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Oxytocin and positive couple interaction affect the perception of wound pain in everyday life

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Abstract

A large body of animal and human laboratory research has linked social interaction and support to pain perception, with a possible role for the neuropeptide oxytocin as a neuroendocrine mediator. However so far, it has been unclear whether these effects translate to ecologically valid everyday life behavior and pain perception. In a randomized placebo-controlled study, a standard suction blister skin wound was induced to N = 80 romantic couples (N = 160 individuals). Couples then received intranasal oxytocin or placebo twice daily and were either instructed to perform a positive social interaction (partner appraisal task, PAT) once in the laboratory and two times during the following five days, or not. During these days, all participants reported their subjective pain levels multiple times a day using ecologically momentary assessment. Results from hierarchical linear modeling suggest that pain levels within the couples were inter-related. In men, but not in women, oxytocin reduced pain levels. Women reported lower pain levels in the group of positive social interaction, while this effect did not show in men. These results suggest that intranasal oxytocin might have sex-specific effects with pain reducing effects in men but the opposite effects in women. In contrast, especially women benefit from positive interaction in terms of dampened pain levels after positive interaction. The results add to the evidence for health-beneficial effects of positive couple interaction and point to underlying neuroendocrine mechanisms in everyday life pain specifically. The sex-specific effects, in particular, may have implications for psychopharmacological treatment of pain in men and women.

Keywords

Suction blister wounds, couples, oxytocin, ecological momentary assessment, partner appraisal task

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Introduction

Social interactions with significant others have a profound impact on our ability to cope with emotional and physical distress.[1,2] Being married or living in a committed relationship appears to be one of the most powerful sources of social support in humans.[3] In line with this, emerging evidence suggests that the presence of and affective interaction with the romantic partner can reduce responses to acute painful stimuli.[4]

With a focus on the underlying psychobiological mechanisms, a large body of research has linked the neuropeptide oxytocin (OT) to social attachment behavior, such as couple interactions as well as pain perception. Several reviews on animal studies suggest that OT impacts specific brain regions which are involved in fear processing and attachment behavior (e.g., amygdala and insula[5]), as well as stress and pain responses.[6–8] Recent experimental studies confirmed these results to be applicable to humans by showing that a single dose of intranasally administered OT can affect stress regulation and prosocial behavior in the laboratory.[9,10] However, while reviews highlight the potential positive therapeutic impact of exogenous OT on pain patients,[11–13] studies with healthy men and women, subjected to experimentally induced pain found mixed results: Inconsistent reports ranging from analgesic effects, pain-empathy effects, placebo-effects, and no effects at all, might in part be explained by the different methods of pain induction, namely cold pressure, electrodes, heat stimuli, and Quantitative Sensory Testing (QST).[14–17] To date, no study has investigated the effects of repeated OT administration or OT on pain perception in everyday life.

Social safety cues, such as viewing the face or feeling the touch of the own romantic partner,[4,18] have been shown to reduce pain experiences in women, an effect which was enhanced by intranasal OT.[19] However, studies on the effects of affective partner contact in chronic pain patients (particularly women) have found mixed results with decreased,[20–22] but also increased pain to solicitous behavior from the partner.[23] This suggests that affective couple behavior has differential effects with the potential to work either as a distractor and shift attention away from pain perception or as an intensifier when related to pain expression. How OT might be involved in either effects or both has not been investigated yet. One important moderating factor for the effects of OT and social interaction on pain perception seems to be sex. Numerous studies found sex to be a differentiating factor for endogenous OT variability[24] as well as tolerance to experimentally induced pain.[25,26]

With the aim to translate the existing laboratory data on OT and couple interaction to pain perception in real life, we investigated the effects of repeated long-term OT administration on pain in couples' everyday life using an ecological momentary assessment (EMA) approach. Specifically, this study was designed to investigate the beneficial effects of intranasal OT and instructed positive couple interaction on momentary pain levels following the application of standard small blister wounds to the skin. Based on previous findings on co-regulation in couples or interacting dyads,[27–29] we expected the perceived pain to co-vary stronger within actual couples in comparison to randomly scrambled opposite-sex dyads.

