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Victory is its own reward: oxytocin increases costly competitive behavior in schizophrenia

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Original Article

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Abstract

Background. Aberrant sensitivity to social reward may be an important contributor to abnormal social behavior that is a core feature of schizophrenia. The neuropeptide oxytocin impacts the salience of social information across species, but its effect on social reward in schizophrenia is unknown.

Methods. We used a competitive economic game and computational modeling to examine behavioral dynamics and oxytocin effects on sensitivity to social reward among 39 men with schizophrenia and 54 matched healthy controls. In a randomized, double-blind study, participants received one dose of oxytocin (40 IU) or placebo and completed a 35-trial Auction Game that quantifies preferences for monetary *v.* social reward. We analyzed bidding behavior using multilevel linear mixed models and reinforcement learning models.

Results. Bidding was motivated by preferences for both monetary and social reward in both groups, but bidding dynamics differed: patients initially overbid less compared to controls, and across trials, controls decreased their bids while patients did not. Oxytocin administration was associated with sustained overbidding across trials, particularly in patients. This drug effect was driven by a stronger preference for winning the auction, regardless of monetary consequences. Learning rate and response variability did not differ between groups or drug condition, suggesting that differences in bidding derive primarily from differences in the subjective value of social rewards.

Conclusions. Our findings suggest that schizophrenia is associated with diminished motivation for social reward that may be increased by oxytocin administration.

Introduction

Abnormal social behavior is a core feature of schizophrenia that leads to marked functional impairment (Couture *et al.*, 2006). Multiple deficits – in social cognition, motivation, decision-making, and learning – are thought to interfere with patients' ability to navigate a wide range of socially relevant tasks, from maintaining basic hygiene to negotiating a raise at work. Disentangling the processes driving abnormal social behavior in order to uncover treatment targets has proven difficult, unfortunately, largely due to the complexity of studying dynamic interpersonal interactions. Multiplayer economic games and computational modeling are increasingly leveraged to address this challenge (Lee, 2013), as these approaches allow quantification of specific aberrancies in cognitive and social processes that are relevant to real-world behavior yet difficult to measure.

The value of a reward, for example, must be estimated from observed actions rather than measured directly (Schultz, 2016). Rewards are critical for motivating actions that are necessary for survival, and the rewarding properties of social interaction, in particular, shape the relationships and social organizations that are essential for healthy functioning among mammals (Krach *et al.*, 2010; Trezza *et al.*, 2011). Dysregulation of the mechanisms underlying social reward are hypothesized to contribute to the abnormal social behavior observed in multiple neuropsychiatric disorders, including schizophrenia (Bora *et al.*, 2009). People with schizophrenia demonstrate reduced neural sensitivity to social *v.* nonsocial reward (Lee *et al.*, 2018) as well as impaired motivation for social interaction that is thought to reflect dysregulated reward processing (Fulford *et al.*, 2018). Though the mechanisms underlying reward processing in social contexts are not fully understood (Noritake *et al.*, 2018), dysregulated dopamine signaling in schizophrenia (Carlsson, 2006) is hypothesized to underlie deficits in the ability to form mental representations of reward (Gold *et al.*, 2008) and to assign salience to social information (Palaniyappan *et al.*, 2013), both of which may contribute to aberrant sensitivity to social reward. Importantly, how this aberrancy impacts social behavior in schizophrenia and whether it represents a viable treatment target is unclear.

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Recent advances in the experimental study of competitive behavior open the door to answering these questions. Competition is a fundamental part of social life, facilitating comparisons that help people make sense of their place in a social hierarchy (Festinger, 1954; Liu *et al.*, 2018). Competitive interactions can reflect not only the drive to maximize payoff (in money or other tangible rewards) relative to others (Messick and McClintock, 1968), but also the desire to attain social status by winning, an end in itself (Huberman *et al.*, 2016). Thus, competitive interactions provide an opportunity to examine sensitivity to social reward in a dynamic context. The Auction Game is an economic paradigm that creates a tension between monetary and social reward to allow investigation of people's preferences in a competitive environment. The game leverages the phenomenon, observed both in real-world (Ashenfelter and Genesove, 1992; Capen *et al.*, 2013) and experimental settings (Bazerman and Samuelson, 1983; Kagel and Levin, 2009), that people tend to overbid at auctions. While overbidding increases the chance of winning an auction, it also leads to monetary losses. Several explanations for overbidding have been proposed (Sheremeta, 2013), but evidence that it persists even after people are told how to avoid it (van den Bos *et al.*, 2013*a*), increases when competition is highlighted (van den Bos *et al.*, 2013*a*), and virtually disappears when people believe they are competing against computers instead of other humans (van den Bos *et al.*, 2008), all suggest that motivation for the social reward of winning is a primary driver. In economic terms, people derive utility not only from obtaining an item at auction, but also from beating their competitors.

The salience of social reward is thought to be regulated by the hypothalamic neuropeptide oxytocin (Shamay-Tsoory and Young, 2016), a potent modulator of social behavior across species. Evidence from animal models that oxytocin-containing projections innervate multiple structures in the mesocorticolimbic dopaminergic pathway (Boccia *et al.*, 2013; Dumais *et al.*, 2013) suggests that oxytocin may exert some of its behavioral effects via influence on reward circuitry (Groppe *et al.*, 2013). Oxytocin receptors in the nucleus accumbens (NAc), for example, are critical for pair bonding in voles (Young and Wang, 2004) and oxytocin activity in the NAc is necessary for social interactions to be rewarding in mice (Dölen *et al.*, 2013). In the ventral tegmental area (VTA), another key node in reward circuitry, oxytocin activity enhances NAc dopamine levels in rats (Shahrokh *et al.*, 2010) and regulates social reward salience in hamsters and mice (Song *et al.*, 2016; Hung *et al.*, 2017). In humans, oxytocin administration has been shown modulate processing of social cues in the VTA (Groppe *et al.*, 2013), and neural responses to social reward correlate with plasma oxytocin levels (Strathearn *et al.*, 2009). Recent evidence also suggests that oxytocin system dysfunction may play a role in the pathophysiology of neuropsychiatric disorders that involve core social impairments, such as schizophrenia (Peñagarikano *et al.*, 2015; Kohli *et al.*, 2018) and autism (Gordon *et al.*, 2016), generating interest in oxytocin's potential as a treatment. Though oxytocin may ameliorate aspects of abnormal social behavior in schizophrenia (Burkner *et al.*, 2017), a lack of sensitive, objective measures designed to illuminate its mechanisms of action has limited our ability to determine whether oxytocin has clinical utility (Bradley and Woolley, 2017).

Given that motivation for social reward is a driver of competitive behavior and oxytocin impacts the salience of social reward, we investigated oxytocin's effects on competitive interactions with the goal of determining whether modulation of social reward may be a mechanism by which oxytocin impacts social behavior in schizophrenia. We used the Auction Game and computational modeling to test whether a single dose of oxytocin could enhance sensitivity to social reward among men with schizophrenia and healthy controls in a randomized, placebo-controlled study. We expected that the social reward associated with winning the auction would be less salient for patients compared to controls, and therefore hypothesized that patients would overbid less than controls in the placebo condition. We also hypothesized that oxytocin would increase the salience of the social reward associated with winning, increasing overbidding in both patients and controls.

