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Intranasal oxytocin reduces reactive aggression in men but not in women: A computational approach

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ABSTRACT

Aggression is an important behaviour that concerns individual survival and large-scale social stability. It comprises a variety of psychological subcomponents and is modulated by different biological factors. Two factors in particular, gender and oxytocin, appear to play a robust role in aggressive behaviour. However, whether these two factors interact to impact aggressive behaviour is not currently known. The current study investigated the modulating effect of gender on the relationship between oxytocin and aggression and characterized its underlying mechanisms by combining behavioural economic, pharmacological, and computational approaches. Specifically, we employed a double-blind, randomized, placebo-controlled, between-subjects design, in which one hundred participants (50 men and 50 women) completed a norm-training version of the multi-round one-shot ultimatum game (UG) after intranasal oxytocin or placebo administration. Rejection rates in the UG were adopted as an indicator of reactive aggression. The results indicated that oxytocin compared with placebo administration decreased aggression among men but not among women. Further analyses suggested that this decrease in aggression was a result of changes in men's sensitivity to provocation and positive affect, rather than norm adaptation rates or concerns about the cost of aggression. These findings highlight the role of gender in the relationship between oxytocin and reactive aggression and reveal its underlying psychological and computational mechanisms.

1. Introduction

Aggression refers to behaviours that intent to harm others (Baron and Richardson, 2004). On one hand, aggression manifests its adaptive value in protecting oneself and offspring and obtaining social status (Heilbron and Prinstein, 2008). On the other hand, aggression may bring chaos to society and incur severe punishment and social exclusion (Banny et al., 2011). These two sides of aggression, which concern both individuals and society as a whole, have stimulated much interest historically (Craig and Brad, 2002). More recently, there has been a focus on biological factors involved in aggression (e.g. Terranova et al., 2017, 2016). The two that are of primarily concern to this study are sexual dimorphism (Archer, 2004) and the neuromodulator oxytocin (de Jong and Neumann, 2017).

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Despite evidence of its involvement, previous studies revealed inconsistent findings regarding the effect size and directionality of the effect of oxytocin on human aggression[1] (for review, de Jong and Neumann, 2017). Some studies have supported the idea that oxytocin decreases human aggression (Campbell and Hausmann, 2013; Lee et al., 2009). For example, cerebrospinal fluid oxytocin levels are negatively correlated to self-reported life history of aggression (Lee et al., 2009). Other studies have instead suggested that oxytocin increases human aggression (Ne'eman et al., 2016; Romney et al., 2018). For example, Ne'eman et al. (2016) examined the effect of intranasal oxytocin administration on reactive aggressive behaviour measured via the point subtraction aggression paradigm (PSAP), in which participants' money is occasionally stolen by a fictitious player. In this paradigm, participants can react with several different responses, including an aggressive response, which is operationalized by the action of reducing the fictitious player's money with no benefit to the participant. Ne'eman et al. (2016) found that, compared to placebo, oxytocin administration increased the proportion of reactive aggressive responses. Alongside these competing directional hypotheses are studies that have been unable to observe any significant effect of oxytocin administration on human aggression (Alcorn et al., 2015a,b).

These mixed findings may be attributed to the ignorance of the modulating role of gender, which may act as a critical modulator of the oxytocin's effect (Klein et al., 2015; Shamay-Tsoory and Abu-Akel, 2016). Many of the above studies recruited a single gender exclusively, with no possibility to observe potential interactions between gender and oxytocin administration (Alcorn et al., 2015a,b; Campbell and Hausmann, 2013; Pfundmair et al., 2018, Study 1). While some studies recruited both men and women, samples were not balanced (Lee et al., 2009; Pfundmair et al., 2018, Study 2; Romney et al., 2018). Therefore, it is not likely that a gender effect is evident in these studies.

Unlike human studies, non-human animal studies have provided abundant evidence that gender is an important modulator of oxytocin's effect on aggressive behaviour. For instance, in male rodents, oxytocin administration consistently decreases aggression towards intruders (Calcagnoli et al., 2015a, 2013, 2014; Calcagnoli et al., 2015ab; Zoratto et al., 2018). In contrast, oxytocin administration appears to increase aggression towards intruders in female rodents (Bosch, 2013; Ferris et al., 1992), although exceptions to these findings have been noted (Bosch and Neumann, 2012).

Neurobiologically, it has been found that the central amygdala plays a vital role in the anti-aggressive effect of oxytocin among male rodents (Calcagnoli et al., 2015a) and in the pro-aggressive effect of oxytocin among female rodents (Ferris et al., 1992). Likewise, human studies have shown that oxytocin administration dampens the response of amygdala to provocative stimuli (e.g. threatening faces and scenes) among men (Domes et al., 2007; Kirsch, 2005), while it boosts amygdala reactivity among women (Domes et al., 2010; Lischke et al., 2012). Considering the involvement of the amygdala in human aggression (Coccaro et al., 2007; Van Elst et al., 2000, but also see some exceptions Fanning et al., 2017) and aggression-related emotion processing (Frijling et al., 2015; Zink et al., 2010), the neurobiological evidence together with the non-human behavioural literature support the possibility that oxytocin has different effects on behavioural aggression in men and women. However, this possibility has not yet been explored.

In the current study, we examined the effects of oxytocin and gender on human reactive aggression and associated psychological mechanisms, combining intranasal oxytocin administration with self-report measures, computational modelling, and a behavioural economics experiment. The ultimatum game (UG) is a paradigm that assesses retaliatory behavioural responses (i.e. reactive aggression) to social provocation (Güth, 1995; Wang et al., 2011). It involves two players, a proposer and a responder. The proposer proposes how to divide a given monetary endowment. If the responder accepts the offer, each player receives the proposed amounts. If the responder rejects the offer, both players receive nothing. Responders often perceive unfair offers as social provocation and are inclined to reject them (Anderson and Bushman, 2002; Prasad et al., 2017). Rejection in the UG harms the proposer's economic benefit at the cost of the responder's own economic benefit (e.g. Brethel-Haurwitz et al., 2016). Accordingly, a rejection decision in the UG matches the definition of aggression (Baron and Richardson, 2004; Prasad et al., 2017), and parallels the reactive aggressive responses in the PSAP (Geniole et al., 2017). The multi-round one-shot UG has several advantages over other popular aggression measures (e.g. self-report and the PSAP). Firstly, behavioural decisions in the UG are likely to be less affected by social desirability bias than self-reported aggression propensity (Krumpal, 2013). Secondly, the multi-round one-shot UG could better circumvent the possible influence of long-term strategic considerations which may manifest in the PSAP, where participants play against the same player repeatedly (Cueva et al., 2017). Finally, the multi-round one-shot UG allows for computational modelling of responder's reactive aggressive behaviour.

