Oxytocin modulation of self-referential processing is partly replicable and sensitive to oxytocin receptor genotype

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ABSTRACT

Intranasal oxytocin (OXT) has been associated with effects on diverse social-emotional domains in humans, however progress towards a therapeutic application of OXT in disorders with social-emotion impairments is currently hampered by poor replicability. Limited statistical power and individual differences in biological factors, such as oxytocin receptor (OXTR) genetics, may have contributed to these variable findings. To this end, employing a validated oxytocin-sensitive trait judgment paradigm, we present a pharmaco-genetic study aiming at (1) replicating previous findings suggesting that intranasal oxytocin (24 IU) reduces the self-referential bias in a large sample of *n* = 170 male subjects, (2) determining whether variations in common receptor polymorphisms (rs237887, rs2268491, rs2254298, rs53576, rs2268498) influence sensitivity to oxytocin's behavioral effects. We confirmed that in the whole sample oxytocin influenced self-other distinction in terms of reduced decision time. However, oxytocin only influenced decision time in rs53576 G carriers, whereas effects on subsequent memory performance were only found in rs2268498 TT homozygotes. In summary, the current study partially replicates our previous findings showing that oxytocin reduces the self-referential bias and suggests that sensitivity to its effects in this domain are receptor genotype dependent.

Key words: self-other distinction; oxytocin; oxytocin receptor; trait judgment; genotype

INTRODUCTION

During the last decade the number of intranasal oxytocin (OXT) administration studies has steadily increased, with it being proposed to facilitate social interaction by increasing trust (Kosfeld et al., 2005), emotional empathy (Geng et al., 2018b), 'mind-reading' (Domes et al., 2007) and decreasing self-referential bias (Zhao et al., 2016). Such findings have inspired the hypothesis that OXT has the potential to alleviate social interaction deficits in psychiatric disorders and led to initial clinical trials in patients with some promising, but also variable therapeutic outcomes (Keech et al., 2018).

Despite initial promise, in recent years the field has been increasingly faced with critical evaluations of OXT's effects on complex social behavior in humans (e.g. Leng and Ludwig, 2016 but see Quintana and Woolley, 2016). Particularly, low statistical power (Bartz et al., 2011; Walum et al., 2016) and replicability of findings (Nave et al., 2015) of intranasal OXT administration experiments have become a matter of growing concern and impede progress towards the clinical application of intranasal OXT. Indeed, recent comprehensive replication studies in healthy individuals failed to replicate modulatory effects of intranasal OXT on core domains initially associated with OXT, including 'mind reading' (Domes et al., 2007; Radke and de Bruijn, 2015) as well as trust - both when money (Kosfeld et al., 2005; contrasting findings Yao et al., 2014 , critical review Nave et al., 2015) or confidential personal information were at stake (see review Xu et al., 2019).

To explain the variable influence of OXT on social behavior, moderating effects of personal and contextual factors have increasingly moved into focus (Bartz et al., 2011). With respect to personal factors, converging evidence points to the important role of biological factors including sex (Feng et al., 2015b; Gao et al., 2016) and genetic variations, particularly individual differences in oxytocin-receptor gene (OXTR; located on chromosome 3p25, consists of three introns and four exons) polymorphisms (Feng et al., 2015a; Montag et al., 2013).

Molecular genetic studies have reported associations between individual variations in a number of single nucleotide polymorphisms (SNPs) of the OXTR gene and behavioral and neural differences in core social-emotional processes (see Jurek and Neumann, 2018). Several SNPs located in the 3rd or 4th introns of the OXTR gene have been associated with prosociality, trait empathy and autism, most notably rs53576 and rs2254298 which have been associated with autism (Cataldo et al., 2018), deficits in social and emotional processing and anxiety (Jurek and Neumann, 2018; Parker et al., 2014; Yang et al., 2017). However, it should be emphasized that meta-analytic approaches have failed to confirm robust associations between the OXTR rs53576 and rs2254298 on social-emotional behavior (Bakermans-Kranenburg and van IJzendoorn, 2014), although a more recent meta-analysis demonstrated an association between OXTR rs53576 and empathy (Gong et al., 2017). Other intronic SNPs such as rs2268491 and rs237897 have also been associated with autism and trait empathy (see Jurek and Neumann, 2018). However, to date none of these SNPs have been shown to have a regulatory role on the OXTR. Only one SNP located in the 5' promoter region of the OXTR gene, rs2268498, associated with prosociality (Christ et al., 2016; Melchers et al., 2015) and trait autism (Montag et al., 2017) has been shown to regulate mRNA expression (Reuter et al., 2016).

An increasing number of pharmaco-genetic studies have begun to explore whether individual differences in OXTR genetics influence the behavioral and neural sensitivity to intranasal OXT. In healthy subjects modulatory effects have been reported in the domains of facial emotion recognition (Kou et al., 2018; Montag et al., 2013), social salience (Feng et al., 2015a), and cooperation (Feng et al., 2015b) suggesting that individual differences in OXTR genetics may account for the variable effects of intranasal OXT on interpersonal behavior. Initial studies have begun to explore the clinical relevance of OXTR-modulated sensitivity in patient populations and suggest that the therapeutic relevant actions of intranasal OXT vary as a function of OXTR genotype (Kosaka et al., 2016; Watanabe et al., 2017).

Interpersonal behavior is shaped by perception of the interaction partner, yet also by the perceived differentiation between self and others (Zhu et al., 2007). The distinction between self and others is commonly operationalized as self-referential processing (Northoff et al., 2006), that is biased processing of contents that are self-related, including biased evaluation times for (Seger et al., 2004; Zhao et al., 2016) and remembering (Rogers et al., 1977; Zhao et al., 2016; Zhu et al., 2007) personality traits pertaining to the self as opposed to others. Accumulating evidence suggests that OXT regulates self-referential processing (Cardoso et al., 2012b; Colonnello et al., 2013), which together with enhanced emotional empathy (Geng et al., 2018a, 2018b) may underlie OXT facilitation of social interaction. For instance, in a previous study we combined intranasal administration of OXT with a self-referential task including self and other trait judgments and found that it reduced response times for both self and other trait judgments (i.e. facilitated decision making during judgments), decreased the accuracy of the subsequent recall of self-judgments and reduced medial prefrontal cortex responses to self judgments. Together these findings suggest that OXT reduces the self-referential bias and increases responsivity to others (Zhao et al., 2016).

