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Effects of intranasal oxytocin and positive couple interaction on immune factors in skin wounds

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ABSTRACT

Background: Intimate social relationships improve individual health and longevity, an effect which is supposed to be mediated through stress-sensitive endocrine and immune mechanisms in response to positive interaction behavior. On a neuroendocrine level, oxytocin (OT) buffers stress responses, modulates social attachment behavior and has been associated with cytokine expression. Consequently, the aim of the present study was to investigate instructed positive couple interaction, observed behavior, and OT in their effect on immune function.
Methods: In a 4-group design, 80 healthy couples (N = 160 individuals) received four standard dermal suction blister wounds and were randomized to instructed positive interaction/control and intranasal OT/placebo. Unstimulated cytokines (IL-1β, IL-6, TNF-α) were assessed from wound liquid at 40 min, 105 min and 24 hrs after wounding.
Results: Overall, group assignment did not affect friendly or dominant behavior during the interaction sequence. IL-1β and IL-6 levels, however, were moderated by group assignment with lowest levels in women in the positive interaction and OT condition in IL-1 and highest levels in IL-6. TNF-α responses to wounding were not affected from group assignment, however observed friendliness in women was associated with lower TNF-α levels.
Discussion: These findings support the immune-regulating role of friendly behavior in romantic couples. Above this, the data provide the first empirical evidence that an intervention that simultaneously targets neuroendocrine mediators and behavior could affect immune function in a sex specific manner and with potential long-term health relevance.

1. Introduction

A large majority of human adults report to currently live or have lived in a committed romantic relationship at some point in their lives (United Nations Department of Economic and Social Affairs and Population Division, 2019). However, while epidemiological research shows that relationship quality has a substantial impact on mental and physical health and even longevity, the underlying psychobiological mechanisms are less clear to date (Robles et al., 2014).

1.1. Psychobiological mediators

The central psychobiological mechanisms to mediate relationship quality with long-term individual health outcomes are seen in the couples' interaction behavior and stress-dependent endocrine and immunological factors.

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1.2. Couple interaction behavior

Based on interpersonal theory, social interaction can be described via the two major domains agency and communion, operationalized as the dimensions dominance vs submission and friendliness vs un-friendliness (or warmth/coldness). These dimensions define the interpersonal circumplex model (Kiesler, 1983) and convey important information about individual characteristics and the relationship between two interaction partners (Hopwood et al., 2018; Sadler et al., 2011). It is particularly warm and friendly interaction behavior, which has been associated with health-beneficial effects in adult romantic relationships (e.g. Wilson et al., 2017).

1.3. Endocrine factors

On an endocrinological level, effects of interaction behavior are supposed to be mediated through stress-sensitive hormones of the sympathetic nervous system and the hypothalamic pituitary adrenal (HPA) axis. Indeed, early research from Kiecolt-Glaser's group showed that hostile behavior during marital discussions was associated with increases in norepinephrine, epinephrine, and adrenocorticotropic hormone and impaired immune responses (for an overview, see Kiecolt-Glaser, 2018). Investigating positive behavior, our own research suggests that affective touch between partners can reduce cortisol (Ditzen et al., 2007) and the mere instruction to focus on positive aspects in the relationship can improve momentary mood and relationship satisfaction (Warth et al., 2020).

1.4. Immune factors

On an immunological level, health-relevant effects of social interactions are supposed to be mediated through an altered activation of pro- and anti-inflammatory cytokines (Steptoe et al., 2007). Cytokines are key immunological modulators as they mediate the complex interactions of pro-inflammatory and anti-inflammatory cells, hematopoietic cells and lymphoid cells functioning as intercellular messengers. These endogenous proteins are produced in immune-relevant cells such as macrophages, *T*-lymphocytes or fibroblasts – however with differing time lines - and can be measured from body fluids (blood, lymphatic fluid, wound liquid) and skin wounds (Grellner, 2002).

IL-1β as a proinflammatory cytokine is produced and released in the initial stages of the immune response to infection and stress and is primarily produced by monocytes and macrophages, although it can also be secreted by other cells. In mast cells, IL-1β leads to the secretion of histamine, which results in localized inflammation, among other effects.

IL-6 has both proinflammatory and anti-inflammatory functions. It affects processes of tissue repair and metabolism and promotes differentiation of B cells into plasma cells and activates cytotoxic T cells.

Among the proinflammatory cytokines, TNF-α is considered the fastest, anti-tumoral cytokine in the reaction to contaminants. However, permanently increased plasma levels lead to negative effects such as cardiac arrhythmia. In addition to the defense against viral, bacterial or parasitic infections, TNF-α is an important factor in autoimmune reactions (Meager, 1998). It has been shown that local expression of proinflammatory cytokines in skin wounds is highly upregulated during the inflammatory healing phase and the coordinated expression of these cytokines is positively linked with wound repair, inter alia, via stimulation of keratinocyte and fibroblast proliferation, synthesis and breakdown of extracellular matrix proteins, and fibroblast chemotaxis (Werner and Grose, 2003).