Methods

Participants and setting

Eighty heterosexual couples, women mean aged 26.65 (standard deviation (SD) 4.67) years, who had been married or cohabiting with a male partner mean aged 28.65 (SD 5.18) years for at least 12 months at the time of the study, participated in a clinical trial on oxytocin, couple interaction, and wound healing at University of Zurich, Switzerland (more information: clinicaltrials.gov, identifier NCT01594775). Couples were recruited via flyers, information brochures, internet ads, mailing lists of the University of Zurich, and social media. Inclusion criteria comprised being between 21 and 45 years old, rather exclusively dating with a relationship duration between 1 and 15 years, and sharing the same household. Participants were excluded if they had children, were currently pregnant, had a current or chronic physical or psychiatric illness (based on self-report during an initial phone contact), or currently used medication (except for hormonal contraceptives) or drugs (no alcohol intake on a daily basis, or smoking more than five cigarettes a day). Women not using hormonal contraception ($N = 40$) were studied during the early follicular phase of the menstrual cycle in order to minimize effects of the cycle on subjective and endocrine outcomes. All participants gave written informed consent. The study protocol was approved by the ethics committee of the Canton of Zurich, and the study was monitored by the Clinical Trials Center, Zurich and conducted in accordance with the Declaration of Helsinki.

Each couple received 500 CHF for study completion. Couples were randomized into four groups: OT treatment (double blind) and instructed positive interaction (partner appraisal task, PAT; $N = 20$ couples), OT treatment and no interaction instruction ($N = 20$ couples), placebo and instructed positive interaction ($N = 21$ couples), and placebo and no interaction instruction ($N = 19$ couples). Based on a pre-study phone interview, couples were stratified with half of the women in each group using hormonal contraception, the other half were naturally cycling.

Procedure

After inclusion and exclusion criteria had been checked during the initial phone contact, couples were invited to a first session at the laboratory. During this first laboratory appointment, participants provided urine samples to rule out drug consumption and pregnancy and completed electronic questionnaires to assess baseline individual and relationship criteria.

Four standard blister wounds were applied to the participants' inner arm according to established methods.[30,31] First, the areas to be blistered were shaved and cleaned. The blistering apparatus was attached to the arm and then employed a combination of suction and heat to generate small blisters. It took approximately 60 min to raise four 0.7 cm blisters in parallel (see Figure 1). A graduate student in medicine or medical doctor constantly monitored the blistering and the participants' reaction during this time. After blistering, the graduate student extracted the wound liquid from two of the four blisters and separated the upper skin layer of the dermal–epidermal junction. Blister roofs were 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, in order to have the two remaining blister roofs removed and wound liquid extracted. Wounds were then covered with a hydrocolloid band aid. Patients were told to keep the blistered areas covered for three days and then to attach a new plaster. Participants reported a sensation of tingling and warmth, and some mild burning and/or pain associated with blister production but no severe pain.

After wound application, participants self-administered 24 IU OT nasal spray (Syntocinon®, Novartis, Switzerland, 3 puffs per nostril × 4 IU per puff) or placebo. They were then instructed to self-administer the nasal spray at two times in the evening (at around 8 and 12 h after waking up) during the following five days. Participants were advised to administer two puffs in each nostril ($2 \times 2 \times 4\,\text{IU} = 32\,\text{IU}$) per day. The placebo contained all same ingredients as the OT spray except for OT itself.

The positive interaction condition (partner appraisal task, 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) and were asked to discuss these topics with regard to their own relationship. Couples were given 10 min to rate each of these topics on a four-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. When leaving the lab, couples were instructed to use and discuss the list at two other times during the coming week and to add positive points, if any came to mind. In the control condition, couples did not receive any specific instruction on how to interact with each other during the following week.

For data assessment during the following week, an EMA design was used with five consecutive days of data collection for which participants were instructed in the use of a pre-programmed (iDialogPad, G. Mutz, Cologne, Germany) iPod touch®. Each participant was given an iPod touch home and asked to start assessments the day after wounding. In order to match the EMA to participants' daily routine, participants provided information on their general awakening times. During the following five days of ambulatory assessment, they individually provided information on subjective pain, social (partner) contact, mood, stress, and control variables (sleep duration, eating, sports, etc.) at six times per day. Measurement time points were prompted by iDialogPad directly (M = 7:47 a.m.) and 30 min after awakening (M = 8:21 a.m.), after 2.5 h (M = 10:30 a.m.), after 8 h (M = 4:03 p.m.), after 12 h (M = 7:26 p.m.), and before going to bed (M = 11:43 p.m.). At each time point, participants indicated whether they felt current wound pain on a scale from 0 to 9. We summed the levels of reported pain to calculate daily pain scores for the analyses.

