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SHORT COMMUNICATION

A sniff of trust: Meta-analysis of the effects of intranasal oxytocin administration on face recognition, trust to in-group, and trust to out-group

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Summary The neuropeptide oxytocin has a popular reputation of being the 'love' hormone. Here we test meta-analytically whether experiments with intranasal administration of oxytocin provide support for the proposed effects of oxytocin. Three psychological effects were subjected to meta-analysis: facial emotion recognition (13 effect sizes, $N = 408$), in-group trust (8 effect sizes, $N = 317$), and out-group trust (10 effect sizes; $N = 505$). We found that intranasal oxytocin administration enhances the recognition of facial expressions of emotions, and that it elevates the level of in-group trust. The hypothesis that out-group trust is significantly decreased in the oxytocin condition was not supported. It is concluded that a sniff of oxytocin can change emotion perception and behavior in trusting relationships.

The neuropeptide oxytocin has a strong popular and scientific reputation as the 'love' hormone that creates warm feelings for offspring (Carter, 1998; Feldman et al., 2007, 2010; Galbally et al., 2011; Insel, 1992, 2010) and supports empathic concern for conspecifics (MacDonald and MacDonald, 2010) through better recognition of emotional facial expression (Bartz et al., 2010; Hurlemann et al., 2010; Kirsch et al., 2005; Marsh et al., 2010). Moreover, it would elevate the level of trust in other human beings (De Dreu et al., 2010; Kosfeld et al., 2005). Experimental studies on oxytocin have contributed to our knowledge of its associations with human perception and behavior. Here we test meta-analytically whether experiments with intranasal administration of oxytocin indeed confirm the proposed effects of oxytocin.

Whereas early behavioral experiments with intravenous administration of oxytocin were short-lived due to disappointing results (e.g., Bruins et al., 1992), in recent years the number of experiments using intranasal administration of oxytocin to study human perception, emotion, and behavior has increased dramatically. The reason is that intranasal administration indeed seems to induce replicable changes in brain functioning (Perry et al., 2010; Riem et al., 2011), perception (Theodoridou et al., 2009), and behavior (Naber et al., 2010), in contrast to intravenously administered oxytocin for which the blood—brain barrier might have been difficult to pass. Nevertheless, salivary oxytocin might not be an adequate indicator of levels of oxytocin in the brain, and experimental effects of intranasally administered oxytocin

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may be due to the participants' awareness of the administration. Double blind experiments are crucial to counteract these potential biases (Eisenegger et al., 2010).

In oxytocin experiments two areas of human functioning have been investigated most intensively: recognition of facial expression of emotions such as fear, anger, happiness; and feelings of trust in other human beings. Recently trust of members of the in-group and out-group has been differentiated (De Dreu et al., 2010). From an evolutionary perspective it is suggested that oxytocin may enhance the inclination to protect offspring against predators (Carter, 1998), and thus increase (defensive) aggression against threats from out-group members.

Here we take stock of the first wave of experiments with intranasal oxytocin administration, and test whether intranasally administered oxytocin leads to better recognition of facial expressions and more trust in conspecifics, except when they are labeled as out-group members, in which case trust may even decrease after oxytocin administration (De Dreu et al., 2010; but see Chen et al., 2011). We will explore the moderating influence of the following design features on the outcomes of the oxytocin experiments: within-subject versus between-subject design; the use of a saline placebo or a placebo with all ingredients of the oxytocin spray except for the neuropeptide; time delay between oxytocin administration and test of effect; gender of the participants, and their awareness of the experimental manipulation.

1. Method

For our meta-analysis we systematically searched the database Web of Science with the key words oxytocin, intranasal*, and administ* in the title or abstract (the asterisk indicating that the search contained the word or word fragment). We excluded intravenous administration studies, studies on the effects of oxytocin on parturition or breastfeeding (see for a meta-analysis Wei et al., 2009) non-experimental investigations of oxytocin, and studies on clinical samples (such as individuals with autism spectrum disorder, e.g., Hollander et al., 2007). We finished the search on January 1, 2011. We identified 23 original empirical papers with 31 pertinent effect sizes, providing data for three meta-analyses on effects of oxytocin on face recognition (13 effect sizes, $N = 408$), in-group trust (8 effect sizes, $N = 317$), and out-group trust (10 effect sizes; $N = 505$).