Unhappy relationships or repeated conflicts are interpreted as relevant and constant stressors and, consequently, have been suggested to impair immune function and health (Bajaj et al., 2016; Glaser and Kiecolt-Glaser, 2005). There is robust scientific evidence for increased pro-inflammatory markers, such as IL-1β, IL-6, or TNF-α concentrations, in plasma or serum due to acute stress exposure (Linninge et al., 2018; Marsland et al., 2017; Steptoe et al., 2007) but also stimulated IL-6 production in response to mindfulness based stress reduction training (Lindsay et al., 2022, in this journal). However, there are fewer data available on *local* cytokine expression in relation to psychological factors. Some studies however report high and reliable levels of local cytokines from wound liquid in a suction blister wound model, as compared to systemic levels (Kuhns et al., 1992; Smith et al., 2015).

In a notable study comparing marital conflict to instructed supportive couple interaction in their influence on wound healing, the conflict discussion led to extended healing processes by an average of one day (Kiecolt-Glaser et al., 2005), an effect which was associated with peripheral levels of the peptide hormone oxytocin (OT) (Gouin et al., 2010).

1.5. Oxytocin

The nine amino acid neuropeptide OT is mainly synthesized from hypothalamic cells (Jurek and Neumann, 2018). In the CNS, OT serves as a neuromodulator involved in cognition and emotion and intranasally applied OT has been extensively studied in relation to social and attachment related and behavior (for reviews, see Meyer-Lindenberg et al., 2011; Olff et al., 2013). Our own research focusing on romantic couples suggests that intranasal OT increased positive interaction behavior and reduced cortisol levels to instructed couple conflict in the laboratory (Ditzen et al., 2009), affected emotional and sympathetic responses in a sex-dependent manner (Ditzen et al., 2013), increased pupil dilation (as an indicator of norepinephrine driven processes) and eye-gaze to bonding-related and socially neutral stimuli (Eckstein et al., 2019), and increased positive partner appraisals (Aguilar-Raab et al., 2019).

Beside this, OT acts as a hormone in the body and has physiological functions, including uterine contractions during labor and milk-letdown during lactation (see Carter et al., 2020, for a recent overview). More recently, OT has been associated with immune functioning. In animal models, the administration of OT led to improved wound-healing, possibly through a suppression of the HPA axis (Detillion et al., 2004; Vitalo et al., 2009). In a small group of men (N = 10), intravenous OT infusion led to reduced plasma IL-1 receptor antagonist, IL-6, and TNF-α responses to endotoxin stimulation (Clodi et al., 2008). In a suction blister skin wound model in N = 12 men and women, OT from the wound liquid was negatively associated with local IL-6 levels (Deing et al., 2013). In a human cell-culture model, OT activation of the oxytocin receptor (OXTR) reduced secretion of IL-6 in lipopolysaccharide activated macrophages (Szeto et al., 2017). In human couples, Gouin et al. (Gouin et al., 2010) showed that endogenous plasma OT levels were accompanied by more positive communication behavior during a support task in the laboratory and with faster wound healing in female participants.

1.6. Aims and hypotheses

In light of these findings, we aimed to design an intervention and determine the role of oxytocin and instructed positive couple interaction on acute immune responses, as a proxy for long-term health processes.

Table 1
Sample characteristics and descriptive data.

		N	*Range*	*Min.*	*Max.*	*Mean (SD)*	Group Comparisons
Age	Women	80	25	20	45	26.54 (4.66)	Group: $F = 0.638$, $p = .592$, **Sex: $F = 5.712$, $p = .018$**, Group*Sex: $F = 0.080$, $p = .971$
	Men	80	23	20	43	28.59 (5.28)	
Dominance	Women	77	927.54	−736.54	191.00	−267.83 (168.06)	Group: $F = 0.625$, $p = .600$, Sex: $F = 0.050$, $p = .824$, Group*Sex: $F = 2.047$, $p = .110$
	Men	78	805.05	−720.84	84.20	−274.56 (164.64)	
Friendliness	Women	77	440	−152.92	287.08	147.04 (74.38)	**Group: $F = 2.927$, $p = .036$,** Sex: $F = 0.028$, $p = .867$, Group*Sex: $F = 0.046$, $p = .987$
	Men	78	421.16	−122.07	299.08	146.61 (63.57)	
BMI	Women	65	10	17.7	27.7	20.96 (2.06)	Group: $F = 0.072$, $p = .975$, **Sex: $F = 60.573$, $p < .001$**, Group*Sex: $F = 0.198$, $p = .898$
	Men	78	11.60	17.10	28.70	23.82 (2.18)	
Relationship Quality	Women	78	42.00	56.00	98.00	82.85 (9.08)	Group: $F = 0.216$, $p = .885$, Sex: $F = 1.631$, $p = .204$, Group*Sex: $F = 0.722$, $p = .541$
	Men	80	37.00	62.00	99.00	81.07 (8.26)	

Notes: Group: OT/PL (oxytocin/placebo), PAT (PAT/nPAT), and sex (male/female). Dominance and friendliness on a continuous level, as coded by two raters; BMI: Body Mass Index; Relationship Quality: overall score of Marital Quality Questionnaire. ANOVA group comparison, significant comparison marked in bold letters.