Computational models have become increasingly important in psychology and neuroscience (e.g. Sporns, 2014). With the computational approach, we can capture dynamic decision-making and learning processes and reveal latent variables that are not directly observable (Farrell and Lewandowsky, 2010). Recent studies have developed computational models that apply to the UG (Gu et al., 2015; Xiang et al., 2013), providing a basis to investigate the psychological mechanisms contributing to aggressive behaviour. In this way, our experiment was designed not only to assess the potential interaction between gender and oxytocin, but also to identify the mechanistic underpinnings of these potential effects.

We set out to test four candidate psychological processes. In the UG, unfair offers are often provocative for a responder (Prasad et al., 2017). Given that the amygdala is implicated in the sensitivity (Tanaka et al., 2019) and behavioural response (e.g. aggression) (Gospic et al., 2011) to social provocation, and that amygdala's activity is modulated by oxytocin and gender (Domes et al., 2007, 2010; Lischke et al., 2012), oxytocin and gender may affect aggression through influencing an individual's sensitivity to provocation.

Importantly, the provocation of an offer in the UG is a function of subjective expectations (Gu et al., 2015). As individuals are exposed to social information, they develop social expectations and norms over time (Montague and Lohrenz, 2007). Thus if a responder consecutively receives offers lower than expected, they may lower their expectation. Then, the same offers are perceived to be less provocative for the responder, and they may begin to accept the offers that they rejected at the beginning. Individuals with high norm adaptation rates tend to adjust their expectation more quickly (Gu et al., 2015). Given that oxytocin has been found to influence social reward learning process (Clark-Elford et al., 2014), it is possible that oxytocin affects aggressive behaviour by altering the rate at which individuals' social norms adapt.

A third candidate psychological contributor to aggressive behaviour are emotions and moods (Berkowitz and Thome, 1987; Donahue et al., 2014). Oxytocin might alter individuals' emotions and moods (Aydogan et al., 2017; Gospic et al., 2011; Kemp and Guastella, 2011; Quirin et al., 2011; Scheele et al., 2019, but also see some exceptions Lane et al., 2016; Tabak et al., 2019). Moreover, gender modulates oxytocin's effect on emotions, such that oxytocin administration reduces negative affect following social stress among men, while increases anger among women (Kubzansky et al., 2012). Thus, it is possible that oxytocin and gender influences aggression via emotional or mood changes.

Finally, aggressive behaviour can come at a cost (in the UG this is a monetary cost), and higher costs may dissuade aggression (Archer et al., 2010). Two studies showed that oxytocin appears to decrease individuals' concern for money during altruistic decision-making (Barraza et al., 2011; Zak et al., 2007). A meta-analysis revealed that, compared

[1] The basic information (e.g. gender, sample sizes, oxytocin dosages, and effects) of studies on oxytocin and aggression was summarized in Table S1.

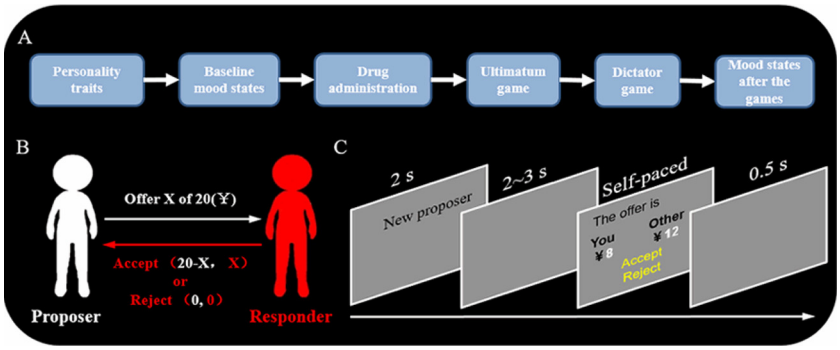

Fig. 1. A) The procedure of the study. B) The rules of the UG. A proposer proposes to a responder how to divide ¥20 between them. If the responder accepts the proposer's offer, both of them receive the proposed amount of money. If the responder rejects the offer, no one receives any money. All participants played the role of the responder. C) The timeline of the UG. At the beginning of each trial, participants were informed they were going to play with a new proposer. After a short while (a blank screen, 2~3 s), they saw the offer proposed by the proposer and decided to reject or accept the offer without time limitaion. In the end, a blank screen was shown for 0.5 s.

with women, men are more inclined to exert costly aggression on others (Archer, 2004), which implies that men may have less concerns about the cost of aggression. Considering both oxytocin and gender have an association with the concerns about the cost of aggression in the UG, they may exert effects on aggression as a result of devaluation of the cost of aggression. Overall, these four candidate psychological processes (sensitivity to provocation, norm adaptation rates, emotions/moods, and concern for money) may contribute to aggressive behaviour in the UG, and thus may be variously responsible for any potential effects of oxytocin and gender on aggression.

The effects of oxytocin on social behaviours have been shown to vary as a function of personality traits and baseline moods (Shamay-Tsoory and Abu-Akel, 2016). For example, oxytocin administration elicited aggression among low trait anxiety and high trait aggression/hostility individuals, but had no significant effect among high trait anxiety or low trait aggression/hostility individuals (Alcorn et al., 2015a; DeWall et al., 2014; Pfundmair et al., 2018). Likewise, oxytocin administration reduced aggression among participants who reported high state anxiety prior to oxytocin administration, but exhibited no effect among participants who reported low state anxiety (Campbell and Hausmann, 2013). Given these potential confounds, the current study also measured and statistically controlled relevant personality traits and moods while examining the potential interaction between gender and oxytocin on reactive aggressive behaviour.

2. Methods

2.1. Design and participants

We employed a 2 (drug administration: oxytocin vs. placebo) × 2 (gender: man vs. woman) between-subjects design.

