Supporting Information Appendix

Placebo treatment facilitates social trust and approach behavior

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Supporting information

Section 1. Expectation formation of oxytocin effects (Exp. 0a)

Self-paced learning of oxytocin related documents was employed to induce expectation of the benefits of intranasal administration of oxytocin on social cognition. To test whether the oxytocin documents delivered the beneficial effects of oxytocin, we conducted a pilot experiment (Exp. 0a) where participants (N = 173; 101 males; mean age ± SD = 27.270 ± 5.450 years) first self-paced learnt oxytocin materials, and then were asked to describe their understanding of oxytocin based on what they had learned (at least 50 words).

To reveal the information delivered by the oxytocin materials, we performed text analysis on participants' descriptions using the tm package (text mining; *ref.* 1) and Snowball package (2) in R. Description scripts from all participants were preprocessed (i.e., converting all characters to lower-case and removing punctuation and stop words) to build up a Document × Term Matrix where *document* referred to each participant's description and *term* referred to each description item. Terms appeared in fewer than 5% of documents were eliminated. The frequency indicated the importance of a specific term, higher the frequency more important the term (3). The most frequently mentioned terms (top 10, Fig. S1A) were: oxytocin (repeated 404 times), people (142 repeats), trust (137 repeats), interpersonal (88 repeats), social (60 repeats), enhance (60 repeats), human (42 repeats), women (38 repeats), moral (35 repeats), behavior (34 repeats).

Moreover, we examined the associations of the top 10 terms by calculating the cosine distance (4), the larger the cosine value the stronger association of two terms. The cosine distance map (Fig. S1B) illustrated the associations among the top 10 terms, suggesting that oxytocin, serving as the core term, was indeed associated with the beneficial social effects, such as "interpersonal", "trust", "social" and "behavior".

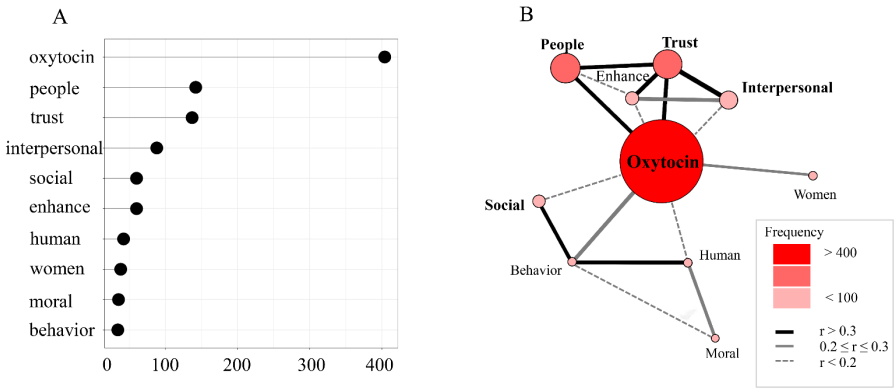

Fig. S1. Expectation formation of oxytocin effects on social cognition. (A) The most frequently mentioned 10 terms in participants' description of oxytocin effect. (B) Cosine distance map of the top 10 terms.

Moreover, we asked participants in Exp. 1 and 2 to report their willingness to trust others and to interact with others induced by the manipulation in each session on an 11-point Likert scale (from 0 = "not willing at all" to 10 = "extremely willing"). The manipulation check questions were designed to check participants' expectation of increased social trust in others and closer interpersonal distance induced by SPE manipulation. We test whether participants would expect beneficial effects of oxytocin on social trust and interpersonal distance from the SPE manipulation. *Spray*$^{+}$ manipulation induced expectation of increased social trust on others and closer interpersonal distance in Exp. 1 (willingness to trust: F (2, 56)[1] = 5.155, P = 0.009, η_p^2 = 0.155; willingness to interact with others: F (2, 52)[2] = 4.963, P = 0.011, η_p^2 = 0.160), similarly in Exp. 2 (willingness to trust: t (30)[3] = 2.974, P = 0.006, Cohen d' = 0.534; willingness to interact with others: t (31) = 1.639, P = 0.055, Cohen d' = 0.289, one tailed), suggesting that participants indeed expected beneficial effects of oxytocin on social trust and social interaction after the SPE manipulation. However, participant's experimental expectation was not correlated with the SPE on social trust (Exp. 1: r(29) = 0.306, P = 0.106; Exp. 2: r(31) = 0.059, P = 0.755) or interpersonal distance (Exp. 1: r(29) = -0.124, P = 0.536; Exp. 2: r(30) = -0.123, P = 0.509) was not participants' perceived experimental expectation.

[1] One participant in Exp. 1 failed to complete the rating of willingness to trust.
[2] Three participants in Exp. 1 failed to complete the rating of willingness to interact with others.
[3] One participant in Exp. 2 failed to complete the rating of willingness to trust.

Section 2. Matched oxytocin and control materials (Exp. 0b)

We used the oxytocin–irrelevant materials, with the topic of robot, as the control materials. The control materials were edited to keep a similar length and format with the oxytocin materials. We conducted a pilot experiment (Exp. 0b, $N = 143$, 95 males) to examine whether participants understood and were interested in the oxytocin and control materials to the same extent, as well as whether the two types of materials induced similar mood change. We adopted a between-subjects design, resulting in 72 participants (50 males; mean age ± SD = 26.680 ± 5.453 years) completed ratings of the oxytocin materials, and 71 participants (45 males; mean age ± SD = 27.267 ± 5.350 years) rated the control materials. The two groups did not differ in age (t (141) = -0.650, $P = 0.517$, Cohen d' = 0.054).

Participants first completed the Positive and Negative Affect Scale (PANAS, *ref.* 5), to assess their baseline mood, then completed the self-paced learning of oxytocin or control materials. After exposure to the materials, participants were asked to complete a post-learning survey, in which participants reported their mood once again, and were asked to report: 1) "How interesting do you think the oxytocin/robot materials are?" (on a 11-point Likert scale: 1 = not interesting at all, 11 = extremely interesting); and 2) "How much do you understand the oxytocin/robot materials?" (1 = not understand at all, 11 = understand extremely well).

We found that the mood changes from baseline to post-learning did not differ between the two groups who learnt the oxytocin or control materials (F (1, 141) = 2.370, P = 0.126, $\eta_p^2 = 0.017$). Furthermore, participants found the oxytocin and control materials were equally interesting (t (141) = -0.276, $P = 0.783$, Cohen d' = 0.023), and participants comprehended the oxytocin and control materials to a similar level (t (141) = -0.510, $P = 0.611$, Cohen d' = 0.043). These effects did not differ between males and females (interesting rating: F (1,139) = 0.346, $P = 0.557$, $\eta_p^2 = 0.002$; *comprehension* rating, F (1,139) = 1.824, $P = 0.179$, $\eta_p^2 = 0.013$).

