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**The addictive appetite model of Bulimia Nervosa and Binge Eating Disorder
a synthesis of basic science and clinical evidence for a new maintenance model of
recurrent binge eating**

Leslie, Monica Rose

Awarding institution:
King's College London

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The Addictive Appetite Model of Bulimia
Nervosa and Binge Eating Disorder:

*A Synthesis of Basic Science and Clinical
Evidence for a New Maintenance Model of
Recurrent Binge Eating*

Monica Rose Leslie

The Institute of Psychiatry, Psychology, and Neuroscience

King's College London

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ABSTRACT

Bulimia nervosa (BN) and binge eating disorder (BED) are psychiatric disorders characterised by recurrent loss-of-control binge eating behaviour, which is associated with the consumption of an objectively large quantity of food for the circumstances. BN is additionally characterised by recurrent inappropriate compensatory weight control behaviours. Both BN and BED cause significant distress and detract from quality of life in affected individuals. To date, however, current treatments do not support full recovery in a considerable portion of individuals with BN or BED, thus highlighting the need for novel treatment approaches which target critical maintenance factors.

The current thesis synthesises current evidence for the maintenance of recurrent binge eating behaviour through neural processes related to reward dysregulation and addiction. Based on previous and original evidence, I will go on to propose a new maintenance model of BN and BED and apply this model to a multi-modal investigation of exogenously-administered intranasal oxytocin in adult women with BN and BED.

Paper 1 presents a narrative review of empirical literature relating to the dysregulation of reward processes in bulimia nervosa and binge eating disorder. Within this paper, I propose a new theoretical maintenance model of recurrent binge eating behaviour: the “addictive appetite” model. Paper 2 presents an additional narrative review of evidence for the novel elements of the addictive appetite model, including evidence for tolerance and withdrawal effects in BN and a central insulin- and dopamine-mediated mechanism underpinning heightened craving. Paper 3 tests hypotheses stemming from the addictive appetite model, which predicts that craving and reward-motivated eating are central to the maintenance of BN and BED. Paper 3 presents a cluster analysis demonstrating that food craving, reward-motivated eating, and eating for coping purposes significantly distinguish women with BN and BED from age- and weight-matched comparison women.

Oxytocin, a neuropeptide and hormone, has previously been found to modulate anxiety and reward processes, which are central components of the addictive appetite model. Paper 4 presents a systematic review and quantitative meta-analysis of the effects of oxytocin on feeding behaviour in both animal and human samples. This meta-analysis demonstrates that a single dose of central or peripheral oxytocin significantly attenuates subsequent feeding in animals, while the effects of oxytocin decrease with chronic administration. The evidence for the effects of oxytocin on feeding in humans is mixed, and moderated by factors including eating disorder status, sex, and food type.

Paper 5 tests the functional significance of exogenous oxytocin in altering palatable food intake, subjective stress, and salivary cortisol in women with BN or BED and healthy comparison women without history of an eating disorder. Contrary to our hypotheses, oxytocin did not significantly affect palatable eating behaviour, 24-hour calorie intake, subjective, stress, or salivary cortisol.

Paper 6 investigates the influence of oxytocin on attentional bias to palatable food images. Contrary to our hypothesis, we found that oxytocin increased vigilance towards palatable, versus neutral, food images. Paper 7 tested the influence of oxytocin on risk-taking behaviours in a computerised task. Contrary to our hypotheses, women with BN and BED did not demonstrate significantly different risk-taking behaviour on the task in the placebo condition. We detected a significant interaction such that oxytocin decreased risk-taking behaviour to a greater degree in women with BN and BED. Paper 8 presents the preliminary outcomes of a study investigating the effect of 40IU intranasal oxytocin on the neural processing of visual and gustatory food stimuli. We did not observe significant differences in neural activation between women with BN or BED, versus healthy control women, in response to the anticipation or receipt of chocolate taste, versus water taste in the brain regions analysed. We did not find a significant effect of 40IU intranasal

oxytocin, versus placebo, on BOLD response to the anticipation or receipt of chocolate milk, versus water.

The results of these original experiments testing the influence of oxytocin indicate that a divided 64IU dose of oxytocin was not effective in reducing calorie consumption in women with BN and BED, although there is preliminary evidence that oxytocin may reduce risk-taking and attentional bias to food in women with BN and BED. Future dose-response studies in women would be helpful in ascertaining whether a different regime of oxytocin treatment may be more effective in treating the symptoms and sequelae of BN and BED. Future research targeting the maintenance factors of BN and BED identified by the addictive appetite model via different treatment methods would be useful to advance treatment for affected individuals and further refine this theoretical model of recurrent binge eating.

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LIST OF ABBREVIATIONS

AN	Anorexia Nervosa
BART	Balloon Analogue Risk Task
BED	Binge Eating Disorder
BMI	Body Mass Index
BN	Bulimia Nervosa
BOLD	Blood-Oxygen-Level-Dependent
CBT	Cognitive Behavioural Therapy
CBT-E	Enhanced Cognitive Behavioural Therapy
CCK	Cholecystokinin
CI	Confidence Interval
DASS	Depression, Anxiety, and Stress Scales
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4 th Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5 th Edition
ED	Eating Disorder
EDE-Q	Eating Disorder Examination – Questionnaire version
FCQ	Food Craving Questionnaire – Trait subscale
fMRI	Functional Magnetic Resonance Imaging

4V	Fourth Cerebral Ventricle
FTO	Fat mass and obesity-related gene
GI	Glycaemic Index
HC	Healthy Comparison
HFD	High-Fat Diet
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
NAcc	Nucleus Accumbens
NTS	Nucleus of the Solitary Tract
OFC	Orbitofrontal Cortex
OT	Oxytocin
OXTR	Oxytocin Receptor Gene
PEMS	Palatable Eating Motives Scale
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
ProWS	The Highly Processed Food Withdrawal Scale
RLCV	Right Lateral Cerebral Ventricle
SNP	Single Nucleotide Polymorphism

SPM	Statistical Parametric Mapping
3V	Third Cerebral Ventricle
UK	United Kingdom
VAS	Visual Analogue Scale
vIPFC	Ventrolateral Prefrontal Cortex
VMH	Ventromedial Hypothalamus
VTA	Ventral Tegmental Area
YFAS	Yale Food Addiction Scale

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Note: The above-listed figures are labelled “Supplementary Figures” to remain consistent with existing and submitted publications associated with each paper.

STATEMENT OF WORK

Introduction: The candidate independently conducted a literature search for relevant theoretical ideas and previous empirical findings. The candidate wrote the introduction independently, before subsequently receiving comments and recommendations for improvement from Professor Janet Treasure and Dr Yannis Paloyelis.

Paper 1: The candidate collaborated with Professor Janet Treasure to develop and refine the theoretical model of eating disorders proposed within the paper. The candidate conducted a literature search of relevant previous findings and wrote the majority of the paper. The candidate and Professor Janet Treasure share first authorship of this paper.

Paper 2: The candidate identified the elements of the addictive appetite model which required further elaboration. The candidate independently researched a central insulin- and dopamine-mediated mechanism hypothesised to underpin bulimia nervosa and binge eating disorder. The candidate wrote the section of the paper describing this neuroendocrinological mechanism, as well as the introduction and conclusion. Ms Ellen Lambert conducted the literature review examining existing evidence for withdrawal and tolerance effects in bulimia nervosa and wrote the corresponding section of the paper. Professor Janet Treasure subsequently provided recommendations to improve the original draft of the paper.

Paper 3: The candidate independently proposed the hypotheses tested with the paper, and conducted all analyses contained within the paper. Dr John Hodsoll (statistician) provided statistical advice and consultation, while all analysis decisions were ultimately made by the candidate. The candidate wrote the paper independently, and subsequently consulted with the co-authors of the paper for additional comments and recommendations for improvement. The candidate holds first authorship of this paper.

Paper 4: The candidate independently proposed the research question examined in the systematic review and meta-analysis. The candidate subsequently developed the systematic search strategy and conducted the systematic search. Abstract and full-text screening was subsequently repeated by Paulo Silva, an MSc student. The candidate consulted with Dr John Hodsoll and Dr Jenni Leppanen for statistical advice. The candidate subsequently conducted the meta-analyses and conducted a qualitative synthesis of the results independently. The candidate wrote the paper independently, before subsequently receiving comments and recommendations for improvements from the paper's co-authors.

Paper 5: The candidate recruited all participants and conducted all data collection for the study. The author refined the study's hypotheses, conducted all statistical analyses, and wrote the paper independently. The candidate subsequently received comments and recommendations for improvement from the paper's co-authors.

Paper 6: The candidate recruited all participants and conducted all data collection for the study. The author refined the study's hypotheses, conducted all statistical analyses, and wrote the paper independently. The candidate subsequently received comments and recommendations for improvement from the paper's co-authors.

Paper 7: The candidate recruited all participants and conducted all data collection for the study. The author refined the study's hypotheses, conducted all statistical analyses, and wrote the paper independently. The candidate subsequently received comments and recommendations for improvement from the paper's co-authors.

Paper 8: The candidate recruited all participants and conducted all data collection for the paper. The candidate subsequently prepared the data for analysis, reoriented the neuroimaging scans, and manually checked realignment and registration parameters. Dr Yannis Paloyelis prepared the scripts for pre-processing. The candidate prepared and

conducted the first- and second-level analyses. The candidate subsequently wrote the paper independently, before receiving comments and recommendations for improvement from the paper's co-authors.

PUBLICATIONS INCORPORATED IN THE CURRENT THESIS

- Paper 1: Treasure, J.[†], Leslie, M.[†], Chami, R., & Fernandez-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:10.1002/erv.2578**
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- Paper 3: 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*, 26(6), 541-550. doi: 10.1002/erv.2621
- Paper 4: Leslie, M.**, Silva, P., Paloyelis, Y., Blevins, J., & Treasure, J. (2018). A systematic review and quantitative meta-analysis of the effects of oxytocin on feeding. *Journal of neuroendocrinology*, 30(8), e12584. doi: 10.1111/jne.12584
- Paper 5: Leslie, M.**, Leppanen, J., Paloyelis, Y., & Treasure, J. (2018). The influence of oxytocin on eating behaviours and stress in women with bulimia nervosa and binge eating disorder. *Molecular and Cellular Endocrinology*. doi:10.1016/j.mce.2018.12.014

[†]JT and ML share first authorship of this manuscript.

* ML and RT share first authorship of this manuscript.

LIST OF PUBLICATIONS COMPLETED DURING THE CANDIDATE'S PHD BUT NOT INCORPORATED IN THE CURRENT THESIS

Peer-Reviewed Articles

- Cardi, V., Leppanen, J., **Leslie, M.**, Esposito, M., & Treasure, J. (2019). The use of a positive mood induction video-clip to target eating behaviour in people with bulimia nervosa or binge eating disorder: An experimental study. *Appetite*. doi:10.1016/j.appet.2018.12.001
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- Nazar, B. P., Trindade, A. P., **Leslie, M.**, Malloy-Diniz, L. F., Sergeant, J., Treasure, J., & Mattos, P. (2018). Eating Disorders impact on vigilance and decision making of a community sample of treatment naive Attention-Deficit/Hyperactivity Disorder young adults. *Frontiers in Psychiatry*, 9. doi:10.3389/fpsy.2018.00531

Conference Presentations

- Leslie, M.**, Leppanen, J., Paloyelis, Y., & Treasure, J. (2018, October). *The influence of oxytocin on eating behaviours and stress in bulimia nervosa and binge eating disorder*. Paper presented at the Eating Disorders Research Society conference, Sydney, Australia.
- Leslie, M.**, Leppanen, J., Cardi, V., Ng, K. w., Paloyelis, Y., Stein, D., Tchanturia, K., & Treasure, J. (2017, July). *The effects of intranasal oxytocin on smoothie intake, cortisol, and attentional bias in anorexia nervosa*. Paper presented at the World Congress on Neurohypophysial Hormones, Mangaratiba, Brazil.

Textbook Chapters

- Leslie, M.** (In press). Serotonin and Feeding Regulation. In D. M. Tricklebank (Ed.), *The Serotonin System: History, Neuropharmacology, and Pathology*. San Diego, USA: Elsevier.
 - Scheduled publication in 2019
- Leslie, M.** & Treasure, J. (2017). Role of Oxytocin in Feeding and Eating Disorders. In T. Wade (Ed.), *Encyclopedia of Feeding and Eating Disorders*. Singapore: Springer Singapore.

OUTLINE OF THESIS

Chapter 1 presents background information about the two disorders which will be the focus of the current thesis: bulimia nervosa and binge eating disorder. More specifically, this thesis chapter will present current evidence regarding the diagnostic criteria, incidence and prevalence, and disorder trajectories of bulimia nervosa and binge eating disorder. This chapter will then go on to discuss the secondary medical complications, common comorbidities, and risk factors for each disorder, followed by a discussion of influential maintenance models for bulimia nervosa and binge eating disorder.

Chapter 2 includes three papers which propose and subsequently defend a novel maintenance model of recurrent binge eating in the context of bulimia nervosa and binge eating disorder.

Chapter 3 discusses the rationale for investigating the influence of oxytocin in curbing binge eating behaviours, through a pathway informed by the addictive appetite model. This chapter subsequently presents a systematic review and meta-analysis of the effects of oxytocin on eating.

Chapter 4 presents the findings of a double-blind, placebo controlled proof-of-concept study with a crossover design. This study investigated the effects of a divided dose of 64IU intranasal oxytocin on eating behaviours and stress in women with and without bulimia nervosa and binge eating disorder.

Chapter 5 presents two papers which tested the influence of intranasal oxytocin on attentional bias to foods images and risk-taking behaviours in women with and without bulimia nervosa and binge eating disorder.

Chapter 6 presents the results of a functional magnetic resonance imaging investigating the effects of oxytocin on the neural processing of taste in women with and without BN and BED.

Chapter 7 presents an overview of key findings, a synthesis of these findings with existing literature, and discusses general limitations and overall conclusions of the current thesis.

Chapter 1

1 Introduction

1.1 Introduction to Feeding and Eating Disorders

Feeding and eating disorders are defined within the Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM-5) as psychiatric disorders which “are characterized by a persistent disturbance of eating or eating-related behaviour that results in the altered consumption or absorption of food and that significantly impairs physical health or psychosocial functioning” (American Psychiatric Association, 2013, p. 329). Feeding and eating disorders specified with the DSM-5 include pica, rumination disorder, avoidant/restrictive food intake disorder, anorexia nervosa, bulimia nervosa, and binge-eating disorder. Additionally, a diagnosis of Other Specified Feeding or Eating Disorder (OSFED) can be administered within the DSM-5 framework for individuals who do not meet full criteria for any of the above-listed disorders but do exhibit a disturbance of feeding or absorption of food that is associated with significant distress or functional impairment. Symptom presentations which may warrant a diagnosis of OSFED include atypical anorexia nervosa, bulimia nervosa (of low frequency and/or limited duration), binge-eating disorder (of low frequency and/or limited duration), purging disorder, and night eating syndrome.

1.2 Bulimia Nervosa

1.2.1 Bulimia Nervosa: Diagnostic Criteria

The DSM-5 specifies that the following five criteria must be met for a diagnosis of bulimia nervosa (BN): A) The individual must exhibit recurrent loss-of-control binge eating behaviour, which is associated with an objectively large amount of food for the circumstances consumed within a two-hour period; B) The individual must engage in recurrent inappropriate compensatory behaviours intended to prevent weight gain (e.g., self-induced vomiting, laxative abuse, fasting, use of diet pills or diuretics, or excessive exercise); C) Both the binge eating and compensatory behaviour must occur, on average,

with a frequency of at least once per week over a period of three months; D) The individual's self-evaluation is unduly impacted by body shape and weight; E) These disturbances must occur in the absence of anorexia nervosa.

Previously, DSM-IV criteria imposed a greater frequency requirement of binge eating and purging for a diagnosis of BN to be met (American Psychiatric Association, 2000). That is, at least two episodes of binge eating and purging per week needed to be present over a period of at least three months for a diagnosis of DSM-IV BN. Furthermore, DSM-IV criteria specified two types of BN: *Purging type*, characterised by self-induced vomiting, laxative abuse, diuretics or enemas, and *Nonpurging type*, characterised by fasting or excessive exercise, but not compensatory behaviours associated with the Purging type of BN. The impact of the expansion of frequency criteria in the DSM-5 on prevalence and incidence rates will be discussed further in section 1.2.2.

1.2.2 Bulimia Nervosa: Incidence and Prevalence

Point prevalence of a disorder refers to the proportion of a given population who meet diagnostic criteria for the specified disorder at a single point in time. Point prevalence estimates for BN differ slightly across Western cohorts, with the most notable demographic difference being a greater prevalence of BN among women, as compared to men (Jaite, Hoffmann, Glaeske, & Bachmann, 2013; Smink, van Hoeken, Oldehinkel, & Hoek, 2014).

Machado, Gonçalves, and Hoek (2013) combined data from two epidemiological studies, including a total of 3,048 female Portuguese high school and university students, estimating the point prevalence of DSM-5 BN to be 0.59%. This point prevalence was approximately replicated by Smink et al. (2014) in a Dutch cohort study including 861 19-year-old women, in which the point prevalence of DSM-5 BN was found to be 0.6%. This point prevalence of 0.59-0.6% represents an increase from previous estimates using

DSM-IV criteria. For example, when Machado et al. (2013) applied DSM-IV diagnostic criteria to the same Portuguese sample of young women, point prevalence of BN was found to be 0.46%. Additionally, when using the International Classification of Diseases system – 10th edition (ICD-10), the prevalence of BN has been recorded to be as low as 0.2% in German girls and young women between the ages of 10 and 21 (Jaite et al., 2013).

It should be noted that point prevalence of BN also varies by age, therefore, cohort studies including multiple ages groups can mask significant differences in point prevalence across different development periods. In a prospective longitudinal study of 9,031 American girls and women, Glazer et al. (2018) found that that across the 18-year assessment period prevalence was highest between the ages of 19 and 23 years of age. When classifying BN using DSM-5 criteria, baseline prevalence among girls aged 9 to 15 years old was found to be 0.10%, increasing to a maximum of 1.1% between the ages of 19 and 22 years old (Glazer et al., 2018).

As previously stated, the point prevalence of BN is lower among men than women. The point prevalence of DSM-5 BN has been found to be 0.1% in 19-year-old Dutch men, compared to 0.6% amongst Dutch women in the same study (Smink et al., 2014). Although raw estimates differed in a separate study using ICD-10 criteria and including participants with a broader range in ages, a similar discrepancy has also been found amongst a sample of German men between the ages of 10 and 21 years old, where point prevalence was 0.02%, as opposed to the 0.20% point prevalence amongst young German women in the same study (Jaite et al., 2013).

Therefore, when men and women are considered together, the prevalence of DSM-5 BN is intermediate between that of the two genders, with overall 12-month prevalence being estimated at 0.14% in a sample of 36,209 American adults (Udo & Grilo, 2018), and 3-month prevalence being estimated at 0.66% in Australian adults (Hay, Girosi, & Mond,

2015). Amongst German adolescents and young adults, baseline 12-month prevalence of ICD-10 BN was found to be 0.11% in 2009 (Jaite et al., 2013). While reasons for the difference in point prevalence estimated in American versus Australian adults are not entirely clear, the relatively lower point prevalence found in the German sample likely reflects differences in the diagnostic classification used to define cases as well as the youth of the sample, which some participants being as young as 10 years old. There appears to be limited evidence for differences in prevalence amongst different race and ethnic groups (Udo & Grilo, 2018), with the exception that white US Latino men have a higher 12-month prevalence of BN when compared to white US non-Latino men (Marques et al., 2011).

In epidemiological terms, incidence refers to the onset of new cases of a disease or disorder within a given time period. There is mixed evidence for changes in the incidence of BN during the course of the 21st century. For example, a Danish study tracking the diagnosis of new cases of BN across all public health services found that, after adjusting for an overall increase in all psychiatric diagnoses, the incidence of BN decreased from 6.3 to 4.2 cases per 100,000 person-years from 1995 to 2010 (Steinhausen & Jensen, 2015). Similarly, a decrease in raw incidence rates of BN has been reported in the Norwegian health service from 2010 to 2016 (Reas & Rø, 2018) and in Dutch primary care service between an initial assessment period from 1985-1989 to the final assessment period in 2005-2009 (Smink et al., 2016).

However, this pattern for decreasing incidence rates was not replicated in a study drawing from data in the United Kingdom (UK) General Practice Research Database, which found that the incidence of BN remained stable for both men and women from 2000 to 2009 (Micali, Hagberg, Petersen, & Treasure, 2013). It should be noted, however, that the UK General Practice Research Database including records of approximately 5% of the UK population, in contrast to the Danish and Norwegian registers recording close to 100% of

new psychiatric diagnoses nationwide (Munk-Jørgensen & Dinesen Østergaard, 2011; Reas & Rø, 2018). While the data included in the UK study is generally representative of the age and gender make-up and geographic distribution of the UK, the possibility that the selection of General Practice surgeries contributing to the database is biased in other ways cannot be excluded.

However, evidence of lifetime risk across the 20th century suggests that the lifetime prevalence of BN may have, in fact, increased from 1944 until 1985, with the pattern for decreasing incidence being a newer phenomenon (Hudson, Hiripi, Pope Jr, & Kessler, 2007). Hudson et al. (2007) administered diagnostic interviews to a sample of 9,282 US adults gauging endorsement for lifetime history of any psychiatric disorder. The authors found significant inter-cohort differences in the sample, with lifetime risk of DSM-IV BN tending to increase from each cohort to the next, such that the relative odds of participants born in 1972-1985 endorsing lifetime history of BN were 16.8, as compared to participants born before 1944. It should be noted that these cohort effects are necessarily confounded by the age of participants, which may detract from recall ability in older adults. However, the fact that cohort effects remain significant from each cohort to the next, where each cohort overlaps over a period of a year (cohorts were determined by age at interview), suggests a true pattern of increasing incidence over the course of the 20th century, despite the potential over-estimation of the magnitude of this cohort effect. Current lifetime prevalence of DSM-5 BN has been estimated to be 0.08% in men and 0.46% in women, with an overall lifetime prevalence of 0.28% (Udo & Grilo, 2018).

1.2.3 Bulimia Nervosa: Disorder Trajectories

The average age of onset of BN has historically been estimated to be between 15 and 20 years old (Micali et al., 2013; Steinhausen & Weber, 2009; Stice, Marti, Shaw, & Jaconis, 2009), with the most recent estimate being 19.6 to 20 years of age (Favaro, Busetto, Collantoni, & Santonastaso, 2019; Udo & Grilo, 2018). However, onset of BN has been

reported in children as young as 11 years old (Schmidt, Hodes, & Treasure, 1992) and as late as 58 years old (Beck, Casper, & Andersen, 1996). Just over a quarter of individuals with BN have a prior history of anorexia nervosa, with a German study finding that 27.6% of the 196 sampled inpatients with BN had a history of anorexia nervosa (Fichter, Quadflieg, & Hedlund, 2008) and an American study finding that 26.8% of women with BN recruited from outpatient clinics and the community had a history of anorexia nervosa (Bardone-Cone et al., 2008).

Estimates of the long-term outcome of BN are complicated by different definitions of “recovery” and various degrees of recovery across studies. A meta-analysis in 2009, including three outcome classifications (recovered, improved, and chronicity), found that across 27 longitudinal studies, 45% of people had achieved recovery by follow-up, 27% achieved improvement, and 23% of people with BN exhibited a protracted chronic course of illness (Steinhausen & Weber, 2009). However, this meta-analysis included studies with follow-up periods as short as 6 months in duration, therefore limiting the insights these findings offer regarding rates of true long-term recovery from BN. Rates of recovery stratified by duration of follow-up period range from 33% recovery at 3-year follow-up (Zeeck, Weber, Sandholz, Joos, & Hartmann, 2011), to 55% at 5-year follow-up (Keski-Rahkonen et al., 2009), and with most recent estimates indicating a 68.2% recovery rate at both 9- and 22-year follow-up (Eddy et al., 2017).

Individuals who do not meet recovery criteria at follow-up tend to fall into one of the following categories: continued demonstration of some, but not all, diagnostic criteria for BN, continued demonstration of all diagnostic criteria for BN, crossover to another eating disorder diagnosis, or natural or premature death. Additionally, it should be noted that there is little correlation between remission at one follow-up time point to another, therefore, it can be argued that an additional category best fits some individuals with a cyclical pattern of remission and relapse over time (Zeeck et al., 2011). An Italian study

of 137 patients with BN found that over a 5-year period 8.4% of patients crossed over to a diagnosis of DSM-5 anorexia nervosa and 8.4% crossed over to a DSM-5 diagnosis of binge eating disorder.

Although the mortality rate associated with BN is lower than that of anorexia nervosa (Arcelus, Mitchell, Wales, & Nielsen, 2011), premature death remains more likely for affected individuals than for the general population. A systematic review of twelve studies measuring the mortality rate of BN found a standardised mortality ratio of 1.93 (Arcelus et al., 2011), and a more recent study recorded an even higher standardised mortality ratio of 2.33 (Franko et al., 2013). Additionally, a systematic review focusing specifically on rates of completed suicide in BN found that, of the 1,768 patients identified amongst eligible studies, there was a suicide rate of 0.030 per 100 person-years, as opposed to the general population suicide rate of .004 per 100 person-years (Preti, Rocchi, Sisti, Camboni, & Miotto, 2011). Standardised mortality ratio for death by suicide was therefore 7.5 for people with BN versus the general population (95% CI [1.6-11.6]).

1.2.4 Secondary medical complications of bulimia nervosa

BN is associated with a wide range of secondary medical complications, largely due to the deleterious effects of compensatory behaviours such as self-induced vomiting, laxative abuse, and insulin omission. Recurrent self-induced vomiting exposes the oral cavity to highly acidic stomach contents, which is commonly associated with the development of oral complications, including tooth erosion (Dynesen, Bardow, Petersson, Nielsen, & Nauntofte, 2008), dental sensitivity (Christensen, 2002), inflammation of oral mucosa (Ximenes, Couto, & Sougey, 2010), enlargement of the parotid glands (Mignogna, Fedele, & Lo Russo, 2004), and a reduced salivary flow rate resulting in oral dryness (Dynesen et al., 2008). Repeated self-induced vomiting can also place undue strain on the larynx, sometimes resulting in a hoarse voice, chronic cough, sore throat, and difficulty swallowing (Ferreira, Gama, Santos, & Maia, 2010).

The trauma of self-induced vomiting has been known to cause tearing of the lining of the oesophagus, known as a Mallory-Weiss tear, which sometimes resulting in bleeding (Cuellar, Kaye, Hsu, & Van Thiel, 1988). However, there is currently limited evidence that Mallory-Weiss tears occur at disproportionate rates in people with BN (Cuellar et al., 1988). More concerning, however, rare cases of Boerhaave syndrome have been reported in BN (Brauer, Liebermann-Meffert, Stein, Bartels, & Siewert, 1997), in which there is full intramural rupture of the oesophagus causing death in approximately 29% of cases where treatment is not immediately administered (De Schipper, Ter Gunne, Oostvogel, & Van Laarhoven, 2009).

Syrup of ipecac is an emetic containing the alkaloids emetine and cephaeline, which was abused by people with BN with increasing frequency from the late 1980s to early 1990s (Greenfeld, Mickley, Quinlan, & Roloff, 1993). Ipecac was commonly kept in households in the mid-20th century for the purpose of causing rapid vomiting in cases of inadvertent poison ingestion, such as by young children (Manno & Manno, 1977). However, the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists have since recommended against the routine use of ipecac in cases of poisoning, both due to low efficacy in preventing poison expulsion, as well as the cardiotoxic and neurotoxic effects of ipecac (Krenzelok, McGuigan, & Lheur, 1997). The cardiotoxic effects of ipecac increase risk of tachycardia and cardiac arrhythmias, while the neuromuscular effects have been known to cause muscle weakness (Manno & Manno, 1977). Given the relatively long 56-hour half-life of ipecac, these toxic effects can therefore cumulate in individuals abusing it on a regular basis (P. C. Ho, Dweik, & Cohen, 1998). Indeed, ipecac has been known to cause death in people with BN (Schiff et al., 1986).

Cardiac complications can also arise in BN due to electrolyte imbalances induced either by self-induced vomiting or laxative abuse. For example, a recent study of 1,026 adults

consecutively admitted to an eating disorders clinic in the US found that, of the 251 patients with BN, 26.6% presented with hypokalaemia on admission (Mehler et al., 2018). Such electrolyte imbalances commonly occur due to the repeated fluid loss caused by self-induced vomiting and laxative abuse, which stimulates activation of the renin-angiotensin system, thus increasing metabolic alkalosis and hypokalaemia (Brown & Mehler, 2012). Severe hypokalaemia can cause cardiac arrhythmias, including fatal ventricular rhythms in some cases (Buchanan, Ngwira, & Amsha, 2011; Piotrowicz et al., 2015).

In addition to self-induced vomiting and laxative abuse, the DSM-5 also includes insulin omission in people with insulin-dependent diabetes as another compensatory behaviour contributing to a diagnosis of BN (American Psychiatric Association, 2013). Insulin omission in the context of BN, sometimes referred to as “diabulimia” (Martin, Darbar, & Mokha, 2008), is associated with health risks including retinopathy, potentially leading to vision impairment, and nephropathy, which can result in kidney failure in severe cases (Takii et al., 2008). A prospective longitudinal study of 234 women with type 1 diabetes mellitus has found evidence for heightened mortality among women exhibiting greater levels of insulin restriction behaviour (Goebel-Fabbri et al., 2008).

1.2.5 Common psychiatric comorbidities of bulimia nervosa

Estimates of the prevalence rates of psychiatric comorbidity with BN vary slightly between samples, likely reflecting differing characteristics of inpatient and outpatient samples versus community samples, as well as country differences. However, research has consistently indicated heightened prevalence of unipolar depression, alcohol and substance abuse, and anxiety disorders among people with BN (Farstad, McGeown, & von Ranson, 2016; Hudson et al., 2007; Patel, Olten, Patel, Shah, & Mansuri, 2018; Ulfvebrand, Birgegård, Norring, Högdahl, & von Hausswolff-Juhlin, 2015).

Amongst a large community sample from the United States, including interviews with 2,980 English-speaking adults, 94.5% of people with BN met DSM-IV criteria for at least one psychiatric comorbidity (Hudson et al., 2007). However, a lower estimate (64.1% comorbidity with BN) has been found more recently amongst a German sample of female children and adolescents (Jaite et al., 2013). This difference in estimates is likely a product of a combination of the differing ages and gender make-up between the two samples, and also possibly reflective of country differences. Indeed, there is evidence to suggest that rates of psychiatric comorbidity with BN differ between men and women. For example, a Swedish study of treatment-seeking people with BN found that 74.4% of women with BN presented with at least one comorbid Axis I psychiatric disorder at initial presentation, compared to 84.5% of men (Ulfvebrand et al., 2015). Taken together, however, these data suggest that the majority of people with BN across countries, ages, and genders have at least one comorbid psychiatric disorder, thus adding to the complexity of appropriate psychiatric formulation for each individual case.

Amongst the previously cited US community sample (Hudson et al., 2007), the odds ratio for a participant with BN having any anxiety disorder was 8.6 (95% CI [3.4-21.6]), as compared to the general population. People with BN had significantly greater odds of having the following specific anxiety disorders: panic disorder (OR 2.9, 95% CI [1.1-7.9]), agoraphobia without panic (OR 8.9, 95% CI [3.0-26.2]), specific phobia (OR 5.4, 95% CI [2.6-11.4]), social phobia (OR 4.7, 95% CI [2.7-8.3]), post-traumatic stress disorder (OR 10.2, 95% CI [5.2-20.0]), obsessive-compulsive disorder (OR 7.5, 95% CI [1.7-37.5]), and separation anxiety disorder (OR 3.5, 95% CI [1.4-9.0]). Amongst treatment-seeking Swedish people with BN, raw prevalence of comorbid anxiety disorders has been estimated at 54.4% in women and 56.9% in men (Ulfvebrand et al., 2015).

The odds ratio for a person with BN having any mood disorder, compared to the general population, has been estimated at 7.8 in a community sample (95% CI [3.6-16.8]) (Hudson et al., 2007). Within this sample, the breakdown regarding the odds ratio of specific mood disorders is as follows: major depressive disorder (OR 4.3, 95% CI [1.7-10.8]), dysthymia (OR 4.4, 95% CI [1.5-12.6]), and bipolar disorder (OR 4.7, 95% CI [2.1-10.8]). Amongst a sample of 3,319 inpatients identified with BN in the US, 23.5% had comorbid depression. This estimate is numerically lower than the raw prevalence estimate of comorbid major depressive disorder in treatment-seeking Swedish women with BN (35.8% comorbidity) and marginally higher than the comorbidity estimate for major depressive disorder among Swedish men with BN (22.4%) (Ulfvebrand et al., 2015). This evidence therefore does not support the existence of overall greater comorbidity for comorbid major depressive disorder in inpatient populations with BN compared to those not receiving residential treatment, although the potential for country differences prohibits firm conclusions to this extent.

There is extensive evidence for deficits in global emotional regulation abilities in BN (Brockmeyer et al., 2014; Gilboa-Schechtman, Avnon, Zubery, & Jeczmiern, 2006; Harrison, Sullivan, Tchanturia, & Treasure, 2010; Svaldi, Griepenstroh, Tuschen-Caffier, & Ehring, 2012), with several studies finding that these deficits confer a general risk for psychopathology, rather than a specific risk for BN (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Svaldi et al., 2012). In addition to the fact that emotional dysregulation acts as a common risk factor for BN, mood disorders, and anxiety disorders, the affect regulation model of BN also posits that strong negative emotions, which characterise mood disorders and anxiety disorders, directly contribute to subsequent incidents of binge eating (Polivy & Herman, 1993). Binge eating is then posited to result in temporary relief from negative affect and is thus maintained over time through a mechanism of negative reinforcement (Polivy & Herman, 1993). A meta-analysis of studies administering

ecological momentary assessment to people with recurrent binge eating has provided partial support for this model, finding lower mood immediately prior to binge eating episodes versus non-binge eating, and lower mood on binge versus non-binge days (Haedt-Matt & Keel, 2011). However, it is unclear to what extent clinically low levels of affect, such as that seen in mood disorders and anxiety disorders, confer additional risk for BN beyond low affect as experienced by people without comorbid mood or affective disorders.

There is evidence for heightened prevalence of impulse-control disorders and substance abuse disorders amongst people with BN versus with general population, as well, with odds ratios calculated at 6.7 (95% CI [3.0-15.2]) and 4.6 (95% CI [2.0-10.8]), respectively (Hudson et al., 2007). The trans diagnostic traits predicting comorbidity with both disorders will be discussed in greater depth in Chapter 2 of the current thesis.

Finally, BN is also associated with borderline personality disorder (now commonly referred to as emotionally unstable personality disorder), avoidant personality disorder, and obsessive-compulsive personality disorder (Farstad et al., 2016). Specifically, a meta-analysis of studies examining personality disorders in adults with eating disorders found a raw prevalence of 26% (95% CI [15-40%]) comorbidity with borderline personality disorder, 14% comorbidity with avoidant personality disorder (95% CI [5-25%]), and 16% comorbidity with obsessive-compulsive personality disorder (95% CI [7-28%]) among adults with BN. Of clinical significance, individuals with BN and a comorbid cluster B personality disorder, such as borderline personality disorder, present a greater likelihood of suicide attempt (Favaro et al., 2008).

Some authors have proposed an aetiological pathway in which borderline personality characteristics, including emotional instability, self-harm behaviour, and impulsivity, emerge early in development and contribute to subsequent risk for impulsive binge-purge

behaviour observed in BN (Sansone & Sansone, 2010). However, there is little evidence supporting the progression from borderline personality disorder to BN. A latent profile analysis, however, has provided supporting evidence that people with BN comorbid with borderline personality disorder report greater incidence of childhood trauma compared to BN without borderline personality disorder (Uttinger et al., 2016). Thus, one can speculate that exposure to childhood trauma may predispose the development of transdiagnostic traits underpinning both BN and borderline personality disorder, such as impulsivity, mood instability, and identity disturbance. However, further research is needed to clarify the nature of the relationship between BN and borderline personality disorder.

1.2.6 Risk factors for bulimia nervosa

The following thesis section will provide a summary of psychological factors, environmental and social factors, and genetic factors which have been linked to heightened risk for BN. Each category of risk factor has been discussed in a separate subsection for clarity; however, it should be noted that cognitive, environmental, and genetic factors do not act independently to confer heightened risk for BN. Rather, each factor interacts at the nexus of the individual in a variety of ways, including cases in which environmental factors alter genetic expression via epigenetic means, cases where passive genetic effects influence the environment because parents, with shared genetic material, shape that environment, and cases where both genetic and environmental factors act upon an individual to shape temperament, personality, and specific risk-related traits. The following discussion of risk factors serves to provide a brief introduction to individual risk factors for BN which have been identified in the empirical literature. Key developmental and maintenance models of BN linking these factors to the progression and perpetuation of BN will be discussed in further detail in Section 1.4 of the current thesis. For the purpose of the current thesis, I will use terminology definitions proposed

by Stice (2002) such that *risk factor* refers to “a variable that has been shown to prospectively predict some subsequent pathological outcome”, as opposed to a *causal risk factor*, which refers more specifically to a variable for which “an experimental increase or decrease results in elevated or reduced symptoms, respectively”. Given the logistic and ethical difficulty in ascertaining a variable’s status as a causal risk factor, the vast majority of the variables discussed in the following thesis section rather refer to risk factors with uncertain causal relation to the disorder, with pure genetic effects, outside of the influence of epigenetics, being a notable exception.

1.2.6.1 Psychological risk factors for bulimia nervosa

There are a number of personality traits and cognitive styles which have been found to confer heightened risk for the subsequent onset of BN or worsening of the symptoms of BN. A meta-analysis of experimental studies and prospective longitudinal studies found that thin-ideal internalisation and body dissatisfaction predict both the subsequent onset of BN and increasing severity of the symptoms of BN (Stice, 2002). Additionally, negative affectivity was found to predict subsequent increasing severity in the symptoms of BN (Stice, 2002). The meta-analysis did not find an overall effect for perfectionism or impulsivity in predicting the subsequent worsening of the symptoms of BN (Stice, 2002). In a conflicting set of findings, an individual case-control study of 102 participants with DSM-IV BN and 204 control participants, as well as a more recent survey study, have found heightened retrospective reporting of premorbid perfectionism (Fairburn, Welch, Doll, Davies, & O’connor, 1997; Hilbert et al., 2014). Nonetheless, it should be noted that these studies are susceptible retrospective report bias, thus the role of perfectionism in predisposing individuals to BN is still unclear.

Other psychological factors which confer risk for the subsequent onset of BN include heightened levels of weight and shape concerns (Field et al., 2008; Killen et al., 1996) and body dissatisfaction (C. M. Anderson, Petrie, & Neumann, 2011; Kluck, 2010; A. R.

Smith, Hames, & Joiner Jr, 2013; Stice, 2002). Retrospective surveys have also indicated that childhood attention-deficit/hyperactivity disorder (ADHD) and premorbid conduct problems are disproportionately present in women with BN versus comparison women without history of an eating disorder, thus providing tentative evidence that impulse control difficulties may predate BN in some women (Hilbert et al., 2014; Seitz et al., 2013). As described in Section 1.2.5, emotion regulation difficulties are also common in BN and likely contribute to the maintenance of the disorder (Haedt-Matt & Keel, 2011). This emotion dysregulation pathway will be described in more detail in the context of the emotion regulation model of eating disorders in Section 1.4 of the current thesis.

[1.2.6.2 Environmental risk factors for bulimia nervosa](#)

The majority of research into environmental risk factors for BN has focused on family and societal factors and the effects of bullying and abuse. Thus, while there are likely to be additional factors predisposing individuals to the onset of BN, the current state of the evidence has not systematically supported the influence of other environmental factors.

One commonly cited risk factor for BN is exposure to, and societal pressure to conform to, an image of the “thin ideal”. Stice, Spangler, and Agras (2001), for example, found that random assignment to receive a subscription to a fashion magazine, which contained images endorsing a thin-ideal body image, was associated with significantly greater increases in the symptoms of BN in a subgroup of adolescent girls with low social support, as compared to random assignment to receive a generic gift card or book subscription. The experimental nature of the study thus provides evidence of a role for exposure to thin-ideal images as a causal risk factor for BN. Additionally, in a 7-year longitudinal study of 6,916 US girls and 5,618 US boys, self-reported attempts to look like same-sex people depicted in media was associated with the subsequent onset of weekly binge eating and weekly purging behaviour in girls (Field et al., 2008). Given the self-report nature of the latter set of data and widespread access to media promoting thin

body image, it is unlikely that such media led to the development of disordered eating in all young people. However, as supported by the Stice et al. (2001) study, such messages promoting the thin ideal likely interact with existing vulnerabilities to further increase the likelihood of the onset of BN symptomology.

Given the societal emphasis on the thin-ideal body shape in Western culture, some authors have argued that BN may be specific to, or a result of exposure to Western culture (Keel & Klump, 2003). A 2003 review of the literature, for example, did not find any previous studies reporting a case of BN in the absence of exposure to Western culture (Keel & Klump, 2003). Indeed, as previously mentioned, there is reason to believe that some combination of factors characterising modern, as opposed to pre-modern, Western culture further enhances risk for BN, as evidenced by increasing risk of BN with successive birth cohorts throughout the 20th century (Hudson et al., 2007). A more recent systematic review has also found that increasing exposure to Western culture among immigrants is associated with heightened BN symptomology (Doris et al., 2015). However, it is important to note that the findings of this latter study are confounded by the stress induced by cultural assimilation and should thus be interpreted with caution. While an absence of evidence should not be equated with evidence of absence, and thus the possibility of cases of BN arising outside of Western culture should not be discounted, evidence on the whole suggests that risk for BN is, to a large degree, associated with exposure to Western culture.

In addition to the societal pressures to conform to the thin-ideal as manifest in media at large, pressures for weight control can also be transmitted more proximally through both behaviour modelling and critical comments from family members and peers (Hilbert et al., 2014; Stice, 2002). While social modelling of disordered eating by family members has been found to be associated with heightened risk for the onset of BN and worsening of the symptoms of BN, this effect is confounded by shared genetic material between

family members (Stice, 2002). It is thus compelling to note that the modelling of disordered eating by unrelated peers is also associated with heightened risk for BN (Stice, 1998). Additionally, risk for BN is associated with childhood bullying (Fairburn et al., 1997; Hilbert et al., 2014) and critical comments about body weight and shape from family members (Fairburn et al., 1997; Kluck, 2010). The effect that family emphasis on weight and shape has on risk for BN is statistically mediated by body dissatisfaction in the individual (Kluck, 2010). However, given that this mediation was found in a survey taken at a single time point, it is unclear whether critical comments, body dissatisfaction, and BN symptomology progress in sequential temporal order.

As might be expected, individuals with BN report a greater likelihood of general psychiatric risk factors in childhood, including parental mental health disorders and abuse, as compared to participants without history of a psychiatric disorder (Fairburn et al., 1997; Hilbert et al., 2014). Additionally, parental alcoholism is specifically associated with a greater likelihood of BN, as compared to other psychiatric disorders (Fairburn et al., 1997). Furthermore, Steiger, Bruce, et al. (2011) have found evidence of a gene X environment interaction such that the risk of BN is heightened further when abuse occurs to individuals carrying a C allele on the BC11 glucocorticoid receptor polymorphism. Micali, Crous-Bou, Treasure, and Lawson (2017) have also found evidence of heightened binge-purge behaviours in women when poor maternal care occurs in conjunction with the AG/GA variant of the rs2254298 oxytocin receptor gene polymorphism. The implications of oxytocin in BN and BED will be discussed in further detail in Chapter 3 of the current thesis.

1.2.6.3 Genetic risk factors for bulimia nervosa

Heritability estimates for BN vary widely: from 18% (Baker et al., 2009) to 62% (Bulik et al., 2010; Yilmaz, Hardaway, & Bulik, 2015) in women, and at approximately 28% in men (Baker et al., 2009). The stability of heritability estimates is likely adversely affected

by relatively low sample sizes in studies so far. The power of previous genome-wide association studies in BN has been limited by low sample size, such that neither a European study of 821 people with BN and 1,968 healthy controls (Boraska et al., 2012) nor an Australian study of 2,564 female twins (Wade et al., 2013) found a significant association at the requisite $p < 10^{-8}$ level.

Nevertheless, it may be the case that some polymorphisms numerically associated with BN would reach significance if investigated with larger sample sizes. For example, the A allele on the rs7624327 polymorphism, which is located in a genetic region associated with birth weight (Freathy et al., 2010) and insulin release (Andersson et al., 2011), has previously been found to reach significance at the $p < 10^{-5}$ level (Boraska et al., 2012). Additionally, the AG genotype on the rs1445130 polymorphism has been found to reach significance at the $p < 5 \times 10^{-7}$ level (Wade et al., 2013). The rs1445130 locus is closest to the NT5B1B gene, which regulates production of adenosine, thus indirectly regulating cellular metabolism (Gass et al., 2010). Therefore, taken together, the genetic polymorphisms so far found to trend towards an association with BN contribute to regulation of insulin metabolism and likely to cellular metabolism as well.

Variants on the fat mass and obesity associated (FTO) gene have been a target of candidate gene studies for eating disorders given previous evidence that variants of the FTO gene are associated with appetite and weight (Cecil, Tavendale, Watt, Hetherington, & Palmer, 2008; Frayling et al., 2007; Hotta et al., 2008; Scuteri et al., 2007; Wardle, Llewellyn, Sanderson, & Plomin, 2009). Indeed, one European study including 477 people with BN and 984 controls found that the A allele on the rs9939609 polymorphism of the FTO gene is indeed associated with greater risk of BN compared to control participants (Müller et al., 2012). However, this finding requires replication before firm conclusions about the role of the FTO gene in predisposing individuals to BN can be drawn.

Early evidence highlighted differences in the serotonin transporter region polymorphisms (5-HTTLPR) in people with BN, as compared to control participants (Di Bella, Catalano, Cavallini, Riboldi, & Bellodi, 2000). However, more recent meta-analyses have not supported an association between 5-HTTLPR polymorphisms and BN across studies (Lee & Lin, 2010; Polsinelli, Levitan, & De Luca, 2012). Nonetheless, the short variant of the 5-HTTLPR polymorphism has been found to be associated with heightened impulsivity and novelty seeking in BN (Steiger, Fichter, et al., 2011; Thaler et al., 2013). Future research would be helpful in clarifying whether 5-HTTLPR polymorphisms play a role in predisposing impulsive eating behaviour in women with BN.

Finally, there is also preliminary evidence to support differences in genetic polymorphisms related to hormone receptors: specifically oestrogen and oxytocin receptors. Nilsson et al. (2004), for example, found greater prevalence of the A allele on the oestrogen receptor beta cx polymorphism and greater prevalence of the A allele on the oestrogen receptor 1730 polymorphism in people with BN versus controls. Additionally, Y.-R. Kim, J.-H. Kim, C.-H. Kim, J.-G. Shin, and J. Treasure (2015) have found heightened risk for BN in people carrying a G allele on the rs53576 oxytocin receptor gene polymorphism, and Micali, Crous-Bou, et al. (2017) similarly found that the GG genotype on the same locus was associated with greater binge-purge behaviour in women. As previously mentioned, Micali, Crous-Bou, et al. (2017) also found a gene X environment interaction where the AG/GA variant of the rs2254298 oxytocin receptor gene polymorphism is associated with greater bingeing and purging behaviour when the individual had experienced poor maternal care. The association between BN and variation in the oestrogen receptor polymorphism is interesting in light of evidence that early menarche, associated with increasing levels of oestrogen, acts as a risk factor BN (Kaltiala-Heino, Rimpel, Rissanen, & Rantanen, 2001), although further evidence is needed to establish the functional effects of the oestrogen receptor beta cx polymorphism

in BN. The implication of oxytocin functioning in BN will be explored in detail from Chapter 3 through Chapter 6 of the current thesis.

1.3 Binge Eating Disorder

1.3.1 Binge Eating Disorder: Diagnostic Criteria

DSM-5 diagnostic criteria for binge eating disorder (BED) are as follows: A) Recurrent loss-of-control binge eating characterised by the consumption of an objectively large amount of food for the circumstances within a two-hour period; B) Binge eating episodes are characterised by at least three of the following features: eating much more rapidly than normal, eating until uncomfortably full, eating large amounts of food when not physically hungry, eating alone due to feelings of embarrassment about how much the individual is eating, and feeling disgusted within oneself, depressed, or very guilty afterward; C) Marked distress as a result of the binge eating behaviour; D) The binge eating occurs with a frequency of at least once a week over a period of at least three months; E) The binge eating is not associated with recurrent use of inappropriate compensatory behaviour (such as behaviours that characterise BN) and does not occur exclusively during the course of BN or anorexia nervosa.

The severity of BED is coded depending of the number of binge-eating episodes per week, with mild BED characterised by 1-3 binge-eating episodes per week, moderate BED characterised by 4-7 binge-eating episodes per week, severe BED characterised by 8-13 episodes per week, and extreme BED characterised by 14 or more binge-eating episodes per week.

DSM-IV criteria listed BED as an example of an eating disorder not otherwise specified, rather than a diagnostic class of eating disorder (American Psychiatric Association, 2000). The proposed research criteria for BED proposed within the DSM-IV text revision are the same as the current DSM-5 criteria, with the exception that DSM-IV research

criteria specify a minimum frequency of binge eating on 2 days per week over a 6-month period.

1.3.2 Binge Eating Disorder: Incidence and Prevalence

Given the recent inclusion of BED as a diagnostic class of eating disorder, there is a relative paucity of research investigating the prevalence and incidence of BED, as compared to BN. Furthermore, given that the DSM-IV imposed more stringent frequency and duration criteria for a diagnosis of BED, as compared to DSM-5 criteria, estimates of the prevalence of BED have correspondingly increased with the instatement of DSM-5 diagnostic criteria (Hay et al., 2015; Trace et al., 2012).

Point prevalence of DSM-IV BED has been estimated at 0.8% in an international World Health Organisation study of 24,124 participants and at 1.2%-1.5% in American samples (Hudson et al., 2007; R. C. Kessler et al., 2013; D. E. Smith, Marcus, Lewis, Fitzgibbon, & Schreiner, 1998). The odds ratio of women to men with BED is lower than that of BN, and has been estimated at 2.3 (R. C. Kessler et al., 2013). An Australian study found that applying DSM-5, as opposed to DSM-IV, diagnostic criteria approximately doubled the reported point prevalence of BED from 2.24% to 5.58% in an Australian sample of 6,041 adults (Hay et al., 2015). However, Udo and Grilo (2018) found a much lower point prevalence of 0.44% using DSM-5 BED criteria in a sample of 36,306 American adults. One can speculate that this difference may be due in part to cultural differences and differences in the food environment between Australia and the US. However, further evidence is required to consolidate these divergent prevalence estimates. To our knowledge, only one study has investigated the incidence of DSM-5 BED, finding an incidence rate of 35 per 100,000 person-years in Finnish women between the ages of 10 and 24 (Mustelin, Raevuori, Hoek, Kaprio, & Keski-Rahkonen, 2015).

Lifetime prevalence of DSM-IV BED has been estimated at 1.9% in the above-described World Health Organisation study (R. C. Kessler et al., 2013) and at 2.8% in an American

sample of 9,282 adults (Hudson et al., 2007). Similarly to BN, the prevalence of DSM-IV BED increased throughout the 20th century, with increased odds of lifetime BED being found with successive birth cohorts from 1944 to 1985 (Hudson et al., 2007). However, cohort effects observed in adults are distinct from differences observed between adults and adolescents at a given time point, as lifetime prevalence rates are somewhat lower in American adolescents as compared to American adults: estimated at 2.3% in girls and 0.8% in boys (Swanson, Crow, Le Grange, Swendsen, & Merikangas, 2011).

In a similar pattern to point prevalence estimates, DSM-5 criteria are associated with roughly double lifetime prevalence rates compared to DSM-IV lifetime prevalence rates. A Swedish study of 13,295 female twins, for example, found a lifetime prevalence of 0.17% using DSM-IV criteria, compared to a 0.35% lifetime prevalence using DSM-5 criteria (Trace et al., 2012). In an American sample of men and women, lifetime prevalence of BED was estimated at 0.85% (0.42% in men and 1.25% in women) (Udo & Grilo, 2018). Lifetime prevalence of BED was significantly lower in non-Hispanic black (0.62%), as opposed to non-Hispanic white (0.94%) participants (Udo & Grilo, 2018).

1.3.3 Binge Eating Disorder: Disorder Trajectories

World Health Organisation data and American-based community samples demonstrate later age of onset for BED versus BN, with mean age of onset estimated between 23.3 and 25.4 years old, and median age of onset estimated at 19.3 and 21.1 years old, respectively (Hudson et al., 2007; R. C. Kessler et al., 2013; Udo & Grilo, 2018). Both personality and family factors have been found to influence the developmental trajectory of BED. Interpersonal difficulties and an excessively affiliative interpersonal style are predictive of an earlier age of onset of BED (Blomquist, Ansell, White, Masheb, & Grilo, 2012). Furthermore, a quadratic function has been reported such that both extremely high and extremely low levels of dominance predict earlier onset of BED (Blomquist et al.,

2012). Distinct developmental trajectories have also been reported in overweight people with BED whose parents had a substance use disorder during the individual's childhood, versus overweight people with BED whose parents did not have a substance use disorder (Blomquist, Masheb, White, & Grilo, 2011). In a retrospective interview study, Blomquist et al. (2011) found that having a parent with substance use disorder was associated with earlier onset of BED, greater likelihood of binge behaviour before dieting behaviour, and a quicker escalation from binge eating to full spectrum BED.

A longitudinal study of 1,383 Australian adolescents recruited pre-birth as part of the Raine study also found differing patterns in the development of binge eating between male and female participants (Allen, Crosby, Oddy, & Byrne, 2013). For female participants, binge eating behaviour remained stable between the ages of 14 and 17, before subsequently increasing to age 20. Additionally, amongst the female participants, having depression at age 14 significantly predicted greater binge eating across the 6-year measurement period from age 14 to age 20. The study identified differential trajectories such that girls without depression at age 14 exhibited a gradual increase in binge eating to age 20, while girls with depression exhibit a gradual decrease in binge eating over the same period. Nonetheless, girls with depression at age 14 maintained higher levels of binge eating compared to girls without depression at age 14 over the entire duration of the study period. By contrast, for male participants in the study, binge eating decreased from age 14 to age 17 and then remained stable to age 20. Having depression at age 14 also predicted greater binge eating across the 6-year measurement period in boys, although no time X depression interaction effect was observed.

Studies consistently find an association between BED and heightened depressive symptoms, although the order of the development of binge eating behaviour versus depressive symptoms is yet unclear. A longitudinal study of 8,594 American girls from ages 9 to 15 found that BED was associated with the subsequent risk of heightened

depressive symptoms (Field et al., 2012), while the Raine study rather found that depression at age 14 predicted greater levels of binge eating compared to girls without depression at age 14 (Allen et al., 2013). Depressive symptoms and BED are therefore likely to be closely intertwined, as will be discussed further in Section 1.4 of the current thesis in the context of the emotion regulation model of binge eating.

Although not all people with BED are overweight, overweight and obesity commonly co-occur with BED. Field et al. (2012) found that girls with BED were more likely to be overweight or obese compared to girls with BN at age 9 to 15. Girls with BED who were not overweight or obese at baseline were also more likely to become overweight or obese over the following year of the study (Field et al., 2012). A separate Finnish study of 2,825 female twins found that two-thirds of adult women with BED were in the highest weight quartile at age 16 (Mustelin et al., 2015). Evidence suggests that weight gain is an influential factor in motivating treatment-seeking, as weight tends to increase substantially in the year prior to treatment-seeking in obese people with BED (Masheb, White, & Grilo, 2013).

Current estimates regarding the average duration of BED vary widely, from a median of 4.3 years for DSM-IV BED (R. C. Kessler et al., 2013) to a mean of 15.9 years in Americans with DSM-5 BED (Udo & Grilo, 2018). Future international studies will help to clarify whether this greater average duration with DSM-5 diagnostic criteria applies across industrialised countries. However, recovery rates are similar when measured either using DSM-IV research criteria or DSM-5 criteria. A study of women recruited from a hospital in Germany found a 78.3% recovery rate for BED at 6-year follow-up using DSM-IV research criteria (Fichter & Quadflieg, 2007), and an Italian clinic has found a 63.8% recovery rate for DSM-5 BED at 6-year follow-up (Castellini et al., 2011). There is evidence to suggest that persistence of BED is shorter in duration for adolescents, with an American study finding that 93% of adolescent girls reached remission within one year

of baseline, although approximately 33% of participants experience recurrence of the disorder within 8 years (Stice, Marti, & Rohde, 2013).

It is relatively common for people with BED to later crossover into an other specified feeding or eating disorder (Fichter & Quadflieg, 2007; Stice, Marti, et al., 2013), such as subthreshold BN and BED, and a 7.1-8.3% crossover rate to BN has been documented at 6-year follow-up (Castellini et al., 2011; Fichter & Quadflieg, 2007). Cases of diagnostic crossover between BED and anorexia nervosa are rare (Castellini et al., 2011; Utzinger et al., 2015; E. Welch et al., 2016); however, a history of anorexia nervosa or BN is associated with greater persistence of eating disorder psychopathology and objective binge eating episodes after treatment (Utzinger et al., 2015). BED is not associated with heightened mortality, with a standardised mortality ratio of 1.50 (95% CI 0.87 – 2.40) (Fichter & Quadflieg, 2016) and an all-cause hazard ratio of 1.77 (95% CI 0.60 – 5.27) (Suokas et al., 2013) compared to the general population. BED is associated with a suicide rate of 0.082 per 100 person-years (Suokas et al., 2013) as opposed to the general population suicide rate of .004 per 100 person-years (Prete et al., 2011).

1.3.4 Secondary medical complications of binge eating disorder

A 2017 systematic review has recently summarised medical conditions found to be associated with BED in both cross-sectional and longitudinal paradigms (Olguin et al., 2017). The majority of studies included in the review adopted a cross-sectional design. Among these cross-sectional studies, BED was found to associated with heightened risk of diabetes mellitus, hypertension, arthritis, chronic back or neck pain, gastrointestinal problems (including stomach ulcers and irritable bowel syndrome), sleep problems, asthma, and other pain disorders. Additionally, after controlling for overweight and obesity, associations with fibromyalgia, pain conditions, irritable bowel syndrome, gastrointestinal symptoms, and sleep problems remained, thus suggesting that these medical complications cannot be attributed to high weight alone. Additionally, after

controlling for psychiatric comorbidity with BED, associations with diabetes, hypertension, chronic back and neck pain, chronic headaches, other pain conditions, and asthma remained significant. In women, BED was also found to be associated with menstrual dysregulation and early menarche.

The latest cross-sectional data, from an epidemiological sample of 36,306 American adults, continues to support the existence of elevated odds of diabetes, hypertension, high cholesterol, and high triglycerides in BED after controlling for demographic factors and other psychiatric comorbidities (Udo & Grilo, 2019). This latest study also reported evidence of greater odds for stomach ulcers, arthritis, sleep problems, anaemia, fibromyalgia, bowel problems, osteoporosis, lung problems, liver disease, nerve problems, and heart conditions other than heart attacks in BED, although these associations did not survive adjustment for other psychiatric comorbidities (Udo & Grilo, 2019).

In terms of the metabolic profile of adults with BED, Succurro et al. (2015) found higher fasting insulin levels, lower HDL levels, and greater concentrations of inflammatory markers in people with obesity and BED, versus adults with obesity alone. However, obese children with binge-eating behaviour exhibit similar glucose and lipid profiles compared to obese children without binge-eating behaviour (Lourenço et al., 2008). Thus, it may be the case that differences in metabolic profiles emerge later in the developmental trajectory of BED. Nonetheless, current evidence does not support different odds of metabolic syndrome in overweight and obese people with and without binge eating disorder (Barber, Schumann, Foran-Tuller, Islam, & Barnes, 2015).

It should be noted that these associations with medical complications observed in cross-sectional studies do not necessarily indicate the direction of effect between BED and associated medical complications. It is therefore of interest to note that a retrospective

World Health Organisation study with 24,000 participants found that BED predicted the later onset of arthritis, chronic back and neck pain, chronic headaches, other chronic pain conditions, diabetes, adult-onset asthma, hypertension, and ulcers (Alonso et al., 2014; R. C. Kessler et al., 2013; D. J. Stein et al., 2014). Primary physical conditions did not significantly predict the subsequent onset of BED (R. C. Kessler et al., 2013). The strongest evidence for the influence of binge-eating behaviour on the development of secondary medical complications, however, comes from longitudinal prospective data. In line with some of the most common associations reported in cross-sectional studies, having BED at baseline has been found to be associated with the subsequent onset of dyslipidaemia, hypertension, and diabetes over the following five years of measurement (Hudson et al., 2010).

1.3.5 Common comorbidities of binge eating disorder

The majority of research studies investigating the prevalence of psychiatric comorbidities among populations with BED has been carried out using DSM-IV research criteria for BED, rather than current DSM-5 diagnostic criteria. However, across both sets of diagnostic criteria, studies consistently indicate elevated rates of unipolar depressive disorders, bipolar disorder, anxiety disorders, and ADHD in people with BED, as compared to participants without history of an eating disorder (Cossrow et al., 2016; Hudson et al., 2007; R. C. Kessler et al., 2013; E. Welch et al., 2016). Indeed, rates of current psychiatric comorbidity in DSM-IV BED tend to vary from 36.6% to 42.8% (Grilo, White, Barnes, & Masheb, 2013; Grilo, White, & Masheb, 2009). One Swedish study found that 75% of participants with BED had a comorbid psychiatric disorder, although this estimate should be treated with caution given the relatively small sample of participants with BED ($n = 28$) (Ulfvebrand et al., 2015). Rates of lifetime psychiatric comorbidity vary from 66.9% to 73.8% (Grilo et al., 2013; Grilo et al., 2009).

Exact odds ratio estimates vary widely for specific psychiatric disorders across samples and differing diagnostic criteria applied. For example, odds ratios comparing the prevalence of major depressive disorder among people with DSM-IV BED versus people without an eating disorder vary from 2.2 (95% CI [1.3,3.7]) in a large American sample to 7.6 (95% CI [6.2, 9.3]) in a sample of treatment-seeking Swedish people with BED. The odds ratio for having major depressive disorder in people with DSM-5 BED, as compared to healthy controls, has been estimated at 3.82 (95% CI [3.06-4.78]) in a large survey study of 22,397 American adults (Cossrow et al., 2016), which falls within the range of existing estimates for comorbidity with DSM-IV BED.

Odds ratio estimates for the co-occurrence of an anxiety disorder in people with DSM-IV BED, as compared to control participants, vary from 3.4 to 5.2 (Hudson et al., 2007; R. C. Kessler et al., 2013; E. Welch et al., 2016). The odds ratio for the comorbidity of anxiety disorders with DSM-5 BED has been estimated to be slightly lower than this range (OR 3.17, 95% CI [2.53-3.97]). One can speculate that people with a shorter frequency and duration of binge eating, as captured by DSM-5 criteria, may exhibit lower levels of overall psychopathology compared to those meeting the strict criteria imposed by DSM-IV research criteria, thus accounting for this difference in comorbidity. Indeed, a positive correlation has previously been observed to exist between binge eating frequency and social anxiety (Sawaoka, Barnes, Blomquist, Masheb, & Grilo, 2012), although future research is needed to clarify the generalisation of this link to other specific forms of anxiety. There is a relative paucity of research investigating the incidence of specific anxiety disorders in DSM-5 BED; however, DSM-IV BED is associated with generalised anxiety disorder, panic disorder, agoraphobia, social phobia, specific phobia, post-traumatic stress disorder, separation anxiety disorder, and obsessive-compulsive disorder (Hudson et al., 2007; R. C. Kessler et al., 2013).

Odds ratios for lifetime impulse-control disorders in people with DSM-IV BED, versus control participants, have been estimated at 2.5 (95% CI [1.4,4.6]) in an American sample and 3.0 (95% CI [2.1-4.4]) in a large international sample (R. C. Kessler et al., 2013). While data in DSM-5 BED is lacking, DSM-IV BED is associated with elevated odds of the following specific impulse-control disorders: ADHD, conduct disorder, oppositional defiant disorder, and intermittent explosive disorder (Hudson et al., 2007; R. C. Kessler et al., 2013). DSM-IV BED is also associated with relatively high rates of personality disorders, with 29% of affected individuals estimated to have a personality disorder (Friborg et al., 2014). The most common type of personality disorder detected in people with DSM-IV BED is avoidant personality disorder, followed by borderline personality disorder and obsessive-compulsive personality disorder (Friborg et al., 2014). However, future studies recruiting control participants are required to more conclusively assess whether the odds of personality disorders are significantly elevated in BED.

1.3.6 Risk Factors for Binge Eating Disorder

The following thesis section will provide a summary of risk factors contributing to the likelihood of the onset of BED. This thesis section will proceed in a similar fashion to section 1.2.6 of the current thesis, in that psychological, environmental, and genetic risk factors will each be discussed in turn. As previously described in section 1.2.6, each category of risk factor has been discussed separately for clarity. Nonetheless, it should be noted that, just as in BN, these factors do not influence risk for BED in isolation, but rather interact in myriad ways within the lives of affected individuals. Further discussion of these interactions and hypothesised pathways to the development of BED will be discussed further in the context of maintenance models for BED, presented in Section 1.4.

1.3.6.1 Psychological risk factors for binge eating disorder

While BED, by definition, often entails intense feelings of depressed mood following binge eating episodes (American Psychiatric Association, 2013), numerous lines of evidence suggest that low affect also increases the likelihood of subsequent binge eating

episodes (Cardi, Leppanen, & Treasure, 2015; Haedt-Matt & Keel, 2011). In addition to bidirectional influences of binge eating and depressed mood within the context of the maintenance of BED, prospective longitudinal studies also indicate that childhood unhappiness predicts the future onset of BED (Micali, Martini, et al., 2017) and depressive symptoms predict the future onset of BED in adolescence and young adulthood (Goldschmidt, Wall, Zhang, Loth, & Neumark-Sztainer, 2016; Stice, Gau, Rohde, & Shaw, 2017; Stice, Presnell, & Spangler, 2002; Zaider, Johnson, & Cockell, 2002). Additionally, depressive symptoms predict quantitative increases in binge eating behaviour in adolescents (Allen et al., 2013) and young adults (Spoor et al., 2006).

