	3.57	0.85
During CPT	57.50	3.31	61.20	3.26	59.60	3.30	51.26	3.42
Post-CPT	31.37	3.03	29.47	2.98	28.05	3.01	24.14	3.13

RMSSD and HR as dependent variables. The analysis with RMSSD did not reveal a significant main effect of avoidance (F(1,168) = 2.01, p = 0.649, partial η^2 < 0.01) and avoidance did not interact with treatment (F(1,168) = 4.20, p = 0.520, partial η^2 < 0.01) or support group (F(1,168) = 0.01, p = 0.933, partial η^2 < 0.01). Neither was there a significant three-way interaction between treatment, support group, and avoidance (F(1,168) = 0.39, p = 0.535, partial η^2 < 0.01). Similar effects were found in the analysis with HR. There was a marginally significant main effect of avoidance (F(1,168) = 3.10, p = 0.080, partial η^2 = 0.02). Participants with higher levels of avoidance tended to show higher HR during CPT (M = 82.50, SD = 1.19) compared to participants with lower avoidance (M = 80.77, SD = 1.17). No significant interactions with treatment (F(1,168) = 0.970, p = 0.326, partial η^2 = 0.01) or support group (F(1,168) = 0.08, p = 0.775, partial η^2 = 0.00) were found. Neither was there a significant three-way interaction between treatment, support group and avoidance (F(1,168) = 0.14, p = 0.714, partial η^2 < 0.01).

Regarding attachment anxiety, analyses with RMSSD did not reveal a main effect of this variable (F(1,168) = 0.75, p = 0.389, partial η^2 = 0.00). Neither were there significant interactions between attachment anxiety and treatment (F(1,168) = 0.35, p = 0.556, partial η^2 = 0.00) or attachment anxiety and support group (F(1,168) = 0.66, p = 0.419, partial η^2 = 0.01) and there was no significant three-way interaction between treatment, support group and attachment anxiety (F(1,168) = 1.26, p = 0.263, partial η^2 = 0.01). Similar results were found with the 2 × 2 ANCOVA with HR. There was a marginally significant main effect of attachment anxiety (F(1,168) = 2.82, p = 0.095, partial η^2 = 0.02). Participants with higher anxiety (median split, median = 3.83) showed higher HR (M = 82.52, SD = 1.15 bpm) than participants with lower anxiety (M = 80.67, SD = 1.19 bpm). No significant interactions between anxiety and treatment (F(1,168) = 0.54, p = 0.464, partial η^2 < 0.01) or attachment anxiety and support group (F(1,168) = 0.99, p = 0.321, partial η^2 = 0.01) were found. Neither was there a significant three-way interaction (F(1,168) = 0.38, p = 0.540, partial η^2 = 0.00).

3.4. Attachment and pain

The 2 × 2 ANCOVA with attachment avoidance as an additional covariate and pain intensity during CPT as dependent variable revealed a significant three-way interaction between treatment group, support group and attachment avoidance (F(1,180) = 3.94, p = 0.009, partial η^2 = 0.06), whereas there was no main effect of attachment avoidance on pain (F(1,180) = 2.02, p = 0.157, partial η^2 = 0.01). For purposes of displaying the data, attachment avoidance was dichotomized using a median split (median = 2.67) in order to interpret the three-way interaction. Fig. 2 shows mean pain intensity levels for participants in the oxytocin alone, oxytocin friend, placebo alone, and placebo friend condition, stratified for individuals with lower or higher attachment avoidance. Planned contrasts showed that oxytocin significantly increased pain intensity relative to placebo for individuals with higher avoidance who were supported by a friend (t(185) = −2.74, p = 0.007). No significant oxytocin effects were found for the other groups (ps > 0.42).

The 2 × 2 ANCOVA with pain intensity during CPT as dependent variable and attachment anxiety as an additional covariate did not show a significant main effect of attachment anxiety on pain (F(1,180) = 0.78, p = 0.380, partial η^2 < 0.01). Attachment anxiety did not interact with treatment (F(1,180) = 2.75, p = 0.10, partial η^2 = 0.02) or support group (F(1,180) = 0.09, p = 0.761, partial η^2 < 0.01) and there was no significant three-way interaction between treatment, support group and attachment anxiety (F(1,180) = 0.91, p = 0.343, partial η^2 < 0.01).

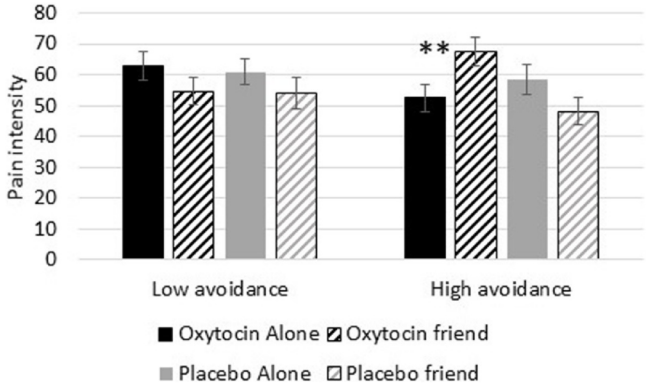

Fig. 2. Mean (SE) pain intensity ratings for participants in the alone-placebo, alone-oxytocin, friend-placebo, friend-oxytocin condition, stratified for individuals with higher or lower levels of attachment avoidance. Subsamples ranged from N = 21 to N = 29. ** = p < 0.01.