Methods and materials

Participants

We recruited 39 male outpatients with schizophrenia and 54 matched healthy controls; see Table 1. Patients met diagnostic criteria for schizophrenia according to the Structured Clinical Interview for DSM-IV-TR (First *et al.*, 2002), were clinically stable, and had no medication changes in the past month. Exclusion criteria for all participants included: (1) substance use disorder in the past month; (2) conditions affecting the nasal passages that would interfere with intranasal administration; (3) history of a neurological or significant medical disorder; and (4) positive urine toxicology test. All participants gave informed consent according to the guidelines of the University of California, San Francisco Committee on Human Research.

Experimental design

Following baseline assessments, we randomized participants to receive either 40 IU of oxytocin or a placebo nasal spray (Wellspring Pharmacy, Berkeley, CA) administered using a standardized procedure (Guastella *et al.*, 2013). Experimental tasks began 30 min after, and ended approximately 70 min after, oxytocin administration.

Measures and procedures

Auction Game

Participants completed a computer-based Auction Game adapted from van den Bos *et al.* (2008), bidding against five other virtual players over 35 trials to win virtual items each with a true common value (X_0); see Fig. 1. We told participants that the other five players were situated at different locations, but in fact they were not bidding against anyone in real time. After explaining the task but before bidding began, we instructed participants in the optimal strategy to maximize their profit from the game: choosing the Risk Neutral Nash Equilibrium (RNNE) bid, the lower bound of the given estimated value range (e.g. if the range is $25–35, the RNNE bid is $25). The RNNE strategy assumes that participants are 'risk neutral' in that they are interested in maximizing their profits from the auction. By bidding the lowest estimated value of the item, a participant avoids the possibility of overbidding and thus losing money. This strategy represents a Nash Equilibrium, as there is no other strategy that would yield a higher payoff for a given participant. All participants completed written tests to confirm that they understood the RNNE strategy and could easily compute RNNE bids.

Table 1. Demographics and clinical information.

	Schizophrenia ($n = 37$)			Controls ($n = 51$)			Controls *v.* schizophrenia	
	Mean (s.d.)		PL *v.* OT	Mean (s.d.)		PL *v.* OT	PL	OT
	PL ($N = 22$)	OT ($N = 15$)		PL ($N = 26$)	OT ($N = 25$)			
Age	46.23 (13.6)	40.47 (12.23)	$p = 0.21$	43.16 (13.69)	44.88 (12.21)	$p = 0.65$	$p = 0.46$	$p = 0.29$
Education years	14.45 (2.35)	13.4 (2.55)	$p = 0.22$	16.48 (2.23)	15.56 (1.54)	$p = 0.10$	$p = 0.01$	$p = 0.01$
PANSS score								
Positive	12.5 (5.61)	12.07 (7.17)	$p = 0.84$	–	–	–	–	–
Negative	13.6 (5.64)	13.6 (7.5)	$p = 0.99$	–	–	–	–	–
General	24.27 (8.78)	24.47 (11.72)	$p = 0.95$	–	–	–	–	–
CPZ equivalents	185.59 (211.54)	166.72 (147.92)	$p = 0.77$	–	–	–	–	–

Shown by group and by placebo (PL) and oxytocin (OT) conditions.

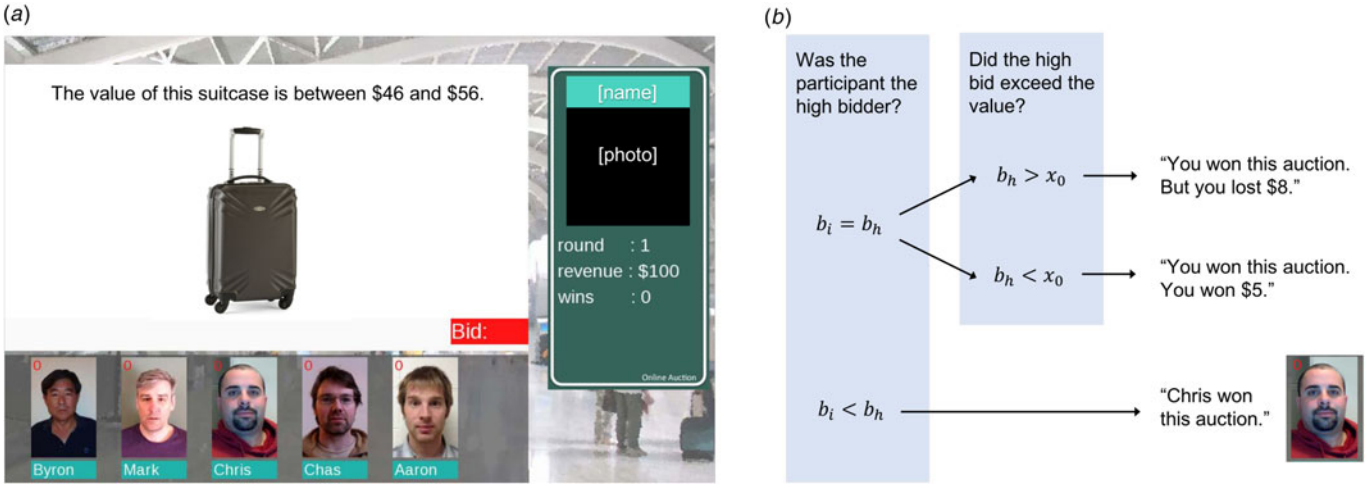

Fig. 1. The Auction Game. Task interface (panel a): The participant's name and photo were displayed in the upper right of the monitor throughout the task. For each trial, a photo of a virtual item, a different closed suitcase, was displayed on the monitor. The participant viewed an estimate of the true value of the suitcase, X_0, within a range of 10 dollars. X_0 was always within this range. Task schematic (panel b): After viewing the item and value range, the participant entered a bid, b_i, followed by a randomized 2–11-s waiting period to simulate gathering the other players' bids. If the participant did not have the highest bid, the picture of the highest bidder and the text '(name) won this auction.' was shown for 3 s. In this case, the participant's endowment did not change. If the participant had the highest bid, there were two possible outcomes. (1) If the participant bid higher than the true value of the suitcase, their picture was shown along with the text 'You won this auction. But you lost $*X*.' (2) If the participant bid lower than the true value of the suitcase, their picture was shown along with the text 'You won this auction. You won $*X*.' The outcome was shown for 3 s, and $x_0 - b_h$ was allocated to the participant's endowment at the end of each trial, where b_h is the winning bid.

