Placebo treatment facilitates social trust and approach behavior

Xinyuan Yan[a], Xue Yong[a], Wenhao Huang[a], and Yina Ma[a,1]

[a]State Key Laboratory of Cognitive Neuroscience and Learning, International Data Group (IDG)/McGovern Institute for Brain Research, Beijing Key Laboratory of Brain Imaging and Connectomics, Beijing Normal University, 100875 Beijing, China

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Placebo effect refers to beneficial changes induced by the use of inert treatment, such as placebo-induced relief of physical pain and attenuation of negative affect. To date, we know little about whether placebo treatment could facilitate social functioning, a crucial aspect for well-being of a social species. In the present study, we develop and validate a paradigm to induce placebo effects on social trust and approach behavior (social placebo effect), and show robust evidence that placebo treatment promotes trust in others and increases preference for a closer interpersonal distance. We further examine placebo effects in real-life social interaction and show that placebo treatment makes single, but not pair-bonded, males keep closer to an attractive first-met female and perceive less social anxiety in the female. Finally, we show evidence that the effects of placebo treatment on social trust and approach behavior can be as strong as the effect of intranasal administration of oxytocin, a neuropeptide known for its function in facilitating social cognition and behavior. The finding of the social placebo effect extends our understanding of placebo effects on improvement of physical, mental, and social well-being and suggests clinical potentials in the treatment of social dysfunction.

social placebo effect | placebo treatment | oxytocin | trust | social approach

Placebo effect refers to health benefits induced by the use of inert treatment and is shaped by the desire for personal well-being and expectations of efficacy of inert (but believed active) treatment (1, 2). Placebo effects have been observed in multiple pain conditions (placebo analgesia; ref. 3), mental disorders (e.g., attenuated affective symptoms of depression and anxiety disorders; ref. 4), and Parkinson's disease (e.g., alleviation of disabling motor symptoms; ref. 5). Although observations in the laboratory and clinical trials have indicated beneficial effects of placebo treatment on individuals' physical and emotional well-being, little is known about whether placebo treatment affects human social functioning—a crucial aspect of well-being for a social species (6, 7). Humans rely strongly on social relations and social interactions (8, 9). Social dysfunctions negatively impact personal health and well-being, and are recognized as integral to various physical and mental conditions (10) and difficult to treat (11). Unveiling whether and how placebo treatment facilitates social functioning is of particular importance in the context of treating social dysfunction, and would shed new light on placebo effects in different domains.

The motivation and expectation of beneficial effects of treatment are essential to induce placebo effects (12). One may expect facilitated social cognition from potential treatment because people have a strong desire of being socially connected, approaching others, and establishing social relationships (13, 14). Moreover, social cognition is context-dependent and influenced by internal thoughts and processing context (15). As placebo effects are often found on dimensions that are sensitive to an individual's internal thoughts (2), the malleability of social cognition provides a basis for placebo effects on social domain.

Social trust and approach behavior are two fundamental aspects of social well-being. Trust signals prosocial approach to others (16) and is an important determinant to establish and maintain interpersonal relationships (17). Trust in others has been proven to be a key predictor of subjective well-being and the quality of interpersonal relationships (18). Social approach behavior, which can be assessed by (close) interpersonal distance (19), provides a basis for social interactions and initiation of interpersonal relationship (20). Thus, the present study tested the presence of social placebo effect (SPE) by examining whether and how placebo treatment would affect social trust and approach behavior. We chose an inert nasal spray (i.e., intranasal administration of saline spray believed by subjects to be oxytocin) as the placebo treatment. Oxytocin, the hypothalamic neuropeptide important for social cognition and behavior, has been shown to promote prosocial approach, such as trust and cooperative behaviors (16, 21, 22, but also see ref. 23) and increase physical approach leading to closer interpersonal distance (24, 25). Thus, testing SPE on social trust and approach behavior would allow us to directly compare the effects of social placebo treatment and active oxytocin and to uncover shared and selective effects.

In real-life situations, keeping too far away from others signals low social motivation (26) and keeping close to others, especially strangers, may induce personal distress or social anxiety (26, 27). Abnormal perception or regulation of interpersonal distance has been linked with social dysfunction (28). In addition, oxytocin is emerging as a pharmacological target for social dysfunction in clinical trials (29, 30). For example, oxytocin down-regulates social anxiety (31) and normalized the abnormal neural responses to negative social stimuli in patients with social anxiety disorder (32, 33). Thus, we further examined SPE on approach behavior in a real-life situation that would cause social anxiety, serving as an extension of SPE in real life, as well as to test potential placebo effects on anxiety during social interactions. This would also provide practical significance in terms of serving oxytocin as an open-label treatment for social dysfunction.

