



OPEN Interdependency between oxytocin and dopamine in trust-based learning in mice

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Oxytocin (OT) is a neuropeptide implicated in complex social behaviors such as trust and attachment, yet the neural mechanisms underlying its effects remain unclear. OT is thought to modulate behavior by enhancing salience of social cues and attenuating prediction error (PE) processing, the discrepancy between expected and actual outcomes that drives learning. Since both salience coding and PE processing involve dopamine (DA), we investigated OT and DA interdependency in social safety learning using the social transmission of food preference (STFP) paradigm. In STFP, mice overcome neophobia towards novel food after a conspecific demonstrator signals its safety. We interpreted STFP acquisition as a functional parallel to human trust-based learning and found that OT enhanced demonstrated food preference in a *trust acquisition* condition, but only when DA signaling was intact. In a *trust violation* condition, the expectation of food safety was violated by pairing demonstrated food with lithium chloride (LiCl)-induced aversion. Updating was blocked after OT administration and non-significantly reduced after DA depletion, resulting in a continued preference for demonstrated food. However, this effect was absent when OT was administered under DA depletion. These findings reveal a functional interaction between the OT and DA systems in social safety learning, which may have important implications for OT's potential in treating disorders involving DA dysfunction.

Keywords Oxytocin, Dopamine, Social learning, Social transmission of food preference, Trust

The hypothalamic neuropeptide oxytocin (OT), identified over a century ago by Sir Henry Dale¹, was initially defined by its hormonal effects on the reproductive system². More recent research has implicated centrally released OT in the modulation of a wide range of social behaviors and socio-cognitive processes such as social recognition, trust and attachment^{3–5}. Putative mechanisms through which OT exerts effects include enhancing the salience of social cues⁶ and attenuating prediction error (PE) processing⁷. PE refers to the discrepancy between expected and actual outcomes that drives learning⁸. Notably, both salience coding and PE processing are thought to involve mesocorticolimbic dopamine (DA) neurons as well^{9,10}. These neurons originate in the ventral tegmental area (VTA) and project broadly to cortical regions, such as the prefrontal cortex (PFC; mesocortical pathway), and to limbic regions, such as the amygdala (mesolimbic pathway)¹¹.

Neurohistological studies show that OT and DA receptor binding sites and neuronal terminals are located in close proximity. The paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus, primary OT production sites, are innervated by DA neurons and express DA receptors^{12,13}. Conversely, DA receptor-expressing brain regions in the mesocorticolimbic pathway receive innervation from PVN OT neurons and express OT receptors^{14,15}. Functionally, PVN OT neurons have been shown to enhance DA activity in the VTA and suppress DA activity in the substantia nigra pars compacta (SNc)¹⁶, an interaction that appears important for modulatory effects of OT on social behavior, including the onset and maintenance of social bonds^{17–19}.

In the current study, we investigate the putative interdependence between OT and DA in social safety learning using the social transmission of food preference (STFP) paradigm^{20,21}. STFP is based on the observation that rodents (observers) display neophobia towards novel food, but develop a preference for it when a conspecific demonstrator signals its safety (i.e., social safety learning). In previous work, we proposed that STFP acquisition

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may involve cognitive processes functionally related to elements of human epistemic trust, in which individuals evaluate and use socially acquired information to guide decision-making or behavior^{22,23}.

Within this framework, we found that OT administered to male mice prior to the observer–demonstrator interaction enhanced preference for the demonstrated food in a *trust acquisition* condition (STFP1), corresponding to the typical STFP paradigm in which observer mice learn about food safety. In contrast, in a *trust violation* condition (STFP2), we violated this learned expectation (i.e., induced PE) by pairing the demonstrated food with lithium chloride (LiCl)-induced nausea after the interaction. In this condition, OT blocked updating, as mice continued to prefer the demonstrated food²⁴.

Mesocorticolimbic DA has recently been conceptualized as a teaching signal that filters out irrelevant information by coding salience and updating expectations based on relevant inputs^{9,25}. Accordingly, DA may potentiate the shift from fear to safety during social safety learning, but also respond to unexpected threats during threat learning^{9,26}. Within the context of STFP acquisition, OT may modulate DA released during social interaction to enhance the salience of social information on safety²⁷, thereby enhancing demonstrated food preference in the *trust acquisition* condition (STFP1) and blocking updating in the *trust violation* condition (STFP2). Complementary, OT may block updating in the *trust violation* condition by attenuating DA released in response to unexpected threats (i.e., LiCl-induced nausea).

Therefore, the current study investigates the effects of OT administration and DA depletion using tetrabenazine (TBZ) on social safety learning during *trust acquisition* (STFP1) and *trust violation* (STFP2) conditions. Building on our previous findings²⁴, we hypothesized that OT would enhance demonstrated food preference in the *trust acquisition* condition but only when DA signaling is intact. Conversely, we expected both OT administration and DA depletion to block updating and retain a demonstrated food preference after *trust violation* (i.e., inducing PE). OT may achieve this effect by enhancing the salience of social information on safety during initial learning and by reducing PE processing, and DA depletion by impairing DA-mediated PE signaling. Additionally, we tested whether any effects of OT and DA system manipulations extended to other behavioral domains such as explorative and anxiety-like behavior, sociability, and spatial working memory.

Materials and methods

Animals

The current study included 72 male C57BL/6J mice (Janvier Labs, France), aged 10–12 weeks upon arrival, randomly divided into three experimental groups (OT, TBZ and OT + TBZ). Instead of testing a new vehicle control (VEH) group, we reused previously collected control data²⁴, a method proposed as valid to reduce the number of animals in research²⁸. Mice in the VEH group (males of the same age; $n = 36$, unless otherwise noted) received phosphate-buffered saline (PBS) or 1% dimethyl sulfoxide (DMSO) diluted in saline (SAL) and were tested under the same conditions as mice in the current study (same experimenters, tested in the same testing room at similar time of day, similar housing conditions). Mice were housed in groups of four in Macrolon cages with wood-shaving bedding and cage enrichment (e.g., nesting material and toilet paper rolls to hide), kept under standard conditions (22–25 °C, humidity 50–70%, 12 h light/dark cycle with lights on at 07:00), with ad libitum access to food and water, unless otherwise noted. Reporting of the current study is in accordance with the ARRIVE guidelines²⁹.

Treatment preparation and administration

All solutions were prepared as stocks and stored in small aliquots at -20 °C. Aliquots were coded to ensure blinded experiments. OT was dissolved in PBS (1 $\mu\text{g}/\mu\text{L}$), and OT or PBS was administered intranasally (2×6 μL) using a micropipette 30 min before each behavioral test. Previous research using this dose demonstrated that central OT levels increase 30 min after intranasal administration³⁰. To ensure proper inhalation, droplets of the respective solutions were applied gradually over the mice's nostrils before proceeding with subsequent portions.