Both generalised anxiety and eating- and body-specific anxieties have also been found to predict the future onset of BED. For example, in a prospective longitudinal study including 45 women with a lifetime history of BN/BED and 1,515 control women, greater levels of perceived stress were found to predate the onset of binge eating across BN and BED (Striegel-Moore et al., 2007). A longitudinal study of 201 American adolescents similarly found that greater anxiety was associated with the subsequent onset of BED (Zaider et al., 2002). Additionally, both prospective longitudinal and retrospective studies indicate that appearance pressure, thin-ideal internalisation, and body dissatisfaction independently predict the later onset of binge eating (Racine et al., 2017; Stice et al., 2017; Stice et al., 2002), and have even greater predictive value in conjunction with high levels of negative urgency (Racine et al., 2017).

Specific forms of impulsivity have also been implicated in the development and psychological profile of people with BED. In particular, negative urgency, which refers to the tendency to act without deliberation when experiencing strong negative emotion, predicts increases in subsequent eating behaviour (Pearson, Combs, Zapolski, & Smith, 2012). This effect has been found to be mediated by the expectation that eating will help to ameliorate low mood (Pearson et al., 2012). Cross-sectional and longitudinal studies

have also found that attentional and motor impulsivity predict binge eating (Meule & Platte, 2015; Sonnevile et al., 2015). Moreover, longitudinal evidence suggests that the effect of hyperactivity and inattention in late childhood impacts binge eating in mid-adolescence via an indirect effect acting via an increase in late-childhood overeating and early-adolescent desire for food (Sonneville et al., 2015).

In light of evidence that emotion dysregulation predicts greater levels of disordered eating in people with BED (Gianini, White, & Masheb, 2013), one can speculate that high levels of anxiety and depression interact with poor coping skills to predict increased likelihood of coping-focused binge eating. Furthermore, evidence suggests that impulsivity interacts with body dissatisfaction, thin-ideal internalisation, and appearance pressure to influence binge eating (Racine et al., 2017). Taken together, this pattern of findings raises the hypothesis that high levels of anxiety and depression combined with poor coping skills additionally act in conjunction with tendencies for impulsivity to increase the risk for binge eating behaviour. This hypothesis will be explored further in both Section 1.4 and Chapter 2 of the current thesis.

Finally, both cross-sectional and longitudinal studies also indicate an association between personality psychopathology and BED. Cross-sectional studies, for example, have found a pattern of high novelty seeking, high harm avoidance, high reward sensitivity, and low-self-directedness compared to normal-weight control participants (Davis et al., 2008; Fassino et al., 2002; Grucza, Przybeck, & Cloninger, 2007; Peterson et al., 2010). However, empirical evidence suggests that the personality profile of overweight and obese people with BED differs little from weight-matched control participants; with only self-directedness being lower in overweight and obese people with BED (Fassino et al., 2002). Of functional significance, however, greater levels of personality psychopathology are associated with frequency of binge eating episodes in people with DSM-IV BED (Picot & Lilenfeld, 2003). Additionally, in a longitudinal study, antisocial and schizotypal

symptoms at age 22 were found to be associated with recurrent binge eating behaviour at age 33 (J. G. Johnson, Cohen, Kasen, & Brook, 2006). While the precise nature of the relationship of specific personality traits and binge eating remains unclear, one can speculate that low levels of self-directedness and high reward sensitivity contribute to reward approach behaviour in BED and that disordered personality traits detract from social functioning, thus further increasing the risk of the anxious and depressive symptoms that contribute to recurrent binge eating behaviour.

1.3.6.2 Environmental risk factors for binge eating disorder

Environmental factors related to poor family functioning, weight and body shape-based teasing, and childhood trauma have all been found to increase risk of BED later in life. For example, a longitudinal study of 1,043 UK women found that low maternal warmth and an oppressive parental relationship significantly predicted the future onset of BED (Micali, Martini, et al., 2017). Additionally, a previous retrospective case-control study found that parental depression significantly predicted BED in adulthood, as compared to healthy control status (Fairburn et al., 1998).

The same case-control study also found that exposure to negative comments around body weight, shape, and eating predicted BED (Fairburn et al., 1998). A similar finding has been replicated with reference to the predictive value of weight stigmatisation to risk for BED (Almeida, Savoy, & Boxer, 2011). Furthermore, non-weight and shape-based bullying in childhood has also been found to confer risk for subsequent binge eating in both longitudinal and retrospective interview studies (Copeland et al., 2015; Striegel-Moore, Dohm, Pike, Wilfley, & Fairburn, 2002).

A meta-analysis investigating the effect of abuse on eating disorder risk, which included a total of 14,169 participants, found significant associations between childhood sexual abuse, childhood emotional abuse, and childhood physical abuse on later onset of BED (Caslini et al., 2016). Abuse appears to be even more prevalent amongst women with

BED with a comorbid personality disorder (Grilo & Masheb, 2002). There is some indication that sexual abuse may confer different risk for BED depending on ethnicity, as greater levels of sexual abuse have been found to differentiate black women with BED from a psychiatric comparison group, while this effect was not found for white women with BED (Striegel-Moore et al., 2002). Nonetheless, it should be noted that almost all findings linking childhood abuse to BED have been found in retrospective studies, and should thus be treated with caution given the possibility of recall bias (Caslini et al., 2016). Future prospective longitudinal studies will help to clarify aetiological pathways from abuse to BED, as well as influential protective factors.

Mixed findings have been reported with regards to the effect of socioeconomic status on BED and binge eating behaviour; however, in sum, existing evidence tends not to support an overall effect of income levels on risk for BED. While one cross-sectional study of 475 people in the Detroit metropolitan area found that lower income was associated with increased frequency of binge eating in women, but not men (Reagan & Hersch, 2005), larger Australian studies of 4,200 and 6,041 people, respectively, found no association between household income and binge eating (Hay, 1998; Mulders-Jones, Mitchison, Girosi, & Hay, 2017). Additionally, a recent study of 35,306 American adults also failed to find an association between income level and risk for BED (Udo & Grilo, 2018). This pattern of findings in BED is therefore in contrast to the increased prevalence of obesity amongst low income groups (Ogden, Lamb, Carroll, & Flegal, 2010), and highlights dissociations between aetiology and risk factors for binge eating versus a more general positive energy balance leading to obesity in the absence of eating psychopathology.

BED is not culturally specific to the West and has rather been observed in approximately 10% of women in an indigenous Fijian community (Becker, Burwell, Navara, & Gilman, 2003). Nevertheless, binge eating behaviour was found to be associated with holding a Westernised view of the body (Becker et al., 2003), which reflects findings in the West

linking body dissatisfaction and thin-ideal internalisation to BED (Racine et al., 2017). This pattern of findings therefore suggests the existence of some sociocultural influence in the development of BED, without going so far as to support the specificity of BED to Western, industrialised societies.

1.3.6.3 Genetic risk factors for binge eating disorder

The heritability of current BED has been estimated between 41% and 57%, with somewhat lower estimates of heritability found in twin studies (Bulik, Sullivan, & Kendler, 2003; K. Mitchell et al., 2010) versus a case-control study (Javaras et al., 2008). Heritability of binge eating behaviour is similar when assessed in terms of frequency of loss-of-control binge eating, versus the binary criterion of BED or non-BED, although the heritability of lifetime binge eating versus no lifetime binge eating of any frequency has been found to be as high as 70% to 74% (Root et al., 2010).

While at least a subset of genetic factors conferring risk to BED are distinct from genetic factors conferring risk for obesity in the absence of BED (Hudson et al., 2006), there is some evidence to suggest that allelic variants associated with polymorphisms on the FTO gene do enhance risk for BED. In a genetic study of 4,916 adolescents enrolled in a UK-based longitudinal study, Micali, Field, Treasure, and Evans (2015) found that binge eating was associated with the AT genotype on the rs1558902 SNP of the FTO gene at the $p = 8 \times 10^{-3}$ alpha level. Furthermore, a weighted allelic score including 32 SNPs across the FTO gene was associated with binge eating at the $p = 8 \times 10^{-4}$ alpha level. A separate study has also found that the AA or AT genotype on the rs9939609 SNP of the FTO gene confers significantly greater risk for BED than the TT genotype, and that AA/AT carriers consumed a significantly greater percentage of energy from fat in a laboratory-based test meal (Tanofsky-Kraff et al., 2009). Associations between BED and allelic variants on the rs9939609 SNP were not replicated by a later study in adults, although this latter study was limited by low sample size ($N = 178$) (Cameron et al., 2018).

Nevertheless, Cameron et al. (2018) did find evidence of an interaction such that a CC or TC genotype on the rs1421085 SNP of the FTO gene, in combination with a high avoidant attachment style, conferred risk for greater frequency of binge eating, whilst the CC/TC variants were not associated with binge eating among those low in avoidant attachment style. On the whole, current evidence therefore suggests that some SNPs on the FTO gene may be related to binge eating, although the influence of specific SNPs has not been consistently supported across studies. Future genome-wide association studies in larger samples will help to clarify the extent to which the FTO gene is related to the development of BED.

Extensive evidence supporting a role for activation of the melanocortin 4 receptor (MC4R) in inhibiting subsequent food intake has also highlighted the MC4R gene as a putative candidate in which genetic variation may lead to disinhibited eating (Garfield et al., 2015). Indeed, two studies have found that a significantly greater proportion of mutation carriers on the MC4R gene present with binge eating, compared with non-carriers (Branson et al., 2003; Potoczna et al., 2004). However, this finding was not replicated by a separate research group (Hebebrand et al., 2004). Associations with BED have also been found on SNPs related to the dopamine D2 receptor (Davis et al., 2012), the serotonin transporter gene (Monteleone, Tortorella, Castaldo, & Maj, 2006), the ghrelin gene (Monteleone, Tortorella, Castaldo, Di Filippo, & Maj, 2007), and the brain-derived neurotrophic factor-related gene (Monteleone, Zanardini, et al., 2006). Nevertheless, a lack of replication in findings supporting an association between these genes, SNPs of the FTO gene, and MC4R genetic variants precludes the possibility of drawing firm conclusions regarding the genetic basis of BED. Future genome-wide association studies with larger sample sizes will be helpful in clarifying allelic variants which pose genetic risk for BED, as well as relevant gene X environment interactions.

1.4 Maintenance models of bulimia nervosa and binge eating disorder

Several theoretical models have been proposed linking the risk factors described above to form coherent explanations of the development and maintenance of BN and BED. The current thesis section will describe four key influential theoretical models which bear relevance to the maintenance of binge eating behaviours in BN and BED: the emotion regulation model (Leehr et al., 2015), the dual-pathway model (Stice, 1994), the interpersonal theory of eating disorders (Rieger et al., 2010), and the trans diagnostic model (Fairburn, Cooper, & Cooper, 1986; Fairburn, Cooper, & Shafran, 2003). The current thesis section will also briefly describe key strengths and limitations of each theoretical model before going on to outline a rationale for a new maintenance model of BN and BED.

1.4.1 The emotion regulation model of bulimia nervosa and binge eating disorder

The emotion regulation model of binge eating, proposed by Leehr et al. (2015) stems from prior specific emotional regulation theories including escape theory (Heatherton & Baumeister, 1991), affect regulation theory (Polivy & Herman, 1993), and the emotional arousal theory of binge eating (Pine, 1985). Each specific emotional regulation theory differs slightly. For example, both escape theory and affect regulation theory purport that heightened negative emotion triggers subsequent binge eating for the purposes of relief. However, escape theory proposes that the improvement in mood occurs during the course of a binge eating episode, while affect regulation theory hypothesises that relief occurs following the conclusion of the binge eating episode. Emotional arousal theory places greater emphasis on the arousal, rather than valence, component of emotion, proposing that overeating is triggered to reduce excessively heightened arousal, regardless of valence. Leehr et al. (2015), in their broader emotion regulation model, however, subsume both escape theory and affect regulation theory by placing less emphasis on the timing of relief, and instead focus on the three components of the emotion regulation process: 1) negative emotion, which is followed by 2) the down-regulation of negative emotion

through binge eating, and finally 3) some relief component from negative emotion, which negatively reinforces binge eating behaviour.

In a systematic review of experimental studies testing the effect of negative mood on binge eating and subsequent improvements in mood in people with BED, Leehr et al. (2015) found that the evidence generally supported the emotion regulation model of binge eating. That is, nine out of fifteen included studies found that experimentally induced negative emotion acted as a trigger for binge eating or overeating in people with BED. More limited evidence was available to support the relief component of the emotion regulation model. Nevertheless, both of the two experimental studies testing changes in mood following overeating or binge eating behaviour indeed found that negative emotions decreased after food intake.

This set of findings differs slightly from those reported in a previous systematic review of naturalistic studies testing the relationship between emotion and binge eating through the use of ecological momentary assessments (Haedt-Matt & Keel, 2011). Haedt-Matt and Keel (2011) indeed found overall greater levels of negative emotion on days in which binge eating episodes occurred, and that greater levels of negative emotion preceded binge eating versus regular meals and snacks. Nevertheless, overall, ecological momentary assessment data did not support an improvement in mood following binge eating. Methodological reasons for this finding will be discussed in more detail in Paper 3 of the current thesis. On the whole, however, both experimental and naturalistic evidence provide strong support for the role of negative emotions in triggering binge eating episodes. This “trigger” component of the emotion regulation model therefore forms an important component of our proposed comprehensive maintenance model of binge eating, which I will expound in Chapter 2.

1.4.2 The dual-pathway model of bulimia nervosa

The dual-pathway model of BN, as the name suggests, proposes that two distinct aetiological pathways act in concert to increase risk for, and maintenance of, BN (Stice, 1994). One pathway entails the transmission of sociocultural pressures for thinness via messages from peers, family, and the media, which is then internalised, leading to body dissatisfaction and dietary restraint. Sustained periods of dietary restraint subsequently increase the likelihood of binge eating episodes. In addition to this sociocultural pathway, the second pathway relates strongly to the emotion regulation model of BN, such that negative affect combines with poor coping skills to increase the likelihood that the individual will engage in binge eating and purging in the pursuit of relief from negative mood.

The dual-pathway model of BN is supported by longitudinal evidence finding that thin-ideal internalisation and perceived pressures to be thin precede subsequent increases in body dissatisfaction, which predicts subsequent increases in dieting and low mood, which predicts subsequent worsening of binge eating and purging behaviour (Allen, Byrne, & McLean, 2012; Stice, 2001). Structural equation modelling of binge eating progression over time has indicated an adequate, but not excellent, fit to the dual-pathway model of BN (Allen et al., 2012).

One significant limitation of the dual-pathway model, however, includes the significant focus on the role of thin-ideal internalisation specifically in women. The original model paper, for example, organised supporting evidence in terms of increasing emphasis on the thin-ideal body type for women throughout the 20th century, the importance of appearance within the female gender-role, and the importance of appearance, and particularly of women's appearance, for societal success (Stice, 1994). The dual-pathway model therefore fails to account for the incidence of BN in men, for whom social standards have tended to favour a muscular body ideal (Labre, 2002).

Additionally, while the affective pathway is supported by a wide array of evidence, as discussed above within the context of the emotion regulation model of binge eating, the sociocultural pathway fails to account for cases of BN and BED in which binge eating precedes dieting behaviour. Indeed, in retrospective studies conducted in participants with BED, 35-81% of participants reported that the onset of binge eating occurred prior to the onset of any dieting (Grilo & Masheb, 2000; Manwaring et al., 2006). Therefore, while the dual-pathway model may indeed encapsulate the aetiology of binge eating well among many women with BN, the model fails to account for significant subgroups with recurrent binge eating, including men and people with BED.

1.4.3 The interpersonal theory of eating disorders

The interpersonal theory of eating disorders postulates first that disturbances in the individual's sense of self, including low self-esteem and negative affect, lead to disordered eating behaviours across the eating disorder spectrum (Rieger et al., 2010). These disturbances in the individual's sense of self are postulated to arise from interpersonal difficulties. Rieger and colleagues' model proposes that the key interpersonal factor maintaining identity disturbances is negative social evaluation, which is exacerbated by specific interpersonal processes including role disputes, role transitions, grief, and interpersonal deficits. Furthermore, insufficient positive social evaluation can also contribute to an overriding perception of negative social evaluation when it is also perceived to communicate a lack of social value.

Where the individual is unable to engage in positive social interactions and achieve a sense of social worth through conventional interpersonal means, the individual is hypothesised to engage in disordered eating behaviours in an attempt to achieve a sense of self-worth and improved affect via alternative means (Rieger et al., 2010). Disordered eating behaviours are then hypothesised to further exacerbate interpersonal difficulties, thus initiating a vicious cycle. Indeed, a previous empirical study has found that

experimental provision of negative social evaluation is associated with the greater consumption of high-caloric foods in a subsequent taste test (Baumeister, DeWall, Ciarocco, & Twenge, 2005). Furthermore, structural equation modelling of 118 students also found that social appearance anxiety and fear of negative social evaluation were significant risk factors for greater eating disorder pathology (Levinson & Rodebaugh, 2012). Nevertheless, these studies fail to establish the primacy of social evaluation concerns in maintaining eating disorder symptoms, as both studies are confounded by general negative affect induced by negative social evaluation and fears. Therefore, one can argue that the emotion regulation model more comprehensively and parsimoniously accounts for binge eating behaviour in BN and BED, where negative social evaluation acts as one of a variety of factors which contributes to the low affect maintaining the eating disorder.

1.4.4 The trans diagnostic model of eating disorders

The trans diagnostic model of eating disorders, originally proposed by Fairburn and colleagues in 1993, proposed that anorexia nervosa and BN were maintained by same core psychological factors, with the most important maintenance factor being the overvaluation of body shape and weight and their control. The model was later revised to suggest that this core maintenance factor can then interact with one or more of four additional factors to influence the course of the eating disorder (Fairburn et al., 2003). These additional four maintenance factors include 1) Clinical perfectionism, defined as “overvaluation of the striving for, and achievement of, personally demanding standards, despite adverse consequences” (Fairburn et al., 2003, p. 515); 2) Core low self-esteem, defined as “having an unconditional and pervasive negative view of oneself which is seen as part of one’s permanent identity” (Fairburn et al., 2003, p. 516); 3) Mood intolerance, defined as “the inability to cope appropriately with certain emotional states” (Fairburn et al., 2003, p. 517); and 4) Interpersonal difficulties, which occur when difficulties with

others, and especially close others, drive a fight for control, heighten stress, and potentially undermine self-esteem in the long-term. A schematic depicting the interaction of these factors in perpetuating disordered eating behaviour is presented in **Figure 1**.

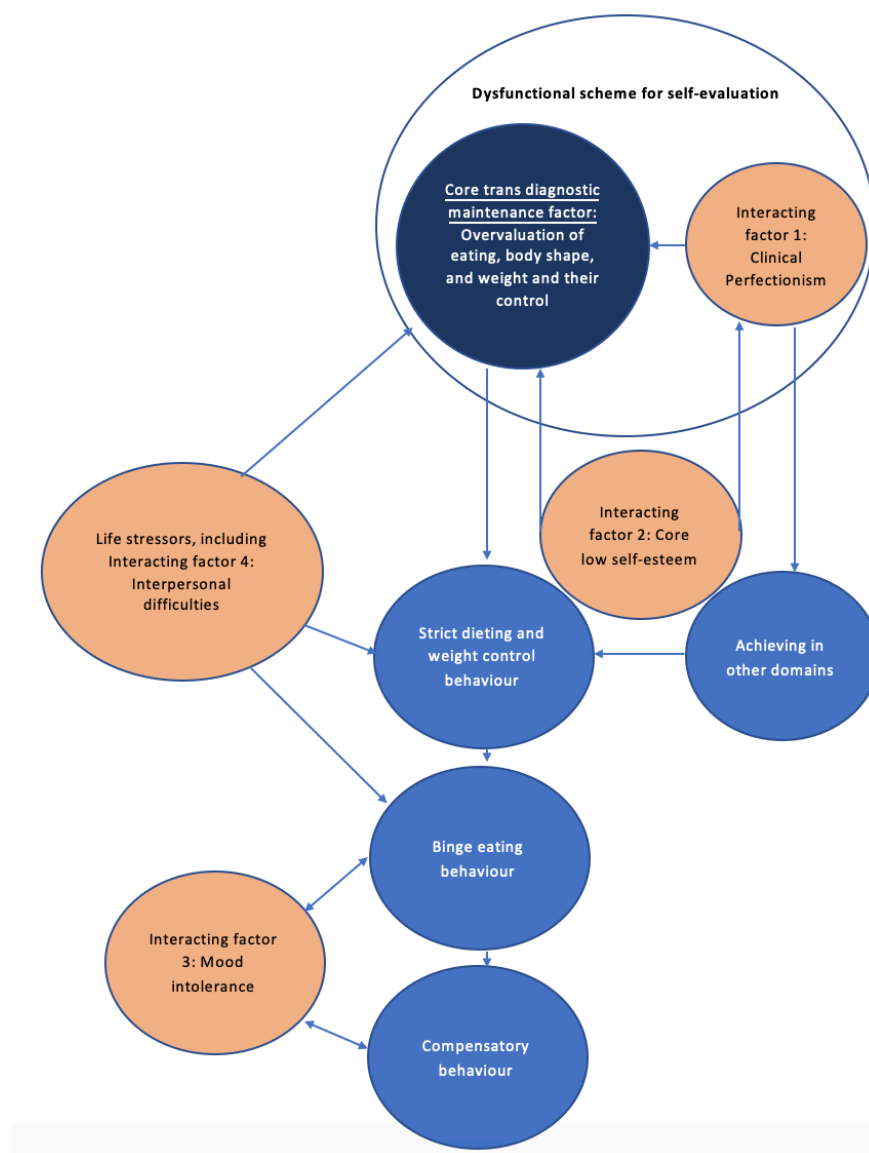


Figure 1. A schematic representation of the trans diagnostic model of eating disorders. Adapted from Fairburn, Cooper, & Shafran, 2003.

In light of the inclusion of BED as a criterial eating disorder, more recent evidence has also provided evidence that at least moderate levels of overvaluation of weight and body shape distinguish a more severe phenotype of BED (Goldschmidt et al., 2010) and that

overvaluation of weight and shape mediates the relationship between low self-esteem and weight bias internalisation in BED (Pearl, White, & Grilo, 2014).

The transdiagnostic model of eating disorders forms the basis for enhanced cognitive behavioural therapy (CBT-E) for BN and BED, which remains the gold-standard treatment for both disorders (National Institute for Health and Clinical Excellence, 2017). The success of CBT-E in treating BN and BED thus provides indirect evidence for the importance of maintenance factors proposed within the trans diagnostic model, as CBT-E is formulated to primarily target these factors. Nonetheless, it is possible that CBT-E achieves therapeutic success via incidental improvement in maintenance factors not proposed within the transdiagnostic model, and that other maintenance factors therefore exert greater influence in perpetuating BN and BED.

Studies testing changes in self-esteem, interpersonal difficulties, perfectionism, and mood intolerance over the course of CBT-E have produced mixed findings regarding the influence of each factor on treatment outcome. For example, one clinical trial found no significant difference in perfectionism and mood intolerance over the course of CBT-E (Byrne, Fursland, Allen, & Watson, 2011), although one later trial did find an improvement in emotion regulation (Wonderlich et al., 2014). However, studies directly testing the mediating effect of changes in each postulated interacting factor on treatment outcome are limited. A recent systematic review found that only two mediators of clinical improvement in BN hypothesised within transdiagnostic model formulation have been directly tested in empirical studies: dietary restraint and body-related concerns (Linardon, de la Piedad Garcia, & Brennan, 2017). Reductions in dietary restraint were found to be associated with better outcome across studies. However, change in body-related concerns, which is arguably more closely related to the transdiagnostic core maintenance factor “overvaluation of weight and shape”, was not found to be related to treatment outcome. The systematic review did not find evidence of any clinical trials of CBT-E for BED

which tested maintenance factors specific to the transdiagnostic model of eating disorders. Thus, while the primary treatment stemming from the transdiagnostic model of eating disorders is indeed effective for many people with BN and BED (Hay, 2013; Peat et al., 2017), evidence supporting its purported mechanism of action is lacking. Additionally, approximately 50% of people with BN do not achieve remission by the end of treatment with CBT-E, thus highlighting the possibility that different maintenance factors from those targeted by CBT-E may perpetuate the BN and BED in a large subgroup of individuals, who may be better served by a different treatment programme.

1.4.5 Rationale for a new maintenance model of BN and BED

Each of the above-described maintenance models of BN and BED serves to elucidate pathways connecting the disparate risk factors described in Sections 1.2.6 and 1.3.6 to produce a coherent formulation of BN and BED, as supported by a range of cross-sectional and longitudinal evidence. Nevertheless, each maintenance model is associated with specific limitations, including: the failure of the dual-pathway model to account for BN and BED amongst significant subgroups of affected individuals, the lack of parsimony associated with the interpersonal theory of eating disorders, and the lack of supporting clinical evidence for the interacting proposed maintenance factors within the transdiagnostic model. Additionally, each of these three maintenance models, as well as the emotion regulation model, also fail to account for the widely different behavioural phenotypes observed across the eating disorder spectrum from anorexia nervosa to BED. That is, while each model predicts how disordered eating behaviour comes to occur, the models have little predictive validity in explaining why this would manifest as weight control behaviour in isolation, weight control behaviour in combination with binge eating behaviour, or binge eating behaviour in isolation. In Chapter 2 of the current thesis, I will further elaborate on the need for a new comprehensive maintenance model of BN and BED, and present both a summary of existing evidence as well as original evidence for a

novel maintenance model of BN and BED: The Addictive Appetite Model of Bulimia Nervosa and Binge Eating Disorder.

1.5 Aims and hypotheses of the current thesis

The overall aim of the current thesis is to propose and investigate a novel maintenance model of BN and BED: The Addictive Appetite Model of Bulimia Nervosa and Binge Eating Disorder. I will first present this novel illness formulation alongside a review of existing evidence for the maintenance model. Subsequently, I aimed to investigate the maintenance model via analysis of motivations for eating behaviour. Furthermore, the model predicts that treatments for substance abuse disorders warrant investigation in individuals with BN and BED. I therefore go on to present the results of an original study investigating the effects of exogenous oxytocin administration in women with BN and BED, based on a burgeoning field of work establishing the relevance of oxytocin in curbing substance addictions and relapse to substance use. The thesis is structured as a series of papers which are each associated with separate but related aims and hypotheses. The aims and hypotheses of each paper are presented in **Table 1**.

Table 1*Aims and hypotheses of the papers in this thesis*

Paper	Title	Aims and Hypotheses
Paper 1	Are trans diagnostic models of eating disorders fit for purpose? A consideration of the evidence for food addiction	This paper aimed to formulate a novel comprehensive maintenance model of bulimia nervosa and binge eating disorder: The Addictive Appetite Model.
Paper 2	Towards a translational approach to food addiction: Implications for bulimia nervosa	The aim of this narrative review was to summarise existing evidence in support of the most novel elements proposed within The Addictive Appetite Model: the existence of tolerance and withdrawal affects in bulimia nervosa and the impact of foods with a high glycaemic index in maintaining elevated food craving.
Paper 3	Testing the addictive appetite model: The importance of craving, reward, and reward enhancement	This original study aimed to test two maintenance processes proposed within The Addictive Appetite Model of binge eating: eating due to enhanced incentive salience and eating for emotion regulation. Our hypotheses were 1) People with BN and BED would show higher levels of craving for food than weight-matched controls; 2) People with BN and BED would endorse eating palatable food as a method of coping with distress and as a means of enhancing mood; and 3) Food craving, eating for emotional coping, and eating for reward enhancement would distinguish individuals with binge-type eating disorders from weight-matched controls.
Paper 4	A Systematic Review and Quantitative Meta-Analysis of the Effects of Oxytocin on Feeding	This paper aimed to conduct a systematic review synthesising the effects of oxytocin on feeding. We used PRISMA guidelines to identify all original published and unpublished experiments testing the effects of exogenous oxytocin on energy intake in wild-type animals and in humans,

		where oxytocin was administered in the absence of other active drugs or surgeries. We also aimed to identify relevant moderators of oxytocin's effects on feeding in order to clarify the conditions under which these anorexigenic effects hold. We hypothesised that exogenous oxytocin administration, as compared to placebo administration, would reduce feeding in both humans and animals.
Paper 5	The influence of oxytocin on eating behaviours and stress in women with bulimia nervosa and binge eating disorder	The aim of the current study was to explore the impact of the administration of oxytocin on both reward and anxiety-related processes. 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.
Paper 6	A Pilot Study Investigating the Influence of Oxytocin on Attentional Bias to Food Images in Women with Bulimia Nervosa and Binge Eating Disorder	This study aimed to test the effect of a divided dose of 64IU intranasal oxytocin on attentional bias to palatable food in women with and without bulimia nervosa and binge eating disorder. Our hypotheses were: 1) Women with BN or BED would demonstrate greater attentional biases towards food images than women without history of an eating disorder; 2) There would be an interaction between time point and participant group, such that the difference in attentional bias to food in the BN/BED, versus healthy control group, would be even greater following food consumption; 3) Oxytocin administration would reduce vigilance towards food images

		in both groups of women, based on previous work suggesting that oxytocin reduces the incentive salience of palatable food in healthy participants (Ott et al., 2013); 4) Oxytocin would reduce vigilance towards food images to a greater degree in women with BN or BED, versus healthy comparison women, due to potential flooring effects in the healthy comparison group.
Paper 7	The Influence of Oxytocin on Risk-Taking in the Balloon Analogue Risk Task Among Women with Bulimia Nervosa and Binge Eating Disorder	This study aimed to compare the performance of women with clinical levels of recurrent binge eating on the BART to that of control women without previous history of an eating disorder. Furthermore, we also aimed to investigate the differential effect of intranasal oxytocin on risk-taking in the BART in women with BN and BED compared to healthy controls. We hypothesised that women with BN and BED would demonstrate greater baseline risk-taking behaviour on the BART in the placebo condition, relative to women without previous history of an eating disorder. Given previous research indicating that oxytocin induces a down-regulation of reward seeking in men, we hypothesised that a divided dose of 64IU intranasal oxytocin, versus placebo, would be associated with reduced risk-taking behaviour in the BART in women, and that this effect would be stronger in women with bulimia nervosa and binge eating disorder due to higher trait levels of risk-taking behaviour.
Paper 8	The effect of oxytocin on the neural processing of taste reward in women with and without binge-type eating disorders	This study aimed to investigate differences in neural activation in response to the anticipation and receipt of chocolate milk, versus water, in women with BN and BED versus healthy comparison women. We also aimed to investigate the influence of 40IU intranasal oxytocin on the neural processing of the anticipation and receipt of chocolate milk, versus water. We conducted whole-brain exploratory analyses to identify regions in which women with BN and BED exhibited different patterns of BOLD response to palatable taste anticipation and receipt, and regions where

40IU intranasal oxytocin moderated neural activation to palatable taste anticipation and receipt.

Chapter 2

2 The Development of a Novel Maintenance Model for Recurrent Binge Eating

Are Trans diagnostic models of eating disorders fit for purpose? A consideration of the evidence for food addiction

Short Title: Neuroadaptation and binge eating

Janet Treasure*¹

Monica Leslie*¹

Rayane Chami¹

Fernando Fernández-Aranda²

* Joint first author

¹ Section of Eating Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

² Eating Disorders Unit, Department of Psychiatry, University Hospital of Bellvitge and CIBERObn (ISCIII), Barcelona, Spain

Corresponding Author:

Professor Janet Treasure

Section of Eating Disorders,

Department of Psychological Medicine

103 Denmark Hill, London, SE5 8AF, King's College London

Email address: janet.treasure@kcl.ac.uk Telephone number: 0044 0207 848 5972

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Abstract

Explanatory models for eating disorders have changed over time to account for changing clinical presentations. The transdiagnostic model evolved from the maintenance model, which provided the framework for cognitive behavioural therapy for bulimia nervosa. However, for many individuals (especially those at the extreme ends of the weight spectrum), this account does not fully fit. New evidence generated from research framed within the food addiction hypothesis is synthesised here into a model that can explain recurrent binge eating behaviour. New interventions that target core maintenance elements identified within the model may be useful additions to a complex model of treatment for eating disorders.

Keywords: Bulimia nervosa, binge eating disorder, food addiction, neuroadaptation, insulin

Introduction

Current treatments for bulimia nervosa and binge eating disorder are only moderately effective, with 30-50% of individuals achieving complete abstinence from binge eating at the end of treatment (Hay, 2013) and a 68% remission rate at 9-year follow-up (Eddy et al., 2017). This suggests that the transdiagnostic model that underpins cognitive behavioural therapy may require modification in order to accommodate the diverse eating patterns and weight across the eating disorder spectrum. Eating behaviour has been relatively neglected (Treasure, Cardi, & Kan, 2012) but the concept of food addiction has brought it into the foreground (Gearhardt, Boswell, & White, 2014; Gearhardt et al., 2012; Granero et al., 2014; Meule & Gearhardt, 2014b; Schulte & Gearhardt, 2017). Nonetheless, the concept of food addiction is controversial (Finlayson, 2017; Hebebrand et al., 2014; Long, Blundell, & Finlayson, 2015; Schulte, Potenza, & Gearhardt, 2017), in part due to the different levels of description being used. For example, the Yale Food Addiction Scale (Gearhardt, Corbin, & Brownell, 2009b) examines behaviours and subjective reports, while the focus of other studies has been on underpinning mechanisms (Colantuoni et al., 2002; Colantuoni et al., 2001). Some of the controversy may stem from semantics: does addiction imply a set of behaviours, or a form of neuroadaptation within hedonic circuits, or an underlying disease process (Lewis, 2017)? If we step aside from the linguistic term “addiction”, with all the stigma and social implications it may carry, and instead focus on the function that related processes serve, this conceptualisation may prove a useful frame for work within the field. Targeting the maintenance factors underpinned by addiction-related neural processes may enhance our ability to prevent and treat these disorders, which lead to misery and disability in many domains (Gramaglia, Brytek-Matera, Rogoza, & Zeppegno, 2017; Simpson & Mazzeo, 2017). In the following account, we suggest an update to the model of binge eating disorder and bulimia nervosa,

which incorporates some of the new evidence that is emerging. First, we consider the profound changes in the epidemiology of eating disorders over the last 50 years.

Epidemiology

An increasing number of people received a diagnosis for bulimia nervosa in the UK in the eighties (Currin, Schmidt, Treasure, & Jick, 2005; Turnbull, Ward, Treasure, Jick, & Derby, 1996) and binge eating disorder in the new millennium (Micali et al., 2013). Possible new forms of eating disorders such as orthorexia nervosa (Gramaglia et al., 2017; Simpson & Mazzeo, 2017) and diabulimia (Wilson, 2012) have been described more recently. This increase in eating disorders parallels the worldwide increase in the prevalence of obesity (Ng et al., 2014). There are several explanations for this rapid increase in eating and weight problems, including changes to the food environment and associated novel interactions with individual vulnerabilities.

In the West, in particular, the evolving food environment has changed what and how we eat (Lewis, 2017). Foods have been modified to become more accessible, cheap, and palatable, while nutrients have been ultra-processed and /or purified (Gramaglia et al., 2017). Food now requires little effort to procure and prepare and is therefore less bound within social processes. At the same time, the relevance of food and eating to health and body image has become a dominant discourse. Fatness is stigmatised (de la Haye, Dijkstra, Lubbers, van Rijsewijk, & Stolk, 2017; Di Pasquale & Celsi, 2017), “fat talk” is associated with body dissatisfaction (Mills & Fuller-Tyszkiewicz, 2017) and abnormal eating practices (Arroyo, Segrin, Harwood, & Bonito, 2017), while thinness and muscularity are valued as the ideal body form (Karazsia, Murnen, & Tylka, 2017). What is the evidence that these changes in the food environment could lead to changes in eating behaviours?

Proof of Concept Animal Models: Changes in the Food environment as Risk

Factors for Binge Eating Disorder

Animal studies have demonstrated proof of the concept that manipulations of the food environment can produce “binge eating”. Putative risk factors including a period of undernutrition, followed by the intermittent addition of palatable food (high sugar and fat combinations) and stress (particularly social stress), have been shown to lead to “binge eating” (Murray, Tulloch, Chen, & Avena, 2015; Razzoli, Pearson, Crow, & Bartolomucci, 2017; Wiss, Criscitelli, Gold, & Avena, 2017). Interestingly, animals exposed to this food schedule exhibit signs of food addiction, such as physical withdrawal symptoms, when intermittent palatable sucrose intake is followed by administration of an opioid antagonist (Colantuoni et al., 2002). These animals are also more vulnerable to developing other addictive behaviours (Avena, 2010; Avena, Bocarsly, & Hoebel, 2012). Moreover, deeper examination of the hedonic circuits involved has shown neuroadaptive changes in dopamine and opiate neurons (Avena, Rada, & Hoebel, 2009; Rada, Avena, & Hoebel, 2005). This is of interest as the mechanisms underpinning substance abuse are also thought to involve “hijacking” of normal hedonic processes (Lewis, 2017).

One theory of addiction processes is that aspects of the pharmacology (more potent agents) or the pharmacokinetics (e.g. rapid rate of change in levels of a psychoactive chemical) leads to greater activation and sensitisation in the “wanting” component of the hedonic system (Volkow, Fowler, Wang, & Swanson, 2004). In turn, this leads to secondary neuroadaptive changes (Sweatt, 2016), including the down-regulation of dopamine and opioid receptors. As tolerance develops along with persistent and increasing craving for the substance, individuals engage in particular behaviours to restore hedonic balance. “Addictive behaviours” are considered out of control and shameful activities and are therefore often carried out in solitude. The repeated occurrence of these behaviours therefore results in a shift in the overall balance between positive and

negative affect, thereby increasing the desire for further activation of the hedonic system (Lewis, 2017; Probst & van Eimeren, 2013). This can lead to the development of a vicious circle of behaviour, where susceptibility is potentially moderated by gender (Jiménez-Murcia et al., 2017).

The Concept of Food Addiction

It follows from this model that certain foods may have an addictive potential because of a similar change in the “pharmacokinetics” of glucose and possibly fat metabolism. For example, foods with a high glycaemic load have the potential to cause greater fluxes in blood glucose. A survey examining the addictive potential of different foods found technologically-processed foods with added refined carbohydrate and fat, and /or with a higher glycaemic load were most implicated (Schulte, Avena, & Gearhardt, 2015). Support for this concept comes from an experimental study in men which found that foods with a high glycaemic load led to greater post meal changes in hunger and activation of reward circuits (Lennerz et al., 2013). Previous evidence has demonstrated individual variation in susceptibility to this effect (Zeevi et al., 2015). For example, insulin resistance or insulin omission (a key behaviour in “diabulimia”) might enhance an individual’s potential to develop a cycle of addictive food consumption because of the wider swings in blood sugar. The same explanation may explain the similar effects of self-induced vomiting. These physiological processes may account for the higher risk of developing an eating disorder in type 1 diabetes (Young et al., 2013), and may also explain the fact that higher levels of binge-purge behaviours in eating disorders worsen prognosis and increase treatment drop-out (Custal et al., 2014; Vall & Wade, 2015).

What is the evidence for similarity in brain circuits between binge eating disorder and substance abuse disorders?

Recurrent binge eating of foods high in fat and sugar has been associated with desensitisation of opioid and dopamine receptors (Colantuoni et al., 2002; Colantuoni et al., 2001). This pattern mimics the neural underpinning of tolerance and dependence observed in substance use disorders (Christie, 2008). Indeed, Broft and colleagues have similarly reported a lower level of dopamine binding in the striatal region for individuals with bulimia nervosa (Broft et al., 2012). Furthermore, they found that lower levels of dopamine binding were correlated with greater severity of bulimic symptoms (Broft et al., 2012).

It is also notable that common neural substrates appear to be relevant in supporting both substance disorders and binge-type eating disorders (Berridge, 2009; R. M. Kessler, Hutson, Herman, & Potenza, 2016; Mameli et al., 2009). The ventral tegmental area and nucleus accumbens play important roles in the processing of reward and maintenance of addictions (Berridge, 2009). Specifically, it has been shown that cocaine use results in the initial potentiation of synapses within the ventral tegmental area (Mameli et al., 2009), which gradually comes to lead to neuroplastic changes within the dorsal striatum (Everitt & Robbins, 2013) (in a path acting via the nucleus accumbens) (Mameli et al., 2009). These changes in the dorsal striatum subsequently consolidate the compulsive nature of the addiction over time. The ventral tegmental area and nucleus accumbens are also highly involved in the processing of taste reward (Berridge, 2009) and, as cited above, reduced dopamine binding in the these same regions of the striatum have been noted in bulimia nervosa (Broft et al., 2012; Steward, Menchón, Jiménez-Murcia, Soriano-Mas, & Fernández-Aranda, 2017) as well as obesity (Wang, Volkow, Thanos, & Fowler, 2004) (as is also seen in individuals with drug addictions) (Wang et al., 2004).

Corresponding with these findings, Gearhardt and colleagues have previously investigated individuals high in food addiction and found that the pattern of neural

activation in response to food cues bears similarity to that observed in individuals with substance disorders in response to drug cues (Gearhardt et al., 2011).

It is interesting to note that these similarities in neural circuits underpinning reward processing are also accompanied by similarities in general neuropsychological traits. Voon used a paradigm that measured aspects of risk taking (valence, probability, and value) and found similarities between people with binge eating disorders and substance abuse, who favoured greater risk taking than healthy controls when anticipating rewards (Voon, Morris, et al., 2015). In the loss domain, however, there were some differences, indicating that individuals with binge eating disorder may not be quite as prone to risk taking when faced with a high probability of loss. Similar findings were obtained when obesity, substance-related disorders and behavioural addictions were compared on decision making tasks (Mallorquí-Bagué et al., 2016).

It has been argued that binge eating disorder and addiction are two clusters of one disorder, with impulsivity and compulsivity as transdiagnostic traits (Figuee et al., 2016; Jiménez-Murcia et al., 2015; R. M. Kessler et al., 2016). Compulsive patterns of behaviour, generally, are believed to be underpinned by anomalies in circuits relating to reward and punishment (particularly among striato-thalamo-cortical circuits (Volkow & Fowler, 2000)).

Building Models for Understanding Bulimia Nervosa and Binge Eating disorder

Fairburn developed a maintenance model for bulimia nervosa in 1981, forming the basis of cognitive behavioural treatment (CBT) (Fairburn, 1981). This was later adapted into the transdiagnostic model, designed to apply to all forms of eating disorder (Fairburn et al., 2003). In these earlier models, the biology and behaviour related to eating and appetite had been largely ignored (Treasure et al., 2012). However, a simple transdiagnostic formulation cannot easily account for the divergent pattern of eating behaviour and

weight between restrictive anorexia nervosa and binge eating disorder. Explanatory models for restrictive anorexia nervosa (AN) (low appetite, aversion to satiety) and both bulimia nervosa (BN) and binge eating disorder (BED) (high appetite, weak satiation) need to account for these differences in the domain of appetitive traits.

The behavioural susceptibility theory has gone some way toward addressing differences between restrictive AN and BN/BED, as it suggests that eating behaviours lie on a continuum (Carnell & Wardle, 2008; Llewellyn & Fildes, 2017). The behavioural susceptibility theory was built upon evidence from precision phenotyping of appetite in large longitudinal studies (Carnell & Wardle, 2008; Llewellyn & Fildes, 2017; Llewellyn & Wardle, 2015). These studies have shown that the variation in appetite is measurable from birth, is highly heritable, and that ‘food-approach’ traits (greater appetite for food) predispose individuals to obesity (Llewellyn & Fildes, 2017). Conversely, ‘food-avoidance’ traits, including poorer appetite and a stronger predisposition to satiety, predispose individuals to being underweight (Llewellyn & Fildes, 2017).

It is possible that this dissimilarity relates to variants of the FTO gene, which has been associated with AN, BN and binge eating (Micali et al., 2015; Müller et al., 2012). This hypothesis is supported by genome-wide association studies and case-control studies indicating that single nucleotide polymorphisms in the FTO gene (including at rs9930506 and rs9939609) are associated with increased body mass index (BMI) in both European American, Hispanic American, British, and Japanese populations (Frayling et al., 2007; Hotta et al., 2008; Scuteri et al., 2007). Furthermore, lab studies have indicated that the A allele at rs9939609 within the FTO gene is associated with significantly greater food intake in test meals (Cecil et al., 2008; Wardle et al., 2009). Thus, there may be biological factors that predispose to the various forms of eating disorders, with the greatest contrasts between binge eating disorders and restricting anorexia nervosa.

New findings from genetic studies suggest that both psychological and somatic aspects may need to feature in our models of eating disorders (Duncan et al., 2017). One example of this is the disordered eating food addiction nutrition guide (DEFANG) (Wiss & Brewerton, 2016), which uses two dimensions, weight and predisposition, as a means of categorising the different forms of eating disorders.

We have developed a maintenance model for binge eating disorder and bulimia nervosa (**Figure 2**), which translates findings from animal studies and builds upon evidence for the theories described above. This differs from the earlier models by including differences in appetitive traits (i.e., the balance between reward and punishment sensitivity) and aspects of executive function (such as impulsivity), while also considering neuroadaptive changes. The five primary maintenance factors proposed within this model are as follows:

(1) The salience of food reward is increased as a result of a predisposing susceptibility. This susceptibility to food addiction reaches the full phenotype following strict dieting behaviour, which further increases the incentive salience of food cues (Berridge & Robinson, 1998). (2) The likelihood of food addiction is further increased within the context of chronic stress and problems with interpersonal relationships, which result in a paucity of other sources of reward. (3) The Western food environment fosters the intermittent consumption of palatable foods with a high glycaemic index in large quantities. Traits of impulsivity and difficulties in delaying action towards rewards can exaggerate susceptibilities to these triggers. (4) Processed foods with added fat and refined carbohydrates produce wide fluxes in blood glucose. These swings in blood sugar can be accentuated by purging behaviours and a lack of, or resistance to, the effects of insulin. (5) In turn, these gradients in blood glucose alter the pattern of dopamine firing (Lennerz et al., 2013). It is thought that these changes in dopamine activity lead to neuroadaptation and the formation of a habitual pattern of behaviour, whereby the drive to eat is no longer dependent on the goal to reduce hunger and is rather triggered by food

cues in the environment. Eating behaviour becomes compulsive (Robbins, Gillan, Smith, de Wit, & Ersche, 2012; Voon, Derbyshire, et al., 2015) and a vicious circle is set in motion. This model can be used as a framework for treatment (**Figure 2**).

Implications for Treatment

This updated model for binge eating suggests there is potential for adaptations to the traditional treatment approaches. Specifically, we identify five potential maintaining mechanisms within the updated model that provide potential targets for treatment within the domains of psychotherapy and nutrition guidance (presented in **Figure 3**). These treatment targets are as follows:

- *Target 1:* An important maintenance factor within the model is the large amount of glucose flux induced by the intermittent consumption of foods with a high glycaemic index. A major difference in the updated model would be the recommendation to avoid and abstain from technologically-modified foods that trigger over-eating, or to manage them in a way that reduces harm (Wiss & Brewerton, 2016) rather than encouraging an absolute “no dieting approach”.
- *Target 2:* Another mechanism that promotes the maladaptive neuroadaptation is the limitation and restriction of all forms of food. While individuals would be recommended to avoid highly-processed foods, treatment based on this new model would continue to discourage individuals from restricting healthy foods, to prevent them from reaching a state of semi-starvation.
- *Target 3:* In order to counteract habit formation that entrenches stimulus-responses association between food cues and eating, another addition may be to add treatments which target impulsivity and habitual patterns of responding. Pilot studies for computerised approaches such as stop signal and go/no-go training have potential (Adams, Lawrence, Verbruggen, & Chambers, 2017; Lawrence,

Verbruggen, Morrison, Adams, & Chambers, 2015; Preuss, Pinnow, Schnicker, & Legenbauer, 2017; Schag, Schönleber, Teufel, Zipfel, & Giel, 2013), but also virtual reality cue exposure (Ferrer-García et al., 2017) and emotional regulation video game training (Fernandez-Aranda et al., 2015) and modification to make these training programmes accessible, more rewarding, and personalised are in progress (Forman et al., 2017). The updated model also opens up the possibility for new pharmacological treatments targeting the sensitisation to food cues, while preventing receptor tolerance triggered by binge eating. For example, Lisdexamphetamine, which targets dopamine systems in binge eating disorder, is already available in the US (Ágh, Pawaskar, Nagy, Lachaine, & Vokó, 2016; McElroy et al., 2016). Work is in progress to further examine drugs which act on the opiate system (Cambridge et al., 2013) and the impact of oxytocin (Y.-R. Kim, J.-S. Eom, J.-W. Yang, J.-W. Kang, & J. Treasure, 2015; Leppanen, Cardi, et al., 2017a; Russell et al., 2018) (which is known to interact with the opiate system) (Flanagan, Verbalis, & Stricker, 1988).

- *Target 4:* Binge eating is partially maintained, following a negative reinforcement model, by high levels of stress and reward seeking that is not satisfied in other domains of life. The model therefore highlights the importance of developing positive anxiety management and coping mechanisms. It is also beneficial to support positive social connections and identify sources of meaning in other areas of life.
- *Target 5:* Maladaptive compensatory behaviours, such as vomiting and insulin omission, further contribute to the large swings in blood glucose that maintain the disorder. Psychoeducation and supporting the development of coping mechanisms to deter these behaviours is therefore also recommended.

Suggestions for Future Research

While the body of evidence described above currently provides a sound basis for this updated model of binge eating behaviour, our understanding of and ability to effectively treat bulimia nervosa and binge eating disorder would benefit from further research in a number of areas. These suggestions are summarised in **Table 2**.

We recommend future research continue to refine our understanding of the ‘food approach’ phenotype. Future work specifically identifying the profiles of traits that are most closely linked to the development of recurring binge eating behaviour would be particularly beneficial in elaborating upon the currently proposed model, in order to further clarify links between traits, environmental cues, thoughts, and disordered eating behaviour. Clarifying which food avoidance traits are most relevant to the onset and maintenance of anorexia nervosa would be similarly useful for the field.

Based on the recognition of neural similarities between substance addiction and binge eating in the proposed model, we would further encourage future research to draw inspiration from interventions previously developed within the addiction sciences and investigate their relevance and effectiveness for curbing binge eating behaviour.

Finally, further research into pharmacological and hormonal treatments that prevent the sensitisation to binge cues and/or reduce receptor tolerance to the ‘liking’ of food stimuli is warranted based on the current model. Relevant research into the potential therapeutic effects of oxytocin and opioid antagonists for binge eating is currently underway; however, research into pharmacological treatments for eating disorders is still nascent and would benefit from further investigation.

Conclusion

We have argued from the impressive evidence from clinical and preclinical science that it is time to put eating behaviour into a central place in models of eating disorders.

Changes in the food environment interacting with individual vulnerability are recognised to be key predisposing risk factors. However, neuroadaptive changes in reward circuits are thought to maintain these disorders. The next step is to develop the evidence for interventions targeting these risk and maintenance factors, with the hope of reversing the increasing prevalence of these problems.

Table 2

Outstanding Questions for Future Research:
• What are the most relevant ‘food approach traits’ determining susceptibility to bulimia nervosa or binge eating disorder? • What are the most relevant ‘food avoidance traits’ determining risk for anorexia nervosa? • What programmes of behavioural intervention would be most effective for breaking automatic stimulus-response associations in bulimia nervosa and binge eating disorder? • What pharmacological treatments would be effective in curbing recurrent binge eating behaviour?

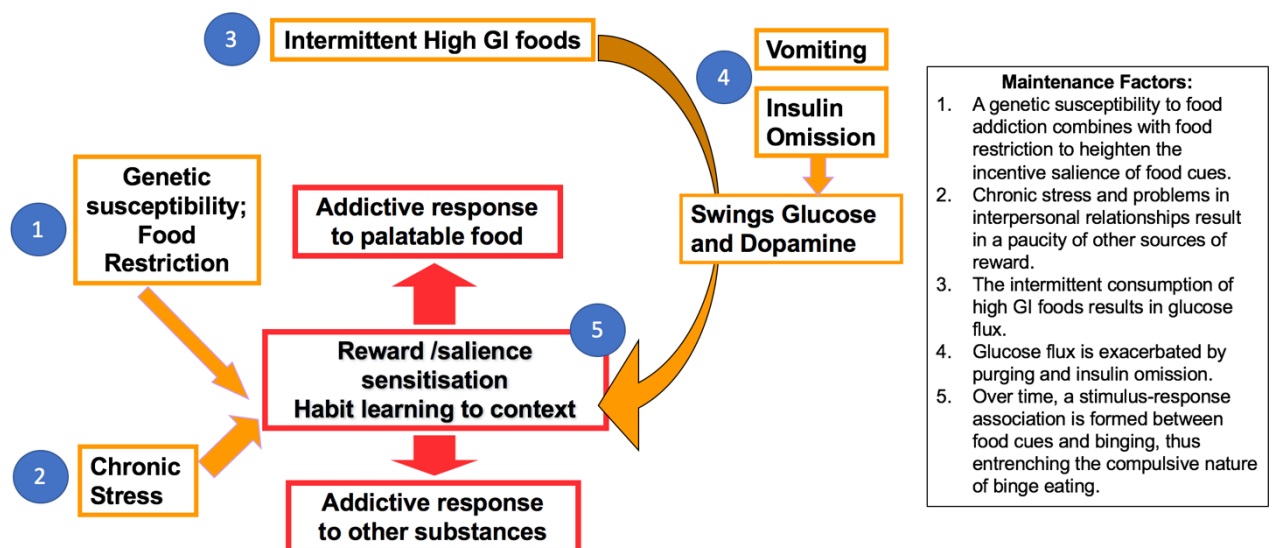


Figure 2. A food addiction model of binge eating behaviour. GI = glycaemic index.

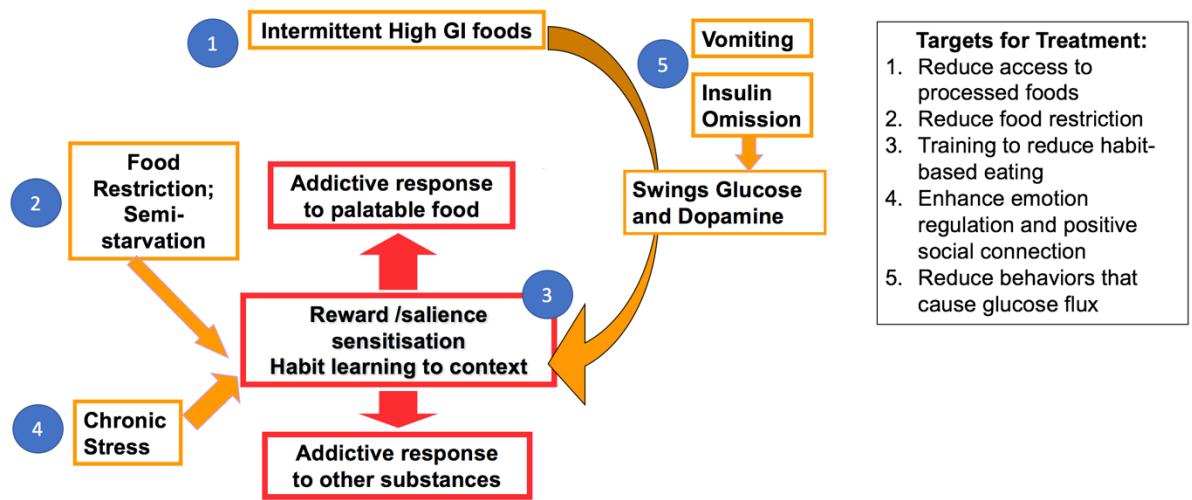


Figure 3. The targets for treatment within a food addiction model of binge eating behaviour. GI = glycaemic index.

Towards a Translational Approach to Food Addiction: Implications for Bulimia Nervosa

Leslie, Monica ^a;

Lambert, Ellen ^a;

Treasure, Janet ^a

Affiliations:

^a Institute of Psychiatry, Psychology and Neuroscience (IoPPN) - King's College London (KCL), London, United Kingdom

Corresponding Author: Monica Leslie – monica.leslie@kcl.ac.uk; - 103 Denmark Hill, Section of Eating Disorders, London SE5 8AF, United Kingdom, +44 20 7848 0604

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Abstract

Purpose of review: In recent years, the food addiction hypothesis of loss-of-control eating has gained traction in the field of eating disorders. In particular, the neural process of food addiction plays a dominant role in the recently formulated “addictive appetite” model of bulimia nervosa and binge eating disorder. Nonetheless, several components of the food addiction hypothesis, including the presence of withdrawal and tolerance effects, as well as the proposition that some foods possess “addicting” properties, remain highly controversial. In response, the current review synthesises existing evidence for withdrawal and tolerance effects in people with bulimia nervosa.

Recent findings: The recent development of a validated tool to measure withdrawal from highly processed foods will aid in measuring withdrawal symptoms and testing hypotheses related to withdrawal in the context of food addiction. We subsequently describe preclinical and human evidence for a central insulin- and dopamine-mediated pathway by which recurrent loss-of-control binge eating is maintained in bulimia nervosa.

Summary: Evidence in populations with bulimia nervosa and loss-of-control eating provides preliminary support for the role of food addiction in the maintenance of bulimia nervosa. Future longitudinal research is needed to develop a clearer profile of illness progression and to clarify the extent to which dysregulation in glucose metabolism contributes to food craving and symptom maintenance in bulimia nervosa.

Keywords: Food addiction; bulimia nervosa; eating disorders; sugar; dopamine

Background

The concept of “food addiction” has received increasing attention in the scientific literature of recent years. While cogent arguments have been made against the establishment of food addiction as a psychiatric diagnosis in its own right (Finlayson, 2017), there is substantial evidence to suggest that processes similar to those observed in substance abuse disorders play a significant role in the maintenance of eating disorders in which loss of control of eating is a feature (e.g., anorexia nervosa -binge purge type, bulimia nervosa and binge eating disorder) (Treasure, Leslie, Chami, & Fernández-Aranda, 2018). In this article, we will use bulimia nervosa (BN) as the exemplar. The “Addictive Appetite Model” proposes that three primary processes maintain psychopathology in BN: 1) The high salience of palatable foods (Berridge & Robinson, 1998), which is moderated by a genetic susceptibility to food approach tendencies, reduced efficiency in satiation processes (Carnell & Wardle, 2008), and/or episodes of food restriction; 2) Chronic stress and interpersonal difficulties resulting in a deficiency of alternative rewards and a primed stress system (Turton, Chami, & Treasure, 2017); and 3) Large swings in blood glucose, caused by the consumption of foods with a high glycaemic index, self-induced vomiting or insulin resistance (and insulin omission in diabetes mellitus). These pathways may contribute to compulsive binge eating behaviour through aberrations in dopaminergic function in a similar way to substance addictions.

The current review presents a synthesis of the literature investigating some of the controversial aspects of applying the food addiction paradigm to eating disorders. For instance, there is uncertainty as to whether tolerance and withdrawal criteria for an addictive disorder, as specified within the DSM-5, are met. We also present a synthesis of molecular, preclinical, and clinical evidence illustrating how fluxes in glucose and insulin moderate central dopaminergic functioning.

Does Bulimia Nervosa Meet DSM-5 Criteria for an Addictive Disorder?

The DSM-5 criteria for an addictive disorder are presented in **Table 3**. The extent to which BN meets these criteria has been reviewed extensively elsewhere (Brewerton, 2014). In his 2014 review, Brewerton acknowledges significant phenotypic overlap between disorders of substance dependence and BN but highlights a paucity of systematic clinical evidence for tolerance and withdrawal in the latter, a point frequently cited as a major weakness of the food addiction hypothesis (Ziauddeen, Farooqi, & Fletcher, 2012). Much research on tolerance and withdrawal symptoms in humans to date has been largely anecdotal (Gearhardt et al., 2009b). However, herein we synthesise the evidence from new assessment methods.

Tolerance

The most compelling evidence for food tolerance is demonstrated in animal models, as previously reviewed by Murray, Gordillo, and Avena (2014). Rats who voluntarily overeat highly palatable food exhibit evidence of a neural reward deficit due to downregulated dopamine D2 receptors, which worsens as weight is gained (Colantuoni et al., 2001; P. M. Johnson & Kenny, 2010; M. J. Robinson et al., 2015). This decreased sensitivity to reward is directly linked to the onset of compulsive food seeking in rats (P. M. Johnson & Kenny, 2010). Repetitive bingeing on sucrose interspersed with periods of dietary restriction causes rats to triple their overall daily sugar consumption (Rada et al., 2005), a finding which may be of particular importance to BN, as it is characterised by intermittent fasting and binge episodes (American Psychiatric Association, 2013). A similar downregulation of dopamine D2 receptors is found in humans addicted to drugs of abuse (Koob & Volkow, 2016) and is thought to be a key driver of compensatory overconsumption in the Reward Hyposensitivity Theory (Blum et al., 2000; P. J. Rogers, 2017). Behavioural observations in people with substance use disorders mirror these findings.

Individuals with BN endorse higher levels of tolerance-like symptoms measured using the Yale Food Addiction Scale (YFAS) (Gearhardt et al., 2009b), compared with healthy controls (de Vries & Meule, 2016; Meule & Gearhardt, 2014a). There are clinical reports of subthreshold BN patients initiating larger and more frequent binge episodes over time (Stice et al., 2009). Consistent with these accounts is cross-sectional evidence of the correlation between higher body weight and frequency and severity of binge eating episodes (Picot & Lilenfeld, 2003). Individuals with binge-type eating disorders endorse significantly greater levels of eating for purposes of reward enhancement compared with weight-matched controls (Leslie, Turton, Burgess, Nazar, & Treasure, 2018). Such evidence, although compelling, remains indirect and is insufficient to prove the existence of tolerance in humans.

A preference for intensely sweet food and larger quantities of sweeteners in individuals with BN is a characteristic often presented as an indicator of tolerance (Berridge & Robinson, 1998; Drewnowski, Bellisle, Aimez, & Remy, 1987; Drewnowski, Shrager, Lipsky, Stellar, & Greenwood, 1989; Franko, Wolfe, & Jimerson, 1994). Furthermore this preference remains after ingesting a glucose load (Rodin, Bartoshuk, Peterson, & Schank, 1990). Magnetic resonance imaging (MRI) studies indicate hypofunctioning of gustatory and limbic circuitry in BN patients when tasting palatable food compared with controls (Bohon & Stice, 2011; Frank, Reynolds, Shott, & O'Reilly, 2011) and compared with individuals recovered from BN (Oberndorfer et al., 2013; Radeloff et al., 2014). This evidence is consistent with the idea that individuals with BN ingest more food over time because of a decreased sensitivity to sweet taste resulting from repeated binging on hyperpalatable foods (Bohon & Stice, 2011).

The development of impaired satiety mechanisms may be an indirect indicator of tolerance (Brewerton, 2014; Haedt-Matt & Keel, 2011; Halmi, Sunday, Puglisi, & Marchi, 1989). For example, a recent functional MRI (fMRI) study found that women in

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remission from BN exhibited the same response to taste stimuli in brain regions implicated in translating sensory information about taste into motivated behaviour, regardless of whether the individuals were hungry or sated, whilst healthy controls showed an increased response to taste stimuli when hungry versus when fed (Ely et al., 2017). The authors also found an increased amygdala response in their remitted BN sample when fed compared to healthy controls, which they propose might project to the hypothalamus and motivate eating in the absence of hunger (Ely et al., 2017; Sun et al., 2015). It is possible that brain circuitry in BN fails to de-value food reward when in a fed state, leading to eating beyond metabolic need.

Five years on from Brewerton's 2014 review, there remains a paucity of direct evidence of tolerance in humans in relation to food intake and prospective, longitudinal studies are needed.

Withdrawal Syndromes

Preliminary evidence for a withdrawal syndrome in relationship to palatable food comes from animal models. There are consistent observations of strong physical (e.g., forepaw tremor, teeth chattering) and psychological (e.g., aggression, anxiety) withdrawal responses in rats during periods of withdrawal from sucrose (Avena, Rada, & Hoebel, 2008; Iemolo et al., 2012; Wideman, Nadzam, & Murphy, 2005). The same observations, however, are not found with removal of high-fat foods (Bocarsly, Berner, Hoebel, & Avena, 2011) and have not yet been studied with removal of highly processed foods (Schulte, Smeal, Lewis, & Gearhardt, 2018). Neuroimaging studies show patterns consistent with this behavioural data. Sugar-dependent rats show a significant increase in extracellular acetylcholine and a decrease in dopamine release in the nucleus accumbens shell, as compared to control groups, during a 36-hour period of food deprivation (Avena et al., 2008), effects which are similar to withdrawal from morphine, nicotine, and alcohol.

Traditionally withdrawal symptoms have not been clearly defined in the context of addictive-like eating, prompting criticism of the food addiction framework (Ziauddeen & Fletcher, 2013). To date, the food addiction field has largely relied on observational and anecdotal clinical reports based on small cohorts or single case studies (Davis & Carter, 2009; Gearhardt, Corbin, & Brownell, 2016; Hansen, 2016; Ifland et al., 2009; Lingswiler, Crowther, & Stephens, 1989; Thornley & McRobbie, 2009) and on self-reported endorsement of withdrawal symptoms on the YFAS (Meule & Gearhardt, 2014a) and other withdrawal scales (Gilbert, Gilbert, & Schultz, 1998). Cross-sectional self-report accounts are consistent in describing physiological symptoms of withdrawal similar to those experienced during opiate withdrawal (Farrell, 1994; Gearhardt et al., 2009b). Headaches, irritability and flu-like symptoms are reported by individuals abstaining from sugar (Davis & Carter, 2009), stomach pains, muscle spasms and shakiness by individuals abstaining or reducing intake of carbohydrates (Ifland et al., 2009; Thornley & McRobbie, 2009), and nausea by individuals abstaining from salted food (Tekol, 2006). Furthermore, tiredness and irritability have been cited as motivating factors for eating (Ifland et al., 2009), providing some suggestion of food being used as a “pick-me-up”, or to avoid an experience of negative feelings of withdrawal.

Symptoms of psychological withdrawal are also widely reported. Cross-sectional self-report accounts from patients with BN reveal that most feel tension, loneliness, and physical symptoms of anxiety before a binge, and the majority feel that their negative psychological states are alleviated whilst engaged in a binge (Schulte et al., 2018). Longitudinal studies using Ecological Momentary Assessment technology also report that binge eating and subsequent purging are usually preceded by dysphoric mood states (Anestis et al., 2010; Selby et al., 2012; Smyth et al., 2007). However, there is high prevalence of depression and emotion dysregulation in BN populations (Braun, Sunday, & Halmi, 1994), so it is not clear whether such presentations of low mood represent

psychological withdrawal from food. Future research should aim to elucidate whether dysphoric mood states before bingeing are distinct from more permanent mood-related comorbidities, perhaps by comparing depressed versus non-depressed individuals with BN.