To summarize findings related to attachment, oxytocin increased perceived pain in avoidantly attached individuals in the presence of social support. Oxytocin did not interact with attachment anxiety in predicting pain and the effects on autonomic responses were not influenced by attachment security.

4. Discussion

In the current study, we examined whether intranasal oxytocin enhances stress-buffering effects of social support during experimentally induced pain, taking into account the role of attachment security. Unexpectedly, the findings indicate that oxytocin reduced parasympathetic control, as indicated by reduced RMSSD and increased HR, in individuals who were supported by a friend. Oxytocin did not enhance beneficial effects of social support on perceived pain, but increased pain intensity in avoidantly attached individuals who were supported by a friend.

Previous research shows that oxytocin increases affiliative disposition after stress exposure (Cardoso et al., 2013; Cardoso et al., 2016) and may be a neurobiological means to attain and benefit from social support under stressful circumstances. However, in the current study, oxytocin did not enhance effects of social support on perceived pain during the CPT, which contradicts previous studies showing positive oxytocin effects on affiliative strivings during experimentally induced *psychosocial* stress. For example, oxytocin enhances the buffering effects of social support during stress induced by the Trier Social Stress Test (TSST) (Heinrichs et al., 2003; Riem et al., 2020). Although stress-

reducing effects in the presence of a friend may be centrally mediated and may not show specificity to situations of psychosocial threat (Riem et al., 2020), still little is known about oxytocin's stress-protective effects in the context of *physical* stress. In an fMRI study, Kreuder et al. (2019) examined intranasal oxytocin effects on perceived pain induced with electric shocks while receiving support from a stranger or a romantic partner. They showed that oxytocin augmented the beneficial effects of partner support at the neural level, as evidenced by a stronger decrease of threat-related neural activity. However, consistent with our findings, oxytocin did not reinforce the beneficial effects of support in reducing the self-reported unpleasantness of induced pain.

Interestingly, oxytocin reduced parasympathetic control in individuals who received supported. High HRV refers to greater variability in the interval between successive heartbeats, which is adaptive as high HRV is related to better health and the ability to regulate emotional and behavioral responses to threatening internal and external stimuli (Appelhans and Luecken, 2006). Low HRV, on the other hand, has been related to anxiety or psychiatric illness (Chalmers et al., 2014), although low variability may not necessarily be maladaptive as it has also been related to enhanced attentional state (Luft et al., 2009). Previous studies have shown that intranasal oxytocin affects HRV during social stress (Kubzansky et al., 2012), although the direction of the effect may depend on the level of distress (Riem et al., 2020). For example, Tracy et al. (2018) found that oxytocin reduces HRV during mild mental stress in patients with chronic pain. As for an explanation, the RMSSD-lowering effects of oxytocin in our study may reflect enhanced vigilance and attention devoted to the friend, consistent with the Social Salience Hypothesis (Shamay-Tsoory and Abu-Akel, 2016), stating that oxytocin enhances the salience of external cues of safety and threat.

Notably, oxytocin lowered RMSSD in the presence of social support at baseline, that is, before the start of the CPT. This is consistent with our previous study in which we found that oxytocin's anxiety-reducing effects in the context of support were already present before the start of a TSST (Riem et al., 2020). Moreover, it is congruent 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). Thus, oxytocin's support-enhancing effects do not show specificity to situations of threat or a specific type of threat (physical or psychosocial). Social Baseline Theory, which suggests that proximity to social resources reduces the predicted cost of the environment through load sharing (Coan and Sbarra, 2015), can be used as a framework to explain this pattern of findings. Oxytocin may enhance the salience of social proximity and, as a result, may strengthen feelings of security, regardless of the type of stressor and even in the absence of external stimuli signaling potential threat.

