Neuropsychopharmacological and behavioural mechanisms underlying eating behaviour and disordered eating behaviour

By

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Abstract

The overall aim of this thesis was to understand the mechanisms underlying eating behaviour in healthy and disordered eating samples with a particular focus on homeostatic, reward, and cognitive processes. Chapter 1 provides a general background to the research area. In Chapter 2, experimental findings suggest women with obesity are more sensitive to the beneficial appetitive and mood effects of exogenous insulin compared to lean women. Results of a systematic review and meta-analysis in Chapter 3 suggest that the only drug approved to treat Binge Eating Disorder (BED), lisdexamfetamine dimesylate (LDX), improves binge-eating symptoms through combined catecholaminergic and serotoninergic mediated actions on appetite, reward, and cognitive processes including attention and inhibition. Chapter 4 aimed to experimentally determine the behavioural mechanisms underlying LDX treatment of BED. LDX-induced reductions in food intake, eating rate and palatability, and improvement in sustained attention and impulsive responding supporting the possibility that LDX acts on appetite, reward, and cognition mechanisms to treat binge eating with a specific effect to increase cognitive control. Chapter 5 summarises the main findings of Chapters 2-4 and discusses the implications of the results. The findings of this thesis provide support for an interactive model of appetite control that emphasises cross talk between homeostatic, reward, and cognitive processes. The results suggest that further investigation of IN insulin as a weight management option for women with obesity is warranted and that novel therapeutics aimed at treating BED might target multiple mechanisms including satiety, reward, and cognitive control. The experimental designs used in this thesis also provide a validated paradigm for testing the efficacy of novel compounds to treat BED.

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This thesis is dedicated to my grandmother, Ernestine, who lived selflessly and gave me a better life. I am here today because of the sacrifices you made for me.

Table of Contents

List of Tables

List of Figures

Appendix A

Ethical Approval

Guidelines put forth by the British Psychological Society for human research ethics were adhered to in the design and data collection of each study herein. Ethical approval from the Science, Technology, Engineering, and Mathematics Ethical Review Committee at the University of Birmingham was granted for studies 1 (Chapter 2), 3 (Chapter 3), and 4 (Appendix A). Additional ethical approval was granted by the National Research Ethics Service (NRES), NRES Committee West Midlands – Solihull for studies 1 and 3.

Statement of Authorship

This research was completed through the funding provided by the Biotechnology and Biological Sciences Research Council (BBSRC) awarded to Professor Suzanne Higgs. This research was conducted in collaboration with P1vital Ltd. Chapters 3 and 4 contains material that has been submitted for publication in peer-reviewed journals. Each chapter has been written as a standalone paper. Though efforts have been made to avoid redundancy, some repetition may be present throughout. The authorship of each chapter (published or unpublished) is the product of collaborative work. I designed, collected, analysed, and wrote up the studies. My Supervisors Professor Suzanne Higgs and Dr. Colin Dourish aided in the design, planning, and editing of all the written work and provided supervision.

Chapter 1: General Introduction

1.1 Overweight and Obesity

Overweight and obesity, characterised by having a body mass index (BMI) greater than or equal to 25-29.9 kg/m^2 and greater than or equal to 30 kg/m^2 respectively, is a global epidemic (Nuttall, 2015). Since 1975, worldwide obesity has nearly tripled with recent reports indicating 39% of adults are overweight and 13% have obesity (Afshin et al., 2017). Within the United Kingdom, 36% of adults are classified as overweight, and 29% are classified as obese (Public Health England, 2017b). Overweight and obesity are associated with significant threats to health, including an increased risk of hypertension, type 2 diabetes, heart disease, and stroke (Agha & Agha, 2017). From 2014-2015, these physical health implications cost the United Kingdom government £6.1 billion in healthcare treatment (Public Health England, 2017a). In addition to physical health risks, overweight and obesity have been associated with anxiety, depression, and overall reduced quality of life (Jagielski et al., 2014; McElroy et al., 2004).

1.2 Binge Eating Disorder/Binge Eating

Overweight and obesity has also been linked to Binge-Eating Disorder (BED). BED is defined by recurrent episodes of binge eating and the absence of compensatory behaviours (e.g. laxative use, vomiting, and excessive dieting). An episode of binge eating is characterised by both of the following: 1) eating in a discrete period of time an amount that is definitely larger than what most people would eat in a similar period of time under similar circumstances and 2) a sense of lack of control over eating during the episode (American Psychiatric Association, 2013). Recent evidence suggests that there may be a bidirectional relationship between binge eating and obesity, in which each can precipitate the other (da Luz, Hay, et al., 2018). Indeed, BED is often comorbid with obesity (Citrome, 2019; Hsu et al., 2002; Papelbaum et al., 2019). Additionally,

BED is associated with a myriad of mental health disorders including depression, anxiety, self-harm, substance abuse, and Attention Deficit Hyperactivity Disorder (ADHD) (Kaisari et al., 2017; Kessler et al., 2013; Pearl et al., 2014; Peters et al., 2019; Swanson et al., 2011). Improved understanding of the underlying mechanisms of obesity and binge-eating is essential in prevention of the disorders and to identify effective treatments.

1.3 Approaches to Treatment

Traditional approaches to the treatment of obesity and BED often target single factors. For instance, behavioural weight loss interventions targeting energy intake and expenditure remain the front-line treatment for obesity (Wilfley et al., 2018). Behavioural weight loss treatments, however, do not address eating disorder pathology and some dieting behaviours have been shown to actually induce obesity (Balantekin et al., 2017; Macpherson-Sánchez, 2015). Alternative weight-loss measures such as weight-management pharmacotherapy and gastric surgery are also viable options but are not without limitations. Of the weight loss drugs with European approval (i.e., orlistat (Xenical®, alli®) bupropion/naltrexone (Mysimba®), and liraglutide (Victoza®), the requisite minimum of 5% reduction in weight is achieved, but concerns of safety, efficacy, and long-term weight-loss management are still barriers to effective obesity treatment (Tak & Lee, 2020; Valsamakis et al., 2017). Similarly, weight loss surgery is often found to be more effective in reducing weight loss compared to non-surgical methods (Colquitt et al., 2014), but recent reports indicate 20-40% of patients regain weight 12-18 months post-surgery (Dimeglio et al., 2020). Further, 10 years post bariatric surgery, only 14-25% of weight lost was maintained in sample of 2010 patients (Sjöström et al., 2007). Following a narrative review of the literature, Bryant and colleagues theorised that post-surgery weight gain is likely due to a shift from passive, involuntary weight loss to a gradual need for reliance on an

individual's cognitive efforts to control food intake (Bryant et al., 2020). Moreover, gastric surgery poses significant peri- and postoperative risks to physical health (Lim et al., 2018).

BED is commonly treated with psychotherapy, specifically cognitive behavioural therapy, which largely emphasises psychological factors (Hay et al., 2009; Palavras et al., 2017; Wilson et al., 2010). Though psychotherapeutic treatments for BED can be effective in the short-term reduction of binge-eating episodes, long-term binge-eating abstinence and weight loss outcomes are inconsistent and inconclusive (Brownley et al., 2007; Peat et al., 2017). There are also few available pharmacotherapy options for treatment of BED. The only FDA approved drug is lisdexamfetamine dimesylate (LDX, Vyvanse®), which has shown promise for effectively reducing binge-eating episodes (McElroy et al., 2016). A recent review of BED pharmacotherapies, however, indicated a lack of understanding of the mechanisms underlying the efficacy of LDX, as well as the presence of undesirable side effects, in common with all BED drug therapies (Amodeo et al., 2019). Taken together, treatment approaches to obesity and BED lack efficacy and/or feasible mechanisms for long term maintenance therapy. This lack of consistent and holistic treatment of BED and obesity may be due to the complex nature of appetite control. Appetite – the desire to eat – was initially classified into homeostatic and non-homeostatic (or reward) driven eating, but recent evidence also suggests higher order cognitive processes play an important role in appetite.

1.4 Homeostatic Control of Appetite

Homeostatic eating refers to eating in response to metabolic need whereas reward-related eating refers to eating motivated by learning about the hedonic effects of food consumption (Berthoud, 2006). Meal initiation is largely determined via reward mechanisms, while meal

termination is mostly considered a homeostatic process (Schwartz et al., 2000). In the homeostatic system, the central nervous system (CNS) and peripheral nervous system interact to regulate food intake and achieve energy homeostasis. For instance, once food is consumed, the gastrointestinal tract relays information through neurotransmitters such as serotonin and neuropeptides such as cholecystokinin (CCK) regarding nutritive status and gastric volume to the vagus nerve which is then relayed to the medial nucleus solitarius (mNTS) in the caudal brain stem (Berthoud, 2006). The mNTS then conveys this energy status information to other brain regions including the hypothalamus.

The hypothalamus, specifically the arcuate nucleus (ARC), has historically been implicated in the control of food intake (Stellar, 1954). The ARC processes metabolic signals provided by a range of hormones, neurotransmitters and neuropeptides, including insulin, ghrelin, leptin, glucagon-like peptide 1, (GLP-1), CCK, dopamine (DA), and serotonin (Woods & D'Alessio, 2008). The lateral ARC secretes the orexigens neuropeptide Y (NPY) and agouti-related protein (AGRP), and the medial ARC neurons secrete the anorexigen pro-opiomelanocortin (POMC; Reece, 2011). The ARC has neuronal projections to other areas of the hypothalamus (e.g., the paraventricular nucleus, lateral hypothalamus and perifornical area) and to reward areas such as the DA neurons of the ventral tegmental area (VTA; for reviews on the hypothalamus see Williams et al., 2001 and Stuber & Wise, 2016).

Insulin receptors are also located within the hypothalamus (Werther et al., 1987). While insulin is largely known for its role in peripheral blood glucose homeostasis (Czech, 2017), there is also evidence that the hormone acts centrally to influence energy homeostasis (Woods, Lotter, McKay, & Porte Jr., 1979).

1.4.1 Regulation of Homeostatic Eating by Central Insulin

Peripheral insulin is produced by β cells of the pancreas for the maintenance of blood glucose levels through the process of glucose uptake, regulation of carbohydrates, lipid and protein metabolism, and the promotion of cell division and growth (Wilcox, 2005). Centrally, insulin receptors are found in several areas of the brain including the hypothalamus, cerebral cortex, amygdala, cerebellum, choroid plexus, olfactory bulb and the hippocampus (Hopkins & Williams, 1997; Marks et al., 1991; Unger et al., 1991; Werther et al., 1987). It is significant that insulin receptors are highly expressed in the ARC (Houten et al., 1979). Insulin is transported to the CNS across the blood-brain barrier by a saturable blood transport system (Banks et al., 1997). Insulin is secreted in proportion to the amount of body fat and as such acts as an adiposity signal. Insulin levels also increase during meals, exercise, stress, and other elevated glucose states (Woods & Seeley, 2001). In this way, insulin adjusts to acute metabolic change, as is reflected by insulin's half-life in the blood of approximately 2-3 minutes.

Insulin acts as a metabolic signal to regulate homeostatic feeding. If exogenous insulin is administered to the brain, the response is as if excess fat exists in the body leading to a reduction in food intake and body weight (Woods & D'Alessio, 2008). Insulin injected directly into the ventral hypothalamus of the rat, reduced food intake and decreased body weight (McGowan et al., 1992). In contrast, female mice with insulin receptor gene knockout (NIRKO) showed increased food intake and both sexes had increased body fat (Bruning et al., 2000). Similarly, insulin receptor antagonists and insulin receptor antibodies induced hyperphagia and obesity in mice and rats (Kyriaki, 2003; Strubbe & Mein, 1977). Thus, augmenting or disrupting adiposity signals to the brain through insulin modulation directly influences food intake.

1.5 Food Reward

Berridge and Robinson (1993) defined food reward as a process of learning through 'liking' and 'wanting'; whereby, 'liking' refers to a hedonic reaction to food cues and 'wanting' is the motivation to procure these liked foods. Wanting attaches salience to palatable foods and induces cravings that motivate efforts to consume the desired food. In the brain, 'liking' regions such as the orbitofrontal cortex (OFC), anterior cingulate cortex, anterior insula cortex, ventral pallidum, nucleus accumbens (NAc), and amygdala are activated by the consumption of pleasant foods, as are systems of the lower brainstem (Berridge et al., 2010). These brain regions are innervated by opioid, cannabinoid, and gamma-aminobutyric acid (GABA) neurones (Berridge, 2009). Conversely, DA mechanisms are activated in the process of 'wanting' (Berridge & Robinson, 2016). Together these two reward systems form a larger food reward circuit: the mesocorticolimbic pathway that arises in the VTA and also includes the posterior fusiform, (ventro)medial and dorsolateral prefrontal cortices (Alonso-Alonso et al., 2015; Berthoud et al., 2011). It has been argued that wanting can occur in the absence of liking and may contribute to hyperphagia (Berridge et al. 2010).

1.5.1 Dopamine

Dopamine plays a crucial role in the mediation of reward. Indeed, increased DA activation in response to food stimuli, particularly high-fat, high-sugar foods, has been evidenced across several studies using many different paradigms (Avena et al., 2006; Nasser et al., 2013; Small et al., 2003). DA neurons are highly expressed in the striatum, which is composed of the caudate, putamen, and the ventral striatum containing the NAc. The DA projection from the VTA to the NAc is strongly implicated in the mediation of reward (Wise, 2006) together with other DA projections from the VTA including the dorsal striatum, cortical and limbic regions,

and the lateral hypothalamus (Haber, 2014). When we try a new food item, firing of DA neurones in the VTA increases which in turn increases DA release in the NAc (Norgren et al., 2006). When a food is repeatedly consumed, the DA response habituates and reward properties are transferred to cues associated with the food item (Volkow et al., 2011). Over time, the brain calculates a 'reward prediction error'; whereby, we predict a stimulus's expected reward value and contrast this with the received value (Schultz, 2016). Implications for this conditioned learning of food reward is discussed below.

1.5.1.1 The Relationship between Dopamine, Obesity, and Binge-Eating Disorder

Rodent models of obesity and BED suggest a dysregulated dopaminergic system may underlie both disorders. Rodents fed a high-fat, high-sugar diet become obese which leads to downregulation of striatal DA D_2 receptors (Johnson & Kenny, 2010). Similarly, rats exposed to a model of binge eating have reduced DA D_1 receptors in the caudate putamen (Heal et al., 2017) and decreased striatal DA D_2 receptors compared to healthy controls (Colantuoni et al., 2001).

The relationship between DA and appetite is moderated by weight status. Individuals with obesity have a hypersensitive striatal DA response to visual food stimuli (Martin et al., 2010; Schienle et al., 2009) and a hyposensitive response to the consumption of food (Stice et al., 2008), leading to a proposed 'dynamic model' of striatal modulation to explain DA divergences in individuals with obesity (Carnell et al., 2012). The incentive sensitisation theory proposed by Berridge suggests that the DA response to food cues in people with obesity is initially hypersensitive but becomes hyposensitive through the downregulation of DA D_2 receptors as a consequence of overfeeding (Morales & Berridge, 2020). This theory is in line with previous reports of decreased D_2 receptors in obese rats fed a high-fat, high-sugar diet (Johnson & Kenny, 2010) and decreased D_2 receptors proportional to increased BMI in humans (de Weijer et al.,

2011; Wang et al., 2001). Both theories reflect the complex role of DA in the control of feeding, in which DA exerts effects on eating, in addition to reward, through conditioned responding, learning, motivation, and motor control (Salamone & Correa, 2012; Wise, 2004).

Altered striatal DA responses to food cues have also been observed in BED. When given the dopaminergic stimulant, methylphenidate, in a Positron emission tomography (PET) imaging study, participants with BED had increased DA in the caudate and putamen in response to various food stimuli. This caudate DA increase correlated with binge-eating scores, but not with BMI, suggesting that DA release can predict BED but not BMI (Wang et al., 2011). These dopaminergic mechanisms likely underpin a maladaptive food reward system observed in obesity and BED. LDX, the only drug approved to treat BED, increases striatal DA efflux in rats (Rowley et al., 2012). The efficacy of LDX for the treatment of BED is thought to be, in part, due to LDX restoring deficits in striatal D_1 receptor-mediated signaling (Heal et al., 2017). Similarly, the reduction of chocolate intake by LDX administration in binge-eating rats was partially reversed by D_1 antagonist pre-treatment (Vickers et al., 2015) suggesting the dopaminergic system is a potential target for BED treatments.

1.6 Homeostatic and Reward Interactions

Though homeostatic and reward processes were previously considered as separate independent systems, there is now evidence that they interact to control food intake. This is evidenced in the case of appetite in fasted and satiated states. When we experience hunger, food cues are more salient (Goldstone, 2006). We even experience greater enjoyment of a meal when hungry. Indeed, participants in a 24-hour fasted condition rated consumed foods as tastier than when satiated (Cameron et al., 2014). Similar results were found in a functional magnetic resonance imaging (fMRI) study investigating neural activations in response to viewing food

images in a fasted and satiated state. Participants in the fasted condition had increased activation in the ventral striatum, amygdala, anterior insulin, and the OFC, all of which are areas involved in food reward. Fasting also increased subjective ratings of the attractiveness of high-calorie foods more than low-calorie foods (Goldstone et al., 2009). Similar results were found in leptin-deficient patients where leptin administration modulated activation in reward circuitry areas and increased satiety (Farooqi et al., 2007). Further, the patients rated food images as less appealing following leptin administration (Farooqi et al., 2007). These results indicate that nutritionally depleted states bias the brain to prefer energy-dense foods and to find them more appealing, providing evidence of reward-metabolism crosstalk.

1.6.1 Insulin as a Mediator of Homeostatic-Reward Crosstalk

Recent evidence suggests the existence of an insulin-dependent dopaminergic system, in which insulin acts both metabolically and hedonically (for a review see Kleinridders & Pothos, 2019 and Könner et al., 2009). Findings from rodent studies confirm that central insulin reduces hedonic feeding via signaling within mesolimbic reward circuits (Davis et al., 2010; Figlewicz et al., 2003). Further, insulin administered to mesolimbic areas of the brain decreased hedonic feeding in rodents (Labouèbe et al., 2013; Mebel et al., 2012). Similar effects have been observed in humans. Thus, Hallschmid et al. (2012) administered 160 IU of insulin intranasally to female participants both when hungry and after eating. Once satiated, participants received a palatable snack to measure hedonic food consumption. Insulin decreased intake and rated palatability of the snack in participants in a postprandial state, but not in a fasted state, indicating that insulin affects hedonic eating. Accordingly, in an fMRI study participants who viewed food and non-food pictures following intranasal insulin administration had significantly reduced ratings of food picture palatability and reduced activity in areas of the brain associated with

reward (i.e., mesolimbic regions) (Tiedemann et al., 2017). Though evidence supports insulin's role in food reward, human studies have yet to be conducted that directly explore if insulin's effect on food intake is mediated by modulation of food reward.

While hedonic and metabolic processes are no longer considered divergently, reward and metabolism interactions do not fully explain how a hungry individual is able to forego a salient, high-fat/high-sugar food item and instead eat a healthier food or why an individual continues to eat past satiation. An emerging field of research that evidences a link between appetite and higher order cognitive processes may offer potential explanations (Higgs et al., 2017; Higgs & Spetter, 2018).

1. 7 Cognition and Food Intake

Eating relies upon many conscious and unconscious decisions. Deciding what to eat, when to eat, and how much to eat is dependent upon cognitive processes such as learning, attention, and memory. Cognitive and appetitive processes appear to work in tandem and bidirectionally. Reviving meal memories is associated with reduced snacking while a regular diet of high saturated fat and refined carbohydrates is associated with impairments in processing speed, delayed memory recall, and attention and with neurodegenerative diseases (Francis & Stevenson, 2013; Higgs et al., 2008; Kopp, 2019; Martínez Leo & Segura Campos, 2020). Changes in cognitive processing may explain such phenomena as resisting highly palatable foods or ignoring feelings of satiety.

1.7.1 Learning

The hedonic 'liking' response of consuming palatable foods quickly becomes associated with stimuli related to the desired food. For example, previous enjoyable experiences of eating a donut will cause an association of the smell or sight of a donut with pleasure. Thus, walking past

a donut shop and smelling the scent may provoke a desire to eat a donut. This is a result of learning via Pavlovian conditioning. The process of food consumption and digestion is an unconditioned stimulus (US), and once a cued conditioned stimulus (CS) is associated with this US, appetitive responses are stimulated by the CS (van den Akker et al., 2018). In the case of the donut shop example, the individual learns to associate the donut shop (CS) with pleasant feelings and this promotes future intake of the target item (i.e., donut). After this US/CS association is made, appetitive stimuli can induce conditioned responses (CRs) called cephalic phase responses such as salivation, insulin secretion, approach behaviour, and cravings (Eliasson et al., 2017; Nederkoorn et al., 2000; Van Gucht et al., 2008). Cephalic phase responses are also seen in the brain, specifically the nucleus accumbens, a key structure in food reward, suggesting an interaction between learning and reward processes (Martin-Soelch et al., 2007). These CRs motivate behaviour to procure the food item, and their receipt produces reward responses ('wanting') thus enhancing salience of the CS.

1.7.2 Impulsivity/Inhibition

Though paired associations can create a drive to obtain a craved food, inhibition can override hedonic motivation. Existing goals such as eating healthier or dieting rely on cognitive control areas of the brain, specifically the prefrontal cortex. The ventromedial prefrontal cortex (vmPFC) makes value judgments about the predicted reward of the food item, while the dorsolateral prefrontal cortex (dlPFC) uses this information to initiate inhibition or disinhibition (Hare et al., 2008). Hare et al. (2009) found that activity in the dlPFC increased when participants used greater self-control on a food decision task that had conflicting palatability and healthiness factors and correlated with activity in the vmPFC. This is in line with evidence that people with obesity tend to have poorer dlPFC activation in response to eating (Brooks et al.,

2013; Le et al., 2006, 2007). Similarly, individuals with obesity and individuals with binge eating show greater impulsivity on behavioural tasks of inhibition (Nederkoorn et al., 2006; Schag et al., 2013). These data suggest that underlying disinhibition could explain individual susceptibility to heightened neural and behavioural responsiveness to highly palatable, salient foods.

1.7.3 Working Memory

Resisting temptation of high-fat/high-sugar foods and suppressing food cravings also relies upon working memory (WM). In accordance with the established finding that WM capacity is limited (Miller, 1956), maintaining goals such as dieting or healthy eating when confronted with highly palatable foods could overwhelm the WM capacity. Applying this theory, deficits in WM capacity may impede healthy eating. Indeed, working memory deficits are found in individuals with overweight and obesity and binge-eating symptoms (Coppin et al., 2014; Duchesne et al., 2010; Hofmann et al., 2008). Moreover, chronic dieters, or restrained eaters, forgo dieting and eat more when given a cognitively demanding task as compared to an easier cognitive task (Lattimore & Maxwell, 2004; Ward & Mann, 2000). Lattimore and Maxwell (2004), theorise that the demanding task usurps resources typically available for dieting resulting in disinhibited eating. Conversely, better visuospatial WM is associated with a greater preference for low energy-dense foods (Whitelock et al., 2018) and greater WM capacity leads to quicker satiation (Nelson & Redden, 2017). However, the causal nature of the relationship is unclear, specifically whether WM deficits precipitate overweight/obesity or vice versa (Dohle et al., 2018).

1.7.3.1 Attention

Attention and working memory are closely intertwined (Awh et al., 2006). It is argued that working memory capacity is actually the capacity for sustained and controlled attention when confronted with distracting or interfering stimuli (Engle et al., 2012). Indeed, attention acts as the working memory 'gatekeeper' and biases encoding of information toward items that are most relevant to current goals (Awh et al., 2006). This is relevant to the robust literature of distraction and overeating, whereby distraction refers to the absence of eating attentively (Robinson et al., 2013). When individuals do not attend to eating, for example when watching television while eating or dining with others, food intake is often increased (Braude & Stevenson, 2014; Ogden et al., 2013; Ruddock et al., 2019). Conversely, eating attentively leads to reduced food intake (Alberts et al., 2012; Jordan et al., 2014; Warren et al., 2017). One possible explanation for these findings is that distraction impairs encoding of memories (Chun & Turk-Browne, 2007), which is also important in reducing future food intake. Thus, both preprandial and periprandial attention to food stimuli are key modulators of food intake.

