The Influence of Oxytocin on Eating Behaviours and Stress in Women with Bulimia Nervosa and Binge Eating Disorder

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Abstract

The current study aimed to test the influence of oxytocin on palatable food intake, 24-hour caloric consumption, and stress in women with bulimia nervosa and binge eating disorder. We recruited 25 women with DSM-5 bulimia nervosa or binge eating disorder, and 27 weight-matched comparison women without history of an eating disorder. We employed a double-blind, placebo-controlled crossover design in which each participant attended the lab for two experimental sessions, receiving a divided dose of 64IU intranasal oxytocin in one session and equivalent volume of placebo nasal spray in the opposite session. The order of administration was pseudo-randomised across participants. We hypothesised that a divided dose of 64IU intranasal oxytocin administration would reduce subjective hunger, the immediate consumption of palatable food, 24-hour calorie consumption, and the incidence of binge eating when compared to placebo. We also hypothesised that oxytocin administration would be associated with lower levels of stress and salivary cortisol, and that there would be an interaction with participant group such that oxytocin would reduce eating behaviour and stress to a greater degree in women with bulimia nervosa or binge eating disorder, compared to women without history of an eating disorder. We did not find a significant effect of oxytocin on any of the measurements of eating behaviour, subjective stress, or salivary cortisol. We recommend that future studies test the dose-response effect of oxytocin on eating behaviours and stress in human populations with eating disorders to further clarify the moderating factors for oxytocin's effect on eating.

KEYWORDS: OXYTOCIN; BULIMIA NERVOSA; BINGE EATING DISORDER; EATING; STRESS

Bulimia nervosa and binge eating disorder are DSM-5 eating disorders characterised by recurrent loss-of-control binge eating episodes (American Psychiatric Association, 2013). This recurrent binge eating is a source of significant distress for individuals with bulimia nervosa and binge eating disorder (American Psychiatric Association, 2013; Mitchison et al., 2018), and the disorders are associated with functional impairment and lower health-related quality of life (Ágh et al., 2016; Pawaskar, Witt, Supina, Herman, & Wadden, 2017).

Currently, cognitive behavioural therapy (CBT) and enhanced CBT (CBT-E) are the recommended gold-standard treatments for binge eating disorder and bulimia nervosa, respectively (National Institute for Health and Clinical Excellence, 2017; Peat et al., 2017). However, only 30-50% of people with bulimia nervosa experience full remission from symptoms at the end of treatment with therapist-led CBT-E (Hay, 2013), with a 68% recovery rate at 9-year follow-up (Eddy et al., 2017). The remission rates for binge eating disorder are somewhat better following therapist-led CBT, with a recent meta-analysis finding that 58.8% of people with binge eating disorder achieve remission by the end of treatment (Brownley et al., 2016). Nevertheless, there is additional scope to explore new treatment methods and supplementation in order to better support the significant portion of people who do not respond to treatment.

One promising new avenue of research is the possibility for oxytocin supplementation in binge-type eating disorders (Kim, Eom, Yang, Kang, & Treasure, 2015). Anomalies in oxytocin function have been implicated as risk factors for the development of bulimia nervosa and binge eating. For example, the GG variant of the rs53576 oxytocin receptor gene polymorphism is associated with greater binging and purging behaviour in women (Micali, Crous-Bou, Treasure, & Lawson, 2017). Additionally, the AG/GA variant of the rs2254298 oxytocin receptor gene polymorphism is also associated with greater binging and purging behaviour in the context of poor maternal care (Micali et al., 2017).

Oxytocin is a neuropeptide and hormone, commonly associated with its role in social functioning (Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011). However, oxytocin has recently received further attention for its roles in down-regulating anxiety and palatable food intake (Neumann & Slattery, 2016; Ott et al., 2013), both of which are strongly implicated in the pathology of bulimia nervosa and binge eating disorder (Treasure, Leslie, Chami, & Fernández-Aranda, 2018).

A recent systematic review and meta-analysis has shown that acute administration of oxytocin in animals has a strong, inhibitory effect on subsequent food consumption (Leslie, Silva, Paloyelis, Blevins, & Treasure, 2018). In humans, the evidence suggests that the inhibitory effect of oxytocin on feeding may be specific to reward-driven eating, as opposed to hunger-driven eating (Leslie, Silva, et al., 2018; Ott et al., 2013), and that this inhibitory effect is stronger in overweight and obese populations (Thienel et al., 2016). In a sample of South Korean women with bulimia nervosa, a single dose of 40IU intranasal oxytocin reduced caloric intake over the following 24 hours in a sample of South Korean women with bulimia nervosa (Kim et al., 2015). However, this study did not measure the immediate impact of oxytocin on binge-type foods.

The mechanism for the effect of oxytocin on eating may be explained by the down-regulation of neural circuits related to the processing of hedonic food motivation, including circuits involving the caudate nucleus (Spetter & Hallschmid, 2017). It has recently been proposed that the cycle of binge eating behaviour in bulimia nervosa and binge eating disorder may be primarily maintained by addictive processes, underpinned by reward-related neural circuits (Treasure et al., 2018). Given the implication of oxytocin in regulating reward-driven eating, it may therefore be the case that oxytocin supplementation directly modulates the eating processes most relevant to binge eating behaviour.

