nature neuroscience

SUPPLEMENTARY INFORMATION

https://doi.org/10.1038/s41593-019-0351-1

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Oxytocin modulates social value representations in the amygdala

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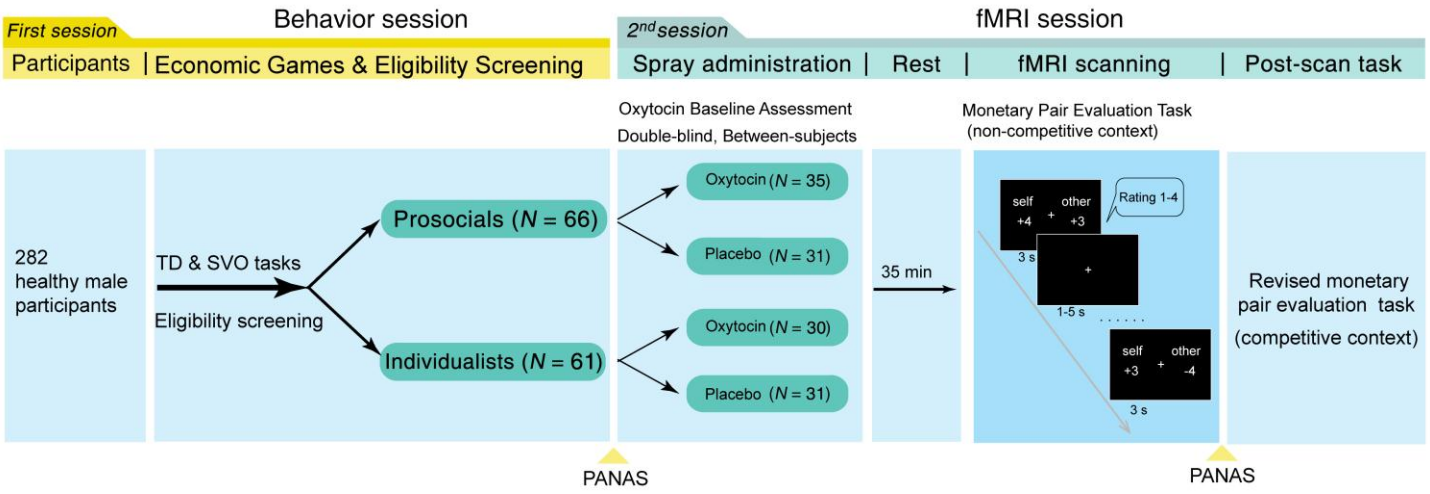

Supplementary Figure 1

General experimental procedure in the fMRI study

There were two sessions: one behavioral session where participants (n = 282) completed two economic games to measure social disposition and were checked for eligibility for the fMRI study; the other fMRI session where prosocials (n = 66) and individualists (n = 61) were randomly assigned to the placebo and oxytocin treatment in a double-blind, placebo-controlled, between-subjects design, and underwent fMRI scanning 35 min later after spray administration. After the fMRI scanning, participants were asked to perform a similar behavioral task in a social competitive context. Note: PANAS, Positive and Negative Affect Schedule to monitor mood (Watson et al., 1988); TD, triple dominance (van Lange, 1999) and SVO, social value orientation (Murphy et al., 2011) to measure individual's disposition of social value orientation.

In the fMRI study, we first invited participants (n = 282) to a behavioral session to identify their dispositions in social value orientation. In the behavioral session, all participants provided demographic information and completed the triple dominance (TD) and social value orientation (SVO) tasks, which were conventional measurements of one's stable disposition in social value orientation (Haruno & Frith, 2010; Hilbig et al., 2014). To incentivize authentic responses during social interactions, participants were recruited in groups of 8-10 individuals (all were strangers to each other). For each economic game, participants were paired with a new, mutually anonymous partner and were asked to make monetary allocation decisions between the self and the partner.

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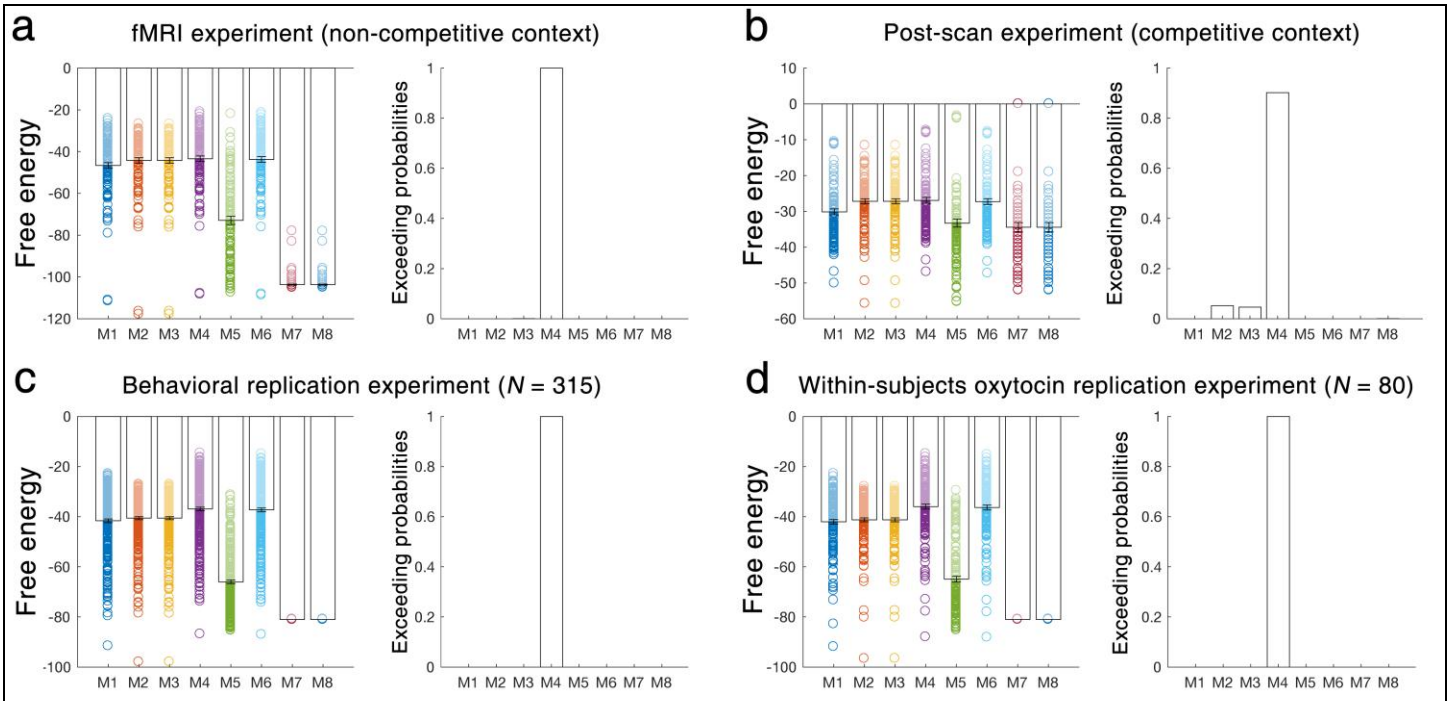

Supplementary Figure 2

Model comparison analysis based on variational free energy

a) fMRI during-scan behavioral data (*n* = 125 males, 180 trials for each participant); **b**) post-scan behavioral data (*n* = 125 males, 90 trials for each participant); **c**) independent online-replication data (*n* = 315 subjects, 82 trials for each participant); **d**) independent oxytocin behavioral replication data (*n* = 80 males, 82 trials for each participant). The social reference model (M4) consistently outperformed other models.