The expectation of beneficial effects of treatment and receiving the inert (believed as active) treatment are necessary to

Significance

The World Health Organization defines health as a state of physical, mental, and social well-being. Although placebo treatment has been widely shown to improve physical and mental well-being, it remains unknown whether placebo treatment facilitates social well-being. Here, we provide evidence that placebo treatment facilitates social approach by increasing trust in others and preference for being physically closer to others. The social placebo effects (SPEs) resemble the effect of intranasal administration of oxytocin, an important neuropeptide for social cognition, on social trust and approach behavior, but the SPE is more sensitive to motivational state. Our findings extend the understanding of placebo effects on improving physical, mental, and social well-being and suggest clinical potentials in the treatment of social dysfunction.

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[1]To whom correspondence should be addressed. Email: yma@bnu.edu.cn.

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induce placebo effects (12). Accordingly, to test the SPE on social trust and approach behavior, we developed and validated a social placebo manipulation that consisted of expectation formation of oxytocin effects on social behavior and self-administered an inert nasal spray (i.e., saline spray but with subjects told it was oxytocin; spray$^+$ condition). We elicited expectations of beneficial effects of oxytocin treatment by presenting participants with oxytocin materials, i.e., articles and a video clip that documented scientific findings of oxytocin effects on social cognition and behavior (*Methods*). We showed in our preparation experiment (Exp. 0a) that the oxytocin materials were able to induce expectations of the beneficial effects of oxytocin (*SI Appendix, Section 1* and Fig. S1). Participants then self-administered nasal saline spray (told it was oxytocin) after acquisition of the beneficial effects of oxytocin. After the expectation formation and administration of inert treatment, participants played a trust game and performed social approach-related tasks. Similar to previous studies (12, 34, 35), in a within-subject design, participants were also invited to a no-treatment control session that was identical to the spray$^+$ session except that they did not receive nasal spray (i.e., spray control condition). Moreover, to avoid potential influence of exposure to the same materials twice, we set up another control (i.e., material control condition) whereby participants were exposed to oxytocin-irrelevant control materials without nasal spray. We conducted two preparation experiments and showed that the oxytocin and control materials were well matched in mood change, self-reported interest, and comprehension (Exp. 0b; *SI Appendix, Section 2*). Furthermore, exposure to oxytocin or control documents alone did not affect social trust ($P > 0.3$) or preferred interpersonal distance ($P > 0.5$, Exp. 0c; *SI Appendix, Section 3*).

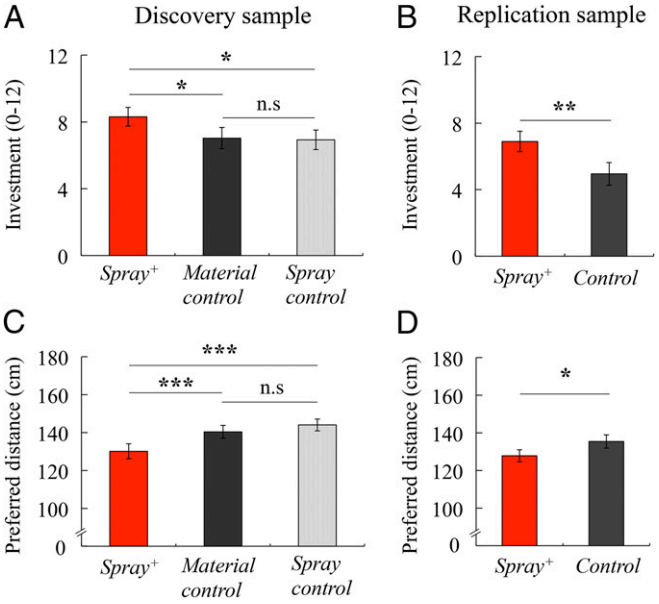

Fig. 1. SPE. Placebo treatment increased participants' social trust (*A* and *B*) and preferences of closer interpersonal distance (*C* and *D*) in the discovery (Exp. 1) and replication (Exp. 2) samples (*$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$; n.s., not significant).

Results

Placebo Treatment Increased Social Trust. We invited participants (Exp. 1, discovery sample) to three sessions (i.e., spray$^+$, spray control, and material control sessions) with ≥7 d between any two sessions (session order counterbalanced across subjects). The spray$^+$ manipulation (vs. controls) did not change general mood from baseline to after the experiment (P values >0.05; *SI Appendix, Section 4* and Table S1), but indeed brought expectations of beneficial effects of oxytocin treatment, with subjects reporting higher levels of willingness to trust others [$F(2,56) = 5.155$, $P = 0.009$, $\eta_p^2 = 0.155$] and to interact with others [$F(2,52) = 4.963$, $P = 0.011$, $\eta_p^2 = 0.160$]. The same pattern whereby spray$^+$ manipulation induced expectations of oxytocin treatment was also observed in Exp. 2 (*SI Appendix, Section 1*).