Statistical analysis

Multilevel models were conducted to test for the hypotheses. Multilevel models account for the non-independent nature of the data, as individuals are likely to differ less

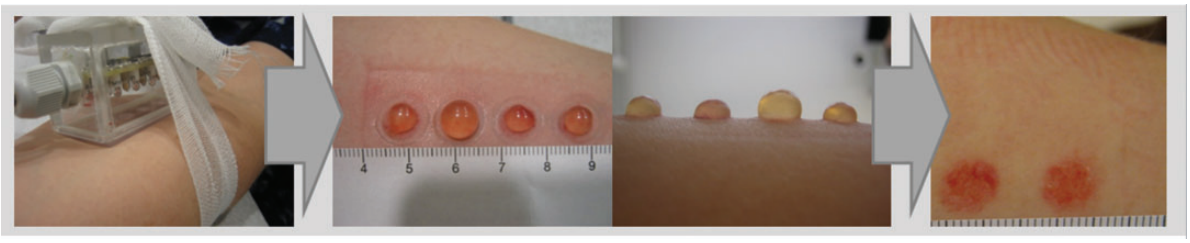

Figure 1. Application of blister wounds.

within their measurements over time as opposed to measurements at a given time between individuals. To answer the question, whether or not experienced pain over time was more related within the couples as opposed to random dyads, multilevel models were conducted where pain perceived by one partner was predicted by pain perceived by the other partner at the same measurement point, as well as type of instructed interaction (PAT vs. no instruction) and oxytocin condition (OT tester vs. placebo). Then, random male partners were assigned to each of the female participants and vice versa over 1000 iterations, and the resulting models were compared to the models utilizing the original dyads.

To answer the question, whether instructed interaction and/or OT would decrease subjective pain levels, multilevel models with measurement points (level 1) nested within individuals (level 2) were conducted. Individual data nested within couples was accounted for by including a third level (level 3) to the primary analysis. This level represents individuals within couples with couples and time points being crossed. We also included model terms for interactions between condition, OT, and sex, as stated in the introduction. The variables were included stepwise into the model, first testing an empty model with just random intercepts, then entering time, OT condition, PAT, and sex, in this order. The models were compared using likelihood ratio tests.

All models included five measurement points, which included the aggregated measures of one day over a five-day period with time centered on day 1. We included time as a predictor in all primary models, thereby disaggregating the effect of variables of interest from non-specific linear trends.

Null Model:
$Ytij = \gamma 000 + u00j + r0ij + \varepsilon tij$

Final Model:
$Ytij = \gamma 000 + \gamma 100(Timetij - 4) + \gamma 010(Partner\ Appraisalij) + \gamma 020(OT\ \ Conditionij) + \gamma 030(Sexij) + \gamma 040\ (Partner\ \ Appraisalij)\ \ (OT\ \ Conditionij)\ \ (Sexij) + u00j + r0ij + \varepsilon tij$

where $Ytij$ denotes the pain score at time t for participant i in dyad j, $(Timetij - 4)$ represents the linear effect of time, $(Partner\ Appraisalij)$ the fixed effect of the PAT at level 2, $(OT\ Conditionij)$ the fixed effect of the OT condition at level 2, $(Sexij)$ the fixed effect of sex at level 2, the three-way interaction term of the level 2 predictors, as well as the random effect estimate at levels 3, 2, and 1, represented by $u00j$, $r0ij$, and εtij, respectively.

While the core outcome of the study was pain over time, a significant proportion of the sample (50.6%) did not experience any pain at any measurement point. The data included 0.38% missing values. Multilevel models naturally handle missing data well, nevertheless we assumed missing at random for all analysis and imputed missing data utilizing multiple imputation by chained equations.[32] In order to be able to perform likelihood ratio tests to compare the models, maximum likelihood was used as estimator, above restricted maximum likelihood, in all models. We computed confidence intervals and significance values for fixed effects using Kenward–Roger approximation.[33] While assuming normality for the errors, we employed a parametric bootstrap approach to compute significance values for random.[34]

Plotting the fitted against the residual values did not indicate non-constant error variance for any of the models. In the same vein, visual inspections of the QQ plots did not show meaningful divergence from normality for any of the models. The open access program R (version 3.4.3 R Development Core Team, 2008) was used for all statistical analyses.

