

Appetite

Intranasal Oxytocin Reduces Attentional Bias to Food Stimuli

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Editor in Chief

Appetite Journal

Dear Sir/Madam,

I am submitting an original manuscript for consideration entitled “Intranasal Oxytocin Reduces Attentional Bias to Food Stimuli”, which I confirm is not under review elsewhere.

All three authors accept full responsibility for all aspects of this work, and I have been nominated as the corresponding author; my full contact details are above.

I also confirm that I can supply all original data for review.

Yours faithfully,

A handwritten signature in black ink, appearing to be 'V. Burmester', written in a cursive style.

Victoria Burmester

Attentional biases to food-related stimuli have been demonstrated in response to hunger as well as during restrained eating. Such biases are often associated with obesity, but healthy-weight individuals who do not self-report hunger have also demonstrated attentional biases to stimuli signalling food using laboratory-based cognitive tasks. Levels of the anorectic neuropeptide oxytocin are elevated by food intake and, when administered intranasally, oxytocin inhibits food intake in the laboratory. Here, 40 healthy adults (29 women; mean age 24.0 years old) self-administered 24 IU of oxytocin or placebo intranasally; 40 mins later they ate a small snack to maintain alertness and ameliorate deprivation-induced hunger before starting a computerized dot-probe attentional bias task that presented 180 trials of paired visual stimuli comprising neutral, food, social and/or romantic images (500 ms presentation time). Reaction times to probe stimuli that appeared after the offset of the visual images indicated a significant attentional bias to food pictures after placebo; this effect was significantly attenuated by oxytocin. The effect of oxytocin on attentional bias to the food pictures was not altered by the type of stimulus paired with the food image, and was independent of BMI, age, sex, self-rated eating behaviour, and self-reported parental bonding; however, the effect was modulated by self-reported food cravings and trait stress. The findings support and extend previous work suggesting that oxytocin can counteract attentional biases to food-related stimuli in a sample with anorexia by demonstrating the same effect for the first time in a cohort who do not have an eating disorder.

Intranasal Oxytocin Reduces Attentional Bias to Food Stimuli

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Abstract

Attentional biases to food-related stimuli have been demonstrated in response to hunger as well as during restrained eating. Such biases are often associated with obesity, but healthy-weight individuals who do not self-report hunger have also demonstrated attentional biases to stimuli signalling food using laboratory-based cognitive tasks. Levels of the anorectic neuropeptide oxytocin are elevated by food intake and, when administered intranasally, oxytocin inhibits food intake in the laboratory. Here, 40 healthy adults (29 women; mean age 24.0 years old) self-administered 24 IU of oxytocin or placebo intranasally; 40 mins later they ate a small snack to maintain alertness and ameliorate deprivation-induced hunger before starting a computerized dot-probe attentional bias task that presented 180 trials of paired visual stimuli comprising neutral, food, social and/or romantic images (500 ms presentation time). Reaction times to probe stimuli that appeared after the offset of the visual images indicated a significant attentional bias to food pictures after placebo; this effect was significantly attenuated by oxytocin. The effect of oxytocin on attentional bias to the food pictures was not altered by the type of stimulus paired with the food image, and was independent of BMI, age, sex, self-rated eating behaviour, and self-reported parental bonding; however, the effect was modulated by self-reported food cravings and trait stress. The findings support and extend previous work suggesting that oxytocin can counteract attentional biases to food-related stimuli in a sample with anorexia by demonstrating the same effect for the first time in a cohort who do not have an eating disorder.

1. INTRODUCTION

Attentional biases towards food that arise from hunger have been demonstrated using an array of attentional-test paradigms, such as the emotional attention-blink test (Piech, Pastorino, & Zald, 2010), the visual dot-probe task (Tapper, Pothos, & Lawrence, 2010) and the word dot-probe design (Mogg, Bradley, Hyare, & Lee, 1998). These hunger-driven attentional biases to food stimuli, and indeed neural sensitivity to food reward, are greater in people who are overweight or obese (Brignell, Griffiths, Bradley, & Mogg, 2009; Stice, Spoor, Ng, & Zald, 2009; Volkow, Wang, & Baler, 2011). Using eye-tracking measures and a visual dot-probe task, people with obesity were also found to have a bias towards food pictures that persisted in the satiated state (Castellanos et al., 2009), a finding replicated by Werthmann et al. (2011), who also found a correlation between the extent of bias and increased food cravings. Further, attentional biases to food-related cues seen in people with obesity may be attributed to enhanced food craving (Roethmund et al., 2007; Stoeckel et al., 2008). Craving may also affect attention to food in healthy-weight participants, as a person's cravings for food might be expected to reflect an increased salience for or preoccupation with food. This is supported by experimentally-enhanced vigilance towards food in a dot probe task being correlated with food salience (Jones & Rogers, 2003; Timmerman & Gregg, 2003) and by increased craving being associated with stronger attentional biases to food (Werthmann, Roefs, Nederkoorn, & Jansen, 2013).

Increased preoccupation with food is also a consequence of restrained eating (Herman & Polivy, 1975), and a number of studies have linked restrained eating to attentional biases for food-related stimuli, although the direction of the effects is not consistent. Thus, some studies have found that restrained eaters demonstrate an increased avoidance of food stimuli (e.g. Boon, Vogelzang, and Jansen, 2000), whilst other experiments have reported elevated attention towards food stimuli (see Hollitt, Kemps, Tiggemann, Smeets, and Mills, 2010). Several parameters, such as cultural norms, procedural differences, participant characteristics, and the instrument used to measure restrained eating, are likely to influence the relationship between restrained eating and attentional bias to food-related stimuli.