Section 3. Effects of exposure to oxytocin and control materials alone (Exp. 0c)

To examine whether exposure to the oxytocin and control materials alone would influence social trust and distance, we conducted a pilot experiment (Exp. 0c, N = 187) where participants were first exposed to oxytocin and control materials in a self-paced manner, and then completed the trust game and the distance preference task. In a between-subjects design, 94 participants (41 males; ages 19-43 years; mean age ± SD = 28.361 ± 5.213 years) were randomly assigned to the oxytocin material group, and 93 participants (63 males; ages 19-49 years; mean age ± SD = 26.98 ± 6.02 years) to the control material group. Participants in the oxytocin and control group did not differ in age (t (185) = 1.66, P = 0.098, Cohen d' = 0.122).

We first examined whether exposure to the oxytocin materials alone would influence social trust by comparing the investment amount in the trust game between the two groups who have leant the oxytocin or control materials. We found that participants sent similar amount of tokens to the trustee after exposure to either oxytocin or control materials (mean difference (oxytocin-control materials) = -0.387 ± 5.895, 95% CI = [-1.237, 0.463], t (185) = -0.898, P = 0.370, Cohen d' = 0.065). We then examined whether exposure to the oxytocin materials alone influenced preferred interpersonal distance. We compared the percentage of choosing closer distance and the preferred distance between groups exposed to oxytocin and control materials. We found that participants exposed to the oxytocin and control materials chose similar percentage of closer distance (mean difference (oxytocin-control materials) = 0.347 ± 55.885, 95% CI = [-7.714, 8.410], t (185) = 0.085, P = 0.932, Cohen d' = 0.006) and showed similar preferred distance (mean difference (oxytocin- control materials) = 2.251 ± 46.753, 95% CI = [-4.493, 8.996], t (185) = 0.658, P = 0.511, Cohen d' = 0.048). These results suggested that exposure to different types of materials did not influence trust in others or preferences of interpersonal distance. Moreover, this is true for both males and females (trust game: F (1,183) = 0.289, P = 0.591, η_p^2 = 0.002; interpersonal distance preference: F (1,183) = 1.367, P = 0.244, η_p^2 = 0.007).

Section 4. Null effect on mood change

In Exp. 1-4, we measured participants' current mood and state anxiety using the PANAS (5) and State Anxiety Inventory (SAI, *ref.* 6) before and after the experiment. The SAI contains 20 items for assessing state anxiety, with higher scores indicating greater state anxiety.

We examined whether the placebo treatment (i.e., *spray*$^+$ manipulation) induced mood and state anxiety change (from baseline to post-experiment) compared to the *control* conditions (Table S1). First, we found that *spray*$^+$ manipulation did not significantly change participants' mood or state anxiety (pair t-test on baseline vs. post-experiment). Moreover, we compared mood change and state anxiety change between *spray*$^+$ session and control sessions (*spray control* and *material control* in Exp. 1; and *material control* in Exp. 2 and 3). In Exp. 4, we also found that double-blind intranasal administration of oxytocin or PL did not lead to mood and state anxiety change.

Table S1. Changes in general mood or state anxiety from baseline to post-experiment in Exp.1-4.

Exp	Condition	Mood change *t/F* (*P*)	State anxiety change *t/F* (*P*)
Exp. 1	*spray*$^+$	-0.368 (0.716)	0.897 (0.377)
	spray$^+$ vs. *material control*	F < 1	F < 1
	spray$^+$ vs. *spray control*	4.432 (0.045)	0.820 (0.746)
Exp. 2	*spray*$^+$	0.865 (0.394)	0.810 (0.424)
	spray$^+$ vs. *material control*	F < 1	3.209 (0.083)
Exp. 3	*spray*$^+$	-0.512 (0.613)	0.215 (0.832)
	spray$^+$ vs. *material control*	F < 1	F < 1
Exp. 4	*oxytocin*	1.924 (0.066)	-0.675 (0.506)
	oxytocin vs. *PL*	2.076 (0.164)	F < 1

Section 5. Using *material control* as control condition in Exp. 2 and 3

In Exp. 1, we included two control conditions, i.e., *spray control* and *material control*. We found that participants' behaviors did not differ in the two control conditions. Participants sent similar amount of tokens in the trust game in the two control sessions (*spray control* vs. *material control*: 6.925 ± 3.139 vs. 7.023 ± 3.426, 95% CI = [-1.542, 1.346], t (28) = -0.139, P = 0.891, Cohen d' = 0.025). In the distance preference task, the percentage of choosing closer distance (*spray control* vs. *material control*: 36.147 ± 19.878 vs. 39.025 ± 21.335, 95% CI = [-9.274, 3.518], t (28) = -0.922, P = 0.365, Cohen d' = 0.171) and the mean preferred distance (*spray control* vs. *material control*: 144.006 ± 16.987 vs. 140.345 ± 18.032, 95% CI = [-1.784, 9.105], t (28) = 1.377, P = 0.179, Cohen d' = 0.255) did not differ in the *spray control* and *material control* conditions.

In Exp. 1, participants were invited to three sessions, and were exposed to the oxytocin materials twice (once in the *spray*$^+$ session and another in the *spray control* session, although order counterbalanced). Although we showed that *spray*$^+$ manipulation did not induce mood change (Table S1), we found that exposure to the same materials twice may induce potential influences on participants' mood as we found influences on mood in the comparison of *spray*$^+$ vs. *material control*, but not *spray*$^+$ vs. *spray control* (Table S1). Moreover, impact on mood was found when comparing the mood change between the first-exposure and second-exposure to the oxytocin materials across *spray*$^+$ and *spray control* sessions (t (27) = 2.105, P = 0.045, Cohen d' = 0.397).

To further confirm such influence, we recruited an independent sample (N = 62, 37 males; ages 18-43 years; mean age ± SD = 26.645 ± 6.148 years). Participants completed two sessions. In each session, participants reported their general mood before and after exposure to oxytocin materials. We found that, exposure to the oxytocin materials for the first time did not lead to mood change (t (61) = 1.564, P = 0.123, Cohen d' = 0.198), however, exposure to the oxytocin materials for the second time led to mood change (t (61) = 2.096, P = 0.040, Cohen d' = 0.266). Thus, exposure to the same materials twice would influence the mood. To avoid the influence of exposure to oxytocin materials twice, we used the *material control* as the control condition in Exp. 2 and 3.

Section 6. Placebo treatment increased the percentage of choosing closer distance

In the main text, we reported that placebo treatment decreased preferred distance in the distance preference task. We showed here that the analysis on another index (i.e., percentage of choosing closer interpersonal distance) showed the same pattern of SPE on interpersonal distance. The repeated-measure ANOVA with Treatment (*spray*$^{+}$, *spray control*, *material control*) as within-subject factor revealed a significant effect of Treatment on the percentage of choosing closer distance (F (2, 56) = 11.296, P < 0.001, η_p^2 = 0.287, Fig. S2A). Participants preferred to choose closer distance in the *spray*$^{+}$ than the *spray control* (t (28) = 3.846, P = 0.002, Cohen d' = 0.714) and *material control* sessions (t (28) = 4.163, P < 0.001, Cohen d' = 0.773; adjusted for multiple comparison using Bonferroni correction). The placebo effect on the increased percentage of choosing closer distance was similarly observed in Exp. 2 (t (30) = 2.112, P = 0.043, Cohen d' = 0.379, Fig. S2B).