TBZ is a selective and reversible inhibitor of vesicular monoamine transporter-2 (VMAT-2) that prevents monoamine storage, with most pronounced effects (75–80% reduction) on striatal DA. TBZ was dissolved in DMSO (7.5 mg/mL in DMSO), and this stock solution was diluted 100 \times with SAL; VEH was 1% DMSO in SAL. TBZ (0.75 mg/kg) or VEH was administered intraperitoneally (i.p.; 1% body weight) 2 h before each behavioral test. This dose and timing were based on research showing the lowest DA levels 2.5 h following TBZ administration, after which they gradually recover^{31,32}. To minimize the risk of persistent behavioral effects associated with daily TBZ injections³³, behavioral tests were scheduled at least one week apart.

LiCl (1 mEq/kg) was dissolved in SAL and administered i.p. (1% body weight) 30 min after STFP2. We previously showed that this low-dose LiCl protocol effectively induced taste aversion learning²⁴.

Behavioral testing

Mouse behavior was evaluated in the following order: explorative and anxiety-like behavior (open field, OF), sociability (social preference, SP), spatial working memory (T-maze), and trust-like behavior (STFP1 and STFP2). Procedures and results of control measures (OF, SP and T-maze) are reported in Supplementary file 1. Thirty minutes prior to each test, mice were habituated to the testing room. In social tests, we evaluated behavior of experimental mice towards unfamiliar mice of the same sex, strain (i.e., strangers), and age in STFP1 and STFP2 (i.e., demonstrators). To prevent transfer of unfamiliar animal scents, tested experimental mice were kept separate from naïve cage mates. For tasks involving different food types (STFP1, STFP2), gloves were changed to avoid contamination. Setups were thoroughly cleaned with 70% ethanol in between mice. To ensure blinding, treatment administration and behavioral testing were performed by different experimenters. All procedures were conducted during the light phase of mice's cycle and approved by the Animal Ethics Committee of the University of Leuven, in accordance with EU directive 2010/63/EU on animal experiments.

Social safety learning

We modified our STFP protocol to model *trust acquisition* and *trust violation*³⁴, as outlined in Budniok et al.²⁴. Briefly, testing for *trust acquisition* (STFP1) and *trust violation* (STFP2) conditions was conducted in a three-compartment setup across three phases (*habituation*, *social interaction* and *test*) over five days (Fig. 1). Throughout, experimental mice (observers) were placed on a scheduled feeding regimen (1 h access to regular food/day), while demonstrators were fed regular crushed food pellets mixed with paprika (1% w/w; STFP1) or rosemary powder (1% w/w; STFP2) for at least five days before the *social interaction* phase.

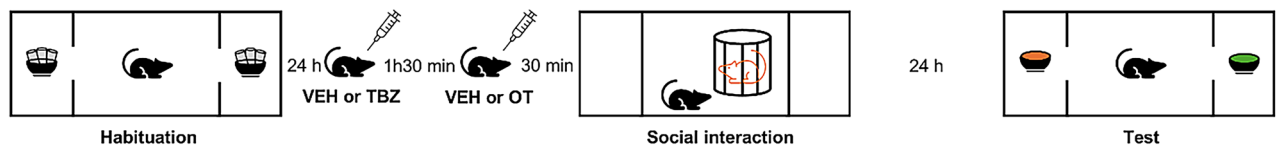
Following two days of scheduled feeding, observers were habituated to the setup during a 20 min *habituation* phase on day 3. On day 4, after receiving treatment, observers interacted for 30 min with demonstrators placed in a round wire cage ($\varnothing = 10$ cm) in the central compartment of the setup during the *social interaction* phase (STFP1). To model *trust violation* (STFP2), we administered LiCl to observers 30 min after this phase to induce nausea. LiCl-induced nausea replaces the positive association with the demonstrated flavor (i.e., food is safe) with an unexpected negative association, inducing PE, which should result in decreased preference for demonstrated food. On day 5, in the *test* phase, observers had 2 h access to demonstrated (i.e., paprika in STFP1 and rosemary in STFP2) and novel food (i.e., oregano in STFP1 and basil in STFP2). Different demonstrators were used in STFP1 and STFP2, and to prevent contamination, demonstrated and novel food flavors were not counterbalanced.

Movements of observers were tracked using the ANY-maze Video Tracking System (Stoelting, Dublin, Ireland) to assess time spent in each compartment of the setup. Additionally, we weighed food cups before and after the *test* phase to measure consumption. Social investigation was assessed as the time the observer spent within the 5 cm area surrounding the cage containing the demonstrator during the *social interaction* phase. Trust-like behavior was evaluated by comparing consumption of demonstrated versus novel food, and by calculating a demonstrated food preference score as the percentage of demonstrated food consumed (demonstrated food preference_{consumption} = demonstrated food consumed / (demonstrated + novel food consumed) x 100) and as time spent near demonstrated food over the whole test period (demonstrated food preference_{time} = time spent near demonstrated food / (time spent near demonstrated + novel food) x 100). Demonstrated food preference_{time} was also calculated for each 10-min time bin to compute the area under the curve relative to the increase from chance level (AUC_{time}³⁵). This calculation allowed us to compare preference to spend time near the demonstrated food during the first hour of the *test* phase, with higher AUC_{time} values indicating stronger preference.

Statistical analysis

Assumptions of normality and homogeneity of variance were formally evaluated using Shapiro–Wilk and Levene’s tests, respectively. No major deviations from these assumptions were observed. Experimental groups (OT, TBZ, OT + TBZ) were compared both with each other and individually against the VEH group (control-based comparisons). Control-based comparisons assessed mean differences (MD) using Dunnett’s *t*-test. Time spent near the demonstrator during the *social interaction* phase of STFP1 and STFP2 was not compared to the

Trust acquisition condition



Trust violation condition

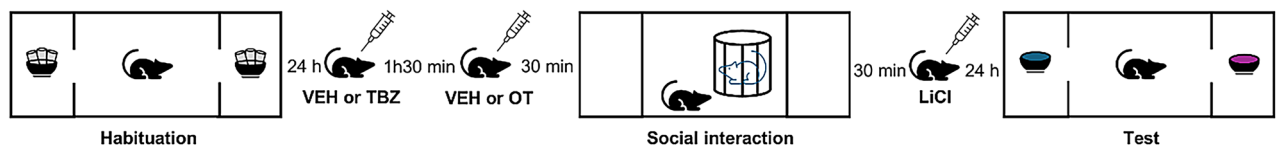


Fig. 1. Overview of the *trust acquisition* and *trust violation* conditions. Testing was conducted in a three-compartment setup across three phases (*habituation*, *social interaction*, and *test*) over five days. During the first two days, observer and demonstrator mice were placed on their respective feeding regimens. On day 3 (*habituation* phase), observer mice were presented with regular food (grey pellets). Two hours, and 30 min before the *social interaction* phase (day 4), observers received their treatment. During *social interaction*, demonstrator mice (inside a circular cage) presented flavored food (e.g., paprika). In the *test* phase (day 5), observers were offered demonstrated food (orange = paprika-flavored) and novel food (green = oregano-flavored). In the *trust violation* condition (STFP2), observers interacted with different demonstrators that had consumed rosemary-flavored food (blue) and received lithium chloride (LiCl) 30 min after the interaction to induce nausea. In this condition, a different novel food (purple = basil-flavored) was presented during the *test* phase. VEH = vehicle; TBZ = tetrabenazine; OT = oxytocin. Adapted from “Oxytocin enhances acquisition in a social trust task in mice, whereas both oxytocin and its antagonist block trust violation learning”, by S. Budniok, Z. Callaerts-Vegh, M. J. Bakermans-Kranenburg, G. Bosmans, R. D’Hooge, 2025, *Neuropharmacology*, 271, p. 3–4.