The first and only tool to evaluate withdrawal in the context of addictive-like eating has been developed recently: The Highly Processed Food Withdrawal Scale – ProWS (Schulte et al., 2018). This, in part, is derived from the premise that specific nutritional ingredients are capable of triggering addictive-like responses (Pursey, Davis, & Burrows, 2017). In a pilot study, the ProWS was found to be positively associated with elevated YFAS symptoms, BMI and weight cycling in a community sample, and responses on the ProWS explained an additional 11.2% of the variance in self-reported dieting success (Schulte et al., 2018). This tool may help differentiate between the withdrawal effects from different types of palatable food (Curtis & Davis, 2014; Schulte et al., 2015) .

The Impact of Glucose Metabolism on Hedonic Eating Behaviour

Preclinical Evidence

Sweet, palatable foods act as an unconditioned rewarding stimulus in humans and rodent models, with evidence suggesting that merely tasting sucrose without digestion produces activation of dopaminergic circuits within the striatum (Avena, Rada, Moise, & Hoebel, 2006). However, there is evidence to suggest that palatable foods with a high glycaemic index further contribute to the development of compulsive binge eating behaviour through changes in dopaminergic functioning triggered by wide swings in blood glucose. One candidate mechanism for this effect relates to the interaction between insulin and dopaminergic functioning.

The role of mesolimbic dopaminergic functioning in food approach behaviours has been reviewed extensively elsewhere (Berridge, Ho, Richard, & DiFeliceantonio, 2010). Dopamine-deficient mouse models exhibit severe aphagia leading to weight loss and death (Q.-Y. Zhou & Palmiter, 1995). Conversely the stimulation of dopaminergic activity within the striatum triggers food consumption in rats without enhancing “liking” responses (e.g., lip-licking and paw licking). Thus, dopaminergic functioning is thought to hold a role in food approach behaviours (wanting) that is discrete from the hedonic response to food receipt (Berridge & Valenstein, 1991). In contrast, central insulin suppresses feeding (Woods, Lotter, McKay, & Porte Jr, 1979). It is thought that the effects of central insulin and dopamine on food intake, are not independent, but rather interact to regulate hedonic eating behaviour.

Dopaminergic neurons within the ventral tegmental area (VTA) express insulin receptors (Figlewicz, Evans, Murphy, Hoen, & Baskin, 2003; Pardini et al., 2006), presenting a possible mechanism by which insulin might influence the dopaminergic induction of feeding behaviour. Furthermore, central insulin enhances the expression of dopamine transporter protein within the VTA via a protein kinase B (Akt) signalling system (Figlewicz, Szot, Chavez, Woods, & Veith, 1994; Williams et al., 2007). The enhanced expression of dopamine transporters on the cell surface induced by insulin exposure is associated with greater dopamine uptake (Carvelli et al., 2002), thus reducing levels of synaptic dopamine.

With regards to the effects of insulin on postsynaptic dopaminergic signalling, in vitro studies have found that insulin exposure invokes long-term depression of excitatory signalling within VTA dopamine neurons extracted from male C57BL/6J mice (Labouèbe et al., 2013). This effect appears to be long-lasting as, once induced, the long-term depression of VTA dopamine cells is not reversed by application of the insulin receptor

antagonist S961 or through a tyrosine kinase inhibitor, which suppresses insulin receptor functioning (Labouèbe et al., 2013).

The effects of central insulin on dopaminergic functioning within the VTA likely have downstream effects in suppressing feeding, and particularly hedonic feeding. For example, Bruijnzeel, Corrie, Rogers, and Yamada (2011) found that injecting insulin directly into the VTA of female rats decreased 24-hour food intake. Mebel, Wong, Dong, and Borgland (2012) have similarly found that injecting insulin directly into the VTA suppresses subsequent feeding in male C57BL/6J mice; however, this effect was dependent on the hunger status of the animals. That is, insulin in the VTA suppressed the quantity of sweetened high fat food consumed by sated mice but did not affect normal chow intake in hungry mice. This pattern of effects therefore suggests that insulin activity in the VTA acts selectively to suppress subsequent hedonic feeding, with weaker evidence for effects on homeostatic feeding behaviour.

Central insulin functioning may play a role in blocking the memory of palatable food reward or attenuating the incentive salience of cues associated with palatable food. Evidence for this hypothesis comes from studies demonstrating that injecting insulin either into the cerebral ventricles (Figlewicz et al., 2004) or VTA (Labouèbe et al., 2013) of rats at the time of memory retrieval reduces conditioned place preference for palatable food. Furthermore, Bruijnzeel et al. (2011) found that injecting insulin at a dose of .005mU/side into the VTA elevated the reward threshold for intracranial self-stimulation, thus indicating a reduction of reward functioning.

Evidence in Humans

Insulin resistance impacts on central dopaminergic systems in humans. For example, Dunn et al. (2012) conducted a positron emission tomography (PET) study using the dopamine D2/D3 receptor radioligand [18F]fallypride, and found that insulin

sensitivity is negatively correlated with dopamine type 2 receptor availability in the ventral striatum in a heterogeneous sample of lean and obese women. In men, Anthony et al. (2006) found that exogenously administered insulin increases metabolism in the ventral striatum and prefrontal cortex, while decreasing metabolism in the right amygdala, hippocampus, and cerebellar vermis. Furthermore, the effect of insulin in increasing metabolism in the ventral striatum and PFC was lower in insulin-resistant, versus insulin-sensitive participants (Anthony et al., 2006). This pattern of findings is thus indicative of trait-level differences in the effects of central insulin on dopaminergic mesolimbic regions, known to be critical for food craving and food approach behaviour (Volkow et al., 2002; Q.-Y. Zhou & Palmiter, 1995).

Interactions between insulin resistance and central dopaminergic functioning may have functional significance for food craving in humans. Chechacz et al. (2009), in an fMRI study, found that people with Type II diabetes mellitus (characterised by insulin resistance) exhibit greater blood oxygenated level dependent (BOLD) response to food versus non-food images in the insula, orbitofrontal cortex (OFC), and basal ganglia, when compared to people without diabetes mellitus. Moreover, this increased activation within the insula and OFC is positively correlated with self-reported external eating. These findings, taken together, thus provide evidence that insulin resistance, commonly observed following repeated excess consumption of fructose in combination with an overall excessive energy intake (MacDonald, 2016), is positively correlated with a pattern of neural response to food stimuli which is associated with greater external cue-driven eating. However, it should be noted that the correlational nature of these findings limits the ability to draw firm causal inferences. Although there is relatively less evidence regarding food craving in Type I diabetes, an fMRI study has found that insulin detemir, which more readily enters the brain compared to standard forms of insulin, is associated with reduced BOLD response to food images in the bilateral insula, a brain region

associated with the regulation of appetite (van Golen et al., 2014). The authors have speculated that insulin detemir may therefore induce a more effective satiety reaction, thus explaining the reduced levels of weight gain observed in people with Type I diabetes mellitus taking insulin detemir (Hermansen et al., 2004).

In a related study, Jastreboff et al. (2013) recruited 25 men and women in the obese weight range and 25 lean controls. Fasting insulin and glucose were taken to measure insulin resistance. During a subsequent fMRI task, audio scripts designed to provoke relaxing imagery or favourite food imagery were played. Food craving was assessed before and after each imagery trial. The degree of food craving following food imagery trials was positively associated with insulin resistance in the obese, but not lean, participant group. Furthermore, the relationship between insulin resistance and food craving within the obese participant group was mediated by BOLD responses in dopaminergic regions including the ventral tegmental area (VTA) and substantia nigra. These studies suggest that insulin resistance moderates craving and associated neural circuits in response to food related imagery.

Thus, the above studies illustrate that interactions between central insulin and dopaminergic systems, known to impact on feeding behaviour in animals, also regulate food craving in humans. While this evidence therefore supports a potential mechanism linking the short- and long-term physiological effects of sugar consumption to food craving in humans, it is also of interest to disentangle the effects of sweet taste on dopaminergic incentive sensitisation from the physiological effects of sugar in food approach behaviour in humans. In support of the physiological effects of glucose consumption on central dopaminergic functioning, regardless of sweet taste, Haltia et al. (2007) found that the intravenous administration of glucose, versus placebo, was associated with increased D2 receptor binding potential in the right caudate nucleus and bilateral putamen in both lean and overweight women. However, intravenous glucose

administration was rather associated with reductions in D2 receptor binding potential in the bilateral caudate nucleus, left putamen, and right thalamus in men. It should be noted that the intravenous method of administration employed in this study bypassed the gastrointestinal system, thus failing to stimulate the production of gastrointestinal hormones, such as glucagon-like peptide 1, which also impact on appetitive functioning (Flint, Raben, Astrup, & Holst, 1998; Vilsbøll, Krarup, Madsbad, & Holst, 2003). This study is therefore limited in the extent to which it directly bears upon the oral consumption of glucose versus calorie-free sweet taste. Nonetheless, these findings provide evidence for the impact of glucose on mesolimbic dopaminergic functioning in the absence of sweet taste. The functional significance of the sexual dimorphism in brain response is not yet clear and would be an interesting avenue for future research.

In another PET study conducted in nineteen participants with BMIs ranging from the lean to obese weight range, dopamine functioning was measured following the consumption of a 75g oral glucose drink versus a calorie-free sucralose drink of equal volume and sweetness. Within the lean participant group, consuming the glucose drink, versus the calorie-free sucralose drink, was associated with increased dopaminergic binding potential within the ventral striatum, while the opposite was observed in the obese participant group (Wang et al., 2014). Thus, there is evidence that glucose impacts upon dopaminergic functioning separately from the effects of sweet taste alone, with BMI modulating the direction of that effect. The reduced activation stimulated by sugar consumption in obese participants is in line with previous evidence of down-regulated striatal response to the receipt of sugar solutions, including chocolate milk and milkshakes (Burger & Stice, 2014; Stice, Yokum, Blum, & Bohon, 2010).

There is a relative paucity of research investigating the effects of glucose metabolism on dopamine-mediated feeding in BN and binge eating disorder without obesity. A recent meta-analysis of studies analysing insulin sensitivity in BN and binge

eating disorders has found significantly reduced insulin sensitivity in both disorders (Ilyas et al., 2018). Such insulin resistance therefore leads to greater flux in blood glucose following the consumption of foods with a high glycaemic index, thus potentially contributing to food craving in a similar manner to that described above for populations with obesity (Jastreboff et al., 2013). The effect of insulin resistance on glucose flux is further exacerbated by the wide swings in blood glucose induced by intermittent fasting followed by objectively large binge eating episodes in people with BN (Monteleone et al., 2000). Frank et al. (2006) found evidence of some trait differences in brain response to a glucose, versus artificial saliva solution, in the anterior cingulate cortex and left cuneus in comparison to the control group. However, this study is confounded by the difference in sweet taste as well as nutritional content (glucose versus calorie-free liquid). It will therefore be critical to carry out similar research to that described above for obesity in populations with bulimia-spectrum disorders in order to clarify the functional role of a glucose metabolism pathway in loss-of-control binge eating versus the chronic overeating which commonly characterises overweight and obesity.

Conclusion

The current literature review has thus far served to illustrate the existing state of the evidence with regards to food tolerance and withdrawal effects in BN. Additionally, preclinical and preliminary evidence in human studies has elucidated an insulin-dependent mechanism whereby foods with a high glycaemic index interact with mesolimbic dopamine systems and heighten food craving in cases of insulin dysregulation. Nonetheless, there are several lines of evidence that should be explored further before definite conclusions can be drawn with regards to withdrawal and tolerance in BN and the physiological mechanisms which maintain addictive responses to palatable food.

Table 3

DSM-5 criteria for an addictive disorder (American Psychiatric Association, 2013)

Criterion Number	Criteria
Criteria 1.	The substance is often taken in larger amounts or over a longer period than was intended
Criteria 2.	There is a persistent desire or unsuccessful efforts to cut down or control use of the substance
Criteria 3.	A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
Criteria 4.	Craving, or a strong desire or urge to use the substance
Criteria 5.	Recurrent use of the substance despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use
Criteria 6.	Continued use of the substance despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use
Criteria 7.	Important social, occupational, or recreational activities are given up or reduced because of use of the substance
Criteria 8.	Recurrent use of the substance in situations in which it is physically hazardous
Criteria 9.	Tolerance, as defined by either of the following: (a) A need for markedly increased amounts of the substance to achieve intoxication or desired effect (b) A markedly diminished effect with continued use of the same amount of the substance
Criteria 10.	Withdrawal, as manifested by either of the following: (a) The characteristic withdrawal syndrome for other substance (b) The substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms

2.3 Rationale for testing the addictive appetite model

Sections 2.1 and 2.2 of the current thesis have presented a novel maintenance model for bulimia nervosa and binge eating disorder and presented evidence for some of the more controversial components of this theoretical model, respectively. However, as highlighted in Paper 2, the state of evidence supporting some elements of the model remains preliminary. The following paper therefore aimed to test psychological, versus metabolic, aspects of the maintenance model, with a specific focus on the importance of food craving, emotional coping, and reward enhancement in bulimia nervosa and binge eating disorder.

Testing the addictive appetite model of binge eating: The importance of craving, coping, and reward enhancement

Short Title: Testing the addictive appetite model of binge eating

Monica Leslie*¹

Robert Turton*¹

Emilee Burgess²

Bruno Nazar^{†1, 3}

Janet Treasure^{†1}

* Joint first author

† Joint senior author

¹ Section of Eating Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

² Department of Psychology, University of Alabama at Birmingham, USA

³ Federal University of Rio de Janeiro – Institute of Psychiatry (IPUB – UFRJ), Rio de Janeiro, Brazil

Corresponding Author:

Monica Leslie

Section of Eating Disorders,

Department of Psychological Medicine

103 Denmark Hill, London, SE5 8AF, King's College London

Email address: monica.leslie@kcl.ac.uk

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Abstract

In the current study, we examine components of the “addictive appetite” model of recurrent binge eating. Specifically, we tested the influence of addictive processes and the influence of emotional regulation processes on recurrent binge eating behaviour. We recruited 79 women in total for the current study; 22 with bulimia nervosa, 26 weight-matched lean comparison women, 15 women with binge eating disorder, and 16 weight-matched overweight/obese comparison women. Participants completed questionnaire assessments of food craving and motivations for eating. Compared to weight-matched comparison women, women with binge-type eating disorders endorse significantly greater levels of food craving, eating for purposes of coping, and eating for purposes of reward enhancement. A cluster analysis revealed that these three traits distinguish women with binge-type eating disorders from weight-matched comparison women. These findings provide support for the addictive appetite model of binge eating behaviour and highlight addictive and emotional regulation processes as potential targets for treatment.

Key Words: Bulimia Nervosa; Binge Eating Disorder; Food Addiction; Research Domain Criteria

The trans diagnostic model of eating disorders has played a dominant role in informing psychological treatment for adults with bulimia nervosa and binge eating disorder over the last several decades (Fairburn et al., 2003). However, treatment informed by the trans diagnostic approach is not effective for many individuals with bulimia nervosa, with only 30-50% achieving abstinence from binge-purge behaviours by the end of treatment (Hay, 2013; National Institute for Health and Clinical Excellence, 2017), and 68% achieving remission at 9-year follow-up (Eddy et al., 2017).

An updated model of recurrent binge eating behaviour has therefore recently been proposed (Treasure et al., 2018), which addresses the dysregulation of appetite in bulimia nervosa and binge eating disorder not previously highlighted within the trans diagnostic model. One of the key factors proposed by this updated “addictive appetite” model of recurrent binge eating behaviour is the increased incentive salience of food cues and habitual response patterns to palatable food cues, which heighten desire and craving for these foods (Berridge, 2007). At a neural level, this pattern of heightened response to food cues and subdued responding to the receipt of pleasant tastes bears resemblance to substance use disorders, in which a similar pattern of neural responding has been observed in relation to drug cues (Gearhardt et al., 2011). For the purposes of the current paper, we define food craving as being characterised by intense desire or urge to eat a particular type of food, where that desire corresponds to a specific flavour and texture (Pelchat, 2002). “Craving”, in its current usage, can therefore be contrasted to both generalised hunger that does not necessarily drive behaviour towards a specific type of food, and to mild preferences for one type of food over another.

There is also thought to be a down-regulation of the response to other rewards in bulimia nervosa and binge eating disorder, such that basal levels of low affect are common in this population (Volkow, Wise, & Baler, 2017). This low affect thus

contributes to heightened likelihood of compensatory reward-seeking, specifically in the form of palatable tastes (Treasure et al., 2018). This model of binge eating behaviour has previously received support from ecological momentary assessment studies, which found that participants reported greater levels of low affect immediately prior to binge eating episodes (Haedt-Matt & Keel, 2011). However, relatively little previous research has explored the relationship between individuals' motivations for eating and eating disorder pathology (Burgess, Turan, Lokken, Morse, & Boggiano, 2014).

The aim of this study was to test two maintenance processes proposed within the addictive appetite model of binge eating: eating due to enhanced incentive salience and eating for emotion regulation. Our hypotheses were as follows:

1. People with BN and BED would show higher levels of craving for food than weight-matched controls.
2. People with BN and BED would endorse eating palatable food as a method of coping with distress and as a means of enhancing mood.
3. Food craving, eating for emotional coping, and eating for reward enhancement would distinguish individuals with binge-type eating disorders from weight-matched controls.

Methods

Participants

Seventy-nine women were recruited through flyers and e-mail circulars at King's College London, as well as through eating disorder clinics in London. Twenty-six women met criteria for the lean control group, 22 women met DSM-5 criteria for bulimia nervosa, 15 women met DSM-5 criteria for binge eating disorder, and 16 women were included in the overweight/obese control group. Of the women with bulimia nervosa or binge eating disorder, 25 had received treatment for their eating disorder within six months prior to

the study. Further details regarding the type of treatment participants received are presented in **Supplementary Table 1**. Of the participants with BN or BED, 15 participants had a comorbid diagnosis of a depressive disorder, 8 participants had comorbid generalised anxiety, 1 participant had a comorbid diagnosis of social anxiety disorder, two participants had borderline personality disorder, two participants had post-traumatic stress disorder, and 1 participant had obsessive-compulsive disorder.

The non-eating disorder comparison groups were age- and weight-matched with the groups with eating disorders as far as possible. Ethical approval for the study was granted by the Hampstead Research Ethics Committee (reference number: 14/LO/2166). All participants voluntarily consented to take part in the study.

Inclusion criteria for the study required participations' age to be between 18 and 65 years old. Participants in the eating disorder sample were required to meet DSM-5 diagnostic criteria for BN or BED (American Psychiatric Association, 2013). Healthy control participants were required to have a body mass index (BMI) of at least 18.5 and have no history of an eating disorder. Exclusion criteria included: current substance abuse, history of an abnormal neurological condition, acute suicidality, and severe comorbidity (e.g., active psychosis). Participants were screened using the Structured Clinical Interview for DSM-5 (SCID) (American Psychiatric Association, 2013). Screening was conducted either by a psychiatrist or graduate-level psychology student who had received specific training in correct use of the SCID. Demographic descriptive statistics for each sample of participants are reported in **Table 4**.

Experimental Design

After signing informed consent and undergoing screening for eligibility, participants were invited to complete an online survey containing the following battery of measures: the Eating Disorder Examination – Questionnaire version (EDE-Q)

(Fairburn & Beglin, 1994b), the Depression and Anxiety Stress Scales (DASS) (Lovibond & Lovibond, 1995), Food Craving Questionnaire – Trait subscale (FCQ) (Cepeda-Benito, Gleaves, Williams, & Erath, 2000), and the Palatable Eating Motives Scale (PEMS) (Burgess et al., 2014). These online questionnaires were conducted prior to a subsequent battery of tests conducted in the lab, the results of which are reported in a previously published paper (Turton et al., 2018). The PEMS has been described in detail below and all other measures are described within the **Supplementary Material**. Participants were also asked to confirm their current binge eating frequency and answer demographic questions, including their age and education level (measured as the total number of years spent in education).

Palatable Eating Motives Scale (PEMS). The Palatable Eating Motives Scale (PEMS) (Burgess et al., 2014) yields a measure of the extent to which individuals tend to eat food for reasons other than maintaining metabolic homeostasis (i.e., in response to hunger). The PEMS consists of 19 items answered in the form of a 5-point Likert scale from 1 (Almost Never/Never) to 5 (Almost Always/Always). The PEMS contains four subscales corresponding to different reasons people consume palatable food (Social, Coping, Conformity, and Reward Enhancement). The social subscale measures motivation to eat for social reasons (e.g., when going out for a meal or to a party with friends), the coping subscale measures motivation to eat in order to regulate negative affect (e.g., to distract oneself and/or improve mood after a bad day), the conformity subscale measures motivation to eat due to social pressures (e.g., to fit in with others, or to be liked), while the reward enhancement subscale measures motivation to eat in order to enhance positive experiences or the intrinsic reward of palatable foods. Within the current sample, the total PEMS scale was associated with excellent internal consistency ($\alpha = 0.92$). All subscales of the PEMS were associated with good internal consistency:

Social ($\alpha = 0.88$), Coping ($\alpha = 0.95$), Enhancement ($\alpha = 0.85$), and Conformity ($\alpha = 0.89$).

Statistical Analysis

In order to account for the potential effect of BMI, the sample with bulimia nervosa was compared against a weight-matched lean comparison group in the following analyses, and the sample with binge eating disorder was likewise compared against an overweight/obese comparison group. Each of the above-mentioned variables were compared across groups using a Student's *t*-test. Multiple comparisons were controlled for by setting the False Discovery Rate at 0.05 (Benjamini & Hochberg, 1995). Exploratory correlation analyses were then conducted to examine relationships between subscales of the EDE-Q, the subscales of the PEMS, BMI, and the FCQ.

A *k*-means cluster analysis was then used to determine whether food craving, eating for emotional coping, and eating for reward enhancement would distinguish individuals with binge-type eating disorders from weight-matched controls. This cluster analysis was conducted using a single-linkage cluster method. Squared Euclidean distance was the chosen distance measure for the cluster analysis. All analyses were performed in SPSS version 23.0.

The data were first analysed for outliers and assumptions of normality. Three outliers ($Z > |3.0|$) were observed in the BMI variable, one in the age variable, two in the social subscale of the PEMS, three in the conformity subscale of the PEMS, and one in the binge frequency variable. These values were excluded case-wise from all relevant analyses.

Results

Demographics. There were no significant differences in age between each sample and its weight-matched comparison group. There were no significant differences in BMI or education between the bulimia nervosa sample and lean control group, although the binge eating disorder group had a significantly higher BMI than the overweight/obese control group ($Z = -2.02, p = .044$) and spent significantly fewer years in education ($t(28.30) = 3.04, p = .005$). The descriptive statistics and effect size comparisons for these variables are presented in **Table 4**.

Eating disorder symptomatology, food craving, depression, anxiety, and eating motivations for each diagnostic group. The descriptive statistics and effect size comparisons for EDE-Q subscales (Eating Concern, Restraint, Weight Concern, Shape Concern, Binge Frequency), FCQ, the PEMS subscales (Social, Conformity, Coping, and Reward Enhancement), and the DASS for each diagnostic group are reported in **Table 5**. The results of the t -tests comparing lean controls with the bulimia nervosa sample on the EDE-Q subscales, FCQ, the PEMS subscales, and the DASS are presented in **Table 6**. Due to excessive skew in the binge eating frequency variable for the lean control sample, this variable was compared to the bulimia nervosa sample using a Mann-Whitney U test. The Mann-Whitney U test for binge frequency revealed that the sample with bulimia nervosa reported a significantly higher binge frequency than the lean control sample ($U = 0.50, Z = -6.20, p < .001$). There were no significant differences regarding the extent to which individuals ate for social reasons measured between these two samples. The sample with bulimia nervosa had significantly higher levels of depression, anxiety, and stress (as measured by the DASS), significantly higher scores on all EDE-Q subscales (restraint, eating concern, weight concern, and shape concern), greater levels of food craving, and reported significantly greater tendencies to eat for purposes of coping, reward enhancement, and conformity than the lean control group.

The results of the *t*-tests comparing the overweight/obese control sample with the binge eating disorder sample on the EDE-Q subscales FCQ, the PEMS subscales, and the DASS are presented in **Table 7**. There were no significant differences between the two groups in eating for purposes of socialising or conformity. However, the binge eating disorder group had significantly higher levels of depression, anxiety, and stress (as measured by the DASS), significantly higher scores on all EDE-Q subscales (restraint, eating concern, weight concern, and shape concern), a significantly greater frequency of binge eating, greater levels of food craving, and reported significantly greater tendencies to eat for purposes of coping and reward enhancement.

The results of the *t*-tests comparing the BN sample with the BED sample on the EDE-Q subscales FCQ, the PEMS subscales, and the DASS are reported in **Table 8**. No significant differences in restraint, shape concern, binge frequency, food craving, eating for social purposes, eating for purposes of coping, eating for purposes of reward enhancement, or depression were observed between participants with binge eating disorder versus participants with bulimia nervosa. Although initial comparisons suggested that participants with binge eating disorder had significantly greater levels of eating concern and weight concern in comparison to participants with bulimia nervosa, these differences did not survive after controlling for multiple comparison. Likewise, while initial the initial *t*-test suggested that people with bulimia nervosa had significantly greater levels of eating for purposes of conformity in comparison to participants with binge eating disorder, this analysis did not hold following correction for multiple comparisons.

Components of food craving for each diagnostic group. The descriptive statistics and effect size comparisons for the FCQ subscales are reported for each diagnostic group in **Table 9**.

The results of the *t*-tests comparing lean controls with the bulimia nervosa sample on the FCQ subscales are presented in **Table 10**. There were significant differences between the two samples for all subscales. The BN sample had significantly greater scores than the lean control sample on all FCQ subscales.

The results of the *t*-tests comparing the obese/overweight comparison group with the BED sample on the FCQ subscales are presented in **Table 11**. (The subscale FCQ – Preoccupation was excluded from the *t*-tests as the data was skewed in the overweight/obese group.) The BED sample had significantly greater scores than the overweight/obese control sample on all FCQ subscales.

Correlations between eating concern, craving, eating motivations, and binge eating. Correlations between eating concern, food craving, binge eating frequency, and each subscale of the PEMS for individuals with bulimia nervosa are presented in **Supplementary Table 2**. Trait levels of food craving were strongly positively correlated with eating for reasons of coping and reward enhancement. The different subscales of the EDE-Q were strongly and positively correlated with each other (with the exception of eating concern and restraint, which were not significantly correlated).

Correlations between eating concern, food craving, binge frequency, and each subscale of the PEMS for individuals with binge eating disorder are presented in **Supplementary Table 3**. As in bulimia nervosa, most subscales of the EDE-Q were strongly and positively correlated with each other (with the exception of restraint and weight concern). Trait levels of food craving were strongly and positively correlated with eating for emotional coping, reward enhancement, and conformity.

Cluster analysis. We next conducted a *k*-means cluster analysis for all participants including the variables FCQ, PEMS-Coping, and PEMS-Enhancement, where the number of clusters to be identified was set to two. Between-subjects ANOVAs subsequently

revealed significant differences between the two clusters on the FCQ ($F = 371.24$, $df = 99$, $p < .001$), PEMS-Coping ($F = 193.07$, $df = 99$, $p < .001$), and PEMS-Enhancement ($F = 48.38$, $df = 99$, $p < .001$).

We then conducted a chi-square test to determine if each of these two clusters contained a significantly different proportion of individuals with and without eating disorders. Cluster 1 contained 42 individuals without an eating disorder, and two with BN or BED. Cluster 2 contained 39 individuals with BN or BED, and 6 without an eating disorder. These proportions were significantly different ($\chi^2 = 60.39$, $df = 1$, $p < .001$), thus indicating that food craving, eating for emotional coping, and eating for reward enhancement significantly distinguished the sample with BN or BED from the lean and overweight/obese comparison samples.

Discussion

The current study aimed to test maintenance processes proposed within the addictive appetite model through an assessment of craving and motivations for eating. Our hypotheses were that women with BN and BED would endorse significantly greater levels of food craving, and tendencies to eat for purposes of coping and reward enhancement, when compared to weight-matched healthy control participants. Our data supported these hypotheses with strong effect sizes for each comparison. A cluster analysis subsequently supported our hypothesis that food craving, eating for purposes of coping, and eating for purposes of reward enhancement would significantly distinguish women with BN or BED from the lean and overweight/obese comparison samples of women without an eating disorder.

These findings, drawn from a clinical population of individuals with eating disorders, corroborate results previously reported by (Boggiano et al., 2014), amongst students: such that eating for purposes of coping and reward enhancement was associated

with exhibiting recurrent binge eating behaviour, and eating for social purposes was not. Differences in the extent to which individuals reported eating for reasons of conformity was significantly different only between individuals with BN versus lean controls and did not differ significantly between the BED group and the overweight/obese control sample. It is not completely clear why this is the case, although one hypothesis may be that in the absence of a visual difference of appearance or weight, the BN group is more highly motivated to mask their disorder by conforming to the eating behaviours exhibited by others in a social setting. This hypothesis requires further research to corroborate.

Our findings provide support for the addictive appetite model of bulimia nervosa and binge eating disorder (Leslie, Turton, et al., 2018) by providing evidence for heightened levels of craving for palatable foods, and the tendency for these individuals to use eating as an emotion regulation strategy. These findings also contribute to the existing field of research testing the affect regulation model of binge eating (Haedt-Matt & Keel, 2011; Leehr et al., 2015). A meta-analysis of ecological momentary assessment studies by Haedt-Matt and Keel (2011) supported the hypothesis that increased negative mood immediately precipitates binge eating episodes, when compared to both average affect and affect preceding non-binge eating. The findings of the present study similarly highlight that eating for purposes of coping is characteristic of individuals with recurrent loss-of-control binge eating behaviour. Furthermore, a meta-analysis of studies inducing negative affect has also supported a causal link between negative affect and binge eating (Leehr et al., 2015)

The effect of binge eating on mood itself is, however, less clear. Haedt-Matt and Keel (2011), in their meta-analysis found that mood worsened following a binge in a heterogeneous population of binge eaters (including those diagnosed with BN, BED, and self-identified binge eaters). On the contrary, Leehr et al. (2015) reported improved mood following binge eating in people with binge eating disorder. These contradictory findings

may be explained by the addictive appetite model of binge eating, which posits that neuroadaptation promotes tolerance for the “liking” hedonic component of tasty foods, which develops over time (Berridge, 2009; Volkow et al., 2004). This process co-occurs with progressive increases in “wanting” (incentive salience) of binge foods (Berridge, 2009; Treasure et al., 2018; Volkow et al., 2004). It may therefore be the case that studies using ecological momentary assessment included in the Haedt-Matt and colleagues’ meta-analysis fail to capture an immediate reduction in negative urgency occurring during the course of a binge eating episode, while succeeding in the capture of guilt and shame following the binge eating episode. This hypothesis receives support from studies demonstrating the influence of negative urgency on binge eating, independent of other facets of negative affect (Anestis, Smith, Fink, & Joiner, 2009; Racine et al., 2013). Within the addictive appetite model of binge eating, this emotional process is posited to be intrinsically underpinned by the large, repeated incidence of addictive appetite. This repeated addictive appetite over time results in the heightened “wanting” of binge foods and directly contributes to the experience of negative urgency.

The addictive appetite model also highlights the relevance of drawing from theoretical models and effective treatments currently employed within the addictions science literature. Heilig et al. (2010), for example, have proposed that alcohol dependency proceeds from “reward craving” in the early phase of the addiction, to “relief craving” as the addiction proceeds. These constructs are conceptually identical to the motivations for Reward Enhancement and Coping, respectively, proposed in relation to eating within the PEMS. It would therefore be interesting to stratify by duration of illness in future research, to determine whether individuals with bulimia nervosa and binge eating disorder demonstrates a similar progression in eating motivation, from Reward Enhancement to Coping.

The prevalence of emotion-triggered eating within this population further highlights the importance of supporting effective emotional regulation strategies among this population. Indeed, it has previously been found that emotion regulation abilities improve throughout the course of treatment for bulimia nervosa, and especially amongst individuals with a better treatment outcome (Mallorquí-Bagué et al., 2018). It can therefore be hypothesised that improvement in emotional regulation strategies is one of the mediating factors in achieving remission from bulimia nervosa, although further studies measuring the time-course of changes are required to determine whether short-term improvements in emotion regulation strategy precede improvements in symptom remission.

It was interesting to note that, after controlling for multiple comparison, there were no significant differences between women with bulimia nervosa versus women with binge eating disorder on measure of food craving, eating disorder psychopathology, or eating motivations. Within the framework of the addictive appetite model of binge eating, this finding can be explained by the fact that the same neural process is hypothesised to underpin binge eating behaviour in populations with eating disorders, and therefore operates identically on a functional level in both bulimia nervosa and binge eating disorder (Treasure et al., 2018). These findings therefore highlight commonalities in the psychological profile and maintenance factors of bulimia nervosa and binge eating disorder, suggesting that similar treatment approaches may be useful in treatment both disorders.

Within the current study, the fact that levels of food craving and eating for mood regulation alone can be used to differentiate individuals with BN/BED from weight-matched controls provides further evidence for the significance of these processes to recurrent binge eating behaviour, even after controlling for overall energy balance, and highlights the importance of targeting emotion regulation in treatment. Individuals with

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BN and BED may need guidance with managing food-related cues in the environment in the early stages of treatment, given their high levels of craving. The continued development of treatment approaches that weaken automatic stimulus-response associations to palatable food would similarly be useful in supporting recovery (Turton et al., 2018).

Limitations of the current study include the small sample size for each diagnostic group, and the use of self-report measures (which are subject to social desirability bias), and the limitations of the participants' memory and understanding of their motivations for eating. Furthermore, as the current study only included women, the current findings are not generalizable to men with bulimia nervosa or binge eating disorder. The subjective perception of the close link between high emotion and eating, however, provides an important indication of the purpose that binge eating serves for women with BN and BED.

We recommend that future studies continue to test other aspects of the addictive appetite model, including the contribution of insulin resistance/sensitivity to the onset of binge eating behaviour. We would also recommend future research to continue to examine the genetic factors accounting for variation in individual risk for binge-eating behaviour. We propose that continued research into the intersection between genetic risk for recurrent binge eating, metabolic dysregulation, and the psychological trait profile of each individual will continue to aid the development of more efficacious and personalised treatment approaches, in line with the burgeoning movement towards 'precision psychiatry' (Fernandes et al., 2017).

In conclusion, the current study identified significantly higher levels of food craving, eating for purposes of emotional coping, and eating for purposes of reward enhancement among women with BN and BED versus weight-controlled women without an eating disorder. A cluster analysis subsequently identified that these three traits

significantly distinguished women with recurrent binge eating behaviour from the general population. These findings provide further support for the food addiction model of recurrent binge eating behaviour and highlight the importance of targeting addictive and emotional regulation processes within treatment.

Table 4

Descriptive Statistics Associated with the Demographic Variables for the BN and BED samples, and Respective Weight Matched Control Groups

	Lean Control <i>N</i> = 26		Bulimia Nervosa <i>N</i> = 22		Overweight/Obese <i>N</i> = 15		Binge Eating Disorder <i>N</i> = 16		Cohen's <i>d</i> (<i>BN</i> vs <i>LC</i>)	Cohen's <i>d</i> (<i>BED</i> vs <i>OC</i>)
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
Age (years)	27.85	7.330	25.41	5.963	30.00	6.831	32.26	8.034	-0.37	0.30
BMI (kg/m ²)	21.70	1.698	22.21	2.582	28.06	4.711	31.60	7.278	0.23	0.58
Education (years)	16.83	3.696	15.36	4.262	19.11	2.213	14.53	5.729	-0.37	-1.05

Note. BMI = Body Mass Index

Table 5*Descriptive Statistics and Effect Size Comparisons for Each Diagnostic Group*

	Lean Control <i>N</i> = 26		Bulimia Nervosa <i>N</i> = 22		Binge Eating Disorder <i>N</i> = 15		Overweight/Ob ese <i>N</i> = 16		Cohen 's <i>d</i> (<i>BN</i> <i>vs LC</i>)	Cohen 's <i>d</i> (<i>BED</i> <i>vs</i> <i>OC</i>)
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
Eating Concern	0.24	0.43 5	3.09	1.45 5	3.99	1.12 4	0.61	0.842	2.65* **	3.40* **
Restraint	0.76	1.06 9	3.06	1.44 5	3.09	1.42 6	0.97	1.063	1.80* **	1.68* **
Weight Concern	0.78	1.20 9	3.65	1.56 5	4.53	0.82 0	1.36	1.216	2.05* **	3.05* **
Shape Concern	1.01	1.33 7	4.38	1.38 7	4.80	0.81 1	1.74	1.453	2.47* **	2.61* **
Binge Frequency	0.08	0.39 2	12.5 2	6.77 7	11.3 7	7.13 5	0.26	0.562	2.59* **	2.20* **
PEMS - Social	8.46	3.31 3	9.27	3.69 4	9.61	2.93 3	11.39	4.667	0.23	-0.46
PEMS – Conformit y	5.65	1.16 4	8.48	3.16 4	6.17	1.94 8	7.06	2.485	1.19* **	-0.40
PEMS – Coping	5.50	1.65 5	13.3 3	4.96 9	15.1 7	4.03 3	6.50	2.995	2.11* **	2.44* **
PEMS - Enhancem ent	8.58	4.33 7	12.5 6	4.46 6	13.8 3	5.36 1	8.56	3.399	0.90* *	1.17* *
FCQ	76.0 8	26.3 71	165. 93	40.4 94	167. 44	29.7 13	77.89	31.088	2.63* **	2.94* **
DASS	8.54	7.34 4	49.6 4	30.7 30	51.1 6	22.0 33	13.79	13.903	1.84* **	2.03* **

Note. BN = bulimia nervosa; LC = lean controls; BED = binge eating disorder; OC = overweight/obese controls; DASS = Depression Anxiety Stress Scale; EDE-Q = Eating Disorder Examination Questionnaire; PEMS = Palatable Eating Motives Scale; FCQ = Food Craving Questionnaire.

** $p < .01$. *** $p < .001$.

Table 6*Results of t-tests comparing the lean control sample with the bulimia nervosa sample*

	<i>t</i>	<i>df</i>	<i>p</i>	<i>Q</i>	Cohen's <i>d</i>
Age	1.33	51	.189	.223	-0.37
BMI	-0.84	51	.403	.411	0.23
Education	1.35	52	.183	.223	-0.37
DASS	-6.87***	30.30 ^a	< .001	< .001	1.84
Eating Concern	-9.89***	32.12 ^a	< .001	< .001	2.65
Restraint	-6.61***	52	< .001	< .001	1.80
Weight Concern	-7.49***	52	< .001	< .001	2.05
Shape Concern	-9.08***	52	< .001	< .001	2.47
PEMS - Social	-0.83	50	.411	.411	0.23
PEMS – Conformity	-4.20***	30.17 ^a	< .001	< .001	1.19
PEMS – Coping	-7.76***	31.90 ^a	< .001	< .001	2.11
PEMS - Enhancement	-3.29**	51	.002	.003	0.90
FCQ	-9.53***	51	< .001	< .001	2.63

Note. BMI = Body Mass Index; DASS = Depression Anxiety Stress Scale; EDE-Q = Eating Disorder Examination Questionnaire; PEMS = Palatable Eating Motives Scale; FCQ = Food Craving Questionnaire.

^a Degrees of freedom adjusted for unequal variances between samples.

** $p < .01$. *** $p < .001$.

Table 7

Results of t-tests comparing the overweight/obese sample with the binge eating disorder sample

	<i>t</i>	<i>df</i>	<i>p</i>	<i>Q</i>	Cohen's <i>d</i>
Age	-0.94	36	.356	.356	0.30
Education	3.04**	28.30 ^a	.005	.007	-1.05
DASS	-6.25***	30.37 ^a	< .001	< .001	2.03
Eating Concern	-10.49***	36	< .001	< .001	3.40
Restraint	-5.21***	36	< .001	< .001	1.68
Weight Concern	-9.42***	31.56 ^a	< .001	< .001	3.05
Shape Concern	-7.99***	28.23 ^a	< .001	< .001	2.61
PEMS - Social	1.37	34	.180	.213	-0.46
PEMS – Conformity	1.20	34	.241	.261	-0.40
PEMS – Coping	-7.32***	34	< .001	< .001	2.44
PEMS - Enhancement	-3.53**	28.77 ^a	.001	.001	1.17
FCQ	-8.84***	34	< .001	< .001	2.94
Binge Frequency	-6.76***	18.22 ^a	< .001	< .001	2.20

Note. DASS = Depression Anxiety Stress Scale; EDE-Q = Eating Disorder Examination Questionnaire; PEMS = Palatable Eating Motives Scale; FCQ = Food Craving Questionnaire.

^a Degrees of freedom adjusted for unequal variances between samples.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 8

Differences in Eating Disorder Pathology, Food Craving, Eating Motivations, and Depression Between Participants with Bulimia Nervosa and Participants with Binge Eating Disorder

	<i>t</i>	<i>df</i>	<i>p</i>	<i>Q</i>	Cohen's <i>d</i>
Eating Concern	-2.28	45	.027	.099	0.69
Restraint	-0.07	45	.944	.944	0.02
Weight Concern	-2.50	42.76 ^a	.016	.088	0.70
Shape Concern	-1.30	44.23 ^a	.202	.444	0.37
Binge Frequency	0.55	42	.588	.847	-0.17
FCQ	-0.14	43	.892	.944	0.04
PEMS – Social	-0.33	42	.745	.911	0.10
PEMS – Conformity	2.96	40.19 ^a	.005	.055	-0.88
PEMS – Coping	-0.51	29	.616	.847	0.41
PEMS - Enhancement	-1.49	29	.147	.404	0.26
DASS	-0.56	35	.577	.847	0.06

Note. DASS = Depression Anxiety Stress Scale; EDE-Q = Eating Disorder Examination Questionnaire; PEMS = Palatable Eating Motives Scale; FCQ = Food Craving Questionnaire.

^a Degrees of freedom adjusted for unequal variances between samples.

Table 9

Descriptive Statistics and Effect Size Comparisons for Each Diagnostic Group on the FCQ Subscales

	Lean Control <i>N</i> = 26		Bulimia Nervosa <i>N</i> = 27		Binge Eating Disorder <i>N</i> = 18		Overweight/Obese <i>N</i> = 18		Cohen's <i>d</i> (<i>BN</i> vs <i>LC</i>)	Cohen's <i>d</i> (<i>BED</i> vs <i>OC</i>)
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
FCQ – Intention to Eat	6.192	3.150	13.74	3.612	13.50	3.417	6.39	3.398	-0.25***	2.09***
FCQ – Positive Reinforcement	10.577	4.692	17.59	6.423	18.89	5.860	9.61	5.066	-0.62***	1.69***
FCQ – Negative Reinforcement	5.115	2.046	11.15	5.005	9.61	3.600	5.56	2.975	0.42***	1.23***
FCQ – Lack of Control	9.654	4.335	27.89	7.371	27.89	6.342	9.89	4.028	0.92***	3.39***
FCQ – Preoccupation	11.538	3.849	29.81	9.604	29.17	9.420	10.56	4.743	0.64***	2.50***
FCQ – Physiological Craving	9.692	3.642	14.48	5.177	14.44	3.761	8.94	3.796	-0.45***	1.46***
FCQ – Emotions	7.692	3.541	18.67	6.051	20.28	3.691	8.67	4.201	-0.05***	2.94***
FCQ – Cue Triggered	9.538	4.207	17.44	4.209	18.22	3.797	11.06	4.917	-0.21***	1.63***
FCQ – Guilt	6.077	3.224	15.15	3.393	15.44	2.572	7.22	4.138	0.23***	2.39***

Note. BN = bulimia nervosa; LC = lean controls; BED = binge eating disorder; OC = overweight/obese controls; DASS = Depression Anxiety Stress Scale; EDE-Q = Eating Disorder Examination Questionnaire; PEMS = Palatable Eating Motives Scale; FCQ = Food Craving Questionnaire.

*** $p < .001$.

Table 10

Results of t-tests comparing lean control sample with the bulimia nervosa sample on the FCQ Subscales

	<i>t</i>	<i>df</i>	<i>p</i>	<i>Q</i>	Cohen's <i>d</i>
FCQ – Intention to Eat	-8.10***	51	< .001	< .001	-0.25
FCQ – Positive Reinforcement	-4.53***	51	< .001	< .001	-0.62
FCQ – Negative Reinforcement	-5.78***	34.72 ^a	< .001	< .001	0.42
FCQ – Lack of Control	- 11.03***	42.35 ^a	< .001	< .001	0.92
FCQ – Preoccupation	-9.15***	34.40 ^a	< .001	< .001	0.64
FCQ – Physiological Craving	-3.91***	46.75 ^a	< .001	< .001	-0.45
FCQ – Emotions	-8.09***	42.23 ^a	< .001	< .001	-0.05
FCQ – Cue Triggered	-6.84***	51	< .001	< .001	-0.21
FCQ – Guilt	-9.97***	51	< .001	< .001	0.23

Note. FCQ = Food Craving Questionnaire.

^a Degrees of freedom adjusted for unequal variances between samples.

*** $p < .001$.

Table 11

Results of t-tests comparing the overweight/obese sample with the binge eating disorder sample on the FCQ Subscales

	<i>t</i>	<i>df</i>	<i>p</i>	<i>Q</i>	Cohen's <i>d</i>
FCQ – Intention to Eat	-6.26***	34	< .001	< .001	2.09
FCQ – Positive Reinforcement	-5.08***	34	< .001	< .001	1.69
FCQ – Negative Reinforcement	-3.68***	34	< .001	< .001	1.23
FCQ – Lack of Control	- 10.16***	34	< .001	< .001	3.39
FCQ – Physiological Craving	-4.37***	34	< .001	< .001	1.46
FCQ – Emotions	-8.81***	34	< .001	< .001	2.94
FCQ – Cue Triggered	-4.89***	34	< .001	< .001	1.63
FCQ – Guilt	-7.16***	34	< .001	< .001	2.39

Note. FCQ = Food Craving Questionnaire.

*** $p < .001$.

Supplementary Materials

Treatment

Twenty-five women with bulimia nervosa or binge eating disorder had received treatment within six months prior to taking part in the study. The type of treatment received by these women is reported in **Supplementary Table 1**.

Supplementary Table 1*Treatment Received by the Sample of Women with Bulimia Nervosa or Binge Eating Disorder*

Type of Treatment	Number of Women Receiving Treatment
Psychiatrist Support	3
Outpatient Support	4
Psychologist Support	7
Counselling	8
Eating Disorder-Specific Group Therapy	2
Non-Eating Disorder-Specific Group Therapy	3
Individual Psychotherapy	3
Family Therapy	2
Community Psychiatric Nurse Support	1
Self-help Support Group	3
Community Nurse	2
Dietician	6
Online Cognitive Behavioural Therapy	1

Measures

Eating Disorder Examination Questionnaire (EDE-Q). The Eating Disorder Examination – Questionnaire version (EDE-Q) (Fairburn & Beglin, 1994a) is a self-report questionnaire. Twelve items are presented as a 7-point scale assessing the number of days within the past month that the participant exhibited a certain eating disorder symptom. Each item scale is anchored from 0 (no days) to 6 (every day). Participants also respond to several open-ended questions regarding the frequency with which they exhibited particular eating disorder-related behaviours within the past month (e.g., binge eating episodes and purging episodes). A greater score on the EDE-Q corresponds with a more severe level of eating disorder psychopathology. The EDE-Q comprises four difference subscales for: Eating Concern, Restraint, Weight Concern, and Shape Concern. The total EDE-Q scale was associated with excellent internal consistency ($\alpha = 0.97$).

Depression and Anxiety Stress Scales (DASS). The Depression and Anxiety Stress Scale (DASS) (Lovibond & Lovibond, 1995) includes a total of 42 self-report items, which are answered in the form of a 4-point Likert scale. The items are anchored from 0 (Did Not Apply To Me At All) to 3 (Applied To Me Very Much). These items gauge the individual's current symptoms of depression, anxiety, and stress. The total DASS was associated with excellent internal consistency ($\alpha = 0.95$).

Food Craving Questionnaire – Trait subscale (FCQ). The trait subscale of the Food Craving Questionnaire (FCQ) (Cepeda-Benito et al., 2000) consists of 39 items answered in the form of a 6-point Likert scale ranging from 1 (Never or Not Applicable) to 6 (Always). This scale assesses the extent to which individuals experience food craving in general, as opposed to the state subscale which measured the amount of food craving experienced in the present moment. The total FCQ scale was associated with excellent internal consistency in this sample ($\alpha = 0.98$).

The FCQ contains 9 subscales, each associated with good internal consistency in the current study: Having Intentions and Plans to Consume Food ($\alpha = 0.88$), Anticipation of Positive Reinforcement That May Result From Eating ($\alpha = 0.87$), Anticipation of Relief From Negative States and Feelings as a Result of Eating ($\alpha = 0.88$), Lack of Control Over Eating ($\alpha = 0.97$), Thoughts or Preoccupation With Food ($\alpha = 0.97$), Craving as a Physiological State ($\alpha = 0.77$), Emotions That May Be experienced Before or During Food Cravings or Eating ($\alpha = 0.96$), Cues That May Trigger Food Craving ($\alpha = 0.85$), Guilt From Cravings and/or for Giving Into Them ($\alpha = 0.94$).

Supplementary Table 2

Correlation Matrix for Eating Concern, Food Craving, Binge Frequency, and PEMS Subscales in Bulimia Nervosa Sample

	Restraint	Weight Concern	Shape Concern	FCQ	Binge Frequency	PEMS-Conformity	PEMS-Social	PEMS-Coping	PEMS-Enhancement	BMI
Eating Concern	.33	.59**	.60**	.52*	.12	.30	.11	.35	.37	.32
Restraint		.50*	.48*	.17	-.43	.04	.03	.16	-.12	-.02
Weight Concern			.86***	.55*	-.10	.45*	.29	.45*	.09	.51*
Shape Concern				.59**	-.10	.34	.19	.58**	.16	.52*
FCQ					.30	.15	.09	.77***	.68**	.24
Binge Frequency						-.16	-.42	.03	.42	.03
PEMS- Conformity							.79***	.12	.17	.37
PEMS- Social								-.004	.02	.31
PEMS- Coping									.60**	.29
PEMS- Enhancement										.13

Note. FCQ = Food Craving Questionnaire; PEMS = Palatable Eating Motives Scale; BMI = body mass index.

N = 21.

p* < .05. *p* < .01. ****p* < .001.

Supplementary Table 3

Correlation Matrix for Eating Concern, Food Craving, Binge Frequency, and PEMS Subscales in Binge Eating Disorder Sample

	Restraint	Weight Concern	Shape Concern	FCQ	Binge Frequency	PEMS-Conformity	PEMS-Social	PEMS-Coping	PEMS-Enhancement	BMI
Eating Concern	.57*	.58*	.66**	.26	.45	.40	.25	.15	.37	.31
Restraint		.41	.54*	.13	.13	.27	-.08	.34	.02	.37
Weight Concern			.75**	.31	.22	.38	.22	.31	.38	.21
Shape Concern				.07	.57*	.31	.16	.20	.42	.32
FCQ					.20	.52*	.15	.51*	.46*	.23
Binge Frequency						-.05	.12	.21	.45	.28
PEMS-Conformity							.54*	-.13	.57*	-.07
PEMS-Social								-.25	.59	-.11
PEMS-Coping									.02	.28
PEMS-Enhancement										-.16

Note. FCQ = Food Craving Questionnaire; PEMS = Palatable Eating Motives Scale; BMI = body mass index.

N = 16.

**p* < .05. ** *p* < .01.

Chapter 3

3 The implication of oxytocin within the addictive appetite model

3.1 Oxytocin

Oxytocin is a nanopeptide hormone and neuromodulator that is primarily produced within the paraventricular nucleus and supraoptic nucleus of the hypothalamus (Swaab, Nijveldt, & Pool, 1975). The structure of oxytocin is depicted in **Figure 4**. As a hormone, oxytocin is synthesised within the hypothalamus and subsequently stored within neurosecretory vessels in the posterior pituitary gland before being released into the bloodstream to reach peripheral targets (Poulain & Wakerley, 1982).

In rats, oxytocin neurons have been found to project to most forebrain regions, including the olfactory system, orbital regions, the insula, the cingulate cortex, basal ganglia, and limbic regions (Knobloch et al., 2012). Parvocellular neurons in the paraventricular nucleus of the hypothalamus of rats also project to as hindbrain regions including the brainstem and the spinal cord (Althammer & Grinevich, 2018). Axonal projections have not been as well-described in humans; however, oxytocin projections to the midbrain, brainstem, and spinal cord are found across basal vertebrates (Althammer & Grinevich, 2018). Oxytocin is also released centrally within the hypothalamus via dendritic emission and somata, which results in non-targeted, dispersed release of oxytocin acting in both a paracrine fashion on proximal sites of actions, as well as on distant sites of action (Ludwig & Leng, 2006).

The oxytocin receptor is a rhodopsin-type G-protein coupled receptor (Gimpl & Fahrenholz, 2001). Depending on the extracellular concentration of oxytocin, oxytocin can act on different G proteins, including Gq, Gi1, Gi2, Gi3, Goa, and GoB proteins (Chini, Verhage, & Grinevich, 2017). Binding at the oxytocin receptor triggers a cascading secondary messenger system to subsequently alter gene transcription within the cell. Oxytocin also has partial binding affinity for the V1a and V1b vasopressin receptor, which are also expressed within the central nervous system (Chini et al., 2017).

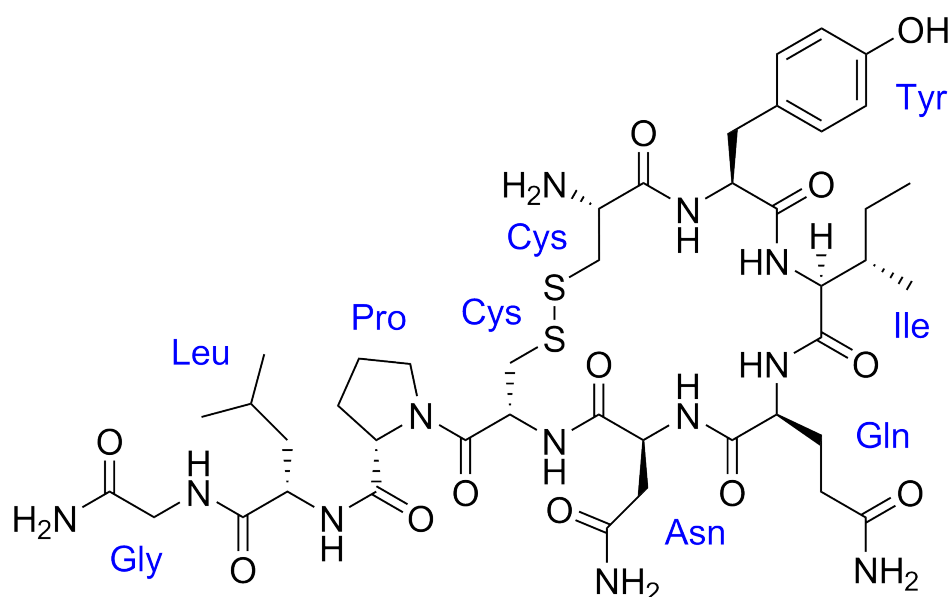


Figure 4. The chemical structure of oxytocin.

Oxytocin receptors are expressed in many peripheral tissues including the kidney, the heart, adipocytes, the thymus, the pancreas, adrenal glands, and sex-specific tissues such as the uterus, ovaries, and myoepithelial cells of mammary glands in women and the prostate and testes in men (Gimpl & Fahrenholz, 2001). Post mortem immunohistological work in humans has identified oxytocin receptors within the cell bodies of neurons in the cingulate cortex, piriform cortex, post-orbital gyrus, subcallosal area, the spinal trigeminal nucleus, the nucleus prepositus, the olfactory nucleus, incus, ventrolateral septal nucleus, basolateral amygdala, central amygdala, posterior cortical nucleus amygdala, medial preoptic area, paraventricular nucleus, ventromedial nucleus, tuberomamillary nucleus, and solitary nucleus (Boccia, Petrusz, Suzuki, Marson, & Pedersen, 2013; Freeman, Smith, Goodman, & Bales, 2017). Oxytocin receptors are also expressed on the nerve fibres of the hippocampus, the subiculum, the supraoptic nucleus and all previously-mentioned brain regions where neuron cell bodies express oxytocin receptors, except for the post-orbital gyrus (Boccia et al., 2013). Autoradiographic studies have identified oxytocin receptors in mesolimbic regions of the human brain including the globus pallidus and ventral pallidum (Loup, Tribollet, Dubois-Dauphin, & Dreifuss, 1991).

In terms of peripherally-mediated effects, oxytocin has long been known for its role in stimulating uterine contractions during parturition and stimulating milk let-down during breast-feeding in mammals (Fuchs, Fuchs, Husslein, Soloff, & Fernstrom, 1982; Soloff, Alexandrova, & Fernstrom, 1979). However, in humans, oxytocin has recently gained greater attention for centrally-mediated effects, such as the processing of social information (Bartz, Zaki, Bolger, & Ochsner, 2011; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), modulating stress responses mediated by the hypothalamic-pituitary-adrenal axis (Ochedalski, Subburaju, Wynn, & Aguilera, 2007), deterring relapse to substance abuse (Zanos et al., 2018), and the regulation of feeding (Olszewski, Klockars, & Levine, 2016). The following thesis section will discuss current animal and human evidence clarifying the role of oxytocin in reward processing and substance addictions, before going on to outline a hypothesised role for oxytocin in food addiction.

3.2 The Role of Oxytocin in Substance Addiction

Oxytocin has been found to directly alter dopamine turnover and neuron firing in reward-related mesolimbic brain regions. For example, in male mice, chronic oxytocin administration has been found to reduce utilisation of dopamine in the basal forebrain in resting conditions (Kovács, Faludi, Falkay, & Telegdy, 1986) and to specifically reduce cocaine-induced dopamine utilisation in the nucleus accumbens, which is associated with the antagonism of cocaine-induced hyperactivity (Kovacs, Sarnyai, Babarcsi, Szabo, & Telegdy, 1990). Oxytocin has also been found to increase the firing rate of neurons within the nucleus accumbens shell of both opiate-naïve and opiate-experienced rats (Moaddab, Hyland, & Brown, 2015) and to increase extracellular dopamine levels in the nucleus accumbens in male rats (Succu et al., 2007). This mixed pattern of effects of oxytocin in alternately increasing or decreasing dopamine release and dopaminergic effects in mesolimbic regions indicates that the effects of oxytocin are likely dependent on dose, particularly given that oxytocin acts on different G proteins depending on the extracellular

concentration of oxytocin (Chini et al., 2017). The effects of oxytocin on central dopaminergic activity may also be dependent on prior experience of opioidergic and dopaminergic drugs and species of the animal under investigation (Zanos et al., 2018).

In terms of behavioural effects, the bulk of the evidence supports a role for oxytocin in attenuating opioid seeking. Three studies have found that pre-treatment with oxytocin reduces subsequent heroin self-administration in heroin-tolerant rats when oxytocin is injected into the nucleus accumbens or ventral tegmental area, the lateral septum, or subcutaneously (Ibragimov & Kovacs, 1987; Ibragimov, Kovács, Szabó, & Telegdy, 1987; Kovács, Borthaiser, & Telegdy, 1985). Furthermore, intraperitoneal oxytocin administration has also been found to prevent stress-induced morphine-seeking and priming-induced reinstatement of a morphine conditioned place preference after a period of abstinence (Georgiou et al., 2015; Zanos et al., 2014).

This pattern of effects, whereby oxytocin prevents reinstatement of opiate self-administration, may be explained by the effect of oxytocin on opioid tolerance. Central injections of oxytocin directly to the dorsal hippocampus and nucleus accumbens have been found to reduce heroin tolerance in mice (Kovacs, Horváth, Sarnyai, Faludi, & Telegdy, 1985; Kovács, Faludi, & Telegdy, 1985; Kovács, Izbéki, Horváth, & Telegdy, 1984; Kovács & Telegdy, 1987). Thus, greater sensitivity to the euphoric and withdrawal-alleviating effects of opioids may explain the reduced opioid-seeking behaviour in opioid-tolerant mice and rats.

However, it should be noted that not all studies have supported a role for oxytocin in deterring opioid-seeking behaviour. For example, a study by Moaddab et al. (2015) found that 0.2 micrograms of oxytocin injected into the cerebral ventricles actually enhanced the expression of morphine-induced place preference after acquisition, and Van Ree and de Wied (1976) found that oxytocin facilitated morphine dependence. However, these findings may be explained by the 0.2 microgram dose of centrally-injected oxytocin in

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the Moaddab et al. (2015), which is substantially larger than the 0.2 nanogram dose of centrally-injected oxytocin which was found to reduce heroin self-administration in the earlier Ibragimov et al. (1987) study. As mentioned above, the difference dose of oxytocin may exert differing effects by acting via different G-protein-coupled secondary messenger systems, or by paradoxical effects induced by binding to V1a or V1b receptors at high doses (Chini et al., 2017). The difference in findings may also be due to the different region of administration: the cerebral ventricles in the Moaddab et al. (2015) study versus the nucleus accumbens and ventral tegmental area in the Ibragimov et al. (1987) study. Furthermore, Van Ree and de Wied (1976) found that oxytocin facilitated morphine dependence in female rats, in contrast to the male rats who exhibited reductions in opioid seeking in other studies. Therefore, this pattern of findings suggests that both dose and sex moderate the effect of oxytocin on opioid seeking.

To date, there are few studies examining the effects of oxytocin on substance addictions in humans. One study has found that a single dose of 40IU oxytocin, in comparison to placebo, had no effect on cue-induced drug craving in opioid-dependent participants undergoing an opioid replacement programme (Woolley et al., 2016). However, it may be the case that longer time frames are needed to observe an effect, as a separate double-blind placebo-controlled crossover trial found that twice-daily doses of 40IU oxytocin significantly reduced cocaine craving at day 15 compared to baseline, although the authors failed to find an effect of oxytocin on heroin craving (Stauffer et al., 2016). Thus, there is some evidence that oxytocin can alleviate cravings in people with cocaine use disorder.

3.3 The Role of Oxytocin in Food Addiction

The evidence described above has provided an overview of some of the neurological pathways by which oxytocin interacts with dopamine and opioid systems to influence reward-seeking behaviour. However, it should be noted that many of the same hedonic

systems implicated in substance use disorders, including neural pathways between the nucleus accumbens and ventral tegmental area, are also relevant to food cravings (Berridge, 2009). Indeed, if food-related appetitive processes interact with oxytocin functioning in a similar manner to drug-related appetitive processes, the evidence described in Section 3.2 would suggest that oxytocin may inhibit palatable food-seeking behaviour just as it has also been found to inhibit opioid-seeking behaviour. For example, recent work has concisely reviewed neural mechanisms by which repeated sucrose consumption ultimately leads to disinhibition of hedonic eating, which include antagonism of the effects of oxytocin in terminating feeding via a sucrose-induced increase in opioid tone (Olszewski, Wood, Klockars, & Levine, 2019).

However, it is possible that any effect of oxytocin on eating may also be mediated via mechanisms other than the modulation of reward, such as through the down-regulation of the stress response and alteration of attentional bias to eating disorder-related stimuli. The following thesis sections will therefore serve to provide an overview of the existing evidence for altered oxytocin functioning, and the effects of exogenously-administered oxytocin, in populations with eating disorders.

3.4 The implication of oxytocin in eating disorders: Genetic and epigenetic evidence

As alluded to in sections 3.1 and 3.3, oxytocin functioning is strongly implicated in the regulation of eating behaviour. Indeed, disruptions in endogenous oxytocin systems have been found to be associated with pronounced, compulsive overeating. For example, mice with mutations on the SIM1 gene, which regulates the development of the paraventricular nucleus of the hypothalamus, exhibit reduced oxytocin synthesis and a pattern of overeating and obesity (Michaud et al., 2001). Similarly, humans with Prader-Willi syndrome present with a reduction in oxytocin-synthesising neurons in the paraventricular nucleus of the hypothalamus, and also present with compulsive overeating behaviour from early in childhood (Swaab, Purba, & Hofman, 1995).

Some differences in genetic and epigenetic oxytocin-related factors have also been observed across the eating disorders spectrum. Women with anorexia nervosa have been observed to exhibit greater levels of methylation at five polymorphisms of the oxytocin receptor gene (OXTR) (Y.-R. Kim, J.-H. Kim, et al., 2015). As DNA methylation can alter transcription of a gene (Zilberman, Gehring, Tran, Ballinger, & Henikoff, 2007), it is possible that altered regulation of the oxytocin receptor gene has functional effects pertaining to cognition and behaviour in anorexia nervosa. Furthermore, women with a history of anorexia nervosa who carry an A allele on the rs53576 and rs2254298 OXTR polymorphisms have been found to exhibit greater eating disorder psychopathology, compared to women with the GG genotype at both loci (Acevedo, Valencia, Lutter, & McAdams, 2015).

However, rather than the G allele being protective from anorexia nervosa, it may be that the G allele is associated with greater food approach behaviour more generally. This hypothesis comes from a study indicating that the G allele on the rs53576 polymorphism confers greater risk for BN (Y.-R. Kim, J.-H. Kim, et al., 2015), and a separate study indicating that the GG genotype on the rs53576 polymorphism is associated with greater bingeing and purging behaviour in women (Micali, Crous-Bou, et al., 2017). Furthermore, a gene X environment interaction has been found in bulimia nervosa such that carrying the AG/GA variant of the rs2254298 polymorphism of the OXTR gene, in combination with poor maternal care, predicts greater bingeing and purging behaviour (Micali, Crous-Bou, et al., 2017).

No direct genetic links have been found between the OXTR gene and populations diagnosed with binge eating disorder. However, at a trait level, the TT genotype on the rs2268493 OXTR polymorphism has been found to be associated with greater overeating behaviour, and the A allele of the rs2268494 OXTR polymorphism has been found to be associated with greater preference for sweet and fat-rich foods (Davis, Patte, Zai, &

Kennedy, 2017). However, the implication of these OXTR polymorphisms in clinical levels of binge eating has not yet been established.

3.5 The implication of oxytocin in eating disorders: Alterations in central and peripheral concentrations of oxytocin

With regards to differences in oxytocin synthesis and secretion, lower night-time serum oxytocin levels have been found in women with current anorexia nervosa, compared to healthy comparison women (Lawson et al., 2011). Furthermore, in women partially recovered from anorexia nervosa, lower fasting serum levels of oxytocin are associated with greater levels of depression, anxiety, and eating disorder psychopathology (Afinogenova et al., 2016). Conversely, serum oxytocin levels were higher in women with anorexia nervosa 60 and 120 minutes after eating compared to healthy control women, and but lower in women weight-recovered from anorexia nervosa 0, 30, and 120 minutes after eating (Lawson et al., 2012). Thus, on the whole, the evidence suggests that women with anorexia nervosa and partially-recovered from anorexia nervosa tend to exhibit lower levels of serum oxytocin, with the exception of women with current anorexia nervosa following food consumption. Nonetheless, while the association with clinical variables might seem to suggest a causal effect on psychopathology, evidence has generally shown that plasma levels of oxytocin are an unreliable indicator of endogenous central oxytocin concentrations (Valstad et al., 2017). Thus, the implication of serum oxytocin for centrally-mediated cognitions related to eating disorder psychopathology is unclear from a biological standpoint.