After the spray$^+$ or control manipulation, participants played a trust game whereby they made a decision on how many tokens they would invest in another player who received triple the amount and decided how many tokens to send back. The amount of investment indicated trust in others (16). Thus, to examine whether placebo treatment increased social trust, we conducted repeated-measures ANOVA of the amount of investment with treatment (spray$^+$, spray control, material control) as a within-subject factor. This analysis revealed a significant main effect of treatment [$F(2,56) = 3.238$, $P = 0.047$, $\eta_p^2 = 0.104$; Fig. 1*A*], as the amount of investment was greater in the spray$^+$ sessions than in controls [spray$^+$ vs. spray control, $t(28) = 2.443$, $P = 0.021$, Cohen $d' = 0.453$; spray$^+$ vs. material control, $t(28) = 2.415$, $P = 0.023$, Cohen $d' = 0.448$]. We further examined SPE on social trust in a replication sample (Exp. 2). As participants' behaviors did not differ between spray control and material control conditions, as well as to avoid the influence of exposure to oxytocin materials twice (*SI Appendix, Section 5*), we employed the material control as the control condition in Exp. 2 and Exp. 3. The SPE on increasing social trust was further replicated in Exp. 2 [$t(31) = 3.540$, $P = 0.001$, Cohen $d' = 0.625$; Fig. 1*B*].

Placebo Treatment Increased Preferences of Closer Interpersonal Distance. In Exp. 1, participants also completed the distance preference task whereby they chose a preferred interpersonal distance from a pair of stimuli that differed only in distance. We examined SPE on interpersonal distance by comparing the preferred distance between the spray$^+$ and control sessions. ANOVA on the preferred distance revealed a significant effect of treatment [spray$^+$, spray control, material control, $F(2,56) = 13.097$, $P < 0.001$, $\eta_p^2 = 0.319$; Fig. 1*C*]. The preferred distance was shorter in the spray$^+$ session than in the spray control [$t(28) = -4.241$, $P < 0.001$, Cohen $d' = 0.787$] and material control sessions [$t(28) = -4.172$, $P < 0.001$, Cohen $d' = 0.774$]. The SPE on the preferred distance was replicated in Exp. 2 [$t(30) = -2.067$, $P = 0.047$, Cohen $d' = 0.371$; Fig. 1*D*]. The analysis of percentage of choosing closer distance showed similar patterns of SPE in Exp. 1 and Exp. 2 (*SI Appendix, Section 6* and Fig. S2). These results demonstrated reliable SPE on increasing preference of closer interpersonal distance.

SPE on Social Trust Mediated Its Effect on Interpersonal Distance Preference. As social trust provides a basis of close interpersonal distance (36), we next examined whether SPE on the preferred distance arose from its effect of enhanced trust. To detect a moderate correlation ($r = 0.4$; ref. 37) between SPE on trust and on interpersonal distance with $\alpha = 0.05$ and 90% power, a sample size of 61 participants was needed (G*Power 3.1; ref .38). Thus, the correlation and mediation analyses were conducted on data collapsed over Exp. 1 and Exp. 2. First, we showed that the SPE on trust ($\text{trust}_{spray^+} - \text{trust}_{control}$) was significantly correlated with the SPE on preferred distance, i.e., spray$^+$ manipulation decreased preferred distance to a greater degree in individuals who showed stronger SPE on trust [$r(60) = -0.367$, $P = 0.004$; Fig. 2]. A mediation analysis (*SI Appendix, Section 7*) further confirmed that the spray$^+$ manipulation impacted interpersonal distance through increasing social trust (Sobel test, $Z = -2.498$, $P = 0.012$, partial mediation; Fig. 2 and *SI Appendix*, Fig. S3 and Tables S2 and S3). A bias-corrected bootstrap resampling analysis (5,000 resamples) of the effect size indicated that the mediator effect was different from zero with 95% confidence.

Placebo Treatment Reduced Interpersonal Distances in Real-Life Social Interaction. Exp. 1 and Exp. 2 revealed SPE on individuals' preference of projected social distance; however, choosing closer projected distance does not necessarily predict interpersonal distance in a real-life situation as a result of potential increases of anxiety (26, 27). We next examined SPE in a real-life situation (Exp. 3) in an adapted stop-distance task that measures real-life interpersonal distance and reflects the willingness to approach others (25–27). In each session, a different female experimenter was instructed to move along the line toward the participant at a natural gait. Similar to previous work (39), participants were asked to determine a distance at which they felt very uncomfortable to

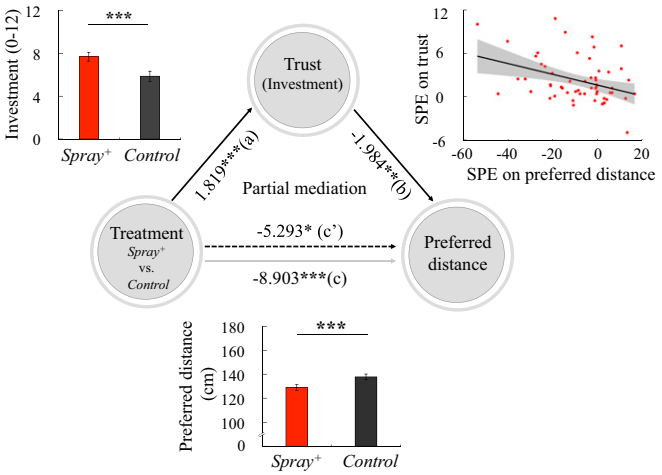

Fig. 2. Placebo treatment increased preferences of closer interpersonal distance through increasing trust in others (*P < 0.05, **P < 0.01, and ***P < 0.001).