Error bars represented standard error of the mean.

In the behavioral analysis, we modeled trial-by-trial preference ratings using 8 different models. Model fits were performed on z-scored preference ratings. The first one was based on the value of monetary outcome to the self ($Self) and to the partner ($Other). The second and third models considered inequality aversion, in addition to the value of $Self and $Other, the third model made a difference between advantage and disadvantage inequality. The fourth model (i.e., M4) is the *social reference model*, considering the cosine similarity between the current offer and the most preferred one. Note that the equation of M4 was equivalent to a model of $a * \cos(\theta - \varphi)$ based on trigonometry, where φ was the reference point, i.e., the angle between the most preferred allocation. The $\cos(\theta - \varphi)$ was actually used in the fMRI analysis as the parametric regressor given it is a more compact measure (we used the distance to this cosine similarity, i.e., $1 - \cos(\theta - \varphi)$). The fifth and sixth models built up the inequality aversion in a compact way of summarizing the offer (similar to the social reference model), i.e., similarity between the potential offer (θ) and equal offer (45°) described as cosine (θ - 45°). The sixth model also considered fixed reference to the pure egocentric ($\cos(\theta - 0°)$, i.e., $\cos(\theta)$) and allocentric ($\cos(90° - \theta)$, i.e., $\sin(\theta)$) offer. The last two models, seventh and eighth models, considered loss aversion with the same or different free parameters for loss aversion to self and to the partner.

Given that BIC tends to overestimate model complexity in the trade-off of a growing number of free parameters and goodness-of-fit, we employed the variational free energy as the model selection criteria, which was insensitive to additional model complexity induced by adding covariance components (Friston et al., 2007) and has shown with better model selection ability relative to AIC/BIC (Rigoux et al., 2014; Penny, 2012). Among these 8 models, the best model for the current design was the *social reference model* (i.e., M4), according to model selection using free energy.

Below listed all the 8 models for behavioral analysis (with *a*, *b*, *c*, and *d* as potential free parameters):

M1: *a* * $Self + *b* * $Other

M2: a * $Self + b * $Other + c * abs ($Self - $Other)

M3: a * $Self + b * $Other + c * max (0, $Self - $Other) + d * max (0, $Other - $Self)

M4: a * cos (θ) + b * sin (θ)

M5: a * cos (θ - 45°)

M6: a * cos (θ) + b * sin (θ) + c * cos (θ - 45°)

M7: a * max (0, $Self) + b * max (0, $Other) + c * min (0, $Self) + c * min (0, $Other)

M8: a * max (0, $Self) + b * max (0, $Other) + c * min (0, $Self) + d * min (0, $Other)

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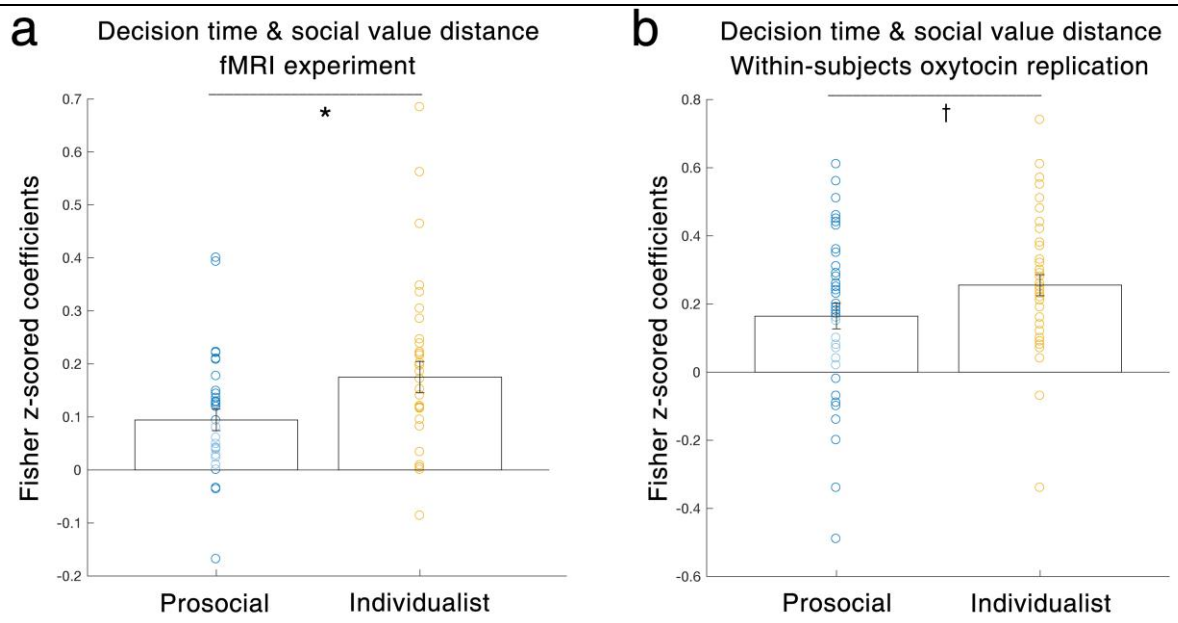
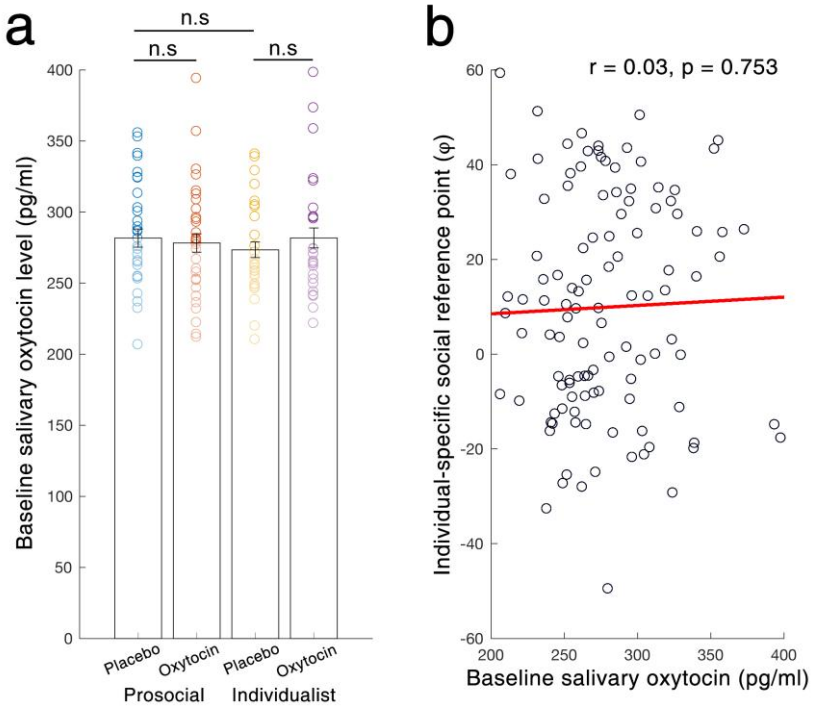