Cerebrospinal fluid levels of oxytocin have not been found to differ significantly between people with or recovered from bulimia nervosa, as compared to the general population (Demitrack et al., 1990; Frank, Kaye, Altemus, & Greeno, 2000). However, cerebrospinal fluid levels of oxytocin do not necessarily reflect the bioavailability of oxytocin to brain regions involved in the regulation of eating and appetitive processes. Furthermore, even in the presence of similar levels of centrally available oxytocin, differential expression

and functioning of the oxytocin receptor gene can still result in functional differences across the oxytocinergic system between people with and without BN. Thus, the extent to which levels of central levels of biologically-available oxytocin, and oxytocinergic functioning, may differ between people with eating disorder versus the general population remains an open question.

3.6 The implication of oxytocin in eating disorders: Social and Emotional Effects

Given the role of oxytocin in modulating the processing of social information, oxytocin treatment has received substantial attention in the context of its potential efficacy in treating social deficits in autism spectrum disorders (Preti et al., 2014). Anorexia nervosa shares several features in common with autism spectrum disorders, including a detail-focused, inflexible cognitive processing style (Lopez, Tchanturia, Stahl, & Treasure, 2008; Westwood, Stahl, Mandy, & Tchanturia, 2016) and deficits in cognitive empathy, which refers to the ability to recognise and understand another person's mental state (Kerr-Gaffney, Harrison, & Tchanturia, 2019). Recent basic psychology and clinical studies have therefore begun to investigate the potential therapeutic effects of oxytocin for social and emotional functioning across the eating disorders spectrum. This literature will be reviewed in the current thesis section.

With regards to anorexia nervosa, one study has found that 40IU intranasal oxytocin attenuated baseline avoidance of images of angry faces in the placebo condition (Kim, Kim, Park, Pyo, & Treasure, 2014). However, later studies have found that exogenous oxytocin had no effect on emotion recognition sensitivity, interpretation of emotion, or expression of emotion in people with anorexia nervosa (Y.-R. Kim, J.-S. Eom, et al., 2015; Leppanen, Cardi, et al., 2017b). Indeed, a 2017 meta-analysis failed to find an effect of oxytocin on emotion interpretation or expression across all studies to have investigated these effects in clinical populations (Leppanen, Ng, Tchanturia, & Treasure, 2017). Thus, while intranasal oxytocin may affect attentional processing of emotional stimuli, the

existing evidence does not support a functional role for exogenous oxytocin in altering higher-level interpretation or emotional behaviour in anorexia nervosa.

A mixed pattern of results has been found in the two studies investigating the effect of intranasal oxytocin on attentional bias to eating and body-related stimuli in anorexia nervosa. Kim, Kim, Cardi, et al. (2014) found that 40IU intranasal oxytocin, versus placebo administration, reduced bias towards both negative body shape images and eating-related images amongst participants with anorexia nervosa. By contrast, Leppanen, Cardi, et al. (2017a) found that participants with anorexia nervosa displayed attentional avoidance of eating-related stimuli at baseline, and that 40IU intranasal oxytocin rather increased vigilance to eating stimuli, compared to the placebo condition, after smoothie consumption. It is therefore possible that the discrepancy between the two sets of findings may be explained by the moderating effect of calorie consumption on the effect of oxytocin on attentional processing of disorder-related stimuli, although future research is required to corroborate this hypothesis.

Oxytocin has been found to reduce the salivary cortisol response to the presentation of food stimuli among people with anorexia nervosa, both when administered as a single dose (Leppanen, Cardi, et al., 2017a) and in the context of a four-to-six-week clinical trial (Russell et al., 2018). Furthermore, after four to six weeks of daily treatment of 36IU intranasal oxytocin, overall eating concern among participants with anorexia nervosa was found to decrease to a significantly greater extent compared to a placebo group (Russell et al., 2018). While oxytocin was not found to affect weight recovery amongst the participants with anorexia nervosa in the latter clinical trial (Russell et al., 2018), overall, the evidence suggests that oxytocin is efficacious in reducing the stress response of people with anorexia nervosa in some circumstances.

Compared to anorexia nervosa, relatively less research has so far been carried out investigating the social and emotional effects of oxytocin for people with BN. A single

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dose of oxytocin has been found to improve emotion recognition specifically for sad faces (Y.-R. Kim, J.-S. Eom, et al., 2015), and to reduce attentional bias to angry, versus neutral, faces in participants with BN (Kim, Eom, Leppanen, Leslie, & Treasure, 2018). Further research is needed to elucidate the clinical significance of these findings.

One clinical trial has investigated the effects of chronic oxytocin treatment in obese people with BED (Agabio et al., 2016). Within this clinical trial, participant received either four doses of 24IU oxytocin daily over a period of eight weeks, or an equal volume of placebo treatment. Oxytocin did not have a significant effect on anxiety, depression, or number of binge eating episodes per week by the end of the study. However, the clinical trial was severely underpowered, with only seventeen participants in total. Thus, the null findings reported in this study should be interpreted with caution.

3.7 Current gaps in knowledge regarding the effect of oxytocin on eating in animals and humans

The preceding thesis section has provided an overview of previous literature investigating the effects of oxytocin on social and emotional functioning in eating disorders. However, it is of great clinical interest to determine if oxytocin can indeed alleviate core symptoms of disordered eating across the eating disorder spectrum. Since the 1970s, a large body of research has documented the effect of exogenous oxytocin on feeding in animals (Blevins & Baskin, 2015). Additionally, in recent years, these findings have gradually been translated to investigations of the effects of oxytocin on eating in both healthy and clinical human populations (Blevins & Baskin, 2015). However, this research has not yet been compiled systematically. The following systematic review and meta-analysis therefore aims to fill this gap in the literature in order to develop a complete picture of the role of exogenous central and peripherally-administered oxytocin in modulating subsequent eating behaviour.

A Systematic Review and Quantitative Meta-Analysis of Oxytocin's Effects on Feeding

Short Title: A systematic review of oxytocin's effects on feeding

Authors:

Leslie, Monica ^a;

Silva, Paulo ^a;

Paloyelis, Yannis ^a;

Blevins, James ^b;

Treasure, Janet ^a

Affiliations:

^a Institute of Psychiatry, Psychology and Neuroscience (IoPPN) - King's College London (KCL), London, United Kingdom

^b VA Puget Sound Health Care System, Office of Research and Development Medical Research Service, Department of Veterans Affairs Medical Center, Seattle, WA 98108, USA; Division of Metabolism, Endocrinology, and Nutrition, Department of Medicine, University of Washington School of Medicine, Seattle, WA 98195, USA

Corresponding Author: Monica Leslie – monica.leslie@kcl.ac.uk; - 103 Denmark Hill, Section of Eating Disorders, London SE5 8AZ, United Kingdom

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Abstract

Purpose: Oxytocin's anorexigenic effects have been widely documented and accepted; however, no paper has yet used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to compile previous findings in a single systematic review and quantitative meta-analysis. The current paper aimed to identify published and unpublished studies examining the effects of oxytocin on energy intake in animals and humans, and the factors that moderate this effect.

Methods: Web of Science, Pub Med, and Ovid were searched for published and unpublished studies reporting the effects of oxytocin on energy intake in wild-type animals and in humans, when administered in the absence of other active drugs or surgery.

Results: 2049 articles were identified through the original systematic literature search, from which 54 articles were identified as relevant for inclusion in this review. An additional 3 relevant articles were identified in a later update of the literature search. Overall, a single dose of oxytocin was found to reduce feeding in animals. Despite several individual studies which found that this effect persists to the end of the third week of chronic administration in rodent models, overall, this anorexigenic effect did not hold in the meta-analyses testing the effects of chronic administration. There was no overall effect of oxytocin on energy intake in humans, although a trend was identified for oxytocin to reduce consumption of solid foods.

Conclusions: Oxytocin reduces energy intake when administered as a single dose. Oxytocin can inhibit feeding over two- to three-week periods in rodent models. These effects typically do not persist beyond the third week of treatment. The anorexigenic effect of oxytocin is moderated by pregnant status, dose, method of administration, and diet composition.

KEYWORDS: OXYTOCIN; ENERGY INTAKE; FEEDING; ANIMALS; HUMANS

Introduction

Verbalis, McCann, McHale, and Stricker (1986) and Kirchgessner, Sclafani, and Nilaver (1988) first proposed a link between oxytocin and the control of food intake almost 30 years ago; which was subsequently corroborated by the Arletti lab (Arletti, Benelli, & Bertolini, 1989). Today, oxytocin has a well-established and well-accepted role in reducing food intake in rodents, although these effects have been found to be conditional on several factors (Olszewski, Klockars, & Levine, 2016).

The reported inhibitory effect of oxytocin on feeding has taken on new relevance in the face of the high prevalence of obesity in developed countries (Arroyo-Johnson & Mincey, 2016) and recognition of the psychological and functional difficulties faced by individuals with binge-type eating disorders, including bulimia nervosa and binge eating disorder (American Psychiatric Association, 2013; Pawaskar, Witt, Supina, Herman, & Wadden, 2017). It has, accordingly, been proposed that oxytocin may be a useful supplement to administer to counter overeating and obesity (Roberts et al., 2017; Spetter & Hallschmid, 2017).

In recent years, several narrative reviews have examined the role of oxytocin in a variety of functions related to the homeostasis of energy status: including its effects on feeding, energy expenditure, lipolysis, glucose homeostasis, and macronutrient preference (Lawson, 2017; Leng & Sabatier, 2017; Sabatier, Leng, & Menzies, 2013; Spetter & Hallschmid, 2017), as well as its potential to regulate disordered eating in humans (Giel, Zipfel, & Hallschmid, 2017). However, systematic reviews and meta-analyses in the style of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines are not commonly used in neurobiology and have not been previously used to estimate the size of the effect of oxytocin on feeding, and its possible moderators. This systematic method offers benefits such as the reproducibility,

accountability of the search methods used, and quantitative precision in the measurement of effect size across different samples (Moher, Liberati, Tetzlaff, & Altman, 2009). De Vries and colleagues have therefore adapted similar guidelines for systematic reviews of animal intervention studies in order to bring these same benefits in methodical rigor to animal research (Vries et al., 2015).

The current paper therefore aimed to use this rigorous methodology to synthesize oxytocin's effects on feeding. We used PRISMA guidelines to identify all original published and unpublished experiments testing the effects of exogenous oxytocin on energy intake in wild-type animals and in humans, where oxytocin was administered in the absence of other active drugs or surgeries. Following this, we then identified subsets of experimental designs conducive to synthesis by quantitative meta-analysis. We also aimed to identify relevant moderators of oxytocin's effects on feeding in order to clarify the conditions under which these anorexigenic effects hold.

Methods

Search Strategy and Eligibility Criteria

Two of the authors conducted a systematic literature search to identify original studies which had administered exogenous oxytocin to either animals or humans and compared its effects on energy intake with a placebo condition. This search was conducted following PRISMA guidelines (Moher et al., 2009). We followed reporting guidelines suggested by de Vries and colleagues for pre-clinical intervention studies in the data extraction and reporting methods described below (Vries et al., 2015).

The search terms included in the literature search were: “oxytocin” AND (“feed*” OR “food” OR “eat” OR “consum*” OR “intake” OR “hunger” OR “satiety” OR “appetite” OR “meal”). The eligibility criteria for studies included in the systematic review are as follows:

Inclusion criteria:

- Original experiment
- Independent variable: Administration of exogenous oxytocin compared to placebo
- Dependent variable: Quantity of food or nutritive substance consumed
- Oxytocin administered in isolation from any other drug or neural stimulation
- Article available in English
- Neurologically typical participants (e.g., participants with Prader-Willi Syndrome were excluded)

Exclusion criteria:

- Studies testing consumption of alcohol/ethanol or methamphetamines
- Studies testing consumption of plain water, saccharin, or sodium solutions
- Studies of breastfeeding neonates
- Studies measuring oxytocin's effect on conditioned taste aversion

In March 2016, these terms were included in a title or topic search in the Web of Science (Core Collection) and in a text word search in PubMed. In November 2016, these same search terms were entered into a literature search using the following Ovid resources: International Pharmaceutical Abstracts, Ovid MEDLINE(R) I-Process & Other Non-Indexed Citations, Ovid MEDLINE R, PsycArticles Full Text, PsycInfo, Ovid MEDLINE(R) Epub Ahead of Print. The PubMed and Web of Science searches were then updated by the first author in December 2016.

The first author then proceeded to screen the reference lists of relevant reviews in order to identify articles not included in the main search results, and independently contacted authors known to have unpublished eligible studies (identified through

individual correspondence, conference attendance, and reference to unpublished data within a published paper). In March 2017, the second author repeated the literature search among the same databases. The first and second authors discussed discrepancies among the identified search results until a consensus regarding each article's eligibility was reached. The literature search was once again updated using the same databases in July 2017. Basic study characteristics (including sample information, dose of oxytocin administration, and duration of feeding measurement) and a qualitative summary of each experiment's findings were extracted by a single author.

Meta-Regression

Given the wide variety of studies identified by the systematic literature search, we opted to conduct five separate meta-regressions in order to maximize the homogeneity within each analysis. The five meta-regressions were then conducted amongst each of the following sets of experiment: 1) single-dose animal studies measuring feeding over one hour after a central injection of oxytocin; 2) single-dose animal studies measuring feeding over one hour after systemic administration of oxytocin; 3) chronic-dosing animal studies administering central injections of oxytocin; 4) chronic-dosing animal studies administering systemic injections of oxytocin; 5) human studies. Effect size data (including raw means and standard deviation or standard error) and sample sizes for each study were necessary for each eligible study to be included in a meta-regression. These data were extracted by a single author directly from tables or text within the paper in cases where they were reported. For papers in which these data were not reported, the authors of the paper were contacted with a request for this information via e-mail, or via Research Gate where a current valid e-mail address was unavailable. Where these data were unavailable, the eligible paper has been described in the results of the systematic review but omitted from the meta-regression by necessity.

As not all of the studies identified in original systematic review were eligible for inclusion in one of these meta-regressions, the full findings of each study included in the systematic review have been reported in separate tables. The moderating and mediating factors influencing oxytocin's effects on energy intake have been summarized in a qualitative synthesis, which follows the quantitative results reported below.

Each meta-regression was conducted as a random-effects multi-level analysis with autoregressive structure, where the second-level corresponded to a specific sample of test subjects. The meta-regressions' results are reported in terms of the standardized mean difference between placebo and oxytocin conditions. The meta-regressions were conducted using the `escalc` and `rma.mv` commands in the `metafor` package for R (Viechtbauer, 2010). The forest plots and bias plots were generated using the Comprehensive Meta-Analysis software. In four experiments within the meta-analysis for human studies, the within-subject correlation was not available. The average within-subject correlation for human studies (0.61) was therefore imputed for these experiments.

Results

Systematic Review

The quantity of papers identified and screened at each step of the PRISMA process during the original systematic literature search is presented in **Figure 5**. Two additional unique papers were identified through the updated literature search, and one additional paper was identified through author correspondence. The original and updated literature searches together identified a total of 57 relevant papers.

Forty-seven papers included at least one experiment that measured the effects of a single dose of oxytocin on feeding. The 114 experiments measuring the effects of a single dose of oxytocin are summarized in **Supplementary Table 4**. Eighteen papers included at least one experiment that administered chronic dosing of oxytocin. The 56

experiments measuring the effects of chronic oxytocin dosing on feeding are summarized in **Supplementary Table 5**.

Meta-Regression

Acute central animal studies. We first conducted the meta-regression for the studies that administered oxytocin centrally, entering moderators for Dose and Body Mass. As all animals were male and housed individually, we did not include moderators for gender or socialization. The Cook's plot generated by this analysis revealed that one study ((Arletti et al., 1989), Experiment 2a) yielded undue influence on the results. This study was therefore excluded from the final analysis, resulting in a total of nine experiments with a pooled sample size of 150 observations. (Note: as several studies incorporated a within-subjects design and/or repeated experiments using the same animals, the number of total observations does not equal the total number of subjects.) The final analysis found a significant main effect of oxytocin, showing that a single dose of centrally-administered oxytocin reduced feeding with a large effect size ($d = -1.26$, $SE = 0.451$, $p = 0.005$, 95% CI [-2.149, -0.380]). The forest plot for this meta-regression is shown in **Figure 6**. Neither of the included moderators was significant: Dose (estimate = -0.003, $SE = 0.017$, $p = 0.857$, 95% CI [-0.036, 0.030]); Body Mass (estimate = 0.000, $SE = 0.000$, $p = .315$, 95% CI [-0.000, 0.000]). There was significant residual heterogeneity: $Q(8) = 22.94$, $p = 0.003$. There was significant residual heterogeneity after controlling for Dose ($QE(7) = 22.94$, $p = 0.002$ and Body Mass $QE(7) = 20.49$, $p = 0.005$).

Acute systemic animal studies. We next repeated the analysis for studies administering a single dose of systemic oxytocin including moderation analyses for Gender, Dose, and Body Mass. This meta-regression included findings from 26 experiments and 510 observations. All animals were individually housed; therefore, socialization was not entered as a moderator. Visual inspection of the Cook's plot did not

reveal undue influence of any study (all values < 0.12). This analysis for single-dose studies administering oxytocin systemically also found that oxytocin significantly reduced feeding with a large effect size ($d = -1.17$, $SE = 0.307$, $p < .001$, 95% CI $[-1.776, -0.574]$). There was significant heterogeneity in the results: $Q(25) = 188.38$, $p < .001$. The moderation analyses revealed a small dose-response effect (estimate = -0.002 , $SE = 0.0005$, $p < .0001$, 95% CI $[-0.003, -0.001]$). The forest plot for this meta-regression is shown in **Figure 7**. Neither of the other included moderators were significant: Gender (estimate = 0.48 , $SE = 1.220$, $p = .694$, 95% CI $[-1.912, 2.872]$); Body Mass (estimate = 0.008 , $SE = 0.005$, $p = .091$, 95% CI $[-0.001, 0.017]$). There was significant residual heterogeneity after controlling for each moderator: Dose ($QE(d24) = 104.31$, $p < .001$); Gender ($QE(24) = 187.81$, $p < .001$); Body Mass ($QE(24) = 131.74$, $p < .001$).

Chronic central animal studies. For the meta-regression of animal studies administering repeated central injections of oxytocin we entered the following moderators: Gender, Dose, Body Mass, and Duration of Oxytocin Administration. The quantity of energy intake on the final day of feeding measurement was compared between oxytocin and placebo conditions. Data were drawn from 20 experiments with a total of 349 observations. As all animals were housed alone, socialization was not included as a potential moderator. Visual inspection of the Cook's plot did not reveal undue influence of any study (all values < 0.30). This analysis did not find a significant main effect of oxytocin on feeding when administered centrally in chronic infusions ($d = 0.15$, $SE = 0.171$, $p = .379$, 95% CI $[-0.185, 0.485]$). The forest plot for this meta-regression is shown in **Figure 8**. There was significant heterogeneity: $Q(19) = 43.08$, $p = 0.001$. None of the included moderators were significant, and there was significant residual heterogeneity after controlling for each moderator. The results of all moderation analyses are presented in **Table 12**.

Chronic systemic animal studies. The same analysis was then repeated for animal studies that administered chronic infusions of oxytocin systemically. The quantity of energy intake on the final day of feeding measurement was compared between oxytocin and placebo conditions. Seventeen experiments with a total of 255 observations were included in this meta-regression. We entered the following moderators: Gender, Dose, Body Mass, Duration of Administration, and Social Condition. Visual inspection of the Cook's plot did not reveal undue influence of any study (all values < 0.90). Again, we did not find a significant main effect of oxytocin on feeding ($d = -1.52$, $SE = 0.963$, $p = .115$, 95% CI [-3.407, 0.369]). The forest plot for this meta-regression is shown in **Figure 9**. The moderators Gender, Dose, and Duration of Administration were significant. Oxytocin had a significantly greater anorexigenic effect in males, and the inhibitory effect of oxytocin on feeding decreased in magnitude over time. The results for dose indicated a reverse dose-response effect, such that greater dose was associated with less inhibition of oxytocin on feeding; however, the effect size was close to zero (estimate = 0.0002, $SE = 0.0001$, $p = 0.039$, 95% CI [0.0000, 0.0003]). There was significant heterogeneity in study results ($Q(22) = 206.88$, $p < .001$) and significant residual heterogeneity after controlling for each moderator. The results of all other moderator analyses are reported in **Table 13**.

Human studies. The meta-regression for human studies included 21 experiments with a total of 1020 observations. We entered the following moderators: Liquid-versus-Solid Food, Gender, Dosage, Fasted-versus-Full condition, Duration of Feeding, and Diagnosis. Visual inspection of the Cook's plot did not reveal undue influence of any study (all values < 0.8). This analysis did not find a significant main effect of oxytocin on feeding (estimate = -0.10, $SE = 0.075$, $p = 0.194$, 95% CI [-0.245, 0.050]). The forest plot for this analysis is shown in **Figure 10**.

There was significant heterogeneity between studies: $Q(df = 20) = 55.82, p < .001$.

All moderators except for Dose and Diagnosis were found to be significant (results shown in **Table 14**). Oxytocin reduced feeding to a greater degree for solid, rather than liquid foods (e.g., nutrient drinks, juice and smoothies). There was a greater inhibitory effect of oxytocin on feeding for males than females, when participants were full, rather than fasted, and when food was presented for a longer period of time (although the effect size was close to zero). There was a marginally significant effect such that oxytocin reduced feeding to a greater degree in obese participants. A greater dose of oxytocin was not associated with quantity of food consumption. There was significant residual heterogeneity after taking each moderator into account. Residual heterogeneity for each moderator is reported in **Table 14**.

Based on the difficulty of interpreting the results given such a range of significant moderators, we then proceeded to repeat the analysis including only studies that had measured the consumption of solid foods. As all but one of the studies in the meta-regression for solid foods included only female participants, the gender moderator was not included in this analysis.

Ten experiments with a total of 486 observations were included in the meta-regression for human studies measuring consumption of solid foods. Visual inspection of the Cook's plot did not reveal undue influence of any study (all values < 0.7). The meta-regression for human studies isolated into the solid food condition found a marginally significant main effect of oxytocin on food consumption with a small effect size ($d = -0.25, SE = 0.132, p = 0.055, 95\% CI [-0.510, 0.006]$). The forest plot for this meta-regression is shown in **Figure 11**. None of the included moderators were significant (results shown in **Table 15**). There was significant residual heterogeneity after controlling for Gender, Fasted or Full condition, Duration of Administration, and Dose. Although the diagnosis moderator was not significant ($Q_m(3) = 3.01, p = 0.391$), there was no longer

significant residual heterogeneity after controlling for diagnosis ($QE(6) = 12.18, p = .058$).

Publication Bias. The funnel plots associated with each meta-regression are shown in **Supplementary Figures 1-5**. The funnel plots indicated that most studies had a moderate degree of precision, with a broad range of effect sizes reported. These findings do not suggest systematic publication bias towards papers with either strong or weak effect sizes.

Mediators and Moderators of Oxytocin's Anorexigenic Effects

Among the systematic review, there were many factors that were found to moderate the effect of oxytocin on feeding in some studies, including: sex of the animal, pregnancy, dose, method of administration, setting, and dietary factors. As not all studies met criteria for inclusion in one of the meta-regressions, the following reported results will focus on a sample of other identified studies that examined a moderating or mediating factor in a controlled experimental design.

Sex differences. Several studies investigated sex differences in oxytocin's effects on feeding. Bjorkstrand and Uvnas-Moberg (1996) found that a 5µg intracerebroventricular injection of oxytocin increased feeding in female, but not male rats. Conversely, L. Zhou, Ghee, See, and Reichel (2015) found that oxytocin induced a greater reduction in feeding in female rats, with anorexigenic effects observed at 0.3, 1, and 3mg/kg doses of oxytocin, while only the 3mg/kg dose was effective at reducing feeding in males. To further add to these mixed findings, Benelli, Bertolini, and Arletti (1991) failed to find any differences in male versus female rats' response to oxytocin's effects on feeding. Previous studies have demonstrated that feeding varies across differing stages of the oestrous cycle in rodents, non-human primates, and humans (Buffenstein, Poppitt, McDevitt, & Prentice, 1995; Dye & Blundell, 1997; Reddy & Kulkarni, 1999).

The feeding response to hunger-related hormones (including ghrelin) and neurosteroids also varies throughout different stages of the oestrous cycle in female rats (Sakurazawa, Mano-Otagiri, Nemoto, & Shibasaki, 2013). It is recommended that future studies continue to investigate the extent to which estrous cycle phase and fluctuations in ovarian hormones may influence the satiety response to oxytocin in female animal models.

Pregnancy. Only one study (Douglas, Johnstone, & Leng, 2007) tested the effect of pregnancy as a moderator for oxytocin's effect on feeding. This study identified that 1µg intracerebroventricular injection decreased feeding in virgin female rats over one hour of measurement, while having no continued effect on feeding over 12 hours. However, a different pattern of effects was observed in pregnant rats, with the same dose of oxytocin exerting no effect on feeding over one hour, while increasing feeding over 12 hours. The authors have proposed that this may be due to changes in the expression and binding affinity of central oxytocin receptors during pregnancy (Douglas et al., 2007).

Dose and method of administration. Most studies testing a dose-response effect of oxytocin found that greater doses of oxytocin were associated with correspondingly lower levels of subsequent feeding. The minimum effective dose required to observe anorexigenic effects of oxytocin depended on the method of administration, with central injections of oxytocin requiring much lower doses than peripheral injections.

Findings of note include that of Ong, Alhadeff, and Grill (2015), who reported that a 1µg/1µL dose of oxytocin injected into the fourth ventricle reduces feeding over 30 minutes only when a dietary preload had been provided, and did not continue to affect feeding over 1.5 hours. By contrast, a 0.3µg dose of oxytocin injected into the nucleus of the solitary tract (NTS) was found to significantly reduce feeding over 30 minutes regardless of whether a dietary preload had been provided. This inhibitory effect on feeding persisted over 1.5 hours in the dietary preload condition. These findings seem to

point to greater sensitivity to oxytocin's effects on feeding within the NTS than within hindbrain receptors accessed via fourth cerebral ventricle, suggesting that the NTS may represent a more proximal site mediating oxytocin's effects on feeding. However, these results contradict those found by J. M. Ho et al. (2014), who reported that oxytocin injection into the fourth ventricle was effective at reducing feeding in the absence of a preload at a dose of 1µg. The differential sensitivity of the NTS and fourth ventricle to oxytocin's anorexigenic effects is therefore a question that would be interesting for future research to explore.

In another study examining the impact of injecting oxytocin into different regions of the central nervous system, Herisson et al. (2016) demonstrated that 1µg and 3µg doses of oxytocin injected directly into the nucleus accumbens core reduces both chow intake and the consumption of a 10% sucrose solution in male rats, while these inhibitory effects are not observed when the same dose is injected into the nucleus accumbens shell. The administration of oxytocin into the nucleus accumbens core was associated with increased Fos-immunoreactivity in both the nucleus accumbens core itself, as well as the paraventricular nucleus and supraoptic nucleus of the hypothalamus: two regions dense in oxytocin neurons and receptors which are involved in feeding regulation (Johnstone, Fong, & Leng, 2006). These findings therefore support a potential role of the nucleus accumbens core in mediating oxytocin's anorexigenic effects, which does not extend to the nucleus accumbens shell.

One point to note, however, are that most studies administered high supraphysiologic doses of oxytocin. While these doses may be required in the case of peripheral administration to increase the chances that some oxytocin will cross the blood-brain barrier, it ought to be noted that these findings may reflect partial oxytocin binding with vasopressin receptors at high doses that would not occur at physiological levels.

Social setting. The social conditions in which animals were housed was also found to impact the effect of oxytocin on feeding. Grippo, Trahanas, Zimmerman, Porges, and Carter (2009) found that isolating female prairie voles from littermates resulted in a decrease in sucrose intake over a period of two weeks in a placebo condition, but that this effect was prevented by oxytocin. In the co-housed group of prairie voles, however, there were no changes in sucrose intake over time, or any differences between the oxytocin and placebo conditions. Additionally, Herisson et al. (2016) found that central oxytocin administration reduced food and sucrose intake in individually-housed male rats, while neither of these effects were observed in male rats allowed some social contact with a conspecific. Both of these studies point to the potential for social housing to prevent oxytocinergic reductions in feeding that would otherwise occur in isolated social settings.

Dietary factors. Finally, diet-induced obesity was also identified as an important moderating factor for oxytocin's effects on feeding in both animals and humans (Blevins et al., 2016; Deblon et al., 2011; Maejima et al., 2011; Morton et al., 2012; Roberts et al., 2017; Thienel et al., 2016). On the whole, direct comparisons of lean animals consuming standard chow with diet-induced obese animals consuming high-fat diets found that oxytocin had more consistent inhibitory effects on feeding in the dietary-induced obese animals (Blevins et al., 2016; Roberts et al., 2017). Blevins and colleagues have shown that this moderating effect persists in high fat diet-fed rats, even when matched for body mass and adiposity with chow-fed controls (Blevins et al., 2016), thus indicating that this moderating effect may be more attributable to the fat-content of the animal's diet than body composition.

Discussion

This review aimed to identify published and unpublished studies testing the effects of exogenous oxytocin on energy intake in wild-type animals and humans, where

oxytocin was administered in isolation from other active drugs and surgery. The systematic review and meta-analysis revealed a robust inhibitory effect of oxytocin on energy intake when administered as a single dose in animals, regardless of whether it was administered via a central or peripheral route. Additionally, while several individual experiments did show a continued inhibitory effect of oxytocin for periods of two or more weeks in rats and mice (Altirriba et al., 2014; Balazova et al., 2016; Beranger et al., 2014; Blevins et al., 2015; Blevins et al., 2016; Roberts et al., 2017; G. Zhang & Cai, 2011), when final-day energy intake was compared between placebo and oxytocin conditions in the quantitative meta-analysis this inhibitory effect did not hold, despite a trend towards inhibition in studies administering oxytocin systemically.

The human studies did not find a main effect of oxytocin on energy intake; however, there was found to be a trend towards a decrease in the consumption of solid foods induced by oxytocin. Additionally, oxytocin had a stronger inhibitory effect on energy intake in male participants, in obese participants, and when participants completed the experiment in the full condition (rather than fasted condition). The specific finding that oxytocin reduced feeding to a greater degree in obese humans (Thienel et al., 2016) is consistent with findings from animal studies, which have also indicated a greater anorexigenic effect in diet-induced obese mice and rats (Roberts et al., 2017).

The moderating effect of liquid versus solid foods was unexpected amongst human studies, particularly given previous animal research demonstrating the inhibitory effect of oxytocin on the consumption of palatable liquid solutions (Herisson et al., 2016; Lokrantz, Uvnas-Moberg, & Kaplan, 1997; Mullis, Kay, & Williams, 2013). The mechanism driving the difference between oxytocin's effect on liquid and solid foods is unclear. One hypothesis is that oxytocin may reduce gastric motility, thus contributing to the sensation of satiety as solid food remains in the gut for a longer period of time. This hypothesis is supported by research demonstrating that oxytocin can reduce gastric

motility in rats (Flanagan, Olson, Sved, Verbalis, & Stricker, 1992; R. C. Rogers & Hermann, 1987; C. L. Wu et al., 2002; C. L. Wu, Hung, Chang, Pau, & Wang, 2003) and mice (M. G. Welch, Margolis, Li, & Gershon, 2014). However, Borg and colleagues have found evidence to the contrary, indicating that oxytocin does not affect gastric emptying rate in humans following consumption of a liquid meal (Borg, Simren, & Ohlsson, 2011). Further research would be useful to test this hypothesis as it pertains to solid foods, and to further investigate the reasons for oxytocin's greater inhibitory effect for solid, versus liquid, consumption in humans.

The pattern for the inhibitory effect of oxytocin on feeding to decrease over time was reflected in a significant moderator analysis carried out for the meta-regression of studies that administered systemic oxytocin to animals chronically over time. This meta-regression, as well as the meta-regression for human studies, were also significantly moderated by sex, such that the effects of oxytocin on reducing feeding were significantly greater for male animals. This overall moderating effect of sex across studies included in the meta-regression is interesting to observe given the highly mixed findings regarding sex differences reported in individual studies (Benelli et al., 1991; Bjorkstrand & Uvnas-Moberg, 1996; L. Zhou et al., 2015). A greater density of oxytocin receptors has previously been reported within the spinal cord and ventromedial hypothalamus of male rats (Uhl-Bronner, Waltisperger, Martinez-Lorenzana, Lara, & Freund-Mercier, 2005), which may potentially explain the greater sensitivity to oxytocin's anorexigenic effects in males. However, the activity of oxytocin and oxytocin receptors also varies across stages of the follicular cycle in female prairie voles (Witt, Carter, & Insel, 1991). Furthermore, it is known that levels of endogenous plasma oxytocin vary across stages of the menstrual cycle in humans (Salonia et al., 2005). One can hypothesize that this natural variation may moderate the effects of exogenously-administered oxytocin. Variation in the follicular stage at which oxytocin was administered to female animals may therefore

partially account for mixed findings reported for feeding effects in previous studies. It would therefore be useful to specifically investigate variation in oxytocin's effect on feeding across different phases of the follicular cycle, and associated variation in plasma levels of other hormones (e.g., oestrogen).

In terms of the mechanisms explaining oxytocin's greater effect in obese animals and humans, it is known that oxytocin receptors exhibit a higher-affinity binding state in the presence of cholesterol (Gimpl, 2016). Therefore, it may be that a greater fat- and cholesterol-rich diet at least partially explains the greater anorexigenic effects of oxytocin observed in obese animals and humans.

The mechanisms and neural circuits explaining the overall anorexigenic effects of oxytocin are still somewhat uncertain. Oxytocin is known to mediate the anorexigenic effects of cholecystokinin (CCK), which acts on oxytocin neurons via vagal afferents from the gut (Verbalis et al., 1986). This finding has received further support from research demonstrating that injections of oxytocin into the third cerebral ventricle enhance the anorexigenic effects of low doses of CCK-8 (Blevins et al., 2016) while, conversely, pre-treatment of an oxytocin receptor antagonist into the fourth ventricle suppresses the anorexigenic effects of CCK (Blevins, Eakin, Murphy, Schwartz, & Baskin, 2003; Olson, Drutarosky, Stricker, & Verbalis, 1991). In addition to this role mediating the effects of CCK, oxytocin has also been implicated in mediating leptin's (Blevins, Schwartz, & Baskin, 2004; Z. Wu et al., 2012) and nesfatin-1's (Saito et al., 2017) inhibitory effects on food intake. The downstream mechanisms by which oxytocin impacts on feeding; however, are less certain.

It is likely that central and peripheral oxytocin exert effects of feeding via different mechanisms. Previous research has identified that only approximately 0.002% of peripheral oxytocin crosses the blood-brain barrier where it might access central receptors

(Mens, Witter, & Greidanus, 1983). However, the extent to which peripheral oxytocin exerts its effects via central versus peripheral receptors, such as those in the gut (Ohlsson, Truedsson, Djerf, & Sundler, 2006), may be species-dependent. In mice, the literature supports a role for vagal afferent nerves in mediating the anorexigenic effect of peripheral oxytocin (Iwasaki et al., 2015; M. G. Welch et al., 2009). This interpretation draws support from research finding that oxytocin receptors are expressed in the nodose ganglion of the vagus nerve (M. G. Welch et al., 2009), as well as further research that has gone on to demonstrate that vagotomy results in an attenuation of the anorexigenic effect of peripherally-administered oxytocin in mice (Iwasaki et al., 2015). In rats, however, Ho and colleagues (2014) have demonstrated that hindbrain receptors accessed via the fourth ventricle are predominantly responsible for mediating the inhibitory effects of peripheral oxytocin on feeding. Further research clarifying which pathway/s predominate this mediating effect in primates and humans has not yet been conducted and would be useful to investigate in future studies.

Brain nuclei including the paraventricular nucleus, NTS, and arcuate nucleus have been implicated as potentially relevant in mediating oxytocin's effects on feeding (Fenselau et al., 2016; Iwasaki et al., 2015; Maejima et al., 2014; Olszewski et al., 2010; Ong et al., 2015). This evidence comes from studies indicating that direct injections of oxytocin into these areas suppresses food intake (Maejima et al., 2014; Ong et al., 2015), as well as immunohistological studies demonstrating that the Fos activation of oxytocin neurons in these regions co-occurs with the termination of feeding (Fenselau et al., 2016; Iwasaki et al., 2015; Maejima et al., 2014; Olszewski et al., 2010). Furthermore, studies have demonstrated that injections of oxytocin directly into the ventral tegmental area, nucleus accumbens core, and ventromedial hypothalamus are effective in inhibiting feeding; thereby indicating that these regions may mediate the anorexigenic effects of oxytocin as well (Herisson et al., 2016; Mullis et al., 2013; Noble, Billington, Kotz, &

Wang, 2014). Given that oxytocin is effective in reducing energy intake when administered both centrally and peripherally, it may be the case that oxytocin acts as a central messenger integrating central and peripheral signals. This hypothesis, however, requires further evidence to corroborate.

It has also been proposed that oxytocin may exert inhibitory effects on energy intake via a physiological pathway mediated by reward-based mechanisms (Klockars, Brunton, Li, Levine, & Olszewski, 2017). This hypothesis is lent support by the high density of oxytocin receptors along the pathways connecting the nucleus accumbens and ventral tegmental area (Mitre et al., 2016; Peris et al., 2017; Shahrokh, Zhang, Diorio, Gratton, & Meaney, 2010), two regions known to be highly involved with processing food reward (Berridge, 2009). Additionally, oxytocin injected directly into the nucleus accumbens has been found to reduce methamphetamine-induced place preference (Baracz et al., 2012) and prevent relapse to methamphetamine-seeking behavior after extinction (Baracz, Everett, McGregor, & Cornish, 2016). Together, these findings point to an ability for oxytocin to disrupt reward-related processing in these regions, which may additionally extend to suppressing reward-based feeding behaviour. This hypothesis, if true, may also explain the stronger effects of oxytocin in reducing hedonic, as opposed to hunger-driven, feeding in human studies (Burmester, 2017; Ott et al., 2013; Thienel et al., 2016). Further research in animals and humans would be useful to test this hypothesis further and elucidate the precise mechanisms of oxytocin's acute action on energy intake.

The confirmation of oxytocin's anorexigenic effects when administered as a single dose echoes conventional understanding in the literature, while highlighting the limits of this effect: such as the reverse (orexigenic) effect observed in pregnancy (Douglas et al., 2007) and when socially-housed animals subsequently undergo separation from litter-mates (Grippio et al., 2009). The null findings revealed in the meta-analysis testing the chronic effects of oxytocin on feeding are disappointing in the context of

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potential hopes for developing oxytocin supplementation as a new treatment for binge-type eating disorders in humans, and conflict with individual studies which have reported the persistence of oxytocin's anorexigenic effects over two to three weeks of measurement in rats and mice (Balazova et al., 2016; Beranger et al., 2014; Blevins & Baskin, 2015; Blevins et al., 2016; Roberts et al., 2017; Guo Zhang et al., 2011), and for two weeks post-treatment in rhesus monkeys (Blevins et al., 2015). It may be the case that a regime of intermittent oxytocin administration would result in the same anorexigenic effects observed within the course of a single experimental administration, without resulting in the same degree of receptor adaptations. Future research testing different temporal regimes of oxytocin administration is recommended to test this hypothesis.

The diminishing effects of oxytocin are in keeping with the results arising from individual studies making use of the repeated administration of oxytocin (Altirriba et al., 2014; Beranger et al., 2014; Blevins et al., 2016; Maejima et al., 2011; Roberts et al., 2017) or an oxytocin agonist (Olson, Drutarosky, Chow, et al., 1991). These findings also concord with social experiments which have found that the anxiolytic effects of oxytocin disappear or reverse over time (Peters, Slattery, Uschold-Schmidt, Reber, & Neumann, 2014). Peters et al. found that the reversal of acute anxiolytic effects over chronic dosing was associated with a concurrent reduction in oxytocin receptor binding. Indeed, previous work has shown that oxytocin receptor binding can reduce by as much as 50% over 10 days of chronic administration, driven largely by down-regulation of the oxytocin receptor (Insel, Winslow, & Witt, 1992). It is therefore likely that this reduced binding potential may explain the dampening of oxytocin's effects on feeding.

The null findings generated from the meta-regressions of chronically-administered oxytocin studies should be interpreted with some degree of caution. Although the final-day analyses used for the meta-regressions maximized the number of

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commensurable studies eligible for inclusion, it may be that noise in the data on the final day data masked smaller effects identified by studies that compared average consumption across several days. It should also be noted that the scope of the current review is limited to oxytocin's effects on energy intake alone, and that oxytocin's effects on other metabolic parameters deterring obesity (e.g., lipolysis, brown adipose tissue thermogenesis, and energy expenditure) may persist with chronic administration (Blevins & Baskin, 2015).

Limitations of the current review include some inherent drawbacks of the methodology chosen for the meta-regressions. We aimed to reach a compromise between maximizing homogeneity of studies included in the meta-regression, while also including the maximum number of experiments. The choice to therefore include only single-dose studies that measured the effects of oxytocin over one hour of feeding therefore constrained these meta-regressions to a reasonable scope and similar effect size. Differences in the exact location of administration and animals included in each experiment, however, may have added to the heterogeneity of effect size observed across studies. Furthermore, the current systematic review did not include findings from non-wild-type animals (e.g., Sim-haploinsufficient rats and mice) or animals whose nervous systems were altered by surgery or direct stimulation. Therefore, although the current findings reveal the effects of exogenous oxytocin in wild-type animals, it should be noted that there are further findings reflecting the implication of oxytocin on feeding that were not included within the scope of the present review.

Regarding the clinical implications of these findings, it is particularly encouraging to have observed that the anorexigenic effects of oxytocin were stronger for populations that suffer from over-eating and binge-eating. These findings suggest that, in the short term, oxytocin may reduce the likelihood of binge-eating and overeating for populations with obesity, bulimia nervosa, and binge eating disorder. However, the null findings from

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the meta-regressions of chronic animal studies cast doubt on the persistence of oxytocin's acute effects. Testing different dosing schedules of oxytocin would be useful for identifying a potential frequency and dose of administration that maintains oxytocin's beneficial effects over time, without resulting in the reduction of receptor binding.

In conclusion, the current systematic review has confirmed the anorexigenic effect of a single dose of oxytocin in animals first documented by the Arletti lab (Arletti et al., 1989), while demonstrating that this anorexigenic effect does not persist throughout chronic dosing. There was a trend for intranasal oxytocin to reduce feeding in humans, and this effect was stronger for individuals with obesity, bulimia nervosa, and binge eating disorder. Future research is needed to further elucidate the mechanisms of these effects, and whether differing dosing schedules might prevent their attenuation with chronic administration.

Table 12*Results of Moderator Analyses for Chronic Central Studies*

	Estimate	SE	p	Confidence Interval		Residual Heterogeneity	
				Lower bound	Upper bound	QE	p
Gender	-0.16	0.580	.787	-1.293	0.980	42.80	< .001
Dose	-0.004	0.025	.881	-0.054	0.046	42.61	< .001
Body Mass	-0.001	0.001	.437	-0.002	0.001	40.52	.002
Duration of Administration	-0.01	0.022	.494	-0.057	0.028	41.56	.001

Table 13*Results of Moderator Analyses for Chronic Systemic Studies*

	Estimate	SE	p	Confidence Interval		Residual Heterogeneity	
				Lower bound	Upper bound	QE	p
Gender	-0.71*	0.292	.015	-1.281	-0.136	200.99	< .001
Socialization	-0.28	0.275	.306	-0.821	0.258	205.83	< .001
Body Mass	0.000	0.000	.456	-0.000	0.000	101.78	< .001
Duration of Administration	0.02*	0.009	.021	0.003	0.038	201.53	< .001

* $p < .05$.

Table 14*Results of Moderator Analyses for All Human Studies*

	Estimate	SE	p	Confidence Interval		Residual Heterogeneity	
				Lower bound	Upper bound	QE	p
Liquid-versus-solid food	-0.30***	0.077	< .001	-0.456	-0.153	40.46	.003
Gender	-0.39**	0.134	.004	-0.650	-0.123	47.70	< .001
Fasted or full condition	-0.14**	0.047	.003	-0.230	-0.047	48.57	< .001
Duration of Food Presentation	-0.0002**	0.0001	.002	-0.0003	-0.0001	50.62	< .001
Diagnosis (Obesity vs AN)	-0.570	0.316	.071	-1.189	0.048	49.08	< .001
Dose	0.01	0.006	.141	-0.003	0.020	53.24	< .001

* $p < .05$; ** $p < .01$; *** $p < .001$.

Table 15*Results of Moderator Analyses for Human Studies in Solid Food Condition*

	Estimate	SE	p	Confidence Interval		Residual Heterogeneity	
				Lower bound	Upper bound	QE	p
Gender	-0.28	0.264	0.300	-0.791	0.241	19.36	.013
Fasted or Full Condition	-0.06	0.057	.266	-0.174	0.048	22.01	.005
Duration of Administration	0.0002	0.0002	.281	-0.0002	0.0006	19.32	.013
Dose	0.02	0.017	.297	-0.015	0.050	19.36	.013

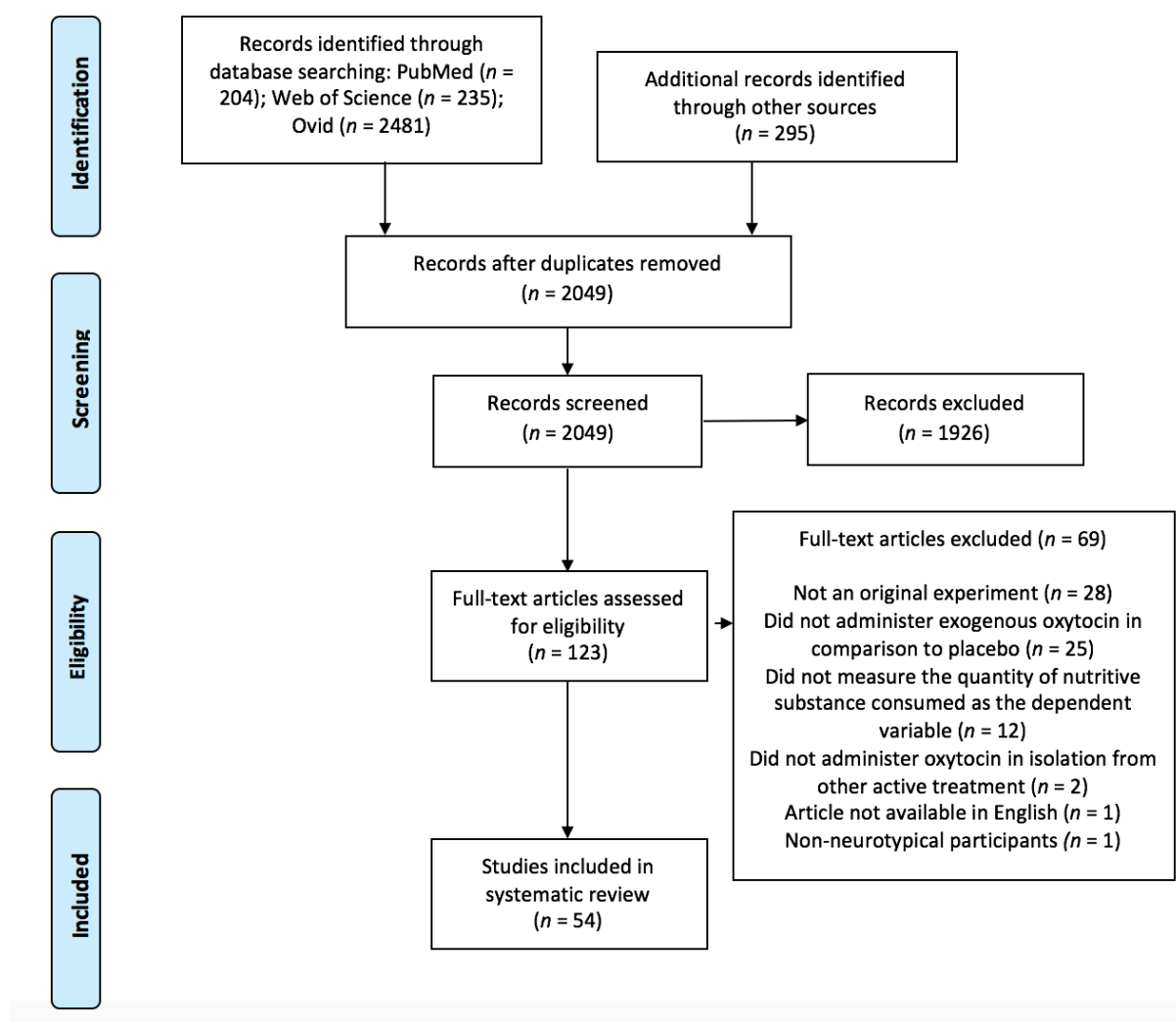


Figure 5. PRISMA flow diagram for the original systematic literature search

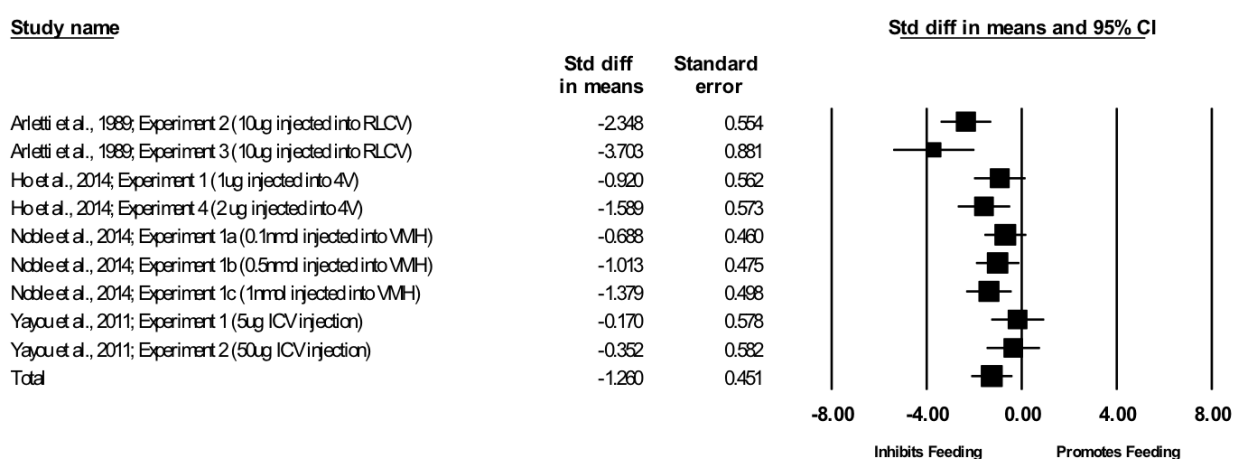


Figure 6. Forest plot of studies measuring the effect of a single-dose of central oxytocin on energy intake over a one-hour measurement duration in animals. RLCV = right lateral cerebral ventricle; 4V = fourth cerebral ventricle; VMH = ventromedial hypothalamus; ICV = intracerebroventricular.

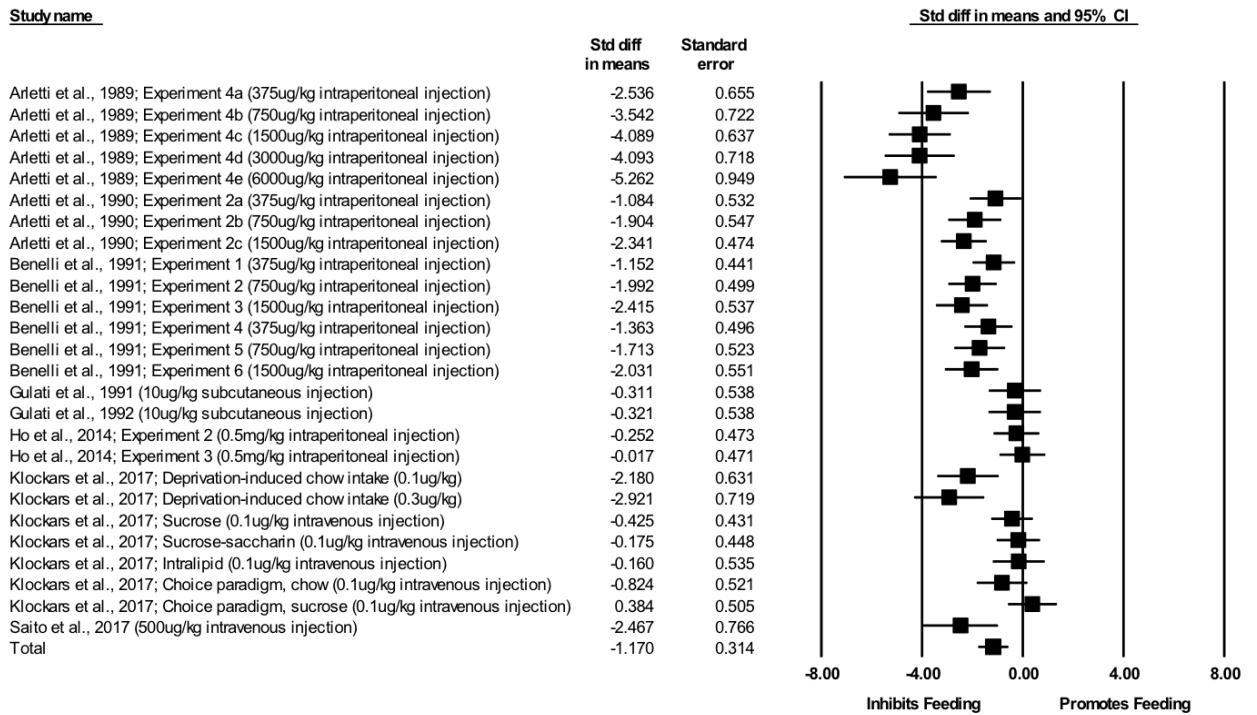


Figure 7. Forest plot of studies measuring the effect of a single-dose of systemic oxytocin on energy intake over a one-hour measurement duration in animals.

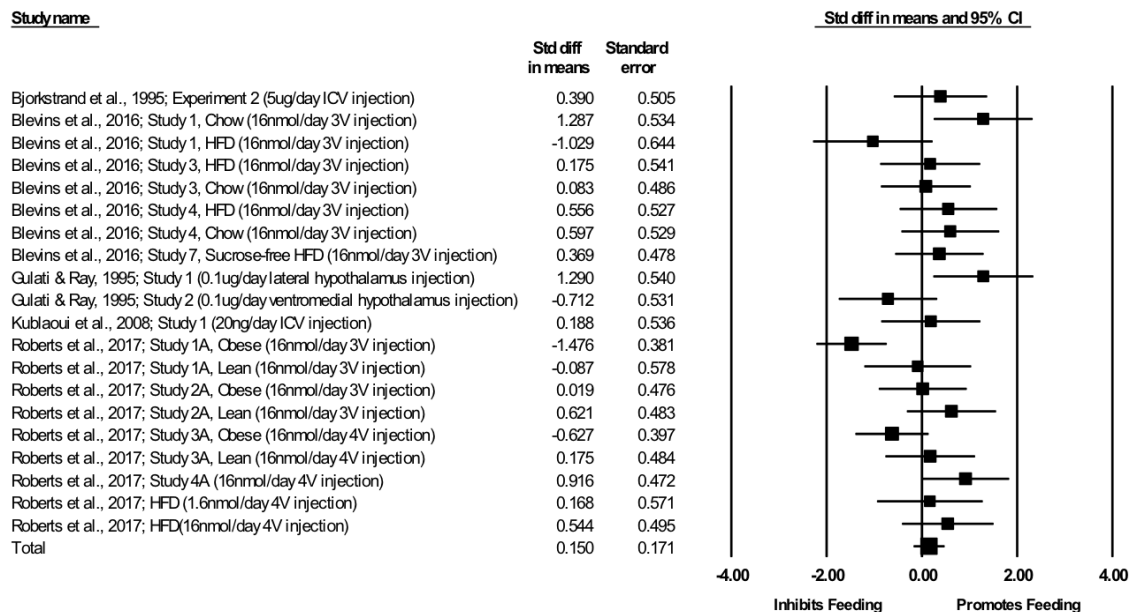


Figure 8. Forest plot of studies measuring the effect of chronic dosing of central oxytocin on energy intake in animals. ICV = intracerebroventricular; 3V = third cerebral ventricle; 4V = fourth cerebral ventricle.

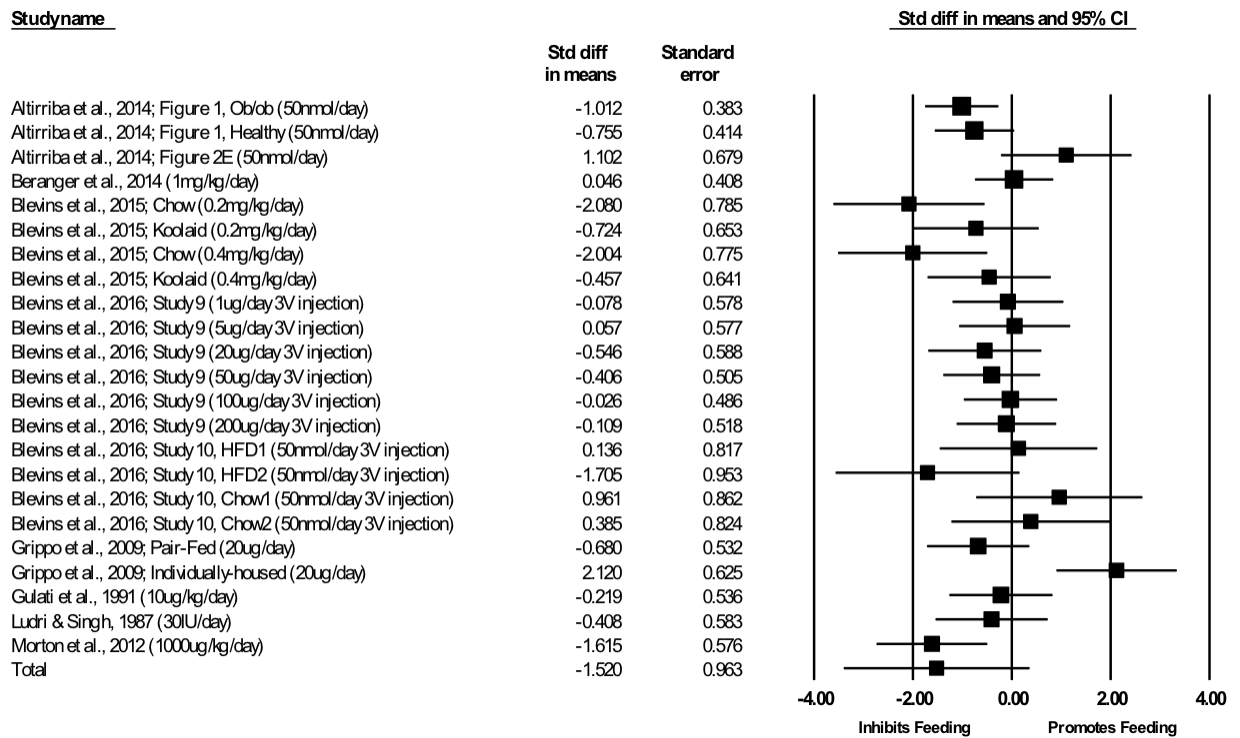


Figure 9. Forest plot of studies measuring the effect of chronic dosing of systemic oxytocin on energy intake in animals.

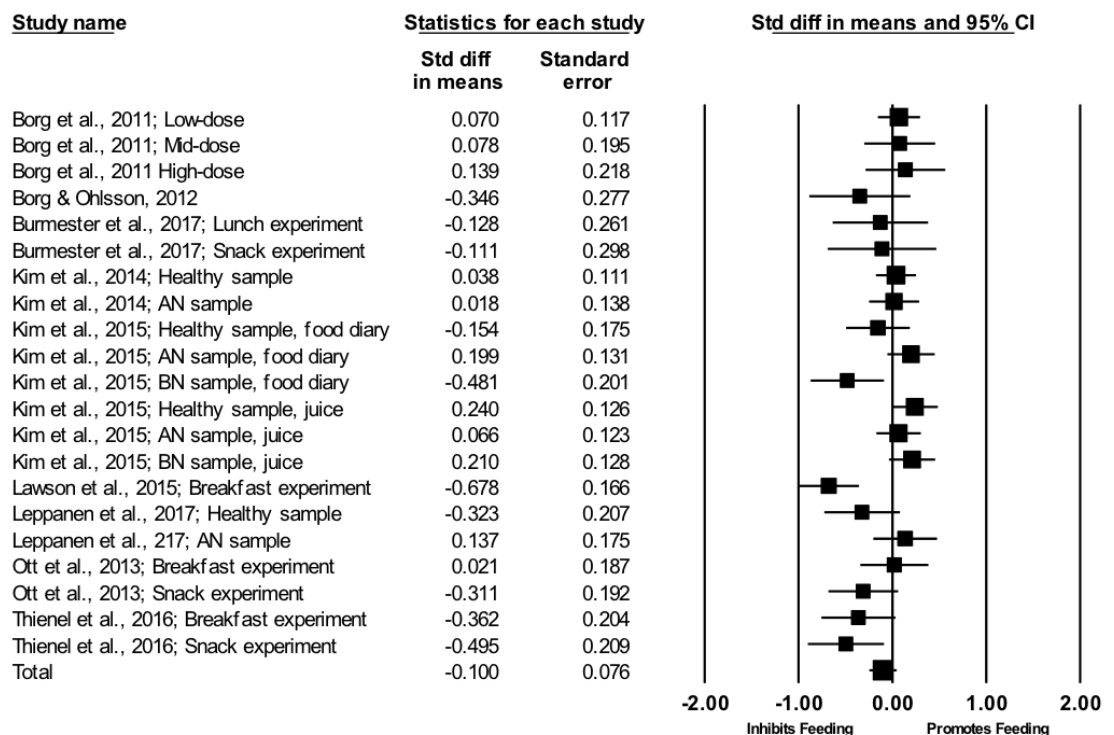


Figure 10. Forest plot of studies measuring the effect of a single dose of intranasal oxytocin on energy intake in humans. AN = anorexia nervosa; BN = bulimia nervosa.

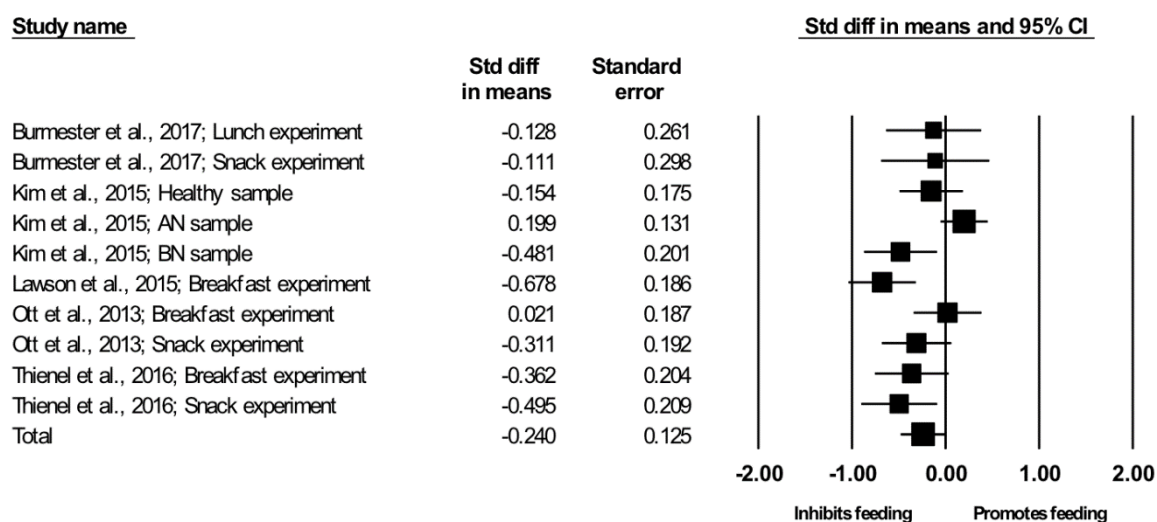


Figure 11. Forest plot of studies measuring the effect of a single dose of intranasal oxytocin on solid food intake in humans. AN = anorexia nervosa; BN = bulimia nervosa.

Supplementary Table 4: Summary of Studies Administering a Single Dose of Oxytocin

Author, Year	Study Title, Experiment Number	Sample Size	Diagnostic Status	Within-Subjects or Between-Subjects Design	Dose	Duration of Feeding Measurement	Route of Administration	Animal	Sex	Type of Food Consumed	Summary of Findings
Arletti et al. (1989)	Influence of oxytocin on feeding behavior in the rat; Experiment 1	OT 1µg (n = 27) OT 2µg (n = 27) OT 10µg (n = 27) PL (n = 27)	Healthy	Between-subjects	1µg; 2µg; 10µg	3 hours	Intracerebroventricular injection	Rats	Male	Chow	Doses of 1µg, 2µg, and 10µg significantly reduced feeding in a dose-dependent manner after 1 hour of measurement. The 10µg dose produced significant reductions in feeding only at hours 2 and 3.
Arletti et al. (1989)	Influence of oxytocin on feeding behavior in the rat; Experiment 2	OT 1µg (n = 11) OT 10µg (n = 11) PL (n = 11)	Healthy	Between-subjects	1µg; 10µg	1 hour	Intracerebroventricular injection	Rats	Male	Chow	The 10µg dose of oxytocin significantly reduced food intake relative to vehicle.