Central and peripheral oxytocin release is triggered by eating (Blevins & Ho, 2013) and multiple mechanisms appear to subserve its anorectic actions (Sabatier, Leng, & Menzies, 2014). In hungry participants, hypothalamic activation occurs in response to high-calorie food pictures and is attenuated by oxytocin (van der Klaauw et al., 2017); moreover, experiments have shown that oxytocin also reduces post-prandial palatable food intake in men and women (Burmester, Higgs, & Terry, 2018; Burmester, Gibson, Butler, Bailey, & Terry, 2019). Additionally, oxytocin-driven attentional shifts away from food-related stimuli in women with anorexia who previously showed biases towards food have been demonstrated in the laboratory (Kim, Y. R. et al., 2014).

In humans and animals, the phylogenetically highly-conserved neuropeptide oxytocin is involved in promoting social behaviours. Neural, genetic, and experimental evidence point towards oxytocin enhancing empathy, social cognition and memory, bonding and attachment, and prosocial behaviour (Li et al., 2015; MacDonald & MacDonald, 2010; Notzon et al., 2016), leading to the social salience hypothesis of oxytocin, whereby oxytocin modulates attention to social cues (Shamay-Tsoory & Abu-Akel, 2016). Although oxytocin's effects are context- and sex-dependent (Dumais & Veenema, 2016; Olff et al., 2013), its promotion of social bias is robust and has even been demonstrated in the rhesus monkey, where reduced attention to negative facial expressions in the dot-probe paradigm was seen after nasally applied oxytocin (Parr, Modi, Siebert, & Young, 2013).

These dual roles for oxytocin of promoting bonding while reducing appetite for food are supported by neural evidence that the ventromedial nucleus of the hypothalamus — a site known to play an important role in energy balance and behaviour related to reproduction — expresses high levels of oxytocin receptors that reciprocally regulate these two functions (Leng & Ludwig, 2008; Leng et al., 2008; McCarthy, Kleopoulos, Mobbs, & Pfaff, 1994; Tribollet, Barberis, Jard, Dubois-Dauphin, & Dreifuss, 1988). Eating is one of a small number of primary reinforcers that stimulate mesolimbic reward circuits without conditioning, and accumbal and striatal dopamine is attenuated by oxytocin (Blevins & Ho, 2013) to reduce motivation for hedonic consumption (McGregor & Bowen, 2012).

1 Although ventromedial hypothalamic neurons appear to contribute to the motivational transfer from
2 food-related incentives to reproductive ones (Leng et al., 2008; McCarthy et al., 1994), this
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4 mechanism cannot wholly explain motivational or attentional shifts mediated by oxytocin. That is, the
5
6 motivational shift from food to sexual targets fails to explain how the administration of intranasal
7
8 oxytocin creates an attentional bias towards social stimuli that are not sexual (Domes et al., 2013;
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10 MacDonald & MacDonald, 2010; Shamay-Tsoory & Abu-Akel, 2016).
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15 Emerging evidence has demonstrated an attentional bias towards food in healthy-weight individuals
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17 that is independent of hunger. Electrophysiological measures assessing postprandial performance on
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19 a word-search paradigm revealed that healthy participants' attention was strongly affected by food
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21 stimuli and correlated with BMI (Kumar, Higgs, Rutters, & Humphreys, 2016). Kim and colleagues
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23 (2014) demonstrated an attentional bias to food not only in an anorexic experimental group but also
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25 amongst healthy controls. In the healthy group, however, the bias was not reduced by oxytocin.
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27 Findings that oxytocin-induced reductions in attentional bias in women with anorexia were preceded
28
29 by decreases in salivary cortisol levels suggest that food-related anxiety may have been lowered by
30
31 the anxiolytic effects of oxytocin in people with anorexia (Leppanen et al., 2017), whereas this effect
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33 may not occur in healthy eaters for whom food is not a threat (Churchland & Winkielman, 2012).
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40 The potential of oxytocin to alter attentional food biases in normal eaters has not been yet explored
41
42 directly. Given the distinct pathways in the medial prefrontal cortex for feeding and bonding that
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44 oxytocin regulates, and the transfer from food-related incentives to reproductive ones via oxytocin
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46 receptors in the ventromedial nucleus of the hypothalamus (Leng et al., 2008; McCarthy et al., 1994),
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48 attentional bias procedures that incorporate stimuli representing food, social, and sexual bonding will
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50 allow comparisons of oxytocin's effects across the three different stimulus types. The current study is
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52 the first time that three types of stimuli relating to different motivations that are modulated by
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54 oxytocin have been examined alongside each other.
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60 A dot-probe task design was adopted, based on two studies that showed effects of oxytocin on
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attention: Leppanen et al. (2017) showed that oxytocin reduced attentional bias to food in people with anorexia, and di Simplicio, Massey-Chase, Cowen, and Harmer (2009) demonstrated that oxytocin reduced reaction times to fearful facial expressions. The experimental aims were concealed, and we measured a number of variables that have been shown to influence endogenous oxytocin effects and that have also been associated with food-related biases. Levels of restraint on the DEBQ, high food cravings, and high trait stress were expected to covary with vigilance to food and, in line with previous research (Kim et al., 2014; Kumar et al., 2016), an overall bias towards food-related stimuli was expected that would be attenuated by intranasal oxytocin. It was also expected that oxytocin would shift attention from food to romantic and/or social stimuli.

2. METHOD AND MATERIALS

The study received a favourable ethical opinion from the Research Ethics Committee at Kingston University in accordance with the principles of the Declaration of Helsinki, 2013.

2.1 Study Design

The experiment was a double-blind, repeated-measures crossover design. The main outcome variable was the effect of oxytocin or placebo on response times to food vs neutral pictures.