Given that oxytocin has *opposite effects* among men and women on the activity of amygdala (Domes et al., 2007, 2010; Kirsch, 2005; Lischke et al., 2012), a brain region closely associated with aggression (Gospic et al., 2011), and that a mean effect size of four previous studies on intranasal oxytocin's effect on aggression is $f = 0.28$ (Alcorn et al., 2015a; Campbell and Hausmann, 2013; Ne'eman et al., 2016; Romney et al., 2018), we expected the between-subjects interaction effect on rejection rates to be medium in our study. For the effect size ($f = 0.30$), type I error rate of 0.05, and statistical power of 0.8, G-Power 3.1 yielded a required minimum sample size of 90 participants (Faul et al., 2007). In total, 100 college students (50 men and 50 women, $M_{age} = 22.35$ years, $SD_{age} = 2.14$) participated in our experiment in exchange for monetary payment. Half of each gender group were assigned to the oxytocin group, the other half to the placebo group.

Exclusion criteria included significant physical illness, psychiatric disorders, substance dependency, or pregnancy. Those who majored in psychology or economics in college or recently participated in any other drug studies were also not recruited. Participants were instructed to abstain from nicotine and caffeine on the day of the experiment and from food and drink (except water) 2 h before the drug administration. None of women participants used contraceptives. All women participants (except one) reported their menstrual period information. Fisher's exact test showed that there was no significant difference in proportion of women in the follicular and luteal phases between the oxytocin (8 in the follicular phase and 16 in the luteal phase) and placebo groups (5 in the follicular phase and 20 in the luteal phase), $p = 0.345$. The study was approved by the Institutional Review Board at Beijing Normal University and written informed consent was obtained from all participants before the experiment.

2.2. Procedure

2.2.1. Personality traits

Participants completed the trait anxiety and trait hostility subscales of the Neuroticism in the NEO Five-factor Inventory (Costa and McCrea, 1992) (Fig. 1A).

2.2.2. Baseline mood states

Paritcipants filled out the state anxiety subscale of the State-Trait Anxiety Inventory (Spielberger et al., 1970) and Positive Affect and Negative Affect Schedule (Watson et al., 1988) prior to drug administration, which respectively measured participants' current state anxiety, positive affect, and negative affect.

2.2.3. Drug administration

Participants intranasally self-administered 24 international units (IU) (three puffs of 4IU per nostril) oxytocin or placebo (saline solution) under an experimenter's supervision. The administation of oxytocin or placebo was randomized across participants, and both the experimenter and participants were blind to the drug administation.

2.2.4. Ultimatum game

Thirty minutes after the administration of the nasal spary, participants played a norm-training version of the multi-round one-shot UG (developed by Xiang et al., 2013). There are two players in the UG, a propser and a responder. The proposer offers a division of an endowment of ¥20 between themselves and the responder (Fig. 1B). If the responder accepts the offer, both players receive the proposed amounts. If the responder rejects the offer, neither player recevies money. Participants played the role of the responder for 60 trials. It was informed that at the end of experiment one trial would be randomly chosen and that the payoff for both the participant and the proposer (whose payment was still pending) would be realized accordingly (e.g. Xiang et al., 2013).

Participants were also told that they interacted with a new anonymous player on each trial, and that each proposal offer was from a different player who had previously visited the laboratory and had their offer recorded (Fig. 1C). However, in fact (but not being aware of by the participants) the porposal offers came from two different Gaussian distributions (Gu et al., 2015; Xiang et al., 2013). In the first and third blocks (20 trials per block), the offers to the participants were

generated from a Gaussian distribution with mean ¥8 and standard deviation ¥1.5; In the second block, the offers were generated from a Gaussian distribution with mean ¥4 and standard deviation ¥1.5. This manipulation was designed to change participants' expectation about the offers across trials and facilitate a norm adaptation process. Additionally, in 60% trials, participants rated their emotion in response to the offers they received after their decision (1 = very unpleasant, 9 = very pleasant). The UG lasted for about 15 min.

2.2.5. Dictator game

Subsequently, participants played the classical one-shot dictator game (DG). There are two players in the DG, a dictator and a receiver. The dictator splits ¥20 between themselves and the receiver. Unlike in the UG, the receiver has to accept the offer. The participants played the role of the dictator with a new anonymous player (the receiver) in a one-shot game. The current study used this task to measure the participants' concern for money in a social interactive context, via the amout given to oneself. One participant's data of the DG was not recorded due to technical issues.

2.2.6. Mood states after the games

Following the DG, the participants completed the state anxiety subscale of the State-Trait Anxiety Inventory and Positive Affect and Negative Affect Schedule to measure their mood states for the second time.

2.3. Data analysis

Trait anxiety, trait hostility, and baseline state anxiety

We examined whether personality traits and baseline state anxiety that have been found to modulate oxytocin's effect on aggression were comparable across subgroups using 2 (between-subjects factor: administration) × 2 (between-subjects factor: gender) analyses of variance (ANOVA) (Alcorn et al., 2015a; Campbell and Hausmann, 2013; DeWall et al., 2014; Pfundmair et al., 2018).

Rejection rates

In accordance with many previous studies (e.g. Cueva et al., 2017; Dreher et al., 2016; Mehta and Beer, 2010), the current study used rejection rates in the UG as an indicator of reactive aggression. Our main hypothesis was tested using an ANOVA on rejection rates in the UG. As a robustness check, we also tested whether our findings changed when trait anxiety, trait hostility, and state anxiety during the baseline were entered as covariates in an analysis of covariance (ANCOVA).

Afterwards, exploratory analyses were conducted to investigate potential psychological mechanisms underlying the effects of oxytocin and gender on rejection rates. We first explored whether drug administration and gender had significant effects on any of the four factors (i.e. sensitivity to provocation, norm adaptation rates, emotions/moods, and concern for money) and then tested whether these factors were correlated with rejection rates.