There is evidence to suggest that attentional biases to food cues increase food intake and hunger (Field et al., 2016). This may explain why individuals with binge-eating symptoms show greater engagement with food items and identify food items quicker than non-food items (Schmitz et al., 2014). Some researchers, however, argue attentional biases to food cues are a result of poor inhibition of salient food cues, a phenomenon that is indeed present in obesity and binge-eating (Hou et al., 2011). Attention can also be biased in non-pathological eating depending upon nutritive state. Thus, in a fasted state, attention is biased to food cues as a motivator to consume food (Tapper et al., 2010). Even when efforts are made to suppress attention to food cues, preprandial food-related stimuli are distracting from task-relevant goals

(Davidson et al., 2018). In fact, a recent meta-analysis found that attentional biases to food cues are more related to appetitive states such as hunger than to individual differences such as BMI (Hardman et al., 2021).

1.7.4 Long-Term Memory

Long-term memory is also a key executive function in eating behaviour. Four types of long term memory have been distinguished: procedural, semantic, autobiographical, and episodic memory (Atkinson & Shiffrin, 1968). Episodic memory is the memory for specific events in time (Wood et al., 2012). As previously noted, initial consumption of a certain food is learned and transferred into long-term memory. Once we make a subsequent meal or snack decision, we retrieve data from our episodic memory to inform the decision to eat this food again in the future. If we remember enjoying a certain food, we are likely to want to eat this food again (Robinson et al., 2012). If we have a goal of healthy eating, we may opt for a healthier item. However, the ability to maintain healthy eating goals relies upon the subsequent retrieval of long-term consequences of behaviour from memory among other requisites (Higgs et al., 2017). Indeed, memory retrieval is critical in affecting future intake. In a study by Higgs (2002), participants were assigned to one of three conditions: recalling a meal from the same day, recalling a meal from the previous day, or unguided thinking (control) and given *ad libitum* access to biscuits. Participants who recalled the meal from the same day ate significantly fewer biscuits than those in the other conditions (Higgs, 2002). This effect was seen in another study in which participants were asked to recall a meal eaten one hour earlier versus 3 hours earlier. Participants in the 3-hour group consumed significantly fewer biscuits, whereas participants in the 1-hour group had no change in their intake. The authors suggested that the results in the 1-hour group were likely due to a lack of time to forget the event highlighting the importance of episodic memory in food

consumption (Higgs et al., 2008). A recent replication study of Higgs et al. (2008) found a reduction in snack intake when participants recalled the meal they had just consumed regardless of their individual memory abilities (Szypula et al., 2020). A similar effect is also seen in amnesic patients who have disrupted episodic memory. Patients with amnesia who were unable to recall having previously eaten consumed significantly more kilocalories compared to control subjects (Higgs et al., 2008).

Individual ability to retrieve episodic memories is positively associated with avoidance of high-fat foods and negatively associated with uncontrolled and emotional eating (Martin et al., 2018). Conversely, high BMI is associated with poorer episodic memory (Cheke et al., 2016). Similar results were seen in an assessment of immediate and delayed recall in women with overweight and obesity (Cook et al., 2017). Again, the causal nature of memory impairments on weight status and overeating or vice versa is unclear but, in either case, can maintain a vicious cycle of overeating (Davidson et al., 2014).

1.8 Cognitive, Metabolic, and Reward Interactions

As noted previously, appetite is mediated by a complex system. When we are hungry, we rate palatable foods as more pleasant (Goldstone et al., 2009) and as less pleasant when we are full (Berridge et al., 2010). We also eat past satiation when we really like a food item (Johnson & Wardle, 2014). Our cognitive processes can also bias our food preferences. Thus, labeling an exercise as ‘fat-burning’ increases later food intake (Fenzl et al., 2014). Taken together, these results suggest an interdependent control system for food intake, in which metabolism, reward, and cognition interact to influence appetite.

1.8.1 Insulin and Cognition

Insulin has also been implicated in cognition. As previously noted, insulin receptors are highly concentrated in the hippocampus, a key area for memory, suggesting a potential role of insulin in memory processes (Parkin, 1996). Central insulin also regulates the release of acetylcholine and noradrenaline, neurotransmitters which are known to influence cognition (Bhattacharya & Saraswati, 1991; Hasselmo, 2006). Exogenous insulin administration has been reported to improve cognition, including enhanced memory recall, inhibition, and verbal memory, in individuals with and without memory impairments (Benedict et al., 2004; Kern et al., 2001; Reger et al., 2006). Conversely, brain insulin resistance is associated with increased risk of dementia and Alzheimer's Disease (Rivera et al., 2005; Talbot et al., 2012; Xu et al., 2009). Some studies have investigated the effects of insulin administration on memory and food intake, but these studies did not examine the potential mediating effects of cognition on food intake (Benedict et al., 2008; Krug et al., 2010). It is thus unclear which mechanisms underlie the effects of insulin on food intake and if cognition mediates these effects.

1.8.2 Dopamine and Cognition

In addition to modulating reward, DA also plays an important role in cognition. Interestingly, DA projections to the striatum and frontal cortex underpin the effects of rewards on approach behaviour and learning, indicating dopaminergic learning mechanisms may mediate reward (Schultz, 2007). When given a single dose of LDX, which is an indirect DA agonist, participants exhibited improved vigilance, accuracy, and reaction time on various cognitive measures (Dolder et al., 2018). LDX is a pro-drug and its active metabolite, d-amphetamine, also reduces impulsivity in healthy adults (De Wit et al., 2002; Weafer & De Wit, 2013). Moreover, as described above LDX decreases binge-eating episodes in individuals with binge-eating

symptoms (Guerdjikova et al., 2016; McElroy, Hudson, et al., 2016) and is FDA approved for the treatment of BED. Given that DA affects learning, reward, and food intake with evidence indicating dopaminergic learning mediates reward (Schultz, 2007) and that DA-agonist drugs influence cognition and binge eating, more research is needed to understand these actions and potential interactions. Specifically, research is needed to examine if the actions of a dopamine-agonist such as LDX on cognition could mediate its effects on binge-eating symptoms.

1.8.3 An Interactive Model of Appetite

Given the highly complex control of eating and the interdependent nature of different mediating mechanisms, an interactive model of appetite has been proposed by Higgs et al. (2017) (see Figure 1). Thus, eating for energy (homeostatic eating) is largely controlled by the hypothalamus which has a bidirectional pathway to reward as in the example of finding foods more palatable in a nutritionally depleted state. Reward is largely controlled by the dopaminergic system of the brain. Mediating both of these pathways is cognition, with specific roles of the prefrontal cortex and the hippocampus. Cognition influences metabolic control as in the case of eating more in the absence of remembering food eaten and exerts an effect on reward by, for example, enabling resistance to the temptation to eat certain foods that are inconsistent with health goals. Moderating these effects, as indicated by the dashed lines in Figure 1, are appetitive signals from the brain and the periphery, such as where insulin modulates metabolism, reward, and cognition. This model provides a framework for research and the rationale for the studies in this thesis. Specifically, the focus of the work is the potential mediating role of cognition mechanisms, an underexplored link, in controlling appetite. The studies proposed may also help to identify improved treatments for disordered eating.

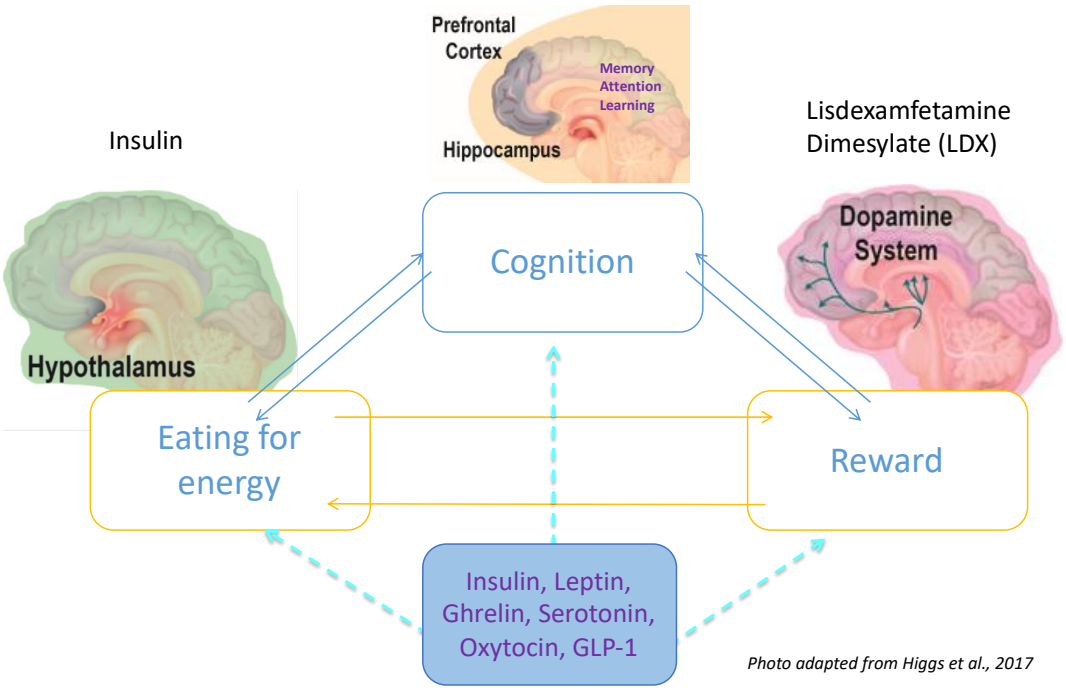


Figure 1: Proposed Interactive Model of Appetite Control

1.9 Thesis Aims and Outline

Based on the model presented above, the aims of this thesis are:

(1) To examine interactions between metabolic, hedonic, and cognitive processes in appetite and their relevance to obesity and BED. Together, these studies will provide new data on the potential mediating role of cognitive processes in the effects of insulin and dopamine manipulations on food intake.

(2) To understand the potential role of weight as a moderator in the effects of intranasal insulin on eating.

(3) To assess the evidence for the efficacy of LDX in the treatment of BED.

(4) To explore the mechanisms underlying the actions of LDX in the treatment of BED.

In the first study (Chapter 2), the hedonic and cognitive mechanisms underlying the effects of the metabolic signal insulin on appetite are examined. The effects of a single intranasal

dose of insulin on appetite, cognition, reward, and mood in lean women and women with obesity are investigated using behavioural and self-report measures. As reviewed in this introduction, insulin is most often associated with metabolic contributions to appetite, though emerging evidence suggests insulin is also instrumental in cognition and reward processes that control eating.

In the third chapter, the efficacy and mechanisms of action of the dopaminergic agonist LDX in the treatment of BED in humans and in animal models of BED are assessed in a systematic review and meta-analysis.

In the second study (Chapter 4), the effects of enhancing dopamine neurotransmission on appetite and the underlying reward and cognitive mechanisms are examined. The effects of a single oral dose of LDX on appetite, cognition, reward, and mood in women with binge-eating symptoms are investigated using behavioural and self-report measures.

The final chapter (Chapter 5) discusses the findings in a broader context, as well as the potential implications of these findings for treatment of overeating pathologies.

All of the hypotheses for the experimental chapters have been pre-registered on either ClinicalTrials.gov (Chapter 2 and 4) or Prospero (Chapter 3).

In Appendix A, a cognitive based intervention is proposed to reduce food cravings in women with binge-eating symptoms. The intervention involves participants engaging with either a low or high cognitive load task, and the effect on subsequent food cravings and food intake is assessed via self-report and laboratory food intake measures. Due to the global pandemic caused by the novel coronavirus SARS-CoV-2, data was not collected for this study and hence only the proposed protocol is included in the appendices.

Chapter 2: The Effect of Intranasal Insulin on Appetite, Cognition, and Mood in Women with and without Obesity

2.1 Introduction

Insulin is known for its role in the regulation of blood glucose in the periphery. However, insulin also has several important functions within the central nervous system (CNS). Insulin receptors are located in the hypothalamus, thalamus, cerebellum, striatum, amygdala, choroid plexus, olfactory bulb, brainstem, and the hippocampus (Hopkins & Williams, 1997; Kleinridders et al., 2014; Marks et al., 1991; Unger et al., 1991; Werther et al., 1987) and are highly expressed in the ARC of the hypothalamus (Houten et al., 1979). The locations of insulin receptors in homeostatic (i.e., hypothalamus), reward (e.g., striatum), and memory-related (i.e., hippocampus) areas of the brain suggest that insulin could play a key role in appetitive, hedonic, and cognitive processes.

Acute administration of intranasal (IN) insulin, which is a non-invasive method for assessing the central actions of insulin, has been reported to reduce food intake in healthy adults given *ad libitum* access to a food buffet (Benedict et al., 2008; Jauch-Chara et al., 2012; Krug et al., 2018; Santiago & Hallschmid, 2017). In addition, chronic administration of IN insulin has been found to suppress hunger in the longer term and decrease BMI (Hallschmid et al., 2004). However, not all studies have found effects of IN insulin on appetite, food intake, and body weight (Hallschmid et al., 2008; Ritze et al., 2018; Rodriguez-Raecke et al., 2020), which suggests that there are moderating factors.

Results from neuroimaging studies suggest that IN insulin has weaker effects or no effects on individuals with obesity (Kullman et al., 2013; Kullmann et al., 2015; Kullmann et al.,

2017; Edwin Thanarajah et al., 2019; Tiedemann et al., 2017; Vidarsdottir et al., 2007). However, the effects of IN insulin on measures of food intake have not been investigated in women with overweight or obesity, despite the fact that women are more likely than men to have obesity (Chooi et al., 2019) and there being evidence for sexually dimorphic effects of insulin. Based on observations that acute administration of IN insulin reduced food intake in men but not women (Benedict et al., 2008) and that daily administration of IN insulin for 8 weeks reduced BMI and body fat in men, but not in women (Hallschmid et al., 2004), it has been suggested that women may be less sensitive than men to the effects of IN insulin on hunger and food intake (Kullmann et al., 2020).

The mechanism of action underlying the effect of CNS insulin administration on food intake remains unclear (Jauch-Chara et al., 2012), but the evidence to date suggests potential contributions from homeostatic, reward, and cognitive processes (Higgs et al., 2017). Indeed, insulin acts on both homeostatic and hedonic pathways. Metabolically, the hypothalamus, a key area for energy regulation, adapts to changing glucose states (Smeets et al., 2005, 2007) and hypothalamic neural activity is inhibited by the delivery of IN insulin. Insulin also modulates the food reward system encompassing the mesocorticolimbic dopaminergic pathways from the ventral tegmental area (VTA), nucleus accumbens (NAc), and prefrontal cortex (PFC), and actions on reward may be an additional mechanism that underlies the effects of IN insulin on food intake (Lutter & Nestler, 2009).

CNS insulin stimulation alters neural activity in regions associated with higher order cognitive processes including the hippocampus and prefrontal cortex, suggesting that changes in food reward could be mediated by changes in cognition (Guthoff et al., 2010; Kullmann et al., 2017; Wallner-Liebmann et al., 2010). Previous studies found an enhancing effect of exogenous

insulin administration on working memory (Benedict et al., 2008; Krug et al., 2010), hippocampus-dependent declarative memory (Benedict et al., 2008; Hallschmid et al., 2008; Ritze et al., 2018), and delayed memory recall (Benedict et al., 2004) in healthy participants. With emerging evidence indicating a mediating role of cognitive processes in appetite control (Higgs et al., 2017; Morris, Yeomans, et al., 2020; Nelson & Redden, 2017), it is possible that the reduction in food intake caused by CNS insulin administration could be mediated by the downregulation of food reward through cognitive control processes.

When assessing the effects of IN insulin on food intake, it is also important to establish the specificity of the effect and whether any decrease in food intake can be explained by a depressed mood or anhedonia. There is some evidence to suggest that insulin may improve, rather than impair, mood (Kern et al., 2001). Enhancements of mood, including improvements in anger, self-confidence, anxiety, and fear response, have been reported after both acute and chronic administration of insulin (Benedict et al., 2004; Ferreira de Sá et al., 2020; Hallschmid et al., 2008). These results suggest that the decrease in food intake after IN insulin is not explained by anhedonia.

In summary, IN insulin has been reported to decrease food intake, but its effects on women with obesity have yet to be established and previous studies have not included detailed measures to determine insulin's mechanism of action on food intake, which remain largely unknown. The current study addresses these gaps by administering an acute dose of 160 IU insulin intranasally to women with and without obesity. IN insulin was administered after a fixed lunch and intake of a palatable snack offered in the absence of hunger was assessed. To examine the effects of IN insulin on homeostatic and reward components of eating, intake of palatable food was assessed alongside additional behavioural measures. Insight into the specific processes

underlying changes in food intake can be gained from assessment of meal microstructure including eating rate and within meal rated palatability using a universal eating monitor (UEM) (Kissileff et al., 1980; Yeomans, 1996). For example, drugs that increase satiety tend to decrease eating rate (Thomas et al. 2014), whereas drugs that decrease palatability have been found to reduce initial rated palatability of a food (Yeomans & Gray, 1997). Reductions in reward-related responding were also assessed using the delay discounting test which assesses the tendency to prefer immediate over delayed rewards (Davis et al., 2010). To examine the effects of IN insulin on cognition, participants completed immediate and delayed memory recall and a working memory task. To examine effects on mood, participants rated their mood throughout the study day using visual analogue scales and the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988). Participants also completed tests of emotional processing from the P1vital® Oxford Emotional Test Battery (ETB) (Harmer et al., 2003; Harmer et al., 2009; Murphy et al., 2008; Thomas et al., 2016). Participants also had fMRI scans but the fMRI data from this study is not reported, as it is not the focus of this thesis. We predicted that IN insulin would reduce palatable snack intake eaten in a satiated state. Further, we predicted IN insulin may decrease eating rate and rated palatability and improve mood and cognitive performance. Finally, based on limited evidence, we tentatively predicted that these effects may be less pronounced in participants with obesity.

2.2 Methods

2.2.1 Participants

Fifty-four participants took part in this study, but one participant withdrew after the first test day due to discomfort with having blood samples taken (lean participant), and another participant withdrew during the first test day due to a migraine (participant with obesity). The

resulting sample consisted of thirty-five lean women (M_{BMI} = 22.211 kg/m^2 ± 1.91, M_{age} = 23.66 ± 4.80) and seventeen women with obesity (M_{BMI} = 34.035 kg/m^2 ± 3.38, M_{age} = 26.00 ± 7.91). Assuming a small to medium effect size for a repeated-measures design, we aimed to recruit 35 in each BMI group to allow for data loss/dropouts, however, difficulties in recruitment resulted in a smaller sample size for women with obesity. Therefore, effect sizes are presented with all statistical outcomes. Participants were recruited from the University of Birmingham and the surrounding community via posters and social media platforms. Participants were informed via study advertising posters and the information sheet that the purpose of the study was to measure the 'effect of intranasal insulin on memory, mood, and taste perception'. Participants received £100 compensation for completion of the study. This study was approved by the University of Birmingham Research Ethics Committee and the National Research Ethics Service and was conducted in accordance with Good Clinical Practice and the principles outlined in the 1964 Declaration of Helsinki. All participants gave written informed consent to participate.

This study was pre-registered on ClinicalTrials.gov (Identifier: NCT03632681).

2.2.1.1 Inclusion/Exclusion

Participants were included if they were female, aged 18-65, fluent English-speaking, and met the BMI specifications for lean (18.5-25 kg/m^2) or obese (≤30 kg/m^2) status. Participants were excluded if pregnant or breastfeeding, allergic or intolerant to study foods, smoker, vegan or vegetarian, diagnosed with an eating disorder, lost more than 5 kg of weight in the three months prior to the study, disliked the test day meal or snack. Participants were also excluded if they had a diagnosis or were prescribed medications for a metabolic, neurological, or psychological disorder. The following exclusion criteria are related to the functional magnetic resonance imaging (fMRI) restrictions: left-handed, claustrophobia, non-removable metal in the

body, sensitivity to loud noises, surgical operations three months prior to the study, and tattoos older than 15 years. Sixty-four participants underwent screening but ten participants were excluded prior to the test days for either: relocating to a new city (n=1), not attending a test day (n=1), not responding to scheduling emails (n=3), vegetarian diet (n=1), presence of non-removable metal in the body (n=1), BMI exceeding MRI capacity (n=1), current taking of antidepressant medication (n=1), or peanut allergy (n=1).

2.2.2 Design

A randomised, crossover, double-blind, placebo-controlled design was used. All participants were required to pass an initial screening session before being invited to attend two test days that were scheduled at least one week apart to allow for drug washout. All participants received 160 IU/1.6 mL of intransal insulin (Actrapid; Novo Nordisk, Bagsværd, Denmark) or 160 IU/1.6 mL of placebo in a counterbalanced order. This dose has shown efficacy in reducing food intake with minimal side effects (Benedict et al., 2008; Hallschmid et al., 2012; Krug et al., 2010; Krug et al., 2018). The placebo consisted of water, 2.7 mg/ml m-cresol/ml, and 16 mg/ml glycerol (prepared by Guy's and St Thomas' NHS Foundation Trust's Pharmacy Manufacturing Unit). The placebo and insulin were identical in appearance and odour.

2.2.3 Questionnaires

2.2.3.1 Screening Day Questionnaires

The Structured Clinical Interview for DSM-5, Clinical Version (SCID-CV)*:* The SCID-CV is a semi structured interview guide for making DSM-5 diagnoses. This was used to screen the presence of psychological disorders (First, 2015).

The following additional questionnaires were used to characterize the sample:

Beck Depression Inventory – II (BDI-II): The BDI is a 21-item scale measuring depression severity (Beck et al., 1996). In a review of 89 studies, the BDI had an average Cronbach's alpha of 0.90 (Wang & Gorenstein, 2013).

The Dutch Eating Behaviour Questionnaire (DEBQ): The DEBQ is a 33-item self-report questionnaire comprised of three subscales: 'Emotional Eating', 'External Eating', and 'Dietary Restraint' (van Strien et al., 1986). These subscales have been shown to have good reliability. Cronbach's alpha in a sample of 653 women and 517 men ranged from 0.80 to 0.95 across scales and groups (van Strien et al., 1986).

The Power of Food Scale (PFS): The PFS is a 15-item scale that measures the appetite for palatable foods at three levels of proximity (Food Available, Food Present, and Food Tasted) to yield a total score of appetite for palatable foods (Lowe et al., 2009). In a sample of 466 participants, Cronbach's alpha was 0.91 suggesting good reliability (Lowe et al., 2009).

2.2.3.2 Test Day Questionnaires

2.2.3.2.1 Appetite and Mood

Visual Analogue Scales (VAS): VAS were used to assess current appetite, mood, and physical state. The participants rated how they felt at that moment in relation to 14 sensations (alertness, drowsiness, happiness, hunger, fullness, desire to eat, thirst, disgust, anxiety, sadness, and withdrawn, lightheaded, nausea, faint) by placing a vertical mark through a 10cm horizontal line with left and right anchors indicating the extremes of each sensation ('completely absent' to 'most I could imagine'). Completed questionnaires were then measured from the left end of each horizontal line to the place where the vertical mark was drawn for each question. VAS were completed seven times throughout the test day (see Figure 2).

Positive and Negative Affect Schedule (PANAS): The PANAS is a 20-item scale that measures positive and negative affect (Watson et al., 1988). The resulting PANAS factors are Positive Affect (PA) and Negative Affect (NA). The PANAS has good reliability with a Cronbach's alpha of 0.89 for the PA scale and 0.85 for the NA scale (Crawford & Henry, 2004). PANAS was administered in conjunction with the VAS.

2.2.4 Food intake

In line with previous findings that intranasal insulin decreases consumption in a postprandial state (Hallschmid et al., 2012), participants were given a fixed lunch prior to dosing to achieve satiation. The lunch consisted of cheese sandwiches that comprised 40% of daily energy requirements and the participants were encouraged to consume all of their lunch if possible. The daily energy requirements ratio was calculated via participants' BMI and weekly physical activity rates. One sandwich consisted of two slices of Warburtons® Wholemeal Medium Sliced Bread, four slices of Pilgrim's Choice® Sliced Mature Cheddar Cheese, and 15g of Lurpak® Spreadable Slightly Salted butter (~588 kcal per 1 sandwich). For the palatable snack offered 140 minutes post-dosing, Maryland® Chocolate Chip Cookies were served *ad libitum* to measure eating in the absence of hunger. Cookies were broken up to disguise the portion size and served in 80g sequential servings to limit tracking of amount consumed (80g ~ 407 kcal). Participants were informed that the purpose of the lunch was to ensure similar insulin levels for all participants and that the cookie snack was a taste test but that they could have as much as they would like.