2.2 Participants

Forty-two well-rested, healthy adults aged between 19 years and 38 years ($M = 24.02$ yrs; $SD = 4.78$ yrs) with body mass indexes (BMI) ranging from underweight at 15.43 kg/m^2 to obese at 35 kg/m^2 ($M = 23.73 \text{ kg/m}^2$; $SD = 4.39 \text{ kg/m}^2$) were recruited in exchange for course credits. Two participants were excluded as they did not complete the online surveys, leaving forty participants. There were 11 men and 29 women. Five participants (one male) were left-handed. Individuals on a vegan diet, with diabetes or food allergies were excluded due to the food provided. Pregnant and breastfeeding women (by self-report) were also excluded from participation due to their altered oxytocin function and sensitivity (e.g. Crowley, Parker, Armstrong, Spinolo, & Grosvenor, 1992; Fenelon, Poulain, & Theodosis, 1993). Altered endogenous oxytocin function is associated with high emotional arousal or stress (e.g. bereavement, financial windfall) so participants reporting such events were also excluded

(Engelmann, Ebner, Landgraf, Holsboer, & Wotjak, 1999; Kovacs, 1986). To participate, individuals had to confirm on the day to the researcher that they had not consumed alcohol or non-steroidal anti-inflammatories during the previous 12 hours at least.

2.3 Materials

Intranasal sprays containing 24 IU of oxytocin or vehicle were self-administered by participants; detailed information about the nasal sprays can be found in previous studies by this group (see Burmester, Higgs, and Terry, 2018). All participants consumed a readily catabolisable chocolate bar (Kitkat®, 40g, 233 kcal) and either a carton of apple or orange juice (200ml, 91 kcal or 84 kcal respectively). This food was designed to boost blood-sugar levels during the attention task to minimise fatigue and reduce deprivation-induced hunger that might have increased attention to food pictures. Height was measured using a wall ruler, and Koogeek biometric impedance scales were used to weigh participants. Images were displayed using a 20-inch monitor, table-mounted at head height approximately 60 cm from the participant with a fixed keyboard for responses. For task presentation and recording of the responses, Superlab presentation software (Version 5.0, Cedrus Corporation, CA, USA) was used.

2.3.1 Questionnaires

The Dutch Eating Behaviour Questionnaire (DEBQ; Van Strien, Frijters, Bergers, & Defares, 1986) is a well-validated measure of restrained, emotional, and external eating. A higher score reflects higher levels of the eating dimension. To assess trait levels of food craving, the 39-item Food Cravings Questionnaire trait subscale (FCQ-T) was used, which is the most frequently used instrument for the assessment of food cravings and was developed to assess cravings that relate to palatable food intake in addition to physiological hunger (Cepeda-Benito, Gleaves, Williams, & Erath, 2000). Scores on the FCQ-T have been found to be positively associated with BMI, eating pathology, low dieting success, and increases in state-food craving during cognitive tasks involving appealing food stimuli. The State Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970) measures trait and state anxiety and has been widely used in oxytocin research (Gordon et al., 2008; Heinrichs et al., 2003; Tops, Van Peer, Korf, Wijers, & Tucker, 2007). The 20-item Revised UCLA Loneliness Scale

version 3 (Russell, 1996), was used, which measures subjective feelings of loneliness as well as feelings of social isolation. The scale is widely used in psychology and contains positive and negative statements about social relations. To assess the degree to which participants were ‘in love’, Rubin’s widely validated ‘Romantic Love Scale’ (1970) was completed during both visits to account for possible inter-sessional changes but also to maintain an identical procedure across visits.

2.3.2 Picture Stimuli

Forty pictures of palatable salty and sweet foods were matched carefully for colour and shape with forty neutral common household objects, and the pictures were randomly allocated into two groups of 20 to be used in each session (University of Birmingham food research database: Allen et al., 2016). Social and romantic pictures from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1999) were validated by 215 respondents for typicality within their category, and the top 40 pictures of each category were randomly allocated into two equal sets for each session. All pictures were three inches high and four inches wide.

2.4 Procedure

Participants provided informed consent, followed by self-administration of 24 IU of oxytocin or placebo, depending on session, supervised by a researcher. Participants provided their age and were then blind-weighed by the researcher. Height and weight were measured, and the participant’s age, gender, and handedness were recorded. Participants then watched a neutral video (*Life of Plants*, BBC, David Attenborough) for about half an hour. At 40 minutes post-inhalation, participants consumed the snack and drink before undertaking the dot probe task. After taking part in both laboratory sessions, participants completed the questionnaires online via a link using Qualtrics survey software.

2.4.1. Dot Probe Task

Participants were seated in front of a monitor and informed that they would be presented with a series of pairs of images (trials) presented side-by-side on the screen, and that one image would disappear to be replaced by a black dot (solid circle, Arial, size 50, black on a white background). At the

beginning of each trial a central fixation cross would be presented for 500 ms, immediately followed by a picture pair for 500 ms. To avoid reaction times that reflected responses to the previous set of pictures, the importance of looking at the fixation cross in between trials was emphasised. After picture offset, the dot probe appeared at the location of either the right or the left picture and remained on screen until the participant pressed one of the response keys: the “F” (left) or “J” (right) keys on the keyboard, marked with blue and green tape respectively. Participants were instructed that they should indicate the dot position as quickly as possible without compromising accuracy. After a valid response there was a 500 ms interval, then the fixation cross of the next trial was presented. Practise trials were undertaken by each participant until they were satisfied that they understood the task; typically participants practised for just one or two trials. A total of 180 trials per session were administered, comprising 20 food vs neutral, 20 social vs romantic, 20 romantic vs food, 20 social vs food, and 10 neutral vs neutral. A different set of pictures was used for each session (Set A and Set B), which were presented in a counterbalanced design. Table 1 shows the pairing scheme and position of the probe behind the picture used for both sets. The picture locations (left or right), dot probe locations (left or right) and presentation order were randomised for each participant.

Table 1

Dot Probe Stimulus Presentation Scheme: Stimulus type pairings and their Organisation Across Left/Right Visual Fields.

Left Visual Field	Right Visual Field
10 food	• 10 neutral
10 neutral	• 10 food
10 romantic	• 10 food
10 social	• 10 food
10 neutral	• 10 neutral
10 romantic	• 10 social
10 social	• 10 romantic
10 food	• 10 social
10 food	• 10 romantic
• 10 food	10 neutral
• 10 neutral	10 food
• 10 romantic	10 food
• 10 social	10 food
• 10 neutral	10 neutral
• 10 romantic	10 social
• 10 social	10 romantic
• 10 food	10 social
• 10 food	10 romantic

The dot represents the location of the probe stimulus for that pairing.