Devil's task

The Auction Game is inherently risky in the sense that any bid is only probabilistically associated with a variable range of monetary outcomes. Behavior during the game should therefore depend on the subjective value of winning and losing relative to a participant's risk preferences. To obtain an independent estimate of risk preferences, we had participants complete the Devil's task (Slovic, 1966), which involves making selections that are probabilistically associated with reward, but has no social context. In this task, participants select a number of cards to win money but must avoid a 'disaster card' that results in zero earnings.

See online Supplementary Information for details of experimental design and procedures.

Data analysis

Auction Game

The Auction Game had subjects bid for items with an unknown true value in the range of x_L to x_H (see Fig. 1). We analyzed bids by transforming to a bid factor κ (van den Bos *et al.*, 2008) that is insensitive to x_L to x_H. For each of the 35 auction trials, the bid factor is defined as:

$$\kappa = 2\frac{b_i - x_L}{x_H - x_L}$$

where b_i is the bid placed by participant on trial i. For this study, the range of possible values (x_L–x_H) was always $10. Note that

$\kappa = 0$ corresponds to the optimal RNNE bidding strategy, and $\kappa = 2$ corresponds to bidding x_H.

We used a multilevel linear model to account for interdependence of within-subject data (ICC > 0.37) using R (R Core Team, 2016), package 'nlme' (Pinheiro *et al.*, 2016) with the following structure:

$$Y_{ij} = \pi_{0j} + \pi_{1j}(\text{Group}_i) + \pi_{2j}(\text{Drug}_i) + \pi_{3j}(\text{Trial}_i) + \pi_{4j}(\text{Group}_i{}^*\text{Drug}_i) + \pi_{5j}(\text{Group}_i{}^*\text{Trial}_i) + \pi_{6j}(\text{Drug}_i{}^*\text{Trial}_i) + \pi_{7j}(\text{Group}_i{}^*\text{Drug}_i{}^*\text{Trial}_i) + r_{ij}$$

with $\pi_{0j} = \pi_0 + u_{0j}$ and $\pi_{3j} = \pi_3 + u_{3j}$.

The best fit model by log-likelihood tests allowed random intercepts by participant and random slopes for trial and accounted for heteroscedasticity and autocorrelation. We calculated simple effects for significant interactions using simplified models, described in the Results section.

A computational reinforcement learning (RL) model, described in van den Bos *et al.* (2013*b*), accounts for how participants change their bids over time based on money won and lost. The model assumes that participants maintain estimates of the expected amount of money that would be gained or lost for bidding each bid factor κ. In addition, the model to individual data incorporates parameters that estimate the social value of winning (ρ_{win}) and disutility of losing (ρ_{loss}) beyond the monetary outcome. It is these parameters, (ρ_{win} and ρ_{loss}), that we hypothesized to differ with schizophrenia and oxytocin. Learning across trials is governed by an individual-specific learning rate (α), and choices are subject to a noise parameter (θ). We examined α and θ to test and rule out whether differences in bidding behavior were due to nonsocial factors. We compared individual parameter estimates between controls and patients for oxytocin and placebo using the Kruskal–Wallis test for a difference between the four groups, followed by Mann–Whitney tests.

Devil's task

We compared risk-taking preferences by conducting a 2 (drug: oxytocin *v.* placebo) × 2 (group: controls *v.* patients) analysis of variance.

We used Matlab for RL modeling; all other analyses presented were conducted using R (R Core Team, 2016). See online Supplementary Information for details of models and fitting procedures.

Results

We excluded three controls and one patient from analysis because they did not believe that they were playing against other human players. We excluded another patient who did not appear to attend to the task given that he entered the same bid, regardless of item value, for every trial. The final sample included 51 controls and 37 patients. We did not match groups on education given that decreased educational attainment is a consequence of schizophrenia, and matching may therefore obscure group differences and generate misleading results (Resnick, 1992).

Auction Game

Multilevel linear model

In the Auction Game, participants generally begin bidding near the upper range of possible values for the item under auction (x_H). However, bidding this amount results in monetary losses, and with experience, participants reduce bidding until they reach a stable equilibrium. This equilibrium is generally significantly above the money maximizing strategy (RNNE; $\kappa = 0$). We examined whether these patterns exist in our sample and whether they differ by group or by drug condition.

The 3-way interaction drug × group × trial was not significant ($p = 0.95$), nor was the 2-way interaction drug × group ($p = 0.87$), so we removed these terms from the model. The 2-way group × trial ($b = 0.0053$, $t = 2.18$, $p = 0.029$) and drug × trial ($b = 0.0049$, $t = 2.01$, $p = 0.044$) interactions were significant. To explore these, we first tested the simple effect of group × trial, controlling for drug. Controls reduced their bids over time ($b = -0.0075$, $t = -4.58$, $p = 4.7 \times 10^{-06}$), while patients did not ($b = -0.0026$, $t = -1.35$, $p = 0.18$). We then tested the simple effect of drug × trial, controlling for group. Participants who received placebo decreased their bids over time ($b = -0.0074$, $t = -4.40$, $p = 1.1 \times 10^{-05}$), while those who received oxytocin did not ($b = -0.003$, $t = -1.62$, $p = 0.1$); see Fig. 2.

To better understand changes in bidding over time, we calculated average bid factors per participant for the first five and the last five trials. We compared these using a mixed model with the terms drug, group, trial (first five or last five), group × trial, and drug × trial. The 2-way interactions were significant: group × trial ($b = 0.23$, $t = 2.66$, $p = 0.0094$), and drug × trial ($b = 0.18$, $t = 2.07$, $p = 0.041$). To explore these, we first tested the simple effect of group × trial, controlling for drug. Controls decreased their bids from the first five to the last five trials ($b = -0.21$, $t = -3.64$, $p = 0.00047$), while patients did not ($b = 0.0054$, $t = 0.082$, $p = 0.93$). We then tested the simple effect of drug × trial, controlling for group. Participants on placebo decreased their bids from the first five to the last five trials ($b = -0.19$, $t = -3.16$, $p = 0.0022$) while participants on oxytocin did not ($b = -0.03$, $t = -0.46$, $p = 0.65$). Participants on oxytocin bid higher than those on placebo at the trend level in the last five trials ($b = 0.16$, $t = 1.7$, $p = 0.093$) but not in the first five trials ($b = 0.0041$, $t = 0.044$, $p = 0.97$); see Fig. 3. We conducted identical analyses using the first 10 *v.* last 10 trials and first *v.* second half of trials. All analyses yielded similar results, so these are not reported.

Reinforcement learning model

Visual investigation of bidding across trials shows that bids start high but then temporarily increase before decreasing toward the optimal strategy; see Fig. 2. This pattern of behavior is expected (van den Bos *et al.*, 2013*b*) and results from the social rewards inherent in the task. Namely, losing an auction causes disutility (ρ_{loss}). Chances of winning on any given trial are small due to the number of other bidders, so loss disutility tends to increase bidding in early trials. Additionally, bids are inflated from the additional utility of winning (ρ_{win}) that derives from submitting the high bid.