We hypothesized that instructed positive couple behavior – and especially warm and friendly behavior - would interact with intranasal OT administration and modify local immune responses to suction blister wound application.

2. Material and methods

2.1. Participants

A total of $N = 80$ heterosexual couples ($N = 160$ individuals) were included in the study. To take part in the study, participants had to be aged 21–45 years, exclusively dating with relationship duration between one and 15 years and had to live together. Exclusion criteria were having children, current pregnancy, chronic physical or psychiatric illness (assessed via self-report during initial phone contact) or current medication (except for hormonal contraceptives) or drugs (no more than five cigarettes a day and no alcohol intake on a daily basis, verified via urine multi-drug test upon arrival in the lab). To maximize comparability between naturally cycling women ($N = 40$) and women taking hormonal contraception ($N = 40$), all women were studied in the early follicular phase of their menstrual cycle or within 10 days after pill-break, respectively (Schmalenberger et al., 2021). Study participants were recruited via public media (information brochures, internet announcements, social media, etc.) from the general population of Zurich and the surrounding area. After full explanation of study procedures, participants gave written informed consent. Participants were on average $M = 28$ ($SD \pm 5$) years old. Further sample details are reported in Table 1.

2.2. Procedures

2.2.1. Suction blister wound application

The current study was part of a longitudinal cooperation project at Clinical Psychology University of Zurich and Dermatological Clinic, University Hospital Zurich, Switzerland. After an initial telephone interview and written informed consent, all participants were investigated in the Dermatological Clinic. Laboratory appointments were scheduled in the early evening and took 2.5 hrs. Participants received up to four standard suction blister wounds, administered according to standard protocols (Kiistala, 1968; Kuhns et al., 1992; Pfeifer et al., 2020). The blistering apparatus (see Online Supplementary Figure a) we used, was designed based on a prototype from the US NIH dermatology branch and consisted of a small plexiglass chamber with four wells, which in a combination of suction and heat from small light bulbs generated four small blisters (up to Ø 0.7 cm each, see Online Supplementary Figure b).

To create the blisters, first, the skin was shaved and cleaned and the apparatus was attached to the arm. After blister-production, which took approximately 60 min, wound liquid from 1) one of the four blisters was taken with a syringe at 40 min after blistering (*cytokine measure t1, baseline*), and 2) a second blister at 105 min (*cytokine measure t2*). These two blister roofs were then removed using sterile surgical instruments and the blistered sites were covered using sterile bandage. Twenty-four hours later, study participants came back to the lab, to have the up to two remaining blister roofs removed and wound liquid extracted from these remaining blisters (*cytokine measure t3*). Each blister produced 100–200 µl wound liquid and liquid from the two remaining blisters was pooled to have enough liquid available for the cytokine analyses.

Blister liquid was immediately frozen at −80C until shipping on dry ice and analysis. Blistering and the participants' reaction were constantly monitored (from SL or a medical student, named below).

2.2.2. Intranasal oxytocin administration

In a double-blind and placebo-controlled design, both partners were instructed to either self- administer OT as a nasal spray (Syntocinon®, Novartis, Switzerland, OT; 24 IU, 3 puffs per nostril) or a placebo (PL) at 50 min after wounding. Both OT and PL nasal sprays were prepared and blinded at Cantonal Pharmacy Zurich. The PL sprays contained all ingredients but the active OT. In addition, as part of a larger examination of long-term OT effects, couples were given the nasal sprays home and asked to administer 2 puffs per nostril at 2 times per day (i.e. a total of 32 IUs of OT) during the following five days. Compliance and side effects were reported on a daily basis via tablet computers (iPod touch©).

2.2.3. Partnership appreciation task (PAT)

In addition to OT vs PL in a 4-groups design, couples were randomized to a positive interaction condition (Partnership Appreciation Task, PAT) (Warth et al., 2020) or a control condition at 95 min post wounding (=45 min after OT/PL administration). The PAT was conceptualized as an instructed positive appraisal of the relationship and personal characteristics of each partner. With this aim, couples received a list of 23 topics, which can characterize romantic relationships (e.g. trust, planning of joint activities, social support, etc.) and were asked to discuss these topics regarding their own relationship. Couples were given 10 mins to rate each of these topics on a 4-point Likert scale (0 = does not apply to our relationship, 4 = is a frequent/important aspect in our relationship) and to amend further positive aspects, in case any deemed them missing in the list. In the control condition (nPAT), couples spent 10 mins in an adjacent room waiting without the instruction to interact in a specific manner or to a standardized positive interaction. During this discussion/ control condition, couples were videotaped.