3. RESULTS

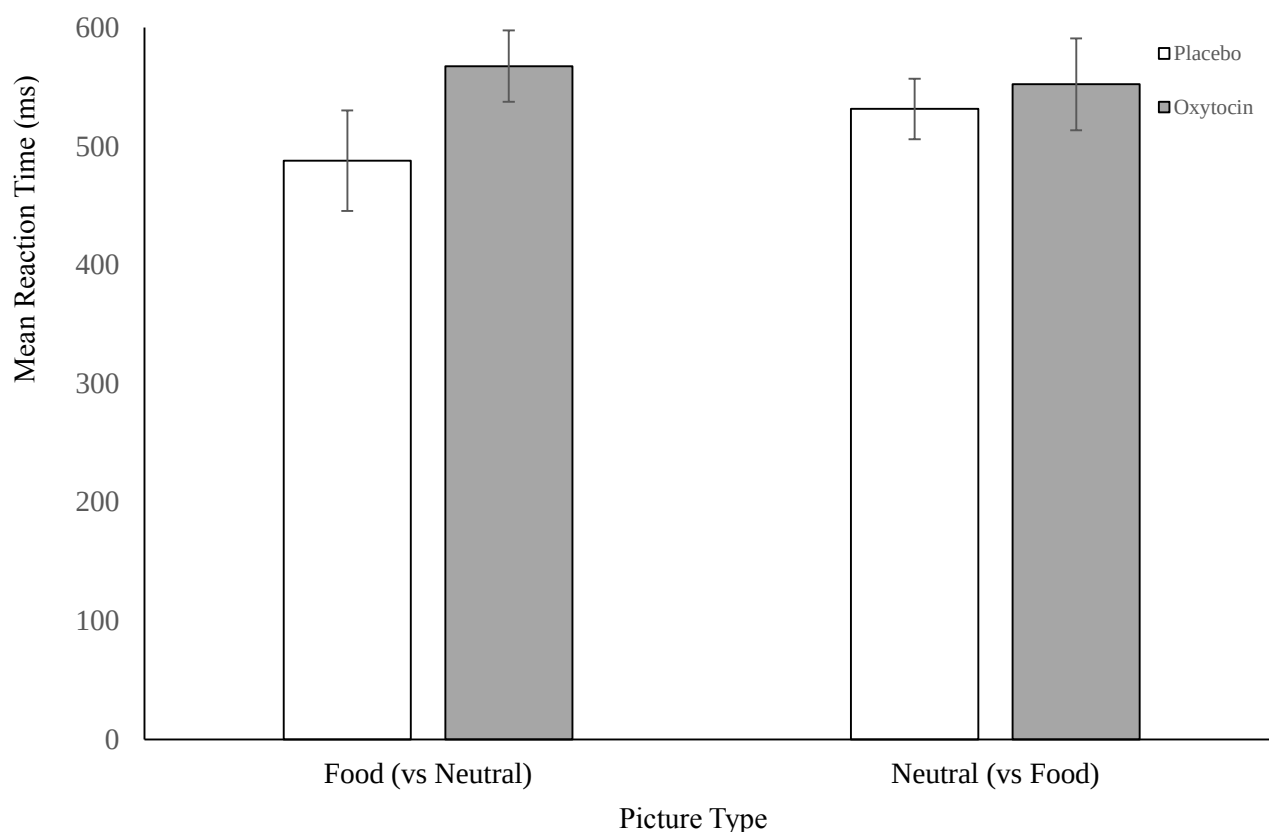
3.1 Data preparation

All trials with error responses or response latencies below 200 ms were removed from the results, as values below 200 ms might indicate that a response was not based on perception of the stimulus (Ehrman et al., 2002). Previous research has commonly eliminated latencies either over 1000 ms or 1500 ms, or on the basis of their standard deviation from the mean. In this data set, there were no outliers between 1000 ms and 1300 ms, but thirty-three cases were greater than 1300 ms, some six

standard deviations above the mean reaction time. The boundary for exclusion was therefore 1300 ms, a set point also used in previous research as a suitable compromise between 1000 ms and 1500 ms (Kujawa et al., 2011). Overall, under 1% of responses were discarded.

3.2 Analysis of Attentional Bias

The means and standard deviations for congruent responses to probes associated with neutral and food picture types, in both the placebo and oxytocin condition are shown in Figure 1. A 2 (drugs: oxytocin or placebo) x 2 (picture: food or neutral) repeated-measures ANOVA was conducted that revealed a main effect of drug [$F(1,39) = 76.89, p < .001$] whereby administration of oxytocin significantly increased response times to the dot probe in comparison with placebo administration. There was also a significant interaction between drug and picture type [$F(1,39) = 20.14, p < .001$]. A paired-samples t test confirmed that response times to the congruent dot probe behind food pictures after oxytocin (see Figure 1) were significantly longer compared with after placebo: $t(41) = 8.40, p < .001$, indicating that oxytocin reduced vigilance to food pictures. A second paired-samples t test confirmed that response times to the congruent dot probe behind neutral pictures after oxytocin compared with placebo ($M = 531.46$ ms, $SD = 23.59$ ms) were also significantly longer: $t(41) = 2.86, p = .007$, indicating that oxytocin reduced vigilance to neutral pictures, too. This suggests that oxytocin has a generalised slowing effect on reaction times that was more pronounced for food stimuli.