These subtleties in bidding behavior may be disentangled by fitting the RL model designed to capture the idiosyncratic effects of trial outcomes from individual differences in preferences for social reward (see the section 'Auction Game'). Model comparisons showed that a full RL model, including two separate parameters for social preferences, ρ_{win} and ρ_{loss}, fit the data better (Bayesian information criterion, BIC = 18 269) than an RL model that included only learning rate (α) and response variability (θ) parameters (BIC = 21 238), RL including ρ_{loss} (BIC = 21 367), or RL including ρ_{win} (BIC = 18 924). This suggests that, as

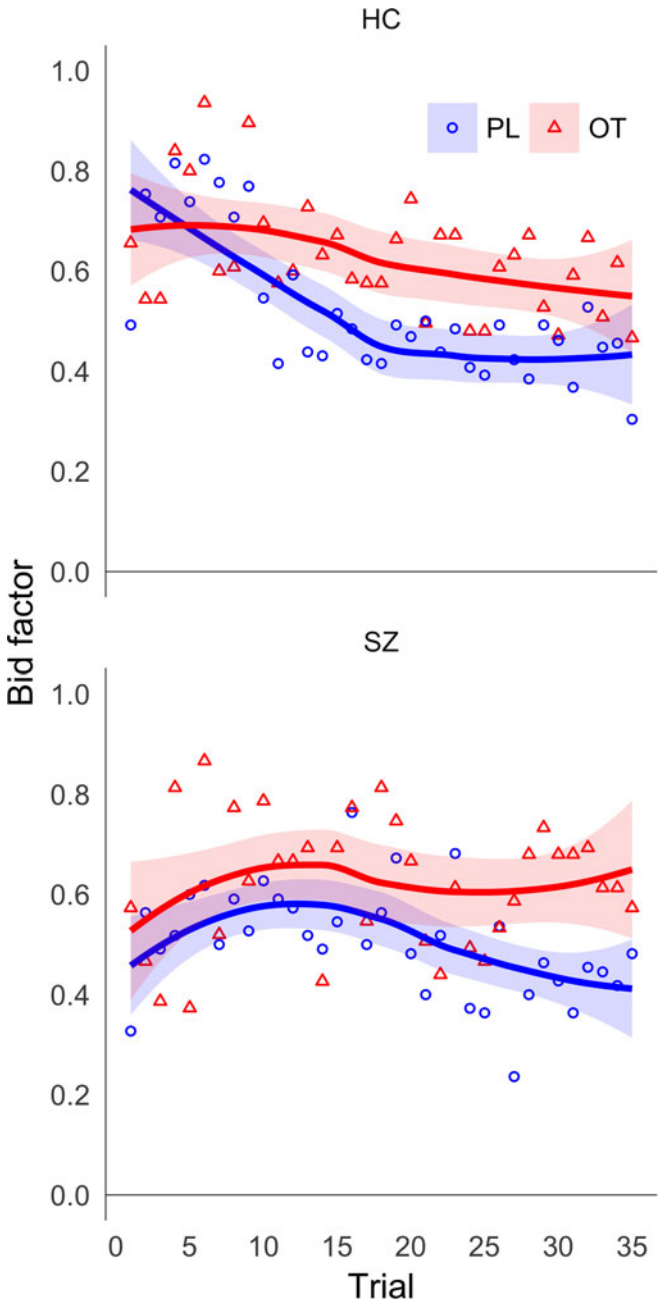

Fig. 2. Auction Game bidding over time. Raw bid factor values for healthy controls (HC) and patients with schizophrenia (SZ) under the placebo (PL) and oxytocin (OT) conditions.

we have found previously (van den Bos *et al.*, 2013*b*), bidding is motivated not only by monetary gains, but also by social motivation to win (ρ_{win}) and to avoid losing (ρ_{loss}).

The Kruskal–Wallis test showed that ρ_{win} differed significantly between groups and drug conditions, $H(3) = 19.49$, $p < 0.001$. Post-hoc, pair-wise Mann–Whitney tests showed that ρ_{win} was not significantly different between controls and patients on placebo ($U = 218.00$, $p = 0.24$), but that oxytocin was associated with higher ρ_{win} in schizophrenia ($U = 30.00$, $p < 0.001$) and at a trend level in controls ($U = 227.00$, $p = 0.10$); see Fig. 4. We found no significant differences between groups or drug conditions for the other parameters (ρ_{loss}, $H(3) = 0.62$, $p = 0.891$; α, $H(3) = 2.89$, $p = 0.442$; θ, $H(3) = 0.51$, $p = 0.918$), suggesting that differences in bidding behavior between the groups and drug conditions are mainly attributable to changes in the value of being the winner.

Devil's task

We found no significant group, drug, or group × drug effects, indicating that differences in bidding behavior between groups and drug condition are unlikely to stem from differences in risk-taking preferences.

Predictors of bidding behavior in schizophrenia

Given that antidopaminergic medication and symptom severity may influence response to oxytocin (Bradley and Woolley, 2017), we explored both as possible predictors of bidding behavior. We examined the effects of antidopaminergic medication dosage quantified as chlorpromazine (CPZ) equivalents (Andreasen *et al.*, 2010) and symptom severity using the Positive and Negative Symptom Scale (PANSS; Kay *et al.*, 1987) on bid factor by trial and drug. The three-way PANSS × drug × trial interaction was not significant ($p = 0.14$). Given the relationship between reward valuation and negative symptoms in schizophrenia (Gold *et al.*, 2013; Kring and Barch, 2014), we also tested the negative symptom subscale of the PANSS and bidding behavior. The PANSS negative subscale × drug × trial was also not significant ($p = 0.45$). The three-way CPZ × drug × trial interaction was significant ($b = 6.2 \times 10^{-05}$, $t = 2.52$, $p = 0.012$), such that patients taking the mean dosage in our sample (CPZ = 75.08) did not change their bids over time on oxytocin ($b = -0.0021$, $t = -0.59$, $p = 0.55$) *v.* placebo ($b = -0.0019$, $t = -0.69$, $p = 0.49$). However, patients on high dosages (CPZ mean + 1 standard deviation = 223.35) decreased their bids over time on placebo ($b = -0.0053$, $t = -2.08$, $p = 0.038$) but not on oxytocin ($b = 0.0037$, $t = 1.13$, $p = 0.26$).

See online Supplementary Information for details of analyses.

Discussion

We found that both men with schizophrenia and healthy controls were willing to lose money in order to win auctions, in line with evidence that the desire for social status is a driver of competitive bidding behavior. Consistent with our first hypothesis, patients overbid less than controls, suggesting impairment in their motivation to pursue the social reward of winning. Consistent with our second hypothesis, oxytocin administration was associated with increased overbidding, particularly in patients. Importantly, the driving force behind this effect was an increased motivation to win the auction, regardless of monetary reward or loss. These findings provide further evidence that oxytocin modulates behavior by increasing the salience of social stimuli and suggest that oxytocin administration may enhance sensitivity to social reward in people with schizophrenia.