Estimation of provocation sensitivity and adaptation rates

Computational model fitting allowed us to test whether drug administration and gender influence individuals' sensitivity to provocation and norm adaptation rates. The inequality aversion model assumes that a responder does not only care about their payoff, but also cares about the extent of inequality in the UG (Fehr and Schmidt, 1999). Based on the inequality aversion model, the responder's utility (U) in trial i can be represented as follows (Xiang et al., 2013):

$$U(x_i) = x_i - \alpha \max\{f_i - x_i, 0\}$$

where $U(x_i)$ is the subjective utility of accepting a proposer's offer x_i. f_i is the offer a responder expects to receive (also called the "internal norm") (Gu et al., 2015). As an offer lower than one's expectation is likely to be considered provocative (or unfair) (e.g. Anderson and Bushman, 2002; Prasad et al., 2017), we used the $\max\{f_i - x_i, 0\}$ to represent provocation. It takes a positive value only when an offer is lower than expected, and zero otherwise. The parameter α reflects sensitivity to provocation ($\alpha \in [0,20]$) (Ahn et al., 2017). The larger the parameter α is, the more unlikely a responder will accept an offer below their expectation.

We complement this utility function with a softmax choice rule, which represents the probability of rejection (e.g. Gu et al., 2015; Xiang et al., 2013):

$$P\text{rejection} = \frac{1}{1+e\tau U(xi)}$$

where τ is inverse temperature parameter ($\tau \in [0,10]$) (Ahn et al., 2017). In essence, this choice rule modifies extent to which individuals base their decision on expected utility.

In the UG, individuals update their expectations of offers as a function of previously received offers (Gu et al., 2015; Xiang et al., 2013), in accordance with the general principle of adaptation to social norms (Montague and Lohrenz, 2007). This means that the perceived provocation (or unfairness) of the same objective offer amount can change over time. To capture this effect, we used the Rescorla-Wagner reinforcement algorithm (Rescorla and Wagner, 1972):$f_i = f_{i-1} + \varepsilon(x_i - f_{i-1})$

where ε is adaption rate (or learning rate) ($\varepsilon \in [0,1]$), which represents the extent to which the previous offer expectation (f_{i-1}) is updated by the experienced offer x_i (Ahn et al., 2017). The initial norm f_0 was fixed to be 10 (Ahn et al., 2017; Gu et al., 2015).

Another possible model may capture the adaptation process is a Bayesian observer model (details could be seen in Xiang et al., 2013). However, it has been found the Rescorla-Wagner model is superior than the Bayesian observer model in the UG (e.g. Gu et al., 2015). We implemented both learning models in our study and performed model comparison using the leave-one-out information criterion (LOOIC) and widely applicable information criterion scores (WAIC) (Ahn et al., 2017). The model-based analyses have two advantages: (i) the model captures the dynamic process of decision-making (e.g. expectation updating) (ii) it provides indicators representing norm adaption rate (ε) and sensitivity to provocation (α).

Parameter estimation was conducted via the hBayesDM package by using data from all participants and from each subgroup (i.e. oxytocin-men group, oxytocin-women group, placebo-men group, and placebo-women group) (Ahn et al., 2017). In the hBayesDM package, posterior inference of the parameters was performed with a Markov Chain Monte Carlo technique implemented in the Stan (Carpenter et al., 2017). We drew 1000 samples from an initial burn-in step and 4000 new samples with four chains. Gelman-Rubin convergence tests were conducted for each parameter (Gelman and Rubin, 1992). All latent variables had $\hat{R} < 1.05$, which indicated all chains converged. The posterior highest density interval (HDI) represented the uncertainty in the estimated parameters. If the 95% HDI did not overlap zero, the effect was considered significant (Carpenter et al., 2017). We tested whether differences in parameter values for each administration group (e.g. $\alpha_{\text{oxytocin}} - \alpha_{\text{placebo}}$) were significantly different between men and women.

2.3.1. Emotion and mood states

To test whether drug administration and gender modulate participants' emotion, we conducted ANOVAs on (i) emotion ratings during the UG (the emotion ratings in the 60% trials were averaged for each participant) and (ii) changes in mood states, including changes in positive affect (i.e. positive affect ratings after the games minus positive affect ratings during the baseline), changes in negative affect, and changes in state anxiety.

2.3.2. Concern for money

To test whether drug administration and gender affect participants' concern for money, an ANOVA was conducted on the amount of money given to participants themselves in the DG.

Table 1
. Mean (± standard deviation) scores of the trait anxiety, trait hostility, and baseline state anxiety in the different conditions.

	Men		Women	
	OT	PBO	OT	PBO
Trait anxiety	7.48 (3.14)	7.52 (3.86)	9.00 (3.01)	8.36 (3.15)
Trait hostility	6.52 (2.66)	6.28 (2.34)	6.76 (2.22)	6.32 (2.70)
Baseline state anxiety	36.44 (7.98)	38.4 (9.45)	38.64 (9.34)	41.16 (9.24)

Note: OT, the oxytocin group; PBO, the placebo group.

2.3.3. Correlations with rejection rates

After identifying significant effects of drug administration and gender on sensitivity to provocation, norm adaptation rates, emotions/moods, or concern for money, we tested whether those factors were correlated with rejection rates.

3. Results

3.1. Trait anxiety, trait hostility, and baseline state anxiety

The ANOVA showed no significant main effect of drug administration, gender, or an interaction effect of these factors on the trait anxiety, trait hostility, or baseline state anxiety, all $F < 1.89$, $p > 0.17$, partial $\eta^2 < 0.017$ (Table 1).

3.2. Rejection rates

The ANOVA showed no significant main effect of drug treatment (F[1,96] = 0.47, p = 0.49, partial η^2 = 0.005) or gender (F[1,96] = 0.63, p = 0.43, partial η^2 = 0.006). Importantly, the interaction effect of administration and gender was significant, F(1,96) = 4.26, p = 0.04, partial η^2 = 0.042 (Fig. 2). A simple effect analysis revealed that oxytocin compared with placebo administration significantly decreased the rejection rates among men (F[1,96] = 3.79, p = 0.05, partial η^2 = 0.038) but not among women (F[1,96] = 0.95, p = 0.33, partial η^2 = 0.010). In addition, the men's rejection rates were significantly higher than the women's rejection rates in the placebo condition (F[1,96] = 4.07, p = 0.04, partial η^2 = 0.041), which was consistent with the findings that men are more likely to engage in costly aggression than women (see meta-analysis by Archer, 2004). This gender difference was eliminated by the oxytocin administration, F(1,96) = 0.81, p = 0.37, partial η^2 = 0.008.