Note. Error bars are standard deviations

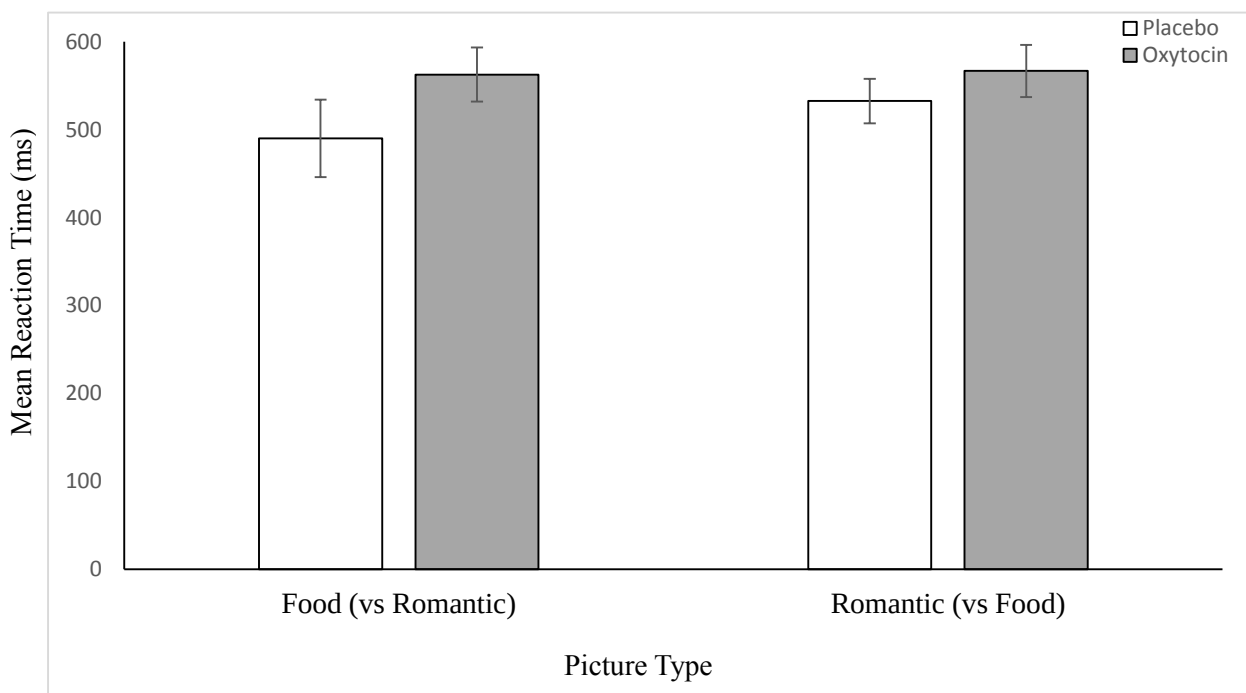
Figure 1

Mean (*SD*) Reaction Times (ms) to Food Congruent vs Neutral Congruent Picture Probes in Placebo and Oxytocin Conditions of Dot Probe Task

3.4 Food versus Social Pictures and Food versus Romantic Pictures

The means and standard deviations for congruent responses to probes associated with food, romantic or social picture types are presented in Figures 2 and 3 for both drug conditions. To compare food and romantic images, a repeated-measures 2 (drug: oxytocin vs placebo) x 2 (picture: food vs romantic) was conducted. The main effect of drug [$F(1,39) = 54.77, p < .001$] was significant meaning that administration of oxytocin lengthened reaction times irrespective of the type of picture viewed. There was no main effect of picture type [$F(1, 39) = 0.63, p = .43$]. Figure 1 illustrates the significant interaction between drug and picture type, which revealed that oxytocin only reduced attention to food stimuli [$F(1,39) = 50.45, p < .001$].

A paired-samples t test confirmed that response times to the congruent dot probe behind food pictures (vs romantic) after oxytocin compared to after placebo were significantly longer: $t(41) = 7.89, p < .001$, indicating that oxytocin reduced vigilance to food pictures. A second paired-samples t test confirmed that response times to the congruent dot probe behind romantic pictures after oxytocin compared to after placebo were not significantly longer: $t(41) = 0.13, p = .90$, indicating that oxytocin did not reduce vigilance to romantic pictures. This suggests that oxytocin had no effect on response times to the dot probe behind romantic pictures but reduced vigilance to food pictures.