2.2.5 Universal Eating Monitor (UEM)

Meals were served on the Sussex Ingestion Pattern Monitor (SIPM) (Yeomans, 1996). The SIPM has been used in previous studies investigating mechanisms of weight-management

drugs to assess eating rate and within meal palatability (Thomas et al., 2014; Thomas et al., 2018). This device consisted of a scale (Sartorius Model CP4201, Sartorius Ltd., Epsom, UK; 0.1 g accuracy) placed underneath the surface of a table that was covered by a placemat on which test meals were placed. The balance was connected to a laptop that recorded the weight of the plate every 2 seconds. The SIPM software (version 2.0.8) was configured to alert participants each time 30g of cheese sandwiches was consumed during the lunch meal, or 10g of cookies was consumed during the snack meal, at which point the participants were instructed to complete visual analogue scales (VAS) ratings of hunger, fullness, and pleasantness of the meal. VAS ratings of hunger, fullness, and meal pleasantness were also measured at the start and end of the meal. Participants were aware that their intake was being measured, as previous research suggests that awareness does not affect food intake and reduces the chance of participants accidentally causing a balance recording error by nudging the table (Thomas et al., 2015). Eating rate was calculated as grams eaten/total time spent eating (minutes).

2.2.6 Computerised Tasks

2.2.6.1 Delay Discounting

Participants completed a delay discounting (DD) task configured so that they made decisions about both monetary and food rewards. The DD task measures the extent to which participants are willing to delay the receipt of a reward in exchange for receipt of a higher value reward, and discounted choices are thought to reflect higher impulsivity (Moreira & Barbosa, 2019). Selection of immediate rewards has also been associated with overeating and obesity (Davis et al., 2010; Rasmussen et al., 2010). The monetary discounting task included nine delays ranging from one day to one year. On a white screen, participants saw the question ‘Which would you prefer?’, with two choices: £xx now or £xx after a delay (varying from one day to one

year) and were asked to select the preferred option. A similar paradigm was used for food, with questions consisting of food variables instead of money. Participants were able to select their favourite food from a bank of food images that included sweet and savoury energy dense palatable foods. Questions required a choice between a smaller amount of food now and a larger amount later, for example 'Which would you prefer?' with the options 'one bite of chocolate now or a bar of chocolate in a month?'. Users selected their choice using the left and right arrow keys on a keyboard. Data are expressed as area under the curve where a value closer to 1.00 indicates a preference for delayed rewards.

2.2.6.2 P1vital® Oxford Emotional Test Battery (ETB)

The ETB (see www.p1vital.com) is a computerised battery consisting of validated emotional cognitive tasks (Thomas et al., 2016) that have been used in previous single-dosing drug experiments (Harmer et al., 2003; Harmer et al., 2009). The following three tasks from the ETB were included:

Emotional Categorisation Task (ECAT): Sixty positive and negative adjectives (e.g., cheerful, hostile) were presented for 500ms (Anderson, 1968). Participants responded with a button box to indicate whether they would like or dislike to be described as such. Words were matched for meaningfulness, length, and frequency of occurrence. Accuracy and reaction times (RT) by valence were measured.

Emotional Recall Task (EREC): Participants were given four minutes to recall as many words from the ECAT task as could be remembered within a 4-minute period. Task instructions and the timer were presented on the computer, and the participant wrote recalled words on paper. Accuracy for correctly recalling words presented in the ECAT were measured as items remembered by valence. Recalling words that were not presented

in the ECAT were labelled as commission errors and were recorded as items incorrectly recalled by valence.

Emotional recognition memory task (EMEM): Participants were presented with 60 personality descriptor words derived from the ECAT, along with 60 matching novel distractor words. Participants were instructed to indicate whether the word had been presented during the ECAT using a dedicated button box. Percentage accuracy for correctly recognising words that appeared in the ECAT, and RT for correct responses were recorded by valence. Commission errors for incorrectly classifying a distractor word as having appeared in the ECAT was recorded as percentage incorrectly recognised by valence.

2.2.6.3 Verbal Paired Associates (VPA)

The VPA task is a measure of immediate and delayed recall (Clark et al., 2018). Participants were instructed to memorise 60 associated word pairs that were presented for 2 seconds on a computer screen presented using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Following word pair presentation, participants received a cue word on the computer screen and responded aloud with the target word to be scored for accuracy by the researcher. After the participant responded, the participant pressed the spacebar to reveal the target word on the screen. Participants were tested again an hour later as a measure of delayed recall. Participants were randomly allocated to one of two word lists on test day one or two to avoid practice effects.

2.2.6.4 N-Back

To measure working memory capacity, a visuospatial n-back task (Kirchner, 1958) was presented via E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA) software. Blue circles were presented on a white 3x3 grid for 500ms. Participants were instructed to indicate if the

circle was in the same position (‘1’ on the keyboard) or a different position (‘2’ on the keyboard) as it was two (2-back) and three trials back (3-back). Accuracy and RT by stimuli (2 and 3-back) were recorded.

2.2.6.5 Picture Rating Task Recall

Participants performed a food and non-food picture rating task in a magnetic resonance imaging (MRI) scanner. Participants viewed a range (36 each category) of low- and high-calorie food (equally distributed in sweet and savoury) and non-food items (visually matched) and rated each image for liking. The results of the picture rating task performed in the MRI scanner are not presented in this thesis. At the end of the test day (see procedure), participants were asked to recall as many of the images as possible from the picture rating task and to record these responses on paper. Accuracy by category (food and non-food) was recorded.

2.2.7 Sniffin’ Sticks

Burghart Sniffin’ Sticks – Threshold Test with n-Butanol were used to determine if insulin-induced changes on food intake were due to changes in olfactory sensitivity. Sixteen trios of scents contained one pen with n-butanol (target scent) and two pens with water (blanks) in each trio. The participant was instructed to choose the pen that contained the target scent after a blindfolded presentation of each pen in the trio. If correct, the participant was presented with a lower concentration pen. If incorrect, the participant was presented with a higher concentration pen. The staircase procedure was used to administer and score the participant’s response to determine overall smell threshold.

2.2.8 Assessment of Blood Insulin and Glucose

All blood samples were collected via an intravenous catheter inserted into a vein of the forearm of the participant’s choice. Four millilitres of blood were collected on the first test day

prior to drug administration for the determination of glycated haemoglobin (HbA1C; mmol/mol) reflecting baseline insulin sensitivity. On both test days, four blood samples (4mL) for the determination of insulin and glucose were collected at baseline, five minutes post-drug administration, 135 minutes post-drug administration, and 155 minutes post-drug administration. Blood samples were kept on ice or stored at -80 ˚C until centrifuged at 1500g for 15 minutes. Capillary blood glucose was measured throughout the day as a safety precaution to monitor hypoglycaemia.

2.2.9 Procedure

2.2.9.1 Screening

Participants arrived at the Wellcome Trust Clinical Research Facility (University Hospitals Birmingham NHS Foundation Trust – Queen Elizabeth Hospital) to confirm eligibility via a screening session. Participants completed the following questionnaires: MRI safety form, DEBQ, PFS, and the SCID. Height, weight, and body fat were measured. The participant then had a medical check with a trained medical doctor that consisted of a pregnancy test, blood pressure, electrocardiogram (ECG), and a verbal medical history. If the participant qualified for the experiment, she was invited to attend the test days.

2.2.9.2 Test Day

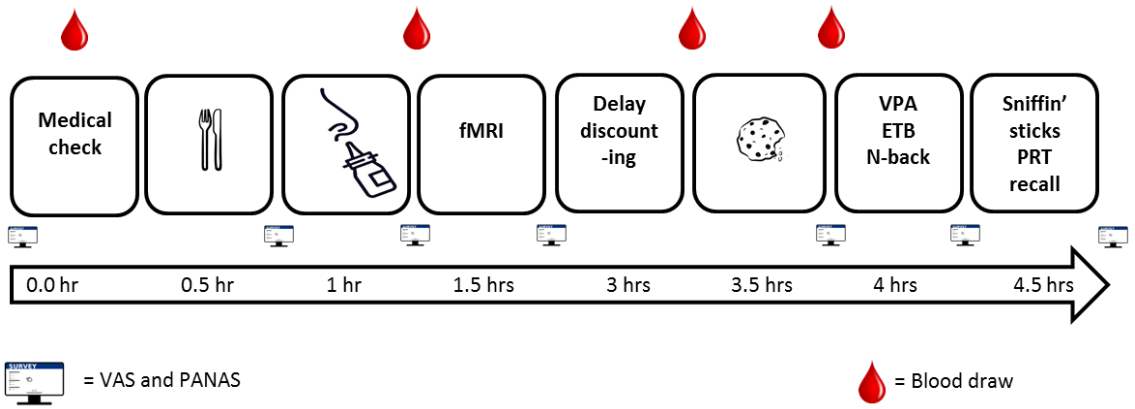
Participants arrived at the Wellcome Trust Clinical Research Facility at 10:30, 11:00, or 12:00. Participants were instructed to eat breakfast as normal prior to the study. Upon arrival, participants completed their first VAS and PANAS and then received a medical check that consisted of documentation of medical changes since the screening appointment, a pregnancy test, and a baseline blood draw for the determination of HbA1C, insulin, and glucose. Following confirmation of negative pregnancy results, participants consumed lunch on the SIPM. After

lunch, participants completed a set of the VAS/PANAS and then self-administered the IN insulin under the guidance of the researcher and a nurse. Following the dosing procedure described by Benedict et al. (2008), participants were instructed to inhale 16 0.1 mL puffs (eight per nostril) of insulin and placebo respectively at 30-second intervals, amounting to a total dose of 1.6 mL insulin or placebo. Five minutes post-drug administration, a blood draw was taken and then another set of the VAS/PANAS was completed.

Participants then underwent an fMRI scan for 1.5 hours. During the scan, participants completed an inhibition task and a picture rating task. Following the fMRI scan, participants completed the DD task. Participants then completed another set of the VAS/PANAS and had another blood draw (135 minutes post-dose). The participants then consumed *ad libitum* chocolate cookies to measure hedonic eating on the SIPM. The final (155 minutes post-dose) blood draw was taken following the snack and the participants completed another set of VAS/PANAS.

The participants then completed the immediate recall phase of the VPA task. Following the VPA, participants completed the ECAT, N-back, EREC, and EMEM followed by a set of VAS/PANAS and the Sniffin' Sticks test. The delayed recall phase of the VPA was then completed. Next, the participants were given five minutes to recall as many of the images that were presented during the food rating task completed in the scanner and to record these responses on paper. These images included food and non-food items. Percentage of recalled items of food and non-food was calculated for accuracy. The participants then completed a final set of VAS/PANAS and a blood glucose safety check before concluding the test day. See Figure 2 for a schematic of the test day procedure.

Figure 2: Test Day Procedure



2.2.10 Data Loss

Several blood samples were missing due to having haemolysed or technical issues with cannulation. Six participants (3 lean participants and 3 participants with obesity) were missing more than 75% of blood draws and so they were removed from the analysis of blood draws. There were technical issues with the Sniffin' Sticks and so the results were not analysed. Smaller degrees of freedoms are reported for the N-back task and ETB-EMEM task due to deletion of outliers and results below chance.

2.2.11 Data and Statistical Analysis

Performance based exclusion criteria were determined prior to data analysis. Cognitive data with RTs below 200ms were removed as outliers. For the ETB tasks, RTs ≥ 6000ms were removed as outliers. For the cognitive tasks, outliers within 3*interquartile range of the lower and upper grand mean values were removed. Because there is a 50% chance for accuracy on the EMEM and N-back tasks, scores at or below 50% on each task were removed for unreliable responding. Comparisons between the effects of insulin and placebo for lean women and women with obesity were computed using a mixed factorial ANOVA where 'BMI status' was the between subjects factor and 'drug condition' was the within-subjects factor, and the factors 'time' or 'stimulus type' as appropriate. Main effects of time, stimuli, or BMI status were not

reported or followed-up. Violations of sphericity were addressed using the Greenhouse-Geisser correction. After confirming that missing data were missing completely at random, regression imputation was used to remedy missing VAS and blood data. VAS were analysed using the factor structure calculated by Thomas et al. (2014) in a previous study: 'Arousal' (alertness, drowsiness, and happiness), 'Appetite' (hunger, fullness, and desire to eat), 'Negative Effects' (disgust, anxiety, sadness, and withdrawn), 'Physical Effects' (lightheaded, nausea, and faint) (Thomas et al., 2014). Though thirst was reported as a negative effect by Thomas et al. (2014), thirst was treated as a separate factor in this study, as thirst does not always theoretically indicate a negative effect. Post-dose VAS and PANAS results were converted to area under the curve (AUC) values using the trapezoid method. To compare the effects between lean women and women with obesity, planned follow-up paired sample *t* tests were computed when an overall condition effect was detected, and multiple comparisons were Holm-Bonferroni corrected. A *p*-value less than 0.05 was considered statistically significant. A mediation analysis was originally proposed to statistically determine the mechanism(s) underlying the effect of IN insulin on food intake, but the resultant smaller sample size precluded this possibility. Instead, exploratory correlation analyses were performed between significant outcomes and cookie intake to determine IN insulin mechanism of action on appetite. Where exploratory correlation analyses are performed, the variables are always placebo minus IN insulin to determine insulin-specific effects.

2.3 Results

2.3.1 Demographics

Participant demographics are presented in Table 1. As expected, BMI was statistically different between the two groups ($p < 0.05$). Women with obesity self-reported higher ratings on the Restraint and Emotional Eating Factors of the DEBQ than lean women ($p < 0.05$). All other measures did not differ according to BMI status ($p > 0.05$).

Table 1: Participant Demographics

Factor	Lean (n = 35)	Obese (n =17)	*p*-value
Age	23.66 (4.80)	26.00 (7.91)	0.27
BMI	22.21 (1.91)	34.04 (3.38)	< 0.01*
HbA1c	33.03 (3.16)	34.21 (3.98)	0.34
BDI (Max = 63)	2.63 (3.62)	5.18 (5.43)	0.09
PFS (Max = 75)	36.51 (12.75)	40.35 (11.82)	0.29
DEBQ (Max = 5)			
Restraint	2.31 (.49)	2.82 (.38)	< 0.01*
External	3.04 (.50)	3.16 (.33)	0.32
Emotional	2.06 (.66)	2.65 (.67)	= 0.01*

Table 1. Data are expressed as mean and ± standard deviation. Questionnaire measures are included with the maximum possible score. BMI: Body Mass Index. HbA1c: glycated haemoglobin. BDI: Beck Depression Inventory – II. PFS: Power of Food Scale Total (aggregate of Food Available, Food Present, and Food Tasted factors). DEBQ: Dutch Eating Behaviour Questionnaire. Age is expressed in years. BMI expressed as kg/m^2. HbA1c expressed as mmol/mol. Asterisks denote significance at $p < 0.05$ level.

2.3.2 Cookie Intake

There was a significant main effect of drug condition on cookie intake ($F(1, 50) = 4.59$, $p = 0.04$, $\eta_p^2 = .08$). The interaction between drug condition and BMI was not statistically significant ($F(1, 50) = 2.36$, $p = 0.13$, $\eta_p^2 = 0.05$). Planned follow-up tests revealed no effect for lean women ($t(34) = -0.55$, $p = 0.59$, d 0 .07) and a near-significant difference for women with obesity ($t(16) = -2.12$, $p = 0.05$, $d = 0.46$) (Figure 3).

Figure 3: Cookie Snack Intake

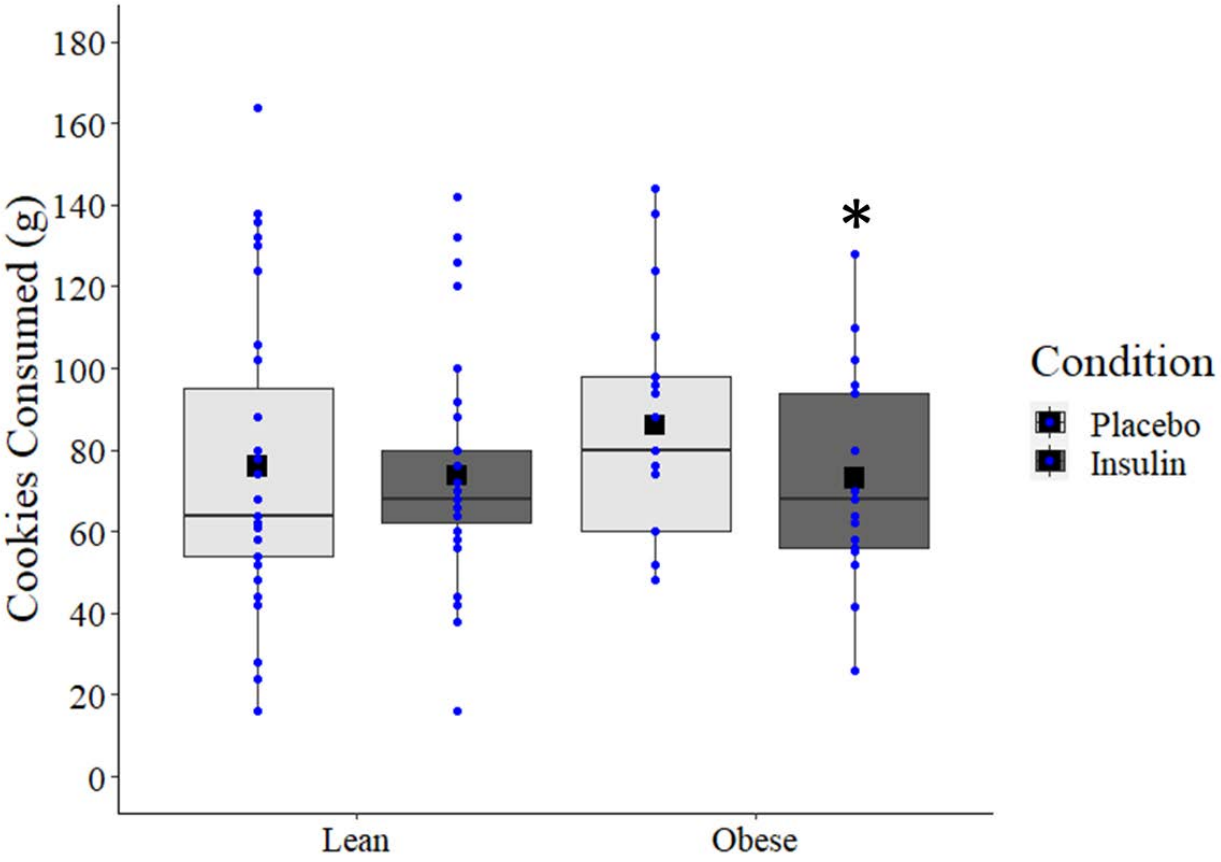


*Figure 3.*Cookie intake data presented with squares denoting means and dots representing individual data points. Light grey fill indicates placebo condition while dark grey fill indicates insulin condition. Asterisk denotes drug condition significance at $p < 0.05$ level.

There was no main effect of intranasal insulin on eating rate ($F(1, 47) = 0.02$, $p = 0.89$, $\eta_p^2 < 0.01$, nor was the interaction between condition and BMI status significant ($F(1, 47) = 0.00$, $p = 0.98$, $\eta_p^2 < 0.01$) (see Table 2). Intranasal insulin had no effect on ratings of cookie pleasantness at the start of the meal or at the end of the meal ($F(1, 47) = 0.95$, $p = 0.34$, $\eta_p^2 = 0.02$). The interaction between condition, BMI status, and rating timing was also not statistically significant ($F(1, 47) = 0.01$, $p = 0.91$, $\eta_p^2 < 0.01$). Planned comparisons revealed a significant difference between drug condition on initial liking for participants with obesity ($t(15) = -2.87$, $p = 0.01$, $d = 0.42$) whereby insulin decreased cookie liking at the start of the meal (see Table 2).

Table 2: Cookie Eating Rate and Palatability Results

	Lean				Obese			
	Placebo		Insulin		Placebo		Insulin	
Measure	*M*	± *SD*	*M*	± *SD*	*M*	± *SD*	*M*	± *SD*
Eating Rate	15.12	6.18	14.95	6.20	19.02	7.71	18.90	9.93
Palatability								
Meal Start	74.55	16.21	73.85	18.69	79.75	13.57	73.06*	17.72
Meal End	63.36	27.25	66.09	23.65	71.38	19.18	68.69	24.12

Table 2. Mean and ± standard deviations presented. Eating rate is represented as grams/minutes. Palatability ratings given at the start of the meal and end of the meal. The rated palatability for cookies at the start of the meal was significantly lower in the insulin condition for the group with obesity. Asterisks denote follow-up significance at $p < 0.05$.

2.3.3 Appetite and Mood

2.3.3.1 VAS Ratings

Analysis of pre-dose AUC VAS ratings revealed no main effect of condition on VAS ratings for arousal ($F(1, 50) = 1.63$, $p = 0.29$, $\eta_p^2 = 0.02$; $M_{Placebo} = 206.37$, $SD = 33.16$; $M_{Insulin} = 200.06$, $SD = 33.09$), appetite ($F(1, 50) = 0.05$, $p = 0.83$, $\eta_p^2 = < 0.01$; $M_{Placebo} = 90.80$, $SD = 36.35$; $M_{Insulin} = 92.02.12$, $SD = 42.30$), negative effects ($F(1, 50) = 0.32$, $p = 0.58$, $\eta_p^2 = 0.01$; $M_{Placebo} = 17.97$, $SD = 19.37$; $M_{Insulin} = 18.30$, $SD = 22.34$), physical effects ($F(1, 50) = 1.44$, $p = 0.24$, $\eta_p^2 = 0.03$; $M_{Placebo} = 16.67$, $SD = 18.18$; $M_{Insulin} = 19.26$, $SD = 25.22$), or thirst ($F(1, 50) = 0.32$, $p = 0.86$, $\eta_p^2 < 0.01$; $M_{Placebo} = 106.42$, $SD = 43.02$; $M_{Insulin} = 106.06$, $SD = 51.77$). The interaction between condition and BMI status for each factor was not statistically significant ($p > 0.05$).

Analysis of post-dose AUC VAS rating revealed a significant main effect of insulin on appetite ratings ($F(1, 50) = 5.66$, $p = 0.02$, $\eta_p^2 = 0.10$). Planned follow-up tests revealed a near-

significant effect of insulin on appetite ratings for women with obesity ($t(16) = -2.11$, $p = 0.051$, $d = 0.60$), but no effect on lean women ($t(34) = -.74$, $p = 0.47$, $d = 0.11$) (see Figure 4). The main effect of insulin on arousal ($F(1, 50) = 2.16$, $p = 0.15$, $\eta_p^2 = 0.04$), negative effects ($F(1, 50) = 1.39$, $p = 0.24$, $\eta_p^2 = 0.03$), physical effects ($F(1, 50) = 0.06$, $p = 0.81$, $\eta_p^2 < 0.01$), and thirst ($F(1, 50) = 0.01$, $p = 0.98$, $\eta_p^2 < 0.01$) ratings, and all interactions between condition and BMI for each factor, was not statistically significant ($p > 0.05$). Post-hoc analyses of post-dose time course data for appetite VAS ratings revealed a significant interaction between condition and time ($F(4, 171) = 3.33$, $p = 0.02$, $\eta_p^2 = 0.06$), in which insulin decreased appetite at 5 minutes post-dose ($t(51) = 2.40$, $p = 0.02$, $d = 0.37$), but this did not survive correction (see Figure 4).