interact with this first-met female, respectively, when there was or was not eye contact (as eye contact signals social motivation and has been shown to play an important role in real-life social interaction; ref. 40). We conducted a 2 (treatment, spray$^+$ vs. material control) × 2 (eye-contact, with vs. without) ANOVA of the distance (log10 transformed; *SI Appendix*, *Section 8* and Fig. S4). A significant main effect of eye-contact [$F(1,29) = 9.646$, $P = 0.004$, $\eta_p^2 = 0.250$] suggested longer distance from the female experimenter with vs. without eye contact. The main effect of treatment was significant [$F(1,29) = 4.312$, $P = 0.047$, $\eta_p^2 = 0.129$], as, relative to material control, spray$^+$ manipulation decreased interpersonal distance. Interestingly, a significant treatment × eye-contact interaction [$F(1,29) = 4.515$, $P = 0.042$, $\eta_p^2 = 0.135$; Fig. 3*A*] indicated modulation of eye contact on the SPE on decreasing real-life interpersonal distance. Specifically, participants kept a closer distance with the female experimenter in the spray$^+$ session (relative to control) in the no-eye contact situation [$t(29) = -2.302$, $P = 0.029$, Cohen $d' = 0.420$], but not the eye-contact situation [$t(29) = -1.210$, $P = 0.236$, Cohen $d' = 0.221$]. These results indicated SPE on facilitating approach behavior, especially when eye contact was not involved.

Placebo Treatment Reduced Perceived Anxiety in Others. Next we examined SPE on interpersonal distress during the stop-distance task. We conducted a treatment × eye-contact ANOVA on the level of participants' own anxiety and perceived anxiety in the female experimenter. Neither the main effect of treatment nor its interaction with eye-contact on one's own anxiety was significant (P values >0.3), possibly reflecting that participants set the same standards for a very uncomfortable level to stop the female experimenter in the spray$^+$ and control sessions.

Interestingly, spray$^+$ manipulation reduced perceived anxiety in the female experimenter [$F(1,29) = 4.485$, $P = 0.043$, $\eta_p^2 = 0.134$]. A main effect of eye-contact [$F(1,29) = 5.826$, $P = 0.022$, $\eta_p^2 = 0.167$] suggested that participants perceived less anxiety in the female experimenter in the no-eye contact situation than in the eye-contact situation. Moreover, we showed a significant treatment × eye-contact interaction [$F(1,29) = 5.009$, $P = 0.033$, $\eta_p^2 = 0.147$; Fig. 3*B*], suggesting that the SPE on perceived anxiety was modulated by eye-contact situations. The placebo treatment reduced perceived anxiety in the female experimenter in the eye-contact situation [$t(29) = -2.648$, $P = 0.013$, Cohen $d' = 0.483$] but not in the no-eye contact situation ($P > 0.5$).

Selective SPE on Real-Life Interpersonal Distance in Single Males. Interpersonal distance is crucially influenced by one's relationship with others (41, 42). We next examined whether SPE on real-life distance was modulated by romantic relationship status (single vs. pair-bonded). Interestingly, the treatment × eye-contact × relationship ANOVA revealed a significant treatment × relationship interaction [$F(1,28) = 13.933$, $P < 0.001$, $\eta_p^2 = 0.332$; Fig. 3*C*], suggesting reliable SPE on reducing interpersonal distance in single [$t(12) = -3.739$, $P = 0.003$, Cohen $d' = 1.037$] but not pair-bonded males [$t(16) = 0.697$, $P = 0.496$, Cohen $d' = 0.169$]. There were only 13 single males and 17 pair-bonded males in Exp. 3, so, to further confirm the modulation of relationship status, we recruited an independent sample of 27 males who completed an identical procedure. The modulation of romantic relationship on SPE on interpersonal distance was further confirmed in the pooled sample ($N = 57$; *SI Appendix*, *Section 9* and Fig. S5). Single and pair-bonded males were matched in relevant personality and mood related traits (*SI Appendix*, *Section 10* and Table S4).

Comparable Effects of Placebo Treatment and Active Oxytocin. The SPE on social trust and interpersonal distance resembled the effects of active oxytocin administration reported in previous studies (16, 22, 25). Next, to directly uncover the shared and selective effects of placebo treatment (i.e., SPE, spray$^+$ vs. control) and active oxytocin (referred to as "AOE" in this experiment; AOE vs. placebo, which is referred to as "PL" to differentiate from placebo effect), we conducted Exp. 4 whereby participants completed the trust game, distance preference, and stop-distance tasks after administration of active oxytocin or PL in a double-blind, within-subject design. First, results the of Exp. 4 replicated the previous findings of oxytocin effects on trust and interpersonal distance (*SI Appendix*, *Section 11* and Fig. S6). We then focused on the direct comparison between the AOE (Exp. 4) and SPE on trust, distance preference (data from Exp. 2), and real-life interpersonal distance (Exp. 3). Participants in these comparisons were matched in relevant personality and mood (*SI Appendix*, *Section 10* and Table S4).