Previous work in healthy people shows that overbidding is maximal early in the Auction Game and decreases over time (van den Bos *et al.*, 2013*a*), as monetary losses prompt participants to reduce bids. We found that patients did not follow this pattern, overbidding less compared to controls at the outset of the game. This is consistent with the reduced anticipatory pleasure observed in schizophrenia (Gard *et al.*, 2007), and may reflect dysregulated salience processing that leads to under-valuation of

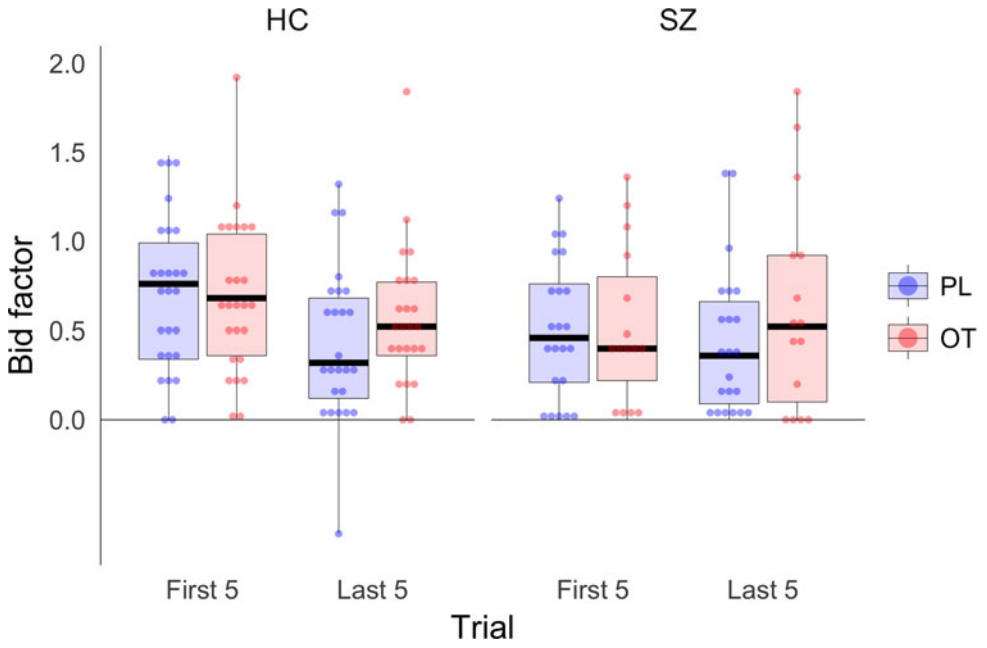

Fig. 3. Auction Game bidding during the first five *v.* last five trials, shown for healthy controls (HC) and patients with schizophrenia (SZ) under the placebo (PL) and oxytocin (OT) conditions.

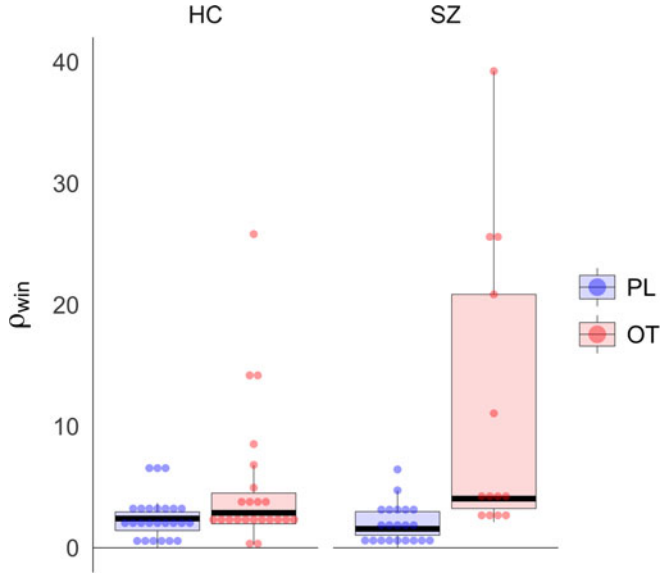

Fig. 4. Motivation to win the auction (ρ_{win}), shown for healthy controls (HC) and patients with schizophrenia (SZ) under the placebo (PL) and oxytocin (OT) conditions. Note that three participants with ρ_{win} values >40 are not shown in this plot: one healthy control on placebo, one healthy control on oxytocin, and one patient with schizophrenia on oxytocin.

the social reward of winning and thus lower bids. It could also reflect impairment in mentalizing, the ability to infer beliefs and intentions of other people, a core deficit in schizophrenia (Green *et al.*, 2015). Mentalizing may play a role in competitive behavior specifically by enhancing the ability to monitor gain and loss of rewards by others. Winning auctions has been associated with increased activity in the right temporoparietal junction (rTPJ; van den Bos *et al.*, 2013*b*), part of a neural network that underlies mentalizing ability (Hampton *et al.*, 2008). In schizophrenia, rTPJ hypoactivation (Lee *et al.*, 2011; Das *et al.*, 2012; Fett *et al.*, 2015) and abnormal functional connectivity between the rTPJ and temporal lobe regions (Bitsch *et al.*, 2018) has been observed during mentalizing tasks. Thus, mentalizing deficits among patients may have led to reduced social comparison during the game, resulting in lower bids. It is also possible that patients' bidding patterns reflect a general impairment in adaptive decision-making. People with schizophrenia tend to make more predictable decisions (Paulus *et al.*, 1999) and have trouble incorporating feedback to inform future decisions (Fett *et al.*, 2012). During iterative decision-making games, for example, they may rely excessively on the most recent outcome rather than integrating the consequences of their decisions over time. These abnormalities amount to a 'strategic stiffness' (Kim *et al.*, 2007) – the tendency to default to a choice based on a recent stimulus – that may have limited patients' ability to discover an optimal decision-making strategy over the course of the game.

Our finding that oxytocin enhanced the motivation to pursue social reward is consistent with previous studies in healthy people showing that oxytocin heightens attention to social preferences during decision-making (Aydogan *et al.*, 2017; Lambert *et al.*, 2017). Interactions between oxytocin and the dopamine system have been implicated in these salience-moderating effects (Love, 2014), which is in line with studies showing that oxytocin administration modulates brain reward circuitry in humans (Groppe *et al.*, 2013; Scheele *et al.*, 2013). Thus, oxytocin may have exacerbated overbidding by shifting attention toward the social reward of winning and away from monetary reward via modulation of dopaminergic signaling. The fact that antidopaminergic medication dosage predicted oxytocin effects on bidding behavior among patients may also reflect oxytocin's interaction with the dopamine system. In animal models of psychosis, oxytocin administration has been shown to reduce dopaminergic signaling in the NAc and striatum (Qi *et al.*, 2008), and administration of certain antidopaminergic medications is associated with an

increase in plasma oxytocin levels (Uvnäs-Moberg *et al.*, 1992). However, the relationship between antidopaminergic medication dosage and response to intranasal oxytocin is unclear (see Bradley and Woolley, 2017). Undoubtedly, endogenous and exogenous oxytocin–dopamine interactions are complex, and further work is needed to understand their implications for administering oxytocin to patients with schizophrenia.