The Comprehensive Meta-Analysis (CMA; Borenstein et al., 2005) program was used to transform the results of the individual studies into the common metric of Cohen's d, or the standardized difference between the intervention and the control condition. Studies could contribute to all three meta-analyses but the same subject was never used twice in the same meta-analysis. The implication however was that some participants were included in two or more meta-analyses; which made it impossible to directly compare effect sizes across the three sets (i.e., effects on face recognition compared to in-group or out-group trust). Therefore the 85% confidence intervals for the point estimates of the combined effect sizes were computed: non-overlapping 85% CI's suggest a significant difference between combined effect sizes that are not independent (Goldstein and Healy, 1995; Van IJzendoorn et al., 2005).

Effect sizes in a set of studies may show smaller or larger variation, and the average or combined effect size across the studies might capture its central tendency more or less adequately. Heterogeneity across studies was assessed using the Q-statistic. Significance tests of combined effect sizes as well as categorical moderator effects were performed with the Q-statistic on the basis of a random effects model (Borenstein et al., 2005). Meta-regression was used to examine the effect of the delay in minutes between oxytocin administration and the test of a behavioral effect on the outcomes of the studies as this was a continuous moderator (Borenstein et al., 2005).

Studies with a small number of subjects and small effect sizes may have a lower chance to be published (publication bias), which might lead to an overestimation of the combined effect size. We used the "trim and fill" method that estimates the number and effect sizes of the potentially non-published studies (Duval and Tweedie, 2000a,b) to calculate the effect of potential data censoring or publication bias on the outcome of the meta-analyses (Sutton et al., 2000). We also computed the fail-safe number of studies needed to reduce a significant combined effect size to non-significance and compared it to Rosenthal's (1991) fail-safe number, $5k + 10$ (k = number of studies included). The fail-safe number is the lowest number of studies with null effects needed to reduce the combined effect size found in the current meta-analysis to non-significance. Moreover, we computed the combined effect size for awareness of condition, i.e., whether the subjects knew if they were administered oxytocin or placebo, as reported in part of the studies.

2. Results

The combined effect size for face recognition amounted to $d = 0.21$ ($p < .01$, 95% CI 0.07, 0.36), in a homogeneous set of studies (Q [$df = 12$] = 10.68). Trim-and-fill did not show a publication bias. Only 19 studies with null effect would be needed to bring the combined effect size down to a non-significant level, a considerably smaller number than Rosenthal's fail-safe criterion. Although the studies with a between-subjects design showed the significant and largest combined effect size ($d = 0.30$, $p = .01$), the difference with the combined outcome of the within-subjects experiments ($d = 0.16$, $p = .10$) was non-significant ($Q_{contrast} = 0.84$, $p = .36$). The other moderator contrasts could not be computed due to too small sets of studies (see Table 1). Time delay between oxytocin administration and behavioral test was not a significant moderator, $z = 0.43$, $p = .67$.

The combined effect size for the in-group trust experiments was $d = 0.48$ ($p < .01$, CI 0.19, 0.77) in a heterogeneous set of studies (Q [$df = 7$] = 15.09, $p < .05$). Trim-and-fill analysis showed a publication bias, and correcting for 1 missing study outcome the combined effect size amounted to $d = .40$ ($p < .05$, CI 0.10, 0.70). Forty-four studies with null effects would be needed to bring the combined effect size down to a non-significant level, still smaller than Rosenthal's fail-safe criterion. Again the six studies with a between-subjects design showed the largest combined effect size ($d = 0.63$, $p < .001$), but the significance of the difference with the outcome of the within-subjects experiments ($d = 0.12$, $p = .53$) could not be tested because only two

Table 1 Effects of oxytocin administration on face recognition, trust to in-group, and trust to out-group.