											The 1µg dose of oxytocin had no significant effect on feeding.
Arletti et al. (1989)	Influence of oxytocin on feeding behavior in the rat; Experiment 3	OT (n = 7) PL (n = 7)	Healthy	Between-subjects	10µg	1 hour	Intracerebroventricular injection	Rats	Male	Chow	Oxytocin significantly reduced food intake relative to vehicle.
Arletti et al. (1989)	Influence of oxytocin on feeding behavior in the rat; Experiment 4	OT 375µg /kg (n = 6) OT 750 µg /kg (n = 8) OT 1500 µg /kg (n = 19) OT 3000 µg /kg (n = 12) OT 6000 µg /kg (n = 8) PL (n = 12)	Healthy	Between-subjects	375µg /kg; 750µg /kg; 1500µg /kg; 3000µg /kg; 6000µg /kg	1 hour	Intraperitoneal injection	Rats	Male	Chow	Oxytocin significantly reduced food intake in a dose-dependent manner. This effect was significant for all doses.
Arletti, Benelli, and Bertolini (1990)	Oxytocin inhibits food and fluid intake in rats; Experiment 1, fed condition	OT 1µg (n = 10) OT 10µg (n = 10) PL (n = 10)	Healthy	Between-subjects	1µg; 10µg	1 hour	Right lateral cerebral ventricle injection	Rats	Male	Chow	Oxytocin significantly reduced food intake relative to vehicle at a dose of 1µg, and completely

											inhibited food intake at a dose of 10µg.
Arletti et al. (1990)	Oxytocin inhibits food and fluid intake in rats; Experiment 2, fasted condition	OT 375µg /kg (n = 6) OT 750µg /kg (n = 8) OT 1500µg /kg (n = 19) PL (n = 12)	Healthy	Between-subjects	375µg /kg; 750µg /kg; 1500µg /kg	1 hour	Intraperitoneal injection	Rats	Male	Chow	Oxytocin significantly reduced the time spent eating at doses of 750µg/kg and 1500µg/kg. No effect on number of meals consumed.
Arletti et al. (1993)	The effect of oxytocin on feeding, drinking, and male copulatory behavior is not diminished by neonatal monosodium glutamate; Experiment 1	OT (n = 10) PL (n = 10)	Healthy	Between-subjects	150µg	1 hour	Intraperitoneal injection	Rats	Male and Female	Chow	Oxytocin significantly reduced food intake.
Arletti et al. (1993)	The effect of oxytocin on feeding, drinking, and male copulatory behavior is not diminished by neonatal monosodium glutamate; Experiment 2	OT 1ng (n = 10) OT 10ng (n = 10) PL (n = 10)	Healthy	Between-subjects	1ng; 10ng	1 hour	Intracerebroventricular injection	Rats	Male and Female	Chow	Oxytocin significantly reduced food intake in a dose-dependent manner at both 1ng and 10ng doses.

Benelli et al. (1991)	Oxytocin-induced inhibition of feeding and drinking: no sexual dimorphism in rats; low-dose, males	Not reported	Healthy	Between-subjects	1µg; 10µg	1 hour	Intracerebroventricular injection	Rats	Male	Chow	Oxytocin significantly reduced feeding in a dose-dependent manner. This effect was significant for both 1µg and 10µg doses.
Benelli et al. (1991)	Oxytocin-induced inhibition of feeding and drinking: no sexual dimorphism in rats; low-dose, females	Not reported	Healthy	Between-subjects	1µg; 10µg	1 hour	Intracerebroventricular injection	Rats	Female	Chow	Oxytocin significantly reduced feeding in a dose-dependent manner. This effect was significant for both 1µg and 10µg doses.
Benelli et al. (1991)	Oxytocin-induced inhibition of feeding and drinking: no sexual dimorphism in rats; Experiment 3	OT 187µg /kg (n not reported) OT 375µg /kg (n = 12) OT 750µg /kg (n = 12) OT 1500µg /kg (n = 12)	Healthy	Between-subjects	187µg /kg; 375µg /kg; 750µg /kg; 1500µg /kg	1 hour	Intraperitoneal injection	Rats	Male	Chow	Oxytocin significantly reduced feeding at doses of 375µg/kg and above.

Benelli et al. (1991)	Oxytocin-induced inhibition of feeding and drinking; no sexual dimorphism in rats; Experiment 3	OT 187µg/kg (n not reported)	Healthy	Between-subjects	187µg/kg; 375µg/kg; 750µg/kg; 1500µg/kg	1 hour	Intraperitoneal injection	Rats	Female	Chow	Oxytocin significantly reduced feeding at doses of 375µg/kg and above.
Bernal, Mahia, and Puerto (2013)	Differential lasting inhibitory effects of oxytocin and food-deprivation on mediobasal hypothalamic polydipsia; Experiment 1, freely-fed condition	OT (n = 8) PL (n = 8)	Healthy	Between-subjects	22µg	9 days	Subcutaneously injected	Rats	Male	Chow	No significant effect of oxytocin on feeding at any day following a single dose of oxytocin.
Bernal et al. (2013)	Differential lasting inhibitory effects of oxytocin and food-deprivation on mediobasal hypothalamic polydipsia; Experiment 1, food-deprived condition	OT (n = 8) PL (n = 8)	Healthy	Between-subjects	22µg	9 days	Subcutaneously injected	Rats	Male	Chow	No significant effect of oxytocin on feeding at any day following a single dose of oxytocin.

Bernal et al. (2013)	Differential lasting inhibitory effects of oxytocin and food-deprivation on mediobasal hypothalamic polydipsia; Experiment 2	OT (n = 7) PL (n = 7)	Healthy	Between-subjects	44µg	6 hours	Subcutaneously injected	Rats	Male	Chow	No significant effect of oxytocin on feeding at any day following single dose of oxytocin.
Bjorkstrand and Uvnas-Moberg (1996)	Central oxytocin increases food intake and daily weight gain in rats; long-term effects, female rats	OT (n = 10) PL (n = 10)	Healthy	Between-subjects	µg	24 hours	Intracerebroventricular injection	Rats	Female	Chow	Oxytocin significantly increased food intake compared to vehicle.
Bjorkstrand and Uvnas-Moberg (1996)	Central oxytocin increases food intake and daily weight gain in rats; long-term effects, male rats	OT (n = 10) PL (n = 10)	Healthy	Between-subjects	µg	24 hours	Intracerebroventricular injection	Rats	Male	Chow	No significant effect of oxytocin on feeding.
Bjorkstrand and Uvnas-Moberg (1996)	Central oxytocin increases food intake and daily weight gain in rats; fasted condition	OT (n = 5) PL (n = 5)	Healthy	Between-subjects	µg	72 hours	Intracerebroventricular injection	Rats	Female	Chow	Oxytocin significantly increased food intake compared to vehicle.
Bjorkstrand and Uvnas-Moberg (1996)	Central oxytocin increases food intake and daily weight gain in rats; effects of three doses	OT 1µg (n = 10) OT 5µg (n = 11) OT 10µg (n = 4)	Healthy	Between-subjects	1µg; 5µg; 10µg	24 hours	Intracerebroventricular injection	Rats	Female	Chow	The 5µg dose of oxytocin significantly increased feeding. No significant effects of oxytocin at

		PL (n = 10)									1µg or 10µg doses.
Bjorkstrand and Uvnas-Moberg (1996)	Central oxytocin increases food intake and daily weight gain in rats; Effects of IP injections of oxytocin	OT (n = 6) PL (n = 6)	Healthy	Between-subjects	5µg	24 hours	Intraperitoneal injection	Rats	Female	Chow	No significant effect of oxytocin on feeding.
Bjorkstrand and Uvnas-Moberg (1996)	Central oxytocin increases food intake and daily weight gain in rats; Experiment 6, fed condition	OT (n = 12) PL (n = 12)	Healthy	Between-subjects	5µg	24 hours	Intracerebroventricular injection	Rats	Male and Female	Chow	No significant effect of oxytocin on feeding.
Borg and Ohlsson (2012)	Oxytocin prolongs the gastric emptying time in patients with diabetes mellitus and gastroparesis, but does not affect satiety or volume intake in patients with functional dyspepsia	OT (n = 12) PL (n = 12)	Diabetes/Gastric Paresis	Within-subjects	40mU/min	Until maximal satiety	Peripheral Infusion	Humans	Male and Female	Mixed macronutrient drink	No significant effect of oxytocin on drink consumption.
Borg et al. (2011)	Oxytocin reduces satiety scores without affecting the volume of nutrient intake or gastric emptying rate in healthy subjects	OT 20mU/min (n = 10) OT 40mU/min (n = 10) OT 80mU/min (n = 10)	Healthy	Within-subjects	20mU/min; 40mU/min; 80mU/min	Until maximal satiety	Peripheral infusion	Humans	Male and Female	Mixed macronutrient drink	No significant effect of oxytocin on drink consumption.

Burmester (2017)	Intranasal oxytocin reduces hedonic eating in satiated males; lunch experiment	OT (n = 20) PL (n = 20)	Healthy	Within-subjects	24IU	20 minutes	Intranasal spray	Humans	Male	Sandwich and crisps	Small reduction in quantity of lunch consumed in oxytocin condition.
Burmester (2017)	Intranasal oxytocin reduces hedonic eating in satiated males; snack experiment	OT (n = 20) PL (n = 20)	Healthy	Within-subjects	24IU	10 minutes	Intranasal spray	Humans	Male	Oat biscuits, crackers, and chocolate	Oxytocin significantly reduced consumption of crackers and chocolate, but not oat biscuits.
Diaz-Cabiale, Narvaez, Petersson, Uvnas-Moberg, and Fuxe (2000)	Oxytocin/alpha(2)-Adrenoceptor interactions in feeding responses	OT (n = 8) PL (n = 8)	Healthy	Within-subjects	1nmol	1320 minutes	Right lateral cerebral ventricle injection	Rats	Male	Chow	No significant effect of oxytocin on feeding at 30, 90, 240 or 1320 minutes.
Douglas et al. (2007)	Neuroendocrine mechanisms of change in food intake during pregnancy: A potential role for brain oxytocin; Pregnant condition	Not reported	Healthy	Not reported	1µg	12 hours	Intracerebroventricular injection	Rats	Female	Chow	No significant effect of oxytocin on feeding after one hour of measurement. Oxytocin significantly increased feeding over 12 hours.

Douglas et al. (2007)	Neuroendocrine mechanisms of change in food intake during pregnancy: A potential role for brain oxytocin; Virgin condition	Not reported	Healthy	Not reported	1µg	12 hours	Intracerebroventricular injection	Rats	Female	Chow	Oxytocin significantly decreased feeding after one hour of measurement. There was no effect of oxytocin on feeding over 12 hours.
K. Gulati and Ray (1995)	Effects of intrahypothalamic morphine and its interactions with oxytocin and vasopressin during food intake in rats; Table 1	OT (n = 6) PL (n = 10)	Healthy	Between-subjects	0.1µg	24 hours	Ventromedial hypothalamus injection	Rats	Male	Chow	No significant effect of oxytocin on feeding at 0-6 hour or 6-24 hour time points.
K. Gulati and Ray (1995)	Effects of intrahypothalamic morphine and its interactions with oxytocin and vasopressin during food intake in rats; Table 2	OT (n = 7) PL (n = 10)	Healthy	Between-subjects	0.1µg	24 hours	Lateral hypothalamus injection	Rats	Male	Chow	No effect of oxytocin on feeding at 0-6 hour or 6-24 hour time points.
Kavita Gulati, Ray, and Sharma (1991)	Effects of acute and chronic morphine on food intake in rats: Modulation by oxytocin and vasopressin	OT (n = 8) PL (n = 8)	Healthy	Between-subjects	10µg /kg	24 hours	Subcutaneous injection	Rats	Male	Chow	No significant effect of oxytocin on feeding at any time point.

K. Gulati, Ray, and Sharma (1992)	Effects of acute and chronic ketocyclazocine and its modulation by oxytocin or vasopressin on food intake in rats	Not reported	Healthy	Between-subjects	10µg /kg	18 hours	Subcutaneous injection	Rats	Male	Chow	No significant effect of oxytocin on feeding at any time point.
Herisson et al. (2016)	Oxytocin acting in the nucleus accumbens core decreases food intake; Deprivation-induced chow intake, AcbC injection	OT 0.3µg (n = 8-9) OT 1µg (n = 8-9) OT 3µg (n = 8-9) PL (n = 9)	Healthy	Between-subjects	0.3µg; 1µg; 3µg	4 hours	Injected into nucleus accumbens core	Rats	Male	Chow	The 1µg and 3µg doses of oxytocin significantly reduced feeding after 1 and 3 hours. The 0.3µg dose of oxytocin had no effect on feeding at 2 or 4 hours.
Herisson et al. (2016)	Oxytocin acting in the nucleus accumbens core decreases food intake; Sucrose solution consumption	OT 0.3µg (n = 12) OT 1µg (n = 12) OT 3µg (n = 12) PL (n = 12)	Healthy	Between-subjects	0.3µg; 1µg; 3µg	2 hours	Injected into nucleus accumbens core	Rats	Male	10% sucrose solution	The 1µg and 3µg doses of oxytocin significantly reduced sucrose consumption. The 0.1µg and 0.3µg doses of oxytocin had no effect

											on sucrose consumption.
Herisson et al. (2016)	Oxytocin acting in the nucleus accumbens core decreases food intake; Deprivation-induced chow intake, AcbSh injection	OT .3μg (n = 8) OT 1μg (n = 8) OT 3μg (n = 8) PL (n = 8)	Healthy	Between-subjects	0.3μg; 1μg; 3μg	2 hours	Injected into nucleus accumbens shell	Rats	Male	Chow	No significant effect of oxytocin on feeding at any dose.
Herisson et al. (2016)	Oxytocin acting in the nucleus accumbens core decreases food intake; Sucrose solution consumption, AcbSh injection	OT 0.3μg (n = 8) OT 1μg (n = 8) OT 3μg (n = 8) PL (n = 8)	Healthy	Between-subjects	.3μg; 1μg; 3μg	2 hours	Injected into nucleus accumbens shell	Rats	Male	10% sucrose solution	No significant effect of oxytocin on sucrose consumption at any dose.
Herisson et al. (2016)	Oxytocin acting in the nucleus accumbens core decreases food intake; Deprivation-induced chow intake, AcbC injection (Figure 2)	OT (n = 7) PL (n = 7)	Healthy	Between-subjects	1μg	4 hours	Injected into nucleus accumbens core	Rats	Male	Chow	Oxytocin significantly reduced food intake after 2 and 4 hours of measurement
Herisson et al. (2016)	Oxytocin acting in the nucleus accumbens core decreases food intake; Sucrose	OT (n = 7 or 8) PL (n = 7)	Healthy	Between-subjects	0.3μg	2 hours	Injected into nucleus accumbens core	Rats	Male	10% sucrose solution	Oxytocin significantly reduced sucrose consumption

	solution, AcbC injection (Figure 2)										compared to vehicle.
Herisson et al. (2016)	Oxytocin acting in the nucleus accumbens core decreases food intake; incomplete socialising condition	OT 1µg (n = 8 or 9 or 10) OT 3µg (n = 8) PL (n = 8 or 9 or 10)	Healthy	Between-subjects	1µg; 3µg	1 hour	Injected into nucleus accumbens core	Rats	Male	Chow	No significant effect of oxytocin on deprivation-induced chow intake.
Herisson et al. (2016)	Oxytocin acting in the nucleus accumbens core decreases food intake; incomplete socialising condition	OT0 0.03µg (n = 6) OT 0.1µg (n = 8) OT 0.3µg (n = 8) PL (n = 8)	Healthy	Between-subjects	0.03µg; 0.1µg; 0.3µg	2 hours	Injected into nucleus accumbens core	Rats	Male	10% sucrose solution	No significant effect of oxytocin on sucrose consumption.
J. M. Ho et al. (2014)	Hindbrain oxytocin receptors contribute to the effects of circulating oxytocin on food intake in male rats; Figure 1	OT (n = 12) PL (n = 12)	Healthy	Within-subjects	.5mg/kg	18 hours	Intraperitoneal injection	Rats	Male	Chow	Oxytocin reduced feeding over 30 minutes, but not at any later time point.
J. M. Ho et al. (2014)	Hindbrain oxytocin receptors contribute to the effects of circulating oxytocin on	OT (n = 7) PL (n = 7)	Healthy	Within-subjects	1µg /µL	30 minutes	4V injection	Rats	Male	Chow	Oxytocin significantly reduced food intake

	food intake in male rats; Figure 2A										compared to vehicle.
J. M. Ho et al. (2014)	Hindbrain oxytocin receptors contribute to the effects of circulating oxytocin on food intake in male rats; Figure 2B	OT (n = 9) PL (n = 9)	Healthy	Within-subjects	5mg/kg	30 minutes	Intraperitoneal injection	Rats	Male	Chow	Oxytocin significantly reduced food intake compared to vehicle.
J. M. Ho et al. (2014)	Hindbrain oxytocin receptors contribute to the effects of circulating oxytocin on food intake in male rats; Figure 2C	OT (n = 12) PL (n = 12)	Healthy	Within-subjects	5mg/kg	30 minutes	Intraperitoneal injection	Rats	Male	Chow	Oxytocin significantly reduced food intake compared to vehicle.
J. M. Ho et al. (2014)	Hindbrain oxytocin receptors contribute to the effects of circulating oxytocin on food intake in male rats; Figure 2D	OT (n = 9) PL (n = 9)	Healthy	Within-subjects	5mg/kg	30 minutes	Intraperitoneal injection	Rats	Male	Chow	Oxytocin significantly reduced food intake compared to vehicle.
J. M. Ho et al. (2014)	Hindbrain oxytocin receptors contribute to the effects of circulating oxytocin on food intake in male rats; Systemic administration of nonpenetrant OTr antagonist fails to block 4V OT-elicited hypophagia	OT (n = 8) PL (n = 8)	Healthy	Within-subjects	2µg /µL	30 minutes	4V injection	Rats	Male	Chow	Oxytocin significantly reduced food intake compared to vehicle.

J. M. Ho et al. (2014)	Hindbrain oxytocin receptors contribute to the effects of circulating oxytocin on food intake in male rats; Figure 6B	OT (n = 11) PL (n = 11)	Healthy	Within-subjects	5mg/kg	30 minutes	Intraperitoneal injection	Rats	Male	Chow	Oxytocin significantly reduced food intake compared to vehicle.
J. M. Ho et al. (2014)	Hindbrain oxytocin receptors contribute to the effects of circulating oxytocin on food intake in male rats; Figure 7A	OT (n = 6) PL (n = 6)	Healthy	Within-subjects	0.5mg/kg	30 minutes	Intraperitoneal injection	Rats	Male	Chow	Oxytocin significantly reduced food intake compared to vehicle.
J. M. Ho et al. (2014)	Hindbrain oxytocin receptors contribute to the effects of circulating oxytocin on food intake in male rats; Figure 7B	OT (n = 8) PL (n = 8)	Healthy	Within-subjects	0.5mg/kg	30 minutes	Intraperitoneal injection	Rats	Male	Chow	Oxytocin significantly reduced food intake compared to vehicle.
Ibragimov, Kadar, and Telegdy (1988)	Effects of neurohypophyseal hormones on food-reinforced classical conditioning in the rat; Figure 3, response acquisition test	Not reported	Healthy	Between-subjects	150mU/kg; 300mU/kg; 600mU/kg	30 minutes	Intraperitoneal injection	Rats	Male	Chow	No significant effect of oxytocin on feeding.
Ibragimov et al. (1988)	Effects of neurohypophyseal hormones on food-reinforced classical conditioning in the rat; Table 1, fasted condition	OT 300mU/kg (n = 10) OT 600mU/kg (n = 10)	Healthy	Between-subjects	300mU/kg; 600mU/kg; 1200mU/kg	30 minutes	Intraperitoneal injection	Rats	Male	Chow	No significant effect of oxytocin on feeding.

		OT 1200mU/kg (n =10) PL (n = 10)									
Iwasaki et al. (2015)	Peripheral oxytocin activates vagal afferent neurons to suppress feeding in normal and leptin-resistant mice: a route for ameliorating hyperphagia and obesity; Figure 1A	OT 200µg/kg (n = 8) OT 400µg/kg (n = 8) PL (n = 8)	Healthy	Between-subjects	200µg/kg; 400µg/kg	6 hours	Intraperitoneal injection	Mice	Male	Chow	Oxytocin significantly reduced feeding at 30 minutes, 1hr, 3hr, and 6hr compared to vehicle. This was true for both doses.
Iwasaki et al. (2015)	Peripheral oxytocin activates vagal afferent neurons to suppress feeding in normal and leptin-resistant mice: a route for ameliorating hyperphagia and obesity; Figure 1C	OT (n = 6) PL (N = 6)	Healthy	Between-subjects	200µg/kg	6 hours	Intraperitoneal injection	Mice	Male	Liquid diet	Oxytocin significantly reduced liquid diet intake at 30 minutes and 1hr, but not 3hr or 6hr time points.
Iwasaki et al. (2015)	Peripheral oxytocin activates vagal afferent neurons to suppress feeding in normal and leptin-resistant mice: a route for ameliorating	OT (n = 6) PL (N = 6)	Obese diabetic db/db mice	Between-subjects	200µg/kg	6 hours	Intraperitoneal injection	Mice	Male	Chow	Oxytocin significantly reduced feeding at 30 minutes, 1hr, and 3hr, but not 6hr time points.

hyperphagia and obesity; Figure 6A											
Jonaidi, Oloumi, and Denbow (2003)	Behavioral effects of intracerebroventricular injection of oxytocin in birds	OT 5µg (n = 7) OT 10µg (n = 7) PL (n = 7)	Healthy	Between-subjects	5µg; 10µg	1 hour	Intracerebroventricular injection	Cockereels	Male and Female	Food	Oxytocin significantly reduced feeding at the 10µg dose at 15min, 30min, 45min, and 60min time points. The 5µg dose decreased feeding at the 30min and 60min time points.
Y.-R. Kim, J.-S. Eom, et al. (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; Juice experiment	OT (n = 33) PL (n = 33)	Healthy	Within-subjects	40 IU	20 minutes	Intranasal spray	Humans	Female	Juice	No significant effect of oxytocin on juice intake.
Y.-R. Kim, J.-S. Eom, et al. (2015)	The impact of oxytocin on food intake and emotion recognition in patients with eating disorders: A double blind single dose within- subject cross-	OT (n = 35) PL (n = 35)	Anorexia nervosa	Within-subjects	40 IU	20 minutes	Intranasal spray	Humans	Female	Juice	No significant effect of oxytocin on juice intake.

over design; Juice experiment											
Y.-R. Kim, J.-S. Eom, et al. (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; Juice experiment	OT (n = 34) PL (n = 34)	Bulimia nervosa	Within-subjects	40 IU	20 minutes	Intranasal spray	Humans	Female	Juice	No significant effect of oxytocin on juice intake.
Y.-R. Kim, J.-S. Eom, et al. (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; Food diary experiment	OT (n = 33) PL (n = 33)	Healthy	Within-subjects	40 IU	24 hours	Intranasal spray	Humans	Female	Normal food environment	No significant effect of oxytocin on caloric intake.
Y.-R. Kim, J.-S. Eom, et al. (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; Food diary experiment	OT (n = 35) PL (n = 35)	Anorexia nervosa	Within-subjects	40 IU	24 hours	Intranasal spray	Humans	Female	Normal food environment	No significant effect of oxytocin on caloric intake.
Y.-R. Kim, J.-S. Eom, et al. (2015)	The impact of oxytocin on food intake and emotion recognition in patients with eating disorders: A double	OT (n = 34) PL (n = 34)	Bulimia nervosa	Within-subjects	40 IU	24 hours	Intranasal spray	Humans	Female	Normal food environment	Oxytocin significantly reduced

	blind single dose within- subject cross- over design; Food diary experiment										caloric intake over 24 hours.
Kim, Kim, Cardi, et al. (2014)	Intranasal oxytocin attenuates attentional bias for eating and fat shape stimuli in patients with anorexia nervosa	OT (n = 33) PL (n = 33)	Healthy	Within- subjects	40 IU	Until maximal satiety	Intranasal spray	Humans	Female	Juice	No significant effect of oxytocin on juice intake.
Kim, Kim, Cardi, et al. (2014)	Intranasal oxytocin attenuates attentional bias for eating and fat shape stimuli in patients with anorexia nervosa	OT (n = 31) PL (n = 31)	Anorexia nervosa	Within- subjects	40 IU	Until maximal satiety	Intranasal spray	Humans	Female	Juice	No significant effect of oxytocin on juice intake.
Klockars et al. (2017)	Intravenous administration of oxytocin in rats acutely decreases deprivation-induced chow intake, but it fails to affect consumption of palatable solutions; Deprivation-induced feeding experiment, chow	OT 0.03µg /kg (n = 8- 9) OT 0.1µg /kg (n = 8- 9) OT 0.3µg /kg (n = 8- 9) PL (n = 8-9)	Healthy	Between- subjects	0.03µg/kg; 0.1µg/kg; 0.3µg/kg	24 hours	Intravenous injection	Rats	Male	Chow	The 0.1µg/kg and 0.3µg/kg doses of oxytocin reduced feeding after 1 and 2 hours of measurement . There was no significant effect for the 0.03µg /kg dose. or for any dose There was not a significant effect of

											oxytocin at any dose after 24 hours of measurement
Klockars et al. (2017)	Intravenous administration of oxytocin in rats acutely decreases deprivation-induced chow intake, but it fails to affect consumption of palatable solutions; Deprivation-induced feeding experiment, chow	OT (n = 7-8) PL (n = 7-8)	Healthy	Between-subjects	0.1µg /kg	2 hours	Intravenous injection	Rats	Male	4.1% Intralipid solution	No significant effect of oxytocin on Intralipid consumption.

Klockars et al. (2017)	Intravenous administration of oxytocin in rats acutely decreases deprivation-induced chow intake, but it fails to affect consumption of palatable solutions; Episodic feeding experiment, Sucrose solution	OT (n = 11-12) PL (n = 11-12)	Healthy	Between-subjects	0.1µg/kg	2 hours	Intravenous injection	Rats	Male	10% sucrose solution	No significant effect of oxytocin on sucrose consumption.
Klockars et al. (2017)	Intravenous administration of oxytocin in rats acutely decreases deprivation-induced chow intake, but it fails to affect consumption of palatable solutions; Episodic feeding experiment, Sucrose-saccharine solution	OT (n = 10) PL (n = 10)	Healthy	Between-subjects	0.1µg/kg	2 hours	Intravenous injection	Rats	Male	0.1% saccharin-10% sucrose solution	No significant effect of oxytocin on saccharin-sucrose solution consumption.

Klockars et al. (2017)	Intravenous administration of oxytocin in rats acutely decreases deprivation-induced chow intake, but it fails to affect consumption of palatable solutions; Episodic feeding experiment, Sucrose solution, high-dose	OT (n = 7) PL (n = 7)	Healthy	Between-subjects	0.3µg/kg	2 hours	Intravenous injection	Rats	Male	10% sucrose solution	No significant effect of oxytocin on sucrose consumption.
Klockars et al. (2017)	Intravenous administration of oxytocin in rats acutely decreases deprivation-induced chow intake, but it fails to affect consumption of palatable solutions; Refeeding experiment, Chow	Not reported	Healthy	Within-subjects	0.1µg/kg; 0.3µg/kg	2 hours	Intravenous injection	Rats	Male	Chow	Oxytocin significantly reduced food intake compared to vehicle.

Klockars et al. (2017)	Intravenous administration of oxytocin in rats acutely decreases deprivation-induced chow intake, but it fails to affect consumption of palatable solutions; Refeeding experiment, Sucrose	Not reported	Healthy	Within-subjects	0.1µg /kg; 0.3µg /kg	24 hours	Intravenous injection	Rats	Male	10% sucrose solution	No significant effect of oxytocin on sucrose consumption.
Klockars et al. (2017)	Intravenous administration of oxytocin in rats acutely decreases deprivation-induced chow intake, but it fails to affect consumption of palatable solutions; Concurrent sucrose and Intralipid presentation	OT (n = 8) PL (n = 8)	Healthy	Between-subjects	0.1µg/kg	2 hours	Intravenous injection	Rats	Male	10% sucrose solution and 4.1% Intralipid solution	No significant effect of oxytocin on consumption of either solution, or preference for either solution.
Kublaoui, Gemelli, Tolson, Wang, and Zinn (2008)	Oxytocin deficiency mediates hyperphagic obesity of Sim1 haploinsufficient mice	OT 50ng (n = 9)	Healthy	Between-subjects	50ng; 250ng; 1µg	6 hours	Intracerebroventricular injection	Mice	Female	Chow	No significant effect of oxytocin on food intake at 2hr, 4hr, or

		OT 250ng (n = 9)									6hr of measurement
		OT 1µg (n = 9)									
		PL (n = 9)									
Lawson et al. (2015)	Oxytocin Reduces Caloric Intake in Men	OT (n = 25) PL (N = 25)	Healthy	Within- subjects	24 IU	30 minutes	Intranasal spray	Humans	Male	Breakfast Buffet	Oxytocin significantly reduced caloric intake.
Leppanen, Cardi, et al. (2017a)	The effects of intranasal oxytocin on smoothie intake, cortisol and attentional bias in anorexia nervosa	OT (n = 29)	Healthy	Within- subjects	40 IU	15 minutes	Intranasal spray	Humans	Female	Smoothie	No significant effect of oxytocin on smoothie intake.
Leppanen, Cardi, et al. (2017a)	The effects of intranasal oxytocin on smoothie intake, cortisol and attentional bias in anorexia nervosa	OT (n = 30)	Anorexia nervosa	Within- subjects	40 IU	15 minutes	Intranasal spray	Humans	Female	Smoothie	No significant effect of oxytocin on smoothie intake.
Lokrantz et al. (1997)	Effects of central oxytocin administration on intraoral intake of glucose in deprived and nondeprived rats; Experiment 1 (fed condition), first intake test	OT (n = 8) PL (n = 8)	Healthy	Within- subjects	20nmol	Until solution rejected	Intracerebroventricul ar injection	Rats	Male	12.5% Glucose solution	No significant effect of oxytocin on glucose consumption.

Lokrantz et al. (1997)	Effects of central oxytocin administration on intraoral intake of glucose in deprived and nondeprived rats; Experiment 2 (deprived condition), first intake test	OT 5nmol (n = 8) OT 10nmol (n = 8) OT 20nmol (n = 8) PL (n = 8)	Healthy	Within-subjects	5nmol; 10nmol; 20nmol	Until solution rejected	Intracerebroventricular injection	Rats	Male	12.5% Glucose solution	Oxytocin at doses of 10nmol and 20nmol significantly reduced glucose consumption. Oxytocin at the 5nmol dose had no significant effect.
Lokrantz et al. (1997)	Effects of central oxytocin administration on intraoral intake of glucose in deprived and nondeprived rats; Experiment 3 (deprived condition)	OT (n = 8) PL (n = 8)	Healthy	Within-subjects	20nmol	Until solution rejected	Intracerebroventricular injection	Rats	Male	12.5% Glucose solution	Oxytocin significantly reduced glucose consumption.
Maejima et al. (2011)	Peripheral oxytocin treatment ameliorates obesity by reducing food intake and visceral fat mass; Figure 1A	OT 200µg/kg (n = 5) OT 400µg/kg (n = 5) PL (N = 5)	Healthy	Between-subjects	200µg/kg; 400µg/kg	24 hours	Intraperitoneal injection	Mice	Male	Chow	Oxytocin significantly reduced feeding at 30 minutes, 1hr, 2hr, 3hr, and 6hr at both doses. This effect was no longer significant after 24 hours.

Maejima et al. (2011)	Peripheral oxytocin treatment ameliorates obesity by reducing food intake and visceral fat mass; Figure 2A	OT (n = 5) PL (n = 5)	Healthy	Between-subjects	1600µg/kg	24 hours	Subcutaneous injection	Mice	Male	Chow	Oxytocin significantly reduced feeding at 30 minutes, 1hr, 2hr, 3hr, and 6hr. This effect was no longer significant after 24 hours
Maejima et al. (2011)	Peripheral oxytocin treatment ameliorates obesity by reducing food intake and visceral fat mass; Figure 2B	OT (n = 5) PL (n = 5)	Obese	Between-subjects	1600µg/kg	24 hours	Subcutaneous injection	Mice	Male	High-fat chow	Oxytocin significantly reduced feeding at 30 minutes, 1hr, 2hr, 3hr, 6hr, and 24hr.
Maejima et al. (2015)	Nasal oxytocin administration reduces food intake without affecting locomotor activity and glycemia with c-Fos induction in limited brain areas; Figure 1a-c	OT 0.1µg (n = 8 or 9) OT 1µg (n = 8-9) OT 10µg (n = 12-13) PL (n = 8 or 9)	Healthy	Within-subjects	0.1µg; 1µg; 10µg	24 hours	Intranasal administration	Mice	Male	Chow	Oxytocin significantly reduced feeding at the 6hr and 24hr time points at the 1µg dose, and at the 30 minute, 1hr, 2hr, 6hr, and 24hr time points at the 10µg dose. No significant effect of oxytocin on

												feeding at the 0.1µg dose.
Maejima et al. (2015)	Nasal oxytocin administration reduces food intake without affecting locomotor activity and glycemia with c-Fos induction in limited brain areas; Figure 1d-e	OT 40µg /kg (n = 4) OT 400µg /kg (n = 4) PL (n =4)	Healthy	Within-subjects	40µg /kg; 400µg /kg	24 hours	Intraperitoneal injection	Mice	Male	Chow	Oxytocin reduced feeding after 30 minutes, 1hr, 2hr, and 6hr (but not 24hr) at the 400µg /kg dose. No significant effect of oxytocin on feeding at the 40µg /kg dose.	
Maejima et al. (2014)	Oxytocinergic circuit from paraventricular and supraoptic nuclei to arcuate POMC neurons in hypothalamus	OT (n = 10) PL (n = 10)	Healthy	Between-subjects	4nmol	6 hours	Lateral ventricle injection	Rats	Male	Chow	Oxytocin significantly reduced food intake after 1hr, 3hr, and 6hr.	
Maejima et al. (2014)	Oxytocinergic circuit from paraventricular and supraoptic nuclei to arcuate POMC neurons in hypothalamus	OT (n = 8) PL (n = 8)	Healthy	Between-subjects	0.4nmol	24 hours	Arcuate nucleus injection	Rats	Male	Chow	Oxytocin significantly reduced food intake at 1hr and 12hr time points, but not 2hr, 3hr, and 24hr time points.	

Maejima et al. (2009)	Nesfatin-1-regulated oxytocinergic signaling in the paraventricular nucleus causes anorexia through a leptin-independent melanocortin pathway	OT (n = 7-9) PL (n = 7-9)	Healthy	Between-subjects	4nmol	6 hours	3V injection	Rats	Male	Chow	Oxytocin significantly reduced food intake over 6 hours.
Maejima et al. (2009)	Nesfatin-1-regulated oxytocinergic signaling in the paraventricular nucleus causes anorexia through a leptin-independent melanocortin pathway	OT (n = 9-10) PL (n = 9-10)	Healthy	Between-subjects	4nmol	1 hour	3V injection	Rats	Male	Chow	Oxytocin significantly reduced food intake over 1 hour.
Morton et al. (2012)	Peripheral oxytocin suppresses food intake and causes weight loss in diet-induced obese rats; Low-fat diet condition	OT (n = 13) PL (n = 13)	Obese	Between-subjects	1µg	18 hours	3V injection	Rats	Male	Chow	Oxytocin significantly reduced feeding after 4hr and 18hr time points.
Morton et al. (2012)	Peripheral oxytocin suppresses food intake and causes weight loss in diet-induced obese rats	OT (n = 5-8) PL (n = 5-8)	Obese	Between-subjects	1µg	18 hours	3V injection	Rats	Male	High-fat chow	Oxytocin significantly reduced feeding after 4hr and 18hr time points.
Mullis et al. (2013)	Oxytocin action in the ventral tegmental area affects sucrose intake; Figure 1A	OT 0.3µg (n = 10) OT 1µg (n = 10)	Healthy	Within-subjects	0.3µg; 1µg; 3µg	30 minutes	Injected into ventral tegmental area	Rats	Male	10% Sucrose solution	The 1µg and 3µg doses significantly reduced sucrose consumption.

		OT 3 μ g (n = 10) PL (n = 10)									The 0.3 μ g dose of oxytocin had no significant effect on sucrose consumption.
Mullis et al. (2013)	Oxytocin action in the ventral tegmental area affects sucrose intake; Figure 3A	OT (n = 7) PL (n = 7)	Healthy	Within-subjects	1 μ g	30 minutes	Injected into ventral tegmental area	Rats	Male	10% Sucrose solution	Oxytocin significantly reduced sucrose consumption.
Noble et al. (2014)	Oxytocin in the ventromedial hypothalamic nucleus reduces feeding and acutely increases energy expenditure; Experiment 1	OT 0.1nmol (n = 11) OT 0.5nmol (n = 11) OT 1nmol (n = 11) PL (n = 11)	Healthy	Within-subjects	0.1nmol; 0.5nmol; 1nmol	1 hour	Injected into ventromedial hypothalamus	Rats	Male	Chow	Oxytocin significantly reduced feeding at all doses at the 3hr and 4hr time points. The 0.5nmol and 1nmol doses reduced feeding after 1hr, and the 0.1nmol dose reduced feeding after 2hr.
Noble et al. (2014)	Oxytocin in the ventromedial hypothalamic nucleus reduces feeding and acutely increases	OT 0.1nmol (n = 10) OT 1nmol (n = 10)	Healthy	Within-subjects	0.1nmol; 1nmol	24 hours	Injected into ventromedial hypothalamus	Rats	Male	Chow	Oxytocin reduced feeding at both doses at the 1hr and

	energy expenditure; Experiment 2	PL (n = 10)										4hr time points. The 1nmol dose also reduced feeding after 2hr.
Noble et al. (2014)	Oxytocin in the ventromedial hypothalamic nucleus reduces feeding and acutely increases energy expenditure; Experiment 3	OT (n = 8) PL (n = 8)	Healthy	Within-subjects	1nmol	12 hours	Injected into ventromedial hypothalamus	Rats	Male	Chow	Oxytocin significantly reduced food intake.	
Olson, Drutarosky, Chow, et al. (1991)	Oxytocin and an oxytocin agonist administered centrally decrease food intake in rats	OT 0.5nmol (n = 4-12) OT 1nmol (n = 4-12) OT 2nmol (n = 4-12) OT 4nmol (n = 4-12) PL (n = 4-12)	Healthy	Within-subjects	0.5nmol; 1nmol; 2nmol; 4nmol	1 hour	Intracerebroventricular injection	Rats	Male	Chow	Oxytocin significantly reduced feeding at all doses.	
Olszewski, Klockars, Klockars, and Levine (2016)	Central oxytocin receptor stimulation attenuates the orexigenic effects of butorphanol tartrate; Experiment 2, lateral ventricle injection	OT 0.1µg (n = 7-9) OT 0.3µg (n = 7-9)	Healthy	Within-subjects	0.1µg; 0.3µg; 1µg	1 hour	Lateral ventricle injection	Rats	Male	Chow	The 1µg dose of oxytocin significantly reduced feeding after 1hr, but not 2 or 4hr of measurement	

		OT 1µg (n = 7-9)											. The 0.1µg and 0.3µg doses had no effect on feeding.
		PL (n = 7-9)											
Olszewski, Klockars, et al. (2016)	Central oxytocin receptor stimulation attenuates the orexigenic effects of butorphanol tartrate; Experiment 2, 4V injection	OT 0.1µg (n = 7-9) OT 0.3µg (n = 7-9) OT 1µg (n = 7-9) PL (n = 7-9)	Healthy	Within-subjects	0.1µg; 0.3µg; 1µg	2 hours	4V injection	Rats	Male	Chow			The 1µg dose of oxytocin significantly reduced feeding after 1hr, but not 2 or 4hr of measurement . The 0.1µg and 0.3µg doses had no effect on feeding.
Ong et al. (2015)	Medial nucleus tractus solitarius oxytocin receptor signaling and food intake control: the role of gastrointestinal satiation signal processing; Experiment 1	OT 1µg (n = 12) OT 3µg (n = 12) OT 6µg (n = 12) OT 12µg (n = 12) PL (n = 12)	Healthy	Within-subjects	1µg; 3µg; 6µg; 12µg	24 hours	4V injection	Rats	Male	Chow			Oxytocin significantly reduced feeding after 30 minutes at the 1µg, 3µg, 6µg, and 12µg doses. The 12µg dose continued to suppress feeding after 1hr. The 1µg dose of oxytocin had

											no effect on feeding.
Ong et al. (2015)	Medial nucleus tractus solitarius oxytocin receptor signaling and food intake control: the role of gastrointestinal satiation signal processing; Experiment 2	OT 0.3µg (n = 12) OT 1µg (n = 12) PL (n = 12)	Healthy	Within-subjects	0.3µg; 1µg	24 hours	Injected into NTS	Rats	Male	Chow	The 1µg dose of oxytocin reduced feeding over 30 minutes. This effect did not continue to 1hr or 2hr of measurement. The 0.3µg dose of oxytocin had no effect on feeding.
Ong et al. (2015)	Medial nucleus tractus solitarius oxytocin receptor signaling and food intake control: the role of gastrointestinal satiation signal processing; Experiment 3	OT (n = 13) PL (n = 13)	Healthy	Within-subjects	3µg	2 hours	4V injection	Rats	Male	Chow	Oxytocin significantly reduced feeding after 30 minutes and 1hr, but not 2hr.
Ong et al. (2015)	Medial nucleus tractus solitarius oxytocin receptor signaling and food intake control: the role of gastrointestinal satiation signal	OT (n = 14) PL (n = 14)	Healthy	Within-subjects	1µg	1.5 hours	4V injection	Rats	Male	Chow	Oxytocin reduced feeding after 30 minutes only when a dietary preload was provided. This

	processing; Experiment 4										effect did not continue to 1hr or 1.5hr time points.
Ong et al. (2015)	Medial nucleus tractus solitarius oxytocin receptor signaling and food intake control: the role of gastrointestinal satiating signal processing; Experiment 4	OT (n = 14) PL (n = 14)	Healthy	Within- subjects	0.3µg	1.5 hours	Injected into NTS	Rats	Male	Chow	Oxytocin significantly reduced feeding in both preload and no- preload conditions after 30 minutes. This was also true for the preload condition after 1.5hr.
Ott et al. (2013)	Oxytocin reduces reward-driven food intake in humans; Fasted condition	OT (n = 20) PL (n = 20)	Healthy	Within- subjects	24 IU	30 minutes	Intranasal spray	Humans	Male	Breakfast buffet	No significant effect of oxytocin on feeding.
Ott et al. (2013)	Oxytocin reduces reward-driven food intake in humans; Fed condition	OT (n = 20) PL (n = 20)	Healthy	Within- subjects	24 IU	30 minutes	Intranasal spray	Humans	Male	Variety of snack foods	Oxytocin significantly reduced snack intake compared to placebo.
Plamondon and Merali (1997)	Anorectic action of bombesin requires receptor for corticotropin-releasing	OT (n = 7- 8) PL (n = 7-8)	Healthy	Within- subjects	10µg	4 hours	Intracerebroventricul ar injection	Rats	Male	Chow	Oxytocin significantly reduced food intake for 1hr, but not at the

	factor but not for oxytocin										2 and 4hr time points.
Saito et al. (2017)	Involvement of central nesfatin-1 neurons on oxytocin-induced feeding suppression in rats	OT (n = 6) PL (n = 6)	Healthy	Between-subjects	500µg /kg	24 hours	Intraperitoneal injection	Rats	Male	Chow	Oxytocin significantly reduced feeding for 0.5-5 hours.
Thienel et al. (2016)	Oxytocin's inhibitory effect on food intake is stronger in obese than normal-weight men; Fasted condition	OT (n = 18) PL (n = 18)	Obese	Within-subjects	24IU	30 minutes	Intranasal spray	Humans	Male	Breakfast buffet	Oxytocin significantly reduced food consumption compared to placebo.
Thienel et al. (2016)	Oxytocin's inhibitory effect on food intake is stronger in obese than normal-weight men; Fed condition	OT (n = 18) PL (n = 18)	Obese	Within-subjects	24IU	10 minutes	Intranasal spray	Humans	Male	Variety of snack foods	Oxytocin significantly reduced snack intake compared to placebo.
van Miert and van Duin (1991)	Feed intake and rumen motility in dwarf goats. Effects of some alpha 2-adrenergic agonists, prostaglandins and posterior pituitary hormones	OT (n = 8) PL (n = 8)	healthy	Within-subjects	0.01IU	210 minutes	Intravenous infusion	Dwarf goats	Females and castrated males	Usual feed	No significant effect of oxytocin on feeding after 30 minutes, or in the 180-210 minute measurement periods.
Verte, McFarlane, McGregor, and Mallet (2004)	Evidence for an interaction between CB1 cannabinoid and oxytocin receptors in food and water intake	OT 0.1IU (n = 8)	Healthy	Within-subjects	0.1IU; 1IU; 10IU	2 hours	Lateral ventricle injection	Rats	Male	Chow	The 1IU and 10IU doses significantly decreased feeding after

		OT 1IU (n = 8) OT 10IU (n = 8) PL (n = 8)									60 minutes and 2 hours. The 0.1IU dose had no significant effect on feeding.
Warren et al. (2015)	Effects on intranasal oxytocin on satiety signaling in people with schizophrenia	OT (n = 16) PL (n = 16)	Schizophrenia	Within-subjects	24IU	Not reported	Intranasal spray	Humans	Male and Female	Test meal	Oxytocin had no effect on consumption of the test meal.
Yayou, Kitagawa, Ito, Kasuya, and Sutoh (2011)	Effect of oxytocin, prolactin-releasing peptide, or corticotropin-releasing hormone on feeding behavior in steers	OT 5µg (n = 6) OT 50µg (n = 6) PL (n = 6)	Healthy	Between-subjects	5µg; 50µg	1 hour	Intracerebroventricular injection	Steers	Male	Usual feed	No significant effect of oxytocin on feeding.
Guo Zhang et al. (2011)	Neuropeptide exocytosis involving synaptotagmin-4 and oxytocin in hypothalamic programming of body weight and energy balance	OT (n = 11) PL (n = 11)	Healthy	Between-subjects	4µg	4 hours	3V injection	Mice	Not reported	Chow	Oxytocin significantly reduced feeding compared to vehicle.
L. Zhou et al. (2015)	Oxytocin differentially affects sucrose taking and seeking in male and female rats	OT 0.3mg/kg (n = 9-10) OT 1mg/kg (n = 9-10)	Healthy	Within-subjects	0.3mg/kg/ 1mg/kg; 3mg/kg	2 hours	Intraperitoneal injection	Rats	Male and Female	Sucrose pellets	The 0.3, 1, and 3mg/kg doses of oxytocin decreased sucrose consumption

OT 3mg/kg (n = 9-10)		in females, while only the 3mg/kg dose reduced sucrose consumption in males.
PL (n = 9- 10)		

Supplementary Table 5: Summary of Studies Administering Chronic Oxytocin

Author, Year	Study Title, Experiment Number	Sample Size	Diagnostic Status	Within-Subjects or Between-Subjects Design	Dose Administered	Route of Administration	Animal	Sex	Duration of Chronic Administration	Type of Food Consumed	Summary of Findings
Altirriba et al., 2014	Divergent effects of oxytocin treatment of obese diabetic mice on adiposity; Figure 1	OT (n = 14) PL (n = 17)	Ob/Ob	Between-subjects	50nmol/day	Subcutaneous injection	Mice	Male	14 days	Chow	Oxytocin significantly reduced food consumption each day during Week 1; and 3/7 days during Week 2.
Altirriba et al., 2014	Divergent effects of oxytocin treatment of obese diabetic mice on adiposity; Figure 1	OT (n = 12) PL (n = 13)	Healthy	Between-subjects	50nmol/day	Subcutaneous injection	Mice	Male	14 days	Chow	Oxytocin decreased food intake only during the first day.
Altirriba et al., 2014	Divergent effects of oxytocin treatment of obese diabetic mice on adiposity; Figure 2E	OT (n = 5) PL (n = 5)	Ob/Ob	Between-subjects	50nmol/day	Subcutaneous injection	Mice	Male	14 days	Chow	No significant effect of oxytocin on feeding.
Balazova et al., 2016	Metabolic effects of subchronic peripheral oxytocin administration in lean and obese Zucker rats	OT (n = 7) PL (n = 7)	Obese	Between-subjects	3.6µg/100g body weight/day	Subcutaneous injection	Rats	Male	14 days	Chow	Oxytocin significantly reduced cumulative 2-week food intake and daily food intake.
Balazova et al., 2016	Metabolic effects of subchronic peripheral oxytocin administration in lean and obese Zucker rats	OT (n = 7) PL (n = 7)	Healthy	Between-subjects	3.6µg/100g body weight/day	Subcutaneous injection	Rats	Male	14 days	Chow	Oxytocin significantly reduced cumulative 2-week food intake and daily food intake.

Beranger et al., 2014	Oxytocin reverses ovariectomy-induced osteopenia and body fat gain	OT (n = 12) PL (n = 12)	Ovariectomized	Between-subjects	1mg/kg/day	Intraperitoneal injection	Mice	Female	10 weeks	Chow	Oxytocin significantly reduced food intake by the 3 rd week of measurement. There were no significant differences at the end of week 10.
Bjorkstrand & Uvnas-Moberg, 1996 ; Experiment 2	Central oxytocin increases food intake and daily weight gain in rats	OT (n = 8) PL (n = 8)	Healthy	Between-subjects	5µg/day	Intracerebroventricular injection	Rats	Female	3 days	Chow	Oxytocin significantly increased cumulative 3-day food intake.
Blevins et al., 2015	Chronic oxytocin administration inhibits food intake, increases energy expenditure, and produces weight loss in fructose-fed obese rhesus monkeys; Low-dose chow experiment	OT (n = 5) PL (n = 5)	Healthy	Within-subjects	0.2mg/kg/day	Subcutaneous injection	Rhesus Monkey	Male	1 week	Chow	Oxytocin significantly reduced 12-hour food intake after 1 week chronic administration.
Blevins et al., 2015	Chronic oxytocin administration inhibits food intake, increases energy expenditure, and produces weight loss in fructose-fed obese rhesus monkeys; Low-dose Kool-Aid experiment	OT (n = 5) PL (n = 5)	Healthy	Within-subjects	0.2mg/kg/day	Subcutaneous injection	Rhesus Monkey	Male	2 weeks	Kool-Aid®	No significant effect of oxytocin on Kool-Aid® intake.
Blevins et al., 2015	Chronic oxytocin administration inhibits food intake, increases energy expenditure,	OT (n = 5) PL (n = 5)	Healthy	Within-subjects	0.4mg/kg/day	Subcutaneous injection	Rhesus Monkey	Male	1 week	Chow	Oxytocin significantly reduced 8-hour and 12-hour food intake

	and produces weight loss in fructose-fed obese rhesus monkeys; High-dose chow experiment										after 1 week chronic administration.
Blevins et al., 2015	Chronic oxytocin administration inhibits food intake, increases energy expenditure, and produces weight loss in fructose-fed obese rhesus monkeys; High-dose Kool-Aid® experiment	OT (n = 5) PL (n = 5)	Healthy	Within-subjects	0.4mg/kg/day	Subcutaneous injection	Rhesus Monkey	Male	2 weeks	Kool-Aid®	Oxytocin reduced 8-hour and 12-hour Kool-Aid® intake after 2 weeks of chronic administration.
Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by enhancing satiety responses and increasing lipid utilization; Study 1	OT (n = 9) PL (n = 8)	Healthy	Between-subjects	16nmol/day	3V injection	Rats	Male	26 days	Chow	No significant effect of oxytocin on feeding.
Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by enhancing satiety responses and increasing lipid utilization; Study 1	OT (n = 5) PL (n = 6)	Healthy	Between-subjects	16nmol/day	3V injection	Rats	Male	26 days	High-Fat Chow	Oxytocin reduced daily food intake on 10/26 days.
Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by	OT (n = 8) PL (n = 6)	Obese	Between-subjects	16nmol/day	3V injection	Rats	Male	26 days	High-Fat Chow	Oxytocin reduced cumulative food intake over 26-day period; and was

	enhancing satiety responses and increasing lipid utilization; Study 3											maintained during last week of study.
Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by enhancing satiety responses and increasing lipid utilization; Study 3	OT (n = 9) PL (n = 8)	Healthy	Between-subjects	16nmol/day	3V injection	Rats	Male	26 days	Chow	No significant effect of oxytocin on feeding.	
Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by enhancing satiety responses and increasing lipid utilization; Study 4	OT (n = 7) PL (n = 8)	Healthy	Between-subjects	16nmol/day	3V injection	Rats	Male	21 days	High-Fat Chow	Oxytocin reduced food intake on days 1-5, and again on days 9-12. These effects were no longer significant by the end of the 21-day administration period.	
Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by enhancing satiety responses and increasing lipid utilization; Study 4	OT (n = 7) PL (n = 8)	Healthy	Between-subjects	16nmol/day	3V injection	Rats	Male	21 days	Chow	No significant effect of oxytocin on feeding.	
Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by enhancing satiety responses and	OT (n = 10) PL (n = 8)	Healthy	Between-subjects	16nmol/day	3V injection	Rats	Male	28 days	High-Fat Chow Without Sucrose	Oxytocin significantly reduced cumulative food intake. This effect was maintained	

	increasing lipid utilization; Study 7										until the third week of administration.
Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by enhancing satiety responses and increasing lipid utilization; Study 9, 1µg	OT (n = 6) PL (n = 6)	Healthy	Between-subjects	1µg /day	Subcutaneous injection	Rats	Male	3 days	Chow	No significant effect of oxytocin on feeding.
Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by enhancing satiety responses and increasing lipid utilization; Study 9, 5µg	OT (n = 6) PL (n = 6)	Healthy	Between-subjects	5µg/day	Subcutaneous injection	Rats	Male	3 days	Chow	No significant effect of oxytocin on feeding.
Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by enhancing satiety responses and increasing lipid utilization; Study 9, 20µg	OT (n = 6) PL (n = 6)	Healthy	Between-subjects	20µg/day	Subcutaneous injection	Rats	Male	3 days	Chow	No significant effect of oxytocin on feeding.
Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by	OT (n = 8) PL (n = 8)	Healthy	Between-subjects	50µg/day	Subcutaneous injection	Rats	Male	3 days	Chow	No significant effect of oxytocin on feeding.

	enhancing satiety responses and increasing lipid utilization; Study 9, 50µg											
Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by enhancing satiety responses and increasing lipid utilization; Study 9, 100µg	OT (n = 9) PL (n = 8)	Healthy	Between-subjects	100µg/day	Subcutaneous injection	Rats	Male	3 days	Chow	No significant effect of oxytocin on feeding.	
Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by enhancing satiety responses and increasing lipid utilization; Study 9, 200µg	OT (n = 7) PL (n = 8)	Healthy	Between-subjects	200µg/day	Subcutaneous injection	Rats	Male	3 days	Chow	No significant effect of oxytocin on feeding.	
Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by enhancing satiety responses and increasing lipid utilization; Study 10, HFD Sep2013	OT (n = 3) PL (n = 3)	Healthy	Between-subjects	50µg/day	Subcutaneous injection	Rats	Male	12 days	High-Fat Chow	Non-significant trend for oxytocin group to consume less high-fat chow.	

Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by enhancing satiety responses and increasing lipid utilization; Study 10, HFD Oct2013	OT (n = 3) PL (n = 3)	Healthy	Between-subjects	50µg/day	Subcutaneous injection	Rats	Male	13 days	High-Fat Chow	No significant effect of oxytocin on feeding.
Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by enhancing satiety responses and increasing lipid utilization; Study 10, Chow Dec2013	OT (n = 3) PL (n = 3)	Healthy	Between-subjects	50µg/day	Subcutaneous injection	Rats	Male	13 days	Chow	No significant effect of oxytocin on feeding.
Blevins et al., 2016	Chronic CNS oxytocin signaling preferentially induces fat loss in high-fat diet-fed rats by enhancing satiety responses and increasing lipid utilization; Study 10, Chow Jan2014	OT (n = 3) PL (n = 3)	Healthy	Between-subjects	50µg/day	Subcutaneous injection	Rats	Male	13 days	Chow	No significant effect of oxytocin on feeding.
Deblon et al., 2011	Mechanisms of the anti-obesity effects of oxytocin in diet-induced obese rats; Low-dose study	OT (n = 6-7) PL (n = 6-7)	Obese	Between-subjects	1.6nmol/day	Intracerebroventricular injection	Rats	Male	14 days	High-Fat Chow	No significant effect of oxytocin on feeding.

Deblon et al., 2011	Mechanisms of the anti-obesity effects of oxytocin in diet-induced obese rats; High-dose study	OT (n = 6-7) PL (n = 6-7)	Obese	Between-subjects	16nmol/day	Intracerebroventricular injection	Rats	Male	14 days	High-Fat Chow	Oxytocin reduced cumulative food intake over the two-week measurement period.
Deblon et al., 2011	Mechanisms of the anti-obesity effects of oxytocin in diet-induced obese rats; Peripheral administration, lean	OT (n = 6-7) PL (n = 6-7)	Healthy	Between-subjects	50nmol/day	Subcutaneous injection	Rats	Male	14 days	High-Fat Chow	Oxytocin reduced cumulative food intake over the two-week measurement period.
Deblon et al., 2011	Mechanisms of the anti-obesity effects of oxytocin in diet-induced obese rats; Peripheral administration, obese	OT (n = 7-8) PL (n = 7-8)	Obese	Between-subjects	50nmol/day	Subcutaneous injection	Rats	Male	14 days	High-Fat Chow	Oxytocin reduced cumulative food intake over the two-week measurement period.
Grippe et al., 2009	Oxytocin protects against negative behavioral and autonomic consequences of long-term social isolation; Pair-fed experiment	OT (n = 8) PL (n = 7)	Healthy	Between-subjects	20µg/day	Subcutaneous injection	Prairie Voles	Female	14 days	Sucrose Solution	No significant effect of oxytocin on sucrose consumption.

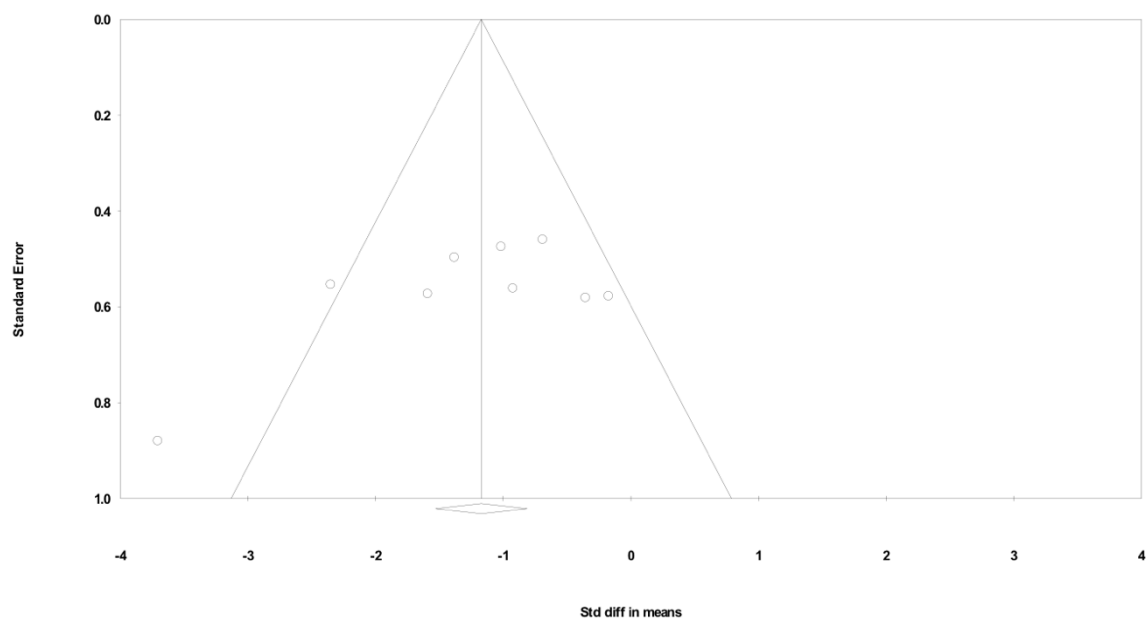
Grippe et al., 2009	Oxytocin protects against negative behavioral and autonomic consequences of long-term social isolation; Individually-housed experiment	OT (n = 8) PL (n = 8)	Healthy	Between-subjects	20µg/day	Subcutaneous injection	Prairie Voles	Female	14 days	Sucrose Solution	The vehicle group decreased food intake over time in comparison to baseline levels. This reduction was not observed in the oxytocin treatment group.
Gulati & Ray, 1995	Effects of intrahypothalamic morphine and its interactions with oxytocin and vasopressin during food intake in rats	OT (n = 7) PL (n = 10)	Healthy	Between-subjects	0.1µg/day	Lateral hypothalamus injection	Rats	Male	7 days	Chow	No significant effect of oxytocin on feeding.
Gulati & Ray, 1995	Effects of intrahypothalamic morphine and its interactions with oxytocin and vasopressin during food intake in rats	OT (n = 6) PL (n = 10)	Healthy	Between-subjects	0.1µg/day	Ventromedial hypothalamus injection	Rats	Male	7 days	Chow	No significant effect of oxytocin on feeding.
Gulati et al., 1991	Effects of acute and chronic morphine on food intake in rats: Modulation by oxytocin and vasopressin	OT (n = 7) PL (n = 7)	Healthy	Between-subjects	10µg/kg/day	Subcutaneous injection	Rats	Male	7 days	Chow	Chronic oxytocin treatment associated with greater food intake during light phase (before controlling for multiple comparisons). No significant differences during dark phase.

Iwasaki et al., 2015	Peripheral oxytocin activates vagal afferent neurons to suppress feeding in normal and leptin-resistant mice: a route for ameliorating hyperphagia and obesity	OT (n = 10) PL (n = 7)	Obese diabetic db/db mice	Between-subjects	1600µg/kg/day	Intraperitoneal injection	Mice	Male	12 days	Chow	Oxytocin significantly reduced food intake between days 2 and 12, compared to vehicle treatment.
Kublaoui et al., 2008	Oxytocin deficiency mediates hyperphagic obesity of Sim1 haploinsufficient mice	OT (n = 7) PL (n = 7)	Healthy	Between-subjects	20ng/day	Intracerebroventricular injection	Mice	Female	12 days	Chow	No significant effect of oxytocin on food intake in wild-type mice.
Ludri & Singh, 1987	Milk-production, dry-matter and water-consumption of crossbred cows milked with and without oxytocin	OT (n = 6) PL (n = 6)	Healthy	Between-subjects	30 IU/day	Intramuscular injection	Cows	Female	10 days	Lean feed	No significant effect of oxytocin on feeding.
Maejima et al., 2011	Peripheral oxytocin treatment ameliorates obesity by reducing food intake and visceral fat mass	OT (n = 5) PL (n = 5)	Obese	Between-subjects	1600µg/kg/day	Subcutaneous injection	Mice	Male	17 days	High-Fat Chow	Oxytocin reduced food intake up to day 6, but not beyond.
Maejima et al., 2011	Peripheral oxytocin treatment ameliorates obesity by reducing food intake and visceral fat mass	OT (n = 14) PL (n = 11)	Obese	Between-subjects	1600µg/kg/day	Subcutaneous injection	Mice	Male	17 days	High-Fat Chow	Oxytocin significantly reduced food intake on days 3 and 4 of administration, but not before or after.
Morton et al., 2012	Peripheral oxytocin suppresses food intake and causes weight loss	OT (n = 8) PL (n = 8)	Obese	Between-subjects	1000µg/kg/day	Peripheral injection	Rats	Male	7 days	High-Fat Chow	Oxytocin significantly reduced food intake on days 2, 3, 4, 6, and 7 of treatment,

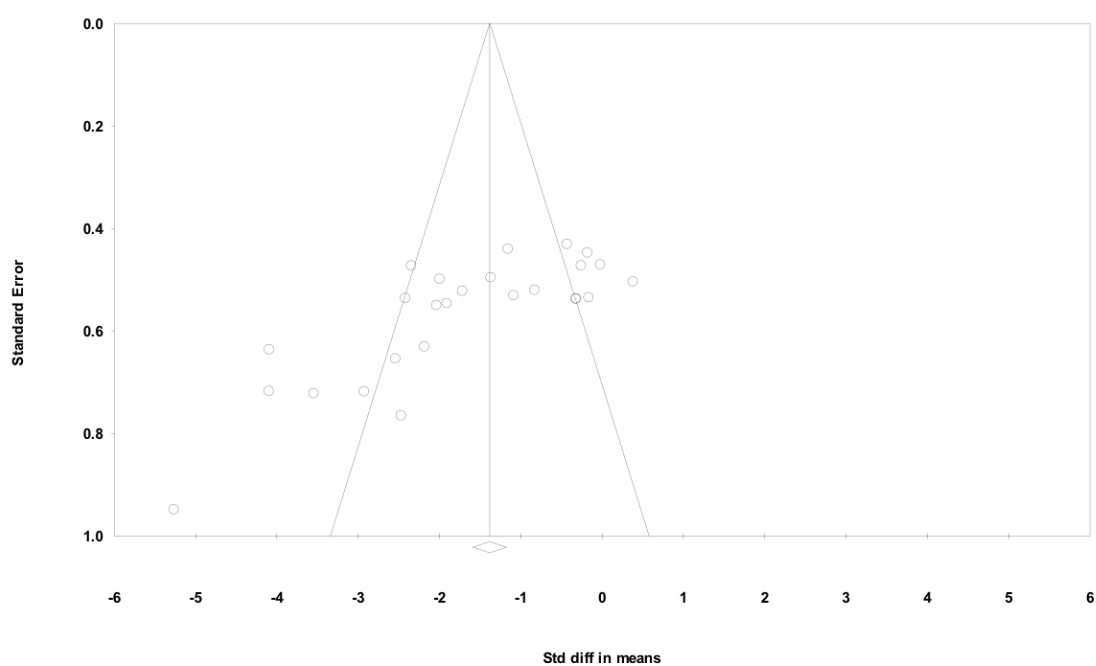
	in diet-induced obese rats										compare to vehicle treatment.
Roberts et al., 2017	Chronic hindbrain administration of oxytocin is sufficient to elicit weight loss in diet-induced obese rats; Study 1A, obese	OT (n = 18) PL (n = 17)	Diet-induced Obese	Between-subjects	16nmol/day	3V injection	Rats	Male	28 days	High-fat chow	Oxytocin significantly reduced feeding.
Roberts et al., 2017	Chronic hindbrain administration of oxytocin is sufficient to elicit weight loss in diet-induced obese rats; Study 1A, lean	OT (n = 6) PL (n = 7)	Healthy	Between-subjects	16nmol/day	3V injection	Rats	Male	28 days	Chow	No significant effect of oxytocin on feeding.
Roberts et al., 2017	Chronic hindbrain administration of oxytocin is sufficient to elicit weight loss in diet-induced obese rats; Study 2A, obese	OT (n = 12) PL (n = 7)	Diet-induced Obese	Between-subjects	16nmol/day	3V injection	Mice	Male	28 days	High-fat chow	Reduction in cumulative feeding over the first two weeks, but not beyond.
Roberts et al., 2017	Chronic hindbrain administration of oxytocin is sufficient to elicit weight loss in diet-induced obese rats; Study 2A, lean	OT (n = 9) PL (n = 9)	Healthy	Between-subjects	16nmol/day	3V injection	Mice	Male	28 days	Chow	No significant effect of oxytocin on feeding.
Roberts et al., 2017	Chronic hindbrain administration of oxytocin is sufficient to elicit weight loss in diet-induced obese rats; Study 3A, obese	OT (n = 12) PL (n = 15)	Diet-induced Obese	Between-subjects	16nmol/day	4V injection	Rats	Male	28 days	High-fat chow	Oxytocin significantly reduced feeding.