Upon study completion, couples were compensated with 500 CHF (approximately 510 USD). The study was realized in accordance with

the Declaration of Helsinki, pre-registered (clinicaltrials.gov, identifier NCT01594775), approved by the Cantonal Ethics Committee Zurich and swissmedics and was monitored by the Clinical Trials Center Zurich.

2.3. Video coding of couple interaction

Couple behavior was videotaped and coded based on the circumplex model (Gurtman et al., 2016; Kiesler, 1983; Leary, 1957). Video-taped behavioral data was available from N = 78 men and N = 77 women. Two independent raters coded the dimensions friendly and dominant behavior as continuous variables using the Joystick-Method (Microsoft Sidewinder Force Feedback 2), as developed by Pamela Sadler (Lizdek et al., 2012). The coding results in two ratings for each dimension every second (in total 1200 ratings for each dimension). Intraclass correlations between raters for dominance and friendliness were $r = 0.651$ and $r = 0.714$, respectively, indicating a moderate inter-rater reliability.

2.4. Cytokine analyses

From the suction blister wound liquid, unstimulated cytokines (IL-1β, IL-6, TNF-α) were assessed at 40 min (before nasal spray administration or PAT), 105 min and 24 hrs after wounding. To account for variation in the amount of the wound liquid, cytokine levels were gauged as a function of the protein concentration (c.f. Kuhns et al., 1992). Cytokine concentrations were analyzed at Cytolab labs, Regensdorf, Switzerland (https://www.cytolab.ch), using ultrasensitive enzyme-linked immunosorbent assays MAP-kits from R&D (Abingdon, OX, United Kingdom). Wound liquid was available from N = 78 men and N = 78 women. The lowest level of detection for cytokines was 0.5 pg/ml. Cytokine levels lower than the assay's detection limit were set at the lower detection limit of 0.5 pg/ml. Overall, cytokine levels in the wound liquid were low and 52.08 % of IL-1, 41.46 % of IL-6 and 30.41 % of TNF-α levels were ≤ 0.5 pg/ml (for detailed descriptive data per measure, see Table 1). To our knowledge, no standards for comparison exist for wound liquid.

2.5. Self-reported relationship quality

Relationship quality was assessed using the Marital Quality Questionnaire, PFB (Hahlweg, 1979), a well-established and validated instrument to measure relationship quality in couples on the three dimensions Quarreling, Tenderness and Companionship/Communication. Previous studies report excellent psychometric properties for the PFB, with a Cronbach's alpha of $\alpha = 0.93$ (Hinz, Stöbel-Richter, & Brähler, 2001). In the present sample, couples reported to be very satisfied with their relationship with a mean satisfaction of $M = 81.94$ (SD ± 8.69).

2.6. Statistical analysis

Overall group differences and baseline characteristics were analyzed using SPSS 24 (IBM Corp, 2016). Here, the main interest was on the association of observable and coded couple behavior (dimensions friendliness and dominance) in the OT/Placebo and PAT/nPAT conditions, respectively. So, ANOVAs with friendliness and dominance as continuous outcomes were calculated. Sex was entered as further group factor in all analyses.

For repeated measures cytokine analyses, because of the nested structure of the data (repeated measures, individuals nested in couples) multilevel growth curve models were calculated using the *"nlme"* package (Pinheiro et al., 2022) for R (R Core Team, 2020), by means of a Restricted Maximum Likelihood estimation method (REML). Three-level models were calculated where measurement points in time (level 1) were nested in individuals (level 2), nested in an empty couple's level (level 3). This third level was used to adjust standard errors because of the variability explained by couples (Kenny et al., 2006). Only the intercepts were set at random, and a heterogeneous compound symmetry structure where each member of the couple had a distinct variance was modeled (Kenny et al., 2006), together with a first order autocorrelation structure. As the cytokine levels were positively skewed, a constant of 1 was added and a transformation to the natural logarithm was calculated for all cytokines. Calculations with the cytokines as dependent variables were done on these log-transformed data. Please note however, that in the figures, un-transformed values are shown.

For each cytokine we calculated the following models: A first model with time, friendliness, and sex as predictors. Also, an interaction between time and friendliness, and sex and friendliness were added into the equation. The same model, but with dominance instead of friendliness as a predictor was also calculated. If any of the predictors showed a statistically significant effect, these were added in the final equation. The third equation included time, OT/PL (oxytocin/placebo), PAT (PAT/nPAT), and sex (male/female) as predictors, together with an interaction between time * oxytocin * PAT, time * sex, and oxytocin * sex.

3. Results

3.1. Descriptive data and baseline characteristics

At the first measure (+40 min after wounding), 55.6 % of the TNF-α values were below the detection limit of 0.5 pg/ml. At the second measure (105 min after wounding), 19.4 % were below the detection limit and 15.6 % at the third time point (24 hrs after wounding). Of IL-6 values, 93.75 % were ≤0.5 pg/ml at the first measure, 8.13 % at the second measure and 22.5 % at the third measure. For IL1, 68.13 % were ≤ 0.5 pg/ml at the first measure, 69.38 % at the second measure and 18.75 % at the third measure. These values were replaced with the detection limit (i.e. 0.5 pg/ml).