	k	*N*	*d*	Confidence interval[a] 95%	Homogeneity *Q*
Face recognition					
Total set	13	408	0.21**	0.07 to 0.36	10.68
Design					
Between-subject	7	276	0.30*	0.06 to 0.53	7.54
Within-subject	6	132	0.16	−0.03 to 0.34	2.30
Gender					
Males	10	306	0.23**	0.06 to 0.40	9.88
Females	1	16	0.09	−0.40 to 0.58	
Mixed	2	86	0.17	−0.26 to 0.60	0.47
Placebo					
Saline	3	113	0.14	−0.15 to 0.42	0.53
OT-	8	243	0.19*	0.01 to 0.37	5.47
Not reported	2	52	0.57*	0.10 to 1.04	2.16
Trust to in-group					
Total set	8	317	0.48**	0.19 to 0.77	15.09*
Design					
Between-subject	6	273	0.63**	0.35 to 0.92	6.78
Within-subject	2	44	0.12	−0.26 to 0.51	1.40
Gender					
Males	7	280	0.44**	0.14 to 0.75	13.70*
Females					
Mixed	1	37	0.81	0.13 to 1.49	
Placebo					
Saline	1	17	0.34	−0.15 to 0.83	
OT	6	263	0.49*	0.11 to 0.86	14.26*
Not reported	1	37	0.73*	0.01 to 1.46	
Trust to out-group					
Total set	10	505	0.21	−0.06 to 0.48	26.70**
Design					
Between-subject	8	431	0.24	−0.10 to 0.57	14.67*
Within-subject	2	74	0.14	−0.42 to 0.71	9.48**
Gender					
Males	7	316	0.24	−0.12 to 0.60	15.97*
Females					
Mixed	3	189	0.16	−0.31 to 0.64	9.36**
Placebo					
Saline	1	18	0.66*	0.15 to 1.17	
OT-	7	408	0.17	−0.15 to 0.50	12.01
Not reported	2	79	0.08	−0.48 to 0.65	6.15*

[a] Based on random effect model unless $k = 1$.
* $p < .05$.
** $p < .01$.

within-subjects experiments were available (see Table 1). Time delay between oxytocin administration and behavioral test was not a significant moderator, $z = -1.93$, $p = .053$.

The combined effect size for the out-group trust experiments was not significant, $d = 0.21$ ($p > .05$, CI −0.06, 0.48) in a heterogeneous set of studies (Q [$df = 9$] = 26.70, $p < .01$). Trim-and-fill indicated a publication bias: two studies needed to be trimmed and filled, resulting in an adjusted combined effect size of only $d = 0.10$ (CI −0.15, 0.36). Studies with a between-subjects design showed the largest but still non-significant combined effect size ($d = 0.24$, $p = .16$). Time delay between oxytocin administration and test of an effect was not a significant moderator, $z = 0.47$, $p = .64$.

Fig. 1 shows the combined effect sizes of the three meta-analyses, with the largest effect sizes for face recognition and in-group trust. From Fig. 1 (showing 85% confidence intervals) it may be derived that the three combined effects were not significantly different, so it cannot be concluded that effects for in-group trust were significantly stronger than effects for out-group trust or face recognition.

In a separate meta-analysis, the awareness tests of seven studies (Alvares et al., 2010; Bartz et al., 2010; Bruins et al., 1992; Fischer-Shofty et al., 2010; Kirsch et al., 2005; Rimmele et al., 2009; Theodoridou et al., 2009) were combined. The combined Odds ratio for the chance that participants would correctly guess the type of administration was 0.91 ($p = .067$, total $N = 265$). Type of placebo (saline versus carrier minus the neuropeptide) did not moderate the awareness outcomes, but the majority (5 out of 7) of the experiments used the carrier minus oxytocin. Design