In the context of improving methodological standards in the field, particularly increased statistical power and replication, as well as increasing evidence for OXTR-modulated individual differences in the sensitivity to intranasal OXT effects, the present randomized placebo-controlled double-blind between-subjects pharmaco-genetic intranasal OXT administration study aimed to (1) determine the replicability of our previous findings (n = 38, male subjects) suggesting that intranasal OXT reduces the bias for self-referential trait judgments (Zhao et al., 2016), in a cohort that is over four times larger (n = 170, male subjects), (2) determine whether the sensitivity to treatment effects in this domain is modulated by individual variations in OXTR genetics. We expected that (1) in line with our previous findings OXT would reduce reaction time for both self and other trait judgments and reduce their subsequent recall, (2) treatment effects would vary as a function of OXTR genotype.

MATERIALS AND METHODS

Participants

In a double-blind, between-subject placebo (PLC) controlled design, a total of 170 (M_{age} = 21.26 years, *SD* = 2.49 years) healthy male participants were randomly assigned to receive a single dose of 24 IU OXT (Sichuan Meike Pharmaceutical Co. Ltd, Sichuan, China; ingredients: oxytocin, glycerine, sodium chloride and purified water) (*n* = 86) or placebo (PLC, supplied by the same company with identical ingredients except for oxytocin) (*n* = 84). Treatment was administered following a standardized administartion protocol. The experimental asessments started 45 minutes after administration, the present paradigm was preceded by another behavioral task reported in a separate publication (Sindermann et al., 2018). Participants could not determine better than chance whether they had received PLC or OXT (χ^2 = 2.35, *p* = 0.13) confirming successful double blinding. Sample size was determined by estimating the power required to detect the primary outcome of interest, that is between-group differences (OXT vs. PLC) in reaction time and memory responses. Our previous study yielded between group differences in reaction times of *d* = 0.59 and memory of *d* = 0.95. Thus, we took a conservative approach and estimated a medium effect size to *d* = 0.5, which resulted in a requirement for 85 subjects to achieve 90% statistical power at *p* = 0.05. This level of statistical power (90%) is considerably higher than the average oxytocin study in healthy controls, which has been reported as 16% (Walum et al., 2016).

A total of *n* = 176 Chinese male (M_{age} = 21.33 years, *SD* = 2.48 years) were enrolled (Chengdu Gene Brain Behaviour Project, CGBBP). Participants were required to abstain from caffeine, alcohol, nicotine or other psychoactive substances in the 24h before the experiment. Exclusion criteria were any self-reported psychiatric illness, drug or alcohol abuse, left-handedness, or missing responses during the paradigm, leading to a sample size of *n* = 170 participants for the final analyses. The study was approved by the local ethics committee of the University of Electronic Science and Technology of China and the procedures were in accordance with the latest revision of the declaration of Helsinki. All

subjects provided written informed consent and received monetary compensation for their participation.

Experimental design, procedures and protocols

Before treatment, participants completed self-report questionnaires to account for potential between group differences in important confounders, including general confounders such as personality (NEO-Five Factor Inventory), depression (Beck Depression Inventory II), current mood and anxiety (Positive Affect and Negative Affect Schedule; State-Trait Anxiety Inventory), as well as traits with direct relevance to the paradigm (Inclusion of Others in Self; Self-Construal Scale). For genotyping all subjects additionally provided buccal swaps.

Subsequently, subjects were randomly allocated to receive either OXT or PLC and underwent a self vs. other trait judgment paradigm. Following a 4s instruction, subjects were asked to judge whether either a positive or negative adjective displayed described themselves, their mother (an extended self in Chinese culture) or a stranger. A "stranger" condition was used rather than a "famous person/celebrity" to include an unfamiliar other category (Zhao et al., 2016). The subjects were asked to imagine a male stranger and judge whether the displayed adjective was suitable to describe him. One of eight adjectives in each block (2 blocks in each judgment condition, i.e. 6 blocks in total) was presented (positive and negative words were balanced) and subjects made a judgment by button press (yes or no) within a time window of 2s. A 'cue' word (self, mother or a stranger) was displayed above the written trait adjective word (presented centered on the screen, **Figure 1**). In the subsequent "surprise" memory test, 24 trait adjectives (half positively and half negatively valenced) were randomly intermixed with 24 new trait adjectives, and subjects required to identify old vs. new items presented in a random order. The stimuli and design were identical to our previous study except for: (1) the number of blocks was decreased due to the high sensitivity observed in the previous study (2) additional conditions that served as baseline or control conditions during the previous fMRI study (classmate, font, and asterisk) were not included. All adjectives were displayed as two Chinese character words and balanced valence and arousal (Zhao et al., 2016).

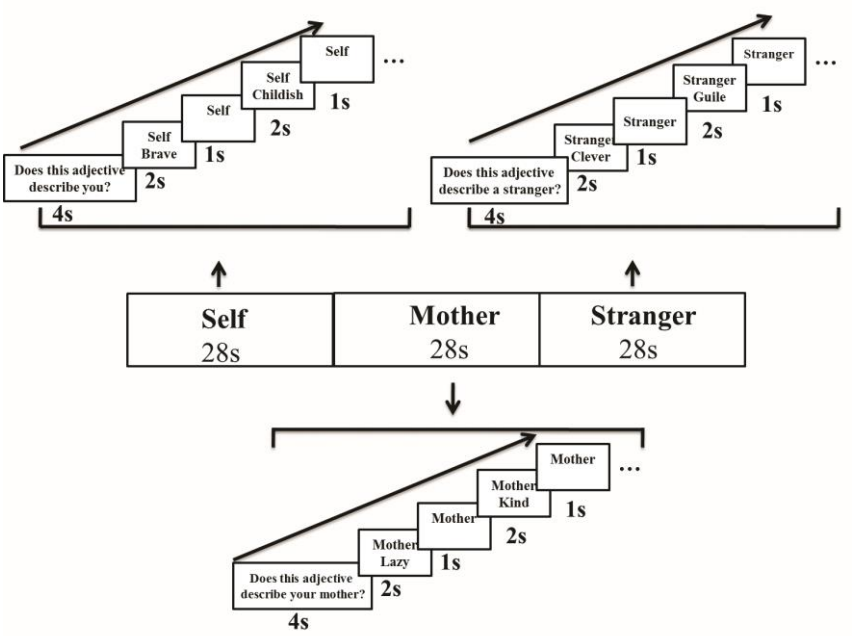

Figure 1. Trait-judgment task.