As a robustness check, the ANCOVA revealed that the interaction effect of drug administration and gender remained significant (F[1,93] = 4.18, p = 0.04, partial η^2 = 0.043), when the trait anxiety, trait hostility, and baseline state anxiety were entered as covariates. No significant covariate effect was found, all Fs < 1.03, ps > 0.31, partial η^2s < 0.011.

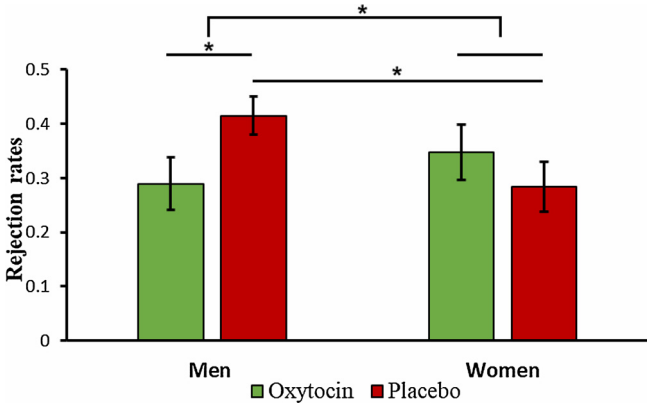

Fig. 2. The mean (± standard error) rejection rates in the different conditions. * denotes significance at the 5% level.

3.3. Provocation sensitivity and adaptation rates

Consistent with previous findings (Gu et al., 2015), the Rescorla-Wagner norm adaptation model fit the data better than the Bayesian norm adaptation model with lower overall LOOIC and WAIC scores (Figure S1). It was also the winning model for the oxytocin-men, oxytocin-women, placebo-men, and placebo-women subgroups separately. Therefore, the parameters from the Rescorla-Wagner model were used for subsequent analyses.

Oxytocin compared with placebo significantly decreased the parameters α among men (the 95% highest density interval [HDI] of the posterior distribution of $\alpha_{oxytocin} - \alpha_{placebo}$: [-2.25, -0.29], zero not covered) but not among women ($\alpha_{oxytocin} - \alpha_{placebo}$ 95% HDI: [-0.41, 2.14]) (Fig. 3). Oxytocin compared with placebo had no significant effect on the parameters ε or τ (see the supplementary material, Figure S2).

3.4. Emotion and mood states

There were no significant main effect of drug administration (F[1,96] = 0.16, p = 0.69, partial η^2 = 0.002) or gender (F[1,96] = 0.22, p = 0.64, partial η^2 = 0.002) on the changes in positive affect. A significant interaction effect of drug administration and gender was found (F[1,96] = 5.34, p = 0.02, partial η^2 = 0.053) (Fig. 4B). A simple effect analysis revealed that, compared with placebo, oxytocin did not significantly alter the changes in positive affect among women (F[1,96] = 1.84, p = 0.18, partial η^2 = 0.019). However, there was a trend towards oxytocin increasing the positive affect among men (F[1,96] = 3.66, p = 0.06, partial η^2 = 0.037). There was no significant main effect of drug administration, gender or their interaction on the emotion during the UG, changes in negative affect, or changes in state anxiety, all Fs < 0.96, ps > 0.33, partial η^2s < 0.010 (Fig. 4A, C, and D). The results of mood states during the baseline and after the games can be seen in the supplementary material (Figure S3), which also implicate that only positive affect was significantly impacted by drug administration and gender.

3.5. Concern for money

The ANOVA showed no significant effect of drug administration (F[1,95] = 1.18, p = 0.28, partial η^2 = 0.012), gender (F[1,95] < 0.01, p = 0.96, partial η^2 < 0.001), or their interaction (F[1,95] = 2.64, p = 0.11, partial η^2 = 0.027), on the amount of money participants allocated to themselves in the DG (Fig. 4E).

3.6. Correlations with rejection rates

Significant positive correlations between the parameters α and rejection rates were found across all participants (Pearson correlation r = 0.94, p < 0.001, n = 100) (Fig. 5A) and within each subgroup (see the supplementary material). There was no significant correlation between the changes in positive affect and rejection rates across all participants (r = -0.13, p = 0.20, n = 100) (Fig. 5B) or within each subgroup (see the supplementary material).

4. Discussion

Combining intranasal oxytocin administration with self-reported, behavioral and computational levels of measures, we examined the role of gender and oxytocin in human reactive aggression with the purpose of uncovering underlying psychological and computational mechanisms. Our results provide evidence that gender modulates the oxytocin's effect on human aggression, specifically, oxytocin administration