No significant differences between the four groups were found at baseline in age ($F = 0.630$, $p = .597$), relationship quality ($F = 0.216$, $p = .885$), baseline IL-1β ($F = 1.876$, $p = .136$), IL-6 ($F = 0.964$, $p = .411$), or TNF-α ($F = 1.517$, $p = .212$).

3.2. Oxytocin, PAT, Dominance, and friendliness during instructed interaction

Dominance. Results from ANOVAs (N = 155, $df_{corrected\ model} = 9$, $df_{error} = 154$) with the conditions OT/PL, PAT/nPAT, sex (male/female), and relationship quality (PFB sum score) and age as covariates revealed no significant 3-way interaction effect on dominance (F = 1.840, p = .177, $\varepsilon^2 = 0.013$). Neither PAT alone (F = 0.043, p = .836, $\varepsilon^2 = 0.000$) nor OT alone (F = 0.123, p = .726, $\varepsilon^2 = 0.001$) affected dominance. Post-hoc analyses suggested that OT and sex interacted with statistical significance on a trend level (F = 3.174, p = .077, $\varepsilon^2 = 0.021$) with women with OT expressing slightly more dominance. Relationship quality (PFB sum-score) was not related to dominance (F = 2.217, p = .139, $\varepsilon^2 = 0.015$), but age was (F = 9. 171, p = .003, $\varepsilon^2 = 0.059$) with higher dominance in older participants.

Friendliness. Results from ANOVAs (N = 155, $df_{corrected\ model} = 9$, $df_{error} = 154$) with the conditions OT/PL, PAT/nPAT, sex (male/female),

and relationship quality (PFB sum score) and age as covariates revealed no significant 3-way interaction effect on friendliness (F = 0.315, p =.575, $\varepsilon^2 = 0.002$). Neither PAT alone (F = 0.039, p =.844, $\varepsilon^2 = 0.000$) nor OT alone (F = 2.073, p =.152, $\varepsilon^2 = 0.014$) increased friendliness. Post-hoc analyses suggested that OT and PAT interacted (F = 4.271, p =.041, $\varepsilon^2 = 0.029$) with participants with OT expressing the lowest friendliness in the nPAT condition and higher friendliness in all other conditions. Relationship quality (PFB sum-score) positively predicted friendliness (F = 9.729, p =.002, $\varepsilon^2 = 0.063$), no association with age was found (F = 0.297, p =.587, $\varepsilon^2 = 0.002$).

3.3. Oxytocin, PAT, friendliness and cytokine-levels

IL-1β. Neither dominance (b = 0.000, t (72) = 0.551, p =.583), friendliness (b = 0.011, t (72) = 1.261, p =.211) or their interactions predicted IL-1β levels, so they were not included in the final equation. On the other hand, significant interactions of PAT/nPAT and OT/PL conditions (b = -0.225, t (305) = -2.144, p =.032), and a significant interaction between time and sex (b = 0.206, t (305) = 3.867, p <.001) on increases in IL-1β was found, with highest IL-1β increases in women in the nPAT PL condition and lowest increases in women in the PAT OT condition.

For mean values and SEs, see Fig. 1 and online supplementary Fig. S1.

IL-6. Neither dominance (b = 0.001, t (72) = 0.813, p =.419), friendliness (b = 0.001, t (72) = 0.453, p =.652) or their interaction predicted IL-6 levels, so they were not included in the final equation. On the other hand, increases in IL-6 were dependent on sex (b = 0.257, t (305) = 2.401, p =.017) with a stronger increase in women. Above this, OT and sex interacted (b = 0.324, t (305) = 2.112, p =.036) with the highest IL-6 values in women in the PAT OT condition at 24 hrs after wounding.

For mean values and SEs, see Fig. 2 and online supplementary Fig. S2.

TNF-α. Neither dominance (b = -0.000, t (72) = -0.380, p =.705) nor friendliness (b = 0.002, t (72) = 1.727, p =.088) predicted TNF-α levels. However, a statistically significant interaction between friendliness and sex was found (b = -0.002, t (72) = -2.968, p =.004) with friendly women showing the lowest TNF-α values.

Therefore, the interaction between sex and friendliness was included into the final model. When OT/PL and PAT/nPAT were included into the equation, the interaction of friendliness and sex remained statistically significant (b = -0.002, t (72) = -2.923, p =.005) with lowest TNF-α levels in women with high friendliness and – on a descriptive level only – in the PAT OT condition (see Fig. 3 and online supplementary Fig. S3 with high vs low friendliness contrasted based on median split for visualization purposes only). No significant effects for group assignment (PAT/nPAT, OT/PL) were found on TNF-α levels.