Data analyses

Independent *t* tests were first conducted to determine whether there were significant differences between the OXT and PLC treatment groups in terms of age, personality, mood, anxiety, depression, self-construct scores and Inclusion of Others in Self for "mother" scores. Based on our previous findings, primary outcome parameters to evaluate the effects of OXT were response time (RT) for the trait judgments and accuracy during the recognition memory test (Zhao et al., 2016). Behavioral indices (RT and memory accuracy) were analyzed using mixed ANOVAs with the between subject factor treatment (OXT vs. PLC) and within subject factor condition (self, mother, stranger) and valence (positive vs. negative). To identify the modulation of OXTR genetic variations, OXTR genotype was included as an additional between-subject factor (i.e. rs2268498 C+ carriers vs. TT genotype) in the subsequent mixed four-way ANOVA models. A total of five SNP-specific mixed ANOVA models were conducted to evaluate the modulation of OXTR genetics on the treatment effects. To control for false positives the *p* values were corrected for the number of SNPs. Post-hoc tests employed appropriate Bonferroni correction to further specify significant main and interaction effects. In addition, to further examine whether the observed effects of OXT on RT and accuracy were

associated, Pearson correlations were conducted in separate treatment groups as well as the different OXTR SNPs groups.

Genotyping analyses

DNA was extracted from participants' buccal cells. Automated purification of genomic DNA was conducted using a MagNA Pure 96 machine and commercial extraction kits (Roche Diagnostics, Mannheim, Germany). Five common OXTR SNPs were chosen based on previous studies suggesting associations with social behavior (OXTR rs237887, rs2268491, rs2254298, rs53576, rs2268498; see. Jurek and Neuromann, 2018; Feng et al., 2015b). Genotyping of the OXTR SNPs was performed by real-time polymerase chain reaction (PCR) and subsequent melting curve detection using a Cobas Z 480 Light Cycler (Roche Diagnostics, Mannheim, Germany). With the melting curve analyses, the alleles in each SNP were distinguished by different fluorescent labels of allele-specific oligonucleotide probe pairs. Simple probe assay designs from TIBMolBiol (Berlin, Germany) were used.

RESULTS

There were no significant differences between the OXT (n = 86) and PLC (n = 84) treatment groups in terms of age, personality, mood, anxiety, depression or self-construct scores. Importantly, there were also no significant differences between scores on Inclusion of Others in Self for "mother" between the two groups (ps > 0.12) (**Table 1**).

Table 1 Ages and questionnaire scores for study subjects in both groups (mean ± SD).

Measurements	Placebo (n = 84)	Oxytocin (n = 86)	t-value	p-value
Age (years)	21.26±2.49	21.16±2.43	0.26	0.79
Positive and Negative Affective Scale -Positive	30.17±5.65	29.15±6.58	0.70	0.49
Positive and Negative Affective Scale -Negative	17.35±5.54	18.20±6.79	0.90	0.37
Beck Depression Inventory	5.90±6.91	6.12±7.34	0.19	0.85
State-Trait Anxiety Inventory -State	38.04±7.88	38.39±9.04	0.27	0.79
State-Trait Anxiety Inventory -Trait	41.00±7.76	40.50±8.03	0.41	0.69
NEO-Five Factor Inventory				
Neuroticism	33.95±7.15	34.21±7.30	0.23	0.82
Extraversion	38.38±5.22	38.86±5.67	0.57	0.57
Openness to experience	39.80±5.48	39.58±5.13	0.27	0.79
Agreeableness	42.14±4.96	41.81±5.30	0.42	0.68
Conscientiousness	40.68±5.01	40.96±5.55	0.35	0.73
Self-Construal Scale -independent	72.96±9.69	72.81±10.05	0.09	0.93
Self-Construal Scale - interdependent	74.42±9.34	75.63±9.92	0.73	0.47
Inclusion of Others in Self -mother	4.87±1.29	4.57±1.19	1.57	0.12

Distribution of genotypes

In the current sample, distribution of SNP genotypes was in the Hardy–Weinberg equilibrium (HWE); for rs237887, GG = 55, GA = 85, AA = 30 [n = 170, HWE: χ^2 = 0.08, p =0.77]; for rs2254298, GG = 79, GA = 75, AA = 16 (n = 170, HWE: χ^2 = 0.09, p = 0.77); for rs2268491, CC = 80, CT = 74, TT = 15 (n = 169, HWE: χ^2 = 0.13, p = 0.72); for rs2268498, CC = 11, CT = 74, TT = 84 (n = 169, HWE: χ^2 = 0.99, p = 0.32); for rs53576, AA = 87, AG = 65, GG = 13 (n = 165, HWE: χ^2 = 0.03, p = 0.86).

Table 1 Ages and questionnaire scores for study subjects in both groups (mean ± SD).

To increase statistical power and avoid statistical inference errors due to the small sample size of the GG group, we grouped the alleles into G+ (GG/AG, 78 males: 40 in OXT group, 38 in PLC group) and G- (AA, 87 males: 43 in OXT group, 44 in PLC group) for rs53576 in the judgment task analysis (Shao et al., 2018). In addition, there were no significant differences between G+ and G- allele groups across OXT and PLC groups in all questionnaires mentioned above (ps > 0.09), indicating confounders were controlled for. For rs2268498, we grouped the alleles into C+ (CC/ CT, 83 males: 40 in OXT group, 43 in PLC group) and C- (TT, 83 males: 44 in OXT group, 39 in PLC group) in the memory performance

task analysis. No significant group differences between C+ and C- allele groups across OXT and PLC groups were found in confounding factors (*p*s > 0.11).

Intranasal OXT effects on self-other distinction

In an initial analysis step the replicability of the effects of intranasal OXT on self- other processing independent of genotype was evaluated (see Table 2). We performed a mixed three-way ANOVA with treatment (OXT vs. PLC) as between-subject factor, condition (self, mother, stranger) and valence (positive vs. negative) as within-subject factors, and RT as dependent variable. Results revealed a significant main effect of condition [$F_{(2,336)} = 21.67$, $p < 0.001$, $\eta^2 = 0.11$] suggesting faster self ($p < 0.001$, Cohen's $d = 0.48$) and mother ($p < 0.001$, Cohen's $d = 0.36$) judgments compared with stranger judgments across the two treatment groups, as well as significant main effects of valence [$F_{(1,168)} = 16.12$, $p < 0.001$, $\eta^2 = 0.09$] and treatment [$F_{(1,168)} = 5.55$, $p = 0.02$, $\eta^2 = 0.03$]. In addition, condition x treatment [$F_{(2,336)} = 6.46$, $p = 0.002$, $\eta^2 = 0.04$] and condition x valence [$F_{(2,336)} = 18.25$, $p < 0.001$, $\eta^2 = 0.10$] interactions were significant. Post-hoc analysis of the interaction between condition and treatment with Bonferroni correction suggested that OXT decreased RTs across all conditions but only reached significance in the stranger condition ($p = 0.001$, Cohen's $d = 0.54$). In the PLC group, RTs for judging stranger's traits were slower than for self ($p < 0.001$, Cohen's $d = 0.65$) and for mother ($p < 0.001$, Cohen's $d = 0.62$, **Figure 2A**). In the OXT group there was a significant difference between self and stranger ($p = 0.013$, Cohen's $d = 0.30$), but not between self and mother (p = 0.1).