Supplementary Figure 3

Results of decision time

The positive correlation between the social value distance (i.e., deviation from reference point for each allocation) and the decision time was higher in individualists (n = 30 males) than prosocials (n = 31 males) under placebo (revealed by independent-samples t-test on the Fisher z-scored correlation coefficients, t_{59} = 2.33, p = 0.023) in the original study (**a**) and in the additional oxytocin experiment (**b**, n = 80 males, 40 individualists and 40 prosocials, revealed by independent-samples t-test, t_{78} = 1.86, p = 0.067). The greater the dissimilarity between potential and preferred allocations, the longer individualists took to evaluate their preference.

Error bars represented standard error of the mean. * p=0.023, and $^{+}$ p = 0.067.



Supplementary Figure 4

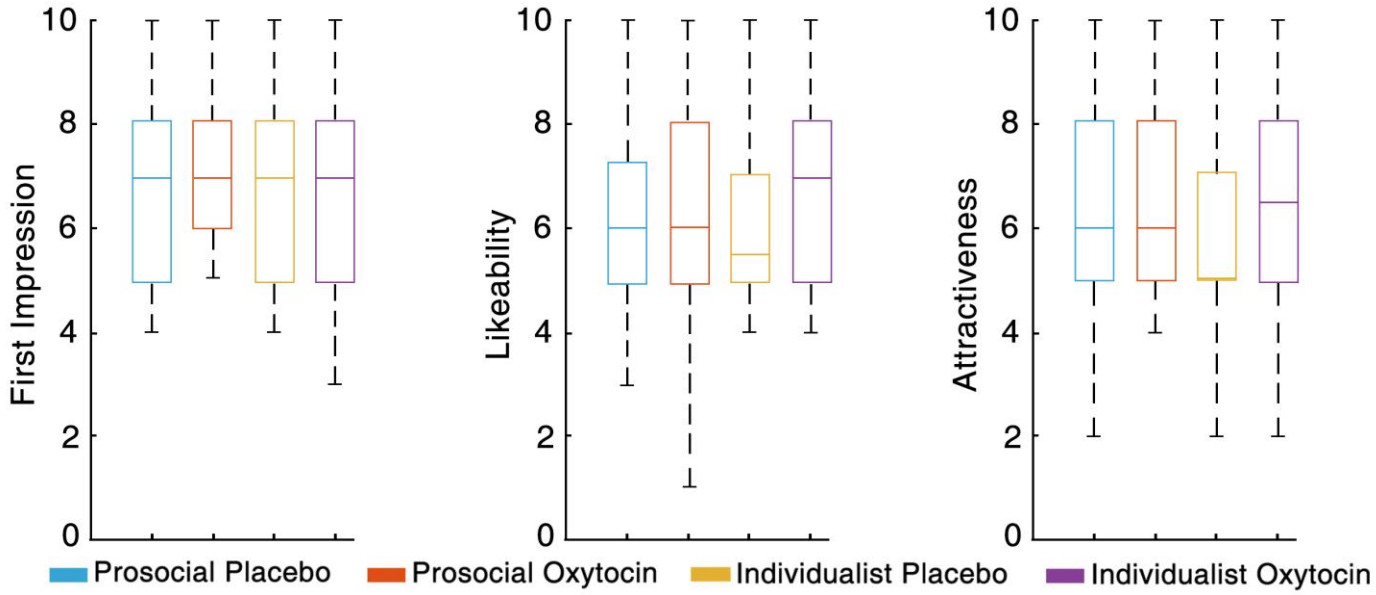
Baseline saliva oxytocin assessment

a) Individual's baseline salivary oxytocin level was measured before the treatment and experiment and did not differ between the prosocials (*n* = 63 males) and individualists (*n* = 51 males) or between oxytocin (*n* = 57 males) and placebo (*n* = 57 males) groups in the result of Treatment x Social Disposition ANOVA. **b**) Pearson correlation analysis showed that the pre-experiment measure of baseline salivary oxytocin level was not related to the reference point in the social value representation (*n* = 114 males).

Error bars represented standard error of the mean (n.s, not significant).

The saliva samples were immediately stored at −20°C until the batch assay. The samples were assayed using standard procedures with a commercially available enzyme immunoassay (EIA) kit (ADI-900-153, Enzo Life Science, Plymouth Meeting, PA). Before the assay, the reagents and the samples were balanced at room temperature 20-28°C. Then, the standard and treated samples were added to a row of wells at 50 µl per well in turn and marked. Then, 25 µl of the enzyme conjugation solution was added to the wells with the standard, and the wells with the samples were assayed and fully mixed. The liquid in the wells and residual liquid were removed after a 60-min incubation reaction at 37°C. The plates were washed with prediluted cleaning liquid 5 times. A 50 µl aliquot of substrate I and substrate II was later added to each well in turn, mixed fully, and kept from light at room temperature for a 15-min reaction. Then, 50µl of stop solution was added to each well and mixed fully to stop the reaction.