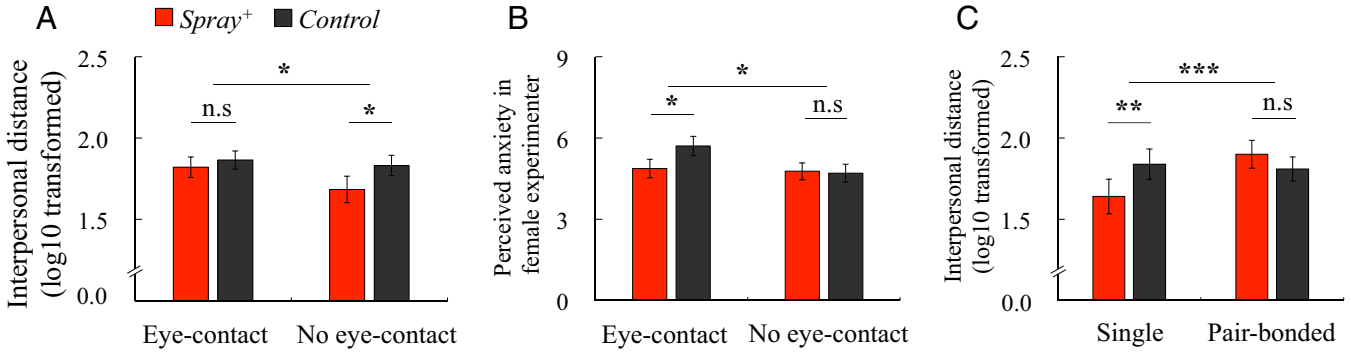

Fig. 3. Placebo effect on real-life interpersonal distance. The spray$^+$ manipulation (*A*) decreased interpersonal distance especially when eye contact was not involved and (*B*) decreased perceived anxiety in the female experimenter only in the eye-contact situation. (*C*) Placebo treatment reduced interpersonal distance selectively in single but not pair-bonded males (*P < 0.05, **P < 0.01, and ***P < 0.001; n.s., not significant).

Social Trust. Given that oxytocin was shown to increase trust and adaptation to trust betrayal, we included trust betrayal manipulation in Exp. 2 and Exp. 4 whereby participants received betrayal feedback (*SI Appendix*, *Section 12*) after six rounds of investment. This allowed us to compare SPE and AOE on trust and responses to betrayal. We conducted ANOVA with treatment (spray$^+$ vs. control or oxytocin vs. PL) and betrayal (before vs. after betrayal) as within-subject factors and group (SPE vs. AOE) as a between-subject factor. The significant main effect of treatment [$F(1,59) = 10.944$, $P = 0.002$, $\eta_p^2 = 0.156$] suggested increased trust by active oxytocin and spray$^+$ treatment. Interestingly, we found a significant treatment × betrayal × group interaction [$F(1, 59) = 5.242$, $P = 0.026$, η_p^2=0.082; Fig. 4], as SPE on trust was only evident before receiving betrayal feedback but not after betrayal [treatment × betrayal, $F(1,31) = 10.055$, $P = 0.003$, $\eta_p^2 = 0.245$] whereas AOE on trust was independent of betrayal [$F(1,28) = 0.079$, $P = 0.781$, $\eta_p^2 = 0.003$]. These results indicated similar SPE and AOE on increased trust, even though SPE was more sensitive to social feedback.

Distance Preference. We next compared SPE and AOE on distance preference. We found a significant main effect of treatment on the preferred distance [$F(1,58) = 5.245$, $P = 0.026$, $\eta_p^2 = 0.083$], but no significant treatment × group interaction [$F(1,58) = 0.641$, $P = 0.426$, $\eta_p^2 = 0.011$], suggesting that placebo treatment and active oxytocin similarly increased participants' preference of a closer distance.

Real-Life Interpersonal Distance. The treatment × eye-contact × group ANOVA on real-life distance revealed a main effect of treatment [$F(1,57) = 6.800$, $P = 0.012$, $\eta_p^2 = 0.107$], suggesting that placebo treatment and active oxytocin made participants get closer to the female experimenter. Interestingly, there was a treatment × eye-contact × group interaction on real-life distance [$F(1,57) = 4.937$, $P = 0.030$, $\eta_p^2 = 0.080$]. The SPE was selectively observed in the no-eye contact situation (Fig. 3*A*) whereas AOE on interpersonal distance was not modulated by eye-contact situations (*SI Appendix*, *Section 11* and Fig. S6). Similar analyses on one's own anxiety and perceived anxiety in others did not show reliable interactive effects (P values >0.05).