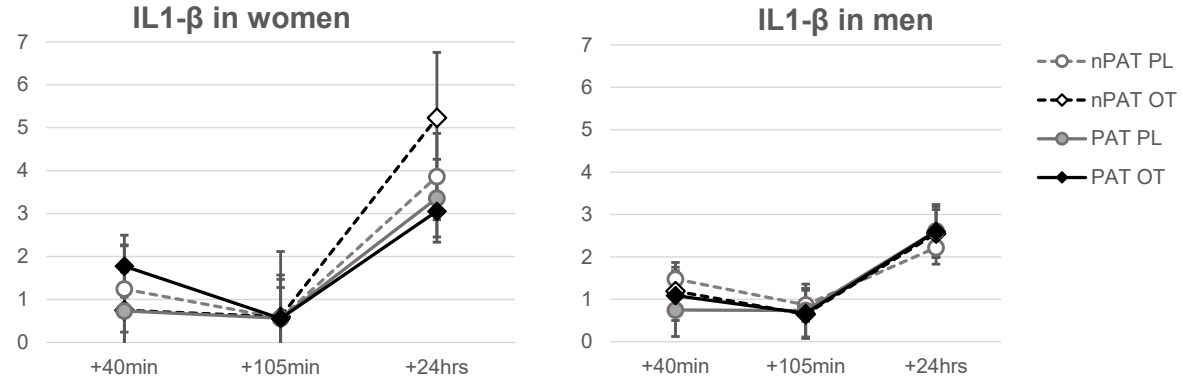

Fig. 1. IL-1β levels from wound liquid (pg/ml) in N = 78 women and N = 78 men, as assessed at t1 (40 min), t2 (105 min) and t3 (24 hrs) after suction blister wound application. Group: OT/PL (intranasal oxytocin/placebo), PAT/nPAT (partnership appreciation task/ control task). For data presented as violin-plots, please see supplementary online material.

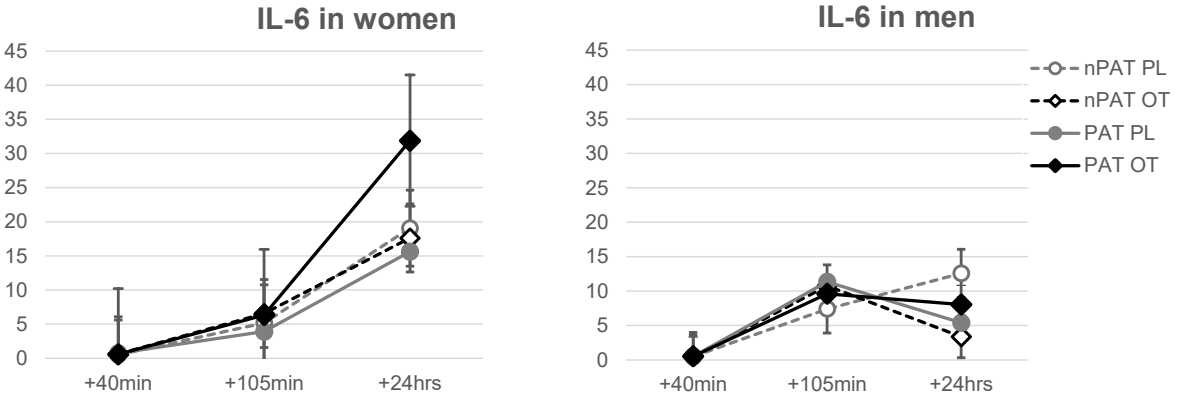

Fig. 2. IL-6 levels from wound liquid (pg/ml) in N = 78 women and N = 78 men, as assessed at t1 (40 min), t2 (105 min) and t3 (24 hrs) after suction blister wound application. Group: OT/PL (intranasal oxytocin/placebo), PAT/nPAT (partnership appreciation task/ control task). For data presented as violin-plots, please see supplementary online material.