Note. Error bars are standard deviations

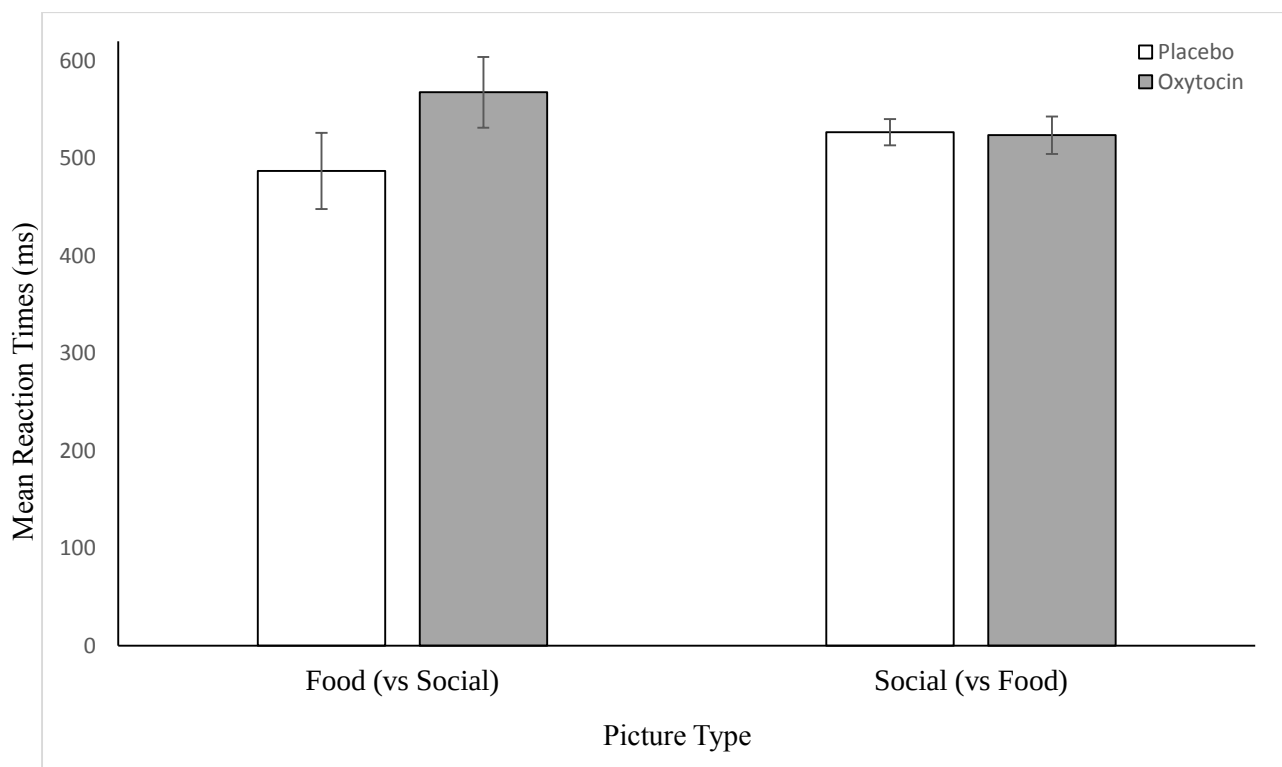
Figure 2

Mean (SD) Reaction Times (ms) to Food Congruent and Romantic Congruent Picture Probes in Oxytocin and Placebo Conditions of the Dot Probe Task

A repeated-measures 2 (drug: oxytocin vs placebo) x 2 (picture: food vs social) ANOVA was conducted to compare food and social stimuli. Administration of oxytocin increased mean response times overall [$F(1,39) = 63.77, p < .001$], but there was no main effect of picture type on response times [$F(1, 39) = 0.08, p = .78$]. Figure 3 shows that there was a significant interaction between drug

and picture type [$F(1, 39) = 81.33, p < .001$] such that oxytocin reduced attention paid to food stimuli only.

Further paired-samples t tests confirmed that response times to the congruent dot probe behind food pictures (vs social) after oxytocin ($M = 567.72$ ms, $SD = 36.29$ ms) compared to after placebo ($M = 486.97$ ms, $SD = 39.12$ ms) were significantly longer: $t(41) = 9.04, p < .001$, indicating that oxytocin reduced attention to food pictures. A second paired-samples t test confirmed that response times to the congruent dot probe behind social pictures after oxytocin ($M = 524.24$ ms, $SD = 16.04$ ms) compared to after placebo ($M = 528.01$ ms, $SD = 8.64$ ms) were not significantly longer: $t(41) = 1.42, p = .17$, indicating that oxytocin did not reduce attention to social pictures. This suggests that oxytocin had no effect on response times to the dot probe behind social pictures but reduced vigilance to food pictures.



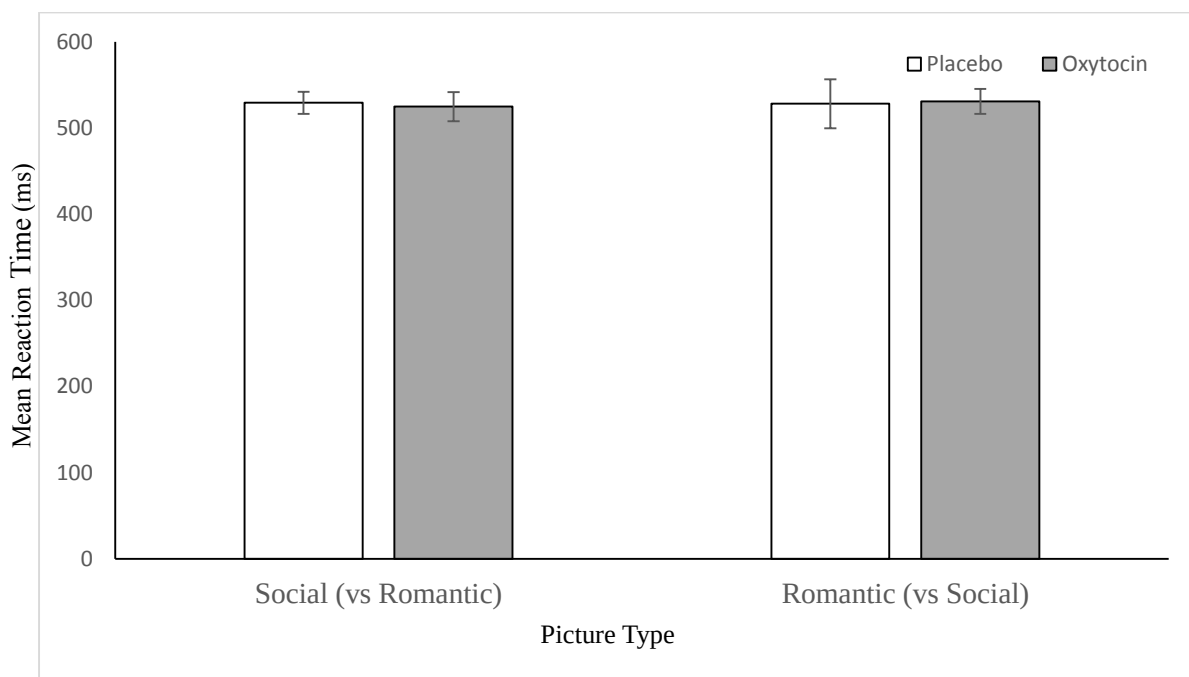
Note. Error bars are standard deviations

Figure 3

Mean (*SD*) Reaction Times (ms) to Food Congruent and Social Congruent Picture Probes in Oxytocin and Placebo Conditions of the Dot Probe Task

3.5 Social and Romantic Pictures

To assess whether oxytocin impacted attention to social and romantic picture probes when paired together, placebo and oxytocin conditions were compared using *t* tests. The means and standard deviations for romantic and social pictures are displayed in Figure 4. Paired *t* test for responses to the romantic pictures revealed no significant difference between the oxytocin or placebo conditions, $t(39) = 0.29, p = .78$. There was also no significant difference between the oxytocin and placebo conditions for the social pictures, $t(39) = 1.63, p = .11$.