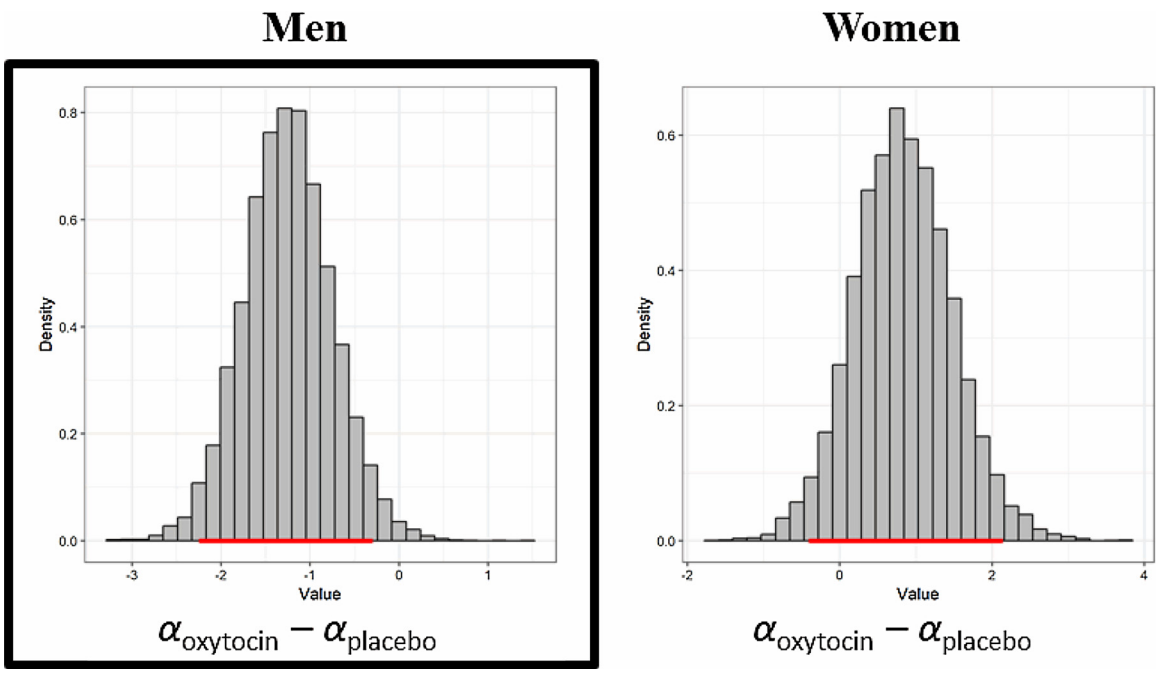

Fig. 3. The posterior distributions of the difference in the parameters α between the oxytocin and placebo groups, among men and women. The red line indicates the 95% HDI. The effect is significant, if the red line does not overlap zero. The significant result is marked with a black frame (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

reduces reactive aggression among men but not among women. Explorations on the underlying mechanisms indicated that oxytocin had distinct effects on men and women's sensitivity to provocation and positive mood changes. Sensitivity to provocation in particular showed a significant association with aggressive behaviour.

Previous studies have painted an inconsistent picture regarding the relationship between oxytocin and human aggression (de Jong and Neumann, 2017; Pfundmair et al., 2018). Considering that the social effects of oxytocin are largely modulated by social contexts and individual differences (for review, see Bartz et al., 2011), a solution to the problem of inconsistency may lie in identifying situational or dispositional features modulating oxytocin's effects. Our study showed that gender modulates oxytocin's effect on human reactive aggression, controlling for other potential modulators (i.e. trait anxiety, trait hostility, and state anxiety). The current results complement two lines of research investigating the links among oxytocin, gender/sex, and social cognition/behaviour. In the first line, many non-human animal studies show that oxytocin consistently inhibits aggression among male rodents, but not among female rodents (Bosch, 2013; Calcagnoli et al., 2015a, 2013; Calcagnoli et al., 2015b). In the second line, among humans, gender modulates oxytocin's effect on various psychological processing (e.g. social information processing) (for review, see Borland et al., 2019) and emotional experience (Kubzansky et al., 2012). Thus, our results extend the findings in non-human animals to humans and provide an important new demonstration that gender can play a critical role in the relationship between oxytocin and human behaviour (i.e. reactive aggression).

It is worth noting that the current findings offer further insights of the psychological and computational mechanisms underlying the effects of oxytocin on human reactive aggression, and its interaction with gender. In particular, our results revealed that oxytocin decreased sensitivity to provocation among men, but not among women. Moreover, we identified a significant correlation between the parameters α (i.e. sensitivity to provocation) and aggressive responses. Taken together, these findings suggest that for men, oxytocin decreases sensitivity to provocation, which drives reductions in aggression. Given that the amygdala is a brain region rich in oxytocin receptors (Boccia et al., 2013) and implicated in aggression (Van Elst et al., 2000), the decreased sensitivity to provocation could be due to the oxytocin's inhibitory effect on the amygdala activity among men. Specifically, functional magnetic resonance imaging (fMRI) studies have shown that oxytocin diminishes amygdala reactivity to provocative stimuli among men, but not among women (Domes et al., 2007, 2010). Some studies have revealed that the amygdala is crucially involved in the processing of and responses to provocative stimuli (Bishop, 2008; Gospic et al., 2011, but also see some exceptions in a nice review, Fanning et al., 2017). For instance, Gospic et al. (2011) reported that benzodiazepine administration dampened amygdala's response to social provocation, which led to reduced aggression. Likewise, previous studies using similar modelling techniques showed that parameters α (i.e. sensitivity to provocation) were correlated with activity in the amygdala (Tanaka et al., 2019). In short, evidence from different lines of research suggests that sensitivity to provocation serves as a critical psychological/computational process underlying the effects of oxytocin on human aggression, and our results add and extend this evidence by demonstrating an interaction with gender.

We next found an interactive effect of gender and oxytocin on changes in positive affect. The identified pattern of the changes in positive affect coincides with the pattern of the aggressive responses across different subgroups, suggesting that oxytocin may influence aggression via changes in positive affect. Previous studies have reported that oxytocin modulates individuals' mood states (Heinrichs et al., 2003; Kubzansky et al., 2012; Mah et al., 2013), which have been independently shown to play an important role in individuals' aggressive responses to provocation (Pillutla and Murnighan, 1996; Van't Wout et al., 2006). For instance, men who receive oxytocin administration report less negative affect following social stress, while women who receive oxytocin administration report more anger (Kubzansky et al., 2012). Moreover, individuals in a negative mood (e.g. sadness) are more inclined to react aggressively to social provocation than individuals in a neutral mood (Harlé and Sanfey, 2007). However, we did not observe a significant linear correlation between the changes in positive affect and rejection rates. Thus, our results partly advocate for the idea that oxytocin may influence aggression by modulating positive