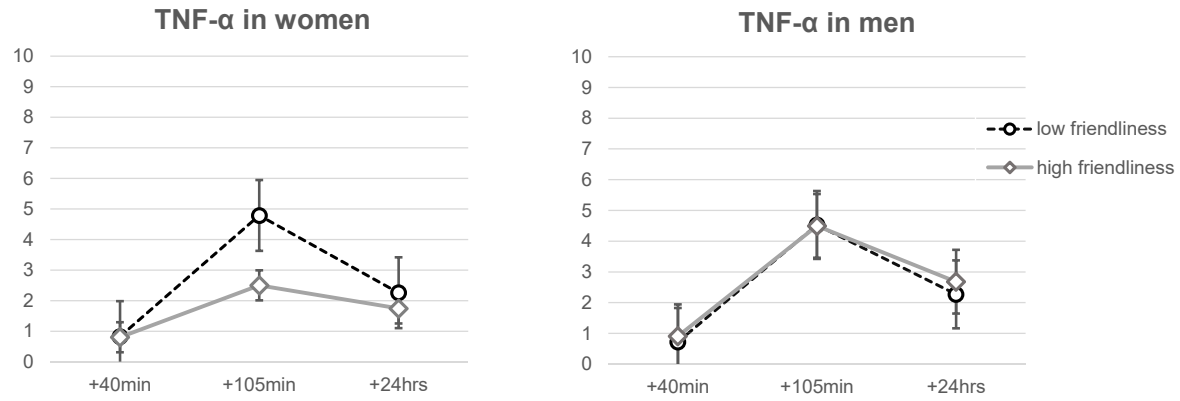

Fig. 3. TNF-α levels from wound liquid (pg/ml) in N = 78 women and N = 78 men, as assessed at t1 (40 min), t2 (105 min) and t3 (24 hrs) after suction blister wound application. Group: Friendliness low vs. high (in Fig. 3 contrasted based on median splits for visualization purposes only), for details see text. For data presented as violin-plots, please see supplementary online material.

4. Discussion

In the present study, in a randomized placebo-controlled four-group design, we examined the effect of intranasal OT and instructed positive couple interaction (PAT) on local immune responses to suction blister wound application in healthy couples.

Results suggest that while neither OT nor PAT directly increased friendly couple behavior in the laboratory, they interacted to reduce local IL-1β and increase IL-6 levels in the wound liquid following wound application. There was no effect of group assignment regarding local TNF-α levels but observed friendliness during couple interaction in the lab was associated with lower TNF-α levels in women. Thereby, these results are mixed regarding individual health implications and partly confirm earlier studies but in part differ.

Indeed, when focusing on intimate relationships and immune functioning in large samples of adults the frequency of positive interactions on a daily basis predicted lower systemic cytokine concentrations (IL-6) (Bajaj et al., 2016) and relationship warmth and support moderated the effects of contextual stress on inflammation markers in blood samples in minorities (Beach et al., 2019). In contrast, negatively perceived social relationships were associated with increased systemic cytokine levels (IL-6 and TNF-α) (Song et al., 2015). Hostile behavior during marital interactions increased plasma levels of pro-inflammatory cytokines, decreased local activation of cytokines in the wound liquid of suction blister wounds and prolonged wound-healing (Kiecolt-Glaser et al., 2005), while supportive behavior and improved wound-healing were positively associated with plasma OT levels (Gouin et al., 2010).

When focusing on the local immune response in suction blisters, the present results in part differ from previous data: We did find increases in IL-1β and IL-6 in the wound liquid over the duration of 24 hrs post wounding, which is in line with previous results (Kiecolt-Glaser et al., 2005; Kuhns et al., 1992; Smith et al., 2015). However, TNF-α decreased again 24 hrs post wounding, which is in contrast to earlier studies. While, overall, reliability of local TNF-α levels has been questioned (Smith et al., 2015), we had expected to find pronounced increases in TNF-α 24 hrs after wounding.

In a mechanistic study using human wound liquid, Deing and colleagues (Deing et al., 2013) found increased local OT levels after light self-touch with a brush and a negative association of local OTmRNA expression with pro-inflammatory cytokines. This suggests that systemic stimulation of endogenous OT, e.g. via affectionate touch in intimate relationships (Eckstein et al., 2020), might be one mechanism through which local immune responses might be affected.

In the present study, the lowest increases in IL-1β were found in women in the PAT OT condition. This is in line with previous results suggesting that local oxytocin reduced proinflammatory cytokine activation (Deing et al., 2013; Szeto et al., 2017), but in contrast to data showing that supportive couple behavior increased local IL-1β levels at 22 hrs after application of a suction blister wound (Kiecolt-Glaser et al., 2005).

The present data on IL-6 responses - vice versa – support the previous behavioral immunology data in couples with higher IL-6 levels 22 hrs post wounding in those, who had had a supportive interaction (Kiecolt-Glaser et al., 2005). However, they are in contrast to findings which suggest that on a local level skin cells depleted of the oxytocin receptor exhibit an increased release of IL-6 (Deing et al., 2013).

Finally, TNF-α levels at 105 min after wounding were lower particularly in women who expressed friendly behavior during couple interaction. Here, no direct effect of group assignment and no influence of behavior on the third measure (24 hrs after wounding) was found.

This time-dynamic might be crucial when seeing the present results in light of the previous findings: While e.g. in Kiecolt-Glaser's 2005 study supportive couple interaction was associated with slightly lower TNF-α levels at 4 hrs and 7 hrs after wounding, this pattern flipped at 22 hrs after wounding. With the surprising decrease in TNF-α at 24 hrs after wounding in the present study, this third measure is difficult to compare and might, indeed, hint towards more equivalent results between studies during the first and second measure points.

Time-dynamics might be important with regard to other aspects of the cytokine response. As published in some papers (Huygen et al., 2002; Huygen et al., 2004; Smith et al., 2015) but different from others (Glaser et al., 1999; Kiecolt-Glaser et al., 2005) , we interpreted unstimulated local cytokine levels taken directly from the wound liquid. This may have affected the results because the cytokines had different time windows to be produced and migrate into the wound than in studies where the blisters had been de-roofed and the wound had been bathed with autologous serum.