An alternative explanation for the effect of oxytocin on feeding posits that this effect may be mediated by the anxiolytic properties of oxytocin (Anestis, Smith, Fink, & Joiner, 2009; Culbert, Racine, & Klump, 2016). In anorexia nervosa, oxytocin has been found to reduce eating concern (Russell et al., 2018) and cortisol reactivity in response to viewing or consuming food (Leppanen et al., 2017). Previous research has also found that intranasal oxytocin administration reduces salivary cortisol in response to interpersonal rejection and conflict with an intimate partner in healthy men and women (Ditzen et al., 2009; Linnen, Ellenbogen, Cardoso, & Joober, 2012). In terms of a physiological mechanism, there is evidence to suggest that oxytocin may affect stress reactivity by modulating the hypothalamic-pituitary-adrenal axis via modulation of neural activity within the amygdala (Viviani et al., 2011).

Subjective stress and cortisol levels are known to be highly related to eating behaviour in healthy women (Epel, Lapidus, McEwen, & Brownell, 2001), and play an even more dominant role in the motivation of eating behaviour in women with bulimia nervosa and binge eating disorder (Leslie, Turton, Burgess, Nazar, & Treasure, 2018). The implication of oxytocin in both reward and anxiety-related processes may therefore explain previous existing implicating abnormal oxytocin functioning in bulimia nervosa.

The aim of the current study was to explore the impact of the administration of oxytocin on both reward and anxiety-related processes. Therefore, we tested the impact of intranasal oxytocin supplementation on subjective hunger, immediate consumption of palatable food, and the 24 pattern of eating in women with binge eating disorder and bulimia nervosa and healthy controls. In order to assess the implication of anxiety in this effect, we also measured the effect of oxytocin on subjective stress, the extent to which participants

reported “feeling fat” (as a disorder-specific indication of anxiety), and on salivary cortisol levels.

We hypothesised that a divided dose of 64IU intranasal oxytocin administration would reduce subjective hunger, the immediate consumption of palatable food, 24-hour calorie consumption, and the incidence of binge eating when compared to placebo. We also hypothesised that oxytocin administration would be associated with lower levels of stress, and that participants would report lower levels of “feeling fat”. Finally, we predicted that participants would have lower salivary cortisol concentrations in the oxytocin, versus placebo, condition. We hypothesised that each of these effects would be moderated by eating disorder status, such that participants with BN or BED would experience greater reductions in food consumption and stress-related variables than participants with no history of an eating disorder.

Methods

Participants

We recruited a total of 52 women for the current study: 25 women met DSM-5 criteria for either bulimia nervosa or binge eating disorder and 27 women had no current or prior history of an eating disorder. Participants were identified via an e-mail circular at King’s College London and through posters placed throughout King’s College London and local community noticeboards. Participants were required to be female, between 18 and 40 years old, proficient in English, and right handed (due to an MRI scan conducted within the current battery of tasks). Exclusion criteria included pregnancy, severe comorbidity (e.g., substance abuse, drug addiction, psychosis, diabetes), history of drug dependence, history of a neurological condition (e.g., epilepsy), a significant visual impairment, which is not corrected by eyewear, currently

suffering from a cold or flu, currently smoking > 5 cigarettes per day (past 6 months), consuming > 21 units of alcohol per week, contraindication to MRI scans (due to an MRI conducted as part of the current battery of tasks), and current intake of medication that might potentially interact with oxytocin (e.g., Prostaglandins).

Participants with bulimia nervosa and binge eating disorder reported an average binge eating frequency of 14.14 episodes over the past 28 days (*SD* = 9.88). The women with bulimia nervosa endorsed an average frequency of self-induced vomiting equal to 10.40 occasions over the past 28 days (*SD* = 13.61), an average laxative abuse frequency of 5.13 occasions over the past 28 days (*SD* = 8.35), an average frequency of "hard exercise intended to control weight or shape" equal to 7.31 occasions over the past 28 days (*SD* = 8.57), and one participant reported using diuretic pills on 4 occasions over the past 28 days.

Of the 25 women with bulimia nervosa and binge eating disorder, 7 women had a comorbid psychiatric disorder. Specifically, 5 women had comorbid depression, 4 women had comorbid generalised anxiety disorder, 4 women had borderline personality disorder, 1 woman had social anxiety, 1 woman had obsessive-compulsive disorder, and 1 woman had an autism spectrum disorder. At the time of the study, 7 women were taking an antidepressant, 1 woman was taking a mood stabiliser, and one woman was taking an antipsychotic drug.

Ethical approval for the study was granted by the London – Camberwell St Giles Research Ethics Committee (Reference: 14/LO/2115).