Figure 4: VAS Ratings

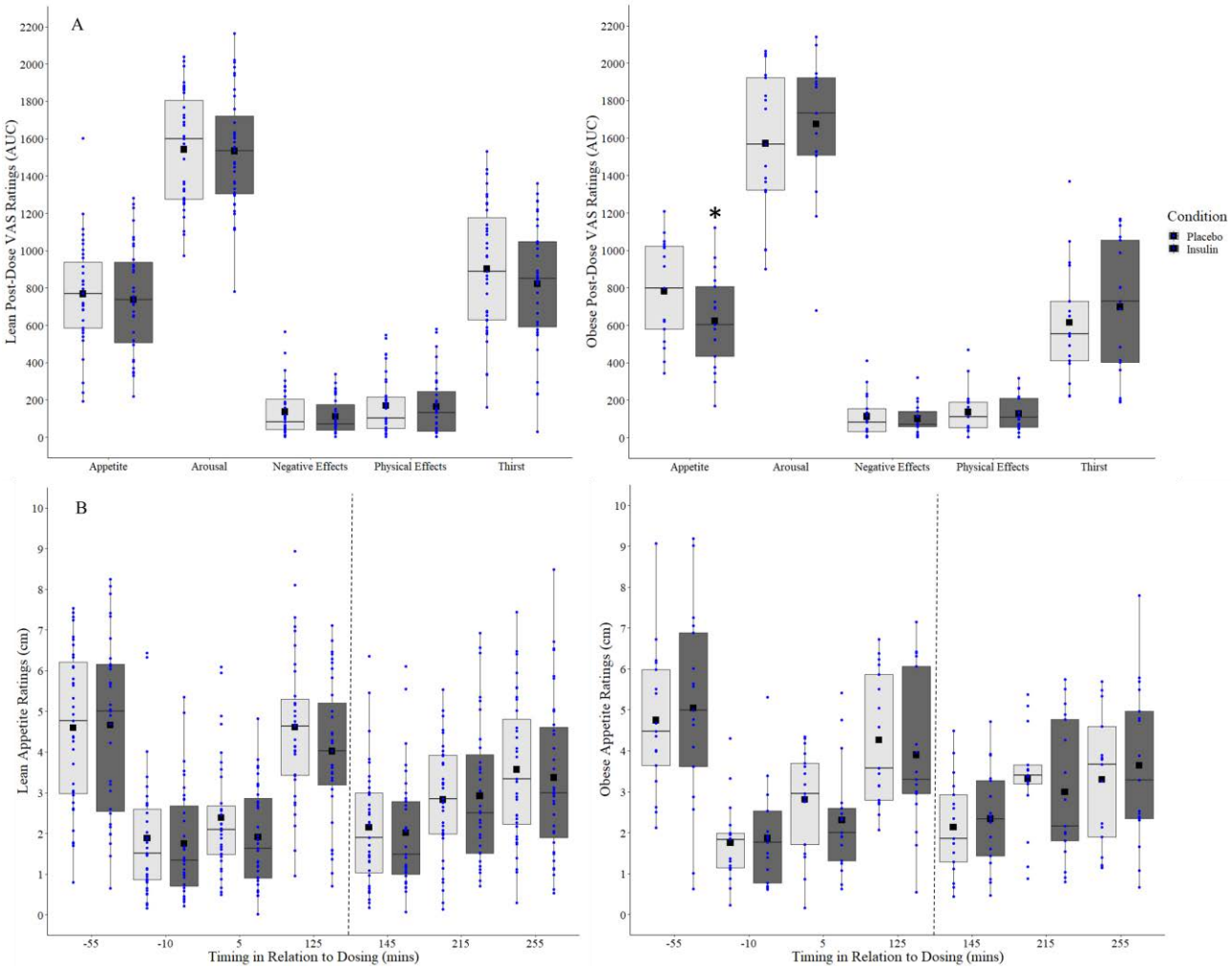


Figure 4. Panel A depicts post-dose area under the curve (AUC) visual analogue scale (VAS) ratings for lean women (left) and women with obesity (right). Panel B depicts appetite VAS ratings throughout the test day. Squares denote means and dots represent individual data points. Light grey fill indicates placebo condition while dark grey fill indicates insulin condition. Dashed vertical lines symbolise timing of the cookie snack. Asterisk denotes follow-up tests significance at $p < 0.05$ level.

2.3.3.2 PANAS Ratings

Analysis of pre-dose AUC PANAS ratings showed no main effect of condition on positive or negative affect ratings ($F(1, 50) = 1.26$, $p = 0.27$, $\eta_p^2 = 0.03$; $M_{Placebo} = 587.46$, $SD = 111.58$; $M_{Insulin} = 594.54$, $SD = 132.16$), and the interactions between condition, BMI, and valence type were also not statistically significant ($p > 0.05$). Analysis of post-dose AUC PANAS ratings revealed a near-significant main effect of condition ($F(1,47) = 3.78$, $p = 0.06$, η_p^2

=0.07), a significant interaction between condition and BMI ($F(1,47) = 5.47$, $p = 0.02$, η_p^2 =0.10), and a near-significant interaction of condition and valence (PA and NA) ($F(1, 47) = 3.71$, $p = 0.06$, $\eta_p^2 = 0.07$). The interaction between condition, BMI status, and valence was not statistically significant ($F(1, 47) = 3.23$, $p = 0.08$, $\eta_p^2 = 0.06$). Follow-up paired samples *t*-tests showed a significant effect for positive affect (PA) for participants with obesity only ($t(16)=2.86$, $p=0.01$, $d = 0.42$). Intranasal insulin increased ratings of PA for participants with obesity (see Figure 5). Post-hoc analyses of post-dose time course data for PA ratings revealed a significant main effect of drug condition ($F(1, 50) = 4.62$, $p = 0.04$, $\eta_p^2 = 0.09$) and an interaction between drug condition and BMI status ($F(1, 50) = 5.04$, $p = 0.03$, $\eta_p^2 = 0.09$), in which women with obesity gave higher ratings of post-dose PA ($t(16) = 2.95$, $p = 0.01$, $d = 0.44$) than lean women ($p > 0.05$). Exploratory analyses of post-dose time points for women with obesity revealed a significant difference ($p < 0.05$) for times 125, 145, 215, and 255 minutes post-dose, but only the 215 minutes post-dose time point survived correction (see Figure 5).

Figure 5: PANAS Ratings

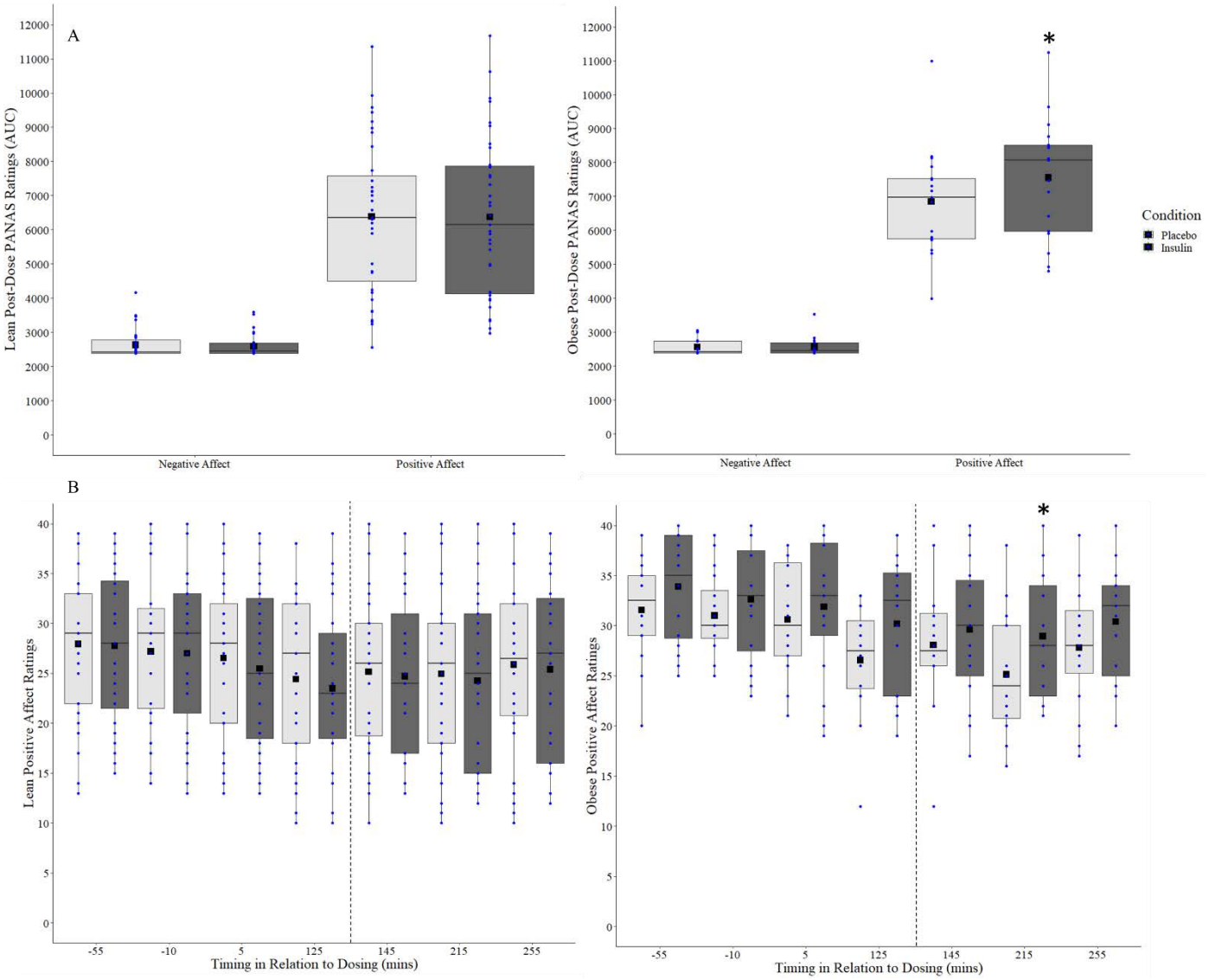


Figure 5. Panel A depicts post-dose area under the curve (AUC) positive and negative affect schedule (PANAS) ratings for lean women (left) and women with obesity (right). Panel B depicts positive affect ratings throughout the test day. Squares denote means. Dashed vertical lines symbolise timing of the cookie snack. Dots represent individual data points. Light grey fill indicates placebo condition while dark grey fill indicates insulin condition. Asterisk denotes follow-up tests significance at $p < 0.05$ level.

2.3.4 Cognitive Tasks

Descriptive statistics for cognitive tasks are presented in Table 3. Results of interactions between drug condition, BMI status, and stimuli/valence are reported only when statistically

significant ($p < 0.05$). If the interaction is not reported, the results were not statistically significant ($p > 0.05$).

VPA: The main effect of drug condition on VPA immediate and delayed recall accuracy was not statistically significant ($F(1, 50) = 0.01$, $p = 0.93$, $\eta_p^2 < 0.01$).

ETB – ECAT: There was a significant main effect of drug condition on ECAT positive and negative valence accuracy ($F(1, 49) = 46.76$, $p = 0.01$, $\eta_p^2 = 0.12$) whereby insulin improved accuracy for selection of positive adjectives for self-reference and rejecting negative adjectives for self-reference. Follow-up tests revealed no significant differences between BMI status and valence type (positive and negative) ($p > 0.05$). The main effect of drug condition on ECAT positive and negative RT ($F(1, 48) = 1.64$, $p = 0.21$, $\eta_p^2 = 0.03$) was not statistically significant.

ETB – EREC: The main effect ($F(1, 50) = 0.67$, $p = 0.42$, $\eta_p^2 = 0.01$) of drug condition on accuracy for positive and negative adjectives recalled from the ECAT task was not statistically significant. The main effect ($F(1, 50) = 0.15$, $p = 0.70$, $\eta_p^2 = 0.03$) of insulin on positive and negative valence commission errors was not statistically significant.

ETB – EMEM: The main effect of drug condition on EMEM positive and negative valence accuracy was not statistically significant ($F(1, 34) = 2.13$, $p = 0.15$, $\eta_p^2 = 0.06$). The interaction between drug condition and BMI status was significant ($F(1, 34) = 5.65$, $p = 0.02$, $\eta_p^2 = 0.14$) but follow-up tests revealed no statistically significant effects on EMEM accuracy for either the lean or obese groups ($p > 0.05$). The main effect of insulin on positive and negative commission errors was also not statistically significant ($F(1, 50) = 1.20$, $p = 0.28$, $\eta_p^2 = 0.02$). The main effect of insulin EMEM positive and negative RT ($F(1, 49) = 0.72$, $p = 0.40$, $\eta_p^2 = 0.02$) was not statistically significant.

N-back: The main effect of drug condition on N-back 2 and 3-back accuracy ($F(1, 27) = 1.08$, $p = 0.31$, $\eta_p^2 < 0.04$) was not statistically significant. The main effect of drug condition on 2-back and 3-back RT ($F(1, 45) = 1.89$, $p = 0.18$, $\eta_p^2 < 0.04$) was not statistically significant, but the interaction between condition and BMI status was significant ($F(1, 45) = 12.36$, $p < 0.01$, $\eta_p^2 = 0.22$). Follow-up tests revealed a significant effect for participants with obesity only ($t(15)=3.33$, $p = 0.01$, $d = 0.56$), in which women with obesity were slower in the insulin condition than the placebo condition.

PRT Recall: The main effect of insulin on PRT recall for non-food and food images ($F(1, 49) = 0.01$, $p = 0.94$, $\eta_p^2 < 0.01$) was not statistically significant.

DD: The main effect of drug condition on the money and food DD task was not statistically significant ($F(1, 48) = 0.47$, $p = 0.50$, $\eta_p^2 = 0.01$).

Table 3: Cognitive Task Results

	Lean				Obese			
	Placebo		Insulin		Placebo		Insulin	
Task	Accuracy	RT	Accuracy	RT	Accuracy	RT	Accuracy	RT
VPA (% correct)								
Immediate	25.57(9.47)	--	25.97(11.25)	--	27.65(9.31)	--	27.12(10.19)	--
Delayed	35.40(10.93)	--	37.11(11.34)	--	40.59(8.85)	--	39.47(9.74)	--
ECAT (% correct)								
Positive	90.00(9.03)	772.62(166.34)	92.06(6.86)	783.56(179.51)	91.17(5.52)	721.19(123.34)	92.55(6.30)	769.00(168.42)
Negative	91.37(6.88)	803.44(185.96)	92.26(7.47)	833.47(162.21)	88.81(7.63)	778.38(132.89)	92.16(5.40)	808.25(150.95)
EMEM (% correct)								
Positive	85.21(8.46)	1046.44(234.86)	87.39(8.53)	1111.38(274.66)	85.36(9.49)	1128.00(157.93)	81.54(9.39)	1135.53(308.08)
Negative	75.80(10.27)	1187.44(269.06)	75.95(10.54)	1239.77(325.47)	76.93(13.93)	1250.76(233.74)	71.03(8.21)	1248.18(310.97)
EREC (items)								
Positive	5.20(2.39)	--	5.03(2.67)	--	5.30(3.12)	--	4.71(2.64)	--
Negative	5.17(2.8)	--	5.37(2.71)	--	5.47(2.62)	--	4.76(1.68)	--
N-Back (% correct)								
2-back	77.42(11.82)	888.16(215.99)	82.16(12.43)	827.32(212.65)	83.70(11.64)	802.41(227.45)	83.50(13.35)	916.22(182.88)
3-back	74.84(11.41)	860.94(247.90)	76.32(12.61)	828.71(246.12)	79.60(16.93)	759.94(190.73)	83.10(13.27)	858.99(210.59)
PRT (% total possible)								
Food	17.39(6.00)	--	17.79(6.94)	--	19.04(6.15)	--	17.87(5.63)	--
Object	10.37(3.57)	--	11.07(4.04)	--	9.93(4.93)	--	10.22(3.65)	--
ETB Commission Errors								
EREC (items)								
Positive	3.46(2.05)	--	4.14(3.22)	--	4.18(2.19)	--	4.24(2.49)	--
Negative	1.89(1.79)	--	1.43(1.61)	--	1.71(1.53)	--	1.76(1.56)	--
EMEM (% incorrect)								
Positive	34.29(18.99)	--	33.72(18.93)	--	42.34(22.27)	--	40.40(21.29)	--
Negative	20.47(12.97)	--	20.19(13.68)	--	23.73(9.86)	--	18.24(11.45)	--
Delay Discounting Results (AUC)								
Money	77.95(16.89)	--	77.70(18.26)	--	74.32(19.99)	--	73.79(15.11)	--
Food	58.46(34.85)	--	57.94(29.67)	--	55.37(31.85)	--	63.39(30.56)	--

Table 3. Data presented as mean ± standard deviation. RT: reaction time, ETB: Emotional Test Battery, ECAT: Emotional Categorisation Task – positive and negative valence, EREC: Emotional Recall Task – positive and negative valence, ECAT: Emotional Recognition Memory Task – positive and negative valence, PRT: Picture Rating Task recall, DD: Delay Discounting. EREC data expressed as items remembered or falsely remembered. DD data expressed as area under the curve. PRT results expressed as percentage correct out of total possible. All other results expressed as percentage correct or incorrect. The main effect of drug condition on ECAT accuracy was statistically significant ($p < 0.05$).

2.3.5 Blood Insulin and Glucose

Analysis of pre-dose blood glucose did not reveal a significant main effect of drug condition ($F(1, 49) = 0.32$, $p = 0.58$, $\eta_p^2 = 0.01$; $M_{Placebo} = 4.77$, $SD = 0.64$; $M_{Insulin} = 4.61$, $SD = 0.56$), nor any interaction between drug condition and BMI status ($p > 0.05$). Analysis of blood glucose across all post-dose time points did not reveal a significant main effect of drug condition ($F(1, 48) = 0.10$, $p = 0.75$, $\eta_p^2 <0 .01$), nor any significant interactions between condition and BMI ($F(1, 50) = 0.06$, $p = 0.81$, $\eta_p^2 < 0.01$); condition and time ($F(3, 50) = 1.67$, $p = 0.18$, $\eta_p^2 = 0.03$); and condition, BMI, and time ($F(3, 50) = 0.29$, $p = 0.80$, $\eta_p^2 = 0.01$) (see Table 4).

Table 4: Blood Glucose Concentration

	Lean				Obese			
	Placebo		Insulin		Placebo		Insulin	
Draw	*M*	± *SD*	*M*	± *SD*	*M*	± *SD*	*M*	± *SD*
-30 minutes	4.72	0.61	4.54	0.50	4.69	0.41	4.79	0.67
5 minutes	4.65	0.71	4.59	0.80	4.74	0.53	4.77	0.77
135 minutes	5.01	0.65	4.84	0.62	4.91	0.73	4.74	0.51
155 minutes	4.74	1.03	5.02	0.74	5.07	0.64	5.09	0.55
300 minutes	5.32	0.65	5.47	0.71	5.09	0.72	5.35	0.62

Table 4: Mean and ± standard deviation presented for glucose concentration values. The main effect of drug condition, and the interaction between drug condition, BMI status, and blood draw were not statistically significant.

Analysis of pre-dose blood draws for insulin concentration revealed a significant difference ($F(1, 44) = 7.03$, $p = 0.01$, $\eta_p^2 = 0.14$) between lean women and women with obesity whereby women with obesity had higher insulin values ($M = 28.01$, $SD = 24.85$) than lean women ($M = 14.35$, $SD = 10.39$). To account for baseline differences observed in the pre-dose analysis, insulin concentration change from baseline was computed. The difference between lean

women and women with obesity was near-significant ($F(1, 44) = 3.76$, $p = 0.06$, $\eta_p^2 = 0.08$) with women with obesity having higher insulin concentrations than lean women throughout the test day. The interaction between drug condition and time of blood draw was near-significant ($F(1, 44) = 3.48$, $p = 0.055$, $\eta_p^2 = 0.07$). Follow-up tests revealed a significant difference between insulin and placebo conditions for the second draw 5 minutes post-dose only ($t(45) = 2.71$, $p = 0.01$, $d = 0.32$), in which insulin concentration at 5 minutes post-dose was higher in the insulin condition for participants with and without obesity than in the placebo condition (see Table 5).

Table 5: Blood Insulin Concentration Results

	Lean				Obese			
	Placebo		Insulin		Placebo		Insulin	
Draw	*M*	± *SD*	*M*	± *SD*	*M*	± *SD*	*M*	± *SD*
-30 minutes	15.75	13.08	12.95	10.42	20.75	12.26	35.28	40.78
Change	--	--	--	--	--	--	--	--
5 minutes	30.60	18.89	37.99	17.09	50.75	29.49	71.71	58.86
Change	14.85	20.13	25.02	16.58	30.01	27.15	36.44*	54.61
135 minutes	24.60	13.71	22.82	12.32	39.13	25.02	48.67	40.08
Change	8.85	17.40	9.88	12.99	18.38	25.92	13.39	24.70
155 minutes	34.92	16.29	33.33	23.18	63.11	55.03	64.54	34.47
Change	19.17	17.99	20.38	25.15	42.37	51.38	29.26	37.18

Table 5. Blood insulin concentration (mIU/L) data presented as mean ± standard deviation. Draw minutes in relation to dosing. Change results derived from draws 2 (5 minutes), 3 (135 minutes), and 4 (155 minutes) subtracted from draw 1 (baseline/-30 minutes). The difference between pre-dose insulin concentration values were statistically different between lean women and women with obesity. The change from baseline value at 5 minutes post-dose was statistically different between the insulin and placebo condition. Asterisks denote follow-up significance at $p < 0.05$ level.

2.3.6 Exploratory Correlation Analyses

An exploratory correlation analysis between cookie intake and cookie liking for participants with obesity did not reveal a significant relationship ($r(16) = 0.16$, $p = 0.55$), nor was the relationship between cookie intake and positive affect ratings for women with obesity significant ($r(17) = -0.08$, $p = 0.77$).

2.4 Discussion

In this study, an acute dose of 160 IU IN insulin reduced cookie intake and self-reported appetite and improved mood for women with obesity but not for lean women. IN insulin did not improve cognitive performance. These results indicate women with obesity may be more sensitive than lean women to the effects of insulin on appetite and mood.

In line with previous findings (Hallschmid et al., 2012), intranasal insulin administration reduced snack intake in the postprandial state i.e. after a fixed lunch that met 40% of daily energy requirements. The observed reduction in intake is not likely to be due to insulin effects in the periphery. Although there was an increase in blood insulin levels 5 minutes after administration, suggesting some spillover of IN insulin into circulation, blood glucose levels were unchanged throughout the test day and blood insulin levels were not elevated before the cookie snack. Hence, the appetite effects observed here likely reflect actions of central insulin. Contrary to the results of Hallschmid et al. (2012), the IN insulin-induced reduction in cookie intake was not observed in lean women and only in women with obesity. The discrepancy in results is likely due to the variety of cookie types presented in the Hallschmid et al. (2012) study that stimulated appetite and allowed for observable differences between the placebo and insulin conditions.

IN insulin decreased self-reported feelings of appetite (composite factor of hunger, fullness, and desire to eat) and this effect was more pronounced for women with obesity. IN

insulin decreased liking for cookies at the start of the meal but did not affect eating rate. This is in line with previous reports that IN insulin decreases rated palatability of food (Hallschmid et al., 2012; Tiedemann et al., 2017; Kullmann et al., 2015). Slower eating rate is associated with self-reported satiety (Argyrakopoulou et al., 2020; Kokkinos et al., 2010) and so this pattern of results suggests that IN insulin may reduce snack intake via a reduction in food reward rather than an enhancement of satiety. Given that the participants were in a post-prandial state when insulin was administered and the cookie snack was offered, it may be that IN insulin enhanced the effects of postprandial signals on food reward. A potential underlying mechanism is an effect of insulin to suppress mesolimbic dopaminergic signaling via insulin receptors on dopaminergic neurones of the ventral tegmental area (Kullmann et al., 2020), which translated into a reduction in food reward.

No effects of IN insulin were observed on the cognitive tasks. The null effects of IN insulin observed on the delay discounting task are similar to those found on the Stroop task after either acute or chronic insulin (Benedict et al., 2004; Hallschmid et al., 2008), which suggests that insulin actions on inhibition are not a primary mechanism in reducing appetite. The lack of augmentation on working memory or memory recall by IN insulin observed in this study contrasts those previously reported by Benedict et al. (2004, 2008), Hallschmid et al. (2008), and Ritz et al. (2018). These differences in results are likely attributed to the heterogeneity of tasks used to measure working memory and memory recall (Benedict et al., 2004, 2008; Hallschmid et al., 2008; Krug et al., 2010). There was also no statistical effect of IN insulin on recall of food and non-food objects on the picture rating task. However, task performance was relatively poor, and it is possible that any small improvements under the IN insulin condition could not be statistically detected. Improved accuracy for selecting positive adjectives and for rejecting

negative adjectives to describe oneself was observed following IN insulin in participants with and without obesity. Given that IN insulin improved accuracy for both valence types, it is more likely that the changes reflect cognitive improvements in reducing ambiguity in word classification rather than changes in emotional biases. The specificity of cognitive improvement observed here may be due to the emotional salience of the target words presented in the ETB ECAT task. Taken together, these results suggest that cognition does not mediate the effects of IN insulin on appetite.