Oxytocin administration has also been shown to enhance sensitivity to social reward in the absence of dopaminergic signaling modulation (Striepens *et al.*, 2014), highlighting the possibility that other mechanisms of action underlie our findings. Oxytocin may have exacerbated overbidding by boosting mentalizing ability, for example. Oxytocin administration improves mentalizing ability in schizophrenia (Burkner *et al.*, 2017), and in macaques, it has been shown to increase sensitivity to rewards received by others (Chang *et al.*, 2012). Another possibility is that oxytocin influenced bidding behavior by altering the adaptive process of reinforcement learning that normally drives down bidding as the Auction Game progresses. Studies in rhesus monkeys (Parr, 2014) and in healthy people (Hu *et al.*, 2015) suggest that oxytocin influences reinforcement learning in social contexts, potentially via increased attention to social cues and feedback. Though we found that oxytocin did not impact participants' learning rate during the Auction Game, it appeared to influence decision-making by shifting their underlying preferences for monetary *v.* social reward.

This study has several limitations. First, despite the interactive nature of the Auction Game and steps we took to maximize the feeling of being in a real social context, it does not reflect the true complexity of real-world interaction. Second, we did not include a condition in which participants played against a computer to control for impairments in nonsocial reinforcement learning. Third, we did not assess cognition, which is relevant given that cognitive limitations are a potential cause of overbidding in healthy people (Fudenberg, 2006) and cognitive impairment has been linked to deficits in reinforcement learning in schizophrenia (Premkumar *et al.*, 2008; Collins *et al.*, 2014). However, by explicitly instructing participants on the optimal bidding strategy, we hoped to minimize the cognitive burden of the task. Fourth, we enrolled only men in this study, and results are not generalizable to women given oxytocin's sexually dimorphic effects (Dumais *et al.*, 2017). Fifth, the pharmacodynamics of intranasal oxytocin are poorly understood (Quintana and Woolley, 2016). Human studies have generally included a 30-min delay after administration before beginning assessments, citing evidence of behavioral and physiological responses using this timing in healthy people (Macdonald and Macdonald, 2010). Elevated cerebrospinal fluid oxytocin levels have been observed 75 min after intranasal administration (Striepens *et al.*, 2013), and oxytocin-induced changes in regional cerebral blood flow are detectable between 25 and 78 min after administration (Paloyelis *et al.*, 2016). Though these findings offer some support for the standard timing used here, the peak and duration of intranasal oxytocin's central nervous system effects remain unclear. Thus, our finding that oxytocin increased overbidding during later trials of the game could reflect suboptimal timing of the task relative to oxytocin administration, resulting in a delayed peak of oxytocin effects. Finally, our sample size is modest; replication and extension of our findings by others is critical.

The robust link between decreased social engagement and poor health outcomes (Holt-Lunstad *et al.*, 2015) underscores the importance of developing targeted interventions for abnormal social behavior among people with schizophrenia. Objective measures of behavior are essential for tackling this challenge (Kapur *et al.*, 2012), given that insensitivity to social reward and other contributors to abnormal social behavior are not well captured by the interview-based symptom rating scales typically used in clinical trials (Freedman *et al.*, 2013). Indeed, we found no correlation between symptom ratings and motivation for social reward in this study, and prior studies have found a similar lack of association between symptom ratings and impaired reward processing in schizophrenia (Waltz *et al.*, 2007; Barch *et al.*, 2017; Lee *et al.*, 2018). Future work is necessary both to explain these incongruities as well as to elucidate the neural mechanisms that underlie oxytocin's effects on social reward. Most critically, we must determine whether oxytocin-induced increases in the perceived value of social reward facilitate social engagement among people with schizophrenia. Enhancing the rewarding value of social interactions may be a mechanism by which we can specifically target impaired social motivation, one of the most robust deficits associated with the disorder. Ultimately, clinical trials that evaluate behavioral changes in large samples will be essential to determine whether pharmacological enhancement of social reward sensitivity improves real-world social behavior and functional outcomes among people with schizophrenia. Given the impact of schizophrenia on patients, caregivers, and society as a whole, further examination of oxytocin's potential as a treatment is a worthwhile undertaking.

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References

Andreasen NC, Pressler M, Nopoulos P, Miller D and Ho B-C (2010) Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. *Biological Psychiatry* **67**, 255–262.

Ashenfelter O and Genesove D (1992) Testing for price anomalies in real estate auctions.

Aydogan G, Furtner NC, Kern B, Jobst A, Müller N and Kocher MG (2017) Oxytocin promotes altruistic punishment. *Social Cognitive and Affective Neuroscience* **12**, 1740–1747.

Barch DM, Carter CS, Gold JM, Johnson SL, Kring AM, MacDonald AW, Pizzagalli DA, Ragland JD, Silverstein SM and Strauss ME (2017) Explicit and implicit reinforcement learning across the psychosis spectrum. *Journal of Abnormal Psychology* **126**, 694–711.

Bazerman MH and Samuelson WF (1983) I won the auction but don't want the prize. *Journal of Conflict Resolution* **27**, 618–634.

Bitsch F, Berger P, Nagels A, Falkenberg I and Straube B (2018) Impaired right temporoparietal junction-hippocampus connectivity in schizophrenia and its relevance for generating representations of other minds. *Schizophrenia Bulletin* **16**, 559.

Boccia ML, Petrusz P, Suzuki K, Marson L and Pedersen CA (2013) Immunohistochemical localization of oxytocin receptors in human brain. *Neuroscience* **253**, 155–164.

Bora E, Yücel M and Allen NB (2009) Neurobiology of human affiliative behaviour: implications for psychiatric disorders. *Current Opinion in Psychiatry* **22**, 320–325.

Bradley ER and Woolley JD (2017) Oxytocin effects in schizophrenia: reconciling mixed findings and moving forward. *Neuroscience and Biobehavioral Reviews* **80**, 36–56.

Burkner P-C, Williams DR, Simmons TC and Woolley JD (2017) Intranasal oxytocin may improve high-level social cognition in schizophrenia, but not social cognition or neurocognition in general: a multilevel Bayesian meta-analysis. *Schizophrenia Bulletin* **43**, 1291–1303.

Capen EC, Clapp RV and Campbell WM (2013) Competitive bidding in high-risk situations. *Journal of Petroleum Technology* **23**, 641–653.

Carlsson A (2006) The neurochemical circuitry of schizophrenia. *Pharmacopsychiatry* **39** (Suppl 1), S10–S14.

Chang SWC, Barter JW, Ebitz RB, Watson KK and Platt ML (2012) Inhaled oxytocin amplifies both vicarious reinforcement and self reinforcement in rhesus macaques (*Macaca mulatta*). *Proceedings of the National Academy of Sciences of the United States of America* **109**, 959–964.