Roberts et al., 2017	Chronic hindbrain administration of oxytocin is sufficient to elicit weight loss in diet-induced obese rats; Study 3A, lean	OT (n = 7) PL (n = 11)	Healthy	Between-subjects	16nmol/day	4V injection	Rats	Male	28 days	Chow	No significant effect of oxytocin on feeding.
Roberts et al., 2017	Chronic hindbrain administration of oxytocin is sufficient to elicit weight loss in diet-induced obese rats; Study 4A	PL (n = 11) OT (n = 9)	Diet-induced Obese	Between-subjects	16nmol/day	4V injection	Rats	Male	28 days	High-fat chow	Oxytocin significantly reduced feeding.
Roberts et al., 2017	Chronic hindbrain administration of oxytocin is sufficient to elicit weight loss in diet-induced obese rats; DIO-prevention study (unpublished dataset)	OT 1.6nmol/day (n = 5) OT 16nmol/day n = 9 PL (n = 8)	Healthy	Between-subjects	1.6nmol/day; 16nmol/day	3V injection	Rats	Male	26 days	High-fat chow	No significant effect of oxytocin on feeding.
Uvnas-Moberg et al., 1996	Dissociation of Oxytocin Effects on Body Weight in Two Variants of Female Sprague-Dawley Rats	OT (n = 5) PL (- = 5)	Slow-growing	Between-subjects	1.5mg/kg/day	Subcutaneous injection	Rats	Female	5 days	Chow	No significant effect of oxytocin on feeding.
Uvnas-Moberg et al., 1996	Dissociation of Oxytocin Effects on Body Weight in Two Variants of Female Sprague-Dawley Rats	OT (n = 18) PL (- = 18)	Rapidly-growing	Between-subjects	1.0mg/kg/day	Subcutaneous injection	Rats	Female	4 days	Chow	Oxytocin significantly reduced food intake over four days, compared to vehicle treatment.

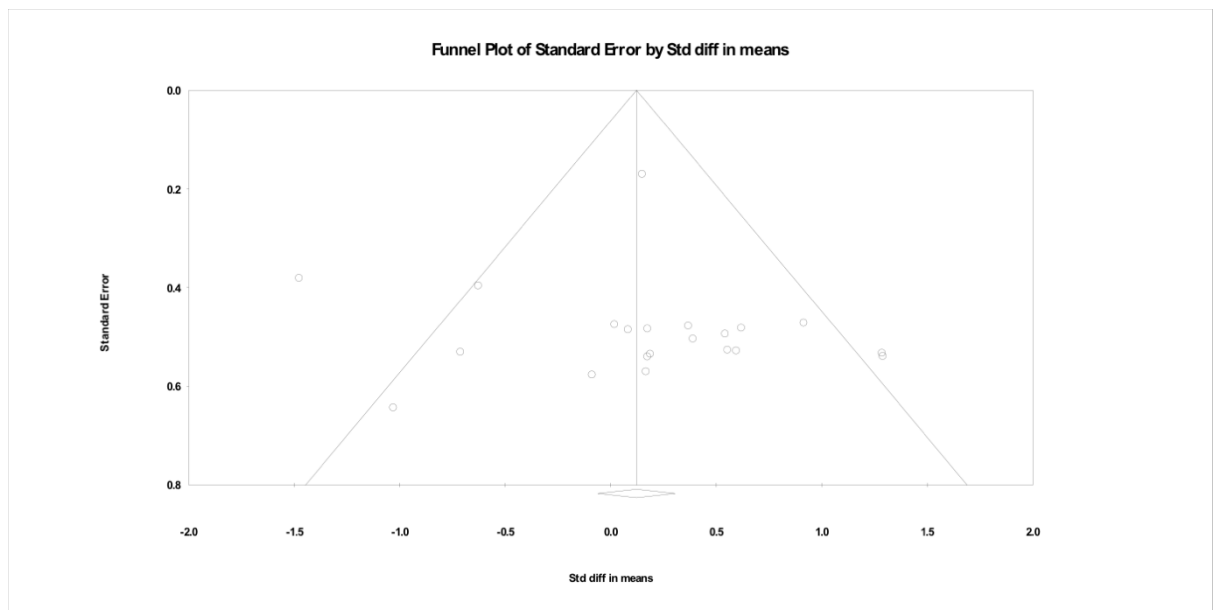
Zhang & Cai, 2011	Circadian intervention of obesity development via resting-stage feeding manipulation or oxytocin treatment; daytime injection	OT (n = 5 or 6) PL (n = 5 or 6)	Obese	Between-subjects	1µg/day	3V Injection	Mice	Male	7 days	High-Fat Chow	Oxytocin significantly reduced food intake over 7 days compared to vehicle treatment.
Zhang & Cai, 2011	Circadian intervention of obesity development via resting-stage feeding manipulation or oxytocin treatment; nighttime injection	OT (n = 5 or 6) PL (n = 5 or 6)	Obese	Between-subjects	1µg/day	3V Injection	Mice	Male	7 days	High-Fat Chow	Oxytocin significantly reduced food intake over 7 days compared to vehicle treatment.
Zhang & Cai, 2011	Circadian intervention of obesity development via resting-stage feeding manipulation or oxytocin treatment	OT (n = 5 or 6 or 7) PL (n = 5 or 6 or 7)	Obese	Between-subjects	1µg/day	Intraperitoneal injection	Mice	Male	6 weeks	High-Fat Chow	Oxytocin significantly reduced food intake in weeks 4, 5, and 6. There were no significant differences in earlier weeks.



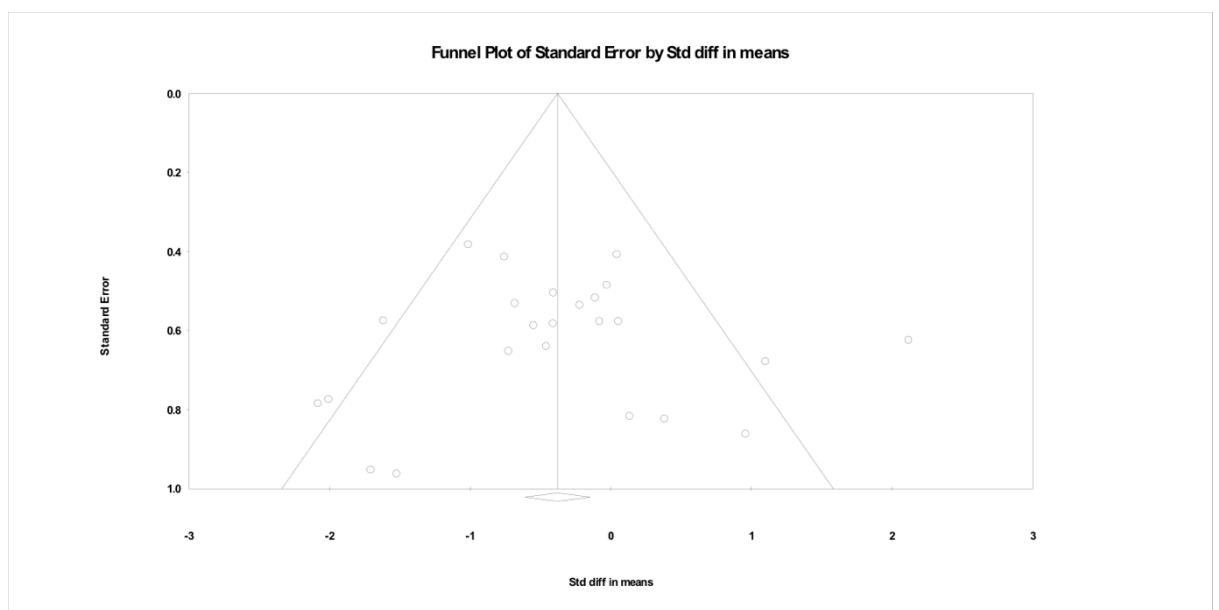
Supplementary Figure 1. Funnel bias plot for animal studies administering a single dose of central oxytocin.



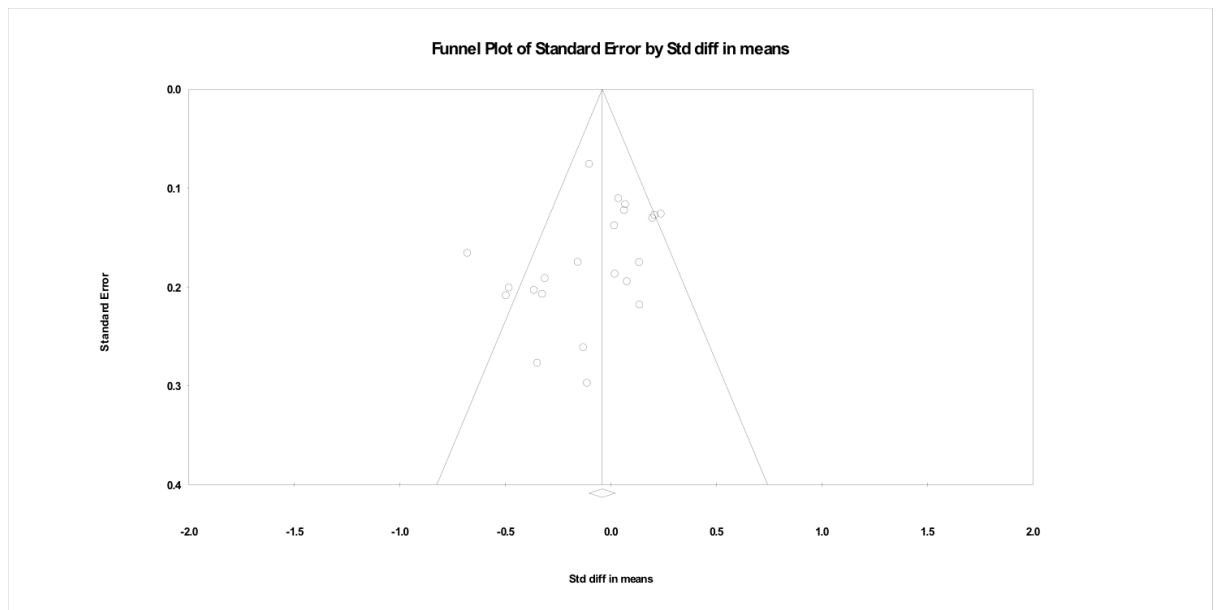
Supplementary Figure 2. Funnel bias plot for animal studies administering a single dose of systemic oxytocin.



Supplementary Figure 3. Funnel bias plot for animal studies administering chronic central oxytocin.



Supplementary Figure 4. Funnel bias plot for animal studies administering chronic systemic oxytocin.



Supplementary Figure 5. Funnel bias plot for human studies measuring the effect of intranasal oxytocin on energy intake.

Chapter 4

- 4 The Functional Significance of Oxytocin Supplementation in Women with Bulimia Nervosa, Binge Eating Disorder, and Healthy Comparison Women

4.1 Rationale for investigating the effect of oxytocin on eating behaviours and stress in bulimia nervosa and binge eating disorder

The systematic review presented in Section 3.7 has synthesised evidence demonstrating an overall inhibitory effect of a single dose of oxytocin on feeding in animals. While the effects of oxytocin on feeding in humans are highly mixed, there is preliminary evidence to suggest that oxytocin may specifically reduce hedonic eating in healthy men and overall caloric intake in women with BN. However, the inhibitory effect of oxytocin on feeding in women with BN has not yet been replicated, nor is the mechanism mediating such an effect clear.

Given the well-established role of oxytocin in supporting abstinence from substance addictions (Zanos et al., 2018), there is reason to believe that oxytocin administration may modulate the very hedonic systems proposed to underpin recurrent binge eating behaviour in BN and BED. Therefore, one hypothesis stemming from the addictive appetite model is that treatments targeting addiction-related neural circuits, potentially including oxytocin administration, should be efficacious in reducing binge eating tendencies in BN.

Furthermore, while initial evidence has found that oxytocin reduces eating-related stress responses in women with anorexia nervosa (Leppanen, Cardi, et al., 2017a; Russell et al., 2018), the effect of oxytocin on stress in women with BN and BED has not yet been investigated. The following study therefore aimed to fill this gap in the literature. Further details regarding the study's rationale and methods are included within the following paper.

4.2 Paper 5: The influence of oxytocin on eating behaviours and stress in women with bulimia nervosa and binge eating disorder

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

Leslie, Monica^a;

Leppanen, Jenni^a;

Paloyelis, Yannis^a;

Treasure, Janet^a

Affiliations:

^a Institute of Psychiatry, Psychology and Neuroscience (IoPPN) - King's College London (KCL), London, United Kingdom

Corresponding Author: Monica Leslie – monica.leslie@kcl.ac.uk; - 103 Denmark Hill, Section of Eating Disorders, London SE5 8AF, United Kingdom

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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, Kovács, et al., 2016; Pawaskar et al., 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 (Y.-R. Kim, J.-S. Eom, et al., 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 bingeing and purging behaviour in women (Micali, Crous-Bou, et al., 2017). Additionally, the AG/GA variant of the rs2254298 oxytocin receptor gene polymorphism is also associated with greater bingeing

and purging behaviour in the context of poor maternal care (Micali, Crous-Bou, 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 et al., 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 (Ott et al., 2013), and that this inhibitory effect is stronger in overweight and obese populations (Leslie, Silva, et al., 2018; 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 (Y.-R. Kim, J.-S. Eom, 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 et al., 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, Cardi, et al., 2017a). 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, & Jooper, 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, et al., 2018). The implication of oxytocin in both reward and anxiety-related processes may therefore explain previous findings 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-hour 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 righthanded (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

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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 12**. 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 sample¹. The need for a second dose of oxytocin at this time point was based on previous neuroimaging research indicating that the central action of a 40IU dose

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.

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 (E. 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 menstrual phase. We therefore conducted preliminary analyses testing the moderating influence of menstrual phase on the effect of oxytocin on each of the following dependent variables. Menstrual 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 16**. 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 13**). Descriptive statistics for the

food consumption data are reported in **Table 17**. Data plots illustrating the distribution of caloric consumption in the taste test are presented in **Supplementary Figure 6**.

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 18**.

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 calorie 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 19**.

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

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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 one², 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 20**. Data plots for the transformed cortisol variable are presented in **Figure 14**.

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 21**.

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 in the healthy control sample (skew = 2.08). Due to skew in the data for subjective

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

stress, a value of one was added to the stress data³ 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 22 and 23**.

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 24**.

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 25**.

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 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

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.

reported significantly greater levels of subjective stress. Fixed effects for the linear mixed model for the transformed stress data are reported in the **Table 26**.

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 calorie 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 (Y.-R. Kim, J.-S. Eom, et al., 2015; Micali, Crous-Bou, 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 that 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, & Joobar, 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) (Y.-R. Kim, J.-S. Eom, 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 (Y.-R. Kim, J.-S. Eom, 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 (Y.-R. Kim, J.-S. Eom, 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 few 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.

Table 16*Descriptive demographic data*

	Healthy Control (<i>n</i> = 27)		BN/BED (<i>n</i> = 25)	
	Median	IQR	Median	IQR
Age	23.50	5.50	23.50	9.75
BMI	22.04	1.76	23.09	3.87
RQF Education Level	6	4	4.5	3

Note. BN = bulimia nervosa; BED = binge eating disorder; IQR = interquartile range; BMI = body mass index; RQF = Regulated Qualifications Framework.

Table 17

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

	Healthy Control (<i>n</i> = 27)				BN/BED (<i>n</i> = 25)			
	Placebo		Oxytocin		Placebo		Oxytocin	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Grape consumption	94.38	77.88	93.72	80.52	60.06	85.63	57.22	91.41
Crisp consumption	136.76	147.28	147.28	117.04	68.38	168.06	52.60	148.86
Chocolate consumption	115.50	264.00	132.00	291.5	98.45	163.35	82.50	192.50
24-hour consumption	1617.63	650.19	1672.90	1119.29	1951.30	1542.66	1606.00	1086.05

Note. Data recorded as number of calories consumed. BN = bulimia nervosa; BED = binge eating disorder.

Table 18

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

	Wald Chi-Square	df	p	Incidence Rate Ratio
Drug Condition	1.11	1	.292	0.780
Eating Disorder Status	0.93	1	.336	0.770
Drug Condition*Eating Disorder Status	3.257	1	.071	1.369

* $p < .05$

Table 19

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

	Wald Chi-Square	df	p	Incidence Rate Ratio
Drug Condition	0.46	1	.498	1.040
Eating Disorder Status	1.40	1	.237	1.235
Drug Condition*Eating Disorder Status	0.04	1	.845	1.033

Table 20*Descriptive statistics for the raw salivary cortisol data*

	Healthy Control (<i>n</i> = 27)				BN/BED (<i>n</i> = 25)			
	Placebo		Oxytocin		Placebo		Oxytocin	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Salivary Cortisol (nmol/L) Time	2.48	1.68-3.03	2.31	1.54-3.13	3.13	1.53-5.72	3.23	2.04-4.89
Point 1								
Salivary Cortisol (nmol/L) Time	1.06	0.63-1.76	1.09	0.54-1.66	1.31	0.63-3.00	1.59	0.92-2.10
Point 2								
Salivary Cortisol (nmol/L) Time	1.43	0.90-1.79	1.17	0.65-1.65	1.48	0.70-2.56	1.04	0.87-1.74
Point 3								

Note. BN = bulimia nervosa; BED = binge eating disorder.

Table 21

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

Fixed Effects	Estimate	SE	df	t	p
Intercept	0.58***	0.050	217.14	11.47	2.16E-16
ED Status	0.12	0.074	226.92	1.67	.097
Drug Condition	-0.01	0.058	247.69	-0.19	.847
Experiment Time Point	-0.08***	0.019	248.30	-4.41	1.56E-5
ED Status * Drug Condition	0.06	0.084	247.44	0.77	.442
ED Status * Experiment Time Point	-0.02	0.028	247.53	-0.88	.379
Drug Condition * Experiment Time Point	-0.01	0.027	247.03	-0.21	.831
ED Status * Drug Condition * Experiment Time Point	-0.03	0.039	246.72	-0.66	.511
Random Effects	Variance				
Individual Participant	0.025				
Residuals	0.019				

Note. ED = Eating disorder.

*** $p < .001$

Table 22*Descriptive statistics for the visual analogue scale data for hunger and feeling fat*

	Healthy Control (<i>n</i> = 27)				BN/BED (<i>n</i> = 25)			
	Placebo		Oxytocin		Placebo		Oxytocin	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Hunger Time 1	2.91	2.127	3.29	2.313	4.04	2.626	2.72	2.313
Hunger Time 2	4.10	2.671	3.96	2.573	5.10	2.487	4.24	2.374
Hunger Time 3	4.95	2.312	5.14	2.553	6.11	2.066	5.02	2.652
Feel Fat Time 1	1.40	1.564	2.04	2.357	7.10	2.295	7.10	1.912
Feel Fat Time 2	1.39	2.033	1.48	2.219	6.44	2.608	6.19	2.308
Feel Fat Time 3	1.23	1.944	1.55	2.311	7.11	2.159	6.42	2.556
Log10 Stress Time 1	0.06	0.406	0.05	0.403	0.57	0.268	0.39	0.554
Log10 Stress Time 2	-0.10	0.437	-0.12	0.419	0.33	0.472	0.30	0.475
Log10 Stress Time 3	-0.26	0.369	-0.13	0.452	0.48	0.353	0.30	0.535

Note. BN = bulimia nervosa; BED = binge eating disorder.

Table 23*Descriptive statistics for the visual analogue scale data for stress*

Healthy Control (<i>n</i> = 27)					BN/BED (<i>n</i> = 25)			
	Placebo		Oxytocin		Placebo		Oxytocin	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Stress Time 1	1.05	1.83	1.33	1.29	3.36	4.03	3.32	4.09
Stress Time 2	0.52	1.22	0.56	1.45	2.53	4.74	1.55	3.71
Stress Time 3	0.40	0.65	0.40	1.37	3.33	4.42	2.41	3.85

Note. BN = bulimia nervosa; BED = binge eating disorder; IQR = interquartile range.

Table 24

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

Fixed Effects	Estimate	SE	df	t	p
Intercept	2.02**	0.636	289.27	3.18	.002
ED Status	1.25	0.916	289.06	1.37	.172
Drug Condition	0.26	0.793	256.02	0.33	.742
Experiment Time Point	1.02***	0.262	255.62	3.90	< .001
ED Status * Drug Condition	-1.64	1.143	256.00	-1.43	.153
ED Status * Experiment Time Point	-0.13	0.376	255.87	-0.34	.732
Drug Condition * Experiment Time Point	-0.10	0.367	255.62	-0.27	.790
ED Status * Drug Condition * Experiment Time Point	0.32	0.528	255.75	0.61	.541
Random Effects	Variance				
Individual Participant	2.262				
Residuals	3.561				

Note. ED = Eating disorder.

** $p < .01$.

*** $p < .001$.

Table 25

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

Fixed Effects	Estimate	SE	df	t	p
Intercept	1.90***	0.479	101.87	3.98	< .001
ED Status	5.22***	0.683	98.386	7.64	< .001
Drug Condition	0.27	0.373	244.61	0.73	.465
Experiment Time Point	-0.12	0.127	243.90	-0.94	.346
ED Status * Drug Condition	-0.17	0.528	244.11	-0.32	.748
ED Status * Experiment Time Point	-0.004	0.177	243.77	-0.02	.981
Drug Condition * Experiment Time Point	-0.09	0.175	244.34	-0.53	.598
ED Status * Drug Condition * Experiment Time Point	-0.11	0.245	243.98	-0.45	.656
Random Effects	Variance				
Individual Participant	4.174				
Residuals	0.731				

Note. ED = Eating disorder.

*** $p < .001$.

Table 26

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

Fixed Effects	Estimate	SE	df	t	p
Intercept	0.42	0.061	220.94	6.99	< .001
ED Status	0.22*	0.087	220.57	2.51	.013
Drug Condition	-0.03	0.068	256.15	-0.51	.612
Experiment Time Point	-0.08***	0.022	255.91	-3.63	< .001
ED Status * Drug Condition	-0.04	0.098	256.13	-0.41	.681
ED Status * Experiment Time Point	0.05	0.032	256.04	1.67	.097
Drug Condition * Experiment Time Point	0.03	0.031	255.91	0.93	.354
ED Status * Drug Condition * Experiment Time Point	-0.03	0.045	255.98	-0.58	.565
Random Effects	Variance				
Individual Participant	0.036				
Residuals	0.026				

Note. ED = Eating disorder.

* $p < .05$.

*** $p < .001$.

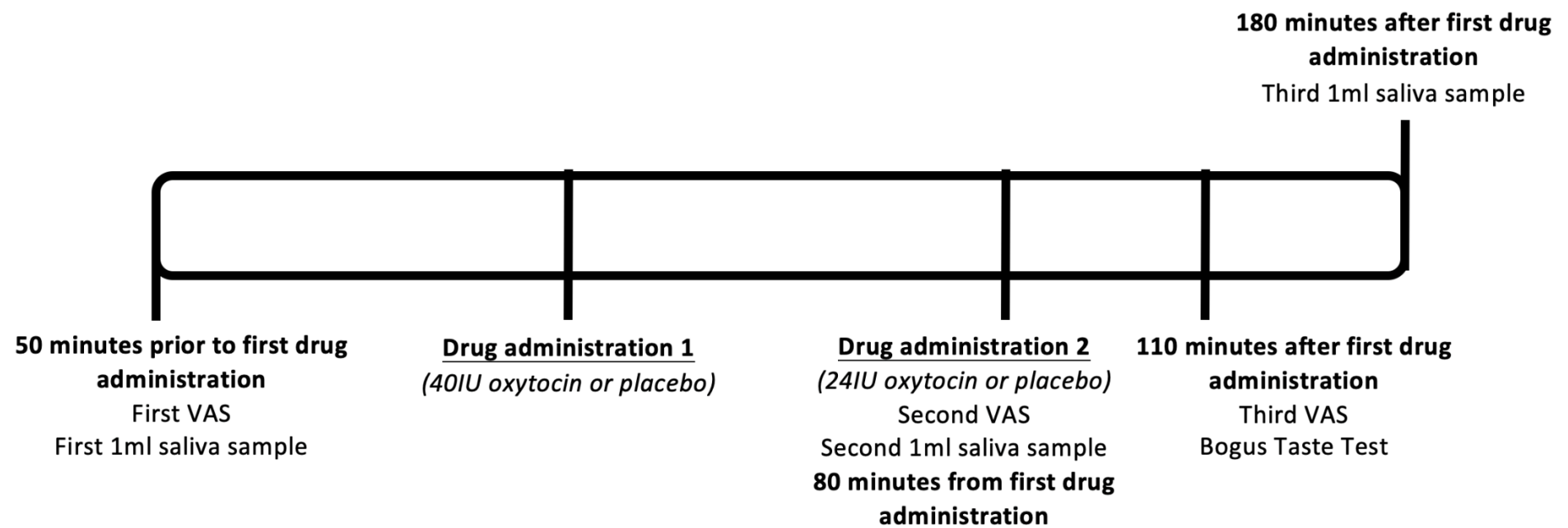


Figure 12. Order of activities for each experimental visit.

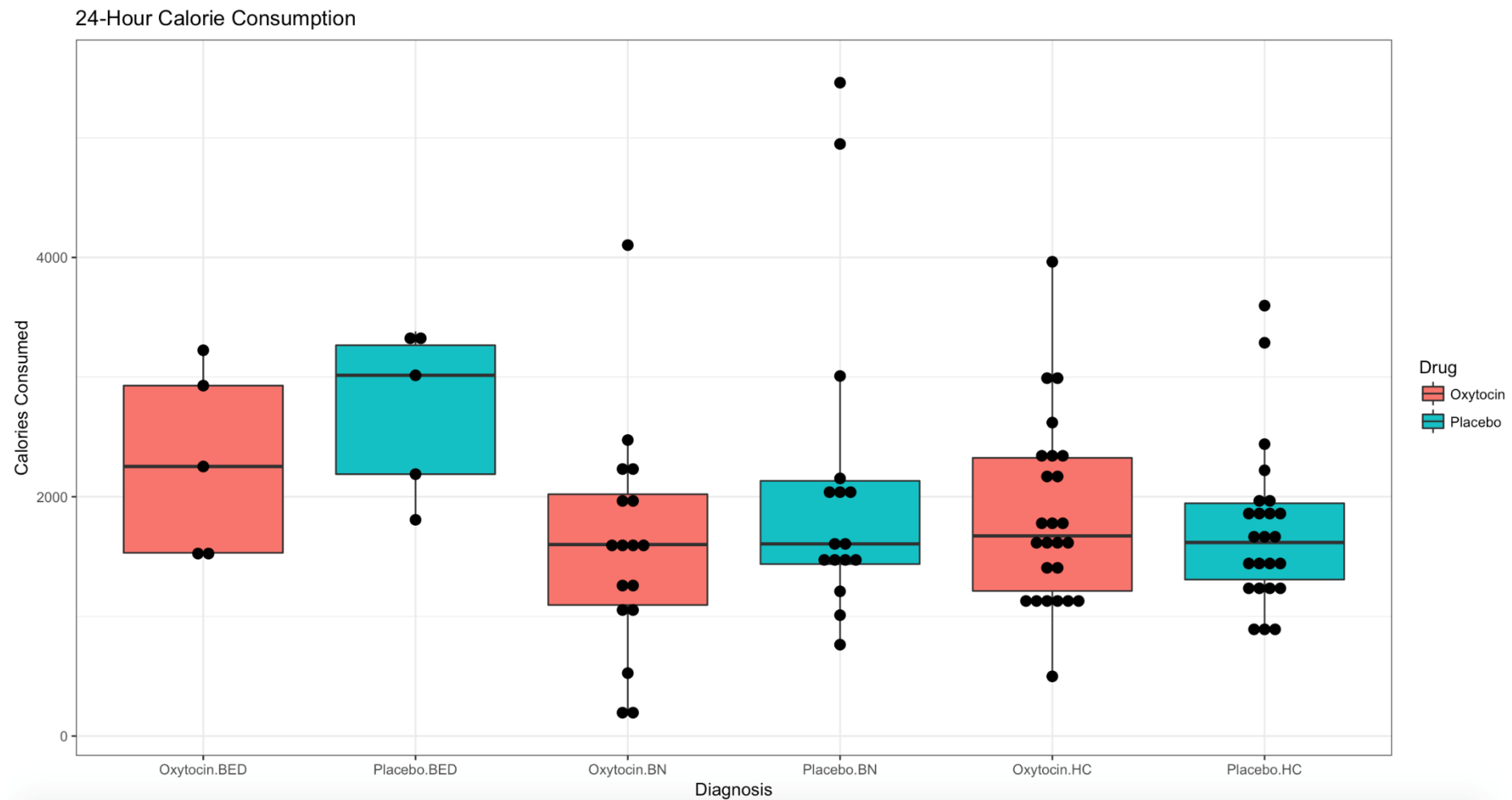


Figure 13. 24-hour caloric consumption by participant diagnosis and drug condition.

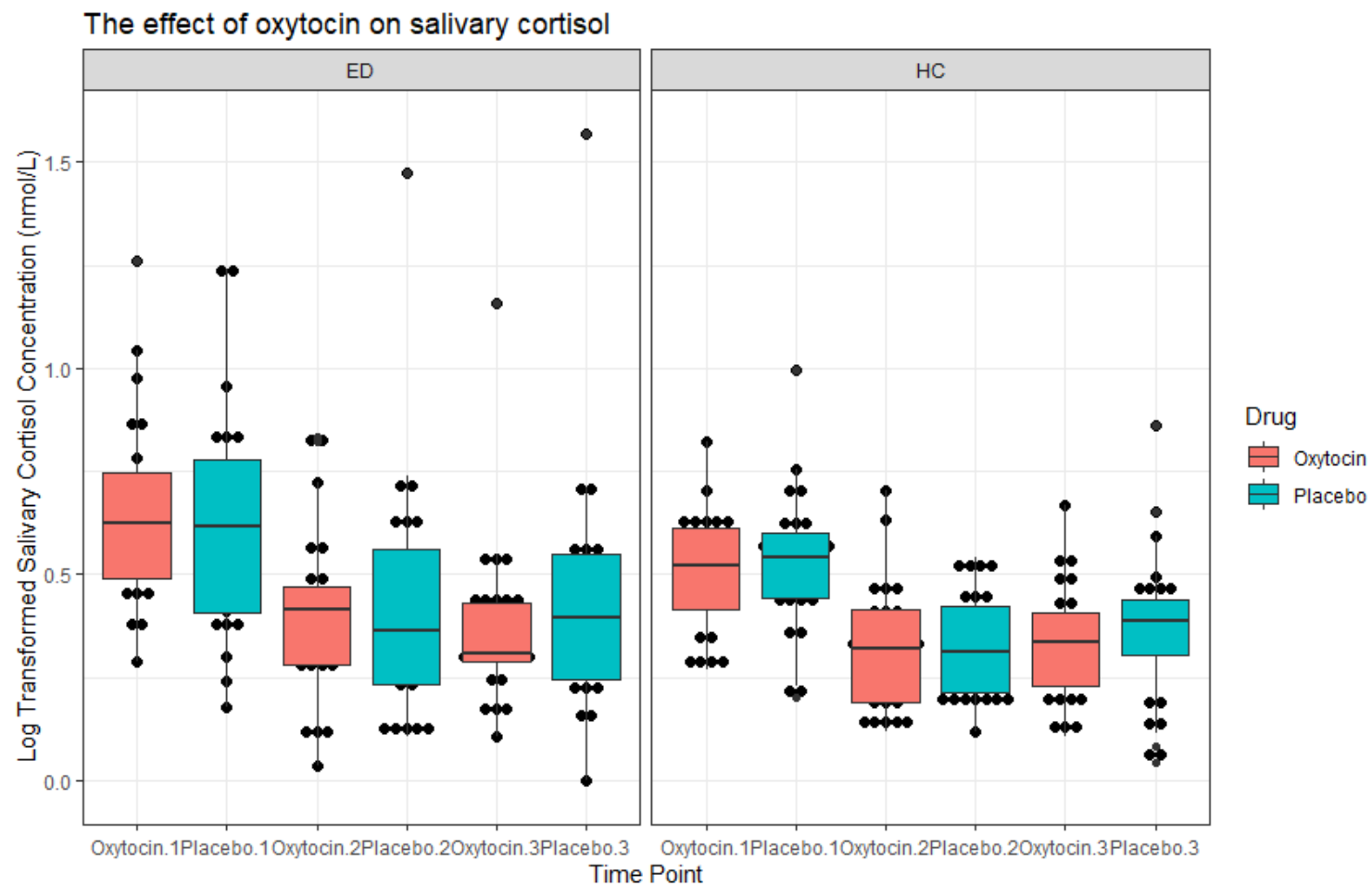


Figure 14. Log transformed salivary cortisol concentration separated by drug condition, time point, and eating disorder status.

Note. ED = eating disorder participant group; HC = healthy comparison group.

Supplementary Material

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

24-hour calorie consumption. Fifteen women completed the study in the follicular phase of the oestrous cycle, thirteen women completed the study in the luteal phase, and twenty-two women were taking hormonal contraception at the time of the study. In order to account for the possible moderating effect of varying oestrous phase on the effect of oxytocin on eating, we first conducted a preliminary negative binomial regression with the predictors Oestrous Phase and Drug Condition. This analysis revealed a main effect of oestrous phase (Wald Chi-Square = 6.88, $df = 2$, $p = .032$), such that women consumed significantly more calories over a 24-hour period when in the luteal phase, as opposed to the follicular phase or when taking hormonal contraception. However, there was not a significant interaction between oestrous phase and drug condition on food consumption reported in the 24-hour food diary (full results of the negative binomial regression are reported in the **Supplementary Table 6**). We therefore proceeded with the main analysis without including oestrous phase as a predictor.

Taste test calorie consumption. We first conducted a negative binomial regression to determine whether oestrous phase and food type interacted with oxytocin to impact caloric consumption in the taste test. There was a significant effect of food type, such that participants consumed significantly fewer calories in grapes, as opposed to crisps or chocolate. This binomial regression did not reveal either a significant main effect of oestrous phase, a significant interaction between oestrous phase and drug condition, or a significant interaction between food type and drug condition on caloric consumption in the taste test. (full results of this negative binomial regression are reported in the **Supplementary Table 7**).

Supplementary Table 6

Results from the preliminary negative binomial regression testing the effect of oestrous phase and oxytocin on calorie consumption in the 24-hour food diaries

	Wald Chi-Square	df	p
Drug Condition	0.16	1	.692
Oestrous Phase	6.88*	2	.032
Drug Condition*Oestrous Phase	3.65	2	.161

* $p < .05$

Supplementary Table 7

Results from the preliminary negative binomial regression testing the effect of oestrous phase and oxytocin on calorie consumption in the taste test

	Wald Chi-Square	df	p
Drug Condition	0.58	1	.448
Oestrous Phase	2.64	2	.267
Food Type	31.05***	2	< .001
Drug Condition*Oestrous Phase	1.30	2	.522
Drug Condition*Food Type	0.33	2	.847

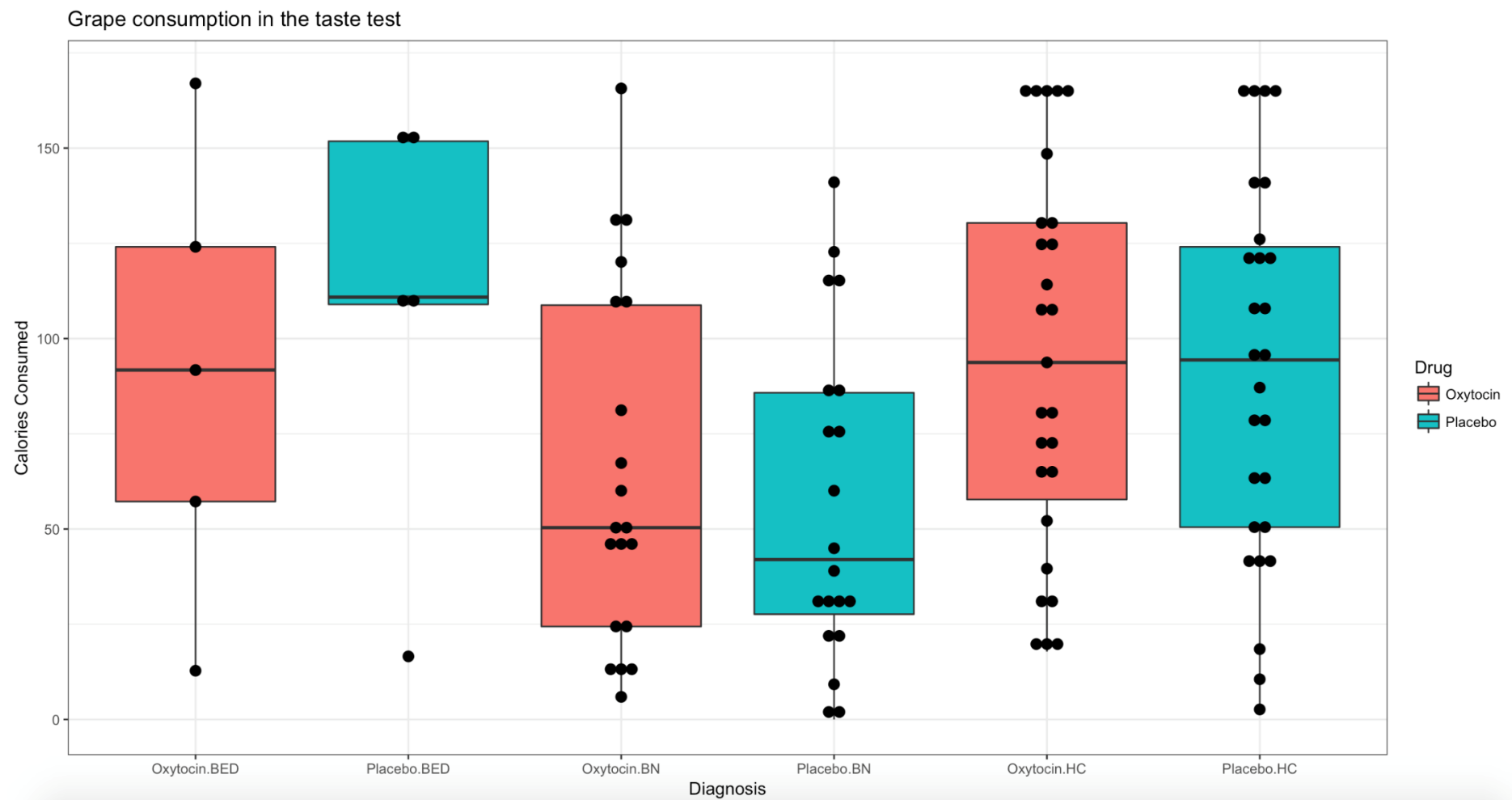
* $p < .001$

Supplementary Table 8

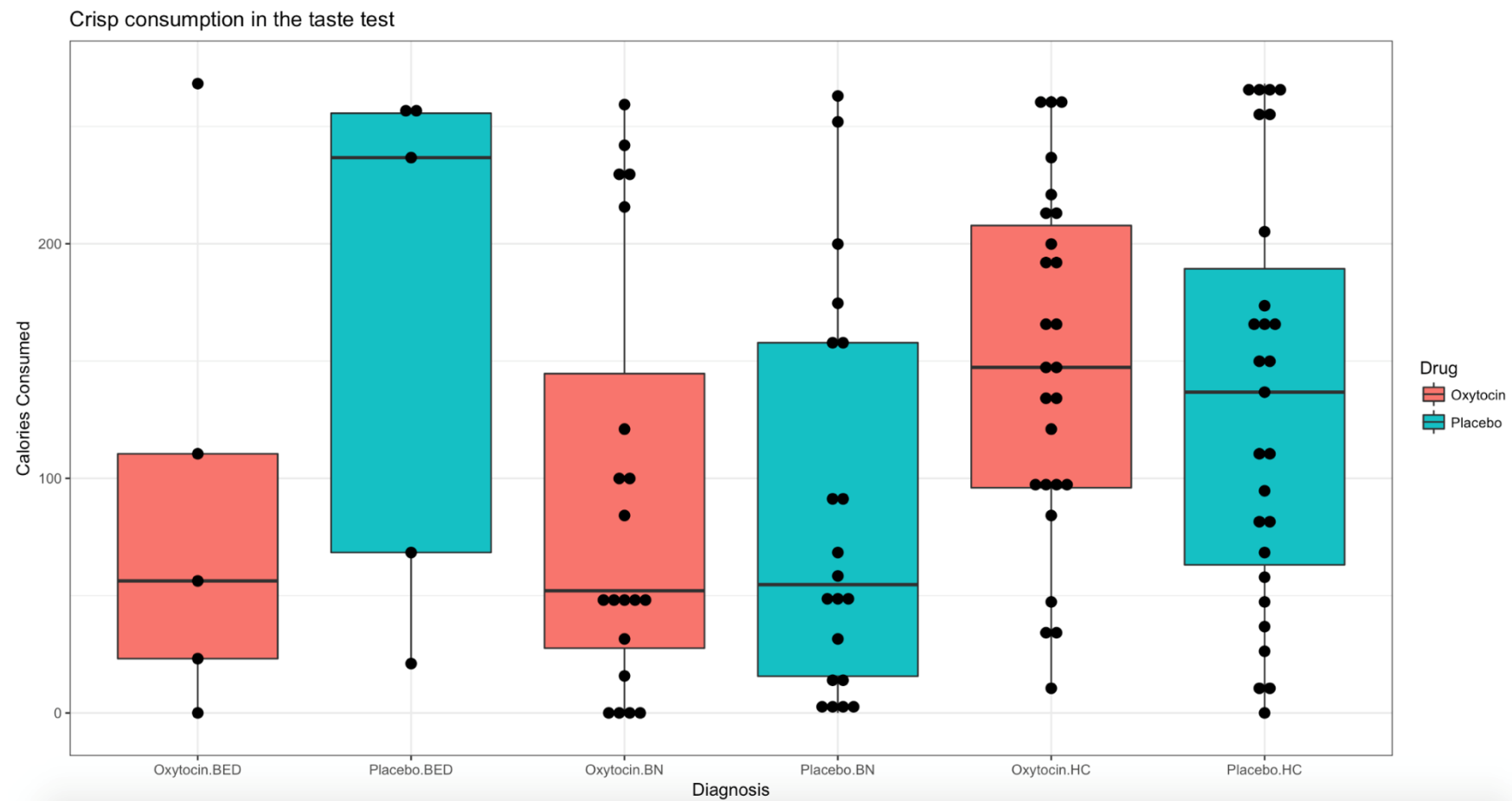
Results of the linear mixed effects analysis testing the moderating effect of follicular phase on the effects of oxytocin on salivary cortisol

Fixed Effects	Estimate	SE	df	t	p
Intercept	0.48***	0.05	80.96	8.71	3.03E-13
Follicular Phase	-0.03	0.02	80.36	-1.11	.272
Drug Condition	3.63E-5	0.05	235.7	0.001	.999
Follicular Phase*Drug Condition	-2.69E-3	0.02	235.7	-0.121	.904
Random Effects	Variance				
Individual Participant	0.01				
Residuals	0.03				

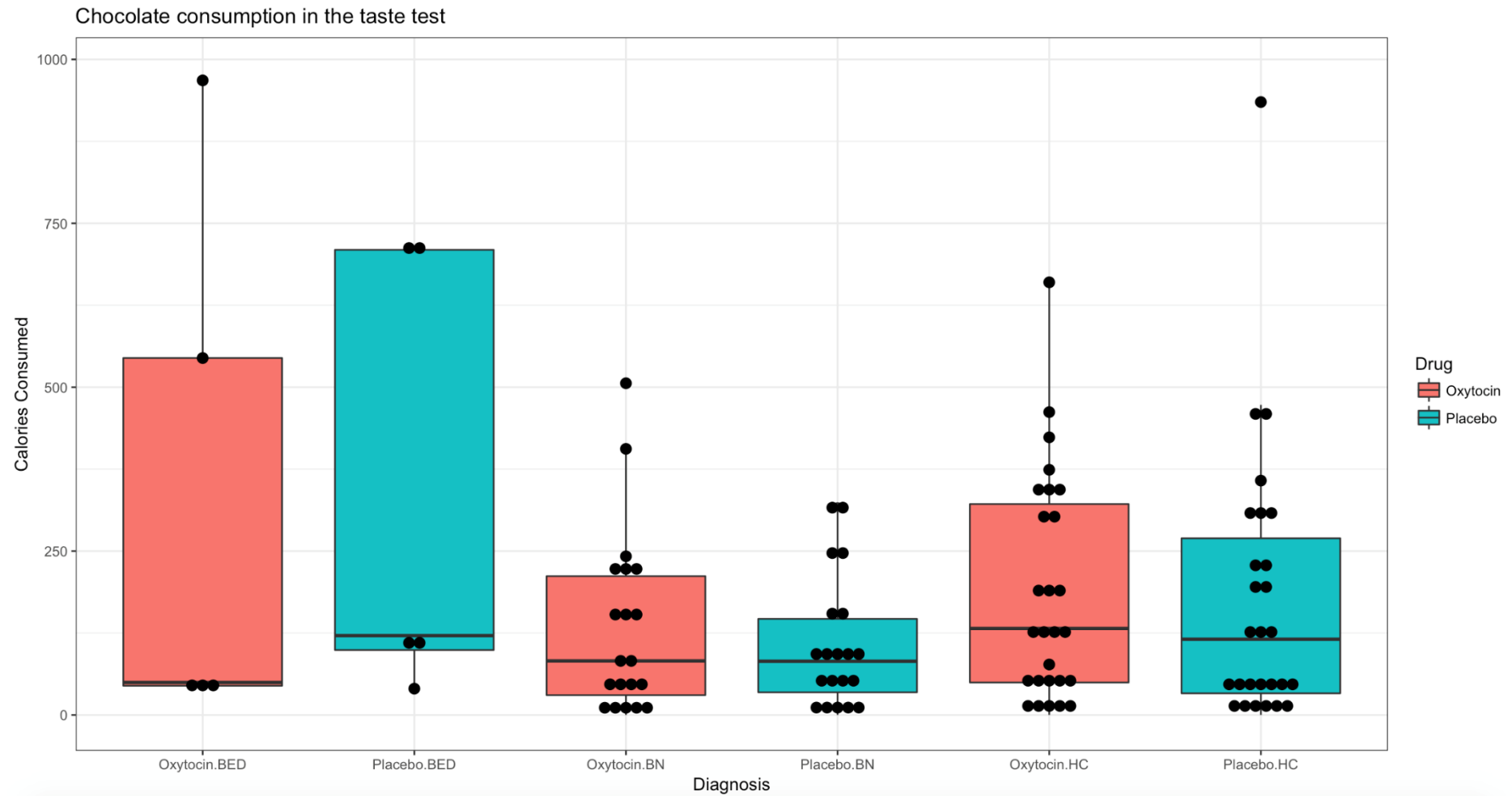
*** $p < .001$



Supplementary Figure 6. Grape consumption in the taste test by participant diagnosis and drug condition. Note: BED = binge eating disorder, BN = bulimia nervosa; HC = healthy control.



Supplementary Figure 7. Crisp consumption in the taste test by participant diagnosis and drug condition. Note: BED = binge eating disorder, BN = bulimia nervosa; HC = healthy control.



Supplementary Figure 8. Chocolate consumption in the taste test by participant diagnosis and drug condition. Note: BED = binge eating disorder, BN = bulimia nervosa; HC = healthy control.

Chapter 5

5 The effects of oxytocin on neurocognitive processes in bulimia nervosa and binge eating disorder

5.1 Rationale for investigating the effects of oxytocin on attentional processing and decision-making in bulimia nervosa and binge eating disorder

One hypothesis proposed within the addictive appetite model is that people with bulimia nervosa and binge eating disorder will exhibit disinhibited stimulus-response pathways in response to palatable food. Thus, despite ongoing efforts towards recovery, the nature of attentional and response patterns in the advanced stage of the disorder continues to contribute to the progression of the disorder. It is therefore of clinical interest to disrupt such automated patterns of responding to palatable food in order to curb loss-of-control binge eating behaviour in both bulimia nervosa and binge eating disorder.

The rationale for using oxytocin supplementation as a treatment approach for unhelpful attentional biases and impulsive decision-making tendencies will be described in further detail in the following papers. That is, while the evidence presented in Paper 5 suggests that a divided dose of 64IU oxytocin does not immediately impact hedonic eating, it remains to be seen as to whether intranasal oxytocin impacts underlying processes which contribute to binge eating behaviour in the long-term.

A Pilot Study Investigating the Influence of Oxytocin on Attentional Bias to Food Images in Women with Bulimia Nervosa and Binge Eating Disorder

Leslie, Monica ^{a*};

Leppanen, Jenni ^a;

Paloyelis, Yannis ^a;

Treasure, Janet ^a

Affiliations:

^a Institute of Psychiatry, Psychology and Neuroscience (IoPPN) - King's College London (KCL), London, United Kingdom

* Corresponding Author: Monica Leslie – monica.leslie@kcl.ac.uk; - 103 Denmark Hill,

Section of Eating Disorders, London SE5 8AF, United Kingdom

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Abstract

Background: Previous research has found that exogenous oxytocin administration has the potential to modulate attentional biases in women with anorexia nervosa. Recent work has indicated that attentional biases to food may reinforce the recurrent binge eating behaviour which characterises bulimia nervosa and binge eating disorder. To date, however, no study has yet investigated the effect of oxytocin on attentional biases to palatable food in women with bulimia nervosa and binge eating disorder.

Methods: The current study employed a single-session crossover design to test the hypothesis that a divided dose of 64IU intranasal oxytocin, versus placebo administration, would reduce attentional biases towards food images in a dot probe task. We further hypothesised that oxytocin administration would reduce vigilance towards food to a greater degree in women with bulimia nervosa or binge eating disorder, versus healthy comparison women, due to potential flooring effects in the healthy comparison group. Twenty-five women with bulimia nervosa or binge eating disorder and 27 comparison women without history of an eating disorder were recruited to take part in the study.

Results: Contrary to our hypothesis, there was no main effect of diagnosis on attentional bias to food (fixed effect = 5.70, $p = .363$), nor a significant interaction between diagnosis and drug condition (fixed effect = -14.80, $p = .645$). There was a main effect of drug condition, such that oxytocin increased vigilance towards food, versus neutral, images in the dot probe task (fixed effect = 10.42, $p = .044$); however, a sensitivity analysis subsequently suggested that this finding was primarily driven by women with binge eating disorder.

Conclusion: The current findings add to a mixed body of literature investigating the therapeutic effects of oxytocin in women. Future research would benefit from dose-

response studies investigating the optimal dose of oxytocin for modulating the attentional processing of palatable food in populations with eating disorders.

Keywords: Bulimia nervosa; binge eating disorder; eating disorders; attentional bias; oxytocin

Introduction

Bulimia nervosa (BN) and binge eating disorder (BED) are DSM-5 eating disorders characterised by recurrent, loss-of-control binge eating behaviour over a period of at least three months (American Psychiatric Association, 2013). Currently, the average remission rate for people with BN and BED remains low and treatment presents a significant challenge (Hay, 2013). The development of new treatment approaches is therefore warranted to address this unmet need.

A meta-analysis has found that people with BN exhibit greater attentional bias towards food words in Stroop tasks when compared to participants without history of an eating disorder (Brooks, Prince, Stahl, Campbell, & Treasure, 2011). More recently, evidence has supported the hypothesis that attentional bias towards food cues is associated with core eating disorder behaviours and psychopathology in BN and BED. For example, Albery et al. (2016) used a Stroop task to measure attentional bias to both food- and body-related words amongst women with BN. They found that the degree of attentional bias towards food-related words was associated with greater frequency of binge-purge behaviour. Additionally Svaldi, Naumann, Biehl, and Schmitz (2015) used a visual priming task to investigate attentional bias to food images, versus neutral images, among obese participants with and without BED. While this priming effect ultimately did not differ between the BED and non-BED groups of overweight participants, they did find that the degree of priming was positively correlated with overall eating disorder psychopathology, as measured using the Eating Disorder Examination – Questionnaire (EDE-Q) (Fairburn & Beglin, 1994b). In a spatial cueing task, Schmitz, Naumann, Trentowska, and Svaldi (2014) also found the same positive correlation between attentional bias to food images and EDE-Q scores in a sample of participants with BED.

It has been proposed that attentional bias toward palatable food cues is a cognitive maintenance factor for BN and BED, as these preconscious biases enhance the salience

of external cues for binge eating (Turton, Bruidegom, Cardi, Hirsch, & Treasure, 2016). Evidence suggests that the link between attention to food cues and subsequent binge eating behaviour may be especially strong in these disorders due to an automatic stimulus-response association that becomes increasingly reinforced with continued binge eating behaviour (Robbins et al., 2012; Treasure et al., 2018). Previous evidence has indicated that attentional biases to food are especially strong following actual food consumption in populations with obesity, as compared to healthy control participants (Castellanos et al., 2009). However, the effect of food consumption on behavioural measures of attentional bias to food has not been investigated in people with BN and BED (Giel, Teufel, Junne, Zipfel, & Schag, 2017). It is therefore of interest to determine whether attentional biases to palatable food occur prior to food consumption, thus supporting the incentive salience hypothesis (Berridge, 2007), or whether attentional biases only or also occur following food consumption, thus potentially highlighting that the onset of food consumption triggers subsequent increases in incentive salience.

Recent research has suggested that the hormone oxytocin may affect the upstream cognitive and emotional processes that contribute to the maintenance of disordered eating behaviour in anorexia nervosa. For example, chronic administration of oxytocin has been found to reduce eating concern (Russell et al., 2018). Additionally, a single dose of oxytocin has been found to reduce attentional bias to disgusted faces and correct avoidance of angry faces in women with anorexia nervosa. (Kim, Kim, Park, et al., 2014). A separate study also found that oxytocin corrected attentional avoidance of food images in women with anorexia nervosa (Leppanen, Cardi, et al., 2017a). This finding potentially carries clinical significance given evidence that attentional avoidance of food stimuli is correlated with disorder severity in anorexia nervosa (Giel et al., 2011), although future research is necessary before causal effects of attentional bias can be determined. To our

knowledge, no study has yet investigated the effects of oxytocin on attentional bias to food images in BN and BED.

It is not entirely clear by what mechanism oxytocin alters attentional bias specifically to food images, although the strength of the effect of oxytocin on attentional bias is related to the anxiolytic effects of oxytocin with a medium effect size (Leppanen, Cardi, et al., 2017a). It may be the case that anxiety primarily drives baseline attentional biases away from food in anorexia nervosa, and the oxytocin-induced reduction in anxiety has the downstream effect of normalising this bias. A current lack of evidence does not allow for the establishment of firm conclusions regarding the mechanism of the effect oxytocin on attentional bias; however, it is reasonable to suspect that oxytocin may exert a similar effect in normalising baseline attentional biases towards food in BN and BED if oxytocin modulates a common anxiety-based mechanism accounting for baseline attentional biases in each disorder, albeit in opposite directions.

Previous evidence that intranasal oxytocin suppresses hedonic eating in overweight men has provided tentative evidence that oxytocin may also suppress the reward salience of palatable food (Thienel et al., 2016), which has previously been found to affect preconscious attentional bias (B. A. Anderson, Laurent, & Yantis, 2011). Furthermore, previous neuroimaging work has found that people recovered from BN exhibit similar blood-oxygenated-level-dependent (BOLD) responses within the left putamen, a neural region strongly associated with the processing of reward, in response to taste stimuli received when either hungry or sated (Ely et al., 2017). This is in contrast to healthy control participants, who exhibit a down-regulated BOLD response in the left putamen following food consumption (Ely et al., 2017). One potential hypothesis stemming from this pattern of effects is that the incentive salience of palatable food, and attentional bias to palatable food, will decrease following food consumption to a greater

degree amongst healthy control participants, as compared to participants with BN or BED.

The current pilot used a double-blind, placebo-controlled crossover design to test the effect of a divided dose of 64IU intranasal oxytocin on attentional bias to food images among women with BN or BED and comparison women without history of an eating disorder. Our hypotheses were: 1) Women with BN or BED would demonstrate greater attentional bias towards food images than women without history of an eating disorder; 2) Oxytocin administration would reduce vigilance towards food images in both groups of women, based on previous work suggesting that oxytocin reduces the incentive salience of palatable food in healthy participants (Ott et al., 2013); 3) Oxytocin would reduce vigilance towards food images to a greater degree in women with BN or BED, versus healthy comparison women, due to potential flooring effects in the healthy comparison group; 4) There would be an interaction between time point and participant group, such that the difference in attentional bias to food in the BN/BED, versus healthy control group, would be even greater following food consumption.

Methods

Participants

Fifty-two women were recruited to take part in the current study. Twenty women met DSM-5 diagnostic criteria for BN, five women met DSM-5 diagnostic criteria for BED, and twenty-seven women had no prior history of an eating disorder at the time of the study. The study was advertised on the website for a major eating disorder charity in the United Kingdom (Beat), via e-mail circulars at King's College London, and on flyers displayed on community bulletin boards. The London – Camberwell St Giles NHS Research Committee granted ethical approval for the current study (reference: 14/LO/2115). All participants gave written informed consent in accordance with the

Declaration of Helsinki. Full inclusion and exclusion criteria for the study are presented in the **Supplementary Material**. Eligibility for the current study was established via a phone screening, which included the Structured Clinical Interview for DSM-5 (American Psychiatric Association, 2013). Seven participants who met diagnostic criteria for BN or BED had at least one comorbid psychiatric disorder. Specifically, 5 women had comorbid depression, 4 women had borderline personality disorder, 4 women had comorbid generalised anxiety disorder, 1 woman had obsessive-compulsive disorder, 1 woman had social anxiety, and 1 woman had an autism spectrum disorder. At the time of the study, 7 women were taking an antidepressant, 1 woman was taking an antipsychotic drug, and 1 woman was taking a mood stabiliser. Twenty-two of the fifty-two participants were taking hormonal contraception at the time of the study. Fifteen women completed the study whilst in the follicular phase of the oestrous cycle and thirteen women completed the study in the luteal phase of the menstrual cycle. Menstrual phase data were missing for two women. Descriptive statistics for the age, body mass index (BMI), and education level of the participant sample are presented in **Table 27**.

Study Design

This study used a double-blind placebo-controlled crossover design. Each participant came to the laboratory for three study visits: one orientation visit and two experimental sessions. During the orientation visit, each participant had the opportunity to discuss any queries with the researcher in person before signing informed consent and practising self-administration of a placebo nasal spray. The height and weight of each participant was also measured during the orientation visit. At the conclusion of the orientation visit, each participant was provided with a link to an online survey, in which participants provided basic demographic data prior to the second study visit.

Each participant subsequently came to the laboratory for two experimental study visits. Participants received a divided dose of 64IU intranasal oxytocin during one experimental study visit, and an equal volume of a placebo nasal spray during the opposite visit. The order in which each participant received each nasal spray was pseudo-randomised, such that an equal number of participants received oxytocin on the first, versus the second, experimental study visit. Both the participant and the researcher were blind to the order in which each participant was allocated the oxytocin, versus placebo, nasal spray. These experimental study visits were held two days apart to ensure that each participant would complete both experimental study visits whilst in the same phase of the menstrual cycle. Perfusion data analysing the central effects of oxytocin suggest that carryover effects from oxytocin administration on the first experimental visit to the second experimental visit are highly unlikely (Paloyelis et al., 2016).

Participants were requested to abstain from consuming alcohol or caffeine from 8.00pm on the evening prior to each experimental study visit. Participants were also asked to eat 2.5 hours prior to the beginning of each experimental study visit, and nothing else between this time and the beginning of the experimental study visit.

Participants arrived for each study visit at 5.00pm. At 5.50pm, each participant self-administered the first dose of the allocated nasal spray for that day: either 40IU oxytocin or an equal volume of the placebo nasal spray. Each participant then underwent a functional MRI scan, the results of which are not reported in the current paper. The functional MRI scan ended at 7.00pm. At 7.10pm, participants self-administered a second dose of the allocated nasal spray for that day: either 24IU oxytocin or an equal volume of the placebo nasal spray. The dose and timing of drug administration was based on previous work finding peak central effects of 40IU oxytocin at 39-51 minutes following administration (Paloyelis et al., 2016), thus suggesting the need for an additional dose at this time. At 7.25pm, each participant then completed a visual dot probe task, which is

described in further detail below. Immediately following the completion of this task, each participant completed a “bogus” taste test, which is also described below. The taste test continued for a standard 15-minute duration. Following the taste test, each participant repeated the visual dot probe task. Subsequently, each participant reported whether they believed they had been allocated the oxytocin or placebo for that study visit.

Visual Dot Probe Task

The visual dot probe task is a common test of attentional bias to disorder-relevant images, which has been used to measure attentional biases across a range of psychiatric disorders (MacLeod, Mathews, & Tata, 1986; Shafran, Lee, Cooper, Palmer, & Fairburn, 2007). The visual dot probe task used in the current study was adapted from Cardi, Lounes, Kan, and Treasure (2013) and presented using E-prime software (Psychology Software Tools, Sharpsburg, USA). Each task run consisted of 96 trials. In each trial, the participant was first presented with two images side by side, with 115mm between the centre of each image. Each image belonged to one of two category types: food images (32 different images) or neutral images (48 different images). Food images depicted close-up photographs of palatable foods on a plate. Food was depicted in a “ready-to-eat” form without any packaging.

Participants were presented with a total of 32 different food-neutral image pairs, and 16 different neutral-neutral image pairs. Each image pair was presented twice (once with the food picture on the left, and once with the food picture on the right; the order of image pairings was randomly determined for each participant). All food images were matched for size and caloric content. Neutral images depicted furniture. Each image had a resolution of 72dpi, measured 45 x 70mm on the computer screen, and was matched for colour saturation. Each picture pair was presented for 500ms.

Immediately following the presentation of each image pair, one of the images was replaced by a visual probe. Visual probes consisted of either a pair of horizontally or vertically oriented dots. Participants were instructed to press the letter ‘z’ as soon as they saw a pair of horizontally oriented dots, or the letter ‘q’ as soon as they saw a pair of vertically oriented dots. Stickers depicting the corresponding dot orientation were attached to the letters ‘q’ and ‘z’ on the keyboard to prevent confusion for participants. The inter-trial interval was 500ms. Reaction time and accuracy was recorded for each trial.

Bogus Taste Test

The bogus taste test is a validated measure of eating behaviour used to test the effect of experimental factors on the consumption of palatable food (E. Robinson et al., 2017). In the current study, each participant was presented with three types of food, each of which was contained in a standardised white ceramic bowl. One bowl contained 250g of grapes, one bowl contained 50g Walker’s ready-salted crisps, and the final bowl contained 220g Cadbury Bitsa Wispa™ chocolate. The bowls were presented in a standard order, with the bowl of grapes on being the leftmost bowl, followed by the bowl of crisps, and the bowl of chocolate being the rightmost bowl. Participants were asked to rate each type of food for tastiness, sweetness, saltiness, richness, and pleasantness on a visual analogue scale anchored from 0 to 10. As the researcher was leaving the room after explaining the instructions for the bogus taste test, the researcher told each participant as an “afterthought” that the participant was welcome to eat as much as they would like, as the remaining food would be thrown away. Participants were then left alone in a room with the three bowls of food for 15 minutes to complete the task.

Following the completion of the bogus taste test, the three bowls of food were brought to a separate room, out of sight of the participant, where a research assistant

weighed the remaining food in each bowl and subtracted this amount from the initial weight of each type of food. The effect of oxytocin on the quantity of food eaten is reported elsewhere (Leslie, Leppanen, Paloyelis, & Treasure, 2018).

Statistical Analysis

Attentional bias scores for each task run were calculated for the dot probe task by subtracting each participant's mean reaction time to probes that were preceded by a food image from those that were preceded by a neutral image. Therefore, positive attentional bias scores indicate vigilance to food images, and negative attentional bias scores indicate avoidance of food images. Trials that presented matching image pairs (e.g., two neutral images) and trials in which the participant responded incorrectly were excluded. All task runs for all participants met the minimum requirement of an 80% correct response rate.

We tested our hypotheses using a 2 x 2 x 2 linear mixed effects model in the lmerTest package for R (Kuznetsova et al., 2017). We included experiment time point (before or after the taste test), eating disorder status (healthy controls or BN/BED), drug condition (placebo or oxytocin), and all associated interactions as fixed effects. The intercept for each participant was entered as a random effect. A preliminary linear mixed effects analysis was conducted to determine whether hormonal state (follicular phase, luteal phase, or current hormonal contraception) moderated the effect of oxytocin on attentional bias. The results of this linear mixed effects analysis are reported in **Supplementary Table 9**. The interaction effect between oxytocin and hormonal state was not significant, and hormonal state was therefore not included as a covariate in the final mixed effects model.

Results

The attentional bias scores were first screened for outliers and violations of the assumption of normality. Four outliers ($|Z| > 3.0$) were found in the attentional bias

variable and excluded from subsequent analyses. Three of these outlier data points were in the BN/BED participant group and one was in the healthy control participant group. Descriptive statistics associated with the attentional bias scores are presented in **Table 28** and visual depictions of the data are presented in **Supplementary Figures 9 and 10**.

The linear mixed model showed that none of the interaction effects reached significance in the full factorial model. The fixed effects associated with the full factorial linear mixed effect analysis are presented in **Table 29**. We did not identify any cases with excessive influence on the model (all Cook's distances < 1.0).

As there were not any significant interaction effects in the full factorial model, we therefore conducted a follow-up linear mixed effects analysis including only main effects. The main effects analysis revealed that neither eating disorder status nor experiment time point significantly affected attentional bias. However, there was a significant main effect of drug condition, such that oxytocin administration, versus placebo administration, was associated with significantly greater vigilance towards food images. The fixed effects associated with the linear mixed effects analysis are presented in **Table 28**. Again, we did not identify any cases with excessive influence on the model (all Cook's distances < 1.0).