Table 2 Tabular presentation of the oxytocin effects in the original study (Zhao et al., 2016) and the present study.

Results from Zhao et al., 2016	Present study
Reaction time (RT)	
(1) OXT decreased RT across all conditions (main effect of treatment)	Replicated
(2) Interaction effect between treatment and condition: OXT decreased RT in the stranger condition	Replicated
(3) In the PLC group, RTs for judging stranger's traits were slower than for self and for mother	Replicated
Memory performance	
(1) Significant three-way interaction effect between treatment, valence and condition: OXT decreased memory accuracy for negatively valenced trait adjectives for 'stranger' relative to PLC.	Three way interaction was not found in the in entire sample. However, it was found in rs2268498 TT homozygotes.

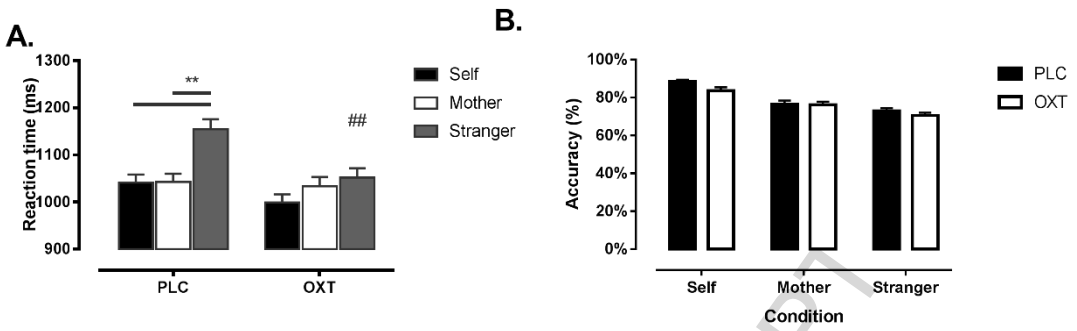

Figure 2. The effects of OXT on reaction time for judging adjectives and memory performance.

Due to technical problems (missing responses), three subjects (n = 1 OXT, n = 2 PLC) were additionally excluded from the subsequent memory analysis. A concordant three-way mixed ANOVA with recognition accuracy as dependent variable revealed significant main effects of condition [$F_{(2,330)}$ = 74.14, p < 0.001, η^2 = 0.31, reflecting better memory performance in self condition compared to mother condition (p < 0.001, Cohen's d = 0.77) and stranger condition (p < 0.001, Cohen's d = 1.07)] and valence [$F_{(1,165)}$ = 14.76, p < 0.001, η^2 = 0.08, due to higher accuracy to positive vs. negative valence adjectives (p < 0.001, Cohen's d = 0.38)] but there was no significant main effect of treatment [$F_{(1,165)}$ = 2.03, p = 0.16]. In addition, there was a significant two-way interaction between condition and valence [$F_{(2,330)}$ = 5.87, p = 0.003, η^2 = 0.03], due to higher accuracy for remembering positive adjective words compared to negative words in self (p = 0.02, Cohen's d = 0.21) and stranger conditions (p < 0.001, Cohen's d = 0.48). In contrast with our previous findings no significant three-way interaction between condition, valence and treatment was observed [$F_{(2,330)}$ = 0.79, p = 0.45]. To increase transparency we additionally added the OXT vs placebo effects on recall memory in Figure 2B [two-way interaction between condition and treatment was not significant, $F_{(2,330)}$ = 1.42, p = 0.24]. However, based on the findings from

our previous study demonstrating an effect of OXT on self-referential memory we specifically explored this effect in the treatment groups separately. Following PLC, a higher accuracy for recognizing both, positively and negatively valenced adjectives for self as compared to mother (*ps* < 0.001) or stranger (*ps* < 0.001) was observed. In contrast, following OXT there was no difference between mother and stranger conditions for recognition accuracy of negative trait adjectives ($p = 0.62$).

To further examine whether the observed effects of OXT on RT and accuracy were associated, a Pearson correlation was conducted but, in agreement with our previous study (Zhao et al., 2016), no significant associations were found within the treatment groups (*r*s = [-0.185, 0.16], *p*s > 0.10), suggesting that effects on the two domains of self- versus other processing are independent.

Interaction effects between OXTR genetics and intranasal OXT effects

To identify the modulation of OXTR genetic variations, OXTR genotype was included as an additional between-subject factor in subsequent SNP-specific mixed ANOVA models.

For RT, we did not find any significant interaction effects across treatment, genotype, condition and valence for OXTR rs2254298, rs2268491, rs237887, rs2268498 (*F*s <1.06, *ps* > 0.38). A significant four-way interaction effect was found for rs53576 [$F_{(4,318)} = 3.91$, $p = 0.004$- ($p_{\text{Bonferroni (corrected for SNPs}} = 0.02$)]. To further disentangle this interaction effect three-way ANOVAs [treatment×condition×valence] were performed for each OXTR rs53576 genotype (AA and G+ carriers). With respect to treatment effects a significant two-way interaction between treatment and condition [$F_{(2,152)} = 4.15$, $p = 0.018$, $\eta^2 = 0.05$, **Figure 3A**] and a significant three-way interaction between treatment, condition and valence [$F_{(2,152)} = 5.35$, $p = 0.006$, $\eta^2 = 0.07$] were observed in the G+ group but not observed in AA [$F_{(2,170)} = 1.80$, $p = 0.17$, **Figure 3B**]. Bonferroni-corrected post-hoc tests of the two-way interaction between treatment and condition revealed that the G+ group under PLC exhibited slower RTs judging trait adjectives of a stranger compared to self ($p < 0.001$, Cohen's $d = 0.74$) or mother ($p < 0.001$, Cohen's $d = 0.64$), whereas no such differences were observed in the G+ group

treated with OXT (all *ps* > 0.29). Post-hoc tests directly comparing the conditions between the G+ treatment groups further revealed significantly decreased RTs for the stranger condition following OXT relative to PLC [$p = 0.002$, Cohen's $d = 0.73$] (**Figure 3A**).