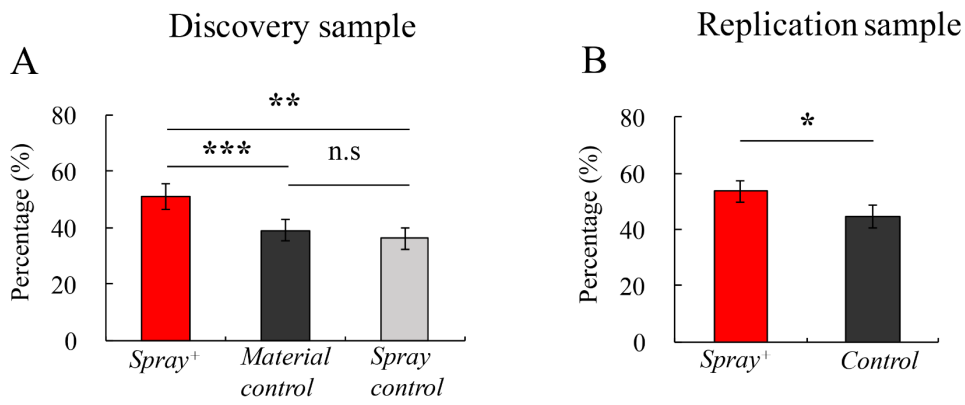

Fig. S2. Placebo effect on increasing the percentage of choosing closer interpersonal distance. The social placebo effect increased the percentage of choosing closer interpersonal distance in discovery sample (Exp. 1, A) and replication sample (Exp. 2, B). * P < 0.05, ** P < 0.01, *** P < 0.001, n.s not significant.

Section 7. Mediation analysis

Mediation analyses were performed to examine whether the SPE on interpersonal distance preference was mediated by social trust. According to the mediation parameter estimation method for repeated measures (7), we construct the following regression model:

$Y_{spray}^{+} - Y_{control} = \beta 11 + e1$ (1)
$Mediator_{spray}^{+} - Mediator_{control} = \beta 21 + e2$ (2)
$Y_{spray}^{+} - Y_{control} = \beta 31\ x + \beta 32\ (Mediator_{spray}^{+} - Mediator_{control}) + \beta 32'\ (Mediator_{spray}^{+} + Mediator_{control})^{*} + e3$ (3)
(*mean centered)

Three conditions for establishing repeated-measures mediation are: (a) in Equation 1, the difference between the dependent variable (preferred distance, results reported in the main text and Table S2; percentage of choosing closer distance, Table S3, Fig. S3) must be significant (β_{11} is significant), that is the SPE on the preferred distance in the distance preference task must be significant; (b) in Equation 2, the difference between the mediator (the amount of tokens invested in the trust game) must be significant (β_{21} is significant), that is the SPE on social trust must be significant; (c) in Equation 3, when regressing the difference on dependent variable onto the difference on mediator, the difference on mediator (i.e., SPE on trust) must predict the difference on dependent variable (i.e., SPE on distance preference), that is the β_{32} must be significant. If there was a significant mediation effect, the effects of the difference between dependent variable must be reduced or even eliminated, $\beta_{31} < \beta_{32}$ (in absolute value, partial mediation) or β_{31} is not significant any more (full mediation). The Sobel test (8) was conducted to further confirm the significance of the mediator, if the Sobel test is significant, which means that the predictor significantly affects the outcome variable via the mediator. Moreover, a resampling method known as bootstrapping was also necessary for evaluate the mediation effect due to the Sobel test was harder to get sucked in to the black-and-white thinking of significance testing. Bootstrapping is a nonparametric approach to effect-size estimation and hypothesis testing that is increasingly recommended for many types of analyses, including mediation (9, 10). Rather than impose questionable distributional assumptions, bootstrapping generates an empirical approximation of the sampling distribution of a statistic by repeated random resampling from the available data, and uses this distribution to calculate p-values and construct confidence intervals (5,000 resamples were taken for these

analyses). Moreover, this procedure supplies superior confidence intervals (CIs) that are bias-corrected and accelerated (11). To maintain congruence with results of more familiar analyses, our description of findings below included data showing that all models conform with Baron and Kenny's criteria, and also include results based on Sobel's test.

Table S2. Results of mediation analysis to test the amount of investment in trust game as a mediator of the social placebo effect on preferred distance.

Variable	Coeff	SEM	t	p	LLCI95	ULCI95
Regression Model 1 (Total effect of Treatment on preferred distance)						
Treatment (*spray*$^+$ vs. *control*)	-8.903***	2.232	-3.988	<0.001	-13.369	-4.436
Dependent: preferred distance						
Regression Model 2 (effect of Treatment on the amount of investment in Trust game)						
Independent: Treatment (*spray*$^+$ vs. *control*)	1.819***	0.433	4.193	<0.001	0.951	2.687
Mediator: investment in Trust game						
Direct effects of mediator on preferred distance						
Independent: Treatment (*spray*$^+$ vs. *control*)	-1.984**	0.637	-3.111	0.002	-3.261	-0.707
Remaining direct effects of Treatment on preferred distance						
Independent: Treatment (*spray*$^+$ vs. *control*)	-5.293*	2.396	-2.209	0.031	-10.091	-0.495
Indirect effect of Treatment on mean preferred distance via trust						
Independent: Treatment (*spray*$^+$ vs. *control*)	-3.609	1.619			-7.099	-0.791
Sobel Test: Indirect effect	-3.609*	1.444	-2.498*(Z)	0.012		

Notes. *P < 0.05, ** P < 0.01, *** P < 0.001
Confidence intervals for indirect Effect are bias-corrected and accelerated; bootstrap resamples = 5000; $N = 60$ for all tests.

Table S3. Results of mediation analysis to test the amount of investment in trust game as a mediator of the social placebo effect on percentage of choosing closer distance.

Variable	Coeff	SEM	t	p	LLCI95	ULCI95
Regression Model 1 (Total effect of Treatment on percentage of choosing closer distance)						
Treatment (*spray*$^{+}$ vs. *control*)	10.409***	2.580	4.034	<0.001	5.246	15.572
Dependent: percentage of choosing closer distance						
Regression Model 2 (Effect of Treatment on social trust)						
Independent: Treatment (*spray*$^{+}$ vs. *control*)	1.819***	0.433	4.193	<0.001	0.951	2.687
Mediator: investment in the Trust game						
Direct effects of mediator on percentage of choosing closer distance						
Independent: Treatment (*spray*$^{+}$ vs. *control*)	2.586***	0.718	3.599	<0.001	1.147	4.025
Remaining direct effects of Treatment on percentage of choosing closer distance						
Independent: Treatment (*spray*$^{+}$ vs. *control*)	5.703*	2.700	2.112	0.039	0.297	11.110
Indirect effect of Treatment on percentage of choosing closer distance via trust						
Independent: Treatment (*spray*$^{+}$ vs. *control*)	4.705	1.833			1.651	8.700
Sobel Test: Indirect effect	4.705**	1.722	2.731**(Z)	0.006		

Notes. *P < 0.05, ** P < 0.01, *** P < 0.001.
Confidence intervals for indirect Effect are bias-corrected and accelerated; bootstrap resamples = 5000; $N = 60$ for all tests.