VEH group, as they had interacted with different demonstrators than the experimental groups. Comparisons among experimental groups used Welch's t -tests. Within-group preference for demonstrated food was evaluated by comparing demonstrated and novel food consumption within each group using paired t -tests, and by comparing demonstrated food preference score_{time} to chance (50%) using one-sample t -tests. Scores above or below chance were interpreted as increased or decreased preference, respectively.

Furthermore, we conducted exploratory analyses to assess the relative influence of observer-demonstrator interaction time in each group on preference for demonstrated food. We analyzed $AUCi_{time}$ using two-way ANOVA, with interaction time (below or above median: short vs. long) and group (and their interaction) as between-subjects variables. Food consumption was analyzed with three-way mixed ANOVA with the addition of food type (demonstrated vs. novel) as within-subjects variable. Interactions between all variables were also analyzed with an exploratory aim. ANOVA results were followed up with Welch's t -tests. The Benjamini-Hochberg method was applied in confirmatory analyses to control for multiple testing when assessing social safety learning (preference for demonstrated food operationalized in terms of time and consumption), both in between- and within-group comparisons^{36,37}. Effect sizes were estimated using generalized eta squared ($\hat{\eta}^2_G$) for ANOVA effects, and Cohen's d for Dunnett's t -tests, Welch's t -tests, paired t -tests, and one-sample t -tests. Statistical significance was set at $\alpha = 0.05$, and the sample size was chosen to achieve a power of 0.80.

Data is visualized using line plots with error bars representing the standard error of the mean, and boxplot diagrams. The boxplots show the median (horizontal line in box), mean (+) and interquartile range (IQR) including the 25th percentile (Q1; lower end of box) and 75th percentile (Q3; upper end of box). Outliers (individual data points) are shown when values are higher or lower than respectively $Q3 + 1.5 \times IQR$ and $Q1 - 1.5 \times IQR$. Extreme outliers ($Q1 - 3 \times IQR$ or $Q3 + 3 \times IQR$) were winsorized to avoid excessive impact on analyses. Analyses were conducted in R³⁸.

Results

Results of control measures (OF, SP, and T-maze) indicated that explorative and anxiety-like behavior (Fig. S1), spatial working memory (Fig. S2), and sociability (Fig. S3) were similar between control and experimental groups, and across experimental groups (Supplementary file 1).

Dopamine depletion reduces the enhancing effect of oxytocin on social safety learning during trust acquisition

Before starting the *trust acquisition* condition, one mouse from the OT group was culled due to severe cage-mate wounding ($N = 71$, $n_{OT} = 23$). The VEH group consisted of 34 mice. In the *social interaction* phase (Fig. 2A), time spent near the demonstrator did not differ between OT-treated mice and those in the TBZ ($t_{45} = 0.49$, $p = 0.62$, $d = 0.14$) or OT + TBZ groups ($t_{41} = -0.06$, $p = 0.95$, $d = 0.02$), nor between the TBZ and OT + TBZ groups ($t_{42,2} = -0.62$, $p = 0.54$, $d = 0.18$). The following day, in the *test* phase, all groups preferred to spend time near (Fig. 2B), and consume demonstrated food (Fig. 2C), indicating successful social safety learning (Supplementary file 1). Demonstrated food preference_{time} appeared elevated in the OT group during the first hour of the *test* phase (Fig. 2B), so we calculated $AUCi_{time}$ over this period to compare groups.

Relative to VEH controls, no differences were observed in preference to spend time near (Fig. 2B) or in the consumption of demonstrated food (Fig. 2C) for mice treated with OT ($AUCi_{time}$: MD = 38.98, $p = 0.35$, $d = 0.53$; food: MD = 0.07, $p = 0.60$, $d = 0.31$), TBZ ($AUCi_{time}$: MD = -3.86, $p = 0.996$, $d = 0.04$; food: MD = -0.10, $p = 0.70$, $d = 0.36$) or OT + TBZ ($AUCi_{time}$: MD = 10.44, $p = 0.93$, $d = 0.13$; food: MD = -0.11, $p = 0.49$, $d = 0.42$), indicating similar social safety learning. Among experimental groups, the OT group had higher $AUCi_{time}$ scores (Fig. 2B) compared to the TBZ and OT + TBZ groups, but these differences were not statistically significant (OT vs. TBZ: $t_{39,8} = 1.90$, $p = 0.07$, $d = 0.55$; OT vs. OT + TBZ: $t_{44,7} = 1.52$, $p = 0.14$, $d = 0.44$). Furthermore, demonstrated food consumption (Fig. 2C) was significantly increased in the OT group, both compared to mice treated with TBZ ($t_{40} = 2.57$, $p = 0.03$, $d = 0.75$), and OT + TBZ ($t_{41,3} = 2.89$, $p = 0.01$, $d = 0.84$). These differences could not be attributed to enhanced total food intake, as novel food consumption was similar in the OT and TBZ groups ($t_{44,8} = -0.49$, $p = 0.62$, $d = 0.14$), and in the OT and OT + TBZ groups ($t_{44,8} = -0.85$, $p = 0.40$, $d = 0.25$).

Oxytocin enhances social safety learning during trust acquisition specifically in mice with shorter interaction times

OT enhanced social safety learning compared to experimental groups, but not compared to previously collected control data. STFP acquisition is influenced by the amount of observer exposure to a demonstrator, with observers only developing a preference for demonstrated food once their interaction time with the demonstrator exceeds a threshold, rather than increasing linearly with longer interaction³⁹. Since OT may affect behavior by modulating salience, its effects may be most pronounced in observers with shorter interaction times, where social information could be less salient⁶.

A post hoc analysis therefore categorized observers into groups with shorter ($x \leq$ median) and longer ($x >$ median) interaction times by calculating the median interaction time over all experimental groups but separately within the previous (median = 911.7s)²⁴ and current experiments (median = 807.3s). Since we did not conduct such an analysis on the OT group of our previous experiment (OT_{prev})²⁴, we included this group in the analysis as well ($n = 12$). Splitting all groups based on the median resulted in approximately equal-sized subgroups (Table 1).

A two-way ANOVA on $AUCi_{time}$ (Fig. 3A) revealed a significant interaction between group and interaction time ($F_{4,107} = 3.16$, $p = 0.02$, $\hat{\eta}^2_G = 0.11$). When interaction time was longer, we found no differences between the VEH group and any experimental group, nor across experimental groups. When interaction time was shorter, only OT-treated groups had a demonstrated food preference_{time} above chance, independent of DA availability (OT: $t_{11} = 3.14$, $p = 0.009$, $d = 0.91$; OT_{prev}: $t_5 = 10.1$, $p < 0.001$, $d = 4.12$; OT + TBZ: $t_{10} = 2.58$, $p = 0.03$, $d = 0.78$).