Note. Error bars are standard deviations

Figure 4

Mean (*SD*) Reaction Times (ms) to Social Congruent and Romantic Congruent Picture Probes in

3.5 Questionnaire Data

The means and standard deviations (SD) for questionnaire scores are presented in Table 2. To assess whether participant characteristics influenced the attenuating effect of oxytocin on attentional bias towards food, questionnaire data were analysed as covariates in a series of repeated-measures ANCOVAs with food bias scores in the two drug conditions as the repeated-measures factor.

Table 2. Means (*SD*) for participants' questionnaire scores (n = 40)

	<i>M</i>	<i>SD</i>
STAI-trait	46.23	5.01
BMI	23.73	4.39
Loneliness	37.68	9.57
PBI Care-Neglect	49.88	15.75
PBI Overprotection	29.63	15.05
Romantic Love	77.53	17.22
FCQ – total	147.60	28.29
DEBQ - Restrained	3.56	1.30
DEBQ - External	1.88	0.82
DEBQ - Emotional	1.95	0.75

BMI did not interact with oxytocin's reduction of food bias $F(1, 38) = 2.04, p = .16$, indicating that oxytocin's effects in this experiment were independent of BMI. The mean STAI-trait score was significantly higher than normative averages [normative: $M (SD) = 40.40 (10.10)$] for trait anxiety in a one-sampled t test: $t(39) = 14.44, p < .001$. Trait anxiety showed a significant interaction with oxytocin's effects on food bias: $F(1,38) = 8.85, p = .005$, suggesting that trait anxiety increased the

effect of oxytocin on bias scores. In the DEBQ, one-sample t tests showed that the mean scores for restraint [$t(39) = 3.54, p = .001$], external [$t(39) = 10.10, p < .001$], and emotional eating [$t(39) = 8.77, p < .001$] were all different from normative scores with restrained eating in the normative samples being lower than this cohort, but the normative scores for external and emotional eating were higher. No interaction, however, was found between oxytocin's reduction of food bias and any of the subscales of the DEBQ: restraint subscale [$F(1,38) = 2.77, p = .10$], external subscale [$F(1,38) = 0.38, p = .54$], emotional eating: $F(1,38) = 1.54, p = .22$. The mean romantic score for romantic love in this cohort was 77.53, which a one-sampled t test showed was below mean normative scores of 89.46 [$t(39) = 4.38, p < .001$]. Romantic scores did not interact with oxytocin's reduction of food bias, though: $F(1, 38) = 0.12, p = .73$. No reliable normative data were found for FCQ scores. There was a significant interaction between overall food cravings and oxytocin's reduction of food bias: $F(1,38) = 5.36, p = .026$, indicating that food cravings decreased the effect of oxytocin on bias scores. Scores on the loneliness not significantly different from normative data $t(39) = 1.07, p = .29$, and did not interact with food bias scores: $F(1, 38) = 0.01, p = .93$.

4. DISCUSSION

In a sample of 40 healthy adults, intranasal oxytocin reduced an attentional bias to food stimuli in a dot probe experiment using neutral and food pictures after ingestion of a snack to boost blood sugar concentrations and help ensure alertness. Despite oxytocin's generalised lengthening of reaction times to both food and neutral picture probes, oxytocin's effect on food stimuli was significantly greater. The oxytocin-led shift away from food and neutral stimuli was independent of BMI, loneliness, and eating behaviour as measured by the DEBQ, but trait stress and food cravings covaried with food bias scores. Response times to food-picture probes in relation to romantic- or social-stimuli probes were greater after oxytocin than after placebo, meaning participants' attention was less focused on the food stimuli after oxytocin when presented alongside affiliative stimuli. No lengthening of reaction times or differential effects were seen after oxytocin with romantic or social picture probes.

1 This finding draws together the work using oxytocin to modify attentional bias and research
2 uncovering an attentional bias towards food in the general population. It is also in line with previous
3 research demonstrating oxytocin's effectiveness at changing attentional bias using food and face
4 pictures presented for 500 ms or above (Brüne et al., 2013; Kim, Youl-Ri et al., 2014). However, in
5 the previous experiments by the Brüne and Kim groups, the cohorts were anorexic, whereas in this
6 study an attentional bias to food was found in normal eaters whose BMI values were predominantly in
7 the normal weight-range (12/40 were overweight or obese).

17 Loeber, Grosshans, Herpetz, Kiefer and Herpetz (2013) proposed two psychological processes
18 underpinning the motivation for food consumption. The first involves the perception of palatable
19 food that initiates cognitive and motivational approach processes, such as attention allocation to food
20 cues that enhances salience attribution. The second process is the self-control required to resist food
21 consumption. It appears that oxytocin may reduce perceptual, motivational, and cognitive processes
22 to alter attentional bias to food, rather than inhibitory mechanisms, since oxytocin has altered
23 attentional biases in those with anorexia but was not successful in potentiating food intake (Kim et al.,
24 2014). However, assessing self-control processes in those with anorexia is problematic and
25 oxytocin's capacity to increase top-down self-control has not been yet been fully explored in healthy
26 participants. Oxytocin's attenuation of the motivation to eat is consistent with preclinical studies and
27 brain imaging research showing that the anorectic effects of oxytocin on ingestive behaviour
28 downregulate activity in reward circuitry, including the ventral tegmental area, putamen, caudate
29 nucleus, NAc and amygdala (Baracz et al., 2012; Sabatier et al., 2014; Striepens et al., 2013). Thus,
30 since oxytocin has also been shown to regulate the cognitive control of inhibitory processes mediated
31 by prefrontal regions (Striepens et al., 2016), further research into oxytocin's modulation of self-
32 control processes using paradigms such as go-no go tasks is warranted.