Study Design

This proof-of-concept study was double-blind and placebo-controlled with a crossover design. Each participant was invited to come to the laboratory on three occasions. The first occasion was a preliminary screening visit in which each participant signed informed consent

and was screened for eligibility for the study. The height and weight of each participant was also measured in this initial screening visit. Each participant was then given a link to an online survey in which they could provide basic demographic data (including age and education level) before the first experimental visit.

Following this screening visit, each participant came to the laboratory for two experimental visits, held two days apart in order to ensure that each participant completed each of the experimental study sessions whilst in the same phase of the oestrous cycle. Each participant was also asked to report the first day of their last menstrual period and any hormonal contraception they were currently taking. Participants were asked to eat 2.5 hours prior to each experimental visit, and both sessions occurred at the same time of day to control for random variance in baseline hunger.

The order of activities for each experimental visit is depicted in **Figure 1**. On arrival at the laboratory for the first experimental session, each participant completed a visual analogue scale indicating their state level of stress, hunger, and the extent to which they "felt fat" on a scale anchored from 0 to 10. At this time participants also provided a 1ml saliva sample, which was used to test for salivary cortisol concentration.

Fifty minutes following this baseline measurement, each participant self-administered 40IU of intranasal oxytocin or identical volume of placebo spray. One hour and twenty minutes after the initial administration of the visit's allocated nasal spray, each participant self-administered an additional 24IU of intranasal oxytocin or identical volume of placebo spray, completed a second visual analogue scale, and provided a second 1ml saliva sample[1]. The need for a second dose of oxytocin at this time point was based on previous neuroimaging research

[1] An MRI scan was conducted in the hour following the initial nasal spray administration for each visit (40IU oxytocin or placebo), and the second nasal spray administration (24IU oxytocin or placebo). This scan is not reported within the scope of the current paper.

indicating that the central action of a 40IU dose of intranasal oxytocin peaks between 39 and 51 minutes following administration (Paloyelis et al., 2016). Thirty minutes after the second administration of the allocated nasal spray, each participant was presented with a bogus taste test (described in further detail below) concurrently with a third visual analogue scale to complete. At the conclusion of each experimental session (180 minutes after first drug administration), each participant provided a third 1ml saliva sample and guessed which spray (oxytocin or placebo) they believed they had been provided with on that day. Participants were then provided with a paper log on which they were requested to record everything they ate or drank, other than water, over the 24 hours following the experimental session. Each participant was then sent a link to an online survey, in which they could input their food and drink intake at the conclusion of the 24-hour period.

The second experimental session followed the same protocol except with the opposite spray to that allocated for the first experimental session (i.e., if a participant received oxytocin intranasal spray on the first experimental visit, the placebo spray was allocated for the second visit and vice versa). The order in which each participant received oxytocin or placebo nasal spray was pseudo-randomised, such that an equal number of participants in both the BN/BED and healthy control samples received the oxytocin spray during the first visit as received the placebo spray during the first visit. Both the experimenter and participant were blind to the order of spray allocation.

Bogus Taste Test

The bogus taste test is a validated task commonly used to measure the effect of factors hypothesised to contribute to palatable food consumption (Robinson et al., 2017). In the current study, participants were presented with three bowls of food in standardised white bowls. One bowl contained 250g grapes, one contained 50g crisps, and the last contained 220g chocolate.

These quantities were chosen in order to standardise the degree to which each food appeared to fill the bowl. The bowls were presented in a standardised order from left to right (first grapes, then crisps, then chocolate). Participants were presented with a visual analogue scale for each of the three types of food, and asked to rate each food for tastiness, sweetness, saltiness, richness, and pleasantness on a scale from 0 to 10. Each participant was instructed to taste each food so that they could complete the visual analogue scales. The participant was left alone in a private room for 15 minutes to complete the task. As the experimenter exited the room, the participant was told as an "afterthought" to eat as much as they would like as the remaining food would be thrown out.

Upon completion of the taste test, the bowls (with the remaining food) were brought to another room, where an assistant weighed the remaining food of each type whilst out of sight of the participant. The remaining weight was subtracted from the exact initial weight to calculate the quantity of each food eaten by the participant. This quantity was then later converted into calories.

Biochemical Analysis

Saliva samples were stored at -20.0C prior to the immunoassay for cortisol levels. The enzyme immunoassay to determine cortisol concentration was conducted using the Salimetrics® Expanded Range High Sensitivity immunoassay kit. This assay method is sensitive to distinguish concentrations of 0.007µg/dl cortisol from 0.

Statistical Analysis

Demographic data. Age and BMI for the BN/BED and healthy control samples were compared using Mann-Whitney U tests due to excessive skew in the Age and BMI variables. Education level was converted to a standardised scale based on the United Kingdom's

Regulated Qualifications Framework (RQF). RQF Education level was compared between groups using an independent-samples median test.

Preliminary analyses of the moderating effect of follicular phase. Due to restrictions associated with availability of the MRI scanner, it was not possible to test all participants during the same follicular phase. We therefore conducted preliminary analyses testing the moderating influence of follicular phase on the effect of oxytocin on each of the following dependent variables. Follicular phase did not have a significant moderating effect for any variable. The full results of these preliminary analyses are reported in the **Supplementary Material**.