Moreover, in genotype-specific three-way ANOVAs [treatment×condition×valence] for rs53576 the following effects that did not involve treatment were observed: In the AA group significant main effects of condition [$F_{(2,170)} = 10.79$, $p < 0.001$, $\eta^2 = 0.11$] and valence [$F_{(1,85)} = 12.54$, $p < 0.001$, $\eta^2 = 0.13$] and a significant interaction between condition and valence [$F_{(2,170)} = 14.77$, $p < 0.001$, $\eta^2 = 0.15$] were observed. For the G+ group a main effect of condition [$F_{(2,152)} = 12.73$, $p < 0.001$, $\eta^2 = 0.14$], valence [$F_{(1,76)} = 4.93$, $p = 0.03$, $\eta^2 = 0.06$], and a significant two-way interaction between condition and valence [$F_{(2,152)} = 9.03$, $p < 0.001$, $\eta^2 = 0.11$] were observed. Significant main effect of treatment was found in G+ group [$F_{(1,76)} = 5.36$, $p = 0.02$, $\eta^2 = 0.07$] but not in AA group [$F_{(1,85)} = 0.89$, $p = 0.35$].

A four-way mixed ANOVA examining subsequent memory accuracy revealed no significant interactions involving treatment, genotype, condition and valence for OXTR rs2254298, rs2268491, rs237887, rs53576 (*F*s < 1.60, *p*s > 0.17). For rs2268498 a significant four-way interaction was found [$F_{(2,324)} = 4.66$, $p = 0.01$- ($p_{\text{Bonferroni}} = 0.05$)]. To further disentangle this interaction three-way ANOVAs [treatment×condition×valence] were performed separately in the rs2268498 C+ and TT groups. With respect to treatment effects a significant three-way interaction involving condition, valence and treatment was found in the rs2268498 TT carriers [$F_{(2,162)} = 3.10$, $p = 0.05$, $\eta^2 = 0.04$, **Figure 3C**] but was not found in C+ carriers [$F_{(2,162)} = 2.52$, $p = 0.09$,**Figure 3D**]. Bonferroni corrected post- hoc analysis suggested that in the TT group OXT decreased memory accuracy for negatively valenced trait adjectives for 'stranger' relative to PLC [$F_{(1,81)} = 6.31$, $p = 0.01$, Cohen's $d = 0.55$] (**Figure 3C**). Moreover, in both treatment groups accuracy of remembering trait adjectives in the self condition was better than for mother and stranger (all *p*s < 0.02).

Moreover, in genotype-specific three-way ANOVAs [treatment×condition×valence] for the rs2268498 the following effects that did not involve treatment were observed: For

rs2268498 C+ carriers significant main effects of condition [$F_{(2,162)} = 33.73$, $p < 0.001$, $\eta^2 = 0.29$] and valence [$F_{(1,81)} = 7.78$, $p = 0.007$, $\eta^2 = 0.09$] were observed. For the TT genotype, main effects of condition [$F_{(2,162)} = 43.28$, $p < 0.001$, $\eta^2 = 0.35$] and valence [$F_{(1,81)} = 6.99$, $p = 0.01$, $\eta^2 = 0.08$] as well as a two-way interaction between condition and valence [$F_{(2,162)} = 3.75$, $p = 0.03$, $\eta^2 = 0.04$] reached significance.

Finally, a correlation analysis between RTs for judging words and accuracy of subsequent memory in these two different OXTR genotype groups across OXT and PLC (*p*s > 0.08) again did not reveal significant associations.

Together, the results from the analyses examining interaction effects between treatment and OXTR polymorphisms suggest that the effects of intranasal OXT on RTs may have been driven by pronounced effects in G carriers of OXTR rs53576, whereas effects on memory performance may have been driven by TT carriers of OXTR rs2268498.

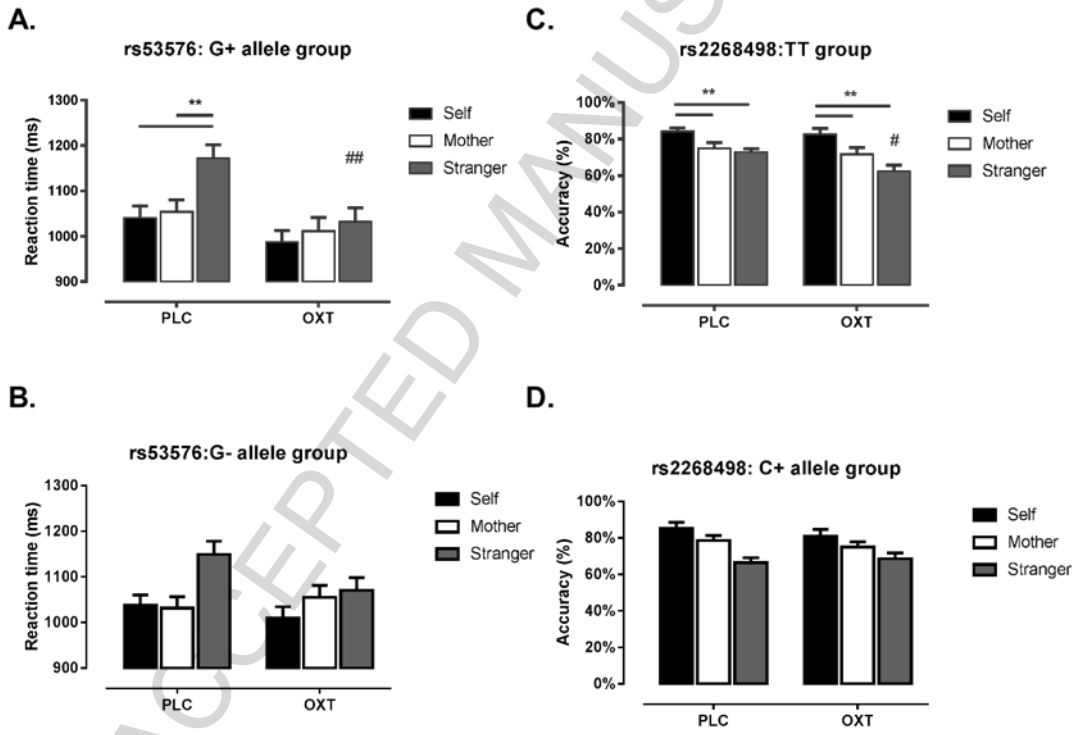

Figure 3. The effects of OXT on reaction time and memory performance were modulated by individual differences in OXTR genotype.