Discussion

The placebo effects on pain analgesia and negative affect reduction have been well-documented (3, 4), and here we provide evidence of placebo effects on facilitating social trust and approach behavior. Our results demonstrated robust SPE on social trust and approach behavior by using different but complementary measures in several independent samples in laboratory and real-life situations. Moreover, SPE remained reliable after controlling session order, relationship status, or attractiveness of the female experimenter (*SI Appendix*, *Section 13* and Table S5). We also showed evidence of comparable effects of placebo treatment and active oxytocin on increasing social trust and approach behavior. In addition, the SPE could not be simply attributed to exposure to oxytocin materials (*SI Appendix*, *Section 3*) or perceived experimenter's expectation (*Experimenter-Blind Procedure*) or social desirability (*SI Appendix*, *Section 14*).

The inclusion of different controls (material control, spray control, and PL spray) clarified necessary elements to induce SPE. The SPE was elicited by the procedure whereby participants learned the beneficial effect of oxytocin and received nasal spray of inert (but believed active) oxytocin. Neither exposure to oxytocin materials without receiving inert treatment nor administration of inert treatment without acquisition of oxytocin expectation (*SI Appendix*, *Section 15*) was able to elicit SPE. Thus, an integration of expectation of social benefits from treatment and receiving the believed active treatment is necessary to induce placebo effect on trust and approach behavior.

Our findings demonstrate robust placebo effects of facilitating trust in others and approach to others. The findings are consistent with the nonspecific effects of placebo treatment observed in multiple pain conditions and different types of negative affect (43, 44). Trust in others and close social distance signal approach to social interactions and provide opportunities to establish close relationships (13). Thus, our findings of SPE on different social aspects may reflect a general effect of placebo treatment on promoting social approach. Moreover, the SPE is modulated by one's motivational state to approaching others: the stronger social motivation, the stronger the SPE. For example, the SPE on social trust was diminished when the initial trust was betrayed, as betrayal signaled untrustworthiness and dampened the motivation to trust. We also found greater SPE in the no-eye contact situation, which provides a stronger approaching motivation according to the intimacy equilibrium (i.e., the less social signal available, the stronger social motivation; ref. 26). Interestingly, the SPE on approaching a first-met female was found only in single males who would have stronger intimacy-seeking motivation (vs. pair-bonded males). Taken together, the SPE is sensitive to social context and personal state linked to social motivation.

Our SPE findings extend placebo effects into the social domain. Regarding the contextual modulations and nonspecific effects, SPE is similar to previous placebo effects on pain and negative affect (3, 4). These findings together indicate that placebo treatment may impact well-being in different domains (physical, emotional, and social) and different dimensions of each domain (e.g., placebo analgesia in multiple pain conditions or placebo effect on different social behaviors). This lends further support to the notion that placebo effect is nonspecifically driven by expectation or belief (43, 45). It has been recognized that placebo treatment reduces pain and negative emotion through a top-down modulation, with "high-level" expectation driving the downstream changes in one's own sensory feelings and affective physiology (2, 46, 47). Here we show that placebo treatment facilitates positive social interactions between the self and others. Thus, placebo treatment not only influences one's own feelings but also influences interactions with others; it not only attenuates negative affect but also facilitates positive aspect. Another interesting issue is whether SPE is mediated by same or different biological systems from the placebo effect on analgesia. The placebo effect on analgesia was linked to the opioid system, which plays an important role in modulating pain (48, 49). Our behavioral results do not allow us to examine the neurobiological system involved in SPE. However, we compared the endogenous oxytocin levels after spray$^+$ or control manipulation, and found that participants in the spray$^+$ session secreted higher levels of endogenous oxytocin than participants in the control session (*SI Appendix*, *Section 16*). This allowed us to speculate that the oxytocinergic system, which has been implicated in social cognition and behavior, may be involved in SPE. Previous studies have provided evidence that the dopaminergic system mediated expectation formation in placebo manipulation (50) and that the opioid system was involved in placebo effect on analgesia (48, 49) and social behavior (51). It is possible that other neural systems such as dopaminergic and opioid systems were also involved in SPE. Future work needs to clarify whether and how SPE was linked to the oxytocinergic system and other neural systems.

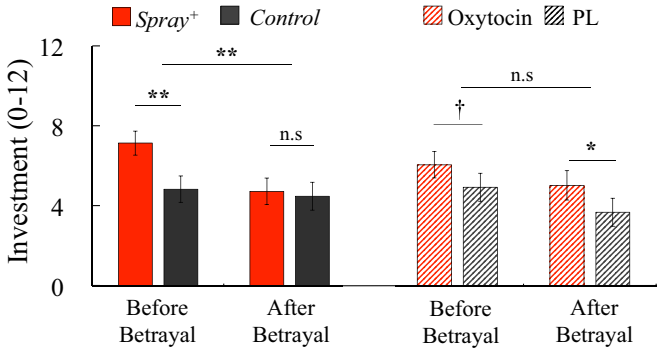

Fig. 4. Comparison of SPE and AOE on social trust. AOE on trust in others was independent of betrayal feedback whereas SPE increased trust only before receiving betrayal feedback but not after betrayal ($^\dagger P < 0.10$, $^* P < 0.05$, and $^{**} P < 0.01$; n.s., not significant).