Results

In Table 1, the means, standard deviations, and ranges for age and individual pain sum scores of all study participants are shown. Female participants were on average younger than their male counterparts and experienced more pain on average across all time points than their male counterparts.

Figure 2 shows the means and standard deviations of pain ratings over time for women and men who received either OT or placebo.

Multilevel models show a significant partner effect on perceived pain. In both the male and the female participants, more pain experienced by the partner was related to more pain experienced by the participant. Estimates for the random effects indicate that a significant proportion of the variance in pain over time were at the within-person level. Table 2 reports the parameter estimates for the multilevel models regarding the question, whether or not pain over time was more strongly related within the couples as opposed to random dyads, suggesting that pain experiences in the couples were related.

In Table 3, the parameter estimates for the primary multilevel models on OT and PAT conditions are reported. Adding time to the empty model (Model 1) was a significant improvement in model fit ($\chi^2(1) = 50.9$, $p < 0.001$). Adding oxytocin condition ($\chi^2(1) = 0.2$, $p = 0.64$), or PAT and its interaction with oxytocin (Model 2, $\chi^2(2) = 0.5$, $p = 0.80$) did not improve model fit. The model fit increased further, when sex and its interaction with the other predictors were added (Model 3, $\chi^2(3) = 9.1$, $p = 0.02$), and even further when

Table 1. Means, standard deviations, and ranges for age and individual pain sum-scores.

	Entire sample			Women only			Men only		
Variable	Mean	SD	range	Mean	SD	range	Mean	SD	Range
Age	27.65	5.02	24	26.65	4.67	24	28.65	5.18	21
Pain T1	1.44	2.26	14	1.88	2.64	14	1.01	1.7	7
Pain T2	0.49	1.44	9	0.66	1.63	9	0.31	1.2	9
Pain T3	0.61	2.44	18	0.75	2.57	18	0.48	2.31	18
Pain T4	0.26	1.4	12	0.3	1.46	12	0.21	1.35	11
Pain T5	0.18	1	10	0.19	0.81	5	0.18	1.16	10

SD: standard deviation.

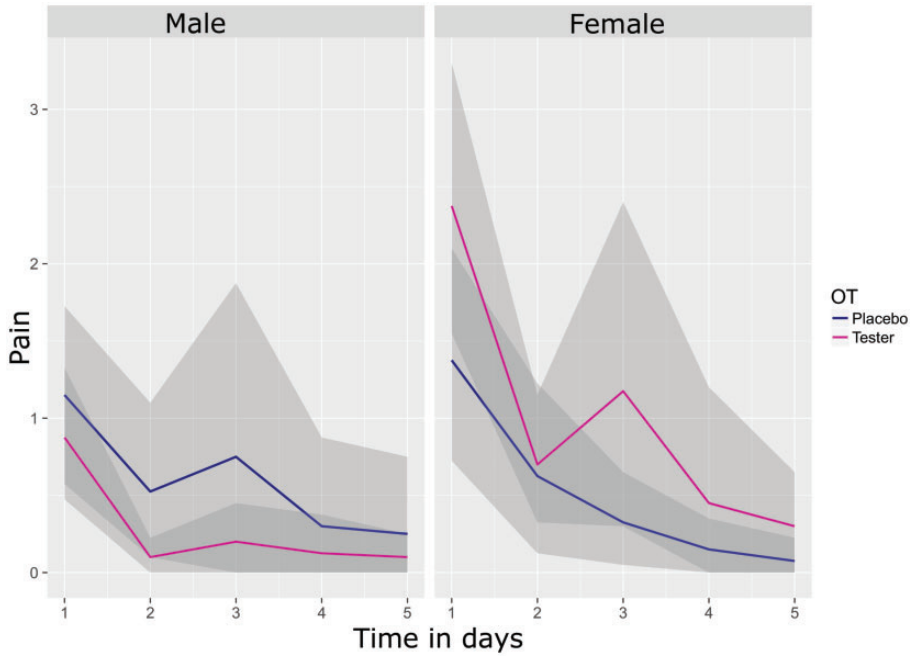

Figure 2. Mean pain ratings for men and women.
OT: oxytocin.

Table 2. Parameter estimates for the multilevel models regarding covariance between real dyads.