Visual inspection of the data revealed a numerically greater difference in attentional bias to food images between the oxytocin and placebo conditions among BED, as opposed to healthy control or BN participants groups. We therefore conducted a sensitivity analysis excluding BED participants. Given that this exclusion would substantially reduce power given the already low sample size, we imputed the mean for each drug condition and experiment time point among the BN participant group for an additional five simulated BN participants. After excluding participants with BED, the effect of drug condition was no longer significant ($p = .084$) although there was a trend

towards an effect in the same direction. Full results of this sensitivity analysis are reported in **Supplementary Table 10**.

Discussion

The current study aimed to test the effect of a divided dose of 64IU intranasal oxytocin on attentional bias to food images in women with and without BN or BED. We hypothesised that women with BN or BED would demonstrate greater vigilance towards food images and that oxytocin administration would reduce vigilance towards food images in both participant groups, but with a stronger effect in the BN/BED versus healthy comparison group.

Our first hypothesis was not supported by the results, as there was no main effect of eating disorder status on attentional bias to food images. Oxytocin was found to have a significant effect on attentional bias; however, this was in the opposite direction to our hypothesis. That is, oxytocin was found to increase vigilance to food images, rather than decreasing vigilance as originally predicted. This finding, however, was primarily driven by the five participants with BED, as the significance of this effect did not survive after excluding participants with BED. Our third hypothesis was also not supported by the results as there was not a significant interaction between oxytocin treatment and eating disorder status on attentional bias to palatable food. Finally, we did not find evidence of an interaction between participant group and time point (before or after the taste test) on attentional bias to food images.

The lack of difference in baseline attentional bias to food stimuli between women with, versus without, BN or BED is in contrast to a previous studies using Stroop tasks (Brooks et al., 2011). This contrast in findings may be due, in part, to differences in the food-related stimuli presented: food images being used in the current study versus food words in the Stroop task. However, previous evidence has suggested that food images are

rather associated with a greater difference in attentional bias to food amongst participants with eating disorders and healthy controls, when compared to word stimuli (Stormark & Torkildsen, 2004). The null effect of eating disorder status in the current study may, therefore, rather be due to the stage of attention processing targeted in the current study. The target for the task was presented 500ms after each image pair, while the nature of the Stroop task necessarily requires that the target be presented simultaneously with the food-related word. This is potentially relevant given previous eye-tracking evidence finding no difference in attention to food images among women with anorexia nervosa at early stages of attentional processing but avoidance of food images at later stages of attentional processing (Giel et al., 2011). If similar variation in attentional biases also exist in populations with BN and BED, it is possible that the current study failed to detect differences in attentional bias before or after the target appeared.

The finding that oxytocin induced greater, rather than less, vigilance towards food stimuli in the current study was surprising, and contrasts with previous research finding that oxytocin attenuated baseline attentional biases away from food images in women with anorexia nervosa, with no effect in healthy comparison women (Leppanen, Cardi, et al., 2017a). However, it should be noted that the increased vigilance observed in the current study was not robust to the exclusion of the five participants with BED, even after imputing the mean for five simulated participants with BN to make up for the loss of power. Although the sample of participants with BED was not large enough to warrant a moderation analysis comparing the influence of oxytocin on participants with BN versus BED, these preliminary results demonstrating numerical divergence in the effect of oxytocin on attentional bias to palatable food among each disorder suggest that attentional biases to palatable food should be investigated separately among samples with BN and BED in future studies. On the whole, given that baseline attentional biases in women with anorexia nervosa were away from food images, rather than towards food images, the

evidence to date suggests that oxytocin increases vigilance to food images in women, with preliminary evidence suggesting that this effect is greater in women with anorexia nervosa and binge eating disorder (Leppanen, Cardi, et al., 2017a).

The mechanism by which oxytocin increases attentional bias to food images in women is yet unclear, but may involve interactions with dopaminergic signalling systems in mesolimbic brain regions (Shamay-Tsoory & Abu-Akel, 2016). Specifically, binding to oxytocin receptors in the ventral tegmental area and nucleus accumbens, two regions strongly related to reward processing, may initiate neural processes ultimately enhancing reward salience of signals (including food) in the immediate environment (Bethlehem, Baron-Cohen, van Honk, Auyeung, & Bos, 2014). However, it should be noted that this hypothesis is still in the speculative stage of proposal and requires additional empirical evidence for corroboration.

This reward salience hypothesis, as well as the finding that oxytocin increases vigilance to food stimuli, is difficult to consolidate with previous findings demonstrating that oxytocin decreases hedonic food consumption (Burmester et al., 2018; Ott et al., 2013; Thienel et al., 2016). That is, one might reasonably hypothesise that reduced hedonic food consumption would be associated with less attentional and motivational orientation to food stimuli. However, previous studies finding a suppression of hedonic eating reported this effect in male participant samples (Burmester et al., 2018; Ott et al., 2013; Thienel et al., 2016), while no effect of oxytocin on feeding was found in the current sample of female participants (Leslie, Leppanen, et al., 2018). An accumulating range of studies has found mixed effects of oxytocin on eating in women, both with and without eating disorders (Kim, Kim, Park, et al., 2014; Leppanen, Cardi, et al., 2017a), therefore suggesting that the inhibitory effect of oxytocin on hedonic eating, and orienting to food stimuli, may be sex-specific in humans. However, further research is necessary to clarify

whether oxytocin may influence reward salience attribution and actual food consumption via different mechanisms.

There is evidence to suggest that the potency of oxytocin on psychosocial functioning has an inverse quadratic function with drug dose (Cardoso et al., 2013). Given the relatively high dose of oxytocin administered in the current study (a divided dose of 64IU), it may therefore be the case that oxytocin administration does have different effects on attentional bias in this population at lower doses. Previous evidence has indicated that the effects of oxytocin on resting neural activation vary over time (Martins et al., Under Review). Therefore, it is possible that the functional effects of oxytocin on attentional biases to palatable food may also differ at other time points after administration given differing bioavailability of exogenous oxytocin to neural regions underpinning the control of attentional bias.

Additional limitations of the current study include the low sample size and our inability to measure the effects of oxytocin on early and late stages of attentional processing due to the nature of the dot probe task. It should be noted that a different pattern of effects may be found at different points within the time course of attentional processing given that different patterns of attentional vigilance versus avoidance have been observed at different stages of attentional processing in other eating disorders (Giel et al., 2011). Future studies of attention bias in BN and BED may be improved through the use of alternative measures of attentional bias, such as eye-tracking tasks. Additionally, as oxytocin has been found to have sex-specific effects in other studies of psychopathology (Feifel et al., 2011), the current findings should therefore not be generalised to men with BN and BED.

In conclusion, this is the first study to our knowledge to investigate the influence of oxytocin on attentional bias to food images in women with BN and BED and healthy

comparison women. A divided dose of 64IU intranasal oxytocin increased vigilance to palatable food images, although a sensitivity analysis suggests that this effect is primarily driven by women with BED. Further studies testing the effects of oxytocin on attentional biases to palatable food at different doses and time courses of administration in larger samples are warranted.

Table 27*Descriptive demographic data*

	Healthy Control (<i>n</i> = 27)		BN/BED (<i>n</i> = 25)	
	Median	IQR	Median	IQR
Age	23.50	5.50	23.50	9.75
BMI	22.04	1.76	23.09	3.87
RQF Education Level	6	4	4.5	3

Note. BN = bulimia nervosa; BED = binge eating disorder; IQR = interquartile range; BMI = body mass index; RQF = Regulated Qualifications Framework.

Table 28

Results of the linear mixed effects analysis testing the main effects of eating disorder status, oxytocin, and food presentation (experiment time point) on attentional bias to food images

		HC ($n = 27$) Mean(SD)	BN/BED ($n = 25$) Mean(SD)	Fixed Effects
Before Taste Test	Oxytocin	10.07(37.200)	10.54(39.720)	ED Status: $Z = 5.70$, $SE = 6.206$, $df = 46.00$, $p = .363$
	Placebo	-0.53(38.897)	0.40(49.889)	Drug Condition: $Z = 10.42^*$, $SE = 5.136$, $df = 142.20$, $p = .044$
After Taste Test	Oxytocin	2.74(31.922)	19.93(42.467)	
	Placebo	-0.26(26.770)	2.29(36.677)	Experiment Time Point: $Z = 1.10$, $SE = 5.14$, $df = 143.76$, $p = .831$
				Random Effects
				Individual Participant
				Residuals
				Variance
				151
				1284

Note. BED = Binge eating disorder; BN = Bulimia nervosa; ED = Eating disorder; HC = Healthy control.

* $p < .05$

Table 29

Results of the linear mixed effects analysis testing a full factorial model with fixed effects for eating disorder status, oxytocin, and food presentation (experiment time point) on attentional bias to food images

Fixed Effects	Estimate	SE	df	t	p
Intercept	-0.45	16.170	163.81	-0.03	.978
ED Status	-1.75	22.868	163.86	-0.08	.939
Drug Condition	17.85	22.536	141.17	0.79	.430
Experiment Time Point	-0.08	10.169	142.17	-0.01	.994
ED Status * Drug Condition	-14.80	32.083	141.71	-0.46	.645
ED Status * Experiment Time Point	2.68	14.382	142.30	0.19	.853
Drug Condition * Experiment Time Point	-7.25	14.301	141.55	-0.51	.613
ED Status * Drug Condition * Experiment Time Point	14.62	20.390	141.91	0.72	.475
Random Effects	Variance				
Individual Participant	159.8				
Residuals	1263.9				

Note. ED = Eating disorder.

Supplementary Material

Participant Inclusion and Exclusion Criteria

Inclusion criteria for the study required participants to be female, aged between 18 and 40 years old, display English fluency, and to be right-handed (due to an MRI scan which was conducted within the 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 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).

Clinical Characteristics of the Participant Sample

Seven participants who met diagnostic criteria for BN or BED had at least one comorbid psychiatric disorder. Five women had comorbid depression, 4 women had borderline personality disorder, 4 women had comorbid generalised anxiety disorder, 1 woman had obsessive-compulsive disorder, 1 woman had social anxiety, and 1 woman had an autism spectrum disorder. At the time of the study, 7 women were taking an antidepressant, 1 woman was taking an antipsychotic drug, and 1 woman was taking a mood stabiliser.

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. Participants with bulimia nervosa or binge eating disorder 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).

Twenty-two of the fifty-two participants were taking hormonal contraception at the time of the study. Fifteen women completed the study whilst in the follicular phase of the oestrous cycle and thirteen women completed the study in the luteal phase of the menstrual cycle.

Supplementary Table 9

Results of the linear mixed effects analysis testing the moderating effect of hormonal state on the effects of oxytocin on attentional bias to food images

Fixed Effects	Estimate	SE	df	t	p
Intercept	12.22	10.90	108.38	1.12	.265
Follicular Phase	-5.16	4.80	107.94	-1.08	.285
Drug Condition	3.12	13.92	135.90	0.22	.823
Follicular Phase*Drug Condition	2.82	6.11	135.51	0.46	.645
Random Effects	Variance				
Individual Participant	156.30				
Residuals	1273.20				

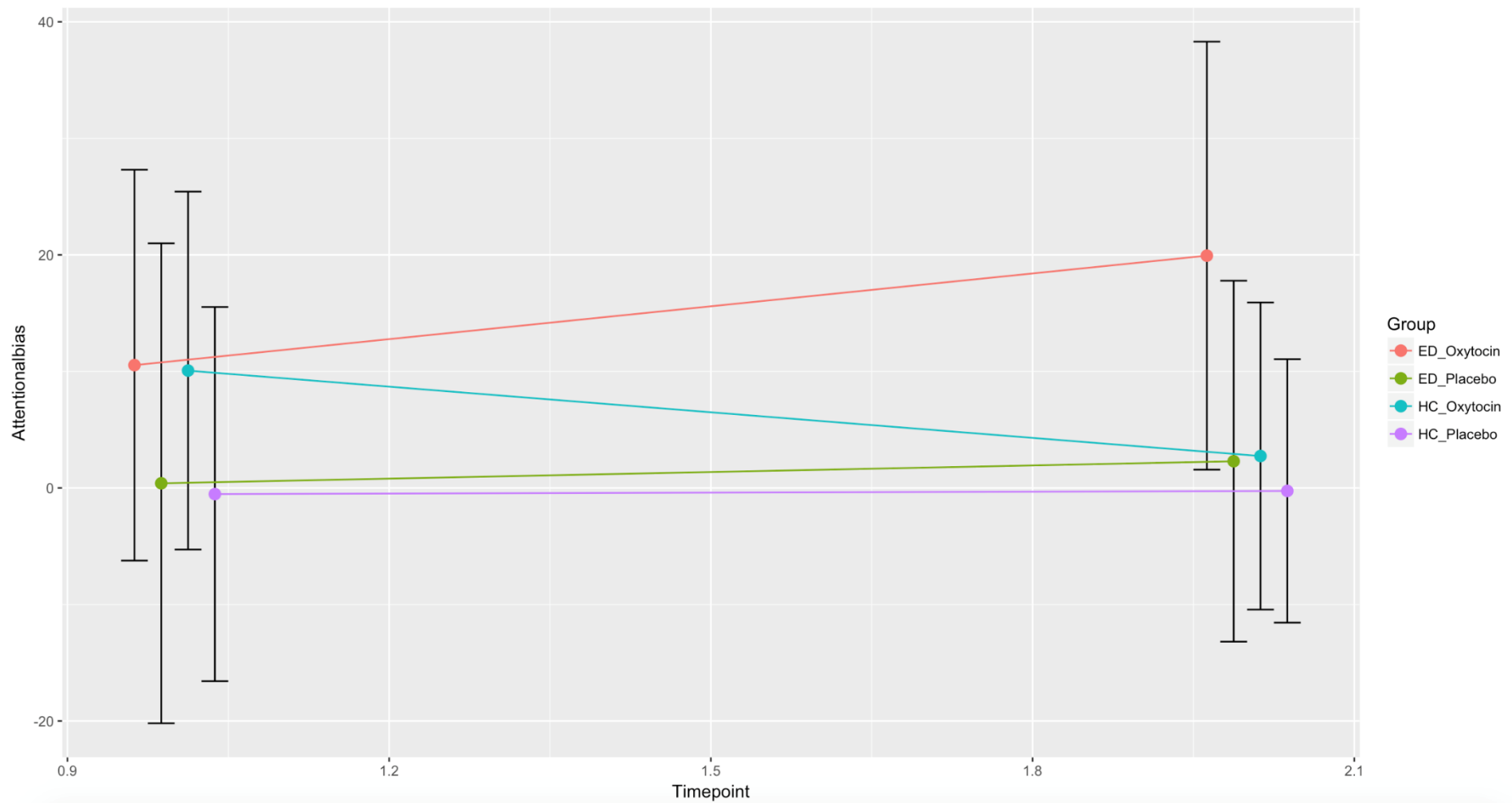
Supplementary Table 10

Results of the linear mixed effects sensitivity analysis testing the main effects of eating disorder status, oxytocin, and food presentation (experiment time point) on attentional bias to food images among healthy control and BN participants

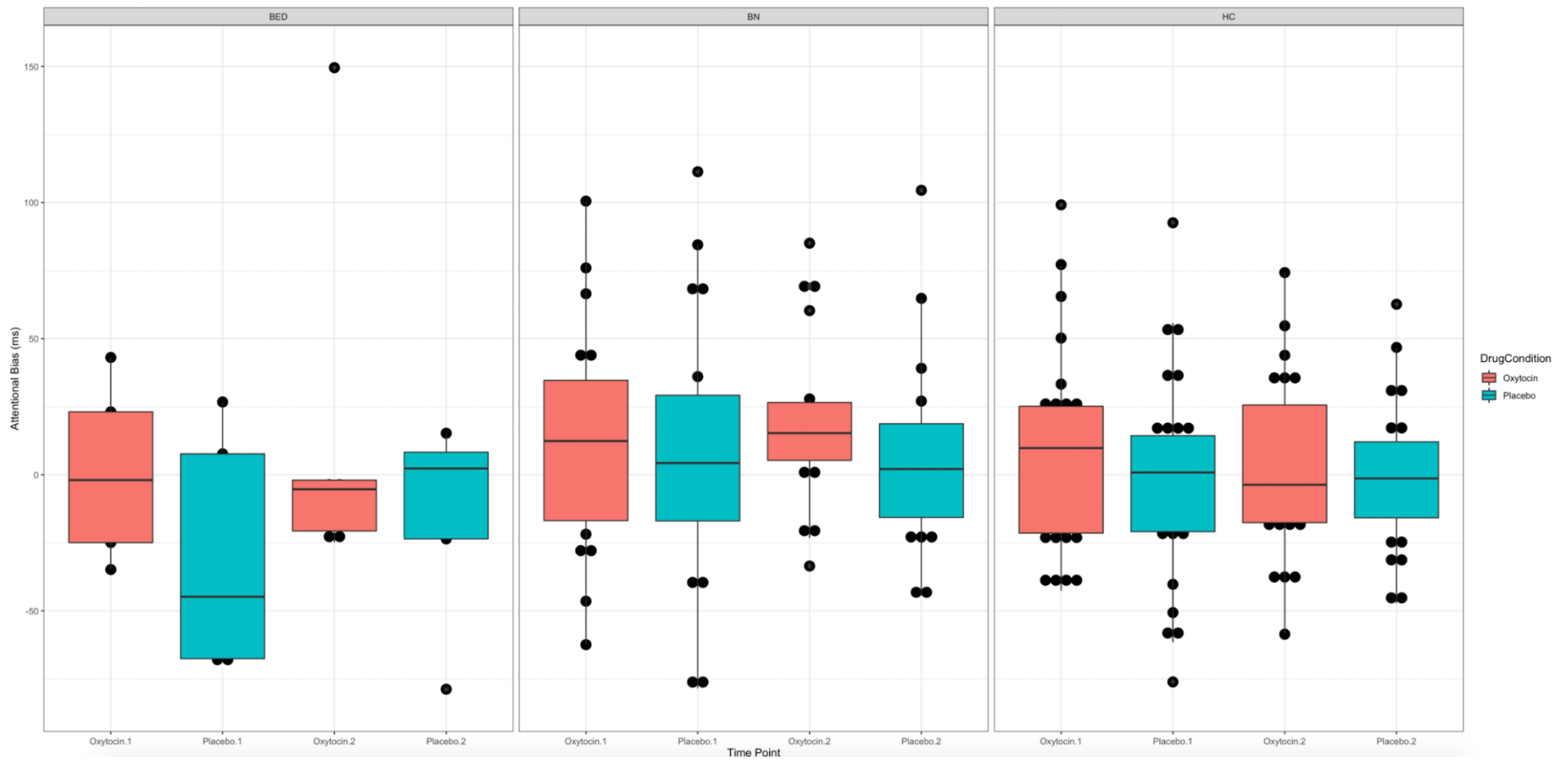
		HC ($n = 27$)	BN ($n = 25^{\dagger}$)	Fixed Effects
		Mean(SD)	Mean(SD)	
Before Taste Test	Oxytocin	10.07(37.200)	13.07(41.827)	ED Status: $Z = 9.39$, $SE = 5.662$, $df = 45.64$, $p = .104$
	Placebo	-0.53(38.897)	7.81(49.470)	Drug Condition: $Z = 8.11$, $SE = 4.662$, $df = 141.79$, $p = .084$
After Taste Test	Oxytocin	2.74(31.922)	20.09(32.629)	
	Placebo	-0.26(26.770)	6.93(35.809)	Experiment Time Point: $Z = -0.17$, $SE = 4.667$, $df = 143.35$, $p = .971$
				Random Effects
				Variance
				Individual Participant
				128.6
				Residuals
				1057.9

Note. BN = Bulimia nervosa; ED = Eating disorder; HC = Healthy control.

[†] Data for five participants was simulated based on the imputed mean for each drug condition and experiment time point among the participant group with bulimia nervosa



Supplementary Figure 9. The effect of oxytocin on attentional bias to food images. Time point 1 occurred after the full dose of oxytocin or placebo had been administered, but prior to the taste test. Time point 2 occurred after the taste test.



Supplementary Figure 10. A box and dotplot of the attentional bias data among each diagnostic group, separated by drug condition.

The Influence of Oxytocin on Risk-Taking in the Balloon Analogue Risk Task Among Women with Bulimia Nervosa and Binge Eating Disorder

Leslie, Monica^a;

Leppanen, Jenni^a;

Paloyelis, Yannis^a;

Nazar, Bruno Palazzo ^{a, b};

Treasure, Janet^a

Affiliations:

^a Institute of Psychiatry, Psychology and Neuroscience (IoPPN) - King's College London (KCL), London, United Kingdom

^b Institute of Psychiatry, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Corresponding Author: Monica Leslie – monica.leslie@kcl.ac.uk; - 103 Denmark Hill, Section of Eating Disorders, London SE5 8AF, United Kingdom

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Abstract

Previous theoretical models of bulimia nervosa (BN) and binge eating disorder (BED) have implicated cross-domain risk-taking behaviour as a significant maintenance factor in both disorders. The current study sought to test this hypothesis by administering the Balloon Analogue Risk Task (BART) to 25 women with BN or BED and 27 healthy comparison women without history of an eating disorder. Furthermore, we tested the effect of a divided dose of 64IU oxytocin on risk-taking behaviour in the BART. Contrary to our hypothesis, women with BN or BED did not exhibit baseline differences in performance on the BART in the placebo condition ($t = 1.42$, $df = 50$, $p = .161$, $d = 0.39$). Oxytocin did not have a main effect on performance in the BART ($F = 0.01$, $df = 1$, $p = .907$, $\eta^2_{\text{partial}} < .001$); however, there was an interaction such that participants in the BN/BED participant group, compared to the healthy comparison group, demonstrated safer behaviour on the BART specifically in the oxytocin condition, but not in the placebo condition ($F = 4.29$, $df = 1$, $p = .044$, $\eta^2_{\text{partial}} = .082$). These findings cast doubt on the common assumption that individuals with BN and BED exhibit greater risk-taking behaviour in all domains and add to evidence that oxytocin plays a functional role in modulating behaviours which entail trade-offs between reward approach and risk in humans. We recommend that future dose-response studies further investigate the effect of oxytocin on reward approach behaviour in women with recurrent binge eating behaviour and the clinical significance of this effect.

Keywords: Bulimia nervosa; binge eating disorder; oxytocin; risk-taking

Introduction

Recurrent loss-of-control binge eating characterises the DSM-5 eating disorders bulimia nervosa (BN) and binge eating disorder (BED) (American Psychiatric Association, 2013). Binge eating behaviour is associated with significant distress, guilt, and shame (American Psychiatric Association, 2013; Haedt-Matt & Keel, 2011; R. I. Stein et al., 2007), and detracts from the overall quality of life of affected individuals (Ágh, Kovács, et al., 2016).

Furthermore, populations with recurrent binge eating behaviour, including those with BN and BED, have been found to exhibit heightened levels of risk-taking behaviour, as evidenced by the high comorbidity of BN and BED with substance abuse disorders and self-harm behaviour (Gómez-Expósito et al., 2016; Hudson et al., 2007). The role of impulsivity in binge eating behaviour has been well-studied, and has been proposed to account for higher levels of risk-taking behaviour in populations with recurrent binge eating (Giel, Teufel, et al., 2017). However, there is evidence to suggest that both generalised reward approach processes and impulsivity contribute to trans diagnostic risk-taking behaviour, and that each set of processes is both conceptually and functionally distinct.

In the domain of adolescent risk-taking behaviour, for example, it has been observed that adolescents exhibit heightened levels of risk-taking in a virtual driving task when observed by peers versus when completing the task alone (Chein, Albert, O'Brien, Uckert, & Steinberg, 2011). These increases in risk-taking behaviour were found to be associated with heightened BOLD responses in the ventral striatum and orbitofrontal cortex, two regions strongly associated with reward processing (O'Doherty, 2004). No difference in BOLD response was observed in prefrontal "cognitive control circuits" between conditions (Chein et al., 2011). Whilst care must be taken when making

inferences from neuroimaging data to the structure of cognitive architecture, these data are at least compatible with the hypothesis that risk-taking is driven by a dual process incorporating the conflicting tendencies for both reward approach and danger avoidance.

The separability of reward-seeking and disinhibition in driving risk-taking behaviour is also supported by previous literature finding that levels of impulsivity and generalised reward-seeking follow separate development curves throughout adolescence and early adulthood (Steinberg, 2010). Indeed, it has been proposed that the convergence of high levels of reward-seeking with high levels of impulsivity account for the greater vulnerability to risk-taking behaviour observed in adolescents (Steinberg, 2010).

However, the role of reward-seeking, versus impulsivity, in driving risk-taking behaviour has received relatively less attention in empirical literature pertaining to adults with recurrent binge eating behaviour. Nonetheless, both conceptual and empirical formulations of risk-taking suggest that reduced reward-seeking should have the consequent effect of also reducing risk-taking behaviour (Rutledge et al., 2016).

One laboratory task measuring risk-taking behaviour is the Balloon Analogue Risk Task (BART) (Lejuez et al., 2002). In the BART, participants aim to maximise a virtual "reward" in a game-like task that entails gambling earnings made within each trial as participants continue to seek greater overall reward. Therefore, the risk posed by continued responding taps into the ratio of participants' tendency for reward approach versus punishment sensitivity (Dissabandara et al., 2014; Gray, 1970). Studies recruiting large community samples have found greater risk-taking behaviour on the BART among disinhibited, as opposed to restrained, eaters (Leitch, Morgan, & Yeomans, 2013; Yeomans & Brace, 2015), although this effect appears to be moderated by prior food consumption (Leitch et al., 2013) and exposure to food images (Yeomans & Brace, 2015).

Studies administering the BART in clinical eating disorder populations, however, have not yielded a clear pattern of results. Manasse et al. (2015), for example, found no differences on the BART between obese individuals with and without BED. Neveu et al. (2016) found that individuals with BN tend to exhibit less risky behaviour in the BART following exposure to food, versus neutral, images, but did not exhibit overall differences in behaviour compared to control participants. The study conducted by Neveu et al. (2016), however, was limited by low sample size, and the study conducted by Manasse et al. (2015) administered only 10 trials in the BART, while the BART was originally validated across 30 trials of balloons with the same probability of explosion. Therefore, limiting the task to 10 trials also limited power to detect differences between individuals with and without binge eating behaviour.

On the whole, however, the general pattern of responding on the BART in samples with subclinical binge eating behaviour has indicated greater levels of risk-taking behaviour, which is in line with studies finding greater risk-taking tendencies on other measures in populations with clinical levels of binge eating behaviour (Giel, Teufel, et al., 2017). In the current study, we therefore sought to investigate whether participants with clinical levels of recurrent binge eating behaviour would, indeed, be found to exhibit greater risk-taking tendencies on the BART given the greater sample size (Neveu et al., 2016) combined with a greater number of BART trials compared to previous investigations (Manasse et al., 2015).

Subsequently, it was of interest to examine whether the hypothesised risk-taking tendencies in women with recurrent binge eating could be reduced via modulation of underlying reward-seeking. Intranasal oxytocin supplementation has emerged as a new investigational approach to manage hedonic and over-eating behaviour in healthy and overweight men (Burmester et al., 2018; Ott et al., 2013; Spetter et al., 2018; Thienel et al., 2016) and in BN (Y.-R. Kim, J.-S. Eom, et al., 2015). While oxytocin may partially

impact food intake via the integration of central and peripheral homeostatic satiety signals (Leslie, Silva, et al., 2018), an increasing body of evidence suggests that the effects of oxytocin on feeding are also mediated by the modulation of reward processes (Burmester et al., 2018; Ott et al., 2013; Spetter et al., 2018). For example, the fact that oxytocin has been found to significantly curb eating of palatable food in sated healthy normal-weight men, but not homeostatic eating in fasted conditions, suggests that exogenous oxytocin administration has a stronger effect on reward-driven, as opposed to homeostatic eating (Burmester et al., 2018; Ott et al., 2013; Thienel et al., 2016).

With regards to the mechanism of effect of oxytocin on reward processing, it may be the case that exogenous oxytocin administration modulates dopaminergic functioning in mesolimbic regions. This hypothesis is supported by a range of pre-clinical studies, which have indicated that oxytocin directly stimulates dopamine release within the striatum, and reduces the likelihood of conditioned place preference to morphine in opioid-tolerant rats after a period of withdrawal (Georgiou et al., 2015). A recent review of the myriad direct and indirect effects of oxytocin in modulating opioid seeking and withdrawal effects has further highlighted the role of oxytocin in modulating reward-related central functions of noradrenaline, methamphetamine, serotonin, and glutamate (Zanos et al., 2018).

In humans, 24IU intranasal oxytocin administration has been found to increase blood-oxygenated-level dependent (BOLD) response to images of high, versus low, calorie foods within the ventromedial prefrontal cortex, supplementary motor area, ventrolateral prefrontal cortex, and anterior cingulate cortex of healthy men (Spetter et al., 2018). Of functional significance, the oxytocin-induced enhanced BOLD response in the right ventrolateral prefrontal cortex when viewing high- versus low-calorie food images was inversely correlated with the consumption of sweet ingredients in a breakfast meal. While hypotheses stemming from these findings are still speculative, it may be the

case that oxytocin enhances cognitive control over hedonic eating behaviour. In a similar study conducted in healthy adult women, the authors found a trend-level effect of 24IU oxytocin administration in successfully supporting the intentional reduction of food craving in response to food images (Striepens et al., 2016). On the whole, previous preliminary evidence has therefore supported a role for oxytocin in modulating reward processing. However, it is not yet clear to what extent oxytocin modulates eating behaviour or general reward approach behaviours in the context of risk-taking tendencies in women with recurrent loss-of-control binge eating (Y.-R. Kim, J.-S. Eom, et al., 2015; Leslie, Leppanen, et al., 2018).

In the current study, we sought to compare the performance of women with clinical levels of recurrent binge eating on the BART to that of control women without previous history of an eating disorder. Furthermore, we also aimed to investigate the differential effect of intranasal oxytocin on risk-taking in the BART in women with BN and BED compared to healthy controls. Based on theoretical models suggesting the existence of cross-domain risk-taking (Pearson, Wonderlich, & Smith, 2015), we hypothesised that women with BN and BED would demonstrate greater baseline risk-taking behaviour on the BART in the placebo condition, relative to women without previous history of an eating disorder. Additionally, given previous research indicating that oxytocin induces a down-regulation of reward seeking in men, we hypothesised that a divided dose of 64IU intranasal oxytocin, versus placebo, would be associated with reduced risk-taking behaviour in the BART in women, and that this effect would be stronger in women with BN and BED due to higher trait levels of risk-taking behaviour.

Methods

Participants

Fifty-two women participated in the current study. Given that recurrent binge eating behaviour was the primary trait of interest in the current study, and that populations with BN and BED are both characterised by recurrent loss-of-control binge eating behaviour, we therefore recruited a heterogeneous sample of women who met criteria for either disorder. Twenty-five women met DSM-5 criteria for BN or BED at the time of the study and twenty-seven comparison women had no history of an eating disorder and no current psychiatric disorder (American Psychiatric Association, 2013). Participants were recruited via the internal research circular at King's College London, the website for the UK eating disorders charity Beat, and through flyers posted on community bulletin boards. By chance, an unequal number of participants with BN ($n = 20$) versus BED ($n = 5$) volunteered to take part in the study during the recruitment period. Ethical approval for the current study was granted by the London – Camberwell St Giles NHS Research Committee (reference: 14/LO/2115).

Inclusion criteria for the study were as follows: age between 18 and 40 years old, English fluency, and right-handedness (due to an MRI scan which was conducted within the battery of tasks). Exclusion criteria included pregnancy, severe psychiatric comorbidity (*e.g.*, current or previous history of substance abuse disorder, psychosis), currently smoking > 5 cigarettes per day (past 6 months), consuming > 21 units of alcohol per week, uncompensated general medical conditions that could alter eating habits (*e.g.*, diabetes, hypothyroidism), history of a neurological condition (*e.g.*, epilepsy), a significant visual impairment not corrected by eyewear, currently suffering from a cold or flu (as this can affect nasal absorption of the oxytocin), contraindication to MRI scans, and current intake of medication that might potentially interact with oxytocin (*e.g.*, Prostaglandins).

Eligibility for the current study was determined through a phone screening, which included an interview using the eating disorders module of the Structured Clinical

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Interview for DSM-5 – Research Version (SCID) (American Psychiatric Association, 2013). Phone screenings were conducted by MSc and PhD students who had received training in the correct use of SCID for DSM-5.

Seven participants in the BN/BED participant group self-reported at least one comorbid psychiatric disorder: 5 women had comorbid depression, 4 women had borderline personality disorder, 4 women had comorbid generalised anxiety disorder, 1 woman had obsessive-compulsive disorder, 1 woman had social anxiety, and 1 woman had an autism spectrum disorder. At the time of the study, 7 women were taking an antidepressant, 1 woman was taking an antipsychotic drug, and 1 woman was taking a mood stabiliser. Participants with BN and BED reported an average binge eating frequency of 14.14 episodes over the past 28 days ($SD = 9.88$). The women with BN 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.

Participants self-reported their use of hormonal contraception or the first day of their most recent menstrual period and this information was used to determine menstrual phase at the time of the study for each participant. Twenty-two participants reported taking hormonal contraception at the time of the study. Fifteen women completed the study in the follicular phase of the menstrual cycle and thirteen women completed the study in the luteal phase of the menstrual cycle. Menstrual phase data were missing for two women. Descriptive statistics regarding the age, BMI, and education level of the BN/BED and comparison participant groups are presented in **Table 30**.

Procedure

The current study used a double-blind placebo-controlled crossover design. Each participant attended the laboratory for an initial orientation visit and two experimental visits. Each participant completed an online battery of psychological tests between the orientation visit and the first experimental visit. Two of the tests, the Depression, Anxiety, and Stress Scales and the Eating Disorders Examination – Questionnaire version, will be described in further detail below. During each experimental visit, participants self-administered a divided dose of 64IU intranasal oxytocin or an equal volume of a placebo nasal spray. The order of oxytocin versus placebo administration was pseudo-randomised for each participant, such that the same number of participants received oxytocin on the first, versus the second, visit. Experimental study visits were held two days apart to ensure that each woman was in the same phase of the menstrual cycle during each visit. Perfusion data analysing the central effects of oxytocin suggest that carryover effects from oxytocin administration on the first experimental visit to the second experimental visit are highly unlikely (Paloyelis et al., 2016).

The first 40IU dose of intranasal oxytocin, or equal volume of placebo, was administered at approximately 5.50pm during each experimental visit. Participants subsequently underwent an arterial spin labelling (ASL) scan and fMRI scan, in which they were presented with images and flavours of water and chocolate milk. These neuroimaging results are not reported in the current paper. We chose to administer a 40IU dose of oxytocin prior to the fMRI scan in order to replicate the Y.-R. Kim, J.-S. Eom, et al. (2015) protocol, which found an effect of oxytocin on eating behaviour in women with BN at this dose. We additionally chose this dose in order to replicate the protocol of a previous study investigating the effects of intranasal oxytocin on cerebral blood perfusion in men (Martins, Mazibuko, et al., 2019). A comparison analysis with the previous ASL data found in men is currently in preparation for publication.

However, previous findings in humans have suggested that peak central effects of 40IU intranasal oxytocin occur 39-51 minutes following administration (Paloyelis et al., 2016), thus suggesting the need for an additional dose after this time. Therefore, following the conclusion of the fMRI scan, each participant self-administered the remaining 24IU of oxytocin or equal volume of placebo at approximately 7.10pm. Following this second dose of oxytocin each participant completed the Balloon Analogue Risk Task, which is described below. At the conclusion of the study, participants were prompted to indicate whether they had received oxytocin or placebo on that occasion to test the effectiveness of drug blinding. Drug blinding was found to be effective, as participants guessed drug condition correctly on 57 out of the total 104 visits (54.8% of visits), which was not significantly different from chance ($p = .377$). There was not a significant difference in the frequency of binge eating episodes in the 24-hr period following oxytocin administration, versus placebo administration, among the participants with BN and BED (see **Supplementary Material**).

The Balloon Analogue Risk Task

The Balloon Analogue Risk Task (BART) is a validated measure of risk taking behaviour, which is presented on a computer (Lejuez et al., 2002). Each participant is presented with a total of 30 balloon trials. During each trial, the participant is informed that each additional click of the computer mouse will add one pump to the balloon, which is associated with an additional virtual £0.05 added to their total task bank. Once the participant believes they have collected enough money for that task trial, they press on a button reading “Collect” to collect their total earnings for that task trial and proceed to the next trial. However, each balloon is programmed to explode after a different random number of pumps. Participants do not collect any money on trials where the balloon explodes before the participant chooses to collect their earnings.

The BART yields three measures of risk-taking tendency: the adjusted average pump count, total pump count, and total explosion count. The adjusted average pump count is sensitive to general risk-taking tendency on trials without a balloon explosion, as the pump count for trials in which the balloon explodes are excluded from the adjusted average pump count measure. A greater adjusted average pump count therefore indicates greater risk-taking tendency. The total number of balloon explosions captures continued risk-taking tendency after experiencing previous “punishment” for that risk-taking behaviour (in the form of prior balloon explosions). The adjusted average pump count is generally considered superior to the total pump count, which has an artificial ceiling on pumps imposed on trials in which the balloon does explode, thus potentially artificially suppressing variance between individuals’ performance (Lejuez et al., 2002). In line with standard administration of the BART, the total pump count will therefore not be considered in the current paper (Lejuez et al., 2002). As both adjusted average pump count and total number of balloon explosions both tap into general risk-taking tendency, these measures are positively correlated with each other ($r = .91$) (Lejuez et al., 2007; Lejuez et al., 2002). However, previous work has found interpersonal differences in responding to “win” versus “loss” trials, depending on whether the balloon exploded in the previous trial. Specifically, compared to adults, adolescents are more sensitive to the previous trial’s outcome, responding with more pumps after win trials and fewer pumps after loss trials (S. H. Mitchell, Schoel, & Stevens, 2008). Additionally, men are more likely to continue to respond with a greater number of pumps after loss trials (Cazzell, Li, Lin, Patel, & Liu, 2012). Given that the total number of balloon explosions taps into continued risk-taking following previous loss trials, there is evidence to suggest that total number of balloon explosions additionally captures risk tolerance following previous loss, which is not captured by the adjusted average pump count. Accordingly, we have

operationalised our hypotheses regarding risk-taking tendency in the BART in terms of both the adjusted average pump count and total number of balloon explosions.

Psychometric Tests

Depression, Anxiety, and Stress Scales. The Depression, Anxiety, and Stress Scales, 21-item version (DASS) is a short measure of negative emotions experienced over the course of the past week for the individual (Lovibond & Lovibond, 1995). Each item is presented as a 4-point Likert scale, anchored as 0 (“Did not apply to me at all”), 1 (“Applied to me some degree, or some of the time”), 2 (“Applied to me to a considerable degree or a good part of the time”), and 3 (“Applied to me very much or most of the time”). The total score for each subscale of the 21-item DASS is calculated by summing participants’ responses to the items for each subscale and multiplying this sum by two. Higher scores for each subscale therefore indicate greater levels of depression, anxiety, and stress, respectively. Each subscale of the DASS was associated with very good or excellent internal consistency reliability in the current study: Depression subscale $\alpha = 0.96$; Anxiety subscale $\alpha = 0.88$; Stress subscale $\alpha = 0.93$. The DASS-21 exhibits good discriminant and convergent validity, when results are compared against other psychometric measures of depression and anxiety (Henry & Crawford, 2005). Descriptive statistics associated with the DASS for each participant group are presented in **Table 31**.

Eating Disorder Examination – Questionnaire Version. The Eating Disorder Examination – Questionnaire Version (EDE-Q) is a self-report questionnaire measuring eating disorder psychopathology and the frequency of eating disorder behaviours (Fairburn & Beglin, 1994a). The psychopathology section of the EDE-Q contains four subscales presented in the form of a 7-point Likert scale: a Restraint subscale, an Eating Concern subscale, a Weight Concern subscale, and a Shape Concern subscale. The Likert scale prompts participants to report on how many days they exhibited each item of eating

disorder psychopathology, in which response to each item are anchored from 0 (“No days”) to 6 (“Every day”). Each subscale of the EDE-Q was associated with excellent internal consistency reliability in the current sample: Restraint subscale $\alpha = 0.92$; Eating Concern subscale $\alpha = 0.93$; Shape Concern subscale $\alpha = 0.97$; Weight Concern subscale $\alpha = 0.94$. The EDE-Q is associated with acceptable criterion validity, with significantly different mean scores for each subscale among individuals with, versus without, a current eating disorder (Mond, Hay, Rodgers, Owen, & Beumont, 2004). Descriptive statistics associated with the EDE-Q subscales for each participant group are reported in **Table 32**.

Statistical Analyses

All analyses were conducted in IBM SPSS Statistics version 24. Differences in performance on the BART in the placebo condition between women in the BN/BED group and comparison women were analysed using Student’s *t*-test. The effects of oxytocin and eating disorder status on the adjusted average pump count and total balloon explosions in the BART were analysed with 2 x 2 mixed-design ANOVAs. The independent variables for each analysis were eating disorder status (healthy control versus BN/BED) and drug condition (placebo versus oxytocin).

Results

The data were first inspected for outliers and assumptions of normality. There were no outliers ($Z > |3.0|$) in the Adjusted Pump Count or Total Explosions variables. Both variables were approximately normally distributed (skew $< |2.0|$, kurtosis $< |9.0|$) (Schmider, Ziegler, Danay, Beyer, & Bühner, 2010). Descriptive statistics for the BART data are presented in **Table 33**. Correlations between the adjusted average pump count variable and the total explosion variable within the healthy control group were $r = .87$ ($p < .001$) and $r = .91$ ($p < .001$), for the placebo and oxytocin conditions, respectively. Correlations between the adjusted average pump count variable and the total explosion

variable within the BN/BED group were $r = .90$ ($p < .001$) and $r = .95$ ($p < .001$), for the placebo and oxytocin conditions, respectively. Given the high correlation between the adjusted average pump count variable and the total explosion variable and the fact that there were only two main analyses, we deemed it excessively conservative to control for multiple comparisons using a Bonferroni correction due to the high risk of a Type II error (Bland & Altman, 1995).

Adjusted Average Pump Count

We tested baseline differences between women with BN/BED and comparison women on the adjusted average pump count using Student's t -test. There was no significant difference between the two participant groups on the adjusted average pump count in the placebo condition ($t = 1.11$, $df = 50$, 95% CI [-2.95, 10.29], $p = .270$, $d = 0.31$). We tested the influence of oxytocin and eating disorder status on the adjusted average pump count using a 2x2 mixed-design ANOVA. Participants without history of an eating disorder did not exhibit a significant difference on the average adjusted average pump count variable compared to participants in the BN/BED group ($F = 2.99$, $df = 1$, $p = .090$, $\eta^2_{\text{partial}} = .059$). The main effect of drug condition on the adjusted average pump count was also non-significant ($F = 0.02$, $df = 1$, $p = .888$, $\eta^2_{\text{partial}} < .001$), as was the Drug Condition*Eating Disorder Status interaction ($F = 0.90$, $df = 1$, $p = .348$, $\eta^2_{\text{partial}} = .018$). A line graph depicting the adjusted average pump count for each participant group and drug condition is depicted in **Supplementary Figure 11**.

Total Explosions

There was no significant difference in balloon explosions between the healthy comparison (HC) and BN/BED participant group in the placebo condition ($t = 1.42$, $df = 50$, 95% CI [-0.58, 3.43], $p = .161$, $d = 0.39$). We tested the influence of oxytocin and eating disorder status on the total number of balloon explosions using a 2x2 mixed-design

ANOVA. The main effect of drug condition on total number of explosions was not significant ($F = 0.01$, $df = 1$, $p = .907$, $\eta^2_{\text{partial}} < .001$). Participants in the HC group exhibited a significantly greater number of balloon explosions ($F = 4.06$, $df = 1$, $p = .050$, $\eta^2_{\text{partial}} = .078$). There was a significant interaction between drug condition and eating disorder status: the HC group exhibited a numerically greater number of balloon explosions in the oxytocin condition compared to the placebo condition, while participants in the BN/BED group had fewer balloon explosions in the oxytocin condition compared to the placebo condition ($F = 4.29$, $df = 1$, $p = .044$, $\eta^2_{\text{partial}} = .082$). A line graph depicting the number of total balloon explosions for each participant group in each drug condition is presented in **Supplementary Figure 12**.

Post hoc *t*-tests revealed that the difference in total balloon explosions between placebo and oxytocin conditions was not statistically significant when the data was isolated among the BN/BED participant group ($t = 1.20$, $df = 23$, 95% CI [-0.42, 1.59], $p = .241$, $d = 0.30$), nor among the healthy comparison participant group ($t = -1.82$, $df = 25$, 95% CI [-1.39, 0.09], $p = .081$, $d = 0.27$). However, the difference in balloon explosions between the two groups did depend on drug condition. As stated previously, there was no significant difference in balloon explosions between the HC and BN/BED participant group in the placebo condition ($t = 1.42$, $df = 50$, 95% CI [-0.58, 3.43], $p = .161$, $d = 0.39$). However, the HC group did have significantly greater balloon explosions than the BN/BED group in the oxytocin condition ($t = 2.50$, $df = 48$, 95% CI [0.51, 4.71], $p = .016$, $d = 0.71$). As reported in **Table 34**, there were no significant correlations between depression, anxiety, stress, or eating disorder psychopathology and balloon explosions in the oxytocin or placebo condition among the BN/BED participant group.

We subsequently conducted a sensitivity analysis to investigate the potential moderating effect of menstrual phase (follicular phase, luteal phase, or hormonal contraception) on the effect of oxytocin on performance in the BART with 3x2 mixed-

design ANOVAs for the adjusted average pump count and the total number of balloon explosions. There was neither a significant main effect nor a significant interaction with oxytocin for either dependent variable. The full results of the ANOVA testing the influence of menstrual phase on adjusted average pump count are reported in **Supplementary Table 11**, and the results of the ANOVA testing the influence of menstrual phase on the total number of balloon explosions are reported in **Supplementary Table 12**.

Discussion

The current study aimed to test differences in risk-taking performance on the BART among women with and without clinical levels of recurrent binge eating, which includes women with both BN and BED, as compared to healthy comparison women. Additionally, we investigated the effect of a divided dose of 64IU intranasal oxytocin on risk-taking behaviours in the BART among women with BN and BED, as well as women without prior history of an eating disorder. We hypothesised that women with BN and BED would demonstrate greater risk-taking behaviour on the BART in the placebo condition. This hypothesis was not supported, as there were no significant differences in performance on the BART between the BN/BED and HC participant groups in the placebo condition. We also hypothesised that prior administration of intranasal oxytocin, versus placebo administration, would be associated with reduced risk-taking behaviour on the BART. Our second hypothesis was also not supported as there was no overall effect of oxytocin on the adjusted average pump count or total balloon explosion count in the BART. Our final hypothesis was that the effect of oxytocin on reducing risk-taking behaviour on the BART would be stronger in women with BN and BED, compared to women without history of an eating disorder. Our final hypothesis was partially supported, as oxytocin was associated with lower risk-taking tendencies among the BN/BED, versus healthy comparison, participant group for the total balloon explosions

count. However, there was no such significant moderating effect for the adjusted average pump count variable.

Despite the fact that the moderation effect between participant group and drug condition did not reach significance for the adjusted average pump count variable, it is interesting to note that the direction of effect was in the same direction as for the balloon count variable. That is, participants in the HC group exhibited numerically greater risk-taking tendency compared to the BN/BED participant group in the placebo condition, and this difference was enhanced further in the oxytocin condition. That is, the healthy control group displayed numerically higher risk-taking in the oxytocin versus placebo condition for both variables, and the BN/BED participant group displayed numerically lower risk-taking in the oxytocin versus placebo condition for both variables. The lack of significant differences observed in the adjusted average pump count variable is likely a result of the greater variability in performance on this measure. It would therefore be interesting to investigate further in future studies with larger sample sizes in order to ensure adequate power. This replication is especially important given that we did not statistically control for the two analyses conducted. On the whole, however, given that the same pattern of effect was observed for both BART variables, these findings therefore suggest that the effect of oxytocin on risk-taking tendencies in the BART is moderated by baseline individual differences.

The differential effect of oxytocin on risk-taking performance in the BART may relate to differences in oxytocin functioning among women with BN compared to healthy comparison women. For example, Y.-R. Kim, J.-H. Kim, et al. (2015) have found that the G allele of the rs53576 oxytocin receptor gene polymorphism is associated with greater risk for BN. Similarly, Micali, Crous-Bou, et al. (2017) found that the GG variant of the same gene is associated with greater bingeing and purging behaviour in women. Micali, Crous-Bou, et al. (2017) also found evidence of a gene X environment interaction, such

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that the AG/GA variant of the rs2254298 oxytocin receptor gene polymorphism is associated with greater binge and purging behaviour specifically in the context of poor maternal care. This pattern of findings suggests that differences in oxytocinergic functioning play a functional role in recurrent binge-purge behaviour. Additionally, one can speculate that the administration of exogenous oxytocin may differentially affect risk-taking tendencies via different patterns of central receptor binding in each participant group. It is possible that these differences may be related to neural circuits including the nucleus accumbens and ventral tegmental area, both of which contain a high density of oxytocin receptors and hold great significance in underpinning appetite behaviour and the processing of reward receipt; however, this hypothesis requires further evidence for corroboration (Grinevich, Knobloch-Bollmann, Eliava, Busnelli, & Chini, 2016).

With regards to the lack of statistically significant baseline differences in risk-taking on the BART between HC and BN/BED groups, the current results add to a mixed field of findings on the BART among participants with disinhibited eating. In non-clinical samples of participants with disinhibited eating, defined by higher scores on the Disinhibition scale of the Three Factor Eating Questionnaire (Stunkard & Messick, 1985), greater levels of risk-taking behaviour on the BART have been observed following prior exposure to food images and food consumption (Leitch et al., 2013; Yeomans & Brace, 2015). The presentation of food stimuli was replicated in the current study given that participants viewed images and received small sips of chocolate milk during the course of the fMRI task conducted prior to the BART. However, we failed to observe greater risk-taking behaviour in the BN/BED participant group in the placebo condition.

By contrast to previous research in sub-clinical samples of disinhibited eaters, previous studies recruiting clinical samples of participants with BN or BED found similar findings to those reported in the current study. That is, there was no difference in responding on the BART among obese participants with or without BED (Manasse et al.,

2015), nor between participants with BN and healthy comparison participants (Neveu et al., 2016). On the whole, these findings demonstrate that individuals with BN and BED do not demonstrate greater risk-taking on the BART and, if anything, instead exhibit numerically smaller risk-taking tendency.

With regards to limitations in interpreting the current findings, it should be noted that tasks such as the BART have been previously criticised for their limited utility in measuring the type of impulsive behaviour generally exhibited by individuals with clinical levels of recurrent binge eating. For example, Leitch et al. (2013) found that women with disinhibited eating tended to display higher levels of “Reflective impulsivity”, defined by a failure to compile and evaluate relevant information before making a decision, as compared to tendencies to perform differently on measures of “Impulsive actions” and “Impulsive choices”. Additionally, it is also possible that laboratory tasks involving virtual rewards may lack the reward value for participants which would elicit behaviours representative of real-world risk-taking, and more general reward-approach behaviours. Indeed, a similar measure of risk-taking behaviour, the Iowa Gambling Task, has recently been criticised for being poorly correlated with self-reported real-life risk-taking behaviour (Schmitz, Kunina-Habenicht, Hildebrandt, Oberauer, & Wilhelm, 2018), leading to increased interest in the BART as an alternative measure of decision-making in risk-taking scenarios. Future validation studies would be useful in more firmly establishing the ecological validity of risk-taking tasks among populations with binge eating behaviour.

Limitations of the current study also include small sample size, which limited our power to detect small effects. Additionally, the neural effects of oxytocin are moderated by dose (Cardoso et al., 2013) time and method of administration (Paloyelis et al., 2016), so it is possible that a different pattern of effects would have been observed using different doses or methods of administration. It would also be interesting to further explore

differences with and without prior exposure to images of food or calorie-dense drinks and without prior administration of the fMRI scan, which may have affected responding on the BART by exposing participants to an unfamiliar stressor. Given differences in hormonal secretion across the course of circadian cycles (Forsling, Montgomery, Halpin, Windle, & Treacher, 1998), which may have interacted with the effect of the exogenously-administered oxytocin, it should also be noted that the current results may not generalise to different times of day (e.g., in the morning or early afternoon). Finally, given the possibility for error inherent in participants self-reporting menstrual phase, future studies can improve accuracy in assessing the interaction between menstrual phase and exogenous oxytocin by testing blood concentrations of follicle stimulating hormone.

Clinical Implications

Previous research has described BN as being characterised by elevated levels of both reward and punishment sensitivity (Harrison, O'Brien, Lopez, & Treasure, 2010). The fact that BN is commonly comorbid with substance use disorders (O'Brien & Vincent, 2003) has contributed to the hypothesis that reward approach behaviours tend to “win out” over fear of punishment across life domains (Treasure et al., 2018; Waxman, 2009). However, the current findings add to previous work using the BART to suggest that elevated risk-taking behaviour is not always evident in BN/BED. Previous work has suggested that elevated levels of risk-taking behaviour may exist predominantly in subgroup of people with BN comorbid with either borderline personality disorder (O'Brien & Vincent, 2003) or attention-deficit/hyperactivity disorder (Nazar et al., 2018). Future research would therefore be helpful to determine whether there is differential responsiveness to reward, versus punishment, in women with comorbid BN and borderline personality disorder versus women without a comorbid personality disorder.

Conclusion

To conclude, the current study aimed to replicate previous studies comparing performance on the BART between women with clinical levels of recurrent binge eating to comparison women without history of an eating disorder. We further aimed to investigate the influence of intranasal oxytocin on risk-taking in the BART among women with BN and BED and comparison women without history of an eating disorder. There were no significant baseline differences in performance on the BART between women with and without BN or BED in the placebo condition. We found evidence of a significant interaction for the balloon explosion variable such that a divided dose of 64IU oxytocin enhanced initial numerical differences in risk-taking between the participant groups: increasing risk-taking in the healthy control group and decreasing risk-taking in the BN/BED participant group. Although not reaching significance, the same trend was observed for the adjusted average pump count variable. Future studies with greater power would be useful in further clarifying whether cross-domain heightened risk-taking is restricted to some subgroups of people with BN.

Table 30*Descriptive demographic data*

	Healthy Control (<i>n</i> = 27)		BN/BED (<i>n</i> = 25)	
	Median	IQR	Median	IQR
Age	23.50	5.50	23.50	9.75
BMI	22.04	1.76	23.09	3.87
RQF Education Level	6	4	4.5	3

Note. BN = bulimia nervosa; BED = binge eating disorder; IQR = interquartile range; BMI = body mass index; RQF = Regulated Qualifications Framework.

Table 31*Descriptive statistics for the Depression, Anxiety, and Stress Scales (21-item version)*

	Healthy Control (<i>n</i> = 26)		BN/BED (<i>n</i> = 25)		<i>d</i>	<i>t</i>	<i>df</i>	<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>				
Depression Scale	1.92	3.08	21.42	11.32	2.37	-8.31	27.53	< .001
Anxiety Scale	1.04	1.54	12.16	9.18	1.69	-5.97	25.35	< .001
Stress Scale	2.88	3.17	20.56	11.20	2.19	-7.59	27.81	< .001

Note. BN = bulimia nervosa; BED = binge eating disorder; EDE-Q = Eating Disorder Examination – Questionnaire Version.

Table 32

Descriptive statistics for the Subscales of the Eating Disorder Examination – Questionnaire Version

	Healthy Control (<i>n</i> = 26)		BN/BED (<i>n</i> = 25)			
	<i>Median</i>	<i>IQR</i>	<i>Median</i>	<i>IQR</i>	<i>U</i>	<i>p</i>
EDE-Q Restraint	0.40	0.70	4.00	2.10	577.50	< .001
EDE-Q Eating Concern	0.00	0.20	4.20	1.90	649.00	< .001
EDE-Q Weight Concern	0.40	0.85	4.80	1.50	623.00	< .001
EDE-Q Shape Concern	1.20	0.63	5.63	1.63	627.50	< .001

Note. BN = bulimia nervosa; BED = binge eating disorder; EDE-Q = Eating Disorder Examination – Questionnaire Version.

Table 33

Descriptive statistics for performance on the Balloon Analogue Risk Task, separated by eating disorder status

Healthy Control (<i>n</i> = 27)					BN/BED (<i>n</i> = 25)			
	Placebo		Oxytocin		Placebo		Oxytocin	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Adjusted Average Pump Count	37.62	10.656	38.43	12.033	33.95	13.061	31.95	10.926
Total Explosions	8.70	3.760	9.19	3.950	7.28	3.422	6.58	3.387

Note. BN = bulimia nervosa; BED = binge eating disorder.

Table 34

Pearson correlations between the total balloon explosions among the BN/BED participant group and the DASS and EDE-Q scales

	1	2	3	4	5	6	7	8
1. Total Explosions(PL)	-							
2. Total Explosions (OT)	.76***							
3. DASS Stress Scale	-.01	-.06						
4. DASS Depression Scale	-.02	-.22	.69***					
5. DASS Anxiety Scale	.22	.27	.67***	.35				
6. Restraint	.05	.27	.10	-.12	.16			
7. Eating Concern	.14	.31	.16	-.18	.27	.48*		
8. Shape Concern	-.04	.17	.08	-.03	.17	.51*	.71***	
9. Weight Concern	.05	.18	.31	-.03	.33	.41*	.78***	.81***

Note. BN = bulimia nervosa; BED = binge eating disorder; DASS = Depression, Anxiety, and Stress Scales; EDE-Q = Eating Disorder Examination – Questionnaire version; OT = oxytocin condition; PL = placebo condition.

* $p < .05$.

*** $p < .001$.

Supplementary Material

Effect of oxytocin on subsequent incidence of binge eating

We conducted an exact binomial test to determine whether oxytocin impacted whether participants with bulimia nervosa or binge eating disorder 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 ($p = .999$).

Supplementary Table 11

Results of the 2x2 mixed-design ANOVA testing the moderating influence of oestrous phase on the effect of oxytocin on adjusted average pump count in the BART

	<i>F</i>	<i>df</i>	<i>p</i>	η^2_{partial}
Drug Condition	0.03	1	.857	.001
Oestrous Phase	1.47	2	.242	.061
Drug Condition*Oestrous Phase	0.44	2	.646	.019

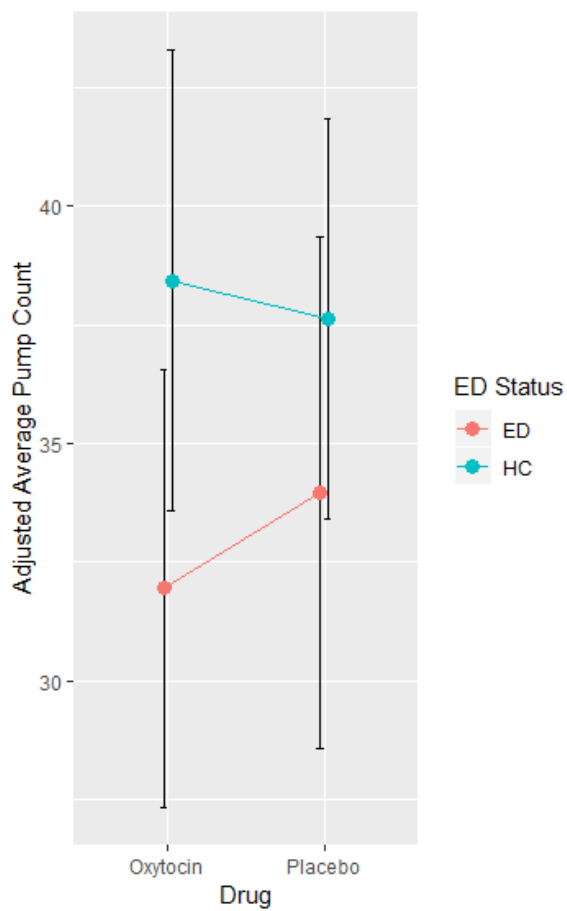
Note. BART = Balloon Analogue Risk Task.

Supplementary Table 12

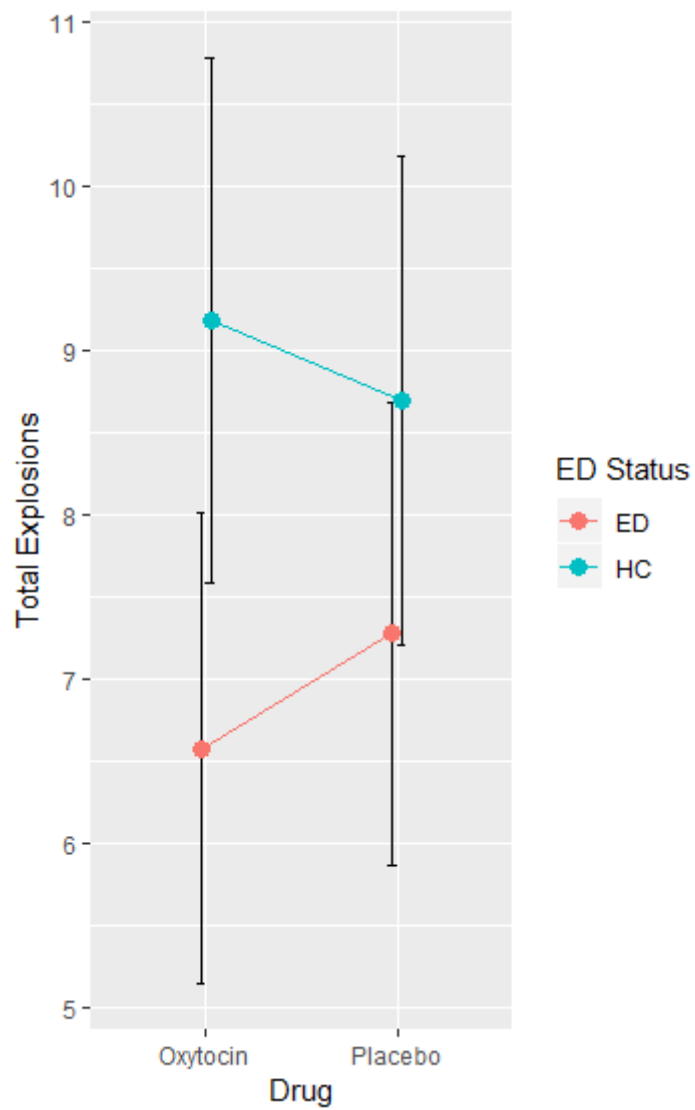
Results of the 2x2 mixed-design ANOVA testing the moderating influence of oestrous phase on the effect of oxytocin on total balloon explosions in the BART

	<i>F</i>	<i>df</i>	<i>p</i>	η^2_{partial}
Drug Condition	0.15	1	.698	.003
Oestrous Phase	0.37	2	.691	.016
Drug Condition*Oestrous Phase	1.92	2	.158	.079

Note. BART = Balloon Analogue Risk Task.



Supplementary Figure 11. The influence of oxytocin on the adjusted average pump count variable. ED = eating disorder participant group; HC = healthy control participant group. Error bars represent confidence intervals.



Supplementary Figure 12. The influence of oxytocin on total balloon explosions. ED = eating disorder participant group; HC = healthy control participant group. Error bars represent confidence intervals.

Chapter 6

6 The influence of oxytocin on the neural processing of palatable taste

6.1 The influence of oxytocin on the neural processing of palatable taste in women with and without bulimia nervosa or binge eating disorder: Preliminary outcomes

The Influence of Oxytocin on the Neural Processing of Palatable Taste in Women With and Without Bulimia Nervosa or Binge Eating Disorder: Preliminary Outcomes

Leslie, Monica^a;

Leppanen, Jenni^a;

Treasure, Janet^a;

Paloyelis, Yannis^a

Affiliations:

^a Institute of Psychiatry, Psychology and Neuroscience (IoPPN) - King's College London (KCL), London, United Kingdom

Corresponding Author: Monica Leslie – monica.leslie@kcl.ac.uk; - 103 Denmark Hill, Section of Eating Disorders, London SE5 8AF, United Kingdom

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Abstract

Background: Bulimia nervosa and binge eating disorder are DSM-5 eating disorders characterized by recurrent loss-of-control binge eating episodes. Recent evidence has suggested that intranasal oxytocin administration can reduce food craving and increase cognitive control over food craving. However, previous research has not yet explored the effect of oxytocin on the neural processing of the receipt of palatable taste or differences in this effect between women with and without loss-of-control binge eating. The current study sought to address this gap in the literature through the use of functional magnetic resonance imaging (fMRI). We hypothesized: 1) That women with BN and BED would exhibit heightened BOLD response in the orbitofrontal cortex (OFC), ventral tegmental area (VTA) and nucleus accumbens (NAcc) in response to the image of chocolate milk, versus the image of water; 2) That women with BN and BED would exhibit lower BOLD response than healthy comparison women in the same regions in response to the actual receipt of chocolate taste, versus water taste; 3) That oxytocin would suppress BOLD response in the OFC, VTA, NAcc, and hypothalamus in response to chocolate images, versus water images, in both groups of women; 4) That there would be a diagnosis x drug interaction such that oxytocin would suppress BOLD activation in the OFC, VTA, NAcc, and hypothalamus to a greater extent in women with BN or BED versus healthy comparison women in response to images of chocolate milk versus images of water.

Methods: We recruited 25 women with bulimia nervosa or binge eating disorder and 25 healthy comparison women. Each participant attended the lab for two experimental sessions, receiving 40IU intranasal oxytocin prior to the fMRI scan during one session, and an equal volume of placebo nasal spray during the opposite session. Both the participant and experimenters were blind to the order of drug allocation. During the fMRI scan participants viewed a series of images of a glass of water or a glass of chocolate milk and received the corresponding drink, water or chocolate milk, through a mouthpiece on a random set of trials.

Results: We did not observe significant differences in neural activation between women with BN or BED, versus healthy control women, in response to the anticipation or receipt of chocolate taste, versus water taste. The administration of 40IU intranasal oxytocin, versus placebo, did not affect the BOLD response to the anticipation or receipt of chocolate taste, versus water taste, in either participant group. However, the ventral striatum and orbitofrontal cortex were not included in the analysis presented here due to a technical issue, thus presenting a significant caveat to interpreting the current preliminary findings.

Conclusions: As we proceed with processing the current dataset, it will be important to conduct region-of-interest analyses including the basal ganglia and orbitofrontal cortex in order to investigate potential differences in neural activation in these reward-related circuits between participant groups and in response to oxytocin, versus placebo, administration.

Bulimia nervosa (BN) and binge eating disorder (BED) are DSM-5 eating disorders characterized by recurrent loss-of-control binge eating (American Psychiatric Association, 2013). Current gold standard treatments for bulimia nervosa and binge eating disorder are associated with only modest remission rates (Hay, 2013; Shingleton, Thompson-Brenner, Thompson, Pratt, & Franko, 2015). The development of more effective treatments for BN and BED is therefore a priority for research and has inspired the recent development of novel approaches to characterizing and addressing core symptomatology (Treasure et al., 2018; Turton et al., 2016).