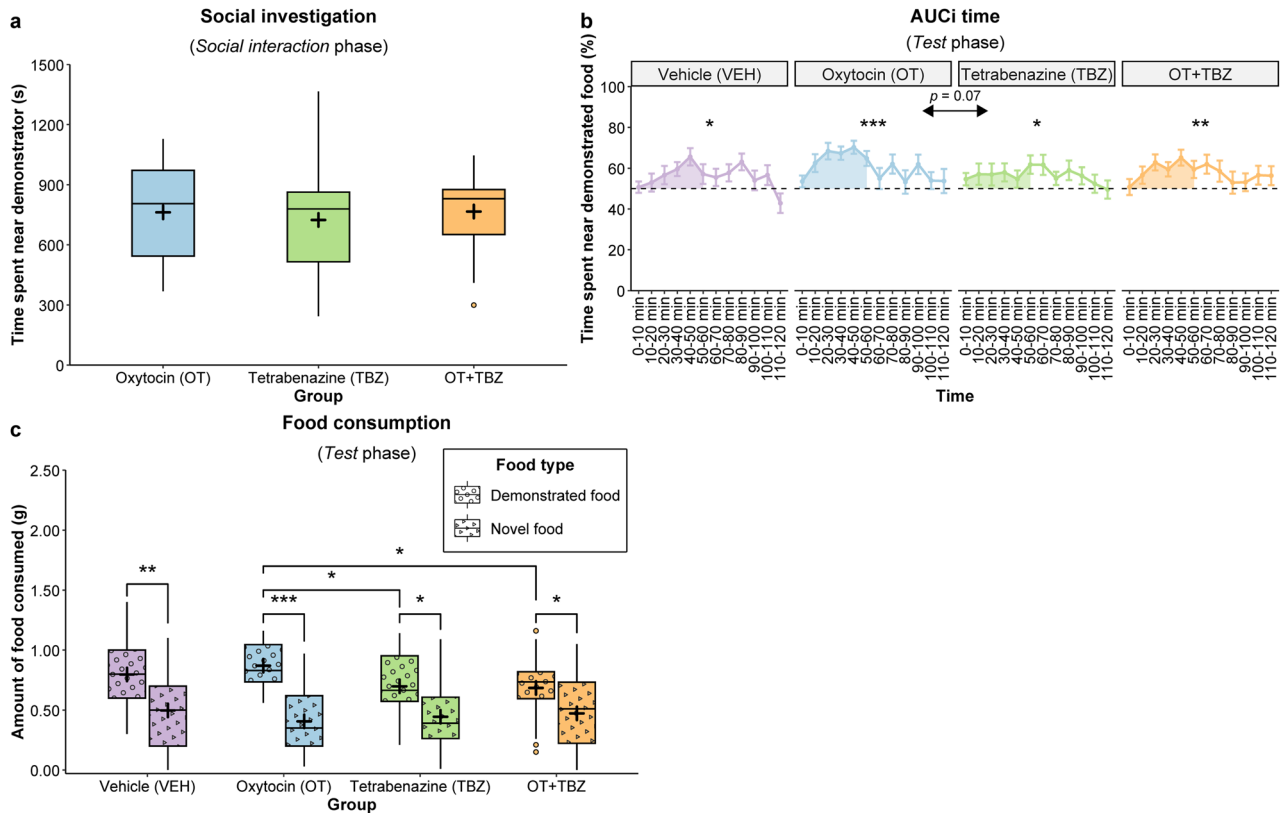


Fig. 2. Dopamine depletion reduces the enhancing effect of oxytocin on social safety learning during trust acquisition. **(A)** In the *social interaction* phase, all experimental groups spent a similar amount of time near the demonstrator. **(B)** In the *test* phase, demonstrated food preference scores_{time} of all groups were significantly above chance, indicating a preference to spend time near demonstrated food (asterisks on top of line graphs). However, during the first hour of the *test* phase (shaded area), these scores were higher in the OT group compared to TBZ- and OT + TBZ-treated mice but these differences did not reach statistical significance. Error bars represent the standard error of the mean. AUCi = the area under the curve relative to the increase from chance level. **(C)** Similarly, all groups preferred to consume demonstrated food during the *test* phase, though this preference was enhanced for OT-treated mice compared to those in the TBZ and OT + TBZ groups. These differences could not be attributed to enhanced total food consumption since novel food consumption was similar in the OT and TBZ groups and in the OT and OT + TBZ groups. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Moreover, AUCi_{time} (Fig. 3A) in both the OT and OT_{prev} groups was significantly higher compared to the VEH (OT vs. VEH: $t_{24.8} = 2.31$, $p = 0.03$, $d = 0.88$; OT_{prev} vs. VEH: $t_{18.5} = 3.32$, $p = 0.004$, $d = 1.36$) and TBZ groups (OT vs. TBZ: $t_{22} = 2.93$, $p = 0.008$, $d = 1.17$; OT_{prev} vs. TBZ: $t_{16.9} = 3.94$, $p = 0.001$, $d = 1.70$). OT_{prev} also increased AUCi_{time} compared to the OT + TBZ group ($t_{14.4} = 2.14$, $p = 0.049$, $d = 1.02$), whereas AUCi_{time} in the OT + TBZ group was higher than in the TBZ group, but this difference did not reach statistical significance ($t_{21.6} = 1.99$, $p = 0.059$, $d = 0.81$).

A three-way mixed ANOVA on food consumption (Fig. 3B) with the addition of food type (demonstrated vs. novel) as within-subjects variable revealed no significant interaction between group, interaction time and food type ($F_{4,107} = 1.30$, $p = 0.27$, $\hat{\eta}^2_G = 0.04$). However, a visual inspection of the data revealed a pattern similar to the results for AUCi_{time} (Fig. 3A). When interaction time was longer, we found no differences between the VEH group and any experimental group, nor across experimental groups. When interaction time was shorter, only mice in the OT ($t_{11} = 4.11$, $p = 0.002$, $d = 1.19$), and OT_{prev} groups ($t_5 = 9.33$, $p < 0.001$, $d = 3.81$) had a preference to consume demonstrated food.

This preference was enhanced in the OT_{prev} group compared to VEH-treated mice, driven by a combination of a non-significant increase in demonstrated food consumption ($t_{18.57} = 1.47$, $p = 0.16$, $d = 0.57$) and a significant decrease in novel food consumption ($t_{18.98} = -2.55$, $p = 0.02$, $d = 1.02$). Differences between the OT and VEH groups did not reach statistical significance. Mice in both the OT and OT_{prev} groups consumed significantly more demonstrated food than mice in the TBZ (OT vs. TBZ: $t_{22,17} = 3.02$, $p = 0.006$, $d = 1.20$; OT_{prev} vs. TBZ: $t_{16,96} = 4.16$, $p < 0.001$, $d = 1.76$), and OT + TBZ groups (OT vs. OT + TBZ: $t_{17,01} = 2.21$, $p = 0.04$, $d = 0.93$; OT_{prev} vs. OT + TBZ: $t_{13,76} = 3.08$, $p = 0.008$, $d = 1.38$). Together, these findings suggested that OT enhanced social safety learning specifically in mice that interacted a shorter amount of time with the demonstrator.