	Pain			Pain		
Predictors	Estimates	CI	p	Estimates	CI	p
Intercept	0.18	−0.27 to 0.63	0.437	0.67	0.12–1.22	**0.017**
Pain of female partners	0.11	0.03–0.18	**0.006**			
Pain of male partners				0.17	0.05–0.30	**0.007**
OT condition (tester)	0.02	−0.63 to 0.66	0.964	0.16	−0.63 to 0.95	0.690
Social condition (positive)	0.76	0.10–1.41	**0.023**	−0.55	−1.36 to 0.25	0.177
OT × Social	−0.80	−1.73 to 0.12	0.089	0.80	−0.33 to 1.93	0.168
Random effects						
Random intercept	0.75_{id}		**<.001**	1.05_{id}		**<.001**
ICC	0.29_{id}			0.26_{id}		

CI: confidence interval; ICC: intraclass correlation coefficient; OT: oxytocin; boldface values are significant at at least $p < 0.05$.

Table 3. Parameter estimates for the primary multilevel models regarding experimental groups.

Outcome: pain	Model 1			Model 2			Model 3			Model 4		
Predictors	Estimates	CI	p	Estimates	CI	p	Estimates	CI	p	Estimates	CI	p
Intercept	1.10	0.80–1.40	**<0.001**	1.04	0.64–1.43	**<0.001**	0.98	0.48–1.47	**<0.001**	0.81	0.29–1.33	**0.002**
Time (in days)	−0.28	−0.35 to −0.20	**<0.001**	−0.28	−0.35 to −0.20	**<0.001**	−0.28	−0.35 to −0.20	**<0.001**	−0.28	−0.35 to −0.20	**<0.001**
OT condition (tester)	0.09	−0.28 to 0.46	0.643	0.10	−0.42 to 0.62	0.708	−0.31	−0.94 to 0.32	0.334	0.03	−0.68 to 0.75	0.928
Social condition PAT (positive)				0.14	−0.39 to 0.67	0.601	0.36	−0.27 to 0.99	0.264	0.71	−0.01 to 1.44	0.054
OT × Social				−0.03	−0.77 to 0.71	0.936	−0.03	−0.76 to 0.70	0.935	−0.73	−1.76 to 0.29	0.162
Sex (female)							0.12	−0.50 to 0.75	0.696	0.46	−0.25 to 1.16	0.204
OT × Sex							0.82	0.09–1.55	**0.028**	0.13	−0.88 to 1.14	0.797
Social × Sex							−0.44	−1.17 to 0.29	0.238	−1.14	−2.17 to −0.12	**0.029**
OT × Social × Sex										1.40	−0.05 to 2.85	0.058
τ_{00}	0.97 ID:IDP		**<.001**	0.98 ID:IDP		**<.001**	0.93 ID:IDP		**<.001**	0.90 ID:IDP		**<.001**
ICC	0.30 ID:IDP		**<.001**	0.30 ID:IDP		**<.001**	0.29 ID:IDP		**<.001**	0.28 ID:IDP		**<.001**

Note: OT condition: Placebo = 0, Tester = 1. Social condition: No instruction = 0, Partner appraisal task = 1. Sex: Male = 0, Female = 1. CI: confidence interval; OT: oxytocin; ICC: intraclass correlation coefficient; PAT: partner *appraisal* task; boldface values are significant at at least $p < 0.05$.

including the three-way interaction between oxytocin condition, PAT, and sex, to the model (Model 4, $\chi^2(3) = 3.8$, $p = 0.05$).

Model 3 suggests a significant interaction of OT and sex with men reporting lower pain levels and women reporting higher pain levels in the OT condition. In Model 3, the PAT condition effect was not significant.

When adding the three-way interaction effect (Model 4), results suggest that there was a significant effect of PAT in women with those in the PAT condition experiencing less pain, than those in the control condition. No such effect was found in men. While the interaction effect of OT with the PAT condition did not reach significance, descriptive data suggest that men, who were given OT and participated in the PAT condition experienced less pain than those who did not (c.f. Figures 3 and 4).

While in Model 4 falling just short of reaching significance, the three-way interaction effect of the OT condition × PAT condition × sex suggests that increases in experienced pain for women receiving OT were reduced by PAT. Again, estimates for the random effects indicate that a significant proportion of the variance in pain over time is at the within-person level.