Eating behaviour data. The food diary data reported by participants was converted into calories using the nutrition label for packaged foods, where possible. For items of produce and where no brand of food was reported by the participant, calorie reference values were drawn from MyNetDiary.com. The incidence of binge eating was defined by the consumption of at least 1000 calories at a single time point reported in the food diary, when this consumption was not part of a main meal. Due to the great variability in calorie consumption observed in both the taste test and food diary data, we therefore proceeded to conduct negative binomial regressions with exchangeable correlation matrix in order to validly retain all possible data points in the analyses for caloric consumption in the taste test, and the 24-hour food diaries (Gardner, Mulvey, & Shaw, 1995). Exact binomial tests were conducted to investigate the association between drug allocation and the incidence of binge eating over the following 24 hours.

Cortisol data. The cortisol data were analysed with a linear mixed effects analysis using the lmerTest package for R (Kuznetsova, Brockhoff, & Christensen, 2017). Salivary cortisol concentration was the planned dependent variable. We tested a full factorial model of the fixed

effects for eating disorder status, drug condition, time point, and all associated two- and three-way interaction effects. Individual participant was entered as a random effect.

Visual analogue scale data. The visual analogue scale data for hunger, stress, and feelings of fatness were analysed with linear mixed effects analyses using the lmerTest package for R (Kuznetsova et al., 2017). We included a full factorial model including fixed effects for the within-subject variables Drug Condition (oxytocin or placebo) and Time Point (measured at time point 1, 2, or 3), and the between-subject variable Eating Disorder Status (healthy control or BN/BED).

Results

Demographic Data

Demographic data for the BN/BED sample and healthy control sample are presented in **Table 1.** There were no significant differences between the healthy control and BN/BED samples in Age ($U = 302.00$, $p = .772$) or BMI ($U = 336.00$, $p = .202$). There were no significant differences in education between groups (test statistic = 1.78, $p = .317$). Participants in the BN/BED group reported having an eating disorder for an average of 10.30 years ($SD = 5.87$ years), with an average age of onset of 15.74 years ($SD = 4.76$ years).

Drug Blinding

Participants guessed drug condition correctly on 57 out of the total 104 visits (54.8% of visits), which was not found to be significantly greater than chance ($p = .377$).

Data for Calorie Consumption

Within the taste test data, one outlier ($Z > |3.0|$) was found in the quantity of chocolate consumed in the oxytocin condition, and another outlier was identified for a separate

participant in the quantity of chocolate consumed in the placebo condition. There was a great deal of variability in the reported calorie consumption in the 24-hour food diaries, particularly by participants with BN (see **Figure 2**). Descriptive statistics for the food consumption data are reported in **Table 2**. Data plots illustrating the distribution of caloric consumption in the taste test are presented in **Supplementary Figure 1**.

Analysis of the Effects of Oxytocin on Calorie Consumption, By Eating Disorder Status

24-hour calorie consumption. We conducted a negative binomial regression with the predictors Drug Condition and Eating Disorder Status to test the effects of oxytocin on 24-hour calorie consumption. Neither Drug Condition, Eating Disorder status, nor the Drug Condition*Eating Disorder Status interaction were significant. The full results of the negative binomial log linked regression for the food diary data are reported in **Table 3**.

Taste test calorie consumption. We conducted a negative binomial regression with the predictors Drug Condition and Eating Disorder Status to test the effects of oxytocin on calorie consumption in the taste test. The negative binomial regression did not reveal a main effect of Drug Condition or Eating Disorder Status on caloric consumption in the taste test, nor was there a significant interaction between Drug Condition and Eating Disorder Status. The full results of the negative binomial log linked regression for the taste test data are reported in **Table 4**.

Effect of oxytocin on subsequent incidence of binge eating

We next conducted an exact binomial test to determine whether oxytocin impacted whether participants in the BN/BED group had a binge eating episode in the 24 hours following oxytocin administration, versus placebo administration. Fifteen participants did not have a binge eating episode on either day. No participant had a binge eating episode following both

respective experimental sessions. Two women experienced a binge eating episode in the 24 hours following oxytocin administration, while three women had a binge eating episode in the 24 hours following placebo administration. An exact binomial test revealed the frequency of binge eating following oxytocin administration versus placebo was not significant (p = .999).

Salivary Cortisol

The salivary cortisol data were screened for outliers and violations of the assumption of normality. It was found that the cortisol data was highly positively skewed. Therefore, the cortisol data was transformed by adding a value of one[2], and then log 10 transforming the cortisol data. Six outliers (Z > |3.0|) were identified in the transformed cortisol data. However, as none of the participants' data had excessive influence on overall model parameters (Cook's distance < 1.0), these outliers were retained in the mixed linear effects analysis. Descriptive statistics for the raw cortisol data are presented in **Table 5**. Data plots for the transformed cortisol variable are presented in **Figure 3**.