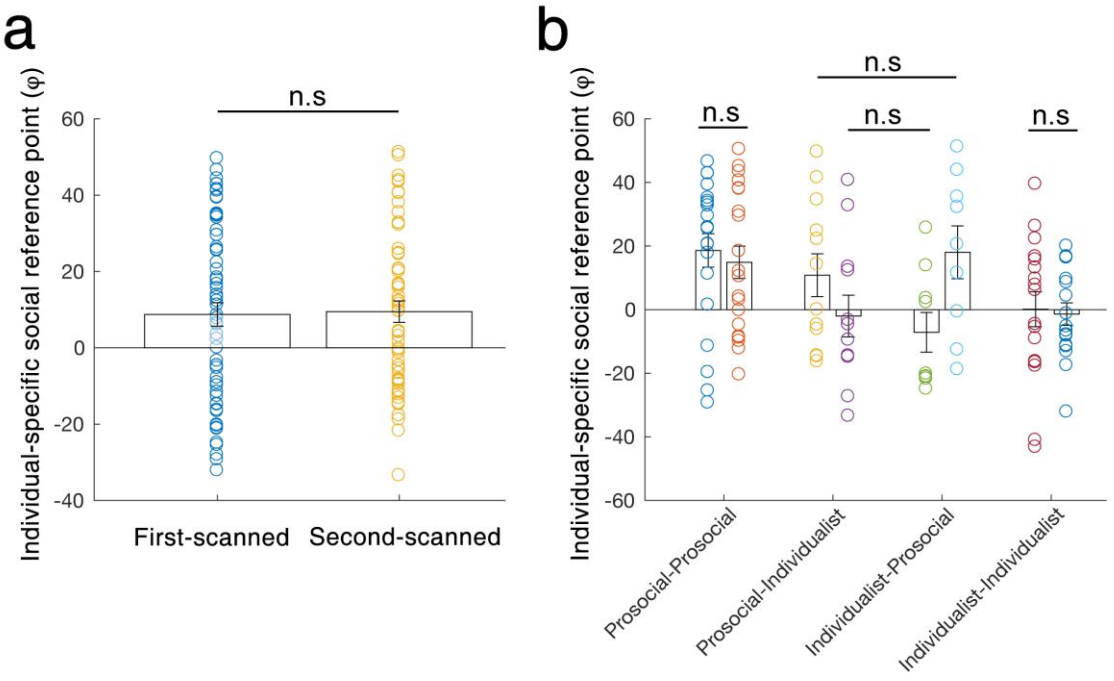
The oxytocin extraction efficiency was 90% (114 out of 127 participants), as determined by spiking with a known amount of hormone and extracting this known amount along with the samples. Oxytocin levels in extracted saliva were then quantified using the oxytocin EIA, in which the salivary oxytocin hormone competed with exogenously added alkaline phosphatase-linked oxytocin, for binding sites on the oxytocin antibody. The optical density (OD) was measured on a Sunrise plate reader (Tecan, Research Triangle Park, NC) at 405 nm after 30 min. The hormone content (in pg/ml) was determined by plotting the OD of each sample against a standard curve.



Supplementary Figure 5

Effects of social perceptions of the partner

participants' social perceptions of their partner, we asked participants to rate their partner on 3 aspects: the first impression, likeability, and attractiveness, on a scale from 0 (lowest) to 10 (highest). There was no significant difference across all groups on any of these measures (n = 125 males). The rating data were analyzed using Treatment x Social Disposition ANOVAs followed by planned two-tailed t tests. Additionally, we asked participants to talk about only their names, hometown, etc. and made sure no topics related to any decision-making, payoff, or task-related information were raised: thus, participants would not be aware of each other's social preferences. Data were plotted as boxplots for each group with boxes indicating 25-75% interquartile range, the inside horizontal lines indicating median values and whiskers indicating the minimum and maximum values. The horizontal line in the attractiveness panel was overlaid with the lower bound of box.



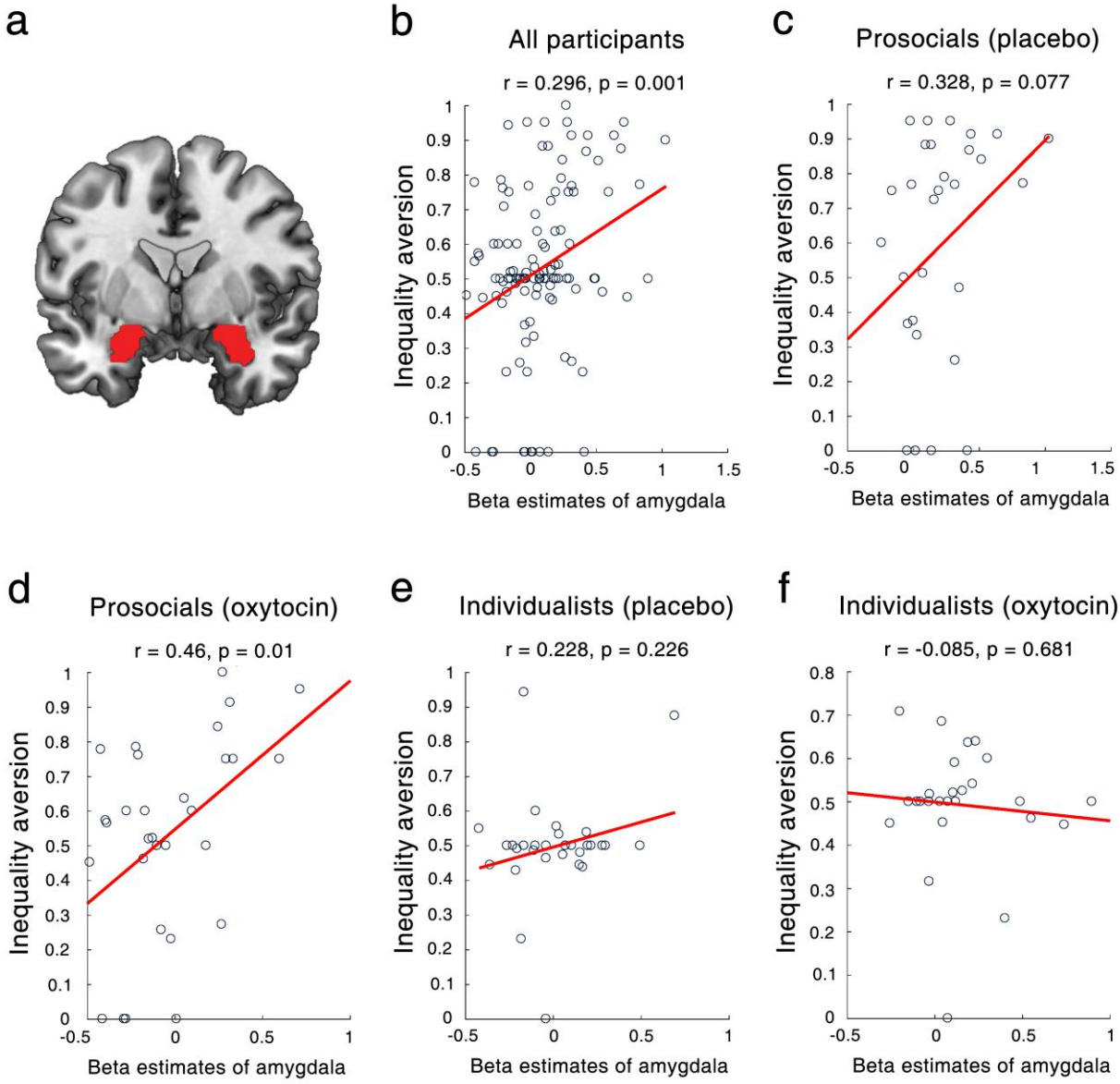
Supplementary Figure 6

Effects of scanning order and partner type on social reference point

a) No effect of scanning order on the social reference point (*n* = 125 males). **b**) No effect of order and partner type on the social reference point.