DISCUSSION

The present study aimed at determining the robustness of effects of intranasal OXT on self-other processing as well as their modulation by individual differences in OXTR genotype. Combining a previously validated and intranasal OXT-sensitive self-referential paradigm with a behavioral genetic approach in a large sample (n = 170) with sufficient statistical power allowed us to replicate that intranasal OXT abolished the self-referential bias in terms of reaction times during trait judgments (Zhao et al., 2016). Sensitivity to the behavioral effects of OXT on the self-referential bias was also modulated by individual differences in OXTR genotype, specifically trait judgment RTs were reduced more in G carriers of rs53576 relative to the AA genotype. The effects of OXT on the additional dimension of memory performance could not be fully replicated in the entire sample, although including genotype in the analysis revealed that T allele carriers of rs2268498 exhibited some of the previously found effects of OXT suggesting that this genotype is specifically sensitive to these memory effects of OXT.

In line with our previous and other findings (Seger et al., 2004; Zhao et al., 2016) we confirmed that there is a self-referential bias in terms of faster RTs when evaluating self vs other (stranger) trait adjectives. We also confirmed that intranasal OXT reduced this self-referential bias by decreasing RTs for judging the traits of a stranger thereby replicating our previous study (Zhao et al., 2016). Although initial studies reported that intranasal OXT may enhance positive self-evaluation (Cardoso et al., 2012a) or increase differential neural processing of self vs. celebrity judgements (Liu et al., 2013), the present findings demonstrated that OXT may rather attenuate the self-referential processing bias. These findings are in line with a growing number of recent studies reporting that intranasal OXT promotes self-other integration (Ruissen and de Bruijn, 2015), facilitates perception of other- but not self-experienced pain (Chen and Johnson, 2012), and increases other-orientation (Bartz et al., 2015). Studies that concurrently assessed eye gaze or neural activity suggest that OXT-enhanced other orientation specifically affects implicit processing (Pfundmair et al., 2018) and is mediated by modulatory effects on brain regions engaged in self-referential processes, particularly the medial prefrontal cortex (Zhao et al., 2017, 2016).

An overarching aim of the present study was to determine the robustness of OXT's effects on self-referential processing using a sufficiently powered design (Bartz et al., 2011; Nave et al., 2015; Walum et al., 2016). Despite failed replication attempts of OXT's modulatory effects in the domains of 'mind reading' (Domes et al., 2007; Radke and de Bruijn, 2015) and trust (Kosfeld et al., 2005; Nave et al., 2015) the present findings resonate with recent findings demonstrating the replicability of OXT-enhanced emotional empathy (Hurlemann et al., 2010; Geng et al., 2018b). It is unlikely that OXT exerts effects on all aspects on social cognition, thus it is important to identify which specific aspects it does modulate robustly. Together with the present results, these current findings indicate an important role of OXT in increasing other-orientation which may represent a common denominator underlying its potential to facilitate social interaction.

In line with increasing evidence for the modulation of intranasal OXT effects by biological factors including OXTR genetics (Feng et al., 2015a; Montag et al., 2013) and that OXTR expression patterns in the human brain are associated with social cognition (Quintana et al., 2019), a second aim of the present study was to determine whether the sensitivity to the behavioral effects of intranasal OXT varies as a function of individual differences in OXTR genotype. Of the five common OXTR variants that were examined only rs53576 and rs2268498 modulated individual sensitivity to intranasal OXT. Specifically, in G carriers of rs53576 accelerated trait judgements were observed in the non-self referential condition, suggesting that subjects with this polymorphism may have an increased sensitivity to intranasal OXT effects on speed of making social evaluation decisions. The OXTR rs53576 SNP has been associated with affiliative behaviour (Feldman et al., 2016), with GG carriers demonstrating more sensitive parental interaction (Bakermans-Kranenburg and van IJzendoorn, 2008), continuous attachment security (Lee Raby et al., 2013), higher sociability (Li et al., 2015) and empathy (Rodrigues et al., 2009) as well as higher psychological resources and prosocial temperament (Tost et al., 2010). Together with a previous report on pronounced effects of intranasal OXT-enhanced preference for highly salient social stimuli (infant faces) (Marsh et al., 2012) and social cooperation in male participants (Feng et al.,

2015b) as well as neural and behavioural effects in autistic individuals (Watanabe et al., 2017), the present findings suggest that the G allele promotes effects of intranasal OXT on other orientation. While G- carriers have primarily been associated with prosocial attributes, A- carriers have been associated more with impaired social attributes in the context of autism and empathy (Jurek and Neumann, 2018). A study reported that intranasal oxytocin suppression of amygdala responses to fear faces and behavioural ratings of fear intensity to were restricted to AA homozygotes of OXTR rs53576 (Kou et al., 2018). This may reflect a greater association of OXT effects on the amygdala in A-carriers and those on the medial prefrontal cortex on G-carriers. Thus, specific OXTR genotype modulation of intranasal OXT effects may be both region and task specific.

Although previous findings on interaction effects involving self-other condition, valence and treatment during the subsequent recognition memory test in the paradigm could not be replicated (Zhao et al., 2016), including OXTR genotype as an additional factor in the analysis revealed that intranasal OXT decreased memory performance for negatively valenced words during the stranger condition specifically for rs2268498 T homozygotes but not C carriers. Previous studies reported that the rs2268498 T homozygotes had higher scores of empathic concern relative to those carrying a C allele (Christ et al., 2016) and that T-allele variant associates with better social perception (Seeley et al., 2018) and lower trait autism scores (Montag et al., 2017). On the other hand, C carriers have a greater association with higher trait autism (Montag et al., 2017).

Interestingly, OXT effects on trait decisions and subsequent memory were found to be modulated by different OXTR polymorphisms. In agreement with previous findings (Zhao et al., 2016) the current study showed that self-referential bias effects on trait decision RTs and subsequent memory were independent of one another. Thus the effects of OXT on these two domains of self-referential processing may also be independent and this may underlie their different patterns of OXTR sensitivity. Indeed, previous studies suggest that both types of processing rely on different neural systems, with effects of intranasal OXT on self-referential processing being mediated by modulatory effects on the medial prefrontal cortex (Zhao et al.,

2017, 2016), whereas OXT effects on emotional modulation of memory formation may be mediated by the insula (Striepens et al., 2012).

Some limitations in the current study need to be considered. Although the results demonstrate robust effects of exogenous OXT on self-referential processing in Chinese men, the replication was carried out by the same research group and within highly similar participant samples. To further increase trust in replicable and general effects of intranasal OXT future studies should aim at independent replications across laboratories, sexes and cultures (initial attempts to generalize treatment effects across cultures in Geng et al., 2018b; or cross-cultural replication of OXTR associations with social behaviour in Montag et al., 2017). Although primary outcomes and analyses were identical to the original study, preregistration of the replication experiment would have improved transparency.