The linear mixed model testing the effect of oxytocin on salivary cortisol levels revealed a significant main effect of experiment time point, such that salivary cortisol tended to decrease from time point 1 to time point 3. Neither the main effects for drug condition or eating disorder status, nor any two- or three-way interaction, were significant. The fixed effects for the linear mixed model testing the moderating effect of eating disorder status on the effect of oxytocin on salivary cortisol are presented in **Table 6**.

Visual Analogue Scales

The data were first analysed for outliers and assumptions of normality. The stress variable in the oxytocin condition at time point 2 was found to be significantly skewed

[2] A value of one was added before log transforming the data in order to retain one case with a cortisol concentration of zero.

in the healthy control sample (skew = 2.08). Due to skew in the data for subjective stress, a value of one was added to the stress data[3] and the data was Log10 transformed before proceeding with the planned analysis. All variables within the data for hunger and the perception of feeling fat were approximately normally distributed (skew < |2.0|, kurtosis < |9.0|). The descriptive statistics for the Visual Analogue Scale data are presented in **Tables 7 and 8**.

None of the data points within the linear mixed model for hunger had undue influence on the model (Cook's distance < 1.0). The linear mixed model for hunger revealed a significant main effect of Time Point, such that hunger linearly increased from time point 1 to time point 3. Neither the main effects for Drug Condition or Eating Disorder Status, nor any of the two- or three-way interactions were significant. Fixed effects of the linear mixed model for hunger are reported in **Table 9**.

None of the data points within the linear mixed model for feeling fat had undue influence on the model (Cook's distance < 1.0). The linear mixed model for the extent to which participants felt fat revealed a main effect of Eating Disorder Status, such that the BN/BED group reported significantly greater levels of "feeling fat", compared to the healthy control group. Neither the main effect for Drug Condition, Time Point, nor any of the two- or three-way interactions were significant. Fixed effects of the linear mixed model for feelings of fatness are reported in the **Table 10**.

None of the data points within the linear mixed model for the transformed stress variable had undue influence on the model (Cook's distance < 1.0). The linear mixed model for the transformed stress variable revealed a significant main effect of Time Point, such that

[3] A value of one was added before log transforming the data in order to retain cases where subjective stress was reported to be equal to zero.

subjective stress tended to decrease from time point 1 to time point 3. There was also a significant main effect of Eating Disorder Status, such that the BN/BED group reported significantly greater levels of subjective stress. Fixed effects for the linear mixed model for the transformed stress data are reported in the **Table 11**.

Discussion

The current study aimed to test the influence of a divided dose of 64IU intranasal oxytocin on eating behaviour and stress in adult women with bulimia nervosa or binge eating disorder. Contrary to our hypotheses, we did not find that oxytocin affected subjective hunger, the immediate consumption of palatable food, 24-hour caloric consumption, or the incidence of binge eating, and eating disorder status did not modify the effect of oxytocin on eating. We also failed to corroborate our hypothesis that oxytocin would reduce subjective stress, the extent to which participants "felt fat", and salivary cortisol levels. The effect of oxytocin on these stress-related variables was also not moderated by eating disorder status.

These findings differ from previous research showing that intranasal oxytocin administration reduced reward-driven food intake in healthy and overweight/obese men (Ott et al., 2013; Thienel et al., 2016). Visual inspection of the data revealed that there were some differences in the distribution of extreme values of caloric intake within the sample of women with bulimia nervosa, such that the very high values tended to occur in the placebo condition while very low values tended to occur in the oxytocin condition. Overall, however, the current findings failed to corroborate a previous study which found that oxytocin reduced 24-hour caloric consumption in Korean women with bulimia nervosa (Kim et al., 2015; Micali et al., 2017).

There are several possible explanations as to why the current study failed to replicate the finding that oxytocin suppresses 24-hour caloric intake in women with bulimia nervosa.

One possible reason may be related to the different dose of oxytocin employed in the current experimental design. Due to previous evidence that the brain response to intranasal oxytocin peaks between 39-51 minutes following administration (Paloyelis et al., 2016), we opted to administer a top-up dose of 24IU following an MRI scan conducted during the current battery of tasks in addition to the original dose of 40IU oxytocin. There is evidence to suggest that the potency of oxytocin may be related to dose by an inverse quadratic function. Specifically, it has previously been shown approximately 24IU intranasal oxytocin significantly reduces plasma cortisol levels relative to placebo, while this effect is not apparent at a dose of 48IU oxytocin (Cardoso, Ellenbogen, Orlando, Bacon, & Joober, 2013). It may therefore be the case that oxytocin does indeed reduce 24-hour caloric intake in women with bulimia nervosa at lower doses (such as the 40IU dose tested in Korean women) (Kim et al., 2015), while failing to produce an effect at higher doses (such as the 64IU dose employed in the current study).