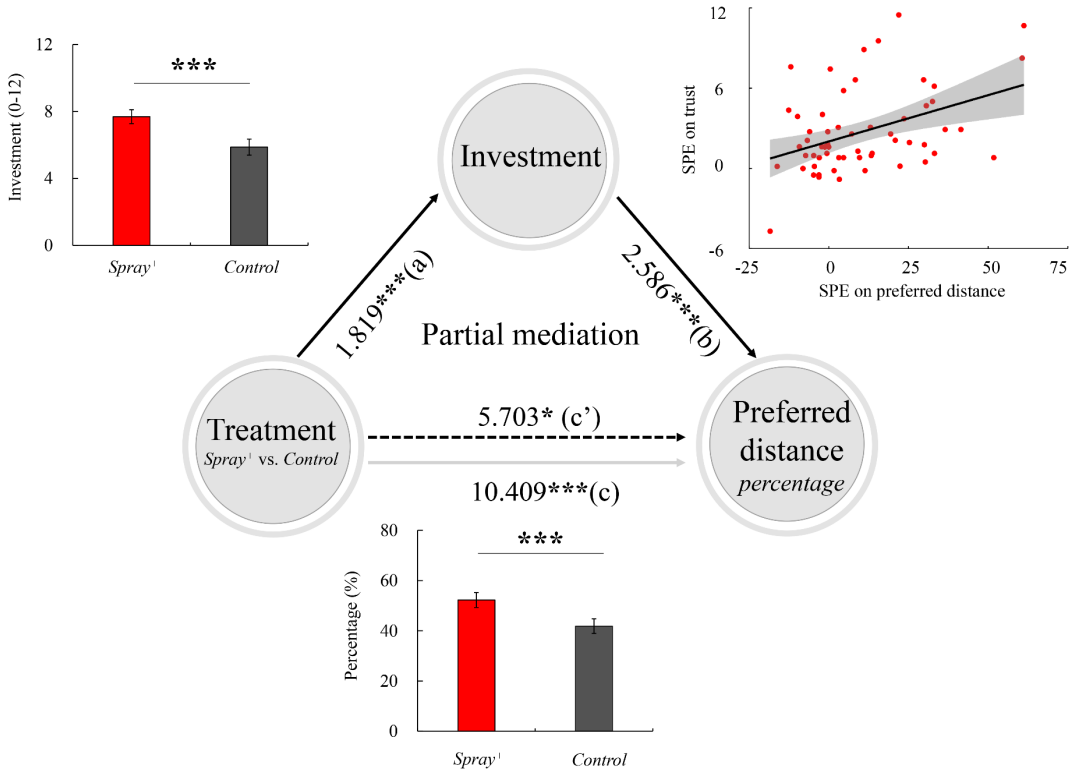

Fig. S3. Placebo treatment increased the percentage of choosing closer distance through increasing trust in others. The SPE on trust ($Trust_{spray+} - Trust_{control}$) was significantly correlated with the SPE on the percentage of choosing closer distance ($r(60) = 0.411$, $P = 0.001$). A mediation analysis further confirmed that the *spray*$^+$ manipulation impacted interpersonal distance through increasing trust in others (Sobel test, $Z = 2.731$, $P = 0.006$, partial mediation; Table S3). * $P < 0.05$, *** $P < 0.001$.

Section 8. Log-transforming distance in real-life situation

In the stop-distance task, the distribution of the raw distance data is right-skewed. Thus linear regression is not appropriate on the raw data. To address this issue, we log10-transform interpersonal distance in all analyses (Fig. S4). Moreover, the placebo effect on interpersonal distance in real-life situation was qualitatively similar when analyzing on the non-transformed distance. Similarly, we conducted a 2 (Treatment: *spray*$^+$ vs. *material control*) × 2 (Eye-contact: with *vs.* without) ANOVA on the non-transformed distance. We found a marginally significant main effect of Treatment (F (1, 29) = 3.996, P = 0.055, η_p^2 = 0.121) and significant interaction of Treatment and Eye-contact (F (1, 29) = 5.067, P = 0.032, η_p^2 = 0.149). Specifically, participants kept a closer distance with the female experimenter in the *spray*$^+$ (relative to *control*) session in the no eye-contact situation (t (29) = -2.522, P = 0.017, Cohen d' = 0.460), but not eye-contact situation (t (29) = -0.827, P = 0.415, Cohen d' = 0.151).

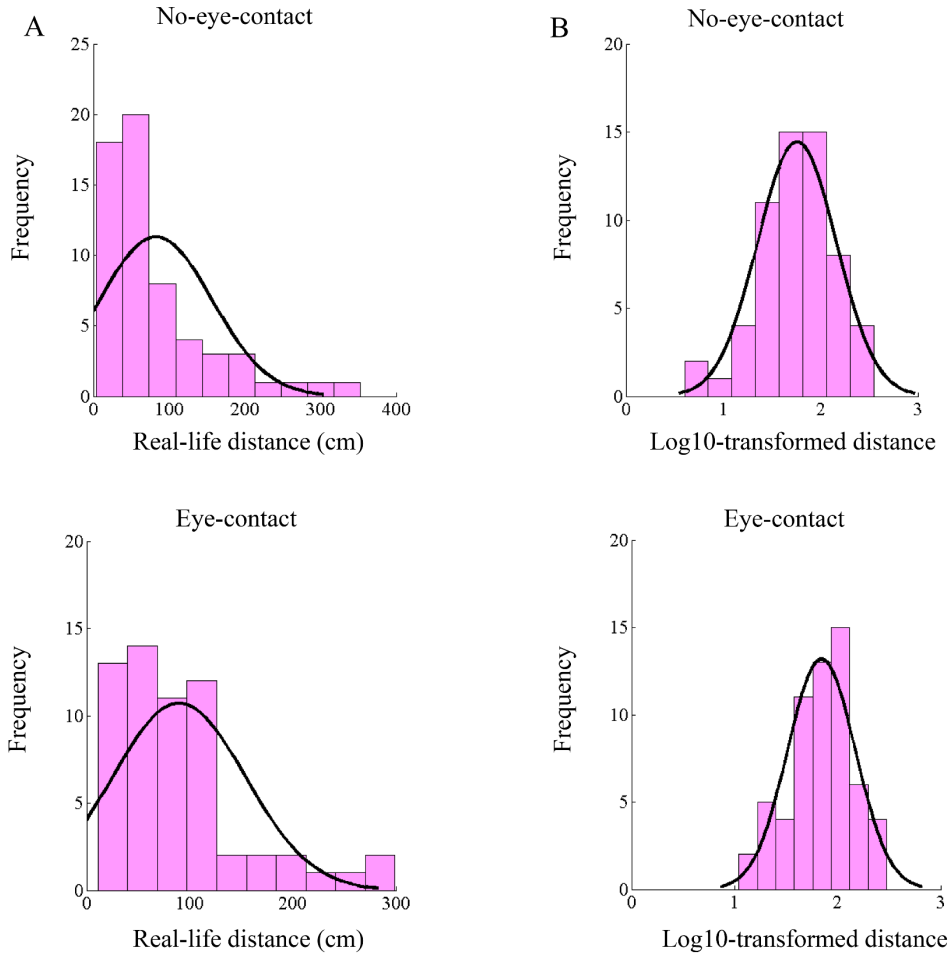

Fig. S4. Distribution of (A) the raw real-life interpersonal distance and (B) log10-transformed distance.