Condition	Group	Interaction time	
		Short	Long
<i>Trust acquisition</i> (STFP1)			
	Vehicle (VEH)	15	19
	Oxytocin previous experiment (OT _{prev})	6	6
	Oxytocin (OT)	12	11
	Tetrabenazine (TBZ)	13	11
	OT + TBZ	11	13
<i>Trust violation</i> (STFP2)			
	Vehicle (VEH)	18	16
	Oxytocin previous experiment (OT _{prev})	5	6
	Oxytocin (OT)	11	12
	Tetrabenazine (TBZ)	13	11
	OT + TBZ	11	11

Table 1. Distribution of mice within each group after median split based on interaction time with the demonstrator. Note. The median interaction time with the demonstrator was calculated over all experimental groups but separately within the previous (VEH and OT_{prev})²⁴ and current experiments (OT, TBZ, OT + TBZ).

Oxytocin requires intact dopaminergic signaling to block updating after trust violation

Before starting the *trust violation* condition, two mice from the OT + TBZ group were culled due to severe wounds caused by their cage mates ($N=69$, $n_{\text{OT+TBZ}}=22$). The VEH group consisted of 34 mice. In the *social interaction* phase (Fig. 4A), time spent near the demonstrator before experiencing LiCl-induced nausea was similar for OT-treated mice and those in the TBZ ($t_{44.9}=1.03$, $p=0.31$, $d=0.30$) and OT + TBZ ($t_{42.9}=0.19$, $p=0.85$, $d=0.06$) groups, and in the TBZ group compared to the OT + TBZ group ($t_{44}=-0.89$, $p=0.38$, $d=0.26$). The following day, in the *test* phase, only mice in the OT group preferred to spend time near (Fig. 4B), and consume demonstrated food (Fig. 4C). In contrast, mice in the VEH and OT + TBZ groups had no such preference, while TBZ-treated mice had a non-significant preference to consume demonstrated food but not to spend time near it (Supplementary file 1).

The loss of demonstrated food preference in the VEH group appeared to be driven by an increase in novel food consumption compared to the experimental groups (Fig. 4C). Therefore, control-based comparisons used $\text{AUCi}_{\text{time}}$ (Fig. 4B) and demonstrated food preference_{consumption} (Fig. 4D) instead of the raw amount of demonstrated food consumed. $\text{AUCi}_{\text{time}}$ was higher in OT- compared to VEH-treated mice, but this difference did not reach statistical significance (MD = 54.56, $p=0.07$, $d=0.71$). Preference to consume demonstrated food was similar between the VEH and OT groups (MD = 7.23, $p=0.41$, $d=0.36$). Mice in the TBZ and OT + TBZ groups did also not differ from VEH-treated mice, neither on $\text{AUCi}_{\text{time}}$ (VEH-TBZ: MD = 12.31, $p=0.90$, $d=0.14$; VEH-OT + TBZ: MD = 16.50, $p=0.99$, $d=0.20$), nor in demonstrated food preference_{consumption} (VEH-TBZ: MD = 5.25, $p=0.90$, $d=0.24$; VEH-OT + TBZ: MD = -1.19, $p=0.99$, $d=0.08$).

Among experimental groups, $\text{AUCi}_{\text{time}}$ (Fig. 4B) was higher in the OT group compared to the TBZ and OT + TBZ groups, but neither difference reached statistical significance (OT vs. TBZ: $t_{42.4}=1.94$, $p=0.12$, $d=0.56$; OT vs. OT + TBZ: $t_{41.1}=1.84$, $p=0.07$, $d=0.55$). Consumption of demonstrated food (Fig. 4C) was similar for OT-treated mice compared to mice in the TBZ group ($t_{43.6}=1.47$, $p=0.15$, $d=0.43$), but enhanced compared to mice in the OT + TBZ group ($t_{41.8}=2.76$, $p=0.02$, $d=0.83$). This difference could not be attributed to enhanced total food consumption since novel food consumption was similar in the OT and OT + TBZ groups ($t_{41.8}=-0.95$, $p=0.35$, $d=0.28$).

Trust violation reduces preference for demonstrated food specifically in mice with longer interaction times

In the *trust violation* condition, preference to spend time near (Fig. 4B), and consume demonstrated food (Fig. 4C) was reduced in the VEH, TBZ (only in terms of time) and OT + TBZ groups. Given the effect of interaction time on preference for demonstrated food in the *trust acquisition* condition, we conducted a post hoc analysis to explore whether *trust violation* specifically influenced preference for demonstrated food in mice with shorter or longer interaction times with the demonstrator. Similar as in the *trust acquisition* condition, we split the treatment groups based on the median of our previous (median = 884.6s)²⁴ and current experiments (median = 498.9s), and included the OT group of our previous experiment (OT_{prev})²⁴ as well ($n=11$). This procedure resulted in approximately equal-sized subgroups (Table 1).

A two-way ANOVA on $\text{AUCi}_{\text{time}}$ (Fig. 5A) revealed no significant interaction between group and interaction time ($F_{4,104}=0.54$, $p=0.71$, $\hat{\eta}^2_G=0.02$). Similarly, a three-way ANOVA on food consumption (Fig. 5B) revealed no significant interaction between group, interaction time and food type ($F_{4,104}=0.33$, $p=0.86$, $\hat{\eta}^2_G=0.01$). In line with the above-reported effects of the current OT group (Fig. 4B and C), OT_{prev} retained preference to spend time near ($t_{10}=2.91$, $p=0.02$, $d=0.88$), and consume demonstrated food ($t_{10}=3.05$, $p=0.02$, $d=0.92$) at the group level. These results indicated that mice with longer interaction times in the VEH, TBZ, and OT + TBZ groups, who had developed a preference for demonstrated food in the *trust acquisition* condition, lost this