The discrepant findings may also be explained by some demographic and clinical differences between the current sample and the sample recruited by Kim et al. (2015). For example, the inhibitory effect of oxytocin on caloric consumption in women with bulimia nervosa may be moderated by cultural and/or unexplored genetic factors differing between women of Eastern Asian origin and Caucasian women. Additionally, it should be noted that there was a longer average duration of illness in the current sample (10.3 years as opposed to 4.8 years in the study by Kim and colleagues) and a younger average age of onset (15.74 years, as opposed to 18.74 years in the study by Kim and colleagues). That being said, given the short-acting effects of a single dose of oxytocin, it is unclear what mechanism could explain the continued effect of oxytocin on feeding approximately 23 hours following its peak physiological potency (Paloyelis et al., 2016). It may, therefore, rather be the case that the previous findings by Kim et al. (2015) represent a Type I error, which was not replicated in the current study.

One notable difference between the current study design to that of previous studies demonstrating an inhibitory effect of oxytocin on palatable food intake (Burmester, Higgs, & Terry, 2018; Ott et al., 2013; Thienel et al., 2016) was the gender of participants included, with the current sample including only female participants, while studies conducted by Ott et al. (2013), Thienel et al. (2016), and Burmester et al. (2018) included only male participants. Another difference between the current study and these previous studies was the lack of a full meal before provision of the snack foods used to test palatable food intake. While the current null findings may be partially due to the influence of hunger-driven eating in the current paradigm, the current experimental design bears closer resemblance to the circumstances in which binge eating often occurs; that is, after a period of mild to moderate food restriction (with more severe restriction often observed in bulimia nervosa). Therefore, while it may be the case that prior provision of a full meal may have elicited stronger results in the taste test, the current null findings have more valid implications for the effects of oxytocin on real-world binge eating episodes (as reflected in the null effects on subsequent binge eating in the current study).

It should be noted that the current study was affected by low power in light of the small effect size of oxytocin on the dependent variables of interest. For example, given the results of the current cortisol analysis, a sample size of 59 participants across would have been necessary for the overall linear mixed model to have a power of 80%, while the current study had 52 participants. The small effect sizes associated with the association between oxytocin and stress and salivary cortisol in the current study add to an increasingly complex picture in the relevant literature. Oxytocin has been shown repeatedly to reduce the anxiety response in animals (Neumann & Slattery, 2016) and to reduce social anxiety in humans. However, a recent meta-analysis has shown that exogenous oxytocin administration, in fact, increases the startle response in healthy humans (Leppanen, Ng, Kim, Tchanturia, & Treasure, 2018). Furthermore,

research in a clinical population of participants with generalised anxiety disorder has suggested the anxiolytic properties of oxytocin may be specific to men (Feifel, MacDonald, McKinney, Heisserer, & Serrano, 2011). Further research testing the dose-response effect of oxytocin on stress in eating disorders in both men and women with bulimia nervosa and binge eating disorder will be useful in clarifying further moderators of oxytocin's effects on anxiety in human populations.

Limitations of the current study include the adoption of a single session study design. Although commonly used prior to clinical trials in translational science, the current design may not be suitable for populations with binge-type eating disorders. Given that the current DSM-5 definition for both bulimia nervosa and binge eating disorder requires a minimum of one binge eating episode per week, it is perhaps unsurprising that participants (5 out of 25 participants with bulimia nervosa or binge eating disorder) experienced a binge eating episode following one experimental session, while others exhibited a more restrictive pattern of eating (commonly observed in bulimia nervosa). This variable eating pattern contributed to the large standard deviation in subsequent caloric consumption over the following 24 hours, thus potentially masking any true effect that oxytocin may exert on eating patterns in the sample of participants with bulimia nervosa or binge eating disorder. We would therefore recommend that future studies measure the influence of oxytocin on eating behaviours over longer periods of time in populations with binge-type eating disorders to control for the large degree of within-person baseline variability in eating patterns. It would also be helpful to measure early sensitive indicators of the effect of oxytocin on approach bias to food, such as attentional bias.

Additionally, we would also recommend that future studies test populations of women with bulimia nervosa and binge eating disorder separately, as the current study found numerically divergent patterns of results in some analyses. Finally, it should be noted that the current sample consisted exclusively of women, and the current findings should therefore not

be generalised to men with BN or BED, especially in light of previous literature indicating that the response to other treatments for BN is moderated by gender (Agüera et al., 2017).

In conclusion, the current study aimed to investigate the effects of intranasal oxytocin on eating behaviours and stress in a sample of women with bulimia nervosa and binge eating disorder. We did not find that oxytocin significantly affected the consumption of palatable food intake, 24-hour caloric consumption, or subjective measurements of stress. Further studies testing a dose-response of oxytocin in a chronic treatment paradigm will be useful in further clarifying the moderating effects of oxytocin's effects on eating in populations with binge-type eating disorders.

References

Ágh, T., Kovács, G., Supina, D., Pawaskar, M., Herman, B. K., Vokó, Z., & Sheehan, D. V. (2016). A systematic review of the health-related quality of life and economic burdens of anorexia nervosa, bulimia nervosa, and binge eating disorder. *Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity, 21*(3), 353-364.