A surprising finding of the current study was that oxytocin did not reduce pain intensity, but increased perceived pain in avoidantly attached individuals who were supported by a friend. This is in contrast with the affiliation-motivation hypothesis that states that oxytocin stimulates affiliative strivings in particular in individuals who are less inclined to affiliate (Bartz, 2016). One explanation for this increase in perceived pain is that oxytocin may have increased the salience of social presence, which may elicit uncomfortable feelings in avoidantly attached individuals who prefer not to rely upon others to regulate stress (Anders and Tucker, 2000; Sambo et al., 2010). According to the Social Salience Hypothesis (Shamay-Tsoory and Abu-Akel, 2016), increased salience of external social cues may stimulate pro-social behaviors in safe and supportive contexts, such as in the presence of a friend, but may interfere with affiliative strivings when social presence is perceived as threatening or unpleasant (Egito et al., 2020). Enhanced salience of the presence of the friend may trigger negative emotions in avoidantly attached individuals and may in turn result in increases in perceived pain (Tracy et al., 2015). It should be noted that no direct effects of oxytocin on pain intensity were found. This finding adds to previous research pointing to inconclusive evidence for analgesic effects of oxytocin. For example, Rash and Campbell (2014) showed that oxytocin directly reduces pain intensity during the CPT, but other studies failed to replicate these pain-relieving effects (Mameli et al., 2014; Zunhammer et al., 2016; Tracy et al., 2017; Skvortsova et al., 2018). Considering this mixed pattern of findings, the analgesic effects of oxytocin remain questionable. Rather than directly impacting on the sensory experience of pain, it seems more plausible that oxytocin influences affective dimensions of pain (Zunhammer et al., 2016), for example due to anxiolytic properties and dampening effects on HPA axis reactivity, which consequently influence pain perception (Tracy et al., 2015). Alternatively, oxytocin may influence attentional focus on a noxious stimulus (Tracy et al., 2015). Research shows that oxytocin enhances the salience of socially relevant cues and can direct attention to potential signals of safety or threat (Shamay-Tsoory and Abu-Akel, 2016). This may either result in a less intense pain experience when an individual is distracted from a stimulus (Terkelsen et al., 2004) or lead to greater perceived pain when the focus is directed towards the painful experience. Indeed, Tracy et al. (2017) showed that intranasal oxytocin increased pain sensitivity in women with chronic pain.

Our findings may have clinical implications. Substantial evidence for the prosocial and stress-reducing effects of oxytocin has resulted in a strong interest in its therapeutic potential, especially for stress-related psychopathology, such as anxiety disorders and post-traumatic stress disorder and in conditions characterized with impaired social behavior (e.g. autism and schizophrenia) (Peled-Avron et al., 2020). There is also increasing interest in oxytocin's therapeutic benefits for modulating pain, for example in patients with chronic pain (Tracy et al., 2015). Moreover, an oxytocin adjunct to therapy may improve sense of security with therapist and therapeutic alliance (Flanagan et al., 2018). However, in light of the modulatory role of both individual and contextual factors, caution about oxytocin's therapeutic promise is warranted. A recent meta-analysis showed that intranasal oxytocin has diverse effects depending on context and symptoms and highlights the role of attachment security as an important factor moderating oxytocin effects across disorders (Peled-Avron et al., 2020). Thus, an oxytocin adjunct to therapy may only be helpful in a safe surrounding, for example when therapists and patients have had opportunities to develop rapport (Flanagan et al., 2018). Large-scale clinical trials applying a personalized medicine approach are needed to clarify whether therapeutic use is a future possibility.

4.1. Limitations

A few limitations should be acknowledged. First, we examined oxytocin effects only in female participants. Future studies are needed to include both sexes in order to test whether oxytocin shapes stress-buffering effects of support differentially in men and women. Second, the use of a between-subject design implies the risk of pre-existing differences between the oxytocin and placebo groups, although randomization reduced this risk. Accordingly, we did not find group differences in state anxiety, attachment, friendship quality, and pain before intranasal administration. Third, it should be noted that self-reported pain may differ from levels of experienced pain and can not be accurately measured in objective ways. Previous studies suggest that self-reported pain may be influenced by social context. For example, Kállai et al. (2004) showed that pain reporting during the CPT is influenced by characteristics of the person to whom the pain is expressed and that pain tolerance is higher in the presence of an opposite-sex experimenter. It therefore remains unclear whether oxytocin increased the experience of pain or levels of expressed pain in avoidantly attached individuals. Furthermore, the temperature of the water in the CPT was 4°–8 °C, which slightly higher than previous CPT studies (Mitchell et al., 2004). However, pain intensity did significantly increase from baseline

in this study, indicating that the task was effective in triggering a pain response. Lastly, attachment was measured with a self-report questionnaire and not a structured interview.

5. Conclusions

Although social bonding and soothing behaviors mitigate the destructive effects of negative environmental stressors on health and well-being, still little is known about physiological mechanisms underlying beneficial effects of support. This study adds to accumulating evidence for the role of the oxytocinergic system as a potential pathway underlying social influences on mental and physical health. Insight into physiological mechanisms mediating the effects of supportive relationships on health will improve understanding of why some individuals fail to benefit from support. Our results showed that oxytocin administration reduced parasympathetic control and increased HR in individuals who were supported by a friend, possibly reflecting increased salience of social presence and attention devoted to the friend. However, oxytocin interacted with attachment avoidance in predicting the response to pain, which is consistent with previous studies pointing to a role of attachment as an individual difference factor in shaping affiliative effects of oxytocin (Peled-Avron et al., 2020). The present data suggest that oxytocin may have paradoxical effects depending on interpersonal insecurities. The therapeutic promise of oxytocin is therefore complicated because oxytocin does not facilitate affiliative behavior for all individuals under all circumstances.

Author contributions

Madelon Riem acquired funding, designed the study, collected the data, analyzed the data, wrote the manuscript. **Laura Kunst** collected the data, analyzed physiological data, reviewed and commented on the manuscript. **Wijo Kop** wrote the manuscript, supervised data analysis, reviewed and commented on the manuscript. All authors contributed to and have approved the final manuscript.

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Declaration of Competing Interest

The author declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.09.057.

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