Intranasal insulin improved positive affect for women with obesity only. Our findings corroborate previous reports of mood improvements after acute and chronic IN insulin (Benedict et al., 2004; Cha et al., 2017; Ferreira de Sá et al., 2020; Kern et al., 2001). Improvements of mood have been previously observed in men with obesity who were administered IN insulin and reported decreased introversion and anxiousness (Hallschmid et al., 2008), but this is the first report for women with obesity. These data suggest that IN insulin may have therapeutic potential for treating mood disorders particularly in patients with altered metabolic function. The enhanced mood effects are especially significant given that some extant weight management drugs are associated with psychiatric incidences (Singh & Singh, 2020). Hence, IN insulin shows promise as a new drug candidate with a favourable safety profile and potentially a mood enhancing action for treating individuals with obesity and co-morbid depression. Future studies should investigate the effects of IN insulin on women with obesity comorbid with subclinical and/or clinical depression to determine if insulin-induced improvements in mood are augmented in this group.

We had tentatively hypothesised that participants with obesity might be less responsive to the effects of IN insulin. This prediction was based on previous reports of absent or reduced

effects of IN insulin on behavioural and neuroimaging measures when comparing lean individuals with individuals with obesity (e.g. Guthoff et al., 2011; Kullmann et al., 2015, 2017; Edwin Thanarajah et al., 2019; Tiedemann et al., 2017), potentially due to insulin resistance. However, a recent study found that IN insulin reduced regional cerebral blood flow in parts of the hippocampus, insula, putamen, parahippocampal gyrus, and fusiform gyrus in an overweight but not lean group (Wingrove et al., 2021) suggesting that, at least according to some measures, participants with overweight may be more sensitive than lean participants to the effects of IN insulin. Other recent evidence suggests that individuals with insulin resistance are responsive to exogenous insulin, but effects may appear later than in lean individuals (Edwin Thanarajah et al. 2019). Individuals with overweight/obesity typically present with peripheral hyperinsulinaemia (Reaven, 1988) and hyperglycaemia (Kahn et al., 2006). In our sample, participants with obesity did not differ statistically on blood glucose concentrations from lean participants but did have elevated levels of insulin. One explanation for the present results is that an initial response to peripheral hyperinsulinaemia is that transport of insulin into the brain is reduced, resulting in reduced levels of brain insulin that can be supplemented by IN insulin treatment.

A strength of this study was the direct comparison of the effects of IN insulin in both lean women and women with obesity. Additionally, the incorporation of multiple measures, including microstructural measures of appetite, provided insight into potential mechanisms of action. However, the current study has limitations. It is unclear whether the absence of any effects of IN insulin on cognition related to the time course of the study. However, the finding that IN insulin improved positive mood up until the end of the test day suggests that long lasting effects can be observed, but these effects may vary depending on the outcome measured. Another limitation is the uneven and smaller sample size for participants with obesity, although the large effect sizes

for the near significant effects suggest that with a larger sample size significant effects would be detected. Indeed, the smaller sample size precluded a mediation analysis to determine IN insulin mechanism of action. Instead, exploratory correlation analyses were performed. Neither the initial rated palatability of the cookie snack nor the self-reported positive affect ratings significantly correlated with cookie intake. The limited statistical power indicates that these results need to be replicated with a larger sample size.

In summary, for the first time, we demonstrated that women with obesity benefit from IN insulin through appetite reduction on food intake measures and self-reported ratings. Previously, behavioural measures of food intake have only been measured in lean women or men with obesity, and these accounts suggested women and individuals with obesity might be resistant to the anorexigenic effects of IN insulin. In contrast, the evidence presented here, suggests that IN insulin could be an effective therapeutic for reducing appetite, food intake and body weight in women with obesity. Further, unlike other weight management drugs that depress mood, we show that IN insulin heightens positive affect. Given the observed reduction in hedonic snack intake, and initial rated palatability of the snack, combined with the null effect of IN insulin on eating rate, it is likely that IN insulin reduces appetite through decreasing motivation to eat when satiated. However, the results found in this study need to be replicated with a larger sample size.

Chapter 3: Lisdexamfetamine and Binge-Eating Disorder: A systematic review and meta-analysis of the preclinical and clinical data with a focus on mechanism of drug action in treating the disorder.

3.1 Introduction

Binge-eating disorder (BED) is defined by recurrent episodes of binge eating in the absence of compensatory behaviours (e.g. vomiting, laxative use, excessive dieting) (American Psychiatric Association, 2013). An episode of binge eating is characterised by eating in a discrete period of time an amount that is definitely larger than that which most people would eat in a similar period of time under similar circumstances (American Psychiatric Association, 2013). Binge-eating episodes are also usually accompanied by a sense of lack of control during the episode and an individual may experience rapid eating, uncomfortable fullness, eating in the absence of hunger, embarrassment, disgust, depression, and guilt (American Psychiatric Association, 2013). BED is the most common eating disorder and the estimated lifetime global prevalence is between 0.9-2.2.% (Erskine & Whiteford, 2018; Qian et al., 2013). BED is often co-morbid with obesity and obesity-related physical symptoms (Citrome, 2019; Kessler et al., 2013; Papelbaum et al., 2019). In addition to impairing physical health, BED is associated with mood and anxiety disorders, bipolar disorder, self-harm, and addiction disorders (Grilo et al., 2013; Peters et al., 2019; Schulz & Laessle, 2010; Swanson et al., 2011).

Current treatments for BED include cognitive behavioural therapy (CBT) and behavioural weight loss therapy (BWLT) (Wilson et al., 2010). CBT is effective in reducing binge-eating frequency but not in reducing weight, while BWLT is effective in reducing weight but not in decreasing binge-eating frequency (McElroy et al., 2015a; Palavras et al., 2017; Peat et al., 2017). Pharmacotherapy options for BED include antidepressants (e.g., sertraline and

bupropion) and the anticonvulsant topiramate. These treatments show modest short term efficacy in reducing binge eating, but antidepressants do not cause weight loss and topiramate use is limited by adverse effects and thus discontinuation rates are high (McElroy et al., 2015a).

In 2015, the United States Food and Drug Administration (FDA) approved lisdexamfetamine dimesylate (LDX) (Vyvanse®, Takeda) as the first and, to date, only drug for the treatment of BED (FDA, 2015). LDX is a pro-drug of *d*-amphetamine that was first approved by the FDA in 2007 for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). Taken orally, LDX is hydrolysed to the active metabolite, *d*-amphetamine (Adler et al., 2017), which crosses the blood-brain barrier to increase central noradrenergic, dopaminergic, and serotonergic neurotransmission (Ermer et al., 2016; Hutson et al., 2014). Approval for the use of LDX in the treatment of BED was based on a Shire (now Takeda) clinical development program that included an 11-week phase II randomised controlled clinical trial assessing doses of 30, 50, and 70mg/day LDX (McElroy et al., 2015b) and two 12-week phase III randomised controlled clinical trials investigating 50 and 70mg/day doses (McElroy et al., 2016a) for the treatment of BED. Both these studies demonstrated a reduction in binge-eating episodes and BED-related symptoms after 50 and 70mg LDX. Subsequent studies have confirmed the efficacy of LDX in the treatment of BED (Citrome, 2015; Fleck et al., 2019; Gasior et al., 2017) . Although LDX is approved to treat BED, little is known about the specific neural, pharmacological, and behavioural processes that are responsible for its efficacy in treating BED symptoms. An improved understanding of the pharmacological and neuropsychological processes that mediate the therapeutic effects of LDX could aid in the development of novel medications to treat BED which have improved efficacy and fewer side effects.

For example, LDX reduces self-reported binge-eating symptoms in individuals with BED (Hudson et al., 2017; McElroy et al., 2016b), which could be due to effects of the drug on appetite, as self-reported appetite is decreased following LDX administration (McElroy et al., 2016a; McElroy et al., 2015c). Thus, LDX increases monoamine neurotransmission, and there is extensive evidence for a role of dopamine, noradrenaline, and serotonin in the control of appetite (Dourish et al., 2008). Further, LDX reduces palatable food intake in preclinical models of binge eating, suggesting a possible effect of LDX on food reward (Vickers et al., 2015). In clinical studies, LDX reduced self-reported impulsivity symptoms (McElroy et al., 2015b), which may be significant as emerging evidence suggests higher order cognitive processes such as attention, memory, and cognitive inhibition, modulate food intake (Higgs & Spetter, 2018). Increased impulsivity is also associated with BED and is considered a contributing factor to binge-eating episodes (Fischer et al., 2008; Giel et al., 2017). To investigate the mechanism of action of LDX in the treatment of BED, effects of the drug on appetite, reward, and cognition will be examined. To date, there have been several narrative reviews of the efficacy of pharmacological treatment of BED (Goracci et al., 2015; Heo & Duggan, 2017; McElroy et al., 2015d; Ward & Citrome, 2018), but only two systematic reviews of the efficacy of LDX. The first systematic review to assess the safety and efficacy of LDX in the treatment of BED concluded that the drug had robust effects on binge-eating symptoms and low discontinuation rates (Citrome, 2015). A subsequent systematic review and meta-analysis reported that LDX was more effective than placebo in reducing binge-eating days per week, BED-related obsessive-compulsive symptoms, weight, and remission rates, but also that discontinuation rates were higher for LDX than for placebo (Fornaro et al., 2016). These reviews focused on the safety and efficacy of LDX rather than mechanism of action and neither included results from preclinical studies. To investigate

pharmacological and behavioural mechanisms of therapeutic drug action, it is recommended that both preclinical studies and clinical studies are included (Sena et al., 2014). The current systematic review and meta-analysis extends the scope of previous reviews by 1) including more recently published clinical studies 2) assessing both the efficacy of LDX in binge eating and the neural mechanisms that may underlie its therapeutic effects and 3) including both preclinical and clinical studies.

3.2. Experimental Procedures

The protocol for this meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) as a preclinical (CRD42020198117) and clinical (CRD42020198102) review.

3.2.1. Literature Search

A search for original research articles in English was performed in June 2020 by a single researcher (ES). The databases used to perform the search were Web of Science, PubMed Central, PsycInfo, and Ovid SP. The following search terms were used: lisdexamfetamine, lisdexamfetamine dimesylate, lisdexamphetamine dimesylate, lisdexamphetamine, SPD489, Vyvanse, Elvanse, or LDX and binge, binge-eating disorder, binge eating disorder, binging, bingeing, binge eating, binge-eating, or binge disorder (see Appendix B for full search terms). The search included human participants of all ages and non-human animal subjects. The Preferred Reporting items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart was used to guide the search of articles (Liberati et al., 2009) (see Figure 6). Supplemental article searches were performed by searching reference lists of related articles and reviews.

3.2.2. Study Selection

All original, peer-reviewed research articles (i.e. no conference abstracts, press releases, reviews or meta-analyses) assessing LDX and binge eating or food intake in humans and non-human animals were included. Studies that were conducted on a different clinical sample (i.e. not BED) were included if a measure of binge eating/food intake was reported. Mechanistic studies, including pharmacokinetic studies that did not recruit participants with BED symptoms or include a binge-eating/food intake measure, were not included. Studies examining the active metabolite of LDX, d-amphetamine, only were not included. There were no restrictions on age, gender, or BED status (i.e. sub-clinical or clinical).

3.2.3. Data Extraction

Data extraction was performed using standardised templates created for the review. Each article was extracted by one investigator (ES) and reviewed by another investigator (SH) for accuracy and completeness. The information extracted from each clinical study included: study design, clinical phase, intervention, duration, eligibility, comparator, sample size, participant characteristics, adverse effects, primary outcome measures, and secondary outcome measures, declaration of interests. Information extracted from preclinical studies included: behavioural model, sex, species and strain, drug regimen (acute versus chronic), dose of drug, route of administration, comparator, sample size, and outcome measures. The quality assessment of each study was completed by two reviewers (ES and SH) using an adapted tool for assessment of clinical studies (Kmet et al., 2004) and an adapted tool for assessment of preclinical studies (Zeng et al., 2015). The quality criteria for clinical studies included: validity of research design, reporting of participant characteristics, randomisation, double-blinding, appropriate reporting of outcomes, and reporting of conflicts of interests. The quality criteria for preclinical studies included: sample size, randomisation, blinding, exclusion reporting, and reporting of conflicts of

interest. Each criterion was rated as 1) met; 2) partially met; or 3) not met to determine an overall quality rating (scored as low, moderate, or high). Scoring was completed by two reviewers (ES and SH) independently. Moderate and large differences in quality ratings were discussed by the two reviewers until a consensus was reached. A third reviewer (CD) was available to arbitrate disagreements, but this was not required.

3.2.4. Data Synthesis

An inverse variance meta-analysis was used to analyse results from both the clinical and preclinical studies. For the clinical studies, randomised controlled trials that compared the efficacy of placebo and LDX were included in the meta-analysis. One measure of LDX efficacy at treatment endpoint was extracted. Efficacy was operationalised as self-reported changes on validated binge-eating symptoms questionnaires (i.e. Binge Eating Scale (BES), Clinical Global Improvement (CGI), and Yale-Brown Obsessive Compulsive Scale – Binge Eating (YBOCS-BE)). Preclinical studies were compared by placebo and LDX effects on chow intake and palatable food intake. Given the variety of study design and assessment measures, a random effects analysis model was used. Revman (Cochrane, 2020) version 5.4 was used to calculate the weight and standardised mean difference (SMD) between the placebo and LDX conditions for both subject types. I^2 values and confidence intervals (95%) were provided to assess statistical heterogeneity. Means that were presented graphically were extracted using WebPlotDigitizer Version 4.3 (Rohatgi, 2020). When standard error was used to represent variance, the Cochrane method for obtaining standard deviation from standard error was used to determine the standard deviation: $SD = SE * \sqrt{N}$ (Higgins et al., 2019). Where relevant data were missing, study authors were contacted to obtain this information. When data for multiple LDX doses were available, the dose with the highest effect size was selected as the LDX comparison for data analysis. When

chronic doses of LDX were reported (Ekstrand et al., 2019; Sachdeo et al., 2019), a single average across all data points was calculated for pooled analysis. All studies reported efficacy measures as endpoint data only; one study (Guerdjikova et al., 2016) reported efficacy endpoint as change from baseline. In this instance, the change from baseline score was included with the other endpoint data, as combining endpoint and change from baseline score has been shown to be an acceptable method for pooling data (Higgins et al., 2019). With the exception of one study (Hudson et al., 2017), all RCTs were placebo-controlled trials investigating the efficacy of LDX for the treatment of BED. However, Hudson et al. (2017) randomly assigned responders from an open-label phase of the study to receive either placebo or LDX to measure BED relapse and is thus a relapse-prevention trial as opposed to a treatment efficacy trial. As such, the Hudson et al. (2017) study data were excluded from the meta-analysis. The preclinical articles included multiple experiments with food intake measures comparing vehicle to LDX, hereafter referred to as comparisons. In these instances, eligible data included any vehicle-LDX comparison regardless of sample type (i.e., transgenic mice, non-bingeing controls).

3.3. Results

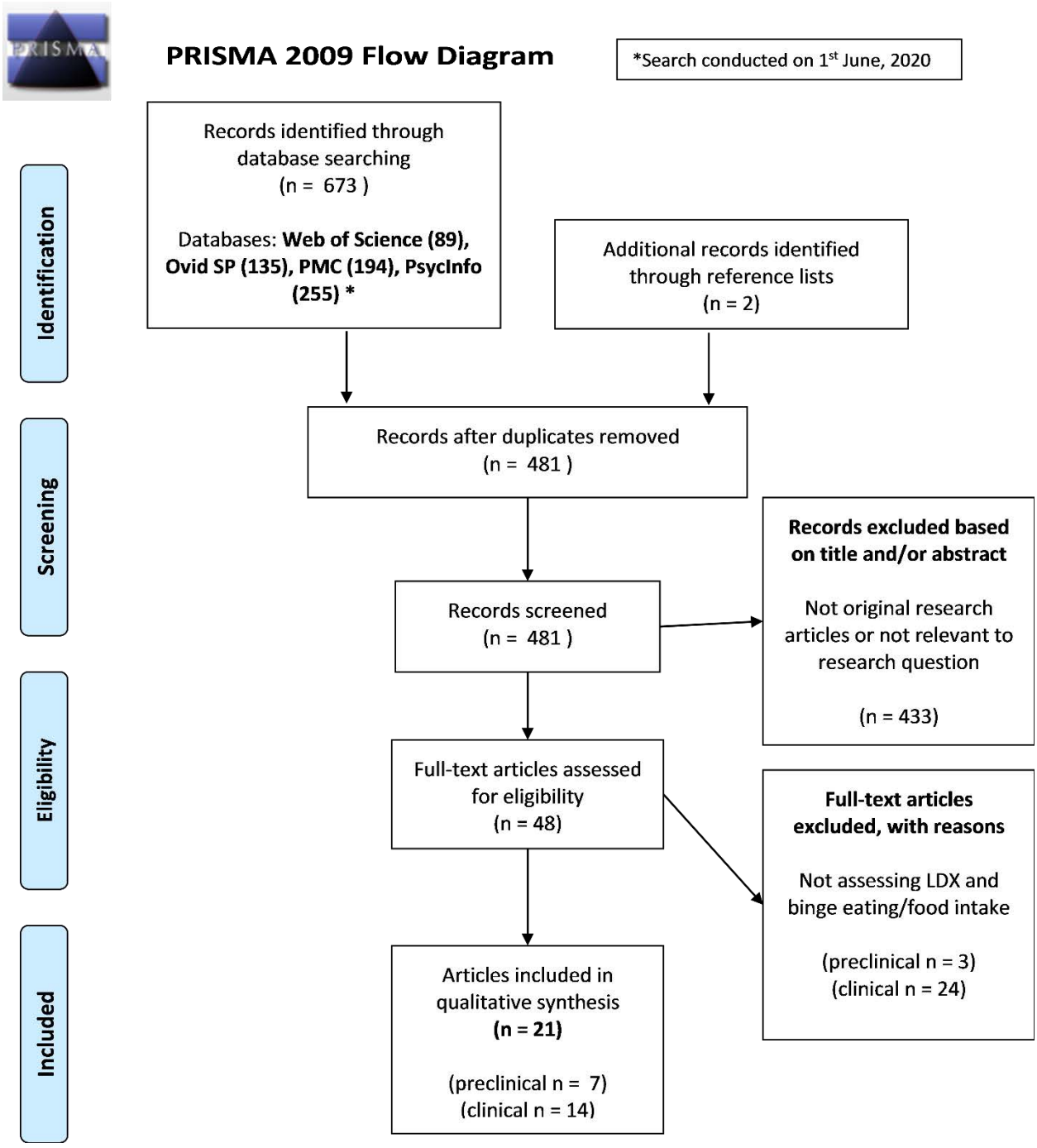
3.3.1. Study Selection

A total of 21 articles were included in this review (see Figure 6). A search of Web of Science, PubMed Central, Ovid SP, and PsycInfo yielded 673 results. After removal of duplicates, 481 records remained. Of these records, 433 were removed after determining the abstracts did not meet the criteria resulting in 48 articles eligible for full-text screening. Twenty-four clinical articles and 3 preclinical articles were removed during full-text screening for lacking a measure of LDX on binge eating/food intake, resulting in 13 clinical and 6 preclinical articles. An additional clinical and an additional preclinical article were included through a

manual search of references of relevant papers and for studies that have cited these papers. This resulted in a final total of 14 clinical and 7 preclinical articles that met inclusion criteria for this review.

A total of 47 comparisons were extracted from the 7 preclinical articles, as some articles included multiple relevant comparisons. Three clinical articles (Kornstein et al., 2019; McElroy et al., 2017; McElroy et al., 2016b) reported secondary analyses from previously published studies. The results of these three studies were excluded from the meta-analysis but are included in Table 12 and are discussed in the narrative synthesis section. One study (Keshen & Helson, 2017) administered extended release amphetamine/dextroamphetamine instead of LDX in one of the six case reports and so this case report is not included in the results.

Figure 6: PRISMA Flow Diagram for Study Selection



3.3.2. Study Characteristics

3.3.2.1. Clinical studies

Of the 14 clinical articles, four (Guerdjikova et al., 2016; Hudson et al., 2017; McElroy et al., 2015a; McElroy et al., 2015c) reported the results of a randomised controlled trial (RCT),

and one reported the results of two RCTs (McElroy et al., 2016a). Three articles reported the results of open-label studies (Fleck et al., 2019; Gasior et al., 2017; Hudson et al., 2017), two were case reports (Brucar et al., 2018; Srivastava et al., 2019), two were retrospective medical record reviews (Guerdjikova et al., 2019; Keshen & Helson, 2017) and three were secondary data analyses (Kornstein et al., 2019; McElroy et al., 2017; McElroy et al., 2016b). Note that Hudson et al. (2017) is included in both the RCT and open label design as results of both designs are reported in the article. As such, the results of Hudson et al. (2017) are included in both sections with accompanying relevant data. BED was a primary diagnosis in all but two studies (McElroy et al., 2015c; Keshan et al., 2017). Primary diagnoses for these two studies were Bipolar Disorder and Bulimia Nervosa.

3.3.2.1.1. Randomised Controlled Clinical Trials

Across the five RCTs, data were collected from a total of 1349 participants who had a clinical diagnosis of BED across 175 sites (North America and Europe). Only adults were eligible to take part and the mean age range was 37.7-43.0 years. All studies recruited men and women, but women represented the majority of participants in all studies. The mean body mass index (BMI) ranged from 33.45-34.90 kg/m^2. Only one study (McElroy et al., 2016a) reported co-morbidities and of these Major Depressive Disorder was the most prevalent. Treatment duration ranged from 8 weeks-26 weeks. Chronic LDX doses ranging from 20mg-70mg were compared against a placebo. Outcome measures for symptom improvement included binge eating days/week (n=4) or binge eating episodes per week (n=2) and changes on the Clinical Global Improvement CGI (n=4), YBOCS-BE (n=4), and BES (n=2). All RCTs were sponsored by the manufacturer of the drug, Shire (now Takeda).

3.3.2.1.2. Non-Randomised Controlled Clinical Trials

Across all non-RCT articles (n=7), data were collected from a total of 1081 participants across 141 sites. Eligibility for participation included a diagnosis of BED (n=4), a score of 21 on the BES (n=1), 45-year history of BED (n=1), and a diagnosis of Bulimia Nervosa (n=1). Ages ranged from 12-56 years. Three studies (Gasior et al., 2017; Guerdjikova et al., 2019; Hudson et al., 2017) recruited men and women (although the majority of participants were women), three studies (Brucar et al., 2018; Fleck et al., 2019; Srivastava et al., 2019) included only women, and one study did not report sex/gender (Keshan et al., 2017). Adult BMI ranged from 33.75-48.89 kg/m^2 and mean paediatric BMI percentile was 97.5 (Guerdjikova et al., 2019). Two studies did not report BMI (Brucar et al., 2018; Keshan et al., 2017). Of the studies that reported co-morbidities (n=2), the disorders reported included: depressive disorders, generalised anxiety disorder, ADHD, developmental delay/autism, milieu instability, marijuana use disorder, dependent traits, avoidant personality traits, dependent personality traits, obsessive-compulsive personality traits, and social anxiety disorder. Treatment duration ranged from 1-19.1 months. Chronic dosing of LDX ranged from 30-70mg LDX and were compared against a control group (n=1) or had no comparator (n=6). Outcome measures of symptom improvement included: binge eating frequency (n=4), CGI (n=2), YBCOS-BE (n=2), BES (n=2), neural activity in relevant brain areas (n=2), self-report BED symptoms (n=1), and binge/purge days per month (n=1). Of the studies that reported a funding source (n=4), three were funded by Shire (now Takeda) the manufacturer of the drug, and five of the seven non-RCTs reported a conflict of interest due to various links with Shire (now Takeda).