Agüera, Z., Sánchez, I., Granero, R., Riesco, N., Steward, T., Martín-Romera, V., . . . Segura-García, C. (2017). Short-Term Treatment Outcomes and Dropout Risk in Men and Women with Eating Disorders. *European Eating Disorders Review, 25*(4), 293-301.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders. *Arlington: American Psychiatric Publishing*.

Anestis, M. D., Smith, A. R., Fink, E. L., & Joiner, T. E. (2009). Dysregulated eating and distress: Examining the specific role of negative urgency in a clinical sample. *Cognitive Therapy and Research, 33*(4), 390-397.

Brownley, K. A., Berkman, N. D., Peat, C. M., Lohr, K. N., Cullen, K. E., Bann, C. M., & Bulik, C. M. (2016). Binge-eating disorder in adults: a systematic review and meta-analysis. *Annals of internal medicine, 165*(6), 409-420.

Burmester, V., Higgs, S., & Terry, P. (2018). Rapid-onset anorectic effects of intranasal oxytocin in young men. *Appetite, 130*, 104-109.

Cardoso, C., Ellenbogen, M. A., Orlando, M. A., Bacon, S. L., & Joober, R. (2013). Intranasal oxytocin attenuates the cortisol response to physical stress: A dose–response study. *Psychoneuroendocrinology, 38*(3), 399-407. doi:https://doi.org/10.1016/j.psyneuen.2012.07.013

Culbert, K. M., Racine, S. E., & Klump, K. L. (2016). Hormonal Factors and Disturbances in Eating Disorders. *Current psychiatry reports, 18*(7). doi:10.1007/s11920-016-0701-6

Ditzen, B., Schaer, M., Gabriel, B., Bodenmann, G., Ehlert, U., & Heinrichs, M. (2009). Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. *Biological psychiatry, 65*(9), 728-731.

Eddy, K. T., Tabri, N., Thomas, J. J., Murray, H. B., Keshaviah, A., Hastings, E., . . . Keel, P. K. (2017). Recovery From Anorexia Nervosa and Bulimia Nervosa at 22-Year Follow-Up. *J Clin Psychiatry, 78*(2), 184-189.

Epel, E., Lapidus, R., McEwen, B., & Brownell, K. (2001). Stress may add bite to appetite in women: a laboratory study of stress-induced cortisol and eating behavior. *Psychoneuroendocrinology, 26*(1), 37-49.

Feifel, D., MacDonald, K., McKinney, R., Heisserer, N., & Serrano, V. (2011). A randomized, placebo-controlled investigation of intranasal oxytocin in patients with anxiety. *Neuropsychopharmacology, 36*, S324-S449.

Gardner, W., Mulvey, E. P., & Shaw, E. C. (1995). Regression analyses of counts and rates: Poisson, overdispersed Poisson, and negative binomial models. *Psychological bulletin, 118*(3), 392.

Hay, P. (2013). A systematic review of evidence for psychological treatments in eating disorders: 2005–2012. *International Journal of Eating Disorders, 46*(5), 462-469.

Kim, Y.-R., Eom, J.-S., Yang, J.-W., Kang, J., & Treasure, J. (2015). The impact of oxytocin on food intake and emotion recognition in patients with eating disorders: A double blind single dose within-subject cross-over design. *PLoS ONE Vol 10(9), 2015, ArtID e0137514, 10*(9).

Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. B. (2017). lmerTest package: tests in linear mixed effects models. *Journal of Statistical Software, 82*(13).

Leppanen, J., Cardi, V., Ng, K. W., Paloyelis, Y., Stein, D., Tchanturia, K., & Treasure, J. (2017). The effects of intranasal oxytocin on smoothie intake, cortisol and attentional bias in anorexia nervosa. *Psychoneuroendocrinology*.

Leppanen, J., Ng, K. W., Kim, Y.-R., Tchanturia, K., & Treasure, J. (2018). Meta-analytic review of the effects of a single dose of intranasal oxytocin on threat processing in humans. *Journal of Affective Disorders, 225*, 167-179. doi:10.1016/j.jad.2017.08.041

Leslie, M., Silva, P., Paloyelis, Y., Blevins, J., & Treasure, J. (2018). A Systematic Review and Quantitative Meta-Analysis of Oxytocin's Effects on Feeding. *Journal of neuroendocrinology*, e12584.

Leslie, M., Turton, R., Burgess, E., Nazar, B. P., & Treasure, J. (2018). Testing the addictive appetite model of binge eating: The importance of craving, coping, and reward enhancement. *European Eating Disorders Review*.

Linnen, A.-M., Ellenbogen, M. A., Cardoso, C., & Joober, R. (2012). Intranasal oxytocin and salivary cortisol concentrations during social rejection in university students. *Stress, 15*(4), 393-402.

Meyer-Lindenberg, A., Domes, G., Kirsch, P., & Heinrichs, M. (2011). Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nature Reviews Neuroscience, 12*(9), 524.