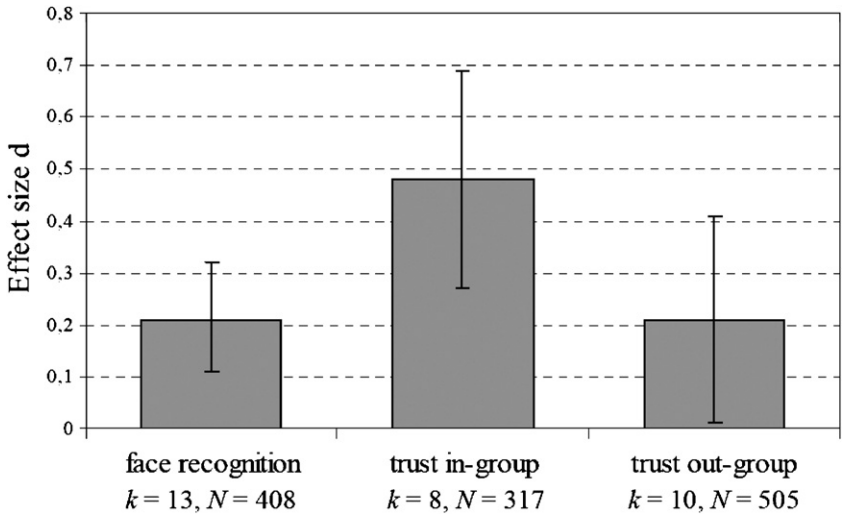

Figure 1 Effects of oxytocin administration on face recognition, trust to in-group, and trust to out-group: combined effect sizes (*d*) and 85% confidence intervals.

(between-subjects versus within-subjects) did not make a difference either ($Q_{contrast} = 0.04$, $p = .84$). It should be noted that in some of the experiments awareness was even negative, that is, more participants guessed that they were administered oxytocin when they were not than chance would allow for (e.g., Theodoridou et al., 2009), showing that it seems rather difficult for participants to know whether they received oxytocin or placebo.

3. Discussion and conclusions

Intranasal oxytocin administration enhances the recognition of facial expressions of emotions, and it elevates the level of in-group trust. The oxytocin experiments conducted to date do however not support the hypothesis that out-group trust is significantly decreased in the oxytocin condition. Intranasal oxytocin administration indeed seems 'a sniff of trust', but the effect sizes are more modest than popular press has suggested. Cohen's *d* ranged from weak ($d = 0.21$, face recognition) to moderate ($d = 0.43$, in-group trust) according to conventional effect size criteria (Lipsey and Wilson, 2000).

Because the fail-safe numbers are rather small compared to the number of studies conducted thus far this area of investigation is not yet saturated. There is an urgent need for replication and extension of the current set of studies, in particular of those studies that differentiate between trust to in-group and trust to out-group members. In the current meta-analysis the number of participants involved in studies on out-group trust was largest and thus the likelihood to find a (negative) effect would be largest in this set of studies. However, the combined effect size of the out-group trust experiments was not significantly different from zero whereas that of the in-group experiments was substantial.

The current meta-analysis is also limited because of the limited room for moderator analyses as a consequence of the small set of effect sizes in each of the moderator subsets. A robust test of the moderating role of design features such as gender, kind of placebo, and participants' awareness of the oxytocin administration was impossible. In the overwhelming majority of studies a dose of 24 IU of oxytocin was used, and a delay of 35—50 min between administration and observation was planned. We therefore do not know whether lower or higher doses of oxytocin have similar effects, and it is unclear how much time outside the 35—50 min window it takes before the oxytocin effects emerge and fade out.

Nevertheless, the use of intranasal oxytocin in experiments on emotion recognition and trust has led to a promising and grounded hypothesis, namely that intranasally administered oxytocin can change emotion perception and behavior in trusting relationships. This first wave of experiments documents a proof of principle of the perceptual and behavioral effects of intranasal administration of an important neuropeptide involved in social-emotional relationships. It opens a myriad of possibilities to uncover the development and dynamics of emotional empathy and trust in close relationships.

One of the most exciting but unexplored areas for future studies is the effect of oxytocin administration on the impact of cognitive or behavioral interventions targeting at the improvement of parent—child or partner relationships. Cognitive behavior therapy of marital problems (Ost, 2008) and interaction-focused parent training (Stein et al., 2006) might become more effective if oxytocin administration would be a component of the treatment and used to sharpen the perception of emotions in partner or child. Oxytocin may lower the level of resistance against dealing constructively with negative emotional signals of partner or child (Riem et al., 2011).

Oxytocin might not be the equivalent of trust and it might not be a stand-alone treatment drug for interpersonal problems but it may prove to be an important catalyst in broader relationship therapies and interventions.

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The Netherlands Organization for Scientific Research had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest

The authors declare that they have no conflicts of interest.

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