Section 9. Reliable modulation of romantic relationship status on SPE on interpersonal distance (*N* = 57)

In the main text, we reported the modulation of romantic relationship status on SPE on interpersonal distance. However, this result was based on a sample of 13 single males and 17 pair-bonded males. To further confirm the effect of romantic relationship status, we recruited an independent sample of 27 heterosexual males (single males = 17, pair-bonded males = 10) who went through the identical procedure as that in Exp. 3. We examined the modulation effect of romantic relationship on a sample of 57 males (30 single males and 27 pair-bonded males, 23.157 ± 3.028 years). The modulation of romantic relationship status on SPE on interpersonal distance was further confirmed. The mix-model ANOVA with Treatment (*spray*$^+$ vs. *control*) and Eye-contact (with vs. without eye-contact) as within-subject factor, Relationship status (single vs. pair-bonded) as between-subject factor showed significant main effect of Treatment (F (1, 55) = 6.025, P = 0.017, η_p^2 = 0.099) and Eye-contact (F (1, 55) = 21.157, P < 0.001, η_p^2 = 0.278). Interestingly, we found an interactive effect of Treatment × Relationship status (F (1, 55) = 5.773, P = 0.020, η_p^2 = 0.095). Simple effect analysis showed that placebo treatment reduced interpersonal distance in single participants (t (29) = -2.970, P = 0.006, Cohen d' = 0.541) but not in pair-bonded males (t (26) = -0.049, P = 0.962, Cohen d' = 0.005, Fig. S5).

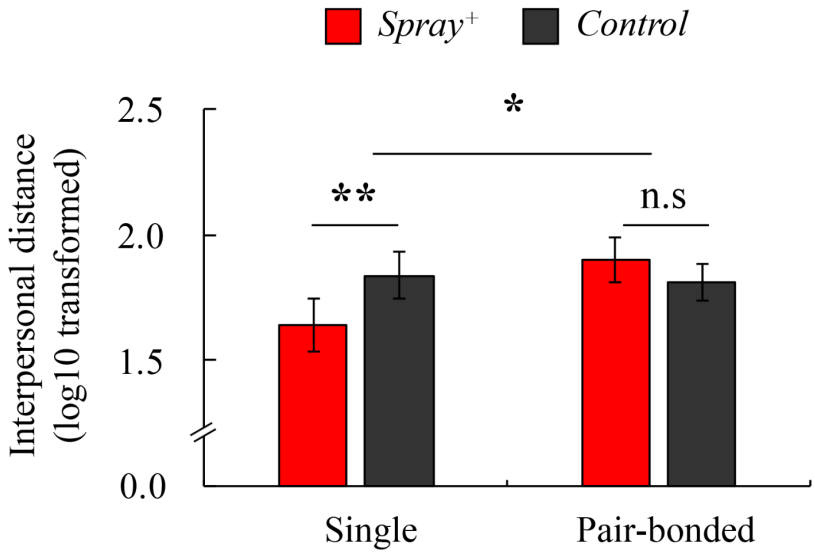

Fig. S5. Modulation effect of romantic relationship status on SPE on real-life interpersonal distance in the combined sample of 57 males. * P < 0.05, ** P < 0.01, n.s not significant.

Section 10. Matched personality and mood-related traits

In the analyses that compared different groups, we checked whether different groups of participants were matched in personality and mood-related traits. In Exp. 3 (on combined sample of 57 participants), we compared single males and pair-bonded males. We also compared SPE and active oxytocin administration (AOE) on trust and distance preference (comparison between Exp. 2 and Exp. 4), and on real-life interpersonal distance (comparison between Exp. 3 and Exp. 4). We showed in Table S4 that participants in these comparisons were matched in prosocial tendency measured by Prosocial Tendencies Measure (PTM, contains 25 items, *ref.* 12); empathic capability measured by Interpersonal Reaction Index (IRI, 28 items, *ref.* 13); interpersonal attachment measured by Attachment Style Scale (AAS, 18 items, *ref.* 14); anxiety trait measured by Trait Anxiety Inventory (TA, 20 items, *ref.* 6); and depressive status measured by Beck Depression Inventory (BDI-II, 21 items, *ref.* 15).

Table S4. Matched personality and mood-related traits.

Questionnaires	**Group comparison**	**Difference *t* (*P*)**
PTM	Single vs. Pair-bonded	1.545 (0.128)
	Exp.2 vs. Exp.4	0.171 (0.865)
	Exp.3 vs. Exp.4	0.953 (0.345)
IRI	Single vs. Pair-bonded	-0.298 (0.767)
	Exp.2 vs. Exp.4	-0.056 (0.956)
	Exp.3 vs. Exp.4	0.980 (0.331)
AAS	Single vs. Pair-bonded	-0.255 (0.823)
	Exp.2 vs. Exp.4	-0.450 (0.654)
	Exp.3 vs. Exp.4	0.123 (0.902)
TA	Single vs. Pair-bonded	-0.647 (0.520)
	Exp.2 vs. Exp.4	1.137 (0.260)
	Exp.3 vs. Exp.4	0.639 (0.525)
BDI	Single vs. Pair-bonded	-0.236 (0.814)
	Exp.2 vs. Exp.4	0.383 (0.703)
	Exp.3 vs. Exp.4	-0.023 (0.982)

Section 11. Effect of active oxytocin on trust and interpersonal distance

To directly compare SPE and active oxytocin (AOE: effects of double-blind oxytocin vs. PL), we conducted Exp. 4 where participants completed trust game, distance preference and stop-distance tasks after administration of active oxytocin or PL in a double blind, within-subject design. The comparison of SPE and AOE was reported in the main text. Here we showed AOE on trust and interpersonal distance.

Trust game. We performed 2 (Treatment: oxytocin vs. PL) by 2 (Betrayal: before vs. after betrayal trust) ANOVA on the amount of investment in the trust game. This analysis revealed a significant main effect of Treatment (F (1, 28) = 4.722, P = 0.038, η_p^2 = 0.144), as oxytocin increased trust in others. However, the Treatment × Betrayal interaction was not significant (F (1, 28) = 0.079, P = 0.781, η_p^2 = 0.003), suggesting AOE on increasing trust remained even when trust has been betrayed (Fig. S6A).