55 The lack of correspondence in this experiment between BMI and an attentional food bias does not
56 agree with previous research suggesting that being overweight or obese is associated with a greater
57 attentional bias towards food (Brignell et al., 2009) or that oxytocin's effects are greater in obese than

1 lean men (Thienel et al., 2016). It is likely that participants in the study were unaware of the
2 experimental aims or the relevance of their body mass to the study. In the Thienel et al. and Brignell
3 et al. studies, obese participants specifically were recruited via targeted advertisements and, as part of
4 the selection procedure, completed eating behaviour questionnaires. Attentional processing by
5 participants who self-select as obese may be different from that of naïve participants. However, the
6 relationship between food bias and BMI may be moderated by other factors. In a sample of
7 overweight participants recruited to a study on slimming, the external eating component of the DEBQ
8 and the personality trait of impulsivity were associated with a greater attentional bias towards food
9 pictures (Bongers et al., 2015).

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22 Motivational states, such as hunger, can alter the magnitude of conditioned responses; moreover, the
23 state of hunger increases attentional bias to food in the general population. A limitation of this study
24 was that hunger and fullness ratings were not obtained from participants. However, to minimise
25 fatigue and prevent deprivation-induced hunger, participants were provided with a snack before
26 completing the dot probe task. It is also possible that consuming palatable food beforehand primed
27 participants to be vigilant towards food cues and the results reflect oxytocin's weakening of the
28 priming effect. Small amounts of food can stimulate the appetite and increase attention to food
29 (Zheng, Lenard, Shin, & Berthoud, 2009) and Konorski termed the ensuing increased locomotor
30 activity and attention to olfactory stimuli related to food a "hunger reflex" (Konorski, 1973; Pavlov,
31 1897). Cornell, Rodin, and Weingarten (1989) first demonstrated this priming effect, or cue reactivity,
32 in humans: Exposure to pizza or ice cream potentiated subsequent eating of that food in food-sated
33 participants. A recent meta-analysis found that consuming palatable food prospectively and
34 significantly alters subsequent eating behaviour (Boswell & Kober, 2016). However, it is not clear
35 that attention to picture probes is a reliable proxy for eating behaviour and thus is altered by prior
36 consumption of palatable food. Future studies should explore whether a snack consumed before an
37 attentional bias task, primes participants to food cues.

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60 Methodological differences between the Kim et al. (2014) study and the present experiment may have
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1 contributed to the lack of attentional bias modification by oxytocin in normal eaters in the Kim group
2 that was demonstrated in this experiment. Increased attention in the dot-probe paradigm within the
3 anorexic cohort may be, at least partly, due to increased threat processing, as has been demonstrated in
4 individuals with anxiety disorders towards, for example, spiders (Öhman & Soares, 1994). However,
5 trait anxiety was higher than normative averages in this cohort and covaried with food bias scores, so
6 oxytocin may, therefore, be effective at attenuating attentional bias differently in people with anorexia
7 than in healthy eaters. In people with anorexia, oxytocin may modulate the increased threat
8 sensitivity present when exposed to food-related cues, whereas in normal eaters, oxytocin may
9 attenuate the reward processes. The food-related images used by the Kim group included items that
10 were related to food (e.g. cooking utensils) and food that was not high valence (e.g. celery). Although
11 both anorexic groups and healthy controls were found to have attentional bias to food-related stimuli,
12 the three types of food-related stimuli were collapsed into one bias result. Low or medium valence
13 stimuli used by Kim et al. (2014) may trigger increased attention in anorexic groups but not healthy
14 controls, meaning that the stimuli were not of equal valence across groups. The high-valence food
15 and neutral pictures in this dot-probe study were from the validated University of Birmingham
16 database, and the romantic and social pictures were rated for typicality by a large number of people
17 (189) compared to other studies that use just four ‘judges’ (e.g. Mogg et al., 2000). The high valence
18 of all non-neutral stimuli used in this experiment may partially account for the significant findings.

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42 In this study, the other salient stimuli presented alongside food images were social and romantic
43 images. Oxytocin did not impact gaze times towards social and romantic images, which were not
44 attentionally impactful after placebo, either. One explanation could be that images of strangers are not
45 meaningful, or even aversive, and this experiment should be repeated using meaningful images of
46 friends and partners. Tactile and vocal social contact trigger oxytocin release in the central nervous
47 system, which leads to the formation or maintenance of conspecific affiliation (Seltzer, Ziegler, &
48 Pollak, 2010), so for these domains oxytocin may not be effective via images.

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60 Although attentional biases to social and romantic stimuli were not explicitly examined in this dot
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probe since no direct comparisons were made with neutral stimuli, response times to romantic and social pictures were as quick as the food response times in the placebo condition, and similar to the attentional bias scores observed when food pictures were viewed alongside neutral pictures. The similarly quick response times to the probes behind romantic, social, and food pictures in the placebo condition suggest that attention across these stimuli was equally distributed in the placebo condition. Given the body of literature showing that oxytocin influences attention toward social stimuli in males (Di Simplicio et al., 2009; Domes et al., 2013), females (Kim, Y. R. et al., 2014; Kim, Youl-Ri, Eom, Yang, Kang, & Treasure, 2015), autistic individuals (Kanat et al., 2017; Xu et al., 2015), and rhesus monkeys (Parr et al., 2013), the finding that social response times did not change after oxytocin is surprising. Previous attentional research on oxytocin's effect on romantic stimuli could not be found. However, Scheele et al. (2013) demonstrated that oxytocin's enhancing effects on men viewing female faces was specific to their romantic partners only. The generic romantic stimuli used in this experiment may not, therefore, convey sufficient valence. Further research could extend this study by contrasting social and romantic images with neutral ones to examine whether attentional bias towards them exists, and whether it persists under oxytocin.

In summary, a significant attentional bias towards food-related stimuli in a healthy non clinical adult population was eliminated with 24 IU of intranasal oxytocin. These results are preliminary evidence of the potential of oxytocin as an agent for modification of attentional bias towards food.

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Ethics Statement for Intranasal Oxytocin Reduces Attentional Bias to Food Stimuli

Ethical approval was granted for the above study by the psychology ethics committee at Kingston University, approval no 151637.