3.3.2.2. Preclinical Studies

Of the 7 articles included in this review, 6 reported measures of food intake after administration of LDX (either free feeding intake or intake of food obtained via lever pressing). One article reported the results of a study that assessed the ability of rats to delay responding on a lever to obtain a larger reward (3 pellets after a delay versus 1 pellet delivered immediately) (Vickers et al., 2017). The number of pellets consumed by the rats was assessed in this study, but given that higher intake in this paradigm reflects a greater ability to delay gratification, any effect of LDX on pellets consumed reflects an effect of the drug on impulsivity rather than on intake *per se.* Therefore, this study was excluded from the narrative synthesis of the efficacy of LDX for treating BED and the meta-analysis and is discussed only in the section on mechanisms. Most articles reported assessment of the effects of acute dosing of LDX on intake of both palatable food (usually chocolate) and standard laboratory rodent chow when offered as a choice in a rat model of binge eating (Presby et al., 2020; Sachdeo et al., 2019; Vickers et al., 2015; Yohn et al., 2016). Of these studies, two used an effort-based choice paradigm that involved rats choosing between lever pressing for palatable food pellets versus free access to chow (Presby et al., 2020; Yohn et al., 2016). One study assessed intake of both palatable food and chow but offered sequentially in a test session (palatable food) and later in the home cage (chow) (Heal et al., 2016). Another study assessed daily home cage chow intake during chronic dosing with LDX (Ekstrand et al., 2019). Comparisons of interest were between LDX treated animals and vehicle treated animals. One article included an assessment of the effects of co-administration of catecholamine receptor antagonists to assess underlying pharmacological mechanisms (Vickers et al., 2015). The results of the comparisons between LDX and vehicle treated rats from these assessments are reported in the section on food intake and the comparisons with the antagonist

drugs are reported in the section on mechanisms. Five articles reported testing female rodents (Heal et al., 2016; Presby et al., 2020; Sachdeo et al., 2019; Vickers et al., 2015, 2017) and 2 male rodents (Ekstrand et al., 2019; Yohn et al., 2016). All studies tested rats except for one that used female transgenic mice with genetically altered μ-opioid receptor signalling (Sachdeo et al., 2019). The doses examined ranged from 0.09mg/kg to 1.5mg/kg LDX which were administered either orally or intraperitoneally (IP). Most animals were not deprived of food but in two reports the animals had food restriction (Sachdeo et al., 2019; Yohn et al., 2016). All but one article (Ekstrand et al. 2019) reported funding from Shire (now Takeda).

3.3.3. Risk of Bias within Studies

For the clinical studies, high quality ratings were given to RCT studies only. Study designs such as open-label, case report, and medical record review are inherently less robust than RCTs due to small sample size, lack of comparator, and lack of randomisation. Thus, study design was a common limitation resulting in a poorer quality score for the non-RCT studies. The overall preclinical study quality was determined to be moderate. This was due to unblinded outcomes and variability among studies in reporting of sample size calculations, randomisation, and lack of reporting of animals excluded from the analysis.

3.3.4. Study Findings

To answer the questions posed by this review, in the following sections we present data on the evidence of the efficacy of LDX for the treatment of BED from clinical studies in humans and any potential moderators of this effect that have been identified. These results are organised according to outcome measure (binge eating frequency, global binge eating symptoms, and body weight and food-intake related outcomes). We then present the data from preclinical studies that have examined the effects of LDX on measures of food intake in rodents. Here, we distinguish

between effects on palatable food intake and effects on standard laboratory chow intake to assess any selective effects of drug administration on different food types. A summary of the studies included in this narrative review are included in Table 12 and Table 13 (Appendix C and D). We then present the results of two meta-analyses: one of the outcomes of the RCTs using change in binge-eating symptoms on validated questionnaires (i.e. BES, CGI, and YBOCS-BE) as the outcome and one of the results of the preclinical studies of the effects of LDX on food intake measures including a subgroup analysis of the effect of LDX on the intake of chow versus palatable food. Finally, we present the results of a narrative synthesis of data that are relevant to understanding the mechanisms of action that might underlie the effectiveness of LDX in treating BED.

3.3.4.1. Narrative Synthesis of the Efficacy of LDX for the Treatment of Binge-Eating Disorder

3.3.4.1.1. Clinical Studies

3.3.4.1.1.1. Binge Eating Frequency

In the five RCTs, binge eating frequency was measured in all but one study (McElroy et al., 2015c). McElroy et al. (2015b) reported a reduction in weekly binge-eating days per week and binge-eating episodes for 50 and 70mg LDX at treatment endpoint. Endpoint one and four-week binge-eating cessation was also reported following 50 and 70mg LDX. Similar results were observed by McElroy et al. (2016a), in which LDX reduced baseline binge-eating days per week and increased 4-week binge-eating cessation rates at treatment endpoint. Secondary analyses of these data reported by McElroy et al. (2016b) concluded that these changes in binge-eating episodes and days and cessation rates were also evident during treatment, in addition to at endpoint (McElroy et al., 2017). In the RCT phase, Hudson et al. (2017) reported a reduction in

binge-eating days per week and a greater time to binge-eating relapse at treatment endpoint following LDX dosing. At treatment endpoint, Guerdjikova et al. (2016) found LDX reduced binge-eating days and episodes per week compared to baseline but found no differences in 4-week cessation rates for LDX and placebo. During treatment, there was a trend for a reduction of binge-eating days/week, but this was not statistically significant (Guerdjikova et al., 2016). Notably, the Guerdjikova et al. (2016) study had a smaller sample size (N=50). The results of the RCTs indicate LDX is more effective than placebo in reducing binge-eating episodes and binge eating days and in increasing cessation rates from baseline to endpoint. Interestingly, the results of Guerdjikova et al. (2016) suggest that LDX may be more effective with longer use. Across the seven non-RCT studies (including the open-label phase of Hudson et al., 2017), LDX was shown to significantly reduce binge-eating days and episodes in two studies (Fleck et al., 2019; Hudson et al., 2017). The remaining studies reported only frequency data. In two case studies, Srivistava et al. (2019) did not measure binge eating frequency, while Brucar et al. (2018) reported that LDX reduced binge-eating episodes and induced cessation of binge eating. An analysis of 25 records showed LDX reduced binge eating frequency in 6 cases (Guerdjikova et al., 2019). One study investigating the effects of LDX in participants with Bulimia Nervosa found that the drug reduced combined binge/purge days per month from one month of treatment onward (Keshen et al., 2017). In an Open-Label, 12-Month Extension Safety and Tolerability study, Gasior et al. (2017) reported a reduction in binge-eating days for the previous 28 days at the end of 52 weeks of LDX treatment in participants with BED.

3.3.4.1.1.2. Global Binge-Eating Symptoms

A range of global BED symptom measures were used across all RCTs. In studies that administered a version of the CGI (n=4), LDX improved BED symptoms at endpoint in three

studies compared to placebo (Hudson et al., 2017; McElroy et al., 2015b; McElroy et al., 2016a). Similarly, in studies that measured obsessive-compulsive BED symptoms via the YBOCS-BE (n=4), LDX reduced YBOCS-BE scores at treatment endpoint in three studies compared to placebo (McElroy et al., 2015b; McElroy et al., 2016a; Hudson et al., 2017). Notably, an extension study investigating symptom changes over the course of treatment also confirmed improvements in symptoms following LDX administration using the CGI and YBOCS-BE during treatment (McElroy et al., 2017). However, Guerdjikova et al. (2016) reported LDX improved symptoms on the CGI, but not on the YBOCS-BE during treatment. Only two studies (McElroy et al., 2015b; McElroy et al., 2015c) reported BES data and both studies reported improvements in ratings following LDX treatment. Two non-RCT studies did not use validated BED symptom measures (Keshan et al., 2017; Guerdjikova et al., 2019). These studies reported percentage improvements in self-reported symptoms in most of the participants, but a worsening of symptoms after LDX treatment in 2 of 25 cases (Guerdjikova et al., 2019). The results of Brucar et al. (2018) did not include a symptom improvement outcome. Fleck et al. (2019) reported that LDX improved BED symptoms using the CGI, YBOCS-BE, and BES. Gasior et al. (2017) reported a percentage improvement in symptoms on the CGI following LDX treatment. In the open-label phase, Hudson et al. (2017) reported an improvement in CGI scores following LDX treatment. Finally, LDX numerically improved BES scores in a paediatric case study (Srivastava et al., 2019).

3.3.4.1.1.3. Body weight and food-intake related outcomes

Across the five RCTs, LDX reduced weight/BMI compared to placebo (Guerdjikova et al., 2016; Hudson et al., 2017; McElroy et al., 2015b; McElroy et al., 2016a; McElroy et al., 2015c). Weight was also reduced in a majority of the non-RCT studies (Gasior et al., 2017;

Srivastava et al., 2019; Hudson et al., 2017; Fleck et al., 2019). However, one study found no reduction in BMI following LDX treatment (Guerdjikova et al., 2019). In five participants with Bulimia Nervosa, weight gain was reported in one case following LDX treatment (Keshen et al., 2017). LDX also reduced triglyceride levels (McElroy et al., 2016a; McElroy et al., 2015c) and cholesterol levels (McElroy et al., 2015c) at study endpoints. During treatment, Guerdjikova et al. (2016) reported a reduction in weight and triglyceride levels following LDX treatment but no differences on measures of cholesterol, glucose, insulin, and HbA1c. In measurements of general eating pathology, LDX reduced food cravings (Srivastava et al., 2019), food sneaking (Guerdjikova et al., 2019), disordered eating (Gasior et al., 2017), stress-triggered binge eating (Guerdjikova et al., 2019), and reaction time on an emotional eating cognitive task (Fleck et al., 2019). However, two studies found LDX did not change self-reported food cravings (Guerdjikova et al., 2016; McElroy et al., 2015c). Conflicting results were found on measures of eating disinhibition and eating restraint with one study reporting improvement following LDX (McElroy et al., 2015b) and the other reporting no change (Guerdjikova et al., 2016).

3.3.4.1.1.4. Moderators of LDX Effects

No studies formally analysed potential moderators of the relationship between LDX and BED improvement. Only one study (Kornstein et al., 2019) directly assessed sex/gender and age differences in the effects of LDX using previously published RCT data (McElroy et al., 2016b). These authors found that neither sex/gender nor age (18-40 years versus ≥ 40 years) moderated the effects of LDX on binge eating frequency or BED symptoms (CGI and YBOCS-BE). Paediatric participants were generally responsive to treatment with LDX as indicated by improved symptoms and greater weight loss (Srivastava et al., 2019; Guerdjikova et al., 2019).

However, as noted previously, two participants had a worsening of symptoms and in four cases there were no changes in BED symptoms with LDX treatment (Guerdjikova et al., 2019).

3.3.4.1.2. Preclinical Studies

3.3.4.1.2.1. Food Intake

The first study to assess the effects of LDX in a rat model of binge eating reported 7 assessments where LDX was compared with a vehicle control condition (Vickers et al., 2015). In one cohort of rats, the effects of a range of LDX doses on food intake in a 2-hour binge session and over 24 hours was assessed. In the binge session, LDX reduced chocolate but not chow intake and reduced total food intake over 24 hours (chow intake plus chocolate consumption in the binge-eating session). In another cohort of rats, the pharmacological characteristics of the actions of LDX on binge-eating behaviour were investigated using selective dopamine receptor and adrenoceptor antagonists. The antagonist effects are discussed below in the section on pharmacological mechanisms (Vickers et al., 2015). Four comparisons in this cohort between LDX and vehicle only showed that LDX reduced chocolate intake in 2/2 comparisons and reduced chow intake in 1/2 comparisons. Another article from the same group using a food reward/punished responding conflict model of binge eating reported that LDX reduced intake of chocolate in the conflict test and reduced intake of chow in the home cage in both binge eating and non-binge eating female rats (Heal et al., 2016). Two studies examined the effect of LDX on effortful responding for palatable pellets (progressive ratio lever responding) versus freely accessible chow in either a binge-like eating model (Presby et al., 2020) or in food restricted rats (Yohn et al., 2016). Free intake of chocolate and chow (when presented as a choice) was also examined. In the binge-eating model, rats were either pre-exposed to chocolate (binge-like model), pre-exposed to lab chow, or had no pre-exposure (control groups). Free intake of chow

and chocolate decreased after LDX administration in the chocolate exposed group, and chow was decreased in the group that only had access to chow (chow pre-exposed group). Lever pressing for chocolate was reduced in both the LDX and combined control groups (chow pre-exposed group and no- exposure group), and chow intake was also reduced in the chocolate exposure group. There was no reduction of chow intake in the control group, but levels of chow intake were low and so floor effects may have been evident. In contrast, using a similar paradigm, Yohn et al. (2016) found that LDX had no effect on intake of pellets or of chow for one reported set of comparisons and increased responding for pellets while decreasing chow intake for another comparison. No effects of LDX (either acute or chronic dosing) were observed in groups of transgenic mice that were subjected to different feeding regimes (bingeing or restricting and their combination) (Sachdeo et al. 2019). Finally, a study by Ekstrand and colleagues (2019) assessed the effect of chronic dosing with LDX on performance in a spatial working memory task and also measured home cage intake of chow. These authors reported that body weight, but not chow intake, was reduced significantly by LDX during the drug treatment period (20 days).

3.3.4.1.2.2. Body weight

Heal et al. (2016) and Vickers et al. (2015) reported no changes in weight with LDX treatment, while Ekstrand et al. (2019) reported that LDX-treated rats weighed less than vehicle-treated rats at endpoint. Further, LDX-treated rats also had lower renal and mesenteric adiposity scores, as well as less epididymal fat mass (Ekstrand et al., 2019). Notably, the studies that reported no effect of LDX on body weight were acute designs where weight loss would not be expected in such a short duration of drug treatment (Heal et al., 2016; Vickers et al., 2015), whereas Ekstrand et al. (2019) used a chronic dosing design.

3.3.5. Meta-Analysis Results

3.3.5.1 Clinical studies

There were five RCTs, but one study did not report the means and standard deviations for binge-eating symptom outcome (McElroy et al., 2015c). All RCTs utilised a placebo-controlled design to assess treatment efficacy, but in Hudson et al. (2017) after an open-label phase of treatment with LDX, drug responders were randomly assigned to placebo or continued LDX during a randomised withdrawal phase to measure relapse-prevention efficacy as opposed to treatment efficacy. Given that McElroy et al. (2016a) reported the results of two RCTs separately, these two data sets were also treated separately in the current meta-analysis. Thus, three articles and four data sets were eligible for inclusion in the meta-analysis (Guerdjikova et al., 2016; McElroy et al., 2015b; McElroy et al., 2016a). All the RCTs were sponsored by Shire (now Takeda) with the exception of Guerdjikova et al. (2016) which was an investigator-initiated study funded by Shire but designed prior to the Shire BED clinical development program conducted from 2011 to 2013. The meta-analysis revealed an overall significant effect of LDX on binge-eating symptom change ($Z = 9.51$; $P < 0.001$; SMD = 0.93, 95% CI: 0.74, 1.12; Figure 7). The forest plot suggests that LDX improved binge-eating symptoms compared to placebo. A low level of heterogeneity was detected ($I^2 = 38\%$). This heterogeneity is likely explained by the variability in doses (ranging from 20-70mg LDX) and the scales used for binge-eating symptom measurements, which were the Clinical Global Improvement (Guerdjikova et al., 2016), Binge Eating Scale (McElroy et al., 2015b), or the Yale-Brown Obsessive Compulsive Scale – Binge Eating (McElroy et al., 2016a). A visual inspection of the funnel plot (Figure 8) shows overall symmetry suggesting there was no publication bias.

Figure 7: Forest Plot of Binge-Eating Symptoms in Clinical Studies

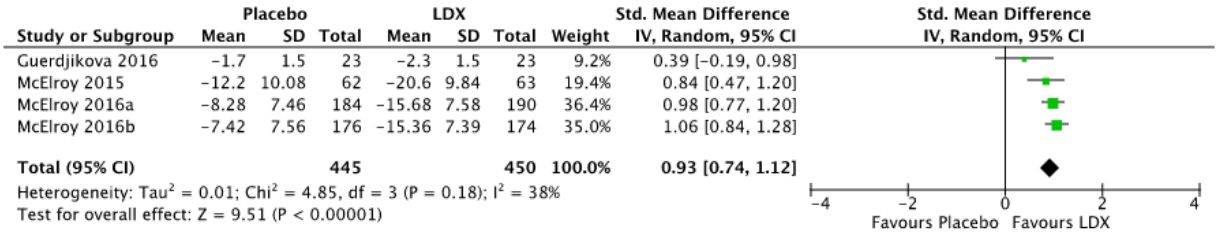
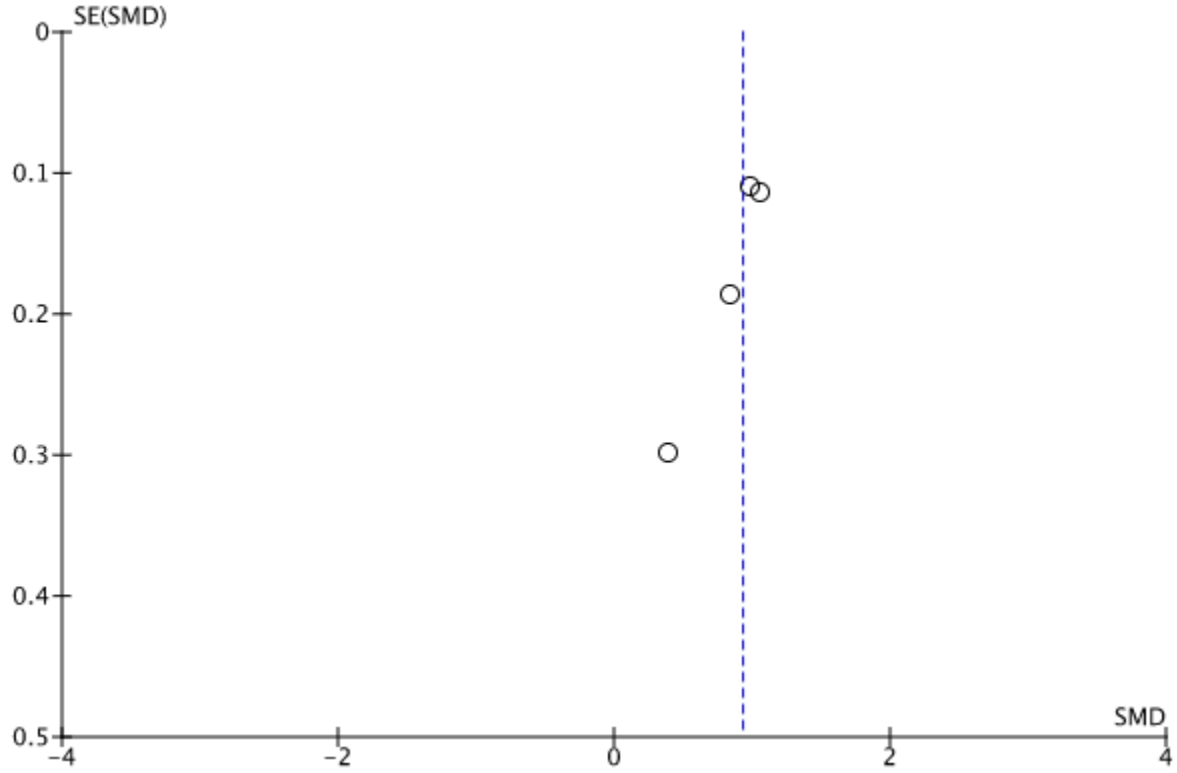


Figure 8: Funnel Plot of Binge-Eating Symptoms in Clinical Studies



3.3.5.2. Preclinical studies

Six preclinical articles (Ekstrand et al., 2019; Heal et al., 2016; Presby et al., 2020; Sachdeo et al., 2019; Vickers et al., 2015; Yohn et al., 2016) reporting 46 LDX-vehicle comparisons were pooled for analysis of the effects of LDX on food intake (the Vickers et al., 2017 delay discounting article was excluded, see above). Subgroup analyses of chow and palatable food intake (i.e., chocolate, shortening, high-carbohydrate pellets) were performed to identify potential differential effects of LDX on food types. Given that the majority of eligible

comparisons (24/46) are extracted from the Sachdeo et al. (2019) article, which is the only study that tested mice, two separate preclinical meta-analyses (with and without the Sachdeo et al. 2019 data sets) were performed to control for homogeneity within published data.

The results from the first preclinical meta-analysis (excluding the Sachdeo et al., 2019 data sets) revealed an overall significant effect of LDX on food intake ($Z = 6.10$; $P < 0.01$; SMD = 0.87, 95% CI: 0.59, 1.15; Figure 9), indicating LDX reduces food intake compared to vehicle. A high level of heterogeneity was detected across comparisons ($I^2 = 64\%$). Pooled analysis of chow intake revealed a significant effect of LDX ($Z = 7.07$; $P < 0.01$; SMD = 0.76, 95% CI: 0.55, 0.98; Figure 9), suggesting LDX reduces chow intake. Heterogeneity was low across comparisons ($I^2 = 0\%$). The reduction of palatable food intake by LDX was also significant ($Z = 3.25$; $P = 0.001$; SMD = 1.04, 95% CI: 0.41, 1.66; Figure 9). A high level of heterogeneity was detected across comparisons ($I^2 = 82\%$). The test for subgroup differences revealed no significant difference between the effects of LDX on chow intake and palatable food intake ($\chi 2 = 0.65$, P = 0.42) with a low level of heterogeneity across subgroups ($I^2 = 0\%$). The high heterogeneity detected within the palatable food intake data sets likely reflects differences in preclinical models (binge-eating and non-binge-eating models), LDX doses, palatable food types (chocolate, shortening, and high-carbohydrate pellets), and quantitative measures of chocolate intake (grams, kilojoules, and lever presses). Determining the source of the heterogeneity through subgroup analyses was not feasible due to the small sample size. Inspection of the funnel plot (Figure 10) revealed approximate symmetry suggesting low risk of publication bias.