Distance preference task. Similar to previous findings of oxytocin effect (16) we found that oxytocin (relative to PL) made participant more likely to choose closer distance (t (28) = 1.385, P = 0.088 (one-tailed), Fig. S6B).

Stop-distance task. The ANOVA on the log10 transformed distance showed that oxytocin decreased interpersonal distance between the participants and the female experimenter, although this effect did not reach significant, in the same trend with previous study (17) and SPE (F (1, 28) = 2.852, P = 0.102, η_p^2 = 0.092, Fig. S6C). However, there was no reliable Treatment × Eye-contact interaction (F (1, 28) = 1.464, P = 0.236, η_p^2 = 0.050), suggesting that AOE on real-life distance was not modulated by the eye-contact situation.

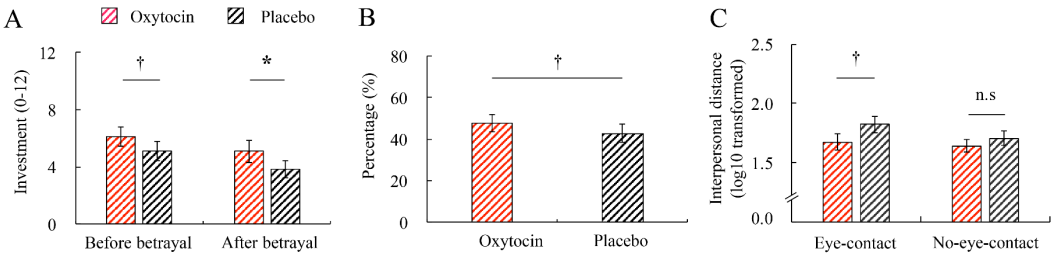

Fig. S6. Administration of active oxytocin enhanced the invested tokens in trust game independent of betrayal feedback (A), increased the percentage of choosing closer interpersonal distance (B), and decreased real-life interpersonal distance independent of eye-contact situation (C). † P < 0.10, * P < 0.05, n.s not significant.

Section 12. Trust betrayal manipulation

In Exp. 2 and 4, we introduced trust betrayal by presenting unfair return of investment of the first 6 rounds. After being betrayed, participants played another 6 rounds with 6 other different partners without feedback. To determine the unfair feedback, we conducted a pilot study where participants were asked to report the minimal amount of investment return they would feel fair after they made the investment in the trust game. Based on the pilot result, the unfair feedback is set as the total amount of invested tokens multiply a random number between 0.85~0.95, i.e., 85% - 95% of participants' investment was returned. Given that the investment will be tripled to the trustee, thus trustee returns back 28.3% - 31.6% of what he gets from the participants.

In Exp. 2 and 4, participants were asked to rate the fairness of the feedback at the end of experiment on an 11-point Likert scale (0 = extremely unfair, 10=very fair offer). Post-experiment fairness rating in Exp. 2 confirmed that participants indeed perceived the feedback as unfair in both the *spray*$^+$ (M ± SD = 4.437 ± 1.899) and control sessions (M ± SD = 4.125 ± 2.282), and the perceived fairness was not different between *spray*$^+$ and *control* sessions (t (31) = 0.744, P = 0.462). Similarly, fairness rating in Exp. 4 also showed that participants perceived the feedback as unfair in both the oxytocin (M ± SD = 4.270 ± 2.273) and PL (M ± SD = 4.241 ± 2.627) sessions, and the perceived fairness was not different between oxytocin and PL sessions (t (28) = 1.206, P = 0.238).

Section 13. Reliable SPE after controlling for covariates

We further examined whether SPE remained significant after controlling for session order, participants' relationship status and personality traits, as well as female experimenter's attractiveness in stop-distance task. We showed in Table S5 that the SPE on trust and distance remained significant after controlling for these variables.

Table. S5 SPE after controlling for covariates

Effect	Exp	Control variables	Effect	F (*P*)	η_p^2
SPE on trust	Exp. 1	Relationship status, Session Oder	Treatment*	3.221 (0.048)	0.114
	Exp. 2	Relationship status, Oder	Treatment*	6.665 (0.015)	0.192
SPE on distance preference	Exp. 1	Relationship status, Oder	Treatment***	10.753 (<0.001)	0.301
	Exp. 2	Relationship status, Oder	Treatment†	3.677 (0.066)	0.120
SPE on real-life distance	Exp. 3 (combined dataset, $N = 57$)	Female attractiveness, Oder	Treatment* Eye*** Treatment × Eye Treatment × Relationship*	4.282 (0.044) 19.688 (<0.001) 2.705 (0.106) 5.506 (0.023)	0.076 0.275 0.049 0.096
SPE *vs.* AOE	Trust game	Relationship status, Order, Personality	Treatment × Betrayal × Group*	4.787 (0.033)	0.087
	Stop distance task	Relationship status, Order, Female attractiveness, Personality	Treatment × Betrayal × Group*	7.127 (0.010)	0.127

Notes. † P < 0.10, * P < 0.05, *** P < 0.001.

Section 14. Eliminate influence of social desirability in SPE

We measured social desirability in 32 participants. We asked them to report to what extent they completed the experimental tasks according to their own thoughts or others' expectation.

Participants were presented with four options and asked to choose the most influential factor in their decisions/performance in the experiment. There are two self-oriented options (A. One's own traits, thoughts/feelings in daily-life, B. One's own thoughts/feelings on the specific experimental day) and two other-oriented options (C. General tendency to align with others' expectation (general social desirability), D. Perceived experimenters' expectation). Among the 32 participants who completed this survey, 13 participants chose option A, 18 chose option B, and 1 chose option D, suggesting that most (31 out of 32) participants performed according to their own traits, thoughts/feelings in the experiment.

Furthermore, we asked participants to choose separately for the *spray*$^+$ and control sessions. We found that 3 participants reported that no specific influential factor for their performance, and 29 (18 chose option A) participants reported that they performed accordingly to their own thoughts/feelings in the *spray*$^+$ session. In the control session, 3 participants reported that no specific influential factor for their performance, and 29 (23 chose option A) participants reported that they performed accordingly to their own thoughts/feelings in the control session. Thus most participants behaved in align to their own thoughts/feelings in both sessions, and this was not influenced by the *spray*$^+$ manipulation.

Section 15. SPE in the contrast of *spray*$^{+}$ vs. *PL spray*

The SPE in the current study was elicited by the procedure where participants learnt the beneficial effect of oxytocin and received intranasal administration of inert (but believed active) oxytocin. The comparison between *spray*$^{+}$ and *spray control* revealed that acquisition of the beneficial effect of oxytocin without receiving inert treatment was not sufficient to induce placebo effect. Here we examined whether intranasal administration of inert treatment (i.e., saline) without acquisition of oxytocin expectation could elicit SPE by comparing the *spray*$^{+}$ (Exp. 1) and the double-blind placebo (Exp. 4, referred as PL). We found that *spray*$^{+}$, compared to PL, significantly increased participants' investment in the trust game in both Exp. 1 (mean difference (*spray*$^{+}$ vs. PL) = 3.424 ± 4.793, t (56) = 3.848, $P < 0.001$, Cohen d' = 0.714) and Exp. 2 (mean difference (*spray*$^{+}$ vs. PL) = 2.255 ± 7.140, t (59) = 2.466, $P = 0.017$, Cohen d' = 0.315).