Discussion

In this study, couples received small suction blister wounds to the skin and were then randomized to either daily self-administer OT nasal spray or placebo and practice an instructed positive couple interaction during the lab assessment and once or twice again during the following five days or no instructed interaction. Compliance with the study was high and overall pain levels to the standard wounds were low to non-existent. Compared to randomly assembled dyads, pain levels within the couples were related. Intranasal OT decreased pain perception in men; however, increased pain perception in women. In contrast, women seemed to benefit from the instructed partner appraisal task (PAT), while men did not show any difference in pain perception based on PAT assignment.

Our first result shows that couples reached higher levels of similarity in their pain estimates than randomly assembled dyads. This is in line with previous findings showing that couples co-vary not only in behavior and affect, but above this in their levels of stress and hypothalamic–pituitary–adrenal axis (HPA) activity.[27,35] One hypothesized mechanism might be a tendency toward a joint psychobiological homeostasis,[36] which might show on an emotional, behavioral, and physiological level. Another explanation could be empathic joining.[29] Spouses of pain patients tend to report higher pain levels themselves,[37,38] and fatigue[27] and depressive symptoms have been shown to co-vary within couples.[39]

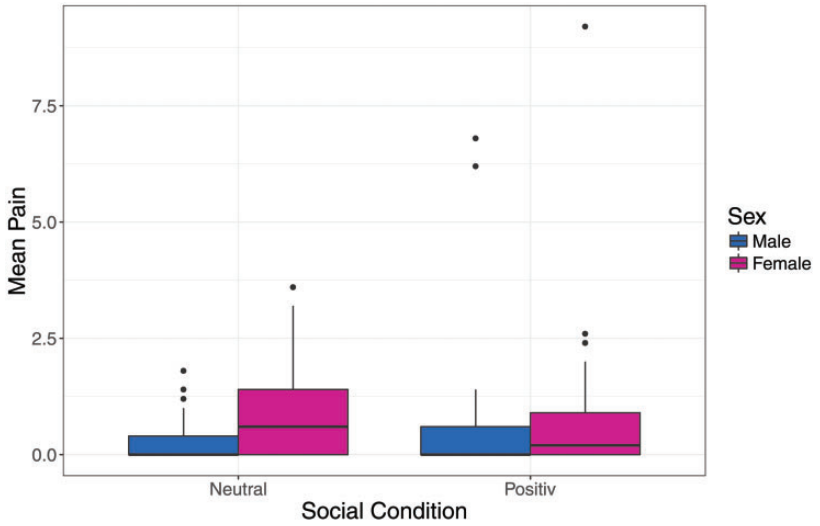

Figure 3. Mean pain ratings in the social interaction groups.

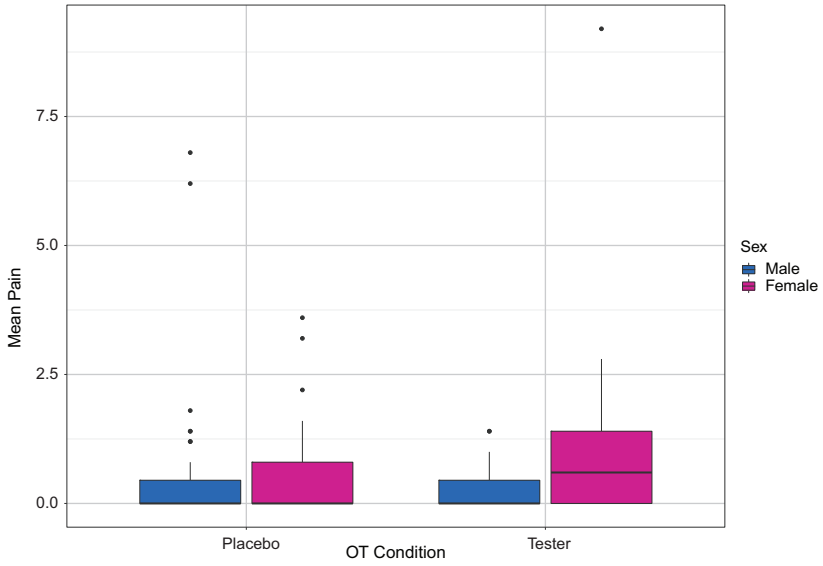

Figure 4. Mean pain ratings in the treatment groups.