Micali, N., Crous-Bou, M., Treasure, J., & Lawson, E. A. (2017). Association Between Oxytocin Receptor Genotype, Maternal Care, and Eating Disorder Behaviours in a Community Sample of Women. *European Eating Disorders Review, 25*(1), 19-25. doi:10.1002/erv.2486

Mitchison, D., Rieger, E., Harrison, C., Murray, S. B., Griffiths, S., & Mond, J. (2018). Indicators of clinical significance among women in the community with binge-eating disorder symptoms: Delineating the roles of binge frequency, body mass index, and overvaluation. *International Journal of Eating Disorders, 51*(2), 165-169.

National Institute for Health and Clinical Excellence. (2017). Eating Disorders: recognition and treatment. *NICE Guideline (NG69)*.

Neumann, I. D., & Slattery, D. A. (2016). Oxytocin in general anxiety and social fear: a translational approach. *Biological Psychiatry, 79*(3), 213-221.

Ott, V., Finlayson, G., Lehnert, H., Heitmann, B., Hallschmid, M., & et al. (2013). Oxytocin Reduces Reward-Driven Food Intake in Humans. *Diabetes, 62*(10), 3418-3425.

Paloyelis, Y., Doyle, O. M., Zelaya, F. O., Maltezos, S., Williams, S. C., Fotopoulou, A., & Howard, M. A. (2016). A spatiotemporal profile of in vivo cerebral blood flow changes following intranasal oxytocin in humans. *Biological Psychiatry, 79*(8), 693-705.

Pawaskar, M., Witt, E. A., Supina, D., Herman, B. K., & Wadden, T. A. (2017). Impact of binge eating disorder on functional impairment and work productivity in an adult community sample in the United States. *International Journal of Clinical Practice, 71*(7).

Peat, C. M., Berkman, N. D., Lohr, K. N., Brownley, K. A., Bann, C. M., Cullen, K., . . . Bulik, C. M. (2017). Comparative Effectiveness of Treatments for Binge-Eating Disorder: Systematic Review and Network Meta-Analysis. *European Eating Disorders Review, 25*(5), 317-328. doi:doi:10.1002/erv.2517

Robinson, E., Haynes, A., Hardman, C. A., Kemps, E., Higgs, S., & Jones, A. (2017). The bogus taste test: Validity as a measure of laboratory food intake. *Appetite, 116*, 223-231.

Russell, J., Maguire, S., Hunt, G. E., Kesby, A., Suraev, A., Stuart, J., . . . McGregor, I. S. (2018). Intranasal oxytocin in the treatment of anorexia nervosa: Randomized controlled trial during re-feeding. *Psychoneuroendocrinology, 87*, 83-92.

Spetter, M. S., & Hallschmid, M. (2017). Current findings on the role of oxytocin in the regulation of food intake. *Physiology & behavior, 176*, 31-39. doi:10.1016/j.physbeh.2017.03.007

Thienel, M., Fritsche, A., Heinrichs, M., Peter, A., Ewers, M., Lehnert, H., . . . Hallschmid, M. (2016). Oxytocin's inhibitory effect on food intake is stronger in obese than normal-weight men. *International Journal of Obesity November, 40*(11), 1707-1714.

Treasure, J., Leslie, M., Chami, R., & Fernández-Aranda, F. (2018). Are trans diagnostic models of eating disorders fit for purpose? A consideration of the evidence for food addiction. *European Eating Disorders Review, 26*(2), 83-91. doi:doi:10.1002/erv.2578

Viviani, D., Charlet, A., van den Burg, E., Robinet, C., Hurni, N., Abatis, M., . . . Stoop, R. (2011). Oxytocin selectively gates fear responses through distinct outputs from the central amygdala. *science, 333*(6038), 104-107.

Figure and Table Legends

Figure 1. Order of activities for each experimental visit.

Figure 2. 24-hour caloric consumption by participant diagnosis and drug condition.

Table 1: *Descriptive demographic data*

Table 2: *Descriptive statistics for calorie consumption data in the bogus taste test and 24-hour food diary*

Table 3: *Results from the negative binomial regression testing the effect of oxytocin and eating disorder status on 24-hour calorie consumption*

Table 4: *Results from the negative binomial regression testing the effect of oxytocin and eating disorder status on calorie consumption in the taste test*

Table 5: *Descriptive statistics for the raw salivary cortisol data*

Table 6: *Results of the linear mixed effects analysis testing a full factorial model with fixed effects for eating disorder status, oxytocin, and experiment time point on the transformed salivary cortisol variable*

Table 7: *Descriptive statistics for the visual analogue scale data for hunger and feeling fat*

Table 8: *Descriptive statistics for the visual analogue scale data for stress*

Table 9: *Results of the linear mixed effects analysis testing a full factorial model with fixed effects for eating disorder status, oxytocin, and experiment time point on subjective hunger*

Table 10: *Results of the linear mixed effects analysis testing a full factorial model with fixed effects for eating disorder status, oxytocin, and experiment time point on feelings of fatness*

Table 11: *Results of the linear mixed effects analysis testing a full factorial model with fixed effects for eating disorder status, oxytocin, and experiment time point on the transformed stress variable*