Section 16. Placebo treatment increased the endogenous oxytocin level

We measured participants' endogenous oxytocin level by collecting their salivary samples (18). Saliva samples were collected from 57 participants in Exp. 3 and 29 in Exp. 4, two samples for each participant. In Exp. 3, salivary samples were collected 20-min after the *spray*$^{+}$ and *material control* manipulation. In Exp. 4, salivary samples were collected 35-min after intranasal administration of oxytocin and PL.

The saliva samples were immediately stored at −20°C until batch assay. The samples were assayed using the standard procedures by commercially available Enzyme Immuno Assay (EIA) kit (ADI-900-153, Enzo Life Science, Plymouth Meeting, PA). Before assay, the reagents and the samples were balanced at room temperature 20-28°C at least 30 minutes. Then, the standard and treated samples were added to a row of wells at 100μl per well in turn, and marked. After that, a 50μl of the Enzyme conjugation solution was added to the wells with the standard and the wells with the samples to be assayed respectively and fully mixed. The liquid in the wells and residual liquid were removed after 18-24 hours incubation reaction at 4°C. Plates were washed with pre-diluted cleaning liquid for 3 times. A 50μl of substrate I and substrate II was later added to each well in turn respectively, mixed fully, and kept from light at room temperature for 15min reaction. After that, a 50μl of stop solution was added to each well after the reaction, mixed fully to stop the reaction.

Oxytocin extraction efficiency was 85.8% (146 out of 170 samples; 94 out of 114 samples in Exp. 3 and 52 out of 56 samples in Exp. 4), as determined by spiking with a known amount of hormone and extracting this known amount along with the samples. Oxytocin levels in extracted saliva were then quantified using the oxytocin EIA, in which the endogenous oxytocin hormone competes with exogenously added alkaline phosphatase linked oxytocin, for binding sites on oxytocin antibody. The optical density (OD) was measured on a Sunrise plate reader (Tecan, Research Triangle Park, NC) at 405 nm after 30min. The hormone content (in pg/ml) was determined by plotting the OD of each sample against a standard curve.

Results

Forty participants' oxytocin extraction was successful in both *spray*$^{+}$ and *control* sessions in Exp. 3, and 24 participants' oxytocin extraction was successful in both

oxytocin and PL sessions in Exp. 4. The endogenous oxytocin level in the *control* session indicated the baseline endogenous oxytocin level, and the effect of *spray*$^{+}$ manipulation on endogenous oxytocin level was calculated as change ratio from control session to *spray*$^{+}$ session, i.e., (*spray*$^{+}$ - *control*) / *control*. We found that *spray*$^{+}$ manipulation increased the endogenous oxytocin level (One-sample T test, mean difference = 1.860 ± 5.692, t (39) = 2.067, P = 0.045, Cohen d' = 0.326). Similarly, we calculated AOE on endogenous oxytocin level, using PL as the baseline, i.e., (oxytocin - PL) / PL. We showed that intranasal administration of oxytocin (relative to PL) increased participants' endogenous oxytocin level (mean difference = 63.929 ± 109.748, t (23) = 2.854, P = 0.009, Cohen d' = 0.582).

Section 17. Reason for choosing no-treatment control

We considered a control condition identical to *spray*$^+$ manipulation expect that participants were told they sprayed a saline spray (i.e., told-saline spray control) at the beginning of experimental design. However, previous studies showed that such a told-inert treatment control would raise participants' doubts about the truth of the manipulation information, especially in skeptical participants and in the context resembling the treatment manipulation (19). It could be the case that the ritual of taking the nasal spray was a salient aspect of the treatment, which may increase the perception of having received powerful treatment. In our study, to make participants have a strong belief about the placebo manipulation was critical, we thus implemented the placebo (told as oxytocin) using the same procedure as the typical oxytocin administration. These external contexts were necessary to trigger the expectation of treatment effects (20, 21), but may raise participants' doubts about the told-saline spray.

Thus we first conducted a pilot study (N = 20, 13 females, age ± SD = 24.150 ± 1.899) to examine whether participants would suspect they self-administered saline in such a context. To keep the same procedure as in the main experiments, participants were told that they were invited to the lab twice, receiving oxytocin or saline administration on each session. In reality, participants only need to visit once and administered with saline. Similar as the *spray*$^+$ manipulation, participants were first exposed to the oxytocin materials. After self-paced learning of oxytocin materials, they nasally sprayed saline (told as saline) in the same procedure in *spray*$^+$ condition and had 20-min rest. After the told-saline control manipulation, participants were asked to report: 1) whether they thought they self-administered saline (yes vs. no); if yes, to what extent they believed that they sprayed saline (0 = not at all, 10 = totally believed it); 2) whether they have doubt about the saline spray; if yes, to what extent they doubted that they were sprayed with saline (0 = no doubt at all, 10 = extremely doubt about it). After the self-report, participants were debriefed and informed about the real purpose of the experiment.

This pilot study revealed that 12 out of 20 (60%) participants believed they sprayed saline (belief: M ± SD = 8.50 ± 1.834). Among the 12 participants, 7 believed in saline spray with no doubt (belief: 9.714 ± 0.487) whereas 5 participants believed in

saline spray (belief: 6.80 ± 1.643) with doubt (doubt: 4.60 ± 2.607). However, 8 of 20 (40%) participants reported that they did not believe they sprayed saline and doubted that they may spray oxytocin (doubt: 8.00 ± 1.195). In total, 13 of 20 participants (65%) reported doubt about the saline spray (doubt: 6.692 ± 2.462).

These results suggested that about half of the participants did not believe or doubt about the saline spray. Participants' belief on the spray is very important for placebo effect induction, thus the results showing doubts about the told treatment in this pilot study made us to decide not to employ the told-saline spray as the control condition, so as to eliminate the potential influences of uncertainty in expectation on SPE. Instead we decided to employ two conventional "no treatment control" as the control conditions (22, 23), i.e., *spray control* and *material control* in the current study.

Section 18. Placebo effect on the first-round investment in trust game

In the trust game, participants made investment decisions in 6 rounds of trust game. We analyzed and reported results from the averaged investment of the 6 rounds (in the main text), and reported here the results on the first-round investment. The results of first-round investment replicated the results of averaged investment and showed reliable social placebo effect on trust.