We conducted ANOVA with scanning order or partner type as between-subjects factors on individual-specific social preference point (φ). There was no effect of Scanning-order (**a**), or effect of partner type (e.g., prosocial-prosocial; prosocial-individualist; individualist-prosocial; individualist-individualist), i.e., no main effect of Order or interaction effect between Order and Social Disposition on the prosocialityindex(**b**).

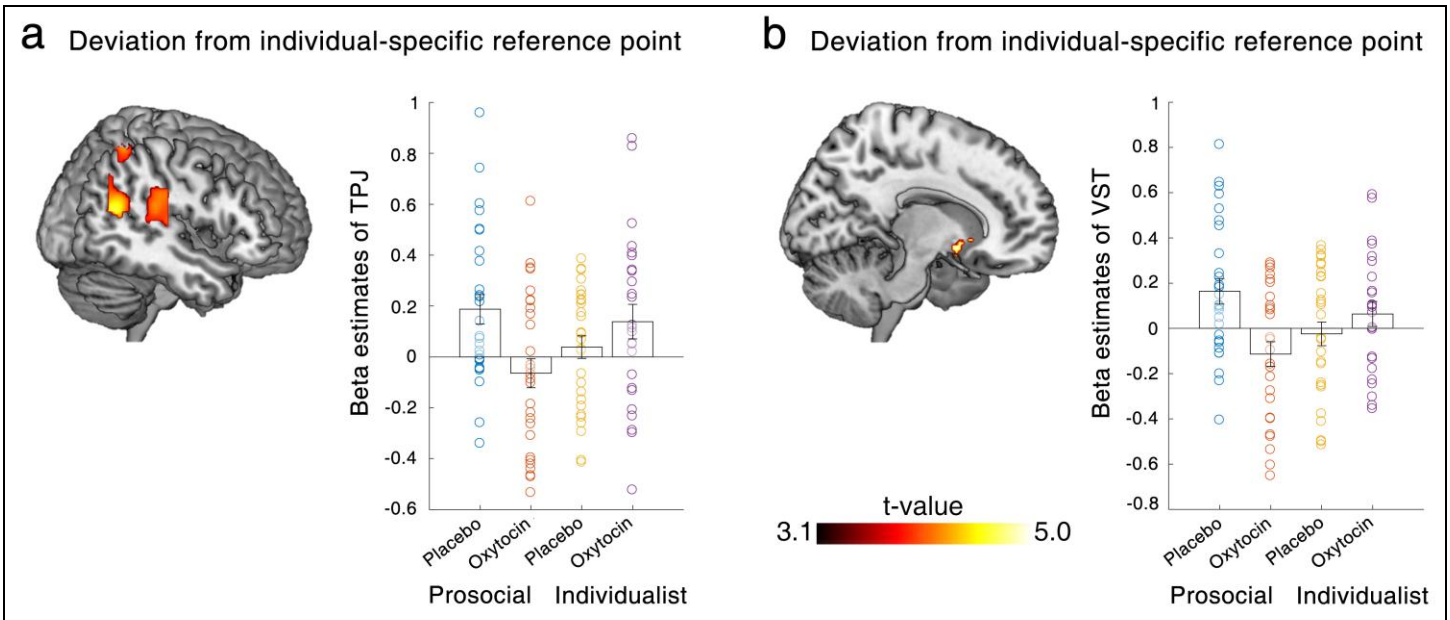
Error bars represented standard error of the mean (n.s, not significant).



Supplementary Figure 7

Amygdala responses predicted inequality aversion in prosocials

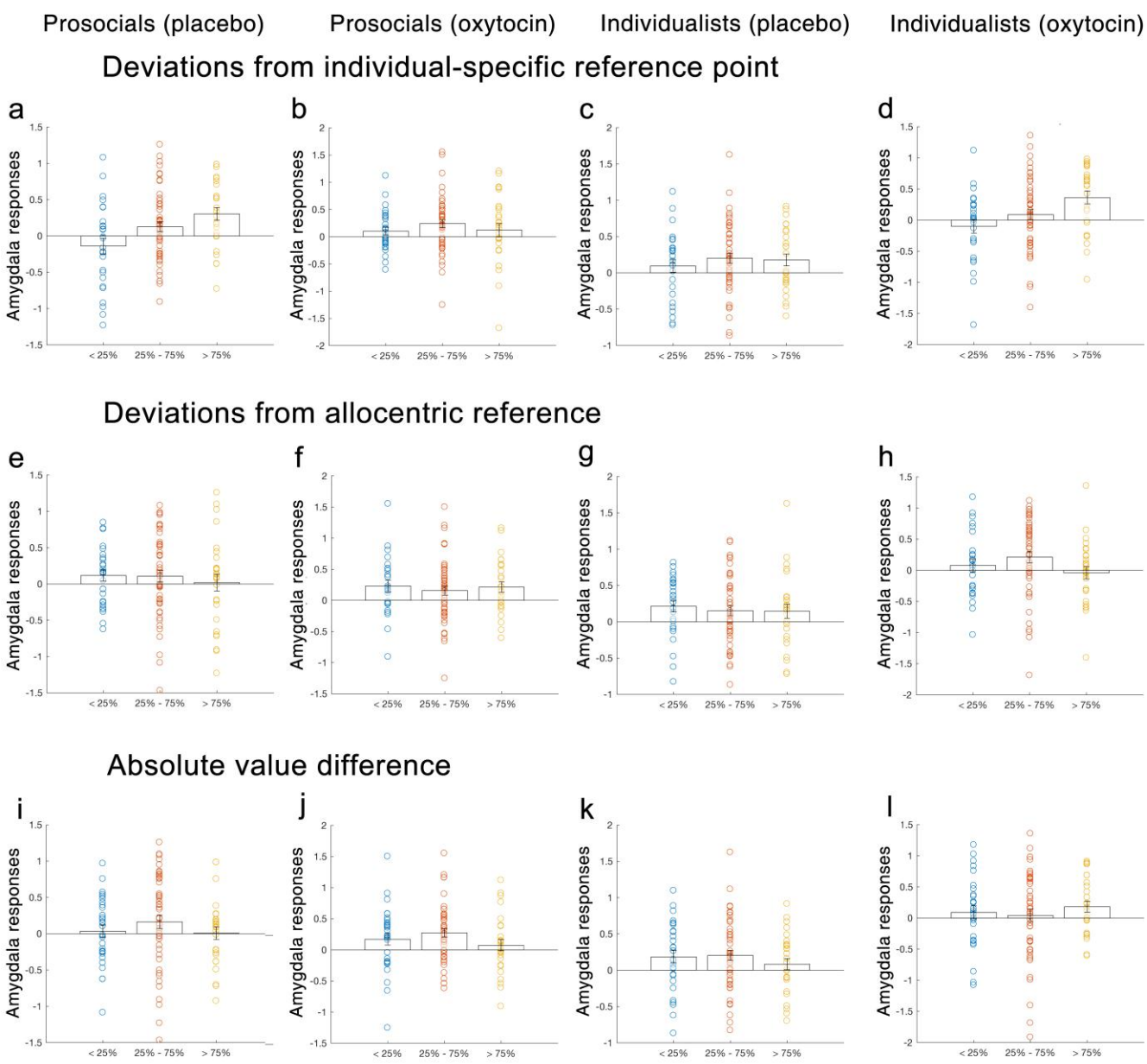
a) Coronal view of bilateral anatomically defined amygdala ROI (red). Pearson correlation analyses showed that amygdala activity was positively correlated with inequality aversion across all participants (n = 116 males, **b**) but was only significant in prosocials (*n* = 30 males under placebo, **c**, and *n* = 30 males under oxytocin, **d**) and not in individualists (*n* = 30 males under placebo, **e**; *n* = 26 males under oxytocin, **f**).