Figure 9: Forest Plot of Preclinical Food Intake Data

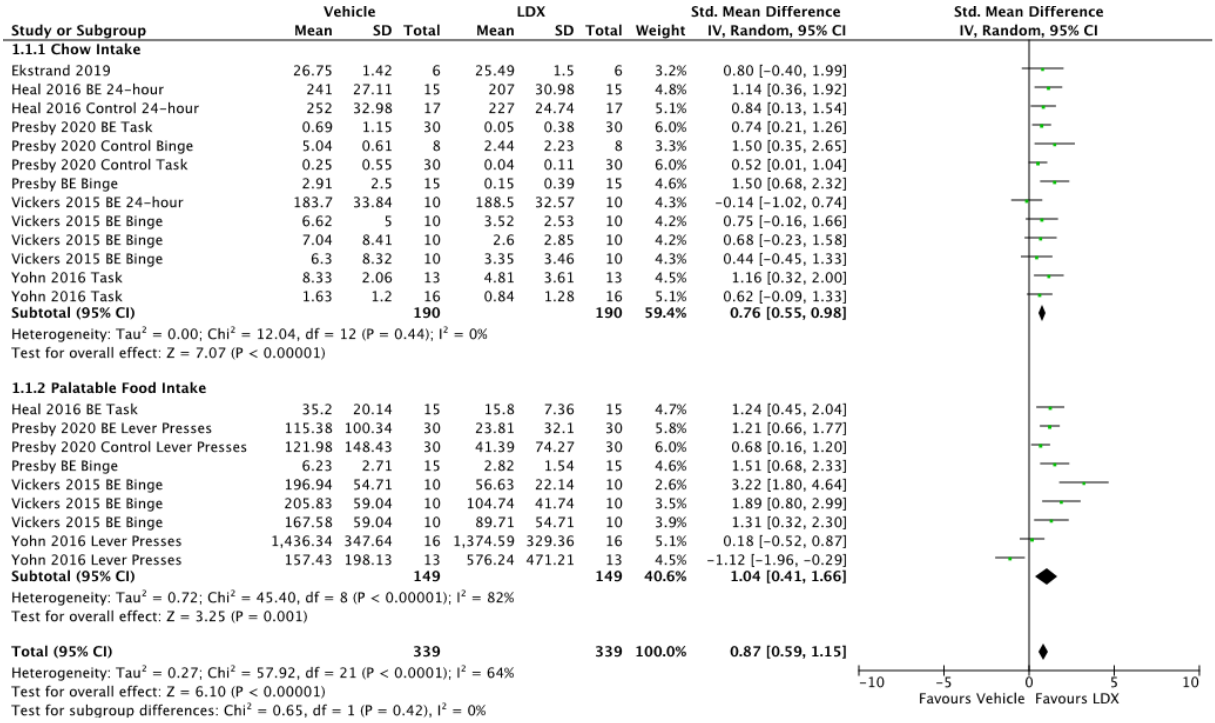
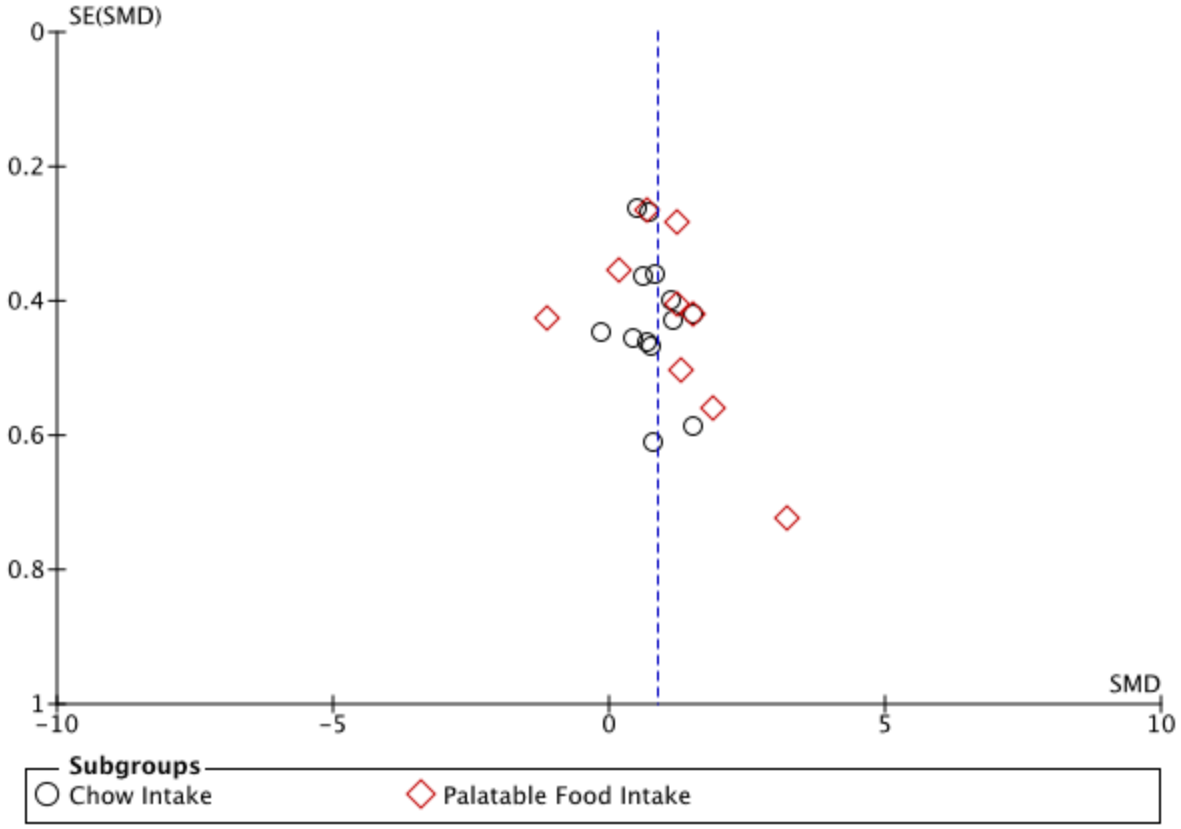


Figure 9. Data label presented as: author, year, rodent model (i.e., control or binge eating (BE)), intake session (i.e., binge or 24-hours) or task.

Figure 10: Funnel Plot of Preclinical Food Intake Data



Analysis of all eligible preclinical comparisons (with Sachdeo et al., 2019 data sets included) revealed a similar pattern, whereby LDX reduced food intake compared to vehicle ($Z = 4.55$; $P < 0.01$; SMD = 0.47, 95% CI: 0.27, 0.67; Figure 11). A moderate-high level of heterogeneity was detected across comparisons ($I^2 = 58\%$). Pooled analysis of chow intake revealed a significant effect of LDX ($Z = 4.45$; $P < 0.01$; SMD = 0.45, 95% CI: 0.25, 0.65; Figure 11), suggesting LDX reduces chow intake. Heterogeneity was low across comparisons ($I^2 = 31\%$). The reduction of palatable food intake by LDX was also significant ($Z = 2.43$; $P = 0.02$; SMD = 0.54, 95% CI: 0.10, 0.97; Figure 11). A high level of heterogeneity was detected across comparisons ($I^2 = 76\%$). The test for subgroup differences revealed no significant difference between the effects of LDX on chow intake and palatable food intake ($\chi_2 = 0.12$, P = 0.73) with

a low level of heterogeneity across subgroups ($I^2 = 0\%$). Inspection of the funnel plot (Figure 12) revealed approximate symmetry suggesting low risk of publication bias.

Figure 11: Forest Plot of All Eligible Preclinical Comparisons

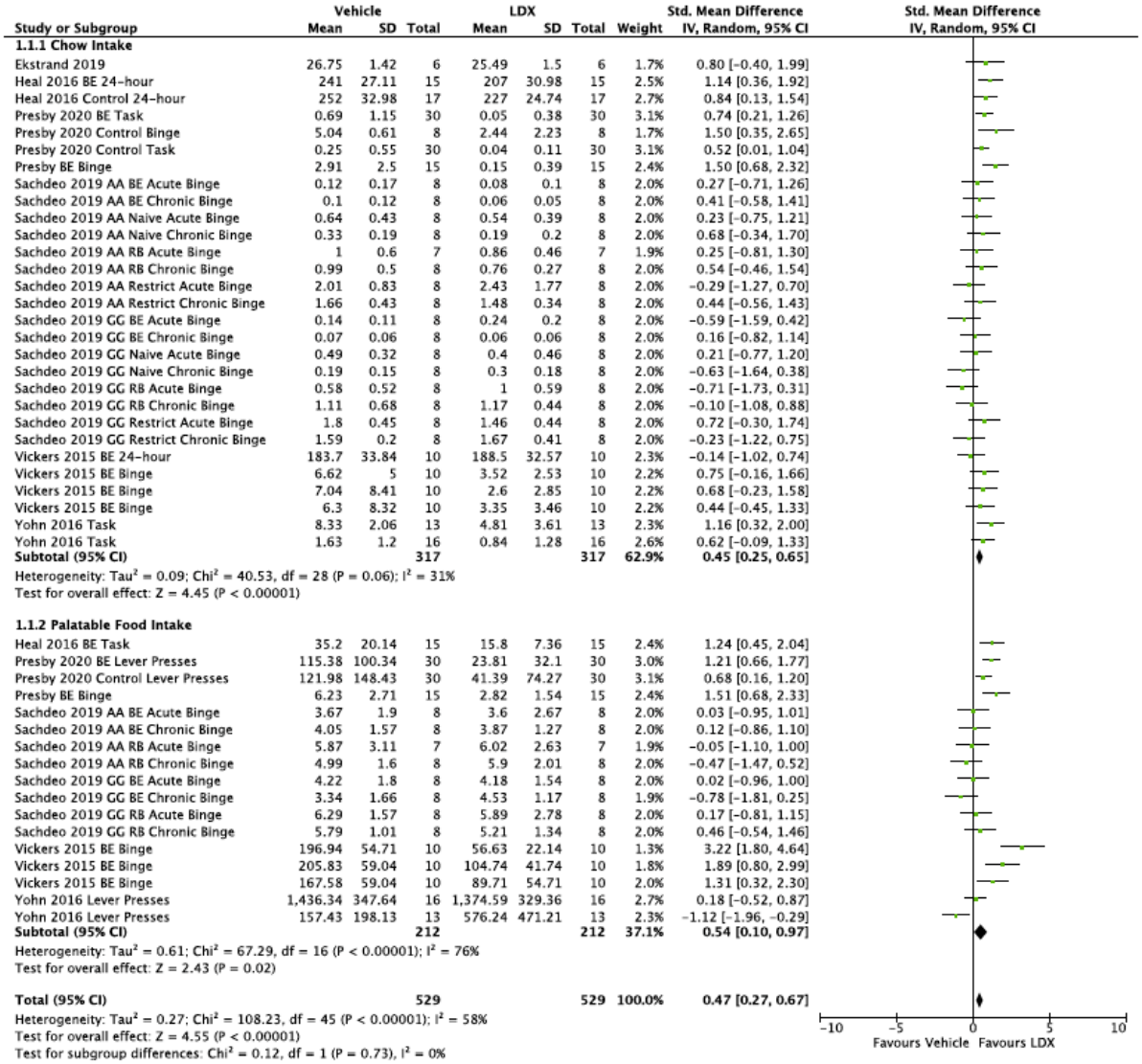
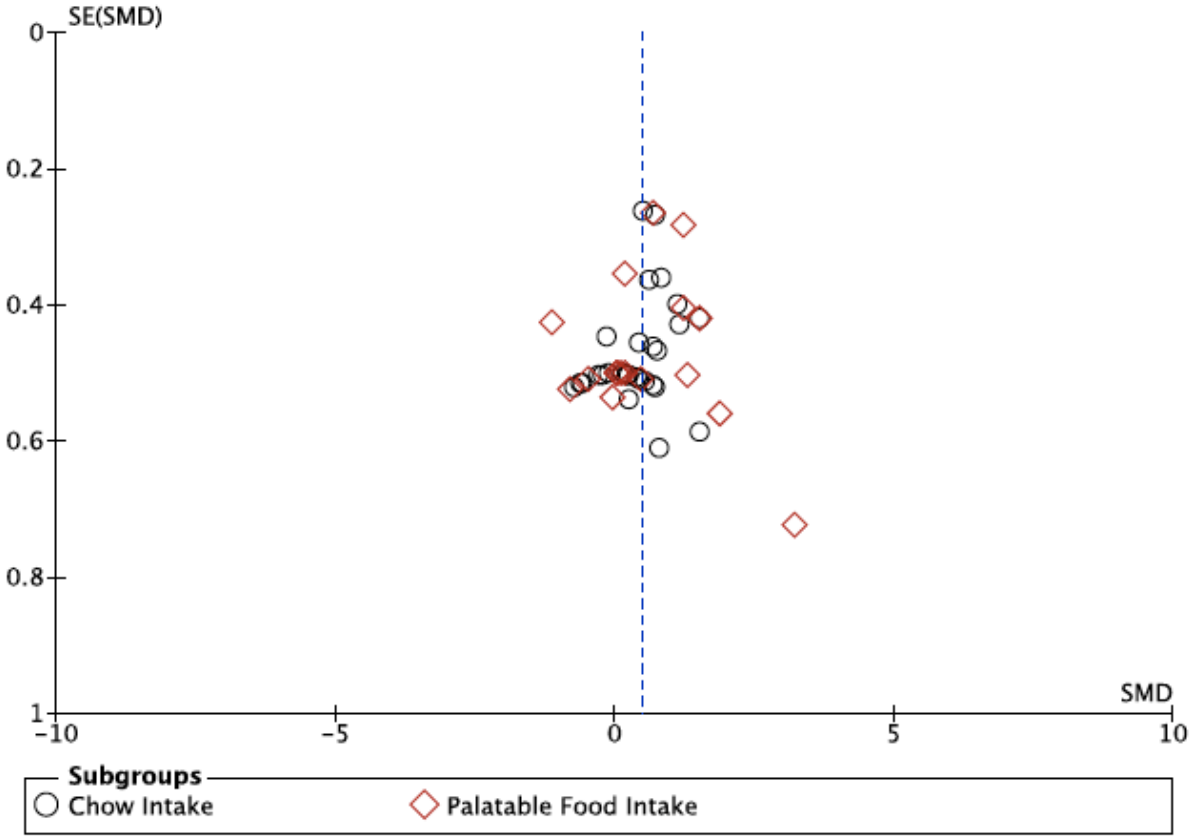


Figure 11. Data label presented as: author, year, genotype (i.e., AA or GG) where relevant, rodent model (i.e., control/naïve, binge eating (BE), restrict binge (RB), restrict), dosing regimen (i.e., acute or chronic) where relevant, intake session (i.e., binge or 24-hours) or task.

Figure 12: Funnel Plot of All Eligible Preclinical Comparisons



3.3.6. Mechanisms of Action of LDX in the Treatment of Binge-Eating Disorder

3.3.6.1. Pharmacological mechanisms

One preclinical study has reported data relevant to understanding the pharmacological mechanisms underlying the effects of LDX on binge eating (Vickers et al., 2015). In this study, the dopamine D_1 receptor antagonist SCH-23390, the dopamine D_2 receptor antagonist raclopride, the α_1 adrenoceptor antagonist prazosin, and the α_2 adrenoceptor antagonist RX821002 were co-administered with LDX (except for SCH-23390 which was given 45 minutes after LDX due to its short half-life in rats). LDX decreased chocolate intake across 4 phases of the antagonist assessment. Prazosin partially reversed the effects of LDX on chocolate intake.

There was also evidence to suggest that SCH-23390 may partially attenuate the effects of LDX on chocolate intake at the lowest dose administered. Thus, chocolate intake in the LDX/ SCH-23390 condition was not significantly less than that of the control group but was also not significantly greater than the LDX/vehicle group. Raclopride, and RX821002 had no effect on the ability of LDX to decrease chocolate intake. Neither prazosin nor SCH-23390 reversed the reduction in chow intake after LDX administration. These results suggest that LDX may reduce chocolate binge eating via enhanced transmission at α_1 adrenoceptors and possibly dopamine D_1 receptors.

3.3.6.2. Behavioural mechanisms

3.3.6.2.1. Drug-induced adverse effects

Common side effects of treatment with LDX such as nausea, constipation, and diarrhoea have been reported to reduce food intake and so could explain at least in part its effect on binge eating (Crozier et al., 2017; Islam et al., 2008). In the three RCTs that reported an overall percentage of treatment-emergent adverse events (TEAE), percentages of participants experiencing any TEAE ranged from 23.5% (Hudson et al., 2017) to 67.75% (McElroy et al., 2016a) and 84.7% (McElroy et al., 2015b). A list of all TEAEs reported in the RCTs can be found in Table 12. Symptoms such as dry mouth (range 5.1-38%), nausea (range 4.4-18%), diarrhoea (range 1.5-16%), and constipation (range 0-7.1%) were reported by participants across all RCTs (Guerdjikova et al., 2016; Hudson et al., 2017; McElroy et al., 2015b; McElroy et al., 2016a; McElroy et al., 2015c). Reductions in food intake can also be brought about by changes in mood or stress (Kazes et al., 1993; Oliver & Wardle, 1999). Two studies reported no effect of LDX on self-reported depression and anxiety (Fleck et al., 2019; McElroy et al., 2015c) whereas in other studies, LDX was reported to reduce self-reported depression (McElroy et al., 2015c),

anxiety (Srivastava et al., 2019), stress-triggered binge eating (Guerdjikova et al., 2019), and stress (Srivastava et al., 2019) which suggests there are no consistent effects of the drug on mood and/or stress.

3.3.6.2.2. Appetite

A general reduction in hunger or enhanced satiety could contribute to the ability of LDX to attenuate binge eating. Across the five RCTs, LDX was found to decrease self-reported appetite in 0-21.4% of participants (reported as an adverse event), suggesting that up to a quarter of participants on LDX experienced a general reduction in appetite. In preclinical studies, LDX was also found to reduce standard chow intake in both bingeing and non-bingeing rats which suggests that the drug may have a general appetite suppressant effect (see Figure 9) (Heal et al., 2016; Presby et al., 2020).

3.3.6.2.3. Reward

Binge eating has been linked to increased reward sensitivity in BED (Schienle et al., 2009) and so LDX could attenuate binge eating via an effect on food reward responses. Two clinical studies reported brain neuroimaging data relevant to understanding mechanisms, and both reported some evidence that LDX reduces activity in brain areas associated with reward. However, both studies have limitations and therefore caution must be applied in interpreting the results. In a pilot Blood Oxygen Level Dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) study, LDX significantly reduced activity in globus pallidus in response to viewing of a palatable food in the context of an attentional task. The authors also reported that changes in ventromedial prefrontal cortex (VMPFC) and thalamus activation were positively correlated with changes in binge scores (Fleck et al., 2019). However, this study had a small sample size, did not include a placebo group, and the obese control group had only a baseline

scan and were not scanned at the study endpoint. In an EEG study, LDX treatment normalised neuronal activity in brain reward areas including the insular cortex, VMPFC, and orbitofrontal cortex (OFC) (Brucar et al., 2018). However, these results are derived from a single case study in which the subject was also prescribed sertraline, thus limiting the conclusions that can be drawn. Two preclinical studies used an effort-based operant choice paradigm to assess whether LDX selectively reduces the willingness to work for a palatable food reward, which would be indicative of reduced reward value of the palatable food pellets (Presby et al., 2020; Yohn et al., 2016). In one study, LDX had a general effect to reduce food intake and food-reinforced operant behaviour (Presby et al., 2020), and in the second study LDX actually increased effort expended to lever press for palatable food and decreased concurrent intake of standard chow (Yohn et al., 2016).

3.3.6.2.4. Cognitive Functioning

It is possible that LDX decreases binge eating via a reduction in impulsive responding. BED has been associated with higher scores on measures of the tendency to act without thinking (motor impulsivity) and the tendency to act without regard for future consequences (non-planning impulsivity), and these impulsive traits may contribute to the onset or maintenance of binge eating (Nasser et al., 2004). Only one clinical study included a measure of impulsivity (McElroy et al., 2015b). In this RCT, LDX was reported to reduce total impulsivity on the Barratt Impulsiveness Scale (Version 11 (BIS-11; Patton et al., 1995)). Secondary analysis of the McElroy et al. (2015b) impulsivity results revealed that LDX dose dependently improved total impulsivity symptoms, motor impulsivity, and non-planning impulsivity on the BIS-11 (McElroy et al., 2016b).

The tendency to act without regard for future consequences can be modelled preclinically using the delay discounting task which involves a making a choice between a small immediate reward versus a larger delayed reward (Odum, 2011). The impulsive choice is to take the immediate reward and not the delayed reward. The effects of LDX on delay discounting in rats was assessed by Vickers et al. (2017). Binge-eating rats had greater intolerance of delayed rewards (were more impulsive) and LDX dose-dependently reversed the reduced preference of binge-eating rats for larger delayed rewards but this shift to choice of a larger delayed reward did not translate into an increase in intake (Vickers et al., 2017). BED is also associated with compulsive responding, which is the tendency toward repetitive, habitual actions that are repeated despite adverse consequences (Robbins et al., 2012). In a study by Heal and colleagues (2016), rats were administered a shock after a conditioned stimulus (tone and light) to mimic binge eating despite negative consequences. LDX reduced compulsive and perseverative responding in this model (Heal et al., 2016). In line with this finding, LDX significantly reduced the obsessional and compulsive subscales score of the Yale–Brown obsessive compulsive scale modified for binge eating (Y-BOCS-BE) (McElroy et al., 2016a, 2016b). A reduction in impulsive responding may also have contributed to the ability of LDX to improve scores of eating restraint reported in one clinical study (McElroy et al., 2015b).

The ability to act in a self-controlled rather than impulsive or compulsive manner relies on cognitive processes such as working memory and attention which are associated with binge-like eating (Gisbert Cury et al., 2020; Kaisari et al., 2017; Kaisari et al., 2018). Accordingly, an action of LDX to improve these cognitive functions might also contribute to the efficacy of the drug in reducing binge-eating episodes. In clinical studies, LDX improved reaction time on an attention-demanding target detection task (“visual oddball” paradigm), potentially reflecting

improvements in attention (Fleck et al., 2019) and self-reported focus (Srivastava et al., 2019). Finally, a preclinical study assessed the effect of the drug on spatial working memory and found that LDX-treated rats showed better performance than vehicle treated rats in the Morris Water Maze (Ekstrand et al., 2019).

3.4. Discussion

To the best of our knowledge, this is the first review and meta-analysis to systematically assess both the preclinical and clinical literature on the effects of LDX on BED and to investigate the potential therapeutic mechanism of action of the drug in treating the disorder. This review set out to address three questions: First, what are the strengths and limitations of the preclinical and clinical data on the use of LDX to treat BED; Second, what do the preclinical and clinical data reveal in terms of specificity of the effects of LDX in BED; Third, what is the current level of understanding of the behavioural and neuropharmacological mechanisms of action of LDX in treating BED.

With regard to the third question, it is relevant that LDX was initially approved by the regulatory authorities for the treatment of ADHD in children in 2007 and in adults in 2008. Subsequently, in 2015, the United States FDA approved a supplemental New Drug Application (NDA) to expand the approved uses of the drug to include treatment of BED in adults and, at present, LDX is the only approved drug in the United States for the treatment of BED. As the drug was approved for use in BED on the basis of a supplemental NDA, it had an accelerated development path to approval and thus there are limited data on the mechanism of action of LDX in treating the disorder.

Fourteen clinical articles were identified and included in this review, and the overall evidence suggests that LDX is an effective treatment for BED which is consistent with the

previous findings of a systematic review (Citrome, 2015) and an exploratory meta-analysis of three RCTs (Fornaro et al. 2016).

Our meta-analysis of the four RCT data sets (Guerdjikova et al., 2016; McElroy et al., 2015b; McElroy et al., 2016a) showed an overall significant effect of LDX on binge-eating symptom change. There was a low level of heterogeneity, due to variation in LDX dose and in the scales used for binge-eating symptom measurements, but no evidence of publication bias as indicated by symmetry of the funnel plot.

Body weight was reduced by LDX in all five RCTs (Guerdjikova et al., 2016; Hudson et al., 2017; McElroy et al., 2015b; McElroy et al., 2016a) and in the majority of non-RCTs (Fleck et al., 2019; Gasior et al., 2017; Hudson et al., 2017; Srivastava et al., 2019). There were also reports of LDX-induced reductions in triglyceride and cholesterol levels although these changes were less consistent across studies (McElroy et al., 2016a; McElroy et al., 2015c; Guerdjikova et al., 2016). Similarly, there are reports in some studies of beneficial effects of LDX on food cravings (Srivastava et al., 2019), eating disinhibition, and eating restraint (McElroy et al., 2015b), but these reports are inconsistent and not replicated in other studies (Guerdjikova et al., 2016; McElroy et al., 2015c).

There is limited evidence on the role of potential moderators of the relationship between LDX and BED symptoms. The only study to assess the role of sex/gender and age reported that neither influenced the effects of LDX on BED symptoms (Kornstein et al., 2019).

Seven preclinical articles were identified and included in this review, and the overall evidence suggests that LDX decreases food intake in rodents. Our meta-analysis of 46 comparisons of LDX and vehicle treatment from six articles showed a significant effect of LDX on food intake (Ekstrand et al., 2019; Heal et al., 2016; Presby et al., 2020; Sachdeo et al., 2019;

Vickers et al., 2015; Yohn et al., 2016). Five of the articles reported data from studies in rats and one article (Sachdeo et al. 2019) reported studies in transgenic mice with a mutation of the μ opioid receptor gene. As 52% of the eligible comparisons were from the Sachdeo et al. (2019) article, we were concerned that this could introduce bias in the results. Therefore, the meta-analysis was conducted on two separate occasions with and without the data from this article. LDX significantly reduced consumption of chow and palatable food in both meta-analyses with and without the comparisons from the Sachdeo et al. (2019) article. There was a low level of heterogeneity across chow intake comparisons but a high level of heterogeneity across palatable food intake comparisons and this pattern was evident in both meta-analyses. The high level of heterogeneity across palatable food intake comparisons is likely due to differences in preclinical models, food types, intake measures, and LDX dose used. Despite a previous report to the contrary (Vickers et al., 2015), there was no consistent evidence for a differential effect of LDX on the intake of chow and palatable food in either analysis which has potential implications for understanding the mechanism of action of the drug in treating BED (see below). There was also no evidence of publication bias as indicated by symmetry of the funnel plot.