For Exp. 1, we conducted a one-way ANOVA with Treatment (*spray*$^+$, *spray control*, *material control*) as an independent within-subject variable on the amount of first-round investment. This analysis revealed a significant main effect of Treatment (F (2, 56) = 4.151, P = 0.021, η_p^2 = 0.129, Fig. S7A); *post hoc* analysis showed the first-round investment in the *spray*$^+$ session was higher than that in the control sessions (*spray*$^+$ vs. *spray control*: t (28) = 2.711, P = 0.022, Cohen d' = 0.503; *spray*$^+$ vs. *material control*: t (28) = 2.527, P = 0.034, Cohen d' = 0.469; adjusted for multiple comparison using Bonferroni correction). For Exp. 2, we further showed that *spray*$^+$ (relative to *material control*) also increased first-round investment (t (31) = 3.572, P = 0.001, Cohen d' = 0.631, Fig. S7B).

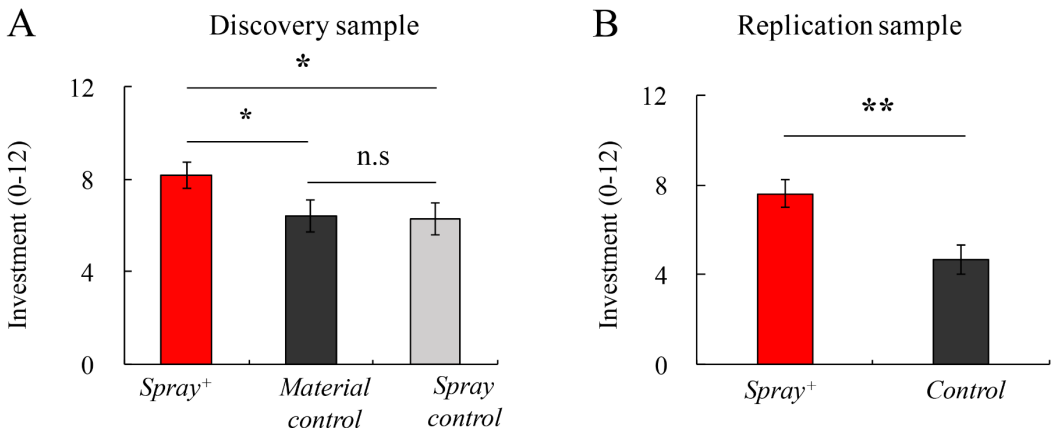

Fig. S7. Placebo treatment increased the amount of the first-round investment in the trust game in Exp. 1 (A) and 2 (B). * P < 0.05, ** P < 0.01, n.s not significant.

Section 19. Matched attractiveness of the female experimenter in the stop-distance task

In Exp. 3 and 4, participants were asked to rate the attractiveness of the female experimenter (1-9, 1 = not attractive at all, 9 = extremely attractive) after they met with each other but before the stop-distance task. We found that the attractiveness of the female experimenters was well matched between the *spray*$^{+}$ and *material control* sessions in Exp. 3 (t (54) = 0.762, P = 0.450, two participants failed to report the attractiveness rating), as well as between the oxytocin and PL sessions in Exp. 4 (t (28) = 0.351, P = 0.729).

Section 20. SPE on real-life distance under slightly uncomfortable situation

In the stop-distance task, participants were required to tell the female experimenter to stop when they felt slightly and very uncomfortable, respectively. The SPE on very uncomfortable distance was reported in the main text, we reported here the results of slightly uncomfortable distance, which were largely the same with that on very uncomfortable distance.

Placebo treatment reduced slightly uncomfortable distance. We conducted a 2 (Treatment: *spray*$^+$ vs. *material control*) × 2 (Eye-contact: with vs. without eye-contact) ANOVA on the slightly uncomfortable distance. Similarly, we found a significant Treatment × Eye-contact interaction (F (1, 29) = 6.497, P = 0.016, η_p^2 = 0.183, Fig. S8A), indicating modulation of eye-contact on the SPE on real-life interpersonal distance. Participants kept a closer distance with the female experimenter in the *spray*$^+$ (relative to *control*) session when walking without eye-contact (t (29) = -2.477, P = 0.019, Cohen d' = 0.452), but not when walking with eye-contact (t (29) = -0.250, P = 0.804, Cohen d' = 0.045).

Placebo treatment reduced perceived anxiety in others in the slightly uncomfortable distance. We conducted Treatment × Eye-contact ANOVA on the level of participants' own anxiety and perceived anxiety in the female experimenter at slightly uncomfortable distance. Similarly, analysis on one's own anxiety did not show significant main effect of Treatment nor its interaction with Eye-contact (ps > 0.299). But we showed SPE on reducing perceived anxiety in the female experimenter (F (1, 29) = 4.485, P = 0.043, η_p^2 = 0.134). Moreover, we showed significant Treatment × Eye-contact interaction (F (1, 29) = 4.265, P = 0.048, η_p^2 = 0.128, Fig. S8B), suggesting that the SPE on perceived anxiety was modulated by eye-contact situations. The placebo treatment reduced perceived anxiety in female experimenter in the eye-contact situation (t (29) = -2.816, P = 0.009, Cohen d' = 0.514) but not in the situation without eye-contact (P > 0.55).

Selective placebo effect on slightly uncomfortable distance in single males. We also performed a Treatment × Eye-contact × Relationship-status ANOVA on slightly uncomfortable distance on the combined sample (N = 57). Similarly, we found significant main effects of Treatment (F (1, 55) = 4.181, P =0.046, η_p^2 = 0.071) and eye contact (F (1, 55) = 24.245, P < 0.001, η_p^2 = 0.306). There was also a significant

Treatment × Relationship-status interaction on slightly uncomfortable distance (F (1, 55) = 5.206, P = 0.026, η_p^2 = 0.086, Fig. S8C), suggesting SPE on reducing slightly uncomfortable distance in single males (t (29) = -2.679, P = 0.012, Cohen d' = 0.487) but not in pair-bonded ones (t (26) = 0.214, P = 0.832, Cohen d' = 0.041).

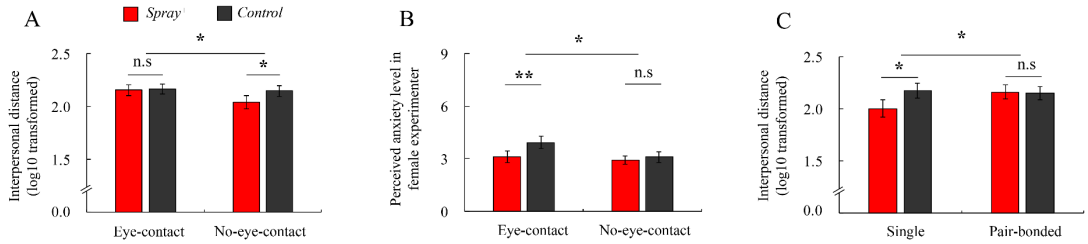

Fig. S8. Placebo effect on real-life interpersonal distance in slightly uncomfortable condition. The *spray*$^+$ manipulation (A) decreased interpersonal distance especially when eye-contact was not involved; and (B) decreased perceived anxiety in others only in the eye-contact situation. (C) Placebo treatment reduced interpersonal distance selectively in single but not pair-bonded males. * P < 0.05, ** P < 0.01, n.s not significant.

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