These findings might help understand the effects of pain disorders in close relationships[20,40] and implicate partner education or couple-based interventions even under such circumstances.[41]

Previous studies suggest that in chronic pain patients, intranasal OT can have dampening effects not only on perception of their regular pain levels[42,43] but also on experimentally induced acute pain in healthy subjects.[17,44] Rash and Campbell found that pain free individuals, who received OT instead of placebo, reported significantly lower pain levels and pain thresholds to standard pain stimuli during QST.[16] However, other research suggests that instead of an analgesic main effect, intranasal OT might have a beneficial effect on placebo-induced pain reduction.[15] The latter finding was also confirmed in both a healthy pain-free sample[14] and fibromyalgia patients.[45] Notably, while recent data suggest an interaction effect of intranasal OT and social support on pain perception in a laboratory study in women,[19] most studies on this topic to date have been done in men. Thus, while lower pain levels to OT in men[46] are in concurrence with previous studies, there is limited data available only to help interpret our results in women and no single study on repeated OT administration in this context has been published yet. In women, endogenous levels vary across the menstrual cycle[24] and

so might effects of externally administered OT. We did not detect differences between women using oral contraception and naturally cycling women in pain levels. However, in our study, the menstrual cycle stage was controlled in those naturally cycling, and OT effects might have been different during the late follicular or the luteal phase.

We here found that the female participants, in particular, benefited from the PAT, an instructed positive couple interaction and reported reduced pain levels. This is in line with previous research and theory to suggest that women respond more sensitively to social modulators of stress or pain, as men do.[47] It seems reasonable to assume that instructed positive couple interaction, such as in this study, and the associated increase in positive affect might prove a protective factor against pain. In line with this, another study by Leong et al.[48] suggested that validating behavior of wives on husbands with pain are linked to greater pain and lower marital satisfaction. However, this was not the case when the wives had pain. The literature on how overall partner interaction influences pain is mixed. Some studies argue that more involvement from the side of the partner might lead to less pain, whereas some find that it increases pain perception. While it might be good to talk about pain, too much involvement with the topic might have adverse effects.[22] A study by Flor et al. suggests that solicitousness of a spouse can have pain increasing effects, especially if the partner shows profound concerns.[20] This effect was also found in an observational study, where patients with solicitous spouses reported higher pain levels, as compared to patients with partners who expressed no or neutral reactions to their pain.[49] Alarmed or distressing behavior of the partner seems to be related to increased pain perception.[20,22,50]

In considering the findings of this study, some limitations have to be mentioned: the sample consisted of healthy young heterosexual couples, reporting high relationship satisfaction. Given the inconsistent effects of instructed couple interaction or social support in clinical samples or couples in therapy,[51] we cannot extrapolate these findings to couples with severe marital problems or chronic pain. Chronic pain has been defined as persistent or recurrent pain lasting longer than 3 months.[52] In this study, we assessed wound pain over one week, which cannot be considered as chronic pain. Moreover, in contrast to our study where both partners received the wounds, in clinical pain samples usually only one of the partners suffers from a specific disease and/or pain. Nevertheless, our study design exceeds investigation of acute pain in laboratory condition and can be directly transferred to everyday life pain.

Above this, while of high ecological validity the suction blister wound application resulted in relatively low pain levels overall: Only 86 of 160 participants rated their pain higher than 0 at the first measurement point (directly after wound application), and this number decreased to 8 of 160 participants at measurement point six. While this is the result of the relatively harmless and ethically uncritical standardized wound application, it nevertheless means that the effects found are rather small and cannot be generalized to high-intense or chronic pain. Future studies might investigate the effects of intranasal OT and instructed positive couple interaction in patients suffering from chronic pain.

Conclusion

Our results suggest that intranasal OT reduced pain experiences to an ecological valid yet minor pain stimulus—skin wounds—in men, but not in women. As predicted, women benefited from instructed positive partner interaction in terms of dampened pain levels to wounding. These results add to the evidence for health-beneficial effects of positive couple interaction[41] and suggest a pain-dampening effect of OT in men. As such, these data are the first to translate the findings from standard laboratory settings to everyday life and natural occurring pain conditions.

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Author Contributions

ACP and ME equally contributed to analysis and interpretation of the data and drafting of the manuscript. PSP contributed to the analysis of the data. ES, SCH, and MS helped interpreting the data. BD, MH, GB, UE, and SL designed the study. BD led the study, including data acquisition, analysis, and interpretation of the data, and drafting of the manuscript. All authors approved the final version of the manuscript.

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Declaration of Conflicting Interests

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