Oxytocin is a neuropeptide which has been found to modulate reward processing in a number of domains, including the prevention of reinstated morphine-seeking in rats following a period of withdrawal (Georgiou et al., 2015; Zanos et al., 2014) and the reinforcement of social behavior (Dölen, Darvishzadeh, Huang, & Malenka, 2013). Oxytocin has recently gained further attention for its potential to curb overeating of rewarding palatable foods (Burmester, 2017; Ott et al., 2013; Thienel et al., 2016). The finding that oxytocin can specifically curb hedonic eating in healthy and overweight men has contributed to the hypothesis that oxytocin may also hold therapeutic potential for the prevention of binge eating behavior in BN and BED (Y. Kim, J. Eom, J. Yang, J. Kang, & J. Treasure, 2015; Leslie, Leppanen, et al., 2018; Thienel et al., 2016).

Currently there is mixed evidence for the effect of oxytocin on binge eating in BN. Y. Kim, J. Eom, et al. (2015) found that 40IU intranasal oxytocin reduces 24-hour caloric intake in participants with BN, but has no short-term effect on consumption of fruit juice. However, we recently failed to replicate the effect of intranasal oxytocin on 24-hour caloric consumption in women with BN and BED at a divided dose of 64IU (Leslie, Leppanen, et al., 2018). We also found that oxytocin did not impact the consumption of palatable foods in the lab 25 minutes after the conclusion of drug administration (Leslie, Leppanen, et al., 2018). However, it is of interest to investigate the effects of intranasal oxytocin on the neural processing of visual and gustatory palatable food cues in BN and BED to further elucidate any subtle effects of oxytocin on appetitive circuits, which may not have reached full behavioural expression at the doses and time points of measurement in existing studies.

The neural effects of oxytocin on the processing of food cues has previously been investigated in healthy men and women. For example, 24IU intranasal oxytocin versus placebo administration is associated with elevated blood oxygen level dependent (BOLD) response in the ventrolateral prefrontal cortex (vlPFC) in response to high versus low calorie food images in healthy men (Spetter et al., 2018). Given that this elevated BOLD response was inversely correlated with the quantity of sweet ingredients the men subsequently consumed in a breakfast meal, the authors have speculated that oxytocin may inhibit hedonic eating via upregulation of prefrontal circuits underpinning cognitive control. Additionally, a study directly testing the effect of oxytocin on food craving found that 24IU intranasal oxytocin, versus placebo administration, was associated with a trend-level effect towards reducing craving for depicted palatable foods in healthy women when instructed to imagine the long-term consequences of food consumption (Striepens et al., 2016). This oxytocin-induced reduction in craving was accompanied by elevated BOLD response in the precuneus, cingulate cortex and precentral gyrus, and superior temporal gyrus, thus leading the authors to hypothesise that these regions may mediate oxytocin-induced enhancements in cognitive control in healthy women (Striepens et al., 2016).

However, the finding that oxytocin suppresses food craving and consumption was not replicated in another mixed sample of healthy men and women (Klaauw et al., 2017). Rather, 24IU oxytocin was observed to suppress BOLD response to high versus low calorie foods in the hypothalamus, with no significant effects observed in the prefrontal cortex (Klaauw et al., 2017). Klaauw et al. (2017) also failed to observe any effect of oxytocin on the quantity of food consumed in a subsequent breakfast meal. Therefore, there is so far a mixed pattern of findings regarding the effects of oxytocin on the neural processing of high versus low calorie foods in healthy men and women. Furthermore, there is reason to believe that the central effects of exogenous oxytocin may differ in women with BN and BED, as compared to healthy comparison women, given evidence of different frequencies of oxytocin receptor gene polymorphisms in women with binge-purge behavior, compared to women without disordered eating (Y. Kim, J. Kim, C. Kim, J. Shin, & J. Treasure, 2015; Micali, Crous-Bou, et al., 2017).

There is a mixed pattern of evidence with regards to differential neural activation in response to palatable food anticipation and palatable food receipt in people with loss-of-control eating, versus the general population. Gearhardt et al. (2011), for example, have found that individuals high in food addiction exhibit heightened activation in reward-related circuits, including the caudate, in response to the anticipation of palatable food, and lower activation within the orbitofrontal cortex (OFC) in response to the actual receipt of palatable taste, when compared to participants low in food addiction, which the authors interpreted to correspond with heightened craving, versus an attenuated “liking” hedonic response, respectively. By contrast, however, Bohon and Stice (2011) found no significant group differences in the basal ganglia or OFC in response to the anticipation or receipt of chocolate milkshake in women with BN, versus healthy control women. Furthermore, Simon et al. (2016) rather found evidence of increased BOLD response in the medial OFC in response to the receipt of food reward in participants with BN and BED versus healthy control participants.

In the current preliminary outcomes report, we therefore aimed to further investigate differences in the neural processing of palatable food cues between women with BN or BED and healthy comparison women. We also sought to clarify the effects of 40IU intranasal oxytocin on the neural processing of palatable food cues in women with and without BN or BED. We chose to administer a 40IU dose of oxytocin prior to the fMRI scan in order to replicate the protocol of a previous study which found an effect of oxytocin on eating behaviour in women with BN at this dose (Y. Kim, J. Eom, et al., 2015). We additionally chose this dose given previous evidence demonstrating that 40IU intranasal oxytocin effectively reduces neural activation in regions of interest, particularly within the basal ganglia (Martins, Mazibuko, et al., 2019; Paloyelis et al., 2016).

We recruited women with BN or BED and comparison women without history of an eating disorder to take part in a functional magnetic resonance imaging (fMRI) study with a double-blind, placebo-controlled, crossover design. Participants self-administered 40IU intranasal oxytocin during the active experimental session and an equal volume of placebo spray during the control session. Participants were subsequently presented with images of either a glass

of water or glass of chocolate milk, which were accompanied by the associated taste of water or chocolate milk, respectively, on some trials. We hypothesized: 1) That women with BN and BED would exhibit heightened BOLD response in the orbitofrontal cortex (OFC), ventral tegmental area (VTA), and nucleus accumbens (NAcc) in response to the image of chocolate milk, versus the image of water; 2) That women with BN and BED would exhibit lower BOLD response than healthy comparison women in the same regions in response to the actual receipt of chocolate taste, versus water taste; 3) That oxytocin would suppress BOLD response in the OFC, VTA, NAcc, and hypothalamus in response to chocolate images, versus water images, in both groups of women; 4) That there would be a diagnosis x drug interaction such that oxytocin would suppress BOLD activation in the OFC, VTA, NAcc, and hypothalamus to a greater extent in women with BN or BED versus healthy comparison women in response to images of chocolate milk versus images of water. Given that we were unable to investigate most regions of interest given a technical issue, for the purposes of the current preliminary outcomes report, we sought to address the main aims of the study by conducting a whole-brain exploratory analysis to identify differences between the participant groups in the neural processing of palatable taste anticipation and delivery. We conducted a separate whole-brain exploratory analysis to identify brain regions in which oxytocin impacted on BOLD response to palatable taste anticipation and receipt.

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. Details regarding the age, education, and body mass index (BMI) of participants are presented in **Table 35**. 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. 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,

Monica Leslie

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, 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 menstrual 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.

Participants presented for each experimental session at 5.00pm. At 5.50pm, each participant self-administered 40IU of intranasal oxytocin or identical volume of placebo spray. The full dose was administered over a series of 10 sprays, each administered 30 seconds apart, alternating nostrils each time. Spray administration was therefore complete at 5.55pm. The eight-minute T1-weighted scan subsequently commenced at 6.00pm. The fMRI task subsequently commenced 24 minutes after the end of drug administration, on average (range: 6.10pm-6.27pm). The fMRI task and set-up are described in detail below.

fMRI Scan Set-Up

Prior to the onset of the scan, each participant was instructed to lay down on the scanning bed. The MRI-compatible flavour-dispensing box, containing separate tanks of cold Evian water and cold Galaxy chocolate milk, was placed underneath the participant's knees. A hose delivering the chocolate and water flavours protruded from left side of the flavour-dispensing box. This hose terminated in a disposable plastic mouthpiece, which the participant kept in their mouth throughout the duration of the scan. This mouthpiece was further secured with a plastic clamp attached to the participant's head coil. The participant was provided with a button box, which had left and right response buttons. The fMRI scans were conducted with a field strength of 3.0 Tesla.

fMRI Task

Prior to each run of the fMRI scan, the participant completed baseline ratings of the chocolate and water flavours. Each participant first received 0.5mL of the chocolate milk delivered through the mouthpiece. The participant was immediately presented with a visual

analogue scale (VAS) asking them to rate the hedonic aspect of the flavor on a scale anchored from “very unpleasant” to “very pleasant”. Other than a central demarcation, there were no other indicators between the two anchors at the left and right extremities of the VAS. The participant responded by either holding down the left button to move a central cursor towards the “very unpleasant” end of the VAS, or the right button to move the cursor towards the “very pleasant” end of the VAS. After thirty seconds this VAS was replaced with another VAS asking the participant to rate the intensity of the chocolate flavor. This VAS was anchored on a scale ranging from “not at all intense” to “very intense”. The participant responded by holding down the left and right buttons in the same manner as for the previous VAS. Finally, the participant was asked to rate their current level of anxiety on a VAS anchored from “not at all anxious” to “very anxious”. The participant responded using the left and right buttons as for the previous two visual analogue scales. The participant then received 0.5mL of the water through the mouthpiece. The participant then completed the same three visual analogue scales described above for the chocolate condition.

Following the baseline ratings of flavor, the first run of the fMRI task began. The participant was presented with a series of pictures of either a glass of chocolate milk or a glass of water. The participant was instructed to press the left button each time they were presented with a picture of chocolate milk, and to press the right button each time they were presented with a picture of water to ensure attention to each image. Each image was presented for 3 seconds, regardless of the participant’s reaction time. The image of water or chocolate milk was then followed by a fixation cross, which was presented for a random jitter period between 1 and 9 seconds in duration. For “invalid” trials, the fixation cross would then remain on the screening for a standard period of 5 seconds, and the next trial would then commence without any further stimuli.

For “valid” trials, however, the presentation of the picture of water or chocolate milk was followed by a squirt of the drink corresponding with the image they had just seen (i.e., if they had just been presented with a picture of a glass of water they would subsequently receive a squirt of water through the mouthpiece, and vice versa for chocolate milk). The participant was instructed

to hold the drink in their mouth for 3 seconds. This 3-second flavour delivery period was then followed by another fixation cross, which was presented for a random jitter period between 1 and 9 seconds. At this point the participant was presented with a visual instruction to “Swallow”. A fixation cross was then presented for 2 seconds prior to the onset of the next trial.

The participant was presented with a total of 50 images for each run in a pseudo-randomised order, such that each participant was presented with 25 images of water and 25 images of chocolate milk. The trials in which the participant received a squirt of water or chocolate milk were chosen pseudo-randomly, such that each participant received a total of 30 squirts during each scanning run in a random order. Following the first valid trial the participant was presented with a squirt of water or chocolate milk and a VAS in which they were instructed to rate the hedonic aspect and intensity of the flavour they had just received. This VAS was repeated following each subsequent set of 10 valid trials. The participant responded to these visual analogue scales in the same manner to the visual analogue scales presented prior to the onset of the task.

The participant then repeated all visual analogue scales performed at baseline prior to the onset of the second run of the scan. The second run of the scan proceeded in an identical manner to the first run, except that the images and squirts of water and chocolate milk were presented in a different random order.

fMRI Scanning Protocol

Each fMRI scanning run lasted for a total of 14 minutes and included 422 volumes. Four dummy scans were acquired prior to each run. Dummy scans were subsequently discarded. Images within the fMRI scans were acquired with a slice thickness of 3mm and a slice gap of 0.3mm. A total of 41 slices were acquired in a top to bottom order. The field of view was 240mm² with a 64 x 64 matrix size. The resulting voxel size was therefore 3.75mm x 3.75mm x 3mm. The scan was conducted with an echo time of 30ms and a repetition time of 2,000ms. The flip angle was set to 75 degrees.

A 3D high- spatial-resolution, Magnetisation Prepared Rapid Acquisition (3D MPRAGE) T1-weighted scan was also acquired. Field of view was 270mm², TR/TE/TI = 7.328/3.024/400ms. The final resolution of the T1-weighted image was 1.1 x 1.1 x 1.2 mm.

Statistical Analysis

All neuroimaging analyses were conducted in the Statistical Parametric Mapping software, version 12 (SPM). The functional images were slice-time-corrected and realigned using the mean functional image as a reference. Each participant's T1-weighted scan image was then co-registered to the mean functional image, then segmented using unified segmentation. The functional images were then normalized to Montreal Neurological institute (MNI) space using the segmentation parameters. Finally, images were smoothed using a Gaussian kernel of full width at half maximum (FWHM) 6mm.

At the single subject level, the data were modeled using the general linear model framework. We constructed a design matrix with separate regressors for correct and incorrect chocolate anticipation, chocolate receipt, water anticipation, and water receipt. We also included regressors for the "Swallow" instruction and VAS completion. The six motion parameters were also included in the design matrix. The BOLD signal was modeled by convolving our design matrix with the canonical haemodynamic response function. Low frequency drift was filtered out using a high-pass filter set to 1/128 second.

We estimated the following contrasts at the single-subject level: (1) chocolate anticipation versus water anticipation; (2) chocolate delivery versus water delivery; (3) chocolate anticipation versus chocolate delivery; and (4) water anticipation versus water delivery. We excluded trials in which participants did not correctly indicate the presence of the chocolate milk image versus water image to ensure that we only included trials where appropriate attention was paid to the water and chocolate images during anticipation and to avoid the signal noise which might be produced by error signaling.

At the group level, we conducted the following tests: (1) a one-sample F -test for the contrast comparing the anticipation of chocolate to the anticipation of water across all scans; (2) a two-sample F -test comparing the BN/BED and healthy comparison participant groups for the contrast comparing the anticipation of chocolate to the anticipation of water in the placebo condition; (3) a one-sample F -test for the contrast comparing the receipt of chocolate to the receipt of water across all scans; (4) a two-sample F -test comparing the BN/BED and healthy comparison participant groups for the contrast comparing the receipt of chocolate to the receipt of water in the placebo condition. We calculated difference images in which BOLD activation in the placebo condition was subtracted from the oxytocin condition. We then conducted the following additional tests: (5) one-sample F -tests investigating the effect of oxytocin on anticipation of chocolate versus water within each participant group; (6) a two-sample F -test comparing the effect of oxytocin for the chocolate anticipation, versus water anticipation, contrast between the two participant groups; (7) one-sample F -tests investigating the effect of oxytocin on receipt of chocolate versus water within each participant group; and (8) a two-sample F -test comparing the effect of oxytocin for the chocolate receipt, versus water receipt, contrast between the two participant groups.

For all tests we conducted exploratory whole brain analyses using cluster level inference, reporting significant clusters at $p < .05_{\text{FWE-corrected}}$ and a cluster forming threshold of $p < .001$ uncorrected (or $p < .001_{\text{FWE-corrected}}$ where the clusters were too big). Two participants' data were excluded from the current analyses as one participant did not complete the scan in the oxytocin condition and the other participant did not respond correctly to confirm attention to task images on a minimum threshold of 70% of task trials.

Results

Anticipation of chocolate taste versus water taste

We first conducted a one-sample F -test for the contrast comparing the anticipation of chocolate taste versus the anticipation of water taste across participant groups (BN/BED and healthy control) and treatment conditions (oxytocin and placebo drug conditions). We applied a

cluster-forming threshold of $p = .001$ (uncorrected), which revealed three significant clusters. However, given that one cluster extended over 69,018 voxels, we therefore decided to use a more conservative cluster-forming threshold of $p = .001_{\text{FWE-corrected}}$ in order to investigate more anatomically specific regions of neural activation. This subsequent, more conservative, whole brain analysis revealed eight significant clusters. We then followed this F -test with two one-sample t -tests to investigate directional differences. We found significantly greater BOLD response to chocolate anticipation, versus water anticipation, in the bilateral visual association area and right extrastriate cortex. We found significantly greater BOLD response to water anticipation, versus chocolate anticipation in the bilateral primary visual cortex, bilateral extrastriate cortex, right insula, bilateral inferior parietal cortex, right primary auditory cortex, left inferior frontal gyrus, and left caudate. Full results of these one-sample t -tests are reported in **Table 36**.

We were surprised by the lack of activation in the ventral striatum given previous evidence finding significant contrasts in BOLD response to the presentation of visual depictions of sweet taste versus control images. We therefore further investigated the mask of included voxels for the group analysis and discovered that it did not include the ventral striatum or OFC. Inspection of a random sample of individual participant masks revealed that most participants' masks did include voxels with signals in these regions. Therefore, the missing voxels are likely a result of one or more aberrant scans. While we did not have time to inspect each mask individually for the current preliminary outcomes report, the identification and exclusion of aberrant scans will form the next steps of the analysis so that we may investigate BOLD signal within the ventral striatum and the OFC.

Anticipation of chocolate taste versus water taste: Between-groups comparison in the placebo condition

Following the observation of significant clusters in response to the anticipation of chocolate taste, versus water taste, across all conditions and groups, we next sought to investigate group differences between participants with BN/BED and healthy comparison participants in the placebo condition given previous evidence of altered activation in reward-related circuits in

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populations with loss-of-control eating (Gearhardt et al., 2011). This analysis did not reveal any significant clusters.

Receipt of chocolate taste versus water taste

We then conducted a one-sample F -test for the contrast comparing the receipt of chocolate taste versus the delivery of water taste across all participant groups and treatment conditions (including both participant groups in both oxytocin and placebo drug conditions). The analysis revealed five significant clusters. We therefore followed this F -test with two one-sample t -tests to investigate directional differences. We detected significantly greater BOLD response to chocolate milk receipt, versus the receipt of water, in the following regions: bilateral somatosensory cortex, right inferior parietal cortex, right premotor cortex, right supplementary motor area, the cerebellum, right putamen, right hippocampus, and right insula. We detected significantly greater BOLD response to the receipt of water, versus chocolate milk, in the bilateral primary motor cortex, right somatosensory cortex, and right dorsomedial frontal cortex. The full results of the whole-brain exploratory analysis for the receipt of chocolate taste versus water taste are presented in **Table 37**.

Delivery of chocolate taste versus water taste: Between-groups comparison

Following the observation of significant clusters in response to the delivery of chocolate taste, versus water taste, across all scans, we next sought to investigate group differences between participants with BN/BED and healthy comparison participants in the placebo condition. This analysis did not reveal any significant clusters.

The effect of oxytocin on anticipation of chocolate taste versus water taste: Main effect of treatment condition and treatment $\times$ group interaction

We then conducted separate whole-brain exploratory analyses within each participant group examining the effect of oxytocin, versus placebo, on neural activation in response to the anticipation of chocolate taste, versus water taste. We calculated contrast images reflecting the effect of treatment for each participant, by subtracting the chocolate versus water anticipation

contrast image in the placebo condition from the same contrast image in the oxytocin condition using *imcalc* in SPM and conducted a one-sample *F*-test. We did not observe any significant clusters within either the BN/BED or healthy control participant groups. A two-sample *F*-test comparing the effect of oxytocin, versus placebo, on neural activation in response to the anticipation of chocolate taste, versus water taste, did not reveal any significant clusters corresponding to differences between the BN/BED versus healthy control participant groups.

The effect of oxytocin on receipt of chocolate taste versus water taste: Main effect of treatment condition and treatment x group interaction

We then conducted separate whole-brain exploratory analyses within each participant group examining the effect of oxytocin, versus placebo, on neural activation in response to the receipt of chocolate taste, versus water taste. We calculated contrast images reflecting the effect of treatment for each participant, by subtracting the chocolate versus water receipt contrast image in the placebo condition from the same contrast image in the oxytocin condition using *imcalc* in SPM and conducted a one-sample *F*-test. We did not observe any significant clusters within either the BN/BED or healthy control participant groups. A two-sample *F*-test comparing the effect of oxytocin, versus placebo, on neural activation in response to the receipt of chocolate taste, versus water taste, did not reveal any significant clusters corresponding to differences between the BN/BED versus healthy control participant groups.

Discussion

The current study aimed to clarify the effects of 40IU intranasal oxytocin on the neural processing of palatable food cues in women with and without BN or BED. The current findings revealed significant differences in BOLD activation when participants observed images of chocolate, versus images of water, and received the taste of chocolate, versus the taste of water. The pattern of BOLD activation did not significantly differ between the BN/BED and healthy control participant groups in response to viewing or tasting chocolate, versus water. The prior administration of 40IU intranasal oxytocin, versus placebo, had no impact on BOLD activation in response to either viewing or tasting chocolate, versus water, in either the BN/BED or healthy

control participant groups. The effect of oxytocin on BOLD activation in response to viewing or tasting chocolate, versus water, also did not significantly differ between participant groups.

Given that the presentation of a visual stimulus was constant between the chocolate anticipation and water anticipation conditions, we were surprised to observe that five out of the eight significant clusters in the one-sample *F*-test were in the primary visual cortex and visual association areas. One possible explanation is that the image of chocolate may have been more enticing than the image of water, thus encouraging a greater degree of visual processing. Additionally, the image of the glass of chocolate milk was a more complex shape, such that the glass had a handle and was topped with whipped cream, while the water was contained in a standard glass. This the processing of the more complex shape may partially account for the greater recruitment of visual association areas.

We observed greater BOLD response in the premotor cortex and supplementary motor area, as well as regions of the parietal lobe anatomically close to the representation of the tongue on the somatosensory cortex in response to the anticipation of chocolate versus water, although separate clusters within the primary motor cortex and somatosensory cortex were associated with greater BOLD response to the anticipation of water, versus chocolate. These differences partially corroborate previous evidence showing greater BOLD activation among healthy control participants in the postcentral gyrus in response to tasting a milkshake, versus a tasteless solution (Stice, Burger, & Yokum, 2013). One can speculate that this pattern of effects may pertain to anticipation of the taste and viscosity of chocolate milk versus water, or the potential for preconscious motor planning pertaining to drink chocolate milk versus water. However, given that we used an encoding design, we cannot validly draw reverse inferences to this extent.

We did not observe significant differences between participant groups in BOLD activation in response to viewing or tasting chocolate milk, versus water. This current finding adds to an existing mixed set of findings with regards to altered neural processing of palatable taste anticipation and receipt in women with BN or BED. Out of two prior fMRI studies examining BOLD response to the sight and taste of palatable food, compared to a neutral taste, in people with current BN or BED, one study also failed to observe differences in the anticipation

of chocolate taste, versus a control taste, between women with BN versus healthy control women (Bohon & Stice, 2011). The other study, however, observed a reduced BOLD response in the posterior cingulate cortex in participants with BN and BED, compared to healthy control participants, in response to the anticipation of food reward, and heightened BOLD response in the medial OFC, anterior medial prefrontal cortex, and posterior cingulate cortex to the receipt of palatable taste. This study, in addition to a separate set of findings indicating heightened activation in the OFC and caudate in response to visual food cues in people high in food addiction (Gearhardt et al., 2011), let us to believe that we might see differences in the pattern of BOLD activation to the anticipation and receipt of chocolate taste, versus water taste, within reward-related circuits in women with BN and BED, compared to healthy control women. However, the fact that the OFC and basal ganglia were not included in the mask for the analyses precluded the possibility of detecting differences in BOLD signal in these regions in the current set of analyses. The next step proceeding from this preliminary outcomes report will therefore be to identify and exclude aberrant participant where for technical reasons their mask of inclusive voxels did not include signal from the anterior ventral brain regions including the ventral striatum and the OFC, beyond the loss that is expected due to the susceptibility artefact. The inclusion of even a single aberrant participant would have biased the group mask of included voxels as group analyses are based on the conjunction of masks of included voxels from all participants. This will allow us to meaningfully investigate hypotheses pertaining to these anatomical regions. Furthermore, given that previous evidence gives us *a priori* reason to expect to see differences in the BOLD response to the anticipation and receipt of chocolate taste, versus water taste, in participants with BN/BED, versus healthy control participants, in the OFC and caudate (Gearhardt et al., 2011; Simon et al., 2016), we will therefore also investigate these hypotheses using corresponding region-of-interest analyses in the next stages of the data analysis.

The primary limitation of the current study was our inability to investigate differences in BOLD signal in regions of interest for the processing of taste reward, specifically the OFC and ventral striatum. Additionally, previous evidence has indicated that hormonal contraception can suppress the effects of exogenous oxytocin on BOLD response to images of a

partner's face within reward-related mesolimbic brain regions (Scheele, Plota, Stoffel-Wagner, Maier, & Hurlemann, 2015). Going forward with the analysis of the current data, it will therefore be important to investigate the potential moderating effect of hormonal status for the influence of oxytocin on the neural processing of the anticipation and delivery of chocolate milk in future analyses, along with region of interest analyses, following the exclusion of aberrant scans.

In conclusion, the current study aimed to investigate differences in the neural processing of the anticipation and delivery of chocolate taste, versus water taste, in women with BN and BED versus healthy control women. We also sought to investigate the influence of oxytocin on the neural processing of the anticipation and receipt of chocolate taste, versus water taste, in women with BN/BED versus healthy control women. We did not observe significant differences in neural activation between women with BN or BED, versus healthy control women, in response to the anticipation or receipt of chocolate taste, versus water taste within the regions of the brain included of our analyses. The administration of 40IU intranasal oxytocin, versus placebo, also did not affect the BOLD response to the anticipation or receipt of chocolate taste, versus water taste, in either participant group within brain regions included in the current set of analyses. It will be important in the next stages of the analysis to repeat these analyses with the OFC and basal ganglia included in the analysis masks and to investigate relevant regions of interest.

Table 35*Descriptive demographic data*

	Healthy Control (<i>n</i> = 27)		BN/BED (<i>n</i> = 25)	
	Median	IQR	Median	IQR
Age	23.50	5.50	23.50	9.75
BMI	22.04	1.76	23.09	3.87
RQF Education Level	6	4	4.5	3

Note. BN = bulimia nervosa; BED = binge eating disorder; IQR = interquartile range; BMI = body mass index; RQF = Regulated Qualifications Framework.

Table 36

Significant clusters identified for the anticipation of chocolate taste, versus water taste: One-sample t-tests conducted across participant groups and treatment conditions.

A $p < .001_{\text{FWE-corrected}}$ cluster-forming threshold was used for the water > chocolate contrast due to excessively large clusters. A $p < .001_{\text{uncorrected}}$ cluster-forming threshold was used for the chocolate > water contrast. We report significant clusters at the $p < .05_{\text{FWE-corrected}}$ threshold.

Cluster Number	Hemisphere	K	P _{FWE}	Peak Coordinates			Description
				x	y	z	
CHOCOLATE > WATER							
Cluster 1	Left	1485	< .001	-14	-92	-8	Visual association area
				-24	-94	4	
				-24	-88	-6	
Cluster 2	Right	821	< .001	24	-86	-14	Extrastriate cortex and visual association area
				40	-76	-12	
				22	-94	2	
WATER > CHOCOLATE							
Cluster 3	Bilateral	8804	< .001	-6	-74	8	Primary visual cortex and extrastriate cortex
				-16	-66	-4	
				16	-62	-2	
Cluster 4	Right	393	< .001	44	-64	6	Extrastriate cortex
				48	-74	18	
Cluster 5	Right	1951	< .001	36	-8	16	Insula and inferior parietal cortex
				54	-12	24	
				58	6	18	
Cluster 8	Left	1598	< .001	-64	-48	12	Inferior parietal cortex

				-62	-26	20	
				-32	-28	10	
Cluster 9	Left	276	< .001	-40	-70	10	Extrastriate cortex
				-52	-70	12	
				-36	-82	22	
Cluster 10	Right	98	< .001	48	-24	8	Primary auditory cortex
				58	-26	12	
Cluster 11	Left	32	< .001	-32	20	16	Inferior frontal gyrus
Cluster 12	Left	173	< .001	-16	6	16	Caudate
				-16	-2	14	
				-26	2	14	

Table 37

Significant clusters identified for the receipt of chocolate taste, versus water taste: One-sample t -tests conducted across participant groups and treatment conditions

A $p < .001$ uncorrected cluster-forming threshold was used for both t -contrasts. We report significant clusters at the $p < .05$ FWE-corrected threshold.

Cluster Number	Hemisphere	K	P _{FWE}	Peak Coordinates			Description
				x	y	z	
CHOCOLATE > WATER							
Cluster 1	Right	1382	< .001	58	-14	24	Inferior parietal cortex, somatosensory cortex, premotor cortex, and supplementary motor cortex
				60	-14	32	
				56	2	32	
Cluster 2	Left	234	.035	-20	-62	-28	Cerebellum
				-26	-50	-32	
Cluster 3	Left	1024	< .001	-56	-14	20	Somatosensory cortex,
				-52	-20	28	
				-58	-20	34	
Cluster 4	Right	755	< .001	26	0	-10	Putamen, hippocampus, and insula
				32	-12	-12	
				38	16	-2	
WATER > CHOCOLATE							
Cluster 5	Bilateral	2500	< .001	-2	-26	62	Primary motor cortex
				30	-26	50	
				12	-32	66	
Cluster 6	Right	247	.029	26	-10	28	Somatosensory cortex
				34	-20	20	

				26	-28	28	
Cluster 7	Right	655	< .001	30	20	34	Dorsomedial frontal cortex
				22	24	54	
				12	30	50	

Chapter 7

7 Discussion

7.1 Summary of Key Findings

The current thesis proposed a novel maintenance model of recurrent binge eating: the addictive appetite model of bulimia nervosa and binge eating disorder. We subsequently tested hypotheses generated by the addictive appetite model. **Figure 15** demonstrates how each data paper of the thesis fits within a specific hypothesis proposed by the addictive appetite model. The key findings of each data paper are subsequently summarised in **Table 38**.

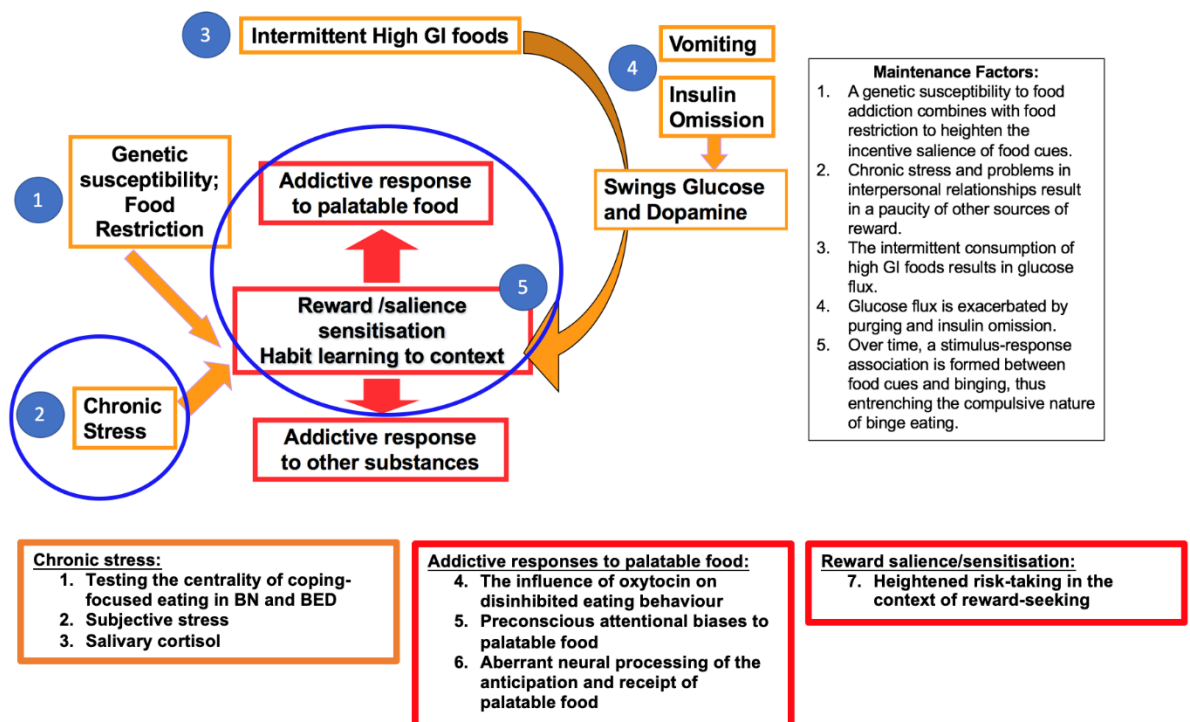


Figure 15. Summary of addictive appetite processes tested in the current thesis.

1) The centrality of coping-focused eating in the profile of bulimia nervosa and binge eating disorder was tested in Paper 3; **2)** The impact of oxytocin administration on subjective stress was tested in Paper 5; **3)** The impact of oxytocin on salivary cortisol was tested in Paper 5; **4)** The influence of oxytocin on the consumption of food was tested in a meta-analysis presented in Paper 4 and an original study in Paper 5; **5)** The presence of preconscious attentional biases to palatable food in women with bulimia nervosa and binge eating disorder and the impact of oxytocin on these attentional biases were measured in Paper 6; **6)** Differences in the neural processing of anticipation and receipt of palatable taste were investigated in Paper 8; **7)** The presence of greater risk-taking in the context of reward-seeking and the influence of oxytocin on risk-taking tendency were investigated in paper 7.

Note. BED = binge eating disorder; BN = bulimia nervosa; GI = glycaemic index.

Table 38*Summary of key findings*

Paper	Aims	Findings
Paper 3: Testing the addictive appetite model: The importance of craving, reward, and reward enhancement	This original study aimed to test two maintenance processes proposed within The Addictive Appetite Model of binge eating: eating due to enhanced incentive salience and eating for emotion regulation. Our hypotheses were: 1. People with BN and BED would show higher levels of craving for food than weight-matched controls; 2. People with BN and BED would endorse eating palatable food as a method of coping with distress and as a means of enhancing mood; 3. Food craving, eating for emotional coping, and eating for reward enhancement would distinguish individuals with binge-type eating disorders from weight-matched controls.	Women with BN and BED endorsed significantly greater levels of food craving and tendencies to eat for purposes of coping and reward enhancement compared to weight-matched women without history of an eating disorder. These differences were each associated with a large effect size. Furthermore, a cluster analysis indicated that considering the variables of food craving and tendencies to eat for purposes of coping and reward enhancement were sufficient to distinguish women with BN or BED from the lean and overweight/obese healthy control women.
Paper 4: A Systematic Review and Quantitative Meta-Analysis of the Effects of Oxytocin on Feeding	This paper aimed to conduct a systematic review synthesising the effects of oxytocin on feeding. We used PRISMA guidelines to identify all original published and unpublished experiments testing the effects of exogenous oxytocin on energy intake in wild-type animals and in humans, where oxytocin was administered in the absence of other active drugs or	Across all studies, a single dose of oxytocin was found to reduce subsequent eating over the following hour in animal studies, both when the oxytocin was administered centrally or peripherally. While some individual studies have supported the anorexic qualities of oxytocin in mice, rats, and rhesus monkeys over a two- to three-week administration period, the effect of chronic oxytocin

	surgeries. We also aimed to identify relevant moderators of oxytocin's effects on feeding in order to clarify the conditions under which these anorexigenic effects hold. We hypothesised that exogenous oxytocin administration, as compared to placebo administration, would reduce feeding in both humans and animals.	on feeding was non-significant across all studies. The main effect of oxytocin on feeding in humans was not significant. However, there was a trend towards an inhibitory effect of oxytocin on the consumption of solid foods. The effect of oxytocin on feeding in humans was moderated by sex, weight status, and prior hunger.
Paper 5: The influence of oxytocin on eating behaviours and stress in women with bulimia nervosa and binge eating disorder	The aim of the current study was to explore the impact of the administration of oxytocin on both reward and anxiety-related processes. We hypothesised that: 1. 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. 2. Oxytocin administration would be associated with lower levels of stress, and that participants would report lower levels of "feeling fat". 3. Participants would have lower salivary cortisol concentrations in the oxytocin, versus placebo, condition. 4. 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.	A divided dose of 64IU intranasal oxytocin did not affect the immediate consumption of palatable food, 24-hour calorie consumption, or the incidence of binge eating in women with and without bulimia nervosa or binge eating disorder. There was no significant effect of oxytocin on subjective stress or salivary cortisol in either participant group.

Paper 6: A Pilot Study Investigating the Influence of Oxytocin on Attentional Bias to Food Images in Women with Bulimia Nervosa and Binge Eating Disorder	This study aimed to test the effect of a divided dose of 64IU intranasal oxytocin on attentional bias to palatable food in women with and without bulimia nervosa and binge eating disorder. Our hypotheses were: 1. Women with BN or BED would demonstrate greater attentional biases towards food images than women without history of an eating disorder; 2. There would be an interaction between time point and participant group, such that the difference in attentional bias to food in the BN/BED, versus healthy control group, would be even greater following food consumption; 3. Oxytocin administration would reduce vigilance towards food images in both groups of women, based on previous work suggesting that oxytocin reduces the incentive salience of palatable food in healthy participants (Ott et al., 2013); 4. Oxytocin would reduce vigilance towards food images to a greater degree in women with BN or BED, versus healthy comparison women, due to potential flooring effects in the healthy comparison group.	There was no baseline difference in attentional bias to food images between women with BN or BED as compared to women without history of an eating disorder. There was a main effect of oxytocin, such that a 64IU divided dose of intranasal oxytocin increased vigilance to food images, as compared to placebo administration; however, this effect was primarily driven by the women with BED.
Paper 7: The Influence of Oxytocin on Risk-Taking in the Balloon Analogue Risk Task Among Women with Bulimia	This study aimed to compare the performance of women with clinical levels of recurrent binge eating on the BART to that of control women without previous history of an eating disorder. Furthermore, we also aimed to investigate the differential effect of intranasal	There were no baseline differences in performance on the BART between women with BN or BED as compared to healthy control women. There was not a significant main effect of a divided dose of 64IU intranasal oxytocin on either the adjusted average

Nervosa and Binge Eating Disorder	oxytocin on risk-taking in the BART in women with BN and BED compared to healthy controls. We hypothesised that: 1. Women with BN and BED would demonstrate greater baseline risk-taking behaviour on the BART in the placebo condition, relative to women without previous history of an eating disorder. 2. Given previous research indicating that oxytocin induces a down-regulation of reward seeking in men, we hypothesised that a divided dose of 64IU intranasal oxytocin, versus placebo, would be associated with reduced risk-taking behaviour in the BART in women; 3. We hypothesised that the effect of oxytocin in down-regulating reward-seeking would be stronger in women with bulimia nervosa and binge eating disorder due to higher trait levels of risk-taking behaviour.	pump count or total number of balloon explosions in the BART. However, there was an interaction such that oxytocin administration reduced the total number of balloon explosions to a greater degree among the women with BN or BED, versus the healthy comparison women. There was no drug x diagnosis interaction for the adjusted average pump count variable.
Paper 8: The effect of oxytocin on the neural processing of taste reward in women with and without binge-type eating disorders	This study aimed to investigate differences in neural activation in response to the anticipation and receipt of chocolate milk, versus water, in women with BN and BED versus healthy comparison women. We also aimed to investigate the influence of 40IU intranasal oxytocin on the neural processing of the anticipation and receipt of chocolate milk, versus water. We conducted whole-brain exploratory analyses to identify regions in which women with BN and BED	We did not observe significant differences in neural activation between women with BN or BED, versus healthy control women, in response to the anticipation or receipt of chocolate taste, versus water taste. The administration of 40IU intranasal oxytocin, versus placebo, did not affect the BOLD response to the anticipation or receipt of chocolate taste, versus water taste, in either participant group. However, the ventral striatum and orbitofrontal cortex were not included in the analysis masks, thus

exhibited different patterns of BOLD response to palatable taste anticipation and receipt, and regions where 40IU intranasal oxytocin moderated neural activation to palatable taste anticipation and receipt. presenting a significant caveat to interpreting the current preliminary findings.

7.2 Synthesis with Existing Literature

7.2.1 The influence of oxytocin on eating behaviour

While previous narrative reviews have provided comprehensive summaries of the effects of oxytocin on eating behaviour (Blevins & Baskin, 2015; Olszewski, Klockars, & Levine, 2016), the study presented in Paper 4 is the first systematic review and meta-analysis of studies investigating the effects of oxytocin on feeding. The primary finding of the systematic review supports general wisdom concerning the anorexigenic effects of oxytocin. We found that a single dose of either centrally- or peripherally-administered oxytocin significantly reduces feeding over the subsequent hour of measurement in animals. While individual studies have indicated the potential for oxytocin to suppress feeding in mice, rats, and rhesus monkeys over periods of two- to three-weeks (Blevins et al., 2015; Blevins et al., 2016), this meta-analysis indicated that this finding is not significant across all animal studies measuring the effects of oxytocin on eating into the long-term.

Due to the relative paucity and wide variety of sample characteristics in studies investigating the influence of oxytocin on eating in humans, it is not surprising that a highly mixed set of findings was observed across all studies. Given that existing studies have been relatively internally homogeneous, the current meta-analysis contributes to current knowledge by indicating that sex, weight status, and hunger status are statistically significant moderators of the effect of oxytocin on feeding. A surprising novel finding is that the liquid- versus solid-state of the food also significantly moderates the effect of oxytocin on feeding. While the reason for this effect is not entirely clear at present, it is possible that oxytocin may reduce gastric motility (Flanagan, Dohanics, Verbalis, & Stricker, 1992; R. C. Rogers & Hermann, 1987; C. L. Wu et al., 2002; C. L. Wu et al., 2003), with a stronger downstream effect in reducing consumption of solid food, in

comparison to liquid food. This finding will be interesting to explore in future studies in order to better understand the mechanism of the effect of oxytocin on feeding.

While previous evidence found evidence of an inhibitory effect of intranasal oxytocin on 24-hr caloric consumption in women with BN (Y.-R. Kim, J.-S. Eom, et al., 2015), the current study failed to replicate this finding. Potential reasons for this difference include the greater dose of intranasal oxytocin used in the current study: 64IU administered as a divided dose, as compared to the single dose of 40IU administered in the previous Y.-R. Kim, J.-S. Eom, et al. (2015) study. As mentioned previously in the current thesis, current evidence suggests that the dose of oxytocin may have an inverse quadratic relationship with the magnitude of its effect due to the rapid internalisation of oxytocin receptors at high doses (Cardoso et al., 2013). Furthermore, unpublished work from our laboratory has indicated that administration of oxytocin via conventional intranasal spray, versus a nebuliser, results in a different pattern of subsequent effects on cerebral blood perfusion. It is therefore also possible that the observed difference in findings between our study and the study conducted by Y.-R. Kim, J.-S. Eom, et al. (2015) are, at least partly, due to differences in the method of oxytocin administration.

Additionally, we provided palatable food with a high caloric density in our taste test, rather than apple juice, as provided in the study conducted by Y.-R. Kim, J.-S. Eom, et al. (2015). Following from the predictions of the addictive appetite model, it is possible that dysregulation in blood sugar following consumption of the provided chocolate, combined with the mere suggestion of snack food, may have predisposed participants to consume a greater quantity of palatable foods during the 24-hour measurement period of caloric intake. Therefore, it is possible that these differences in protocol may have contributed to the failure to replicate previous research findings. Further work will be necessary to identify the optimal protocol, including the optimal dose and method of oxytocin administration, required to curb palatable food consumption in future studies

recruiting women with and without eating disorders. A summary of existing studies to have investigated the effects of oxytocin on eating behaviour and neurocognitive processes in populations with eating disorders is presented in **Table 39**.

Table 39

Summary of Studies Investigating the Effects of Intranasal Oxytocin on Neurocognitive Processes and Eating Behaviour in Populations with Eating Disorders

Author, Year	Study Title	Sample	Dose	Method of Administration	Experimental Design	Sex	Summary of Findings
Eating Behaviour in Binge-Type Eating Disorders							
Leslie et al., 2018	The Influence of Oxytocin on Eating Behaviours and Stress in Women with Bulimia Nervosa and Binge Eating Disorder	Binge eating sample: (n = 25) - BN (n = 20) - BED (n = 5) HC (n = 27)	64IU	Intranasal spray	Double-blind within-subjects crossover design investigating the consumption of palatable snack foods in a bogus taste test, 24-hour caloric consumption, and binge episode frequency following drug administration	Female	No significant effect of oxytocin on palatable food consumption, 24-hr caloric consumption, or binge episode frequency following oxytocin, versus placebo, administration. There was also no evidence of a significant drug x participant group interaction.
Agabio et al., 2016	Oxytocin Nasal Spray in the Treatment of Binge Eating Disorder and Obesity: A pilot, Randomized, Double Blind Trial	BED (n = 17)	24 IU, four times per day	Intranasal spray	Double-blind between-subjects clinical trial investigating the effects of 4 daily doses of 24IU oxytocin, versus placebo, on frequency of binge eating episodes over a period of 8 weeks	16 female, 1 male	Oxytocin administration, versus placebo, had no significant effect on number of binge eating episodes per week.
Kim et al., 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	AN (n = 35) BN (n = 34) HC (n = 33)	40IU	Nebuliser	Double-blind within-subjects crossover design investigating the consumption of apple juice and 24-hr caloric consumption	Female	Oxytocin did not impact juice consumption for any participant group. There was no effect of oxytocin on 24-hr caloric consumption for HC or AN participants. However, oxytocin, versus placebo, decreased 24-hr caloric consumption for participants with BN.

Eating Behaviour in Anorexia Nervosa							
Leppanen et al., 2017	The effects of intranasal oxytocin on smoothie intake, cortisol and attentional bias in anorexia nervosa	AN (n = 30) HC (n = 29)	40IU	Intranasal spray	Double-blind within-subjects crossover design investigating smoothie consumption	Female	Oxytocin administration, versus placebo, had no effect on smoothie consumption in either participant group.
Kim et al., 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	AN (n = 35) BN (n = 34) HC (n = 33)	40IU	Nebuliser	Double-blind within-subjects crossover design investigating the consumption of apple juice and 24-hr caloric consumption	Female	Oxytocin did not impact juice consumption for any participant group. There was no effect of oxytocin on 24-hr caloric consumption for HC or AN participants. However, oxytocin, versus placebo, decreased 24-hr caloric consumption for participants with BN.
Kim et al., 2014	Intranasal oxytocin attenuates attentional bias for eating and fat shape stimuli in patients with anorexia nervosa	AN (n = 31) HC (n = 33)	40IU	Nebuliser	Double-blind within-subjects crossover design investigating the consumption of apple juice	Female	Oxytocin administration, versus placebo, had no effect on apple juice consumption in either participant group.
Attentional Bias to Food Stimuli in Binge-Type Eating Disorders							
Leslie et al. (Paper 6 of the current thesis)	A pilot study investigating the influence of oxytocin on attentional bias to food images in women with bulimia nervosa and binge eating disorder	Binge eating sample: (n = 25) - BN (n = 20) - BED (n = 5) HC (n = 27)	64IU	Intranasal spray	Double-blind within-subjects crossover design investigating attentional bias to food images versus neutral images in a dot probe task	Female	Oxytocin increased vigilance to food images, versus neutral images, across all participants. Although there was not a significant moderating effect of participant group, the results of a sensitivity analysis suggest that this effect is stronger in women with BED.

Attentional Bias to Food Stimuli in Anorexia Nervosa							
Leppanen et al., 2017	The effects of intranasal oxytocin on smoothie intake, cortisol and attentional bias in anorexia nervosa	AN (n = 30) HC (n = 29)	40IU	Intranasal spray	Double-blind within-subjects crossover design investigating attentional bias to food images versus neutral images in a dot probe task	Female	Participants with AN exhibited avoidance of food images versus neutral images, as compared to the HC group, at baseline. Oxytocin administration, versus placebo, reduced the avoidance of food images in the AN group, thus resulting in increased vigilance to food.
Kim et al., 2014	Intranasal oxytocin attenuates attentional bias for eating and fat shape stimuli in patients with anorexia nervosa	AN (n = 31) HC (n = 33)	40IU	Nebuliser	Double-blind within-subjects crossover design investigating attentional bias to eating and body weight and shape related stimuli in a dot probe task	Female	There was no difference in vigilance to eating and body-related stimuli between the AN and HC participant groups at baseline. There was a significant drug x participant group interaction such that oxytocin reduced vigilance to eating and body-related stimuli only in participants with AN.
Generalised Reward-Seeking and Risk-Taking Behaviour in Binge-Type Eating Disorders							
Leslie et al. (Paper 7 of the current thesis)	The influence of oxytocin on risk-taking in the balloon analogue risk task among women with bulimia nervosa and binge eating disorder	Binge eating sample: (n = 25) - BN (n = 20) - BED (n = 5) HC (n = 27)	64IU	Intranasal spray	Double-blind within-subjects crossover design investigating performance on the Balloon Analogue Risk Task (BART)	Female	There were no significant differences in performance on the BART between the BN/BED and HC groups in the placebo condition. There was no main effect of oxytocin on performance in the BART. There was an interaction for the total balloon explosion count, such that oxytocin specifically reduced balloon explosions in participants with BN and BED. However, this interaction was not found for the adjusted average pump count variable.
Attentional Bias to Socio-Emotional Stimuli in Binge-Type Eating Disorders							

Kim et al., 2018	Effects of intranasal oxytocin on the attentional bias to emotional stimuli in patients with bulimia nervosa	BN (n = 31) HC (n = 33)	40IU	Intranasal spray	Double-blind within-subjects crossover design investigating attentional bias to happy and angry faces versus neutral faces in a visual probe detection task.	Female	There were no significant differences in attentional bias to happy or angry, versus neutral, faces between the BN and HC groups in the placebo condition. There was a drug x emotion interaction such that oxytocin reduced attentional bias to angry faces in both participant groups but did not affect attentional bias to happy faces.
Attentional Bias to Socio-Emotional Stimuli in Anorexia Nervosa							
Kim et al., 2014	The impact of intranasal oxytocin on attention to social emotional stimuli in patients with anorexia nervosa: A double blind within-subject cross-over experiment	AN (n = 31) HC (n = 33)	40IU	Nebuliser	Double-blind within-subjects crossover design investigating attentional bias to happy, angry, and disgusted faces, versus neutral faces, in a visual probe detection task.	Female	Participants with AN exhibited avoidance of angry faces in the placebo condition and the HC group exhibited vigilance to angry faces in the placebo condition. No differences in vigilance to disgusted or happy faces were observed between the participant groups in the placebo condition. Oxytocin increased vigilance to angry faces only in the AN participant group. Oxytocin reduced vigilance to disgusted faces in both participant groups.
Interpretation of Socio-Emotional Stimuli in Binge-Type Eating Disorders							
Kim et al., 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	AN (n = 35) BN (n = 34) HC (n = 33)	40IU	Nebuliser	Double-blind within-subjects crossover design investigating emotion recognition sensitivity in a dynamic facial morphing task.	Female	There were no differences in emotion recognition thresholds between the AN, BN, and HC participant groups in the placebo condition. Oxytocin improved overall emotion recognition sensitivity in the HC participant group and improved emotion recognition sensitivity for sad faces in the BN participant group.
Interpretation of Socio-Emotional Stimuli in Anorexia Nervosa							

Leppanen et al., 2017	The effects of oxytocin on the interpretation and expression of emotions in anorexia nervosa	AN (n = 30) HC (n = 29)	40IU	Intranasal spray	Double-blind within-subjects crossover design investigating the interpretation of emotions and mental states using the "Reading the Mind in the Eyes" test	Female	Participants with AN were more accurate on the Reading the Mind in the Eyes test compared to the HC participant group. Oxytocin administration, versus placebo, did not affect accuracy in either participant group. Oxytocin led to a slower reaction time on the task for the AN group in session 2 and a faster reaction time for the HC group in session 2.
Kim et al., 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	AN (n = 35) BN (n = 34) HC (n = 33)	40IU	Nebuliser	Double-blind within-subjects crossover design investigating emotion recognition sensitivity in a dynamic facial morphing task.	Female	There were no differences in emotion recognition thresholds between the AN, BN, and HC participant groups in the placebo condition. Oxytocin had no effect on emotion recognition sensitivity in the AN group.

Note. AN = anorexia nervosa; BED = binge eating disorder; BN = bulimia nervosa. Grey rows highlight studies incorporated in the current thesis.

7.2.2 The influence of oxytocin on attentional bias in populations with eating disorders

The majority of research investigating the effects of oxytocin on attentional biases in populations with eating disorders has so far focused primarily on anorexia nervosa, and no prior studies have investigated the influence of intranasal oxytocin on attentional bias to food stimuli in populations with either BN or BED. However, intranasal oxytocin has previously been found to partially normalise attentional biases in women with anorexia nervosa (Leppanen, Cardi, et al., 2017a), who exhibited attentional avoidance of food images in the placebo condition. In contrast to the study conducted by Leppanen, Cardi, et al. (2017a), which investigated women with anorexia nervosa, and in contrast to previous studies investigating attentional biases to food in populations with binge eating, the study reported in Paper 6 did not find a baseline difference in attentional bias to food between women with BN or BED and healthy comparison women in the placebo condition. It may be the case that attentional biases to food stimuli are specific to early stages in attentional processing, which were not captured in the current study. Future research will therefore be helpful in establishing the variation and functional significance of attentional biases to food stimuli across the entire span of attentional processing in women with BN and BED.

The study reported in Paper 6 also found that a divided dose of 64IU intranasal oxytocin significantly increased attentional bias to food images across the entire participant sample. This finding partially contrasts with evidence from (Leppanen, Cardi, et al., 2017a), who reported that the effect of oxytocin in increasing vigilance to food stimuli was specific to participants with anorexia nervosa. That being said, it should be noted that the effect of oxytocin in increasing vigilance was unduly affected by the women with BED in our study, as sensitivity analyses excluding these five participants or imputing data for these participants based on the BN sample resulted in this main effect becoming

non-significant. Therefore, the evidence to date suggests that intranasal oxytocin may increase vigilance to food images across all women, though to a greater degree in women with anorexia nervosa or binge eating disorder.

7.2.3 The influence of oxytocin on reward approach

Previous evidence has tentatively supported a role for exogenous oxytocin in enhancing the intentional reduction of food craving in women (Striepens et al., 2016). Furthermore, several studies in both healthy and overweight men have found that oxytocin specifically reduces hedonic eating, as opposed to hunger-driven eating (Burmester et al., 2018; Ott et al., 2013; Thienel et al., 2016). While the mechanism for these effects is not yet clear, it may be the case that oxytocin reduces food approach behaviours through some combination of the reduction of incentive salience of food and an increase in cognitive control over food craving (Love, 2014; Striepens et al., 2016). Conversely, a large body of evidence has indicated that oxytocin rather increases the reward value of social stimuli (Dölen et al., 2013). However, previous evidence in humans has not investigated whether the effect of oxytocin generalises beyond domain-specific effects on feeding and social stimuli.

The findings reported in Paper 7 suggest that oxytocin does not decrease impulsive reward-approach behaviours across women with and without BN or BED. However, there was an interaction effect such that oxytocin decreased the total number of balloon explosions to a significantly greater degree among women with BN or BED versus healthy comparison women, thus indicating a greater reduction in risk-taking, and particularly a reduction in persistent risk-taking following “punishment” trials. Based on previous evidence indicating a greater proportion of the G carriers for the OXTR gene among women with BN and BED (Y.-R. Kim, J.-H. Kim, et al., 2015; Micali, Crous-Bou, et al., 2017), we have speculated that this difference may relate to potential underlying differences in the functioning of the oxytocin receptor system between the two

populations of participants. However, further research is necessary in order to replicate our reported effect of oxytocin on risk-taking in a larger sample and elucidate the mechanism of this effect.

7.3 Implications and future directions

7.3.1 Implications and future directions for the addictive appetite model of recurrent binge eating

The addictive appetite model proposed within the current thesis offers a novel formulation of the progression and maintenance of BN and BED. While other authors have previously highlighted the addiction-like properties of some forms of eating behaviour (Gearhardt, Corbin, & Brownell, 2009a; Volkow, Wang, Fowler, Tomasi, & Baler, 2011), the addictive appetite model makes the novel contribution of contextualising these processes within a comprehensive maintenance model of BN and BED.

It should be noted that evidence for the novel components of the addictive appetite model is still in an early stage of development. Our first recommendation for future research pertains to the systematic study of tolerance effects in BN. Future longitudinal studies comparing participants with BN and BED against weight-matched controls would be invaluable in shedding light on the progression of binge size and frequency, expected reward value of binge eating episodes, actual reward value of binge eating episodes, perceived satiety, and weight. Such studies could be conducted with the use of ecological momentary assessments and would ideally commence from the earliest stages of the disorder. As capturing the progression from the earliest stages of the disorder would most likely require the recruitment of participants outside of treatment-seeking settings, this research would likely require large community samples, and may therefore be best-suited to a phone application to minimise required resources.

Additionally, we would recommend that future research also investigate the development of food withdrawal effects through longitudinal studies administering the ProWS, a food withdrawal scale developed by Schulte et al. (2018). The ProWS would provide valuable

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information on food-specific withdrawal effects, independent of trait levels of low mood. Furthermore, we recommend additional research investigating biological and affective withdrawal effects, such as those observed in substance use disorders. Withdrawal effects of interest to investigate include: the presence of anxiety, restlessness, sleep difficulties, depressed mood, and physical discomfort (Budney & Hughes, 2006). The investigation of these biological and affective responses to withdrawal would thus also potentially highlight mechanisms of behavioural withdrawal symptoms endorsed on the ProWS.

With regards to the impact of insulin- and dopamine-mediated food craving, extensive work in populations with obesity and Type II diabetes have illustrated the role of insulin dysregulation in heightening food craving, as mediated by mesolimbic brain regions (Chechacz et al., 2009; Jastreboff et al., 2013). While recent evidence has supported an overall reduction in insulin sensitivity across populations with BN and BED (Ilyas et al., 2018), it is important to replicate links with food craving in people with eating disorders. For example, the combination of measuring fasting insulin levels and food craving within an fMRI design, as previously conducted by Jastreboff et al. (2013) in people with obesity, would help to clarify whether activity in dopaminergic brain regions also mediates the association between insulin resistance and food craving in people with BN and BED.

Furthermore, it is also necessary to investigate the dopamine response of normal-weight individuals with BN to sucrose, versus sucralose, consumption against weight-matched controls before definitive conclusions can be drawn regarding dysregulation of dopamine responses to high GI foods, versus non-nutritive sweet taste, in this population. Such studies could employ a similar design to that previously used by Wang et al. (2014) in a PET study recruiting participants with obesity.

If further investigation ultimately corroborates key components of the addictive appetite model, this would carry important implications for the future treatment of BN and BED. One new treatment recommendation stemming from the addictive appetite model is the recommendation to avoid highly-processed foods during recovery from BN and BED. While many clinicians and current treatment models encourage continued consumption of high GI foods in moderation (Apple & Agras, 2004), the addictive appetite model argues that the addictive nature of eating in the acute phase of BN and BED entails the disinhibition of appetitive processes and continued food craving following the consumption of high GI foods. To provide an analogy to a separate eating disorder, it is commonly accepted that a more prescriptive clinical approach to eating is necessary in the early stages to recovery from anorexia nervosa before intuitive eating develops adequately, thus allowing for greater flexibility whilst still ensuring that basic nutritional needs are met (Richards, Crowton, Berrett, Smith, & Passmore, 2017). Similarly, until normalisation of neural circuits occurs in BN and BED, the addictive appetite model recommends a prescriptive avoidance of high GI foods.

As a key tenet of the addictive appetite model pertains to the role of blood sugar flux in contributing to food craving and subsequent binge eating, another implication of the model is the importance of psychoeducation around maintaining stable blood sugar levels. Clinical practice currently recommends the avoidance of self-induced vomiting and insulin omission to prevent the health risks described in Chapter 1 of the current thesis (National Institute for Health and Clinical Excellence, 2017). However, recommendations stemming from the addictive appetite model would further highlight the importance of maintaining stable blood sugar levels for the additional purpose of contributing to remission from recurrent binge eating behaviours.

The theoretical importance of addictive responses to food, which are highlighted within the addictive appetite model, also provides theoretical support for the continued

advancement of treatments seeking to break automated stimulus-response patterns around palatable food and remove binge triggers from the environment (Turton et al., 2016). Such research might include approach bias modification, attentional bias modification, and interventions informed by behavioural science, which seek to alter the environment to assist in shaping desired behaviour and deter binge eating (MacLeod & Clarke, 2015; Prinsen, de Ridder, & de Vet, 2013; Turton et al., 2018).

7.3.2 Implications and future directions for the investigation of oxytocin in treating disordered eating behaviour

It is important to note that the effect of oxytocin on eating behaviour in humans is influenced by several factors, including dose, sex, weight status, hunger status, and food type (Leslie, Silva, et al., 2018). Thus, while the current study did not find a significant effect of a divided dose of 64IU intranasal oxytocin on the immediate consumption of palatable food or 24-hr caloric consumption in women with and without BN or BED, these findings do not detract from the possibility that oxytocin may curb overeating behaviour at a different dose or method of administration.

A perfusion study drawing from the data presented in this thesis found that 40IU intranasal oxytocin does not affect resting cerebral blood perfusion in women with or without BN or BED 18-24 minutes following drug administration, while intranasal oxytocin did affect resting cerebral blood flow in men at the same dose and timespan following administration (Martins, Leslie, et al., 2019). While these findings regarding cerebral blood perfusion at rest do not indicate the optimal functional dose of oxytocin for curbing palatable eating, this study does indicate that the architecture of oxytocin signalling likely differs between men and women. Therefore, the optimal dose schedule found for men in previous studies will not necessarily apply to women. Our primary recommendation for future research investigating the influence of oxytocin on eating in women is therefore to carry out dose-response studies to titrate the optimal dose of administration in women.

Given evidence reviewed in Paper 4 indicating that oxytocin has a greater inhibitory effect on eating in men, we would strongly recommend future studies to investigate the effect of oxytocin on hedonic eating in men with BN and BED. Men with eating disorders are often underserved by research; however, our knowledge to date suggests that oxytocin administration may be more effective in men with BN and BED versus women with BN and BED. Future studies investigating the differential effect of oxytocin on hedonic, versus hunger-driven eating, in men with BN and BED therefore presents an interesting, and potentially fruitful, avenue for further investigation.

7.4 General limitations

While each study of this thesis has served to contribute new knowledge to the understanding of BN and BED, these studies were also associated with several limitations. Study-specific limitations have been discussed within each individual paper. Other limitations applying across two or more papers will be discussed within the current thesis section.

Papers 1 and 2 presented and defended a novel maintenance model of BN and BED: the addictive appetite model. The theoretical components of this model are based on evidence demonstrating similarities in neural functioning between people with substance dependence and people who score highly on measures of food addiction (Gearhardt et al., 2011), as well as models of insulin- and dopamine-mediated food craving in animal models (Mebel et al., 2012) and people with Type II diabetes and obesity (Chechacz et al., 2009; Jastreboff et al., 2013). However, research testing these effects in populations with BN and BED is currently sparse, and the addictive appetite model therefore requires future investigation to corroborate its central hypotheses.

Papers 5, 6, 7, and 8 of the current thesis presented findings from a double-blind, placebo-controlled crossover study investigating the effects of a single divided dose of 64IU intranasal oxytocin in women with and without BN or BED. While the sample size of 52

women is relatively large for a novel fMRI study, this represents a small sample size for the study of potentially subtle effects of oxytocin on eating behaviours, stress, attentional bias to food, and reward approach behaviours. We therefore cannot rule out the possibility that the current study may have been underpowered to detect true, but small effects on each of these dependent variables. Furthermore, the inclusion of a heterogeneous group of women with BN and BED in our clinical participant sample leaves open the possibility that the current study may have failed to detect some effects which are specific to one disorder or the other, as was indicated by our data in the context of attentional biases. We would therefore recommend future studies investigate BN and BED separately, and particularly when investigating attentional biases to palatable food.

The choice of dose schedule in the current study was based on previous findings indicating that the effects of a 40IU dose of intranasal oxytocin on resting cerebral blood perfusion peak at 39-51 minutes following administration in men (Paloyelis et al., 2016). However, data drawn from the current study of oxytocin has indicated that this finding does not apply to women (Martins, Leslie, et al., 2019). It therefore follows from this finding that the dose of oxytocin chosen in the current study may not have been optimal to observe functional effects on eating behaviour, stress, attentional bias to food, and reward approach behaviours. Future dose-response studies will be needed to identify the best dose schedule of intranasal oxytocin administration for curbing overeating behaviour in women.

Finally, in order to maximise recruitment given limited availability of the fMRI scanner, this proof-of-concept study did not experimentally control for menstrual phase or hormonal contraceptive use. Previous evidence has indicated that hormonal contraception can suppress the effects of exogenous oxytocin on BOLD response to images of a partner's face within reward-related mesolimbic brain regions (Scheele et al., 2015). While we did not find a statistically significant effect of hormonal contraception on any

behavioural outcome in the current study, it is still plausible that including women taking hormonal contraception may have suppressed potential effects on eating behaviour in the current study. We would therefore recommend future studies experimentally control for menstrual phase and exclude women currently taking hormonal contraception.

7.5 Overall conclusions

The current thesis aimed to propose and test a new maintenance model of recurrent binge eating: the addictive appetite model of BN and BED. The evidence herein has supported the importance of food craving and eating for the purposes of coping and reward enhancement as distinguishing features of BN and BED. However, further evidence is required to support the existence of food tolerance and withdrawal in BN and BED, as well as the implication of glucose dysregulation in contributing to heightened food craving.

Based on evidence indicating that the hormone oxytocin impacts reward processing and reward-driven eating, the addictive appetite model predicts that oxytocin should be efficacious in curbing binge-like eating behaviour. While oxytocin did curb reward approach behaviours to a greater degree in women with BN or BED compared to healthy control women, we did not find an overall effect of a divided dose of 64IU intranasal oxytocin on reward approach behaviours in the context of a risk-taking computerised task across all participants. The administration of a divided dose of 64IU intranasal oxytocin did not affect the immediate consumption of palatable food, 24-hr calorie consumption, stress, salivary cortisol, or neural response to palatable taste anticipation or receipt. Furthermore, a divided dose of 64IU intranasal oxytocin had the counterintuitive effect of increasing vigilance to palatable food images.

Overall, the current findings therefore do not support a beneficial effect of oxytocin on binge-like eating behaviour in women with BN or BED at the dose used in this study. Based on evidence that oxytocin has a greater inhibitory effect on eating in men, we

recommend that future studies investigate the effects of intranasal oxytocin on binge eating in men with BED and BED and that future dose-response studies continue to investigate whether a different dose of oxytocin would enhance the beneficial effects of oxytocin for women with BN and BED.

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