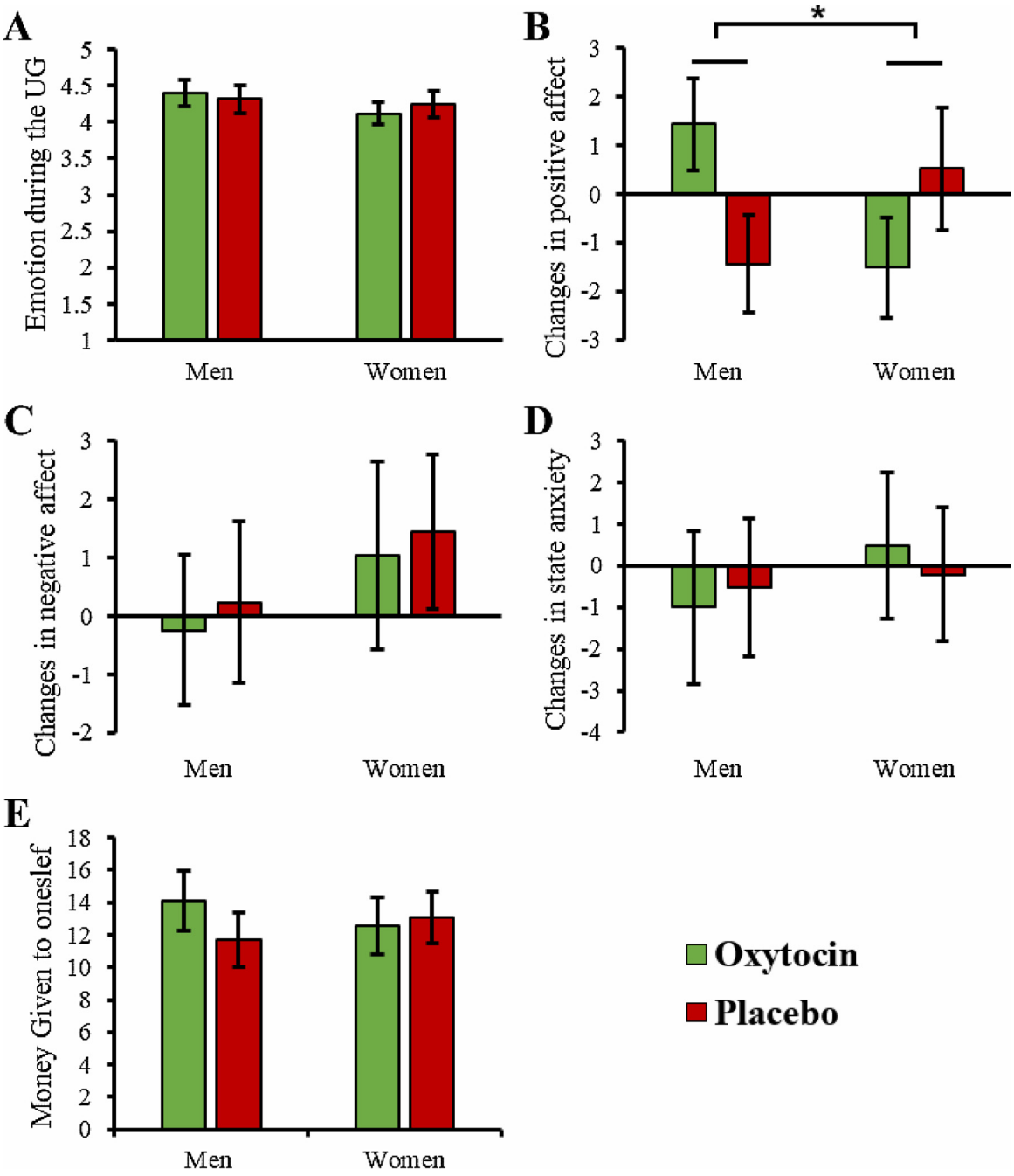

Fig. 4. The mean (± standard error) in the different conditions for A) the emotion ratings during the UG, B) changes in positive affect, C) changes in negative affect, D) changes in state anxiety, and E) amount of money participants allocated to themselves in the DG. * denotes significance at the 5% level.

affect.

Though negative mood and emotion, especially anger, are usually considered to serve as a bridge between provocation and aggression (e.g. Stadler et al., 2006), we did not find any significant effect of gender or oxytocin on changes in negative mood and emotion (i.e. unpleasantness) during the UG. One possible reason is that gender and oxytocin influence anger specifically, but not negative mood or emotion in general. The Positive Affect and Negative Affect Schedule has a item measuring feeling similar to anger (i.e. *"how hostile you feel now"*). Testing whether gender and oxytocin influence hostile mood state may provide some clues about whether gender and oxytocin affect anger mood state. The results showed that gender and oxytocin did not significantly affect the anger-like mood state (see Figure S4). As we did not measure participants' anger emotion during the UG, it leaves an open question whether anger emotion during the game was influenced by gender and oxytocin. Another possible reason is that mood or emotion state can be implicit or nonconscious. For example, a recent fMRI studies showed that participants holding different political ideologies (liberal or conservative) had different neural responses to a set of disgusting pictures, however, they gave similar (no significant difference was found) subjective ratings of disgusting to the pictures (Ahn et al., 2014). Moreover, the neural responses were highly predictive of participants' policical orientation (Ahn et al., 2014). Thus, as to our study, gender and oxytocin might have implicit effects on emotional states, which could be outside of awareness and not be detected by self-report. This hypothesis could be tested by future studies using neuroimaging techniques to investigate the brain mechanisms underlying the effects of gender and oxytocin on reactive aggression.

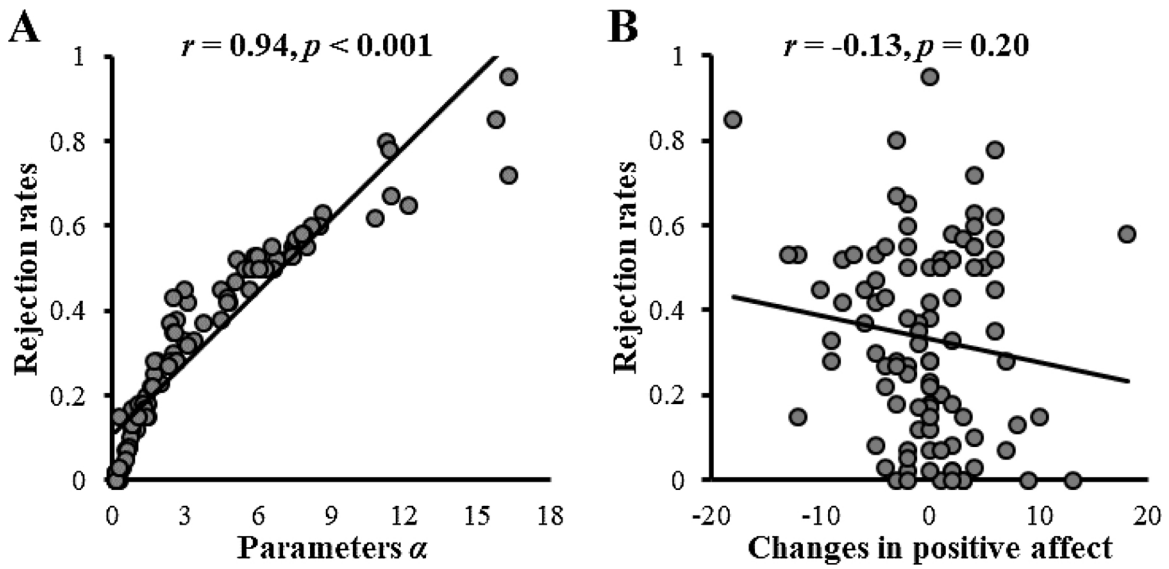

Fig. 5. Correlation scatterplots. A) The correlation between the rejection rates and parameter *α*. B) The correlation between the rejection rates and changes in positive affect.