Collins AGE, Brown JK, Gold JM, Waltz JA and Frank MJ (2014) Working memory contributions to reinforcement learning impairments in schizophrenia. *Journal of Neuroscience* **34**, 13747–13756.

Couture SM, Penn DL and Roberts DL (2006) The functional significance of social cognition in schizophrenia: a review. *Schizophrenia Bulletin* **32** (Suppl 1), S44–S63.

Das P, Lagopoulos J, Coulston CM, Henderson AF and Malhi GS (2012) Mentalizing impairment in schizophrenia: a functional MRI study. *Schizophrenia Research* **134**, 158–164.

Dölen G, Darvishzadeh A, Huang KW and Malenka RC (2013). Social reward requires coordinated activity of nucleus accumbens oxytocin and serotonin. *Nature* **501**, 179–184.

Dumais KM, Bredewold R, Mayer TE and Veenema AH (2013). Sex differences in oxytocin receptor binding in forebrain regions: correlations with social interest in brain region- and sex-specific ways. *Hormones and Behavior* **64**, 693–701.

Dumais KM, Kulkarni PP, Ferris CF and Veenema AH (2017). Sex differences in neural activation following different routes of oxytocin administration in awake adult rats. *Psychoneuroendocrinology* **81**, 52–62.

Festinger L (1954) A theory of social comparison processes.

Fett A-KJ, Shergill SS, Joyce DW, Riedl A, Strobel M, Gromann PM and Krabbendam L (2012) To trust or not to trust: the dynamics of social interaction in psychosis. *Brain* **135**, 976–984.

Fett AKJ, Shergill SS and Krabbendam L (2015) Social neuroscience in psychiatry: unravelling the neural mechanisms of social dysfunction. *Psychological Medicine* **45**, 1145–1165.

First MB, Spitzer RL, Gibbon M and Williams J (2002) *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research version, Non-Patient Edition (*SCID-I/NP*)*. New York: New York State Psychiatric Biometrics Research.

Freedman R, Lewis DA, Michels R, Pine DS, Schultz SK, Tamminga CA, Gabbard GO, Gau SS-F, Javitt DC, Oquendo MA, Shrout PE, Vieta E and Yager J (2013) The initial field trials of DSM-5: new blooms and old thorns. *American Journal of Psychiatry* **170**, 1–5.

Fudenberg D (2006) Advancing beyond advances in behavioral economics. *Journal of Economic Literature* **44**, 694–711.

Fulford D, Campellone T and Gard DE (2018) Social motivation in schizophrenia: how research on basic reward processes informs and limits our understanding. *Clinical Psychology Review* **63**, 12–24.

Gard DE, Kring AM, Gard MG, Horan WP and Green MF (2007) Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. *Schizophrenia Research* **93**, 253–260.

Gold JM, Waltz JA, Prentice KJ, Morris SE and Heerey EA (2008) Reward processing in schizophrenia: a deficit in the representation of value. *Schizophrenia Bulletin* **34**, 835–847.

Gold JM, Strauss GP, Waltz JA, Robinson BM, Brown JK and Frank MJ (2013) Negative symptoms of schizophrenia are associated with abnormal effort-cost computations. *Biological Psychiatry* **74**, 130–136.

Gordon I, Jack A, Pretzsch CM, Vander Wyk B, Leckman JF, Feldman R and Pelphrey KA (2016) Intranasal oxytocin enhances connectivity in the neural circuitry supporting social motivation and social perception in children with autism. *Scientific Reports* **6**, 35054.

Green MF, Horan WP and Lee J (2015) Social cognition in schizophrenia. *Nature Reviews Neuroscience* **16**, 620–631.

Groppe SE, Gossen A, Rademacher L, Hahn A, Westphal L, Gründer G and Spreckelmeyer KN (2013) Oxytocin influences processing of socially relevant cues in the ventral tegmental area of the human brain. *Biological Psychiatry* **74**, 172–179.

Guastella AJ, Hickie IB, McGuinness MM, Otis M, Woods EA, Disinger HM, Chan H-K, Chen TF and Banati RB (2013) Recommendations for the standardisation of oxytocin nasal administration and guidelines for its reporting in human research. *Psychoneuroendocrinology* **38**, 612–625.

Hampton AN, Bossaerts P and O'Doherty JP (2008) Neural correlates of mentalizing-related computations during strategic interactions in humans. *Proceedings of the National Academy of Sciences of the United States of America* **105**, 6741–6746.

Holt-Lunstad J, Smith TB, Baker M, Harris T and Stephenson D (2015) Loneliness and social isolation as risk factors for mortality: a meta-analytic review. *Perspectives on Psychological Science* **10**, 227–237.

Hu J, Qi S, Becker B, Luo L, Gao S, Gong Q, Hurlemann R and Kendrick KM (2015) Oxytocin selectively facilitates learning with social feedback and increases activity and functional connectivity in emotional memory and reward processing regions. *Human Brain Mapping* **36**, 2132–2146.

Huberman BA, Loch CH and Önçüler A (2016) Status as a valued resource. *Social Psychology Quarterly* **67**, 103–114.

Hung LW, Neuner S, Polepalli JS, Beier KT, Wright M, Walsh JJ, Lewis EM, Luo L, Deisseroth K, Dölen G and Malenka RC (2017) Gating of social reward by oxytocin in the ventral tegmental area. *Science* **357**, 1406–1411.

Kagel JH and Levin D (2009) *Common Value Auctions and the Winner's Curse*. Princeton, New Jersey: Princeton University Press.

Kapur S, Phillips AG and Insel TR (2012) Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Molecular Psychiatry* **17**, 1174–1179.

Kay SR, Fiszbein A and Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* **13**, 261–276.

Kim H, Lee D, Shin Y-M and Chey J (2007) Impaired strategic decision making in schizophrenia. *Brain Research* **1180**, 90–100.

Kohli S, King MV, Williams S, Edwards A, Ballard TM, Steward LJ, Alberati D and Fone KCF (2018) Oxytocin attenuates phencyclidine hyperactivity and increases social interaction and nucleus accumben dopamine release in rats. *Neuropsychopharmacology* **53**, 65.

Krach S, Paulus FM, Bodden M and Kircher T (2010) The rewarding nature of social interactions. *Frontiers in Behavioral Neuroscience* **4**, 22. doi: 10.3389/fnbeh.2010.00022.

Kring AM and Barch DM (2014) The motivation and pleasure dimension of negative symptoms: neural substrates and behavioral outputs. *European Neuropsychopharmacology* **24**, 725–736.

Lambert B, Declerck CH, Boone C and Parizel PM (2017) A functional MRI study on how oxytocin affects decision making in social dilemmas: cooperate as long as it pays off, aggress only when you think you can win. *Hormones and Behavior* **94**, 145–152.

Lee D (2013) Decision making: from neuroscience to psychiatry. *Neuron* **78**, 233–248.

Lee J, Quintana J, Nori P and Green MF (2011) Theory of mind in schizophrenia: exploring neural mechanisms of belief attribution. *Social Neuroscience* **6**, 569–581.