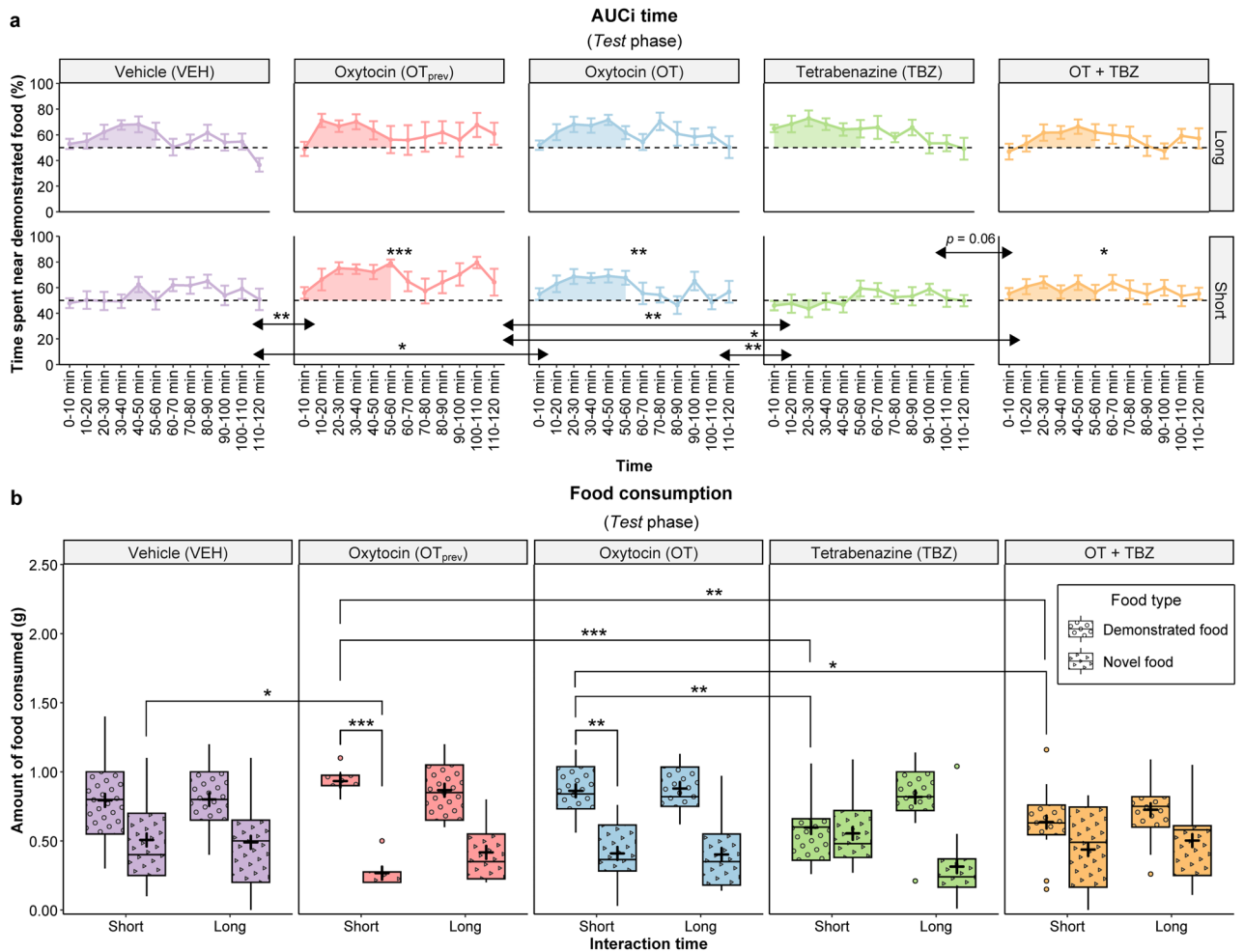


Fig. 3. Oxytocin enhances social safety learning during trust acquisition specifically in mice with shorter interaction times. **(A)** Exploratory analyses revealed in mice with longer interaction times no differences in $AUC_{i\text{time}}$ (shaded area) between the VEH group and any experimental group, nor across the experimental groups. When interaction time was shorter, only OT-treated groups had a demonstrated food preference above chance, independent of DA availability (asterisks on top of line graphs). Moreover, $AUC_{i\text{time}}$ of mice in both the OT and OT_{prev} group was significantly higher compared to mice in the VEH and TBZ groups. OT_{prev} also increased $AUC_{i\text{time}}$ compared to the OT + TBZ group, whereas $AUC_{i\text{time}}$ in the OT + TBZ group was higher than in the TBZ group, but this difference did not reach statistical significance. Error bars represent the standard error of the mean. AUC_i = the area under the curve relative to the increase from chance level. **(B)** When interaction time was longer, we found no differences in consumption of demonstrated food between the VEH group and any experimental group, nor across experimental groups. When interaction time was shorter, only mice in the OT and OT_{prev} groups had a preference to consume demonstrated food. This preference was enhanced in the OT_{prev} group compared to VEH-treated mice, driven by a combination of a non-significant increase in demonstrated food consumption and a significant decrease in novel food consumption. Differences between the OT and VEH groups did not reach statistical significance. Lastly, mice in both the OT and OT_{prev} groups consumed significantly more demonstrated food than mice in the TBZ and OT + TBZ groups. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

preference when we administered LiCl (i.e., *trust violation*) after the observer-demonstrator interaction. This manipulation attenuated the preference to spend time near, and consume demonstrated food at the group level in the VEH, TBZ (only in terms of time), and OT + TBZ groups, while mice receiving only OT were less affected by LiCl-induced nausea and retained preference for demonstrated food.

Discussion

We investigated whether DA is required for OT to modulate social safety learning using the STFP paradigm, interpreting STFP acquisition as a putative functional parallel to human epistemic trust, in which individuals evaluate and use socially acquired information to guide decision-making or behavior^{22,23}. As hypothesized, OT enhanced demonstrated food preference in the *trust acquisition* condition compared to DA-depleted groups. In the *trust violation* condition, updating was blocked after OT administration and non-significantly reduced after