Oxytocin administration alone did not increase friendly behavior or reduce dominance during the interaction task. This contrasts with our previous findings, where OT improved the ratio of positive to negative behavior during instructed couple conflict in the laboratory (Ditzen et al., 2009). Instead in the present study, individuals who received OT nasal spray with no further instruction showed less friendly behavior than those in the placebo group. It is possible that no instruction or the instruction to explicitly focus on positive aspects did not provide enough variance in friendly vs unfriendly behavior to stimulate a mere OT effect. This would support the notion, that OT effects rather than being overall "pro-social" or positive seem to depend on individual attachment experiences and social context (Shamay-Tsoory and Abu-Akel, 2016). Instead, OT seems to modulate salience and serve as "catalysator of social stimuli processing" instead of making all social encounters more pleasurable in general (Kemp and Guastella, 2010).

Notably, group assignment to instructed positive couple interaction (PAT) did not overall increase friendly behavior during a 10 min

interaction task in the laboratory, either. In an attempt to design a minimal intervention to promote positive couple interaction, the partnership appreciation task (PAT) was developed (Warth et al., 2020) and here evaluated with regard to its immune modulating effects.

The missing effect of the PAT on immediate friendliness or dominance is counterintuitive, but consistent with results from clinical samples (Aguilar-Raab et al., 2018): In a study with depressed couples, whereas improving mood and momentary relationship satisfaction – PAT increased cortisol and alpha amylase levels (Warth et al., 2020). Also, while PAT can put the focus on positive aspects within the relationship, it is not a guided cognitive strategy, which would unhappy couples help to re-evaluate their relationship or the partner in fundamental ways. However, focusing on the positive aspects of the partner and the relationship might still promote warmth and closeness between couples and, thereby, affect immune functioning. This, indeed, seems to be reflected in the altered IL-1β, IL-6 and TNF-α responses in those participating in the PAT and OT condition or expressing high friendliness during the interaction task.

The present data suggest effects of OT, PAT or observed couple behavior on cytokine levels particularly in women. In women, nPAT × placebo showed the highest IL1-β responses 24hrs after wounding and PAT × oxytocin women expressed the highest local IL-6 levels 24hrs after wounding, the latter linking oxytocin in women with an intensified local inflammatory response and possibly improved wound healing. Again, however negative associations of friendliness and TNF-α levels at 105 mins after wounding were only found in women and these might point towards impaired wound healing in those who expressed high friendliness. On a statistical level this is validated through the significant sex by group or sex by behavior effects. Sex differences in overall cytokine production and time lines in cytokines have been reported in earlier studies and have been interpreted in light of the evident sex-differences in auto-immune disorders (Klein and Flanagan, 2016). Also, it has been suggested that women might react more sensitive to impaired relationship quality than men (Kiecolt-Glaser and Newton, 2001) or show specific oxytocin mediated response patterns to stress or challenges (Taylor et al., 2000).

4.1. Strengths and limitations

This research needs to be seen considering some strengths and limitations. A large number of men and women were investigated, and repeated cytokine levels were interpreted from an in-vivo immune activation model with high validity for everyday health processes. Above this, rigid controls (day time, menstrual cycle stage vs hormonal contraceptives, medication, drugs) were established which allow for interpretation of behavioral, endocrine, and immune interactions.

One limitation is, that we did not control for endogenous OT in the wound liquid and, thus, cannot interpret local OT-immune interactions or the time line of whether or when systemically administered OT might have ended up in wound liquid. We only had three measures of wound liquid available at 40 mins, 105 mins and 24 hrs after wounding and, thus, probably missed major increases in local cytokine production at around 7 hrs after wounding. Above this, other than the increasingly used attempts which interpret systemic biomarkers of inflammation, as assessed from blood or saliva (Szabo et al., 2020) local unstimulated cytokine responses were interpreted. Therefore, large numbers of measures were below the detection limit of the commercial assays that were used. These values were exchanged with the lowest detection rate (0.5 pg/ml), which reduced power to determine significant interaction effects. Nowadays, availability of more sensitive cytokine assays has much improved (see e.g. Battaglia et al., 2005) and might allow for detection of lower levels in the wound liquid.

5. Conclusion

In a translational approach using a skin suction blister model, we here confirm the immune-regulating role of instructed appreciative couple interaction and friendly interpersonal behavior. To learn more about the possibly underlying biological mediators of this intervention, OT was administered as a nasal spray, with the aim to mimic endogenous CNS-based oxytocinergic mechanisms.

Based on the results, we speculate that systemic OT application alone might not alter local immune responses, but that it might interact with positive interaction in a sex-dependent manner. Also, this data suggests that stimulation of endogenous OT levels might be one mechanism through which positive couple interaction can improve individual health.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2022.08.011.

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