Supplementary Figure 8

Other brain regions showing the interaction effect of treatment and social disposition in coding social-value distance

Whole-brain analysis revealed that (**a**) right temporoparietal junction (rTPJ) and (**b**) ventral striatum (VST) also showed distinct effects of oxytocin in prosocials ($n = 30$ males under placebo and $n = 30$ males under oxytocin) and individualists ($n = 30$ males under placebo, $n = 26$ males under oxytocin) ($P < 0.05$, FWE-corrected at the cluster level after voxel-wise thresholding at $P < 0.001$).

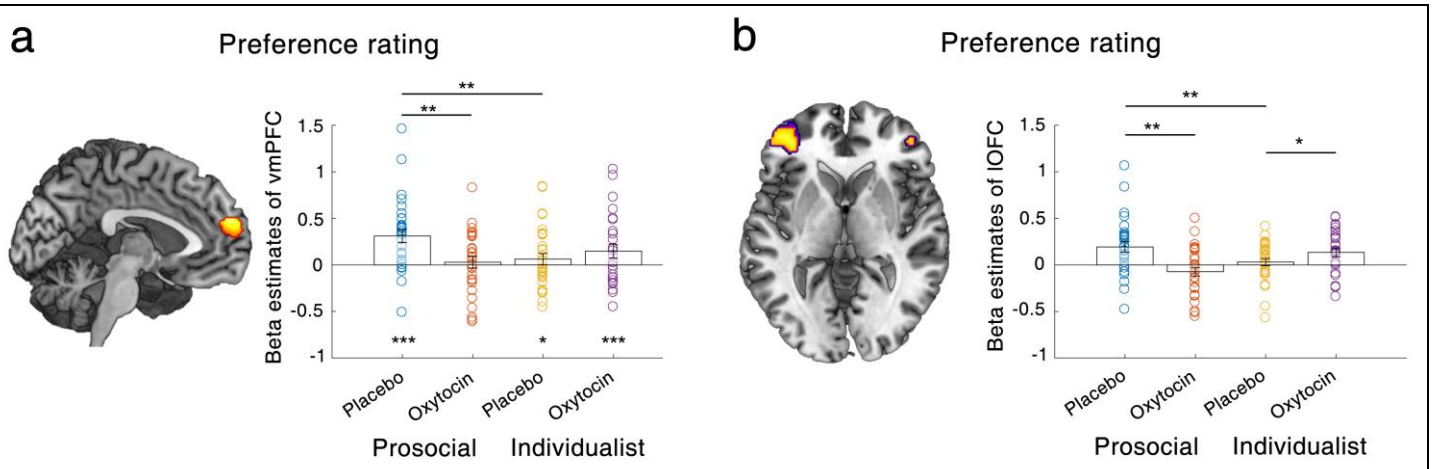


Supplementary Figure 9

Amygdala responses to different parametric regressors

Amygdala responses to different parametric regressors (divided into bins), including the deviations from the individual-specific reference point **(a-d)**; the deviations from allocentric reference point **(e-h)**; and the absolute value difference **(i-l)** in prosocials under placebo (the first column, i.e., **a/e/i**, *n* = 30 males) or oxytocin (the second column, i.e., **b/f/j**, *n* = 30 males), and in individualists under placebo (the third column, i.e., **c/g/k**, *n* = 30 males) or oxytocin (the fourth column, i.e., **d/h/l**, *n* = 26 males). The amygdala activity increased as a function of deviations from individual-specific referent point in prosocials under placebo (slope estimate of the linear fit=0.222, p=0.001, **a**) and this pattern was diminished under oxytocin (slope estimate=0.010, p=0.88, **b**). In contrast, oxytocin increased amygdala responses to deviations from individual-specific referent-point in individualists (slope estimate=0.232, p=0.003, **c**), and this pattern was not found under placebo (slope estimate=0.042, p=0.50, **d**). Monotonically increasing patterns were not present for amygdala responses for absolute value differences or for deviations from allocentric referen ce (all $p > 0.5$, ***e-l***).

Error bars represented standard error of the mean.