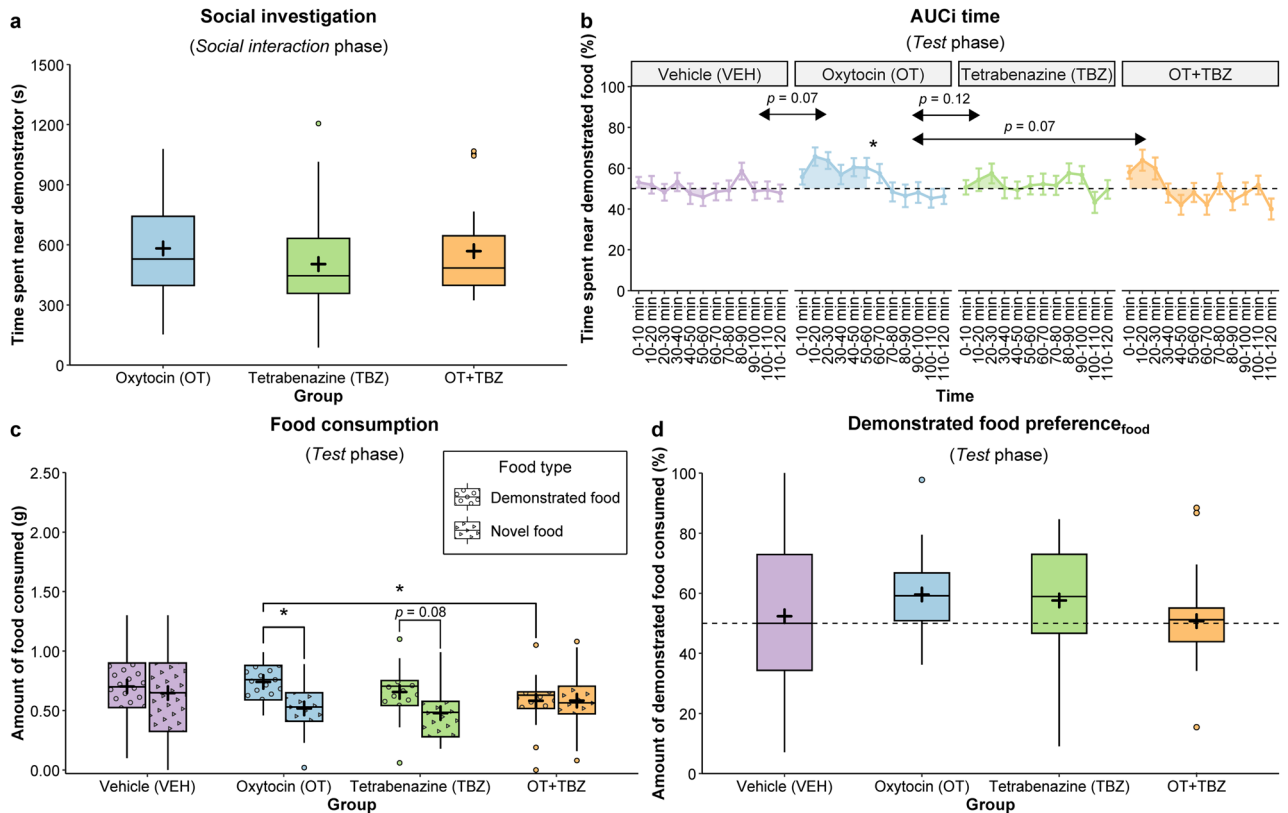


Fig. 4. Oxytocin requires intact dopaminergic signaling to block updating after trust violation. **(A)** In the *social interaction* phase, time spent near the demonstrator before experiencing LiCl-induced nausea was similar for all experimental groups. **(B)** In the *test* phase, only mice in the OT group had a demonstrated food preference score_{time} significantly above chance, indicating a preference to spend time near demonstrated food (asterisk on top of line graph). This preference was higher during the first hour of the *test* phase (shaded area) compared to the VEH, OT + TBZ and TBZ groups, but neither of these effects reached statistical significance. Error bars represent the standard error of the mean. AUCi = the area under the curve relative to the increase from chance level. **(C)** Only mice in the OT group preferred to consume demonstrated food, while TBZ-treated mice showed a non-significant tendency in the same direction. The preference in the OT group was enhanced compared to the OT + TBZ group. This difference could not be attributed to enhanced total food consumption since novel food consumption was similar in the OT and OT + TBZ groups. **(D)** Control-based comparisons failed to indicate differences in demonstrated food preference_{consumption} between the VEH group and any of the experimental groups. * $p < 0.05$.

DA depletion, resulting in a continued preference for demonstrated food. However, this effect was absent when OT was administered under DA depletion.

Exploratory analyses in the *trust acquisition* condition revealed that OT may enhance preference for demonstrated food specifically in mice with shorter interaction times, a group that failed to develop this preference when not treated with OT, or when treated with OT under DA depletion. In the *trust violation* condition, the loss of preference for demonstrated food in the VEH, TBZ, and OT + TBZ groups was driven by reduced preference in mice with longer interaction times. Given that performance in the longer interaction group did not reach maximal levels, it is less likely that the absence of an OT effect in this group reflects a ceiling effect. Rather, OT effects appear most pronounced when social information is less salient (i.e., shorter interaction times), consistent with the social salience hypothesis of OT⁶. Finally, behavior on control measures of explorative and anxiety-like behavior, sociability, and spatial working memory remained largely unaffected by OT and DA manipulations.

Although OT produced similar behavioral outcomes across OT groups, differences between VEH and the current OT group did not reach statistical significance, unlike in our previous experiment²⁴. STFP acquisition was traditionally thought to rely on simple stimulus-response learning, in which carbon disulfide (CS₂), a semiochemical in the demonstrator's breath that signals safety, becomes associated with a food odor⁴⁰. However, STFP acquisition is also influenced by characteristics of the demonstrator transmitting the information (e.g., familiar vs. unfamiliar), which in turn modulate the behavioral effects of OT^{41,42}. While this finding supports our proposed functional parallel with human epistemic trust²², it also highlights the context-sensitive nature of OT effects. Therefore, differences in demonstrators used between the current and previous experiments may have contributed to variability in the magnitude of the OT effect on STFP acquisition.