In addition, the present study administered 24IU of OXT whereas the original study used a higher dosage of 40IU. Both doses are in the typical range of OXT treatment studies (Striepens et al., 2011; Guastella et al., 2013), and although some studies reported dose-dependent effects of OXT (Cardoso et al., 2013; Quintana et al., 2016, 2017; Spengler et al., 2017) others have reported no differences between 24 and 40IU in terms of effects on social-cognitive functions (Zhao et al., 2017; Geng et al., 2018b). We therefore cannot fully exclude that the different doses may have contributed to the lack of a full replication of the memory effects in the entire sample as previously observed using the 40IU dose.

CONCLUSION

Overall, the present study partially replicated previous findings on the effects of intranasal OXT on self- and other- processing, suggesting that OXT blurs self and other distinction. Individual differences in OXTR genotype determined sensitivity to the behavioural effects of OXT. The present findings add to the growing literature on an important role of the OXTR in modulating the effects of OXT administration (Kou et al., 2018; Yamasue et al., 2012) and thus may help to identify individuals with a high responsiveness to OXT treatment in disorders characterized by altered self-referential processing, such as autism.

Acknowledgements

Weihua Zhao and Ruixue Luo contributed equally to this work.

WZ, RL, CS designed the experiments; RL, CS, Y, CL, JL contributed to acquisition of data; WZ, RL, CS and YZ analyzed the data; WZ, KMK, BB drafted the manuscript; ZW, DS, CM, KMK and BB reviewed and revised the paper.

Funding and disclosure

This work was supported by grants from National Natural Science Foundation of China (NSFC) [31530032; 91632117]; Fundamental Research Funds for the Central Universities [ZYGX2015Z002]; Science, Innovation and Technology Department of the Sichuan Province [2018JY0001]; Open Research Fund of the State Key Laboratory of Cognitive Neuroscience and Learning (Beijing Normal University); The Novo Nordisk Foundation [NFF160C0019856]; China Postdoctoral Science Foundation [2018M643432].

Conflict of interest

None.

Ethical statement

The study was approved by the local ethics committee of the University of Electronic Science and Technology of China and the procedures were in accordance with the latest revision of the declaration of Helsinki. All subjects provided written informed consent and received monetary compensation for their participation.

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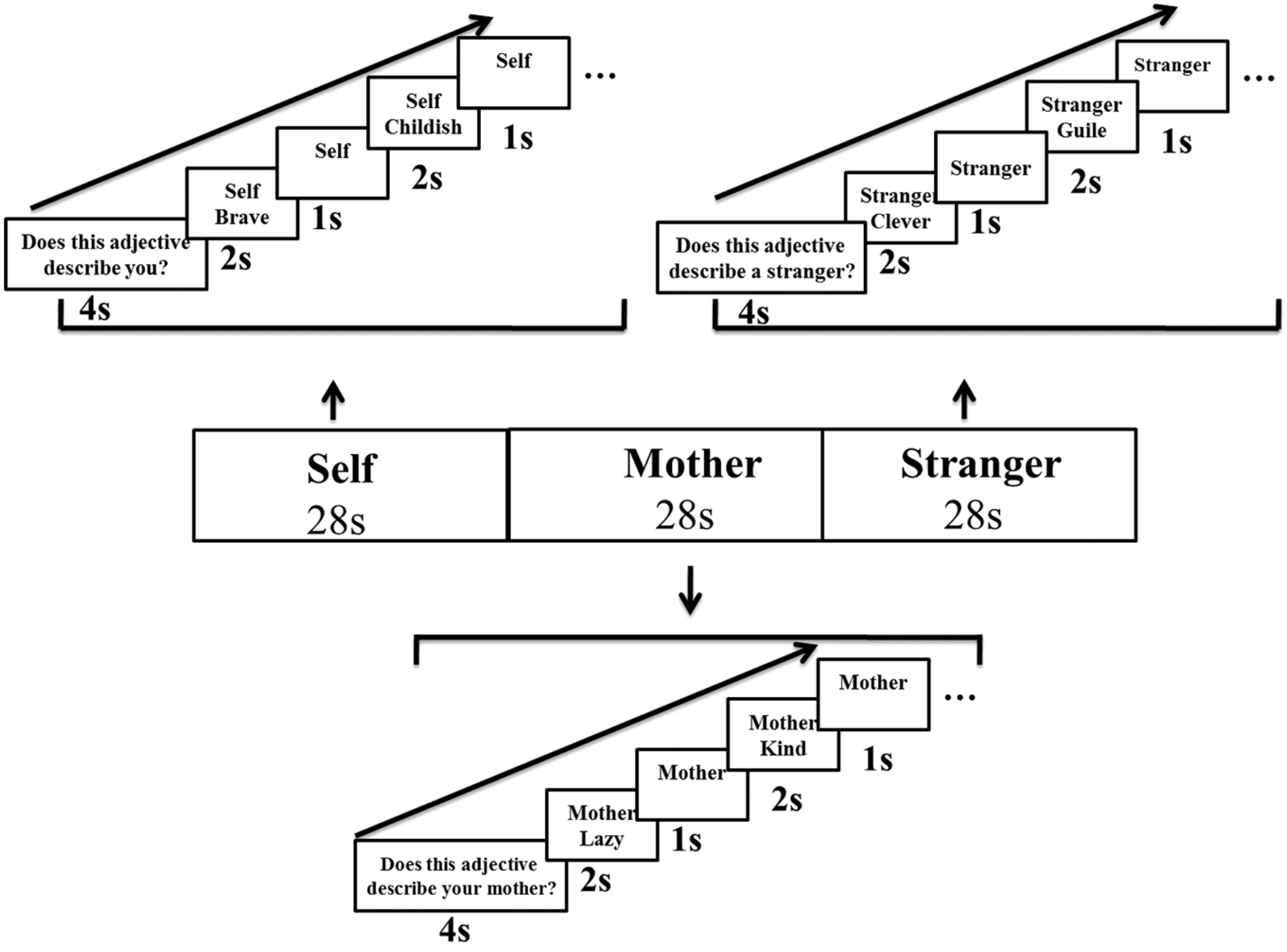
Figure 1. Trait-judgment task. A 4-s instruction that required subjects to judge if an adjective (either positive or negative valence) was appropriate to describe the person (either self, mother or a stranger) was displayed. Eight trait adjectives were presented in each session. Each trial consisted of a 'cue' word (either self, mother or a stranger) above a trait adjective presented for 2s at the center of the screen and it was followed by the cue for 1 s. The total time for each session was 28 s.