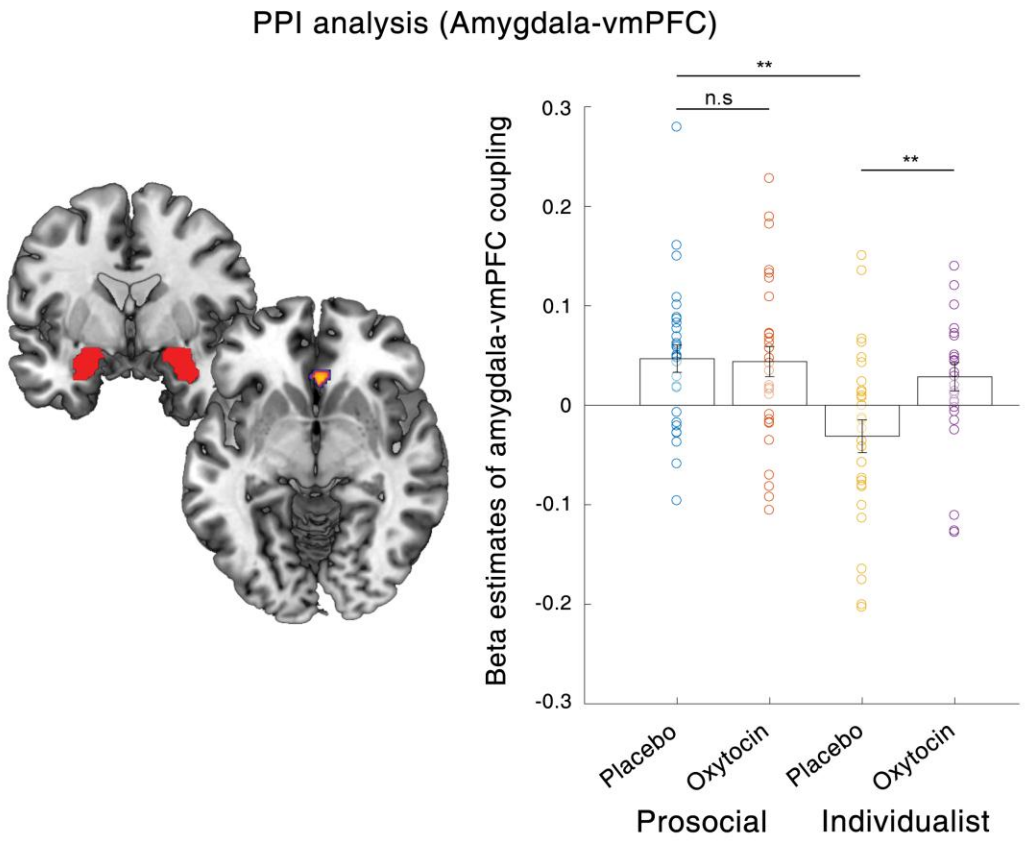


Supplementary Figure 10

Neural activity in the mPFC and lOFC for encoding the preference rating

Neural activity in the mPFC (**a**) and lOFC (**b**), encoding subjective preference ratings on social allocations (height threshold $p<0.001$, cluster-based FWE correction, $p<0.05$), was modulated by Social Disposition and oxytocin treatment (n = 116 males).

Error bars represented standard error of the mean (*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$).



Supplementary Figure 11

Functional connectivity between the amygdala and vmPFC

Functional connectivity between the amygdala and vmPFC was stronger in individualists ($n = 56$ males) than in prosocials ($n = 60$ males) (voxel-wise $p<0.001$, uncorrected). Oxytocin increased the amygdala-vmPFC coupling individualists but not prosocials. Further ROI analysis (functionally defined vmPFC cluster showing different coupling with amygdala between individualists and prosocial under placebo, height threshold $p<0.001$, suggested that oxytocin increased the strength of functional connectivity between amygdala and vmPFC in encoding social value distance in individualists (one-sample t-test, $t_{54} = 2.69$, $p = 0.009$) but not in prosocials ($t_{58} = 0.067$, $p = 0.95$).

Error bars represented standard error of the mean (**$p < 0.01$; n.s, not significant).

Supplementary Table 1. Brain regions involved in encoding social value distance in prosocials under placebo

Brain Regions	L/R	BA	*T* values	MNI Coordinates (x, y, z)		
Prosocials (*n* = 30 males)						
Striatum	R	-	4.93	28	-4	-6
Amygdala/Hippocampus	R	-	5.22	20	-10	-12
Middle Temporal Gyrus	L	21	5.13	-52	-36	-2
Superior Parietal Lobule	R	7	5.55	16	-68	50
	L	7	4.79	-18	-66	44

Only clusters, significant at a height threshold of $p < 0.001$ and an extent threshold of $p < 0.05$ with family-wise error corrections for multiple comparisons, were reported with local maxima in Montreal Neurological Institute (MNI) space. "-", no proper data. L, left hemisphere; R, right hemisphere.

Supplementary Table 2. Brain regions involved in encoding social value distance with parametric modulator centered on egocentric reference (i.e., x-axis) or allocentric reference (i.e., y- axis).

Brain Regions	L/R	BA	*F* values	MNI Coordinates (x, y, z)		
Egocentric reference (i.e., x-axis)						
Main Effects of Social Disposition or Treatment				None		
Social Disposition x Treatment Interaction						
Thalamus	R	-	11.21	6	-18	6
	L	-	11.54	-4	-15	5
Lingual	R	-	14.23	4	-72	0
Allocentric reference (i.e., y-axis)						
Main Effects of Social Disposition or Treatment				None		
Social Disposition x Treatment Interaction				None		

Only clusters, significant at a height threshold of $p < 0.001$ and an extent threshold of $p < 0.05$ with family-wise error corrections for multiple comparisons, are reported with local maxima in Montreal Neurological Institute (MNI) space. "-", no proper data. L, left hemisphere; R, right hemisphere.

Supplementary Table 3a. Scores on emotion-related questionnaire measures and Mood changes from pre- to post-experiment (mean ± standard deviation) in the fMRI oxytocin experiment (*n* = 125).

	Individualists		**Prosocials**		**Main effects** $F_{(p)}$		**Interaction**
	Placebo	Oxytocin	Placebo	Oxytocin	Social Disposition	Treatment	$F_{(p)}$
Wellbeing	42.81 (8.91)	43.45 (10.43)	46.49 (9.85)	46.82 (9.69)	3.98 (0.05)	0.08 (0.78)	0.01 (0.93)
Happiness	18.20 (3.87)	18.90 (4.51)	19.68 (3.74)	19.09 (4.40)	1.26 (0.26)	0.00 (0.94)	0.75 (0.39)
BDI	6.87 (6.04)	8.14 (9.03)	5.16 (4.62)	6.41 (5.68)	2.13 (0.15)	1.15 (0.29)	0.00 (0.99)
TA	37.90 (6.92)	41.24 (10.96)	36.71 (7.38)	36.94 (8.06)	3.30 (0.07)	1.40 (0.24)	1.06 (0.31)
Mood measurement							
Pre	15.07 (5.79)	14.29 (11.58)	17.42 (7.75)	15.94 (8.19)	1.67 (0.20)	0.53 (0.47)	0.05 (0.82)
Post	15.41 (7.38)	15.00 (11.62)	16.30 (9.89)	16.71 (10.54)	0.51 (0.48)	0.00 (1.00)	0.05 (0.82)
Δ Mood	0.34 (6.52)	0.71 (14.24)	-1.13 (8.12)	0.77 (6.19)	0.18 (0.67)	0.47 (0.50)	0.21 (0.65)

Supplementary Table 3b. Scores on emotion-related questionnaire measures and Mood changes from pre- to post-experiment (mean ± standard deviation) in the behavioral oxytocin-replication experiment (*n* = 80).