Lee J, Jimenez AM, Reavis EA, Horan WP, Wynn JK and Green MF (2018) Reduced neural sensitivity to social vs nonsocial reward in schizophrenia. *Schizophrenia Bulletin* **143**, 332.

Liu Z, Zheng L, Li L, Xu J, Cheng X, Guo X, Mulcahy J and Xu M (2018) Social comparison modulates the neural responses to regret and subsequent risk-taking behavior. *Social Cognitive and Affective Neuroscience* **13**, 1059–1070.

Love TM (2014) Oxytocin, motivation and the role of dopamine. *Pharmacology, Biochemistry, and Behavior* **119**, 49–60.

Macdonald K and Macdonald TM (2010) The peptide that binds: a systematic review of oxytocin and its prosocial effects in humans. *Harvard Review of Psychiatry* **18**, 1–21.

Messick DM and McClintock CG (1968) Motivational bases of choice in experimental games. *Journal of Experimental Social Psychology* **4**, 1–25.

Noritake A, Ninomiya T and Isoda M (2018) Social reward monitoring and valuation in the macaque brain. *Nature Neuroscience* **64**, 906.

Palaniyappan L, Simmonite M, White TP, Liddle EB and Liddle PF (2013) Neural primacy of the salience processing system in schizophrenia. *Neuron* **79**, 814–828.

Paloyelis Y, Doyle OM, Zelaya FO, Maltezos S, Williams SC, Fotopoulou A and Howard MA (2016) A spatiotemporal profile of in vivo cerebral blood flow changes following intranasal oxytocin in humans. *Biological Psychiatry* **79**, 693–705.

Parr LA (2014) Intranasal oxytocin enhances socially-reinforced learning in rhesus monkeys. *Frontiers in Behavioral Neuroscience* **8**, 278. doi: 10.3389/fnbeh.2014.00278.

Paulus MP, Geyer MA and Braff DL (1999) Long-range correlations in choice sequences of schizophrenic patients. *Schizophrenia Research* **35**, 69–75.

Peñagarikano O, Lázaro MT, Lu X-H, Gordon A, Dong H, Lam HA, Peles E, Maidment NT, Murphy NP and Yang XW (2015) Exogenous and evoked oxytocin restores social behavior in the Cntnap2 mouse model of autism. *Science Translational Medicine* **7**, 271ra8–271ra8.

Pinheiro J, Bates D, DebRoy S, Sarkar D and EISPACK HS (2016) R Development Core Team (2016) Nlme: linear and nonlinear mixed effects models. R package version (Version 3.1–128).

Premkumar P, Fannon D, Kuipers E, Simmons A, Frangou S and Kumari V (2008) Emotional decision-making and its dissociable components in schizophrenia and schizoaffective disorder: a behavioural and MRI investigation. *Neuropsychologia* **46**, 2002–2012.

Qi J, Yang J-Y, Song M, Li Y, Wang F and Wu C-F (2008) Inhibition by oxytocin of methamphetamine-induced hyperactivity related to dopamine turnover in the mesolimbic region in mice. *Naunyn-Schmiedebergs Archives of Pharmacology* **376**, 441–448.

Quintana DS and Woolley JD (2016) Intranasal oxytocin mechanisms can be better understood, but its effects on social cognition and behavior are not to be sniffed at. *Biological Psychiatry* **79**, e49–e50.

R Core Team (2016) *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing.

Resnick SM (1992) Matching for education in studies of schizophrenia. *Archives of General Psychiatry* **49**, 246.

Scheele D, Wille A, Kendrick KM, Stoffel-Wagner B, Becker B, Güntürkün O, Maier W and Hurlemann R (2013) Oxytocin enhances brain reward system responses in men viewing the face of their female partner. *Proceedings of the National Academy of Sciences of the United States of America* **110**, 20308–20313.

Schultz W (2016) Dopamine reward prediction-error signalling: a two-component response. *Nature Reviews Neuroscience* **17**, 183–195.

Shahrokh DK, Zhang T-Y, Diorio J, Gratton A and Meaney MJ (2010) Oxytocin–dopamine interactions mediate variations in maternal behavior in the rat. *Endocrinology* **151**, 2276–2286.

Shamay-Tsoory S and Young LJ (2016) Understanding the oxytocin system and Its relevance to psychiatry. *Biological Psychiatry* **79**, 150–152.

Sheremeta RM (2013) Overbidding and heterogeneous behavior in contest experiments. *SSRN Electronic Journal*, Available at https://ssrn.comabstract=2197151.

Slovic P (1966) Risk-Taking in children: age and Sex differences. *Child Development* **37**, 169.

Song Z, Larkin TE, Malley MO and Albers HE (2016) Oxytocin (OT) and arginine-vasopressin (AVP) act on OT receptors and not AVP V1a receptors to enhance social recognition in adult Syrian hamsters (*Mesocricetus auratus*). *Hormones and Behavior* **81**, 20–27.

Strathearn L, Fonagy P, Amico J and Montague PR (2009) Adult attachment predicts maternal brain and oxytocin response to infant cues. *Neuropsychopharmacology* **34**, 2655–2666.

Striepens N, Kendrick KM, Hanking V, Landgraf R, Wüllner U, Maier W and Hurlemann R (2013) Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans. *Scientific Reports* **3**, 3440.

Striepens N, Matusch A, Kendrick KM, Mihov Y, Elmenhorst D, Becker B, Lang M, Coenen HH, Maier W, Hurlemann R and Bauer A (2014) Oxytocin enhances attractiveness of unfamiliar female faces independent of the dopamine reward system. *Psychoneuroendocrinology* **39**, 74–87.

Trezza V, Campolongo P and Vanderschuren LJMJ (2011) Evaluating the rewarding nature of social interactions in laboratory animals. *Developmental Cognitive Neuroscience* **1**, 444–458.

Uvnäs-Moberg K, Alster P and Svensson TH (1992) Amperozide and clozapine but not haloperidol or raclopride increase the secretion of oxytocin in rats. *Psychopharmacology* **109**, 473–476.

van den Bos W, Li J, Lau T, Maskin E, Cohen JD, Montague PR and McClure SM (2008) The value of victory: social origins of the winner's curse in common value auctions. *Judgment and Decision Making* **3**, 483–492.

van den Bos W, Golka PJM, Effelsberg D and McClure SM (2013*a*) Pyrrhic victories: the need for social status drives costly competitive behavior. *Frontiers in Neuroscience* **7**, 189.

van den Bos W, Talwar A and McClure SM (2013*b*) Neural correlates of reinforcement learning and social preferences in competitive bidding. *The Journal of Neuroscience* **33**, 2137–2146.

Waltz JA, Frank MJ, Robinson BM and Gold JM (2007) Selective reinforcement learning deficits in schizophrenia support predictions from computational models of striatal-cortical dysfunction. *Biological Psychiatry* **62**, 756–764.

Young LJ and Wang Z (2004) The neurobiology of pair bonding. *Nature Neuroscience* **7**, 1048–1054.