We did not find a significant effect of oxytocin or gender on the rate of adaptation to social norms. However, Clark-Elford et al. (2014) reported that oxytocin decreased the rate of learning rewards from happy faces. This discrepancy in findings could be attributed to the different paradigms or the different psychological and computational mechanisms underlying the two types of learning processes. Our study revealed no significant effect of oxytocin or gender on the amount of money that the participants left for themselves in the DG. Previous studies have provided mixed evidence on the effect of oxytocin on concern for money: some findings suggest that oxytocin decreases individuals' concern for money (Barraza et al., 2011; Zak et al., 2007), yet other findings provided evidence for the opposite effect (Radke and de Bruijn, 2012). Some may argue that individuals' decision in the DG can be influenced not only by their concern for money but also by their attitude towards fairness. A cautious way to understand our finding may be that oxytocin and gender did not change the trade-off between concern for money and fairness. Overall, our results did not support the hypotheses that the decreased aggression among men are caused by the oxytocin's effects on norm adaption rates or concerns about the cost of aggression (i.e. concern for money).

One potential explanation of the gender interaction in oxytocin's effect on aggression is differences in men and women baseline oxytocin levels, and a non-monotonicity in the oxytocin-aggression dose-response curve. Specifically, women have higher baseline cerebrospinal fluid oxytocin levels than men (Altemus et al., 1999), thus if oxytocin acts on aggression as a U-shaped function, women baseline oxytocin levels may correspond to the center (minimal aggression), while men baseline levels may correspond to the left portion of the U-shape (near maximum aggression) (see Borland et al., 2019). Accordingly, augmenting oxytocin levels in women would facilitate aggression (a positive shift from the minimum point of the U-shape), while augmenting oxytocin levels in men would inhibit aggression (a positive shift toward the minimum point of the U-shape). Our findings are somewhat consistent with this explanation, in that we found oxytocin decreases aggression among men. We also observed a tendency towards oxytocin increasing aggression among women, however, this was not significant. In line with this hypothesis, results of previous studies regarding oxytocin's effect on social recognition (Bielsky and Young, 2004) and social reward processing (Borland et al., 2019; Feng et al., 2015; Rilling et al., 2014; Wei et al., 2003) are consistent with a non-monotonic dose-response relationship. Notably, we did not measure oxytocin levels, and therefore cannot provide direct evidence for this hypothesis. Nevertheless, converging evidence suggests the possibility of a U-shaped oxytocin-aggression dose-response curve (Borland et al., 2019), and as such it should be tested in future studies.

Two previous studies investigated the effect of intranasal oxytocin on responders' behaviour in the UG (Radke and de Bruijn, 2012; Zak et al., 2007). Both studies recruited only men as participants and found no significant effect of oxytocin administration on rejection rates. Our study is different from these studies in several vital aspects. In the study of Zak et al. (2007), participants made decisions in hypothetical situations, which may be interpreted and processed differently from decisions with real consequences (FeldmanHall et al., 2012). The study of Radke and de Bruijn (2012) employed a within-subjects design, in which all participants played a modified UG twice, under both administration conditions (oxytocin/placebo) in sequence. In the modified UG, participants were informed that in some conditions proposers had no choice but to offer an unfair division, while in the other conditions proposers were able to choose a fair alternative. The authors found that oxytocin administration tended to decrease aggression responses when proposers had a fair alternative, whereas an opposite pattern was identified when proposers had no alternative. However, these effects were eliminated when the order of drug administration was entered into the ANOVA as a covariate. Similarly, another oxytocin study on aggression also found a significant order effect of drug administration (Ne'eman et al., 2016). Thus, the order of drug administration may bring carry-over effects that confound oxytocin effects to studies employing a within-subjects design.

To broaden the understanding of oxytocin and aggression, future studies may extend our work in the following ways. Besides oxytocin, other neurotransmitters (e.g. testosterone) are also involved in aggressive behaviour (Svare, 2013). Future studies may adopt our paradigm to investigate their underlying mechanisms. As to aggression, we focused on reactive aggression measured by the UG. Another major type of aggression, proactive aggression, which is associated with different expressions, eliciting factors, and neural bases (Wrangham, 2018), is also worth studying in the future.

One limitation of our study is no assessment of anger during the game. Anger can play a predominant role in aggression under some conditions (Anderson and Bushman, 2002; Averill, 1983, also see an exception Zhu et al., 2018). Our study measured general valence (unpleasant/pleasant) instead of anger during the UG, mainly because a previous study using a similar paradigm (multi-round one-shot ultimatum game) showed that unpleasantness was involved in the decision-

making process during the UG (Xiang et al., 2013). Besides, evidence has been found that unpleasantness is significantly associated with aggression (Schultz et al., 2004). Future studies are called for investigating whether anger mediates the effects of gender and oxytocin on aggression. Another limitation is the lack of assessment of sex hormones, which could have allowed for more accurately identifying the menstrual cycle of women compared with self-reported menstrual information. It has been found that menstrual cycle of women affects their endogenous oxytocin concentration (see a nice review, Engel et al., 2019) and emotional experience (e.g. Wu et al., 2014). For future studies, it would be worth assessing sex hormones to better control for potential confounding of the menstrual cycle of women. In addition, our sample size was predetermined for finding a medium interaction effect of drug administration and gender on aggression in the ANOVOA. Larger samples are conductive to test whether there are small but solid effects of oxytocin (Walum et al., 2016).

In conclusion, our results reveal that gender modulates the effect of oxytocin on human reactive aggression, and that the inhibitory effect of oxytocin on reactive aggression in men is achieved via a change in their sensitivity to provocation and positive affect, but not norm adaptation rates or concern for money. These findings deepen our understanding of relationship between oxytocin and reactive aggression, and its underlying mechanisms, which have significant implications for the clinical application of oxytocin treatment in psychiatric aggressive disorders.

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Declaration of Competing Interest

The authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.06.016.

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