	Individualists		**Prosocials**		**Main effects** $F_{(p)}$		**Interaction**
	Placebo	Oxytocin	Placebo	Oxytocin	Social Disposition	Treatment	$F_{(p)}$
Wellbeing	44.08 (12.15)		48.06 (10.52)		2.45 (0.12)	-	-
Happiness	21.55 (6.12)		21.68 (6.23)		0.01 (0.93)	-	-
BDI	7.85 (8.69)		7.23 (7.05)		0.13 (0.73)	-	-
TA	37.89 (9.52)		36.92 (11.06)		0.16 (0.69)	-	-
Mood measurement							
Pre	14.79 (9.26)	13.37 (10.61)	18.11 (9.98)	19.39 (9.41)	4.62 (0.03)	0.01 (0.94)	2.75 (0.10)
Post	14.88 (11.12)	13.62 (10.79)	16.94 (11.98)	16.42 (12.02)	0.91 (0.34)	0.87 (0.35)	0.15 (0.70)
Δ Mood	0.09 (7.00)	0.25 (8.26)	-1.17 (6.49)	-2.97 (7.16)	2.59 (0.11)	0.69 (0.41)	0.98 (0.33)

Wellbeing: Participant's wellbeing measured by the Index of Well-Being questionnaire (Campbell et al., 1976) (*n* = 122 in **a**, *n* = 80 in **b**); Happiness: Participant's happiness was measured by the Satisfaction With Life Scale (Pavot et al., 1991) (*n* = 125 in **a**, *n* = 69 in **b**); BDI: Participant's depression symptoms were measured by in Beck Depression Inventory (Beck et al., 1988) (*n* = 123 in **a**, *n* = 80 in **b**); TA: Participant's trait anxiety measured by the Trait Anxiety (Spielberger & Sydeman, 1994) (*n* = 123 in **a**, *n* = 80 in **b**).

Mood measurement: Pre/Post, Participant's pre-/post-experiment mood measured by Positive and Negative Affect Schedule (Watson et al., 1988) (*n* = 122 in **a**, *n* = 72 in **b**). Δ Mood **=** Post-mood *minus* Pre-mood. Some participants did not complete all the questionnaires, thus the number of participants (*n*) provided differed in each questionnaires.

ANOVAs with Treatment (between-subjects factor in **a**; within-subjects factor in **b**) and Social Disposition (between-subjects factor) was conducted. "-": no test of treatment for the scores of these questionnaires because the within-subject design was employed in the oxytocin-replication study and each participant completed these questionnaires just once. Neither the main effect of Treatment nor the interaction effect was significant for any emotion-related questionnaire scores across two studies. Manipulation check of mood changes after oxytocin/placebo has shown that the main effect of Treatment and Social Disposition and interaction effect were not significant in fMRI experiment (**a**) and oxytocin-replication experiment (**b**).

Reference:

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Supplementary Note 1

Evidence for using intranasal administration of 24 IU oxytocin.

The effect of intranasal oxytocin on alterations in brain oxytocin levels. We administered oxytocin using intranasal delivery. Although limited amounts of oxytocin cross the blood-brain barrier[1], the direct anatomical connection between the nasal cavity and the brain makes it possible to deliver oxytocin to the brain. The intranasal delivery of oxytocin reaches the central nervous system and increases central oxytocin concentrations via channels surrounding trigeminal and olfactory nerve fibers. The quantifiable evidence that intranasal oxytocin alters brain oxytocin activity is provided from findings of cerebrospinal fluid (CSF) oxytocin increases after intranasal oxytocin in rodents[2], monkeys[3-7] and humans[8,9], also well documented in a systematic recent review[10].

Some of the clearest evidence in rat and primate was reported in recent studies[7, 11]. Lee and colleagues[7] measured CSF concentrations of oxytocin after intranasal administration of labeled (d5-deuterated) oxytocin and provided direct evidence for CSF penetrance of intranasal oxytocin administered to nonhuman primates. Another recent study by Tanaka and colleagues[11] systematically examined the pharmacokinetic properties and brain distribution of oxytocin after intranasal application. This study evaluated the disposition, nasal absorption and bioavailability of oxytocin after nasal administration and showed evidence that the nasal bioavailability of oxytocin was approximately 2%, and more than 95% of oxytocin in the brain was directly transported from the nasal cavity.

Moreover, Paloyelis and colleagues[8] measured the availability of intranasal oxytocin to brain tissues in human participants using arterial spin labeling (ASL) to quantify in vivo intranasal oxytocin-induced changes in resting regional cerebral blood flow (rCBF), which reflects changes in neuronal activity rather than simple vascular effects. They showed robust evidence that intranasal oxytocin induced changes in an oxytocinergic network of regions expected to express oxytocin receptors, including limbic and midbrain/brainstem regions, such as the amygdala, hippocampus, caudate nucleus, ventral striatum and pallidum; anterior and middle cingulate, inferior frontal gyrus, anterior insula, and superior temporal gyrus, and these changes were sustained over the entire observation interval of 78 min.

The dosage issue of intranasal oxytocin. The use of 24 IU administration of oxytocin in the current study (the most commonly used dose in the literature) is supported by recent findings:

First, using oxytocin-induced CSF change as an indicator, a recent study by Rault[12] measured cerebrospinal fluid samples before and after intranasal administration of 50 µg oxytocin in pigs (close to human equivalent dose of 24 IU, considering body surface area, pharmacokinetics, and physiological time differences among species,

the pig-to-human dose extrapolations factor of 0.95 is close to 1[13,14]) and showed that 50 ng (approximately 0.001 of the administered 50 µg) reached the CSF. Although a small proportion accesses the brain, the common dose of 24 IU providing 50 ng reaching the CSF impacts neural activity and is already a supra-physiological dose given the commonly reported baseline endogenous CSF OT concentrations in humans[9, 15].

Second, it is also worth noting that a common finding in recent oxytocin studies is that intranasal oxytocin does not produce a linear dose–response curve[16-18]. Although the exact mechanism is unknown, it has been speculated that the nonlinearity of the oxytocin dose response is due to coupling with different G proteins or binding to the Avpr1a receptor when high doses flood available oxytocin receptors. Guoynes and colleagues[17] examined the effect of intranasal oxytocin on the central receptor binding and immunoreactive protein for oxytocin and detected significant changes in the prairie voles receiving a dose similar to the equivalent in human studies but not for lower or higher doses. Moreover, Keech and Hocking[19] suggested that the effect of intranasal oxytocin on social cognition is not modulated by dosage.

Finally, regarding the oxytocin effect on amygdala activity, Spengler and colleagues[20] directly compared effects of different doses of oxytocin on human emotional processing and found evidence that 24 IU oxytocin (compared with 12 or 48 IU) produced the most pronounced effects on amygdala responses underlying emotional processing, as well as on plasma and salivary oxytocin levels, providing evidence for 24 IU as the appropriate dose to target amygdala functioning.

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