The finding that placebo treatment facilitates social interaction suggests clinical potentials of SPE in the treatment of mental disorders characterized by social withdrawal or dysfunction. Specifically, we showed SPE on reduced interpersonal distance and perceived anxiety in others in a real-life situation when individuals felt personal distress. This is of particular interest for patients with social anxiety disorder who show social withdrawal as a result of personal distress and fear of approaching others (52, 53). The placebo-induced expectations of attenuation of one's anxiety and improving one's social function may possibly lead to symptom alleviation. Consistently, previous clinical trials have reported placebo effects on rating scores of social anxiety in patients (54). We provide behavioral (rather than self-reported or evaluated by others) evidence that placebo treatment can increase trust and facilitate social approach, which may serve as a cognitive mechanism underlying the placebo responses observed in clinics. In addition, SPE resembles the effects of active oxytocin on social behavior. This opens an interesting question of whether and how the placebo effect would interact with the oxytocinergic system. It has been suggested that open-label treatment produces better results, whereas hidden drug delivery eliminates expectation and reduces drug efficacy (55). Thus, how the combination of open-label administration of active oxytocin with information about oxytocin effects and expected benefits improves clinical outcomes should be examined in future clinical trials.

Methods

Ethics Approval. The experimental procedures of all experiments met the standards set by the Declaration of Helsinki and were approved by a local research ethics committee at the State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University. All participants provided written informed content after the experimental procedures were fully explained and were informed of their right to withdraw at any time.

Participants. We recruited 651 participants as paid volunteers as follows: n = 503 for Exp. 0a-c (*SI Appendix*, *Sections* 1–3), n = 30 for Exp. 1 (discovery sample for SPE; one participant who failed to complete all sessions was excluded from data analysis; mean age ± SD = 23.33 ± 3.07 y), n = 32 for Exp. 2 (replication sample for SPE; one participant who failed to finish the distance preference task was excluded from data analysis; mean age, 23.06 ± 2.94 y), n = 57 for Exp. 3 (mean age, 23.16 ± 3.03 y), and n = 29 for Exp. 4 (mean age, 23.24 ± 3.39 y). In the formal experiments examining SPE or AOE (Exp. 1–4), heterosexual male participants were recruited given that AOE was modulated by sex (56, 57) and social approach to opposite-sex others was modulated by sexual orientation (58). This allowed us to compare the SPE and AOE. All participants were healthy, right-handed, and had no history of neurological or psychiatric disorders. Those who majored in psychology or economics in college or recently participated in any other drug study were not recruited.

Experimenter-Blind Procedure. In all experiments, experimenters of the placebo manipulations were blind to experimental hypotheses. Moreover, placebo manipulation and experimental tasks were conducted separately by different experimenters or in different settings. In Exp. 1 and Exp. 2, we employed a computerized version of the trust game and distance preference task whereby each participant was seated alone in front of a computer screen and provided with standardized instructions. In Exp. 3, in which participants completed the real-life stop-distance task, the placebo manipulation and experimental tasks were implemented by different experimenters. The experimenter who conducted the stop-distance task was blind to experimental conditions and the hypothesis. In Exp. 4, we employed a standard double-blind, PL-controlled procedure for active oxytocin/PL administration.

Experimental Design. We designed two sets of experiments: three preparation experiments (Exp. 0a-c) and four main experiments (Exp. 1–4). Exp. 0a-c was conducted to identify oxytocin and control materials for SPE manipulation. Four main experiments were conducted to discover SPE on social trust and approach behavior (Exp. 1), replicate SPE (Exp. 2), extend SPE to a real-life situation (Exp. 3), and compare SPE with AOE (Exp. 4). All of the main experiments employed within-subject design whereby subjects were invited to three sessions (Exp. 1, spray$^+$, spray control, and material control) or two sessions (Exp. 2 and Exp. 3, spray$^+$ and material control; Exp. 4, active oxytocin and PL).

General Procedure and Experimental Conditions. In Exp. 1–3, participants were invited to the spray+ and control manipulation sessions ≥7 d apart (Exp. 1, mean ± SD = 7.30 ± 0.65 d; Exp. 2, 7.63 ± 1.07 d; Exp. 3, 7.33 ± 0.61 d; session order counterbalanced across participants). For each session, participants reported their baseline mood and state anxiety upon arrival, and then entered the spray+ or control manipulation.

In the spray$^+$ condition, participants learned oxytocin materials on a self-paced basis and then self-administered a nasal spray (i.e., saline spray they were told was oxytocin) under experimenter supervision. We employed a similar procedure as the typical intranasal administration of oxytocin. Participants were instructed to refrain from smoking or drinking (except water) for 2 h before the experiment. The spray was administered to each participant three times, and each administration consisted of one inhalation into each nostril. Participants took a rest (they were told it was a time period waiting for treatment to produce effects) and then performed the experimental tasks. At the end, participants reported their mood once again, and reported their willingness to trust others and interact with others induced by the manipulation in each session on a scale from 0, indicating "not willing at all," to 10, indicating "extremely willing."