Figure 2. The effects of OXT on reaction time for judging adjectives and memory performance. (A) Histograms show mean ± sem reaction time for judging self-, mother-, stranger-related adjectives following OXT and PLC administration. $^{**}p < 0.01$ for differences within each group (B) Histograms show mean ± sem memory performance for remembering self-, mother-, stranger- related words in OXT and PLC group. $^{\#\#}p < 0.01$ for OXT vs. PLC.

Figure 3. The effects of OXT on reaction time and memory performance were modulated by individual differences in OXTR genotype. (A-B) Histograms show mean ± sem reaction time for judging self-, mother-, stranger-related adjectives in OXT and PLC subgroups for individuals with G+ allele (A) and G- allele (B) of OXTR rs53576 (C-D) Histograms show mean ± sem memory performance for remembering self-, mother-, stranger- related negative words in OXT and PLC for individuals with TT genotype (C) and C+ allele (D) of OXTR rs2268498. $^{**}p < 0.01$ for differences within each group; $^{\#}p < 0.05$ for OXT vs. PLC; $^{\#\#}p < 0.01$ for OXT vs. PLC.

Highlights

- The effects of oxytocin on self-referential processing could be partially replicated.
- Oxytocin reduces the self-referential bias.
- Oxytocin selectively influenced decision time in rs53576 G carriers.
- Oxytocin selectively induced memory effects in rs2268498 TT homozygotes.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Does this adjective describe a stranger?
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Stranger Guile
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Stranger
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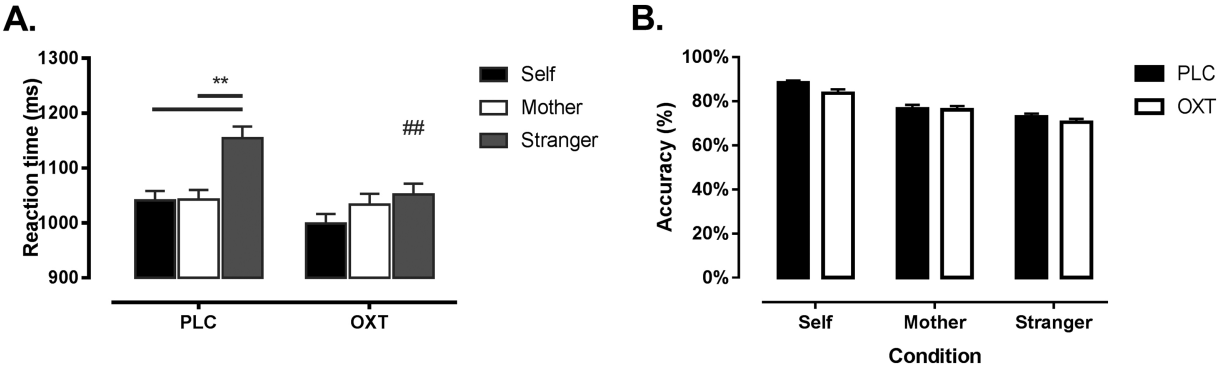
Figure 1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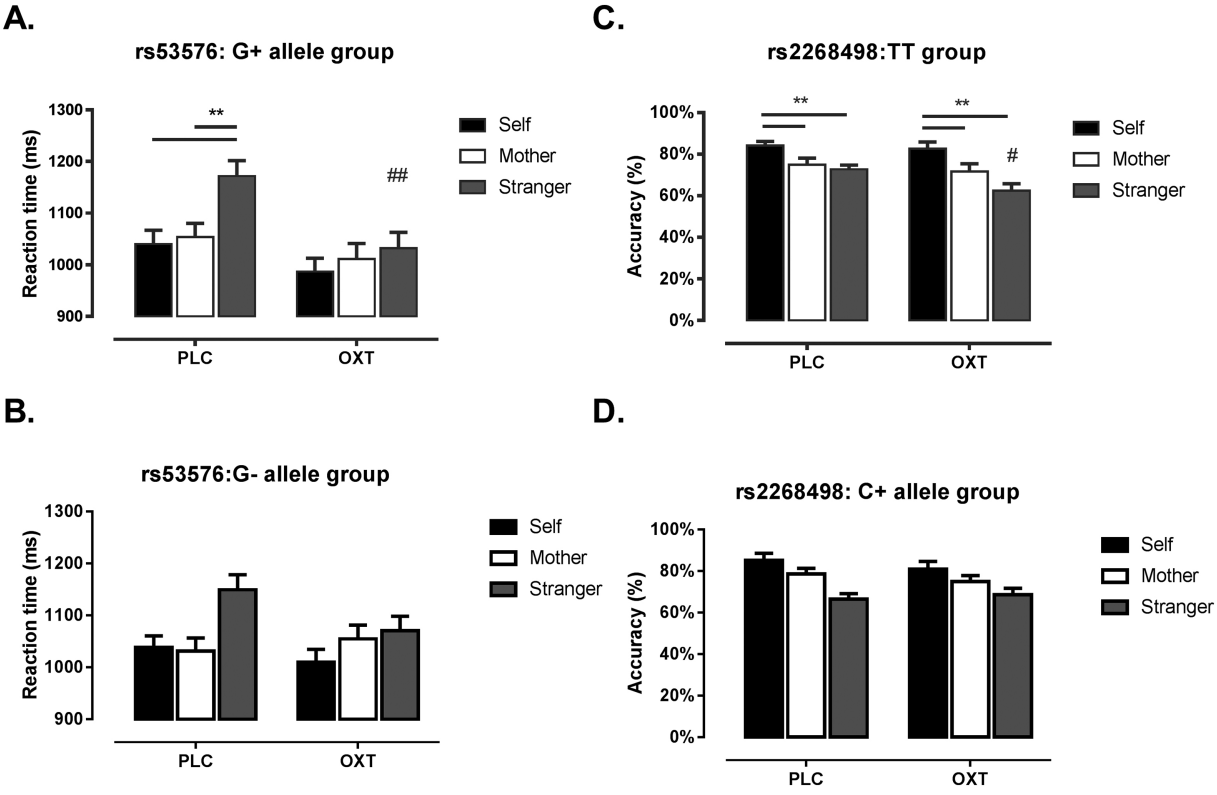
Mother
Stranger
Condition

Figure 2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Self
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Stranger
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80%
60%
40%
20%
0%
Self
Mother
Stranger
PLC
OXT

Figure 3