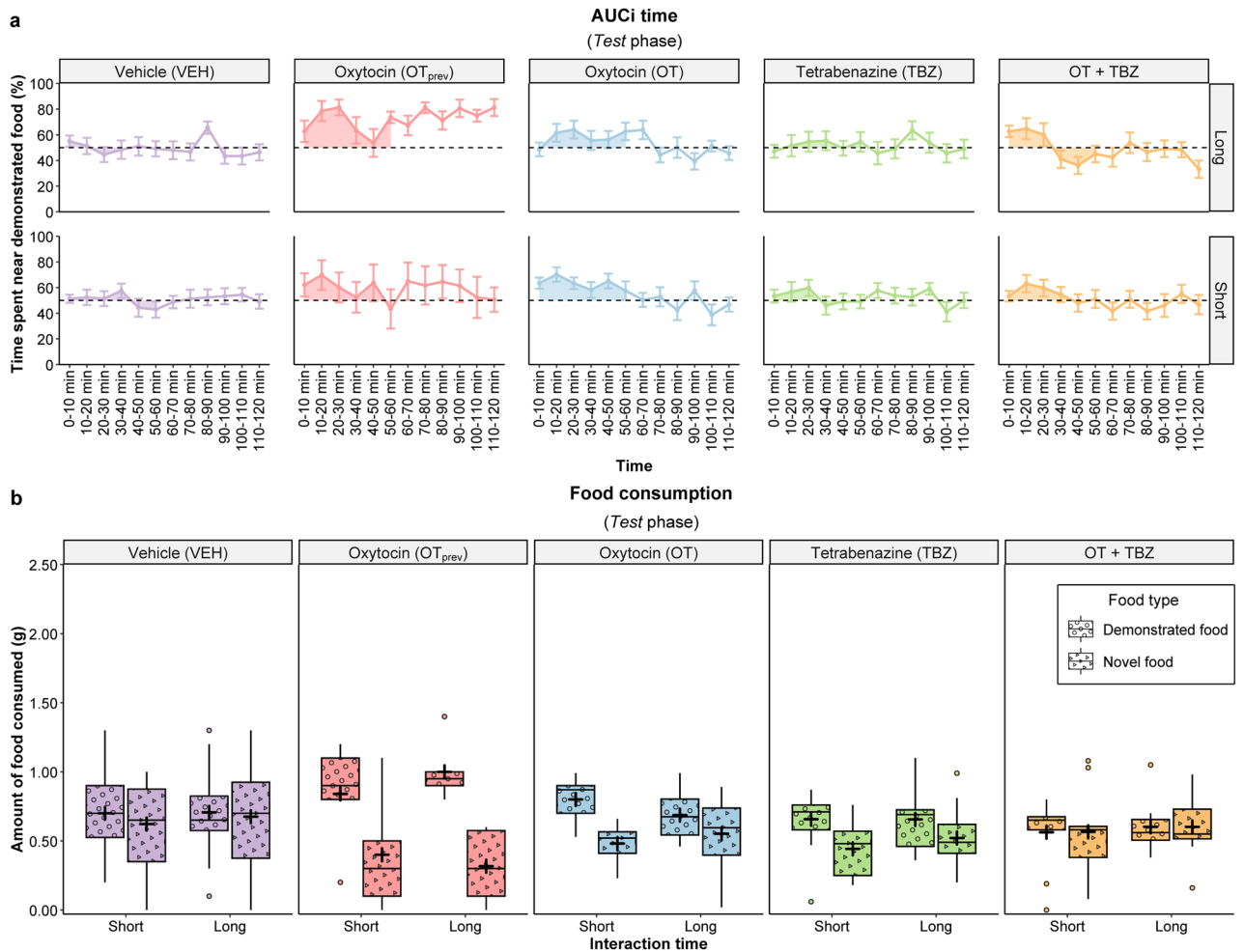


Fig. 5. Trust violation reduces preference for demonstrated food specifically in mice with longer interaction times. Exploratory analyses revealed that mice with longer interaction times with the demonstrator in the VEH, TBZ and OT + TBZ groups, who had developed a preference for demonstrated food in the *trust acquisition* condition, lost this preference when we administered lithium chloride (LiCl; *trust violation*) after the observer-demonstrator interaction. This manipulation attenuated the preference to (A) spend time near, and (B) consume demonstrated food at the group level in the VEH, TBZ (only in terms of time), and OT + TBZ groups, while mice receiving only OT, in our current (see Fig. 4) and previous experiments, were less affected by LiCl-induced nausea and retained preference for demonstrated food. Error bars represent the standard error of the mean. AUCi = the area under the curve relative to the increase from chance level.

The ability of rodents to respond differentially to social information involves coordinated activity across cortical and subcortical regions. Loureiro et al.⁴³ demonstrated that the PFC receives inputs from the amygdala, within a PFC–nucleus accumbens (NAc) circuit that influences demonstrated food consumption. Although the specific role of the amygdala in this network remains unclear, both functional and anatomical evidence of OT-DA interactions in the amygdala suggests that it may represent a likely site for our observed effects⁴⁴. OT neurons in the central amygdala (CeA) have been shown to shift cue encoding from fear to safety⁴⁵, while DA neurons projecting to the basolateral amygdala (BLA) and CeA encode stimulus salience and signal threat PE⁹. Based on these findings, we may speculate that OT–DA interactions in the amygdala are involved in biasing the processing of social information towards perceived safety or threat and in modulating responses to unexpected aversive events, thereby influencing demonstrated food consumption.

We assessed social safety learning through preference for demonstrated food, measured by time spent near, and consumption of, demonstrated food. In the *trust acquisition* condition, OT increased time spent near demonstrated food, independent of DA depletion (Fig. 2B and 3A), but enhanced consumption only when DA was available (Fig. 2C). The incentive-sensitization theory^{46,47} may explain this pattern of results, as it distinguishes between *liking* (value, DA-independent) and *wanting* (motivational drive, DA-dependent) of a reward like demonstrated food. OT mediates entrainment of neutral odors to appetitive social cues⁴⁸, suggesting that under DA depletion, OT may still have modulated *liking* of demonstrated food odor by increasing its social relevance (i.e., neutral food odor becomes social odor). However, without DA, OT may have failed to enhance

the association between the food odor and safety (CS₂ signal) that is required to increase *wanting* (consumption) of demonstrated food (i.e., social safety learning).

In the *trust violation* condition, OT retained preference to spend time near (*liking*; Fig. 4B), and consume demonstrated food (*wanting*; Fig. 4C), but only when DA was available. Under DA depletion alone, mice showed a non-significant tendency to consume demonstrated food (*wanting*; Fig. 4C) but not to spend time near it (*liking*; Fig. 4B). Under DA depletion, *liking* may have been reduced, as mice tend to avoid neutral and social odors paired with LiCl^{49,50}, while *wanting* persisted due to impaired PE updating⁹. Although OT enhances avoidance of negative stimuli to reduce *liking* (e.g., demonstrated food odor paired with LiCl⁴⁸), this effect may have been blocked as OT first supported the positive association between the food odor and safety (CS₂ signal) and complementary attenuated PE processing (LiCl-induced nausea), to increase *wanting*, mitigating LiCl effects, but only when DA was available.

To empirically dissociate *liking* from *wanting*, future research could test whether the demonstrated food odor acquires social relevance, for instance using an odor habituation–dishabituation assay alongside the STFP paradigm. In such assays, mice are exposed to both social and non-social odors and typically investigate socially relevant odors longer than non-social ones. If OT modulates *liking* and *wanting* through distinct neural mechanisms, we would expect OT to enhance interest in the demonstrated food odor (reflecting increased *liking*) even under DA depletion, whereas increased consumption (*wanting*) would require intact DA signaling. Following LiCl pairing, maintenance of both odor interest and food consumption would be expected only when DA is available, while under DA depletion OT may instead reduce interest in the odor by facilitating an aversive association (reflecting reduced *liking*).

Since salience processing is not exclusively attributable to DA^{51,52}, our results may suggest that OT modulates *liking* and *wanting* of social stimuli via distinct neural mechanisms. When replicated in future research, this differential modulation could have important implications for therapeutic interventions. For instance, OT has been proposed as adjunct pharmacotherapy for psychiatric disorders characterized by social deficits, such as autism spectrum disorder (ASD)^{53,54}. However, the success of OT treatment in ASD has been variable⁵⁵, possibly reflecting heterogeneity in ASD etiology and the existence of different ASD subtypes. Our findings tentatively suggest that OT efficacy may be reduced in ASD subtypes involving DA dysfunction⁵⁶. Future studies are needed to directly test this hypothesis.

In conclusion, our results confirm the involvement of OT in social safety learning, demonstrating that OT modulates DA signaling to enhance *trust acquisition* and block updating after *trust violation* by complementary enhancing the salience of social information on safety and reducing PE processing. Notably, OT may exert its salience effect particularly in mice for whom social information is less salient, though further research is required to confirm this hypothesis. Furthermore, the incentive-sensitization theory^{46,47} provides a valuable framework for distinguishing between aspects of social behavior OT influences via DA and those it influences through other neurochemical systems. Given OT's therapeutic potential^{53,57}, elucidating the neurochemical pathways underlying its effects is crucial to optimize clinical outcomes.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Received: 2 October 2025; Accepted: 2 February 2026

Published online: 09 February 2026

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Author contributions

Samuel Budniok: Investigation, Data Curation, Visualization, Formal analysis, Writing - Original Draft, Writing - Review & Editing. Zsuzsanna Callaerts-Vegh: Conceptualization, Formal analysis, Writing - Review & Editing, Supervision. Marian Bakermans-Kranenburg: Conceptualization, Formal analysis, Writing - Review & Ed-

iting. Guy Bosmans: Conceptualization, Formal analysis, Writing - Review & Editing, Funding acquisition. Rudi D'Hooge: Conceptualization, Formal analysis, Writing - Review & Editing, Funding acquisition, Supervision.

Funding

This study was financed by a project grant from Fonds Wetenschappelijk Onderzoek (FWO) Flanders to GB and RDH (G0D6721N), by a KU Leuven C1 Grant (C16/24/003), and by the Excellence of Science (EOS) program of FWO Flanders and Fonds de la Recherche Scientifique (F.R.S.–FNRS; EOS 40007528 / G0I2422N).

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1038/s41598-026-38976-9>.

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