We employed two no-treatment control conditions (*SI Appendix*, *Section 17*). The spray control condition was identical to the spray$^+$ session except that subjects did not receive nasal spray. To avoid potential influence of exposure to the same materials twice, we also set up a material control condition whereby participants were exposed to control materials without receiving nasal spray.

Oxytocin Materials. To induce the expectation of beneficial effects of oxytocin, we selected and edited a *Popular Science* article, a published academic article (a review article about oxytocin), and a TED video ("Trust morality—and oxytocin?" by Paul Zak, Nov. 2011) as the oxytocin materials. In the oxytocin documents, we provided participants with (*i*) a general introduction to oxytocin, such as basic knowledge about oxytocin (e.g., the chemistry of oxytocin, oxytocin structure, oxytocin receptor), the procedure of oxytocin administration, and safety issues of oxytocin administration; and (*ii*) information about the beneficial effects of oxytocin on social behaviors, such as maternal behaviors, pair bonding, interpersonal relationships, anxiety, empathy, and prosocial behavior (e.g., generosity, social trust, cooperation). All of the materials were based on real research without deception.

Control Materials. Oxytocin-irrelevant materials, with the topic of robots, were used as control materials. The control materials were edited to obtain similar length and format as the oxytocin materials (including a *Popular Science* article, a published academic article, and a TED video introducing robots and detailing the functions of robots in daily life).

Active Oxytocin Administration. Exp. 4 employed a randomized, within-subject, double-blind, placebo-controlled design whereby participants were invited to oxytocin and PL sessions ≥7 d apart (8.19 ± 1.17 d, treatment order counterbalanced across subjects). A single intranasal dose of 24 IU oxytocin or PL was self-administered under experimenter supervision. The spray was administered three times, and each administration consisted of one inhalation of 4 IU into each nostril. To be comparable to the SPE experiment, participants self-learned control materials before self-administering oxytocin or PL. Participants performed the trust game, distance preference task, and stop-distance task 35 min later. The inclusion of exposure to the control materials allowed us to use the PL spray in Exp. 4 as an inert spray control to compare with the spray$^+$ condition to reveal SPE.

Trust Game. Participants were told that they were randomly and anonymously paired with other players to play a trust game whereby the investor and the trustee receive an initial endowment of 12 tokens. The investor chooses to send some amount (x) to the trustee. The trustee receives a tripled amount ($3x$) and then chooses to send back some amount, y ($0 \le y \le 12 + 3x$). Participants were told that they would play as either the investor or trustee, randomly determined by computer. As we were interested in the trust behavior, all participants were actually assigned as investors. The amount the investor sent indicated his trust for others. Participants were told they would be paid a certain amount for their participation in the experiment plus earnings in the trust game, but they were actually paid a fixed amount.

Participants in Exp. 1 made investment decisions in six rounds of the trust game. To preserve the one-shot nature, participants were informed that each round was independent and they would not play with the same player twice. We analyzed and reported results from the averaged six-round investment in the main text and from first-round investment (*SI Appendix*, *Section 18* and Fig. S7). In Exp. 2 and Exp. 4, trust betrayal was introduced by presenting unfair return of investment in the first six rounds. After being betrayed, participants played another six rounds with six other different players without feedback. Postexperiment fairness rating confirmed that participants indeed perceived the feedback as unfair (*SI Appendix*, *Section 12*).

Distance Preference Task. Participants were presented with pairs of pictures and asked to choose one picture displaying their preferred interpersonal distance from each pair. There were two types of situations: (*i*) half with two strangers (opposite sex) sitting opposite one another, with participants choosing a preferred distance between them; and (*ii*) another half with a female stranger sitting in one chair opposite an empty chair, which participants would sit in and chat with the female, with participants choosing a preferred distance between themselves and the female. Models in the pictures kept a neutral facial expression and sat up straight. The distance varied from 50 to 190 cm at intervals of 20 cm. Each pair of stimuli comprised two pictures that differed only in distance, with seven types of intervals (interval = $|\text{distance}_{\text{left picture}} - \text{distance}_{\text{right picture}}|$ = 20, 40, 60, 80, 100, 120, or 140 cm). There were 336 pairs of pictures with 48 pairs at each interval, with half of the pairs at the longer distance in the left picture. All pictures were adjusted in luminance and contrast.

Stop-Distance Task. We adopted the stop-distance paradigm to measure real-life interpersonal distance (27, 28). Each participant met different female experimenters in different sessions to avoid familiarity. We matched females' attractiveness across sessions as it may influence interpersonal distance (*SI Appendix, Section 19*). All participants were tested in the same room, with an initial distance of 6.5 m. Participants were required to tell the female to stop when they felt slightly and very uncomfortable, respectively. The SPE on slightly uncomfortable distance was largely the same with that on very uncomfortable distance (*SI Appendix, Section 20* and Fig. S8). At every stop, participants reported the level of their own anxiety on a scale from 0 indicating "not anxious at all" to 10 indicating "extremely anxious" and the level of anxiety they perceived in the female (i.e., perceived anxiety).

Open Practice. All data and materials have been made publicly available via the Open Science Framework and can be accessed at https://osf.io/nvsfr/.

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