3.4.1. Mechanism of Action

3.4.1.1. Pharmacological mechanisms

LDX is a prodrug (a therapeutically inactive molecule) in which d-amphetamine is covalently bonded to L-lysine. After administration of LDX in humans and animals, the mechanism of drug delivery is cleavage of L-lysine by enzymatic hydrolysis in red blood cells to convert the prodrug to the active drug, d-amphetamine (Goodman, 2010). It is well established that d-amphetamine increases the in vivo release of catecholamines and serotonin in rodent brain (Kuroki et al., 1996; Philips et al., 1982). Similarly, in more recent microdialysis studies, LDX

has been shown to increase the in vivo release of dopamine, noradrenaline, and serotonin in the prefrontal cortex (PFC) and striatum of rats (Rowley et al., 2012, 2014). The therapeutic effect of LDX and other stimulants in both BED and ADHD has been proposed to involve catecholamine neurotransmission in the PFC (Berridge et al., 2006; Fleck et al., 2019; Rowley et al., 2012, 2014), and BED has been associated with PFC dysfunction (Fleck et al., 2019; Karhunen et al., 2000; Schienle et al., 2009). This hypothesis is supported by the results of catecholamine receptor antagonist studies in rats where the ability of LDX to decrease the consumption of chocolate was attenuated by the α_1 adrenoceptor antagonist prazosin and the dopamine D_1 receptor antagonist SCH-23390 (Vickers et al., 2015). The dopamine D_2 receptor antagonist raclopride and the α_2 adrenoceptor antagonist RX821002 had no effect suggesting that α_1 adrenoceptors and dopamine D_1 receptors may play an important role in mediating the effects of LDX on chocolate bingeing. As d-amphetamine and LDX also increase the in vivo release of serotonin in rat brain (Kuroki et al., 1996; Rowley et al., 2012, 2014), and given the well-established role of multiple 5-HT receptors in the control of appetite and obesity (Dourish, 1995; Dourish et al., 2008), it is possible that 5-HT receptor mechanisms may play a role in mediating the effects of LDX on binge eating. For example, 5-HT_{2C} receptors were identified over 25 years ago as a target for appetite suppressant drugs (Dourish, 1995), and in 2012 the selective 5-HT_{2C} receptor agonist lorcaserin was approved by the FDA to treat obesity. It has been proposed that patients with BED may consume excessive food at least in part due to disrupted satiety signals (Sysko et al., 2007), suggesting that a 5-HT_{2C} receptor agonist could decrease food intake during a binge-eating episode by enhancing satiety. In addition, in BED palatable foods may be more rewarding, and patients can exhibit greater motivation to consume these foods compared to healthy individuals (Dalton et al., 2013; Finlayson et al., 2011; Schebendach et al., 2013). Thus,

it is possible that the LDX-induced enhancement of satiety signals attenuates subsequent reward value of palatable foods and thereby decreases food intake.

3.4.1.2. Behavioural mechanisms

LDX is a psychostimulant in animals and humans but its stimulant effects are less pronounced than those of d-amphetamine which is thought to be due to the pharmacokinetic profile of the drug (Ermer et al., 2016; Hutson et al., 2014; Jasinski & Krishnan, 2009a, 2009b). In RCTs, LDX was reported to cause nausea, diarrhoea, and constipation (Guerdjikova et al., 2016; Hudson et al., 2017; McElroy et al., 2015b; McElroy et al., 2016a). As adverse gastrointestinal effects and stimulant effects have been reported to reduce food intake (Crozier et al., 2017; Islam et al., 2008; Rasmussen, 2015), it is conceivable that the therapeutic effects of LDX in treating BED are secondary to these actions of the drug. This appears unlikely given the low incidence of gastrointestinal side-effects in RCTs with LDX and its weak stimulant properties in humans (Guerdjikova et al., 2016; Hudson et al., 2017b; Jasinski and Krishnan, 2009a, 2009b; McElroy et al., 2015b; McElroy et al., 2016a).

LDX has effects on appetite/satiety, reward and cognitive processes and it is possible that the therapeutic action of the drug in treating BED may involve one of more of these actions.

3.4.1.3. Appetite and Satiety

LDX reduced body weight in all five RCTs (Guerdjikova et al., 2016; Hudson et al., 2017; McElroy et al., 2015b; McElroy et al., 2016a) and in a majority of the non-RCT studies (Fleck et al., 2019; Gasior et al., 2017; Hudson et al., 2017; Srivastava et al., 2019), indicating a pronounced suppressant effect of the drug on food consumption although this was not measured directly in any of the studies. Furthermore, in the five RCTs up to a quarter of patients reported reduced appetite although this could not be included in the meta-analysis as it was not quantified

and reported only as an adverse event. Interestingly, a low daily dose of 30 mg LDX did not significantly reduce binge-eating frequency but produced a significant decrease in body weight compared to placebo (McElroy et al., 2016a) suggesting that an appetite suppressant effect of the drug may be apparent at a dose that is subthreshold for treating BED.

In preclinical studies, there is one report (Vickers et al., 2015) using a rat binge-eating model that LDX dose-dependently and preferentially reduced the consumption of chocolate compared to standard chow. However, our meta-analyses of 46 comparisons of LDX and vehicle treatment from six articles showed that LDX significantly reduced consumption of both chow and palatable food and overall, there was there was no evidence for a preferential effect of the drug on the intake of palatable food. This is consistent with a previous suggestion (Presby et al., 2020) that LDX has a general appetite suppressant effect in rats.

3.4.1.4. Reward

An extensive body of evidence indicates that brain dopamine, noradrenaline, and serotonin neuronal pathways play an important role in the mediation of food reward processes (Fallon et al., 2007; Fletcher et al., 2010; Higgins et al., 2003; Volkow et al., 2011). There is also extensive evidence that individuals with BED have a dysregulated reward system that is supersensitive to food stimuli (Balodis et al., 2013a; Bodell et al., 2018; Fleck et al., 2019; Geliebter et al., 2016; Karhunen et al., 2000; Lee et al., 2017; Schienle et al., 2009; Wang et al., 2011). As LDX increases the in vivo release of dopamine, noradrenaline, and serotonin in the cortex and striatum of rodent brain (Rowley et al., 2012, 2014), it is plausible that the therapeutic efficacy of the drug in treating BED could be mediated at least in part by an action on brain reward mechanisms to attenuate hypersensitivity to food stimuli. There is some limited evidence to support this hypothesis from recent fMRI and EEG studies with LDX. In an fMRI study,

where BED patients displayed stronger BOLD activations than controls in VLPFC, striatum, and globus pallidus to viewing pictures of palatable food, 12 weeks of treatment with LDX significantly reduced the hyperactivation in globus pallidus but not in VLPFC and striatum (Fleck et al., 2019). Thus, it has been proposed that the globus pallidus could play a crucial role in the functional neuropathogenesis of BED (Fleck et al., 2019) and by implication the efficacy of LDX in treating the disorder. Exploratory analysis of change scores after LDX indicated that changes in VMPFC activation positively correlated with changes on the binge eating scale and changes in thalamus activation were positively correlated with changes on the YBOCS-BE (Fleck et al., 2019). Fleck and colleagues (2019) interpret these correlational results as support for the hypothesis that the ventromedial reward circuit including VMPFC, subgenual ACC, and thalamus is of primary importance in BED and its treatment with LDX. A potential role of the ventromedial reward circuit in mediating the therapeutic action of LDX in BED is also supported by preliminary results of an EEG study. Thus, in a patient with a long history of BED, treatment with LDX prevented binge eating and this action was associated with normalised neuronal activity in brain reward areas including the insular cortex, VMPFC, and OFC (Brucar et al., 2018).

However, both of these studies have limitations that restrict the extent of the conclusions that can be drawn from the results. Fleck et al. (2019) is a pilot study which did not include a placebo treated group or a scan of the control group with obesity at the study endpoint, and Brucar et al. (2018) is a case report in which the patient was also prescribed the antidepressant drug sertraline in addition to LDX.

There is little preclinical evidence for the efficacy of LDX in treating BED being mediated by an action on brain reward mechanisms. As discussed above in relation to appetite,

there is one report that LDX preferentially reduced the consumption of chocolate compared to standard chow in rats (Vickers et al., 2015). In contrast, in an effort-based operant choice paradigm to assess the willingness of rats to work for a palatable food reward, LDX either had a general effect to reduce food intake (Presby et al., 2020) or increased effort to lever press for palatable food and decreased intake of standard chow (Yohn et al., 2016). Similarly, our meta-analyses of preclinical data provided no evidence for a preferential reduction of palatable food consumption by LDX.

3.4.1.5. Cognitive Processes

BED has been described as an impulse control disorder since one of the key symptoms of the disorder is a lack of control over eating (American Psychiatric Association, 2013), and it is possible that LDX may be effective in treating BED at least in part by reducing impulsivity, compulsivity, and the repetitive nature of binge eating. There is extensive evidence that loss of impulse control in BED is a causal factor in provoking bingeing symptoms (Colles et al., 2008; Galanti et al., 2007; Giel et al., 2017; McElroy et al., 2016a; Nasser et al., 2004; Schag et al., 2013). More specifically, BED is associated with motor impulsivity and non-planning impulsivity which could initiate and maintain binge eating (Nasser et al., 2004).

Clinical reports on the effects of LDX on impulsivity in BED patients are limited to a single clinical trial in which a reduction was reported in total impulsivity (McElroy et al., 2015b). Secondary analysis of these data indicated that LDX improved total impulsivity, motor impulsivity, and non-planning impulsivity compared with placebo (McElroy et al., 2016b). Similarly, LDX significantly reduced the obsessional and compulsive subscales score of the Y-BOCS-BE (McElroy et al., 2016b).

The role of impulse control in BED has been investigated in both clinical and preclinical studies using the delay discounting task which measures the discounting of the value of a reward based on how quickly a reward loses its value over time. An inability to delay gratification will result in preference for a small immediate reward relative to a larger delayed reward (MacKillop et al., 2011). BED patients display enhanced delay discounting compared to controls (Davis et al., 2010; Mole et al., 2015). Similarly, binge-eating rats exhibit greater intolerance of delayed rewards and delay discounting in rats has been used as a preclinical model of BED (Vickers et al., 2017). LDX reversed the reduced preference of binge-eating rats for larger rewards at increasingly longer delays (Vickers et al., 2017), a finding that is consistent with the ability of the drug to decrease impulsiveness in patients with BED (McElroy et al., 2015b, 2016a). The finding that LDX treated binge-eating rats did not differ significantly from either the vehicle-treated, non-binge-eating controls, or vehicle-treated, binge-eating rats in their intake of chocolate pellets suggests that there may have been some additional effects of LDX on appetite to reduce overall responding for pellets. Alternatively, the doses at which LDX reduce impulsive responding may be lower than those that have significant effects on appetite and further work is required to test this possibility.

A modified rat shuttle box conditioned avoidance model has been used to explore the effects of LDX on the compulsive and preservative nature of binge eating (Heal et al., 2016). In this model, rats are trained to avoid one compartment of a shuttle box by the administration of foot shock preceded by a conditioned stimulus. When the rats are trained to avoid the shock associated compartment, a conflict is introduced by placing chocolate in this compartment. Binge-eating rats spend a greater proportion of their time in the compartment associated with the negative stimuli, eating more chocolate and receiving more foot shocks than controls as a result.

LDX significantly decreased the consumption of chocolate and the compulsive and repetitive responding in the model (Heal et al., 2016).

The role of cognitive processes in mediating BED has largely focused on the importance of impulsivity and compulsivity in the disorder. However, recent evidence suggests that attentional processes, more specifically inattention, may play an important role in binge eating associated with ADHD (Kaisari et al., 2017, 2018). LDX is approved to treat both ADHD and BED, and it is concievable that an action on attentional processes could contibute to the efficacy of the drug in treating BED and binge eating associated with ADHD. There is limited evidence to date from clinical studies on the effects of LDX on attention in BED. In a visual oddball task that engages the attentional sytem, LDX improved performance of patients with BED (Fleck et al., 2019). Further, a case report of an adolescent patient with BED described improved focus on school-work and other tasks (Srivastava et al., 2019). These results suggest that the efficacy of LDX in treating BED could be related in part to actions of the drug to increase cognitive control but further studies are needed to test this hypothesis.

3.4.2. Strengths and limitations of this systematic review and meta-analysis

This systematic review and meta-analysis has a number of strengths and some limitations. This is the first systematic review of LXD and BED to include both clinical and preclinical studies, and the first review to consider the mechanism of action of LDX in treating the disorder. This is also the first meta-analysis of the results of studies on LDX and BED, and the results of both clinical and preclinical studies are included in the meta-analyses. There are limitations which require the results of this review and meta-analysis to be interpreted with some caution. The number of articles included in the review is relatively small, 14 clinical studies and 7 preclinical articles. Similarly, the number of data sets used in the clinical meta-analysis was

small comprising 4 data sets from RCTs reported in 3 articles and the data were collected by a relatively small number of research groups. The preclinical meta-analysis comprised 46 comparisons of LDX and vehicle treatment but these were obtained from a relatively small number of articles and 24 of these comparisons were from a single article. There was also a relatively small number of studies on the mechanism of action of LDX in treating BED that could be included in the review. There may be a language and a publication bias as the search was limited to studies written and published in the English language.

3.4.3. Clinical Implications

The results of this review and meta-analysis confirm that LDX is an effective treatment for BED and that the drug reduces both the BED symptoms and the body weight of patients with the disorder. Patients with BED can present as underweight, healthy weight, overweight, or obese (Fairburn et al., 2000; Hudson et al., 2007). Given the propensity of LDX to reduce body weight, the BMI of the patient on presentation is an important consideration when prescribing LDX to treat BED. It would be valuable for physicians to have a broad spectrum of drug therapy options available (including for example drugs that can treat BED symptoms without decreasing body weight) to treat patients with BED across a range of BMI categories. LDX is the only approved drug treatment for BED and is approved in only a limited number of countries. Thus, drug treatment options in some countries (such as the United States and Canada) are limited to one marketed drug and in many countries (including most countries in Europe) there is no approved drug therapy for the disorder. Further LDX, like the majority of other commonly prescribed drug treatments for BED, is a stimulant and a Schedule 2 controlled drug in the United States and the United Kingdom. Clearly, there is an urgent need to identify new drug treatment options for BED. An improved understanding of the pathogenesis of BED, and the

mechanism of action of LDX in treating the disorder, which as discussed above is limited, could lead to the discovery of a broader range of improved drug therapies with a lower risk of side-effects and abuse potential.

3.4.4. Future Research

Only one analysis has been published on the role of potential moderators of the relationship between LDX and BED symptoms. This study found that neither sex/gender nor age moderated the effects of LDX on BED symptoms (Kornstein et al., 2019). Thus, there is a clear need for future studies to formally assess potential moderators of the efficacy of LDX in treating BED.

There have been few preclinical or clinical studies on the mechanism of action of LDX in treating BED. Hence, there is considerable potential to use the power of experimental medicine to explore the mechanism of action of LDX in treating BED. However, only a single pilot fMRI study with LDX has been conducted to date (Fleck et al., 2019) and although the results are interesting, its conclusions are limited by a small sample size and the absence of a placebo control group. Therefore, there is an urgent need for adequately powered, placebo-controlled, behavioural and neuroimaging studies with LDX to further investigate the mechanism of action of the drug in treating BED. These studies could recruit patients with BED (as in the study by Fleck et al., 2019) or use an intermediate phenotype approach such as that used successfully to study binge eating associated with ADHD (Kaisari et al., 2018).

3.4.5. Conclusions

There is consistent evidence from this review and meta-analyses that LDX is an effective treatment for BED and that the drug reduces both the BED symptoms and the body weight of patients with the disorder. There is also consistent evidence that LDX reduces food intake in

preclinical studies but no consistent evidence for a preferential reduction of palatable food consumption by the drug in rodents. The evidence from mechanism of action studies suggests that LDX may reduce binge eating through a combination of effects on appetite/satiety, reward, and cognitive processes, including attention and impulsivity/inhibition, that are mediated by catecholamine and serotonin neuronal pathways in the brain. The mechanism of action evidence is limited and an improved understanding of the behavioural and neurochemical mechanisms of action of LDX could lead to the development of improved drug therapies to treat BED.

Chapter 4: The effect of lisdexamfetamine dimesylate on eating behaviour and homeostatic, reward and cognitive processes in women with binge-eating symptoms.

4.1 Introduction

Binge-Eating Disorder (BED) is a disorder of recurrent binge-eating episodes without the use of compensatory behaviours (e.g., purging, laxatives) (American Psychiatric Association, 2013). A binge-eating episode is characterised by both of the following: 1) eating in a discrete period an amount that is definitely larger than what most people would eat in a similar period of time under similar circumstances and 2) a sense of lack of control during the episode. An individual with BED may experience rapid eating, feelings of uncomfortable fullness, eating in the absence of hunger, and/or disgust and shame (American Psychiatric Association, 2013). In additional to psychological distress, BED is co-morbid with obesity, diabetes, hypertension, sleep disorders, and asthma (Mehler et al., 2016; Olguin et al., 2017).

Lisdexamfetamine dimesylate (LDX), the generic name for Vyvanse® (Takeda), was first approved in 2012 by the US Food and Drug Administration (FDA) as a therapeutic agent for the treatment of ADHD and has shown good treatment efficacy (Adler, Lynch, et al., 2017; Frampton, 2016). Subsequently, in 2015, the FDA approved the use of Vyvanse® for the treatment of BED. This approval was based on the results of two phase III, 12-week randomized, double-blind, multi-centre, parallel-group, placebo-controlled, dose-optimization studies in adults with BED (FDA, 2015). In both studies, 50 and 70mg LDX reduced binge-eating episodes, weight, and obsessive-compulsive symptoms (McElroy, Hudson, et al., 2016; McElroy, Mitchell, et al., 2016).

Though LDX has been approved as a treatment for BED, little is known about the neural and cognitive processes that underpin the improvement of BED symptoms following LDX

therapy. An improved understanding of the neuropsychological processes impacted by LDX could aid in development of novel medications to treat BED with improved efficacy and fewer side effects. Pharmacologically, LDX is a pro-drug of d-amphetamine. Following ingestion, the drug is converted via hydrolysis to d-amphetamine in the bloodstream (Adler, Alperin, et al., 2017). This conversion to d-amphetamine has been proposed to be the basis of the drug's prolonged clinical effects (~14 hours) reported by patients (Adler et al., 2008). d-amphetamine increases the in vivo release of catecholamines and serotonin in rodent brain (Kuroki et al., 1996; Philips et al., 1982). In vitro D-amphetamine has been shown to inhibit the dopamine transporter (DAT), the noradrenaline transporter (NET) and the vesicular monoamine transporter 2 (VMAT2). Further, d-amphetamine has weak inhibitory effects on the serotonin transporter (SERT) and monoamine oxidase (MAO) enzyme (for review see Hutson et al., 2014). The actions of LDX on both brain catecholamine and serotonin systems include effects on appetite, reward, and cognitive circuitry that could underlie the improvement of BED symptoms.

Impulsivity is a key feature in the onset and maintenance of BED (Robbins et al., 2012), and it is possible that LDX may be effective in treating BED at least in part by reducing impulsivity. Trait impulsivity is reported more in individuals with BED than in weight-matched controls (Hege et al., 2015; Marek et al., 2014). Further, individuals with BED who reported increased trait impulsivity also reported more severe eating disorder pathology, depressive symptoms, and co-morbidities than individuals with BED who did not report increased trait impulsivity (Boswell & Grilo, 2020). Trait impulsivity might explain the high co-morbidity, with an estimated 1.6-18% co-morbidity prevalence rate, between BED and ADHD (Nickel et al., 2019).

One facet of impulsivity is motor impulsivity, or difficulty in stopping an action already initiated, which could explain the difficulty to stop eating once a binge-eating episode has already begun. Poor performance on impulsive inhibition tasks is linked with trait impulsivity, decreased activation of prefrontal network areas, and increased activation of paralimbic areas (Aichert et al., 2012; Horn et al., 2003). Tasks such as the Stop-Signal Task and the Go/No-go task require withholding a pre-potent motor response, and participants with BED have been found to show poorer performance than matched controls (Grant & Chamberlain, 2020; Wu et al., 2013), especially when the inhibitory targets are food cues (Hege et al., 2015; Svaldi et al., 2014). This is in line with evidence that BED is associated with food-related impulsivity (Schag et al., 2013).

Another facet of impulsivity is negative urgency (NU), which is a rash reaction to emotional distress. NU is recognized as a risk and maintenance factor for BED (Anestis et al., 2007; Claes et al., 2005; Kenny et al., 2019). Indeed, some researchers hypothesize that NU is the main contributor to binge-eating onset (Fischer et al., 2008). NU parallels emotional eating (EE), in which a person experiences an urge to eat in response to emotional cues rather than physical cues (Arnow et al., 1995). Antecedent emotions can be both negative and positive emotions, though negative affect is more often related to a binge-eating episode (Smith & Cyders, 2016; Sultson et al., 2017). EE has also been reported in individuals with co-morbid binge eating and obesity (Haedt-Matt et al., 2014; Turton et al., 2017; Verstuyf et al., 2013), in which intense moods prompt binge eating (Cardi et al., 2015).

Negative urgency and emotional eating have been linked to disinhibition (Momoi et al., 2016) and impaired performance on behavioural decision-making tasks such as the delay discounting task in individuals with BED (Steward et al., 2017). In this task, participants choose

between short-term (smaller rewards) and long-term (larger rewards) and a tendency to choose smaller more immediate rewards over longer, delayed rewards is thought to be an index of impulsive behaviour. The tendency to opt for the short-term reward has been correlated with overeating/BED in some (Davis et al., 2010; Kekic et al., 2020; Manwaring et al., 2011; Steward et al., 2017) but not all studies (Bartholdy et al., 2017; Manasse et al., 2015).

Clinical reports on the effects of LDX on impulsivity in BED patients are limited to a single clinical trial in which a reduction was reported in total impulsivity (McElroy et al., 2015b). Secondary analysis of these data indicated that LDX improved total impulsivity, motor impulsivity, and non-planning impulsivity compared with placebo (McElroy et al., 2016b). Further work is required to verify the effects of LDX on impulsivity and how this may be linked to binge eating.

Enhanced impulsivity toward food in BED could be due to an altered brain reward response to food cues and it is plausible that the therapeutic efficacy of the drug in treating BED could be mediated via attenuation of hypersensitivity to food reward. In fMRI studies, when viewing food and non-food images, individuals with BED, regardless of weight status, viewed food images for longer than controls (Schag et al., 2013). Further, individuals with BED have been reported to have a larger medial orbitofrontal cortex (OFC) region than those without BED and to show greater OFC activation in response to palatable food stimuli (Schäfer et al., 2010; Schienle et al., 2009). In a study of matched binge-eating and non-binge-eating participants, participants with binge-eating symptoms had greater activation in the dorsal anterior cingulate cortex (dACC) when shown images of high-density energy foods, though no differences were found in the striatum and OFC between the two groups (Geliebter et al., 2016). In a PET study, participants with obesity and binge eating who viewed food stimuli after administration of

methylphenidate had increased dopamine in the caudate and putamen but participants with obesity without binge-eating symptoms did not (Wang et al., 2011). To date, there is only limited evidence that LDX attenuates reward responses in BED. In an fMRI study, where BED patients displayed stronger BOLD activations than controls in VLPFC, striatum, and globus pallidus to viewing pictures of palatable food, 12 weeks of treatment with LDX significantly reduced the hyperactivation in globus pallidus but not in VLPFC and striatum (Fleck et al., 2019). However, the study conducted by Fleck et al. (2019) was a pilot study which did not include a placebo treated group or a scan of the control group with obesity at the study endpoint.

Binge eating has also been associated with diverse deficits in cognitive functioning, including working memory and attention which could contribute to problems in controlling food intake (Higgs, 2015). LDX may have therapeutic effects via an ability to improve cognitive functioning (Kaisari et al. 2018). The high prevalence of co-morbid ADHD and BED suggests similar underlying cognitive processes (Brunault et al., 2019; Hanson et al., 2019; Reinblatt et al., 2015) and inattention, a core symptom of ADHD, has also been linked with BED (Kaisari et al. 2018; Christian et al., 2020; Mason et al., 2018; Mobbs et al., 2011; Svedlund et al., 2017). Working memory deficits have also been found in individuals with ADHD (Kofler et al., 2018), but findings for BED and working memory are mixed. Some studies have found that individuals with BED have poorer performance on working memory tasks compared with healthy controls and participants with obesity (Duchesne et al., 2010; Gisbert Cury et al., 2020), while others have found no significant differences between these groups on working memory performance (Eneva et al., 2017; Grant & Chamberlain, 2020; Israel et al., 2015; Manasse, Forman, et al., 2015). A recent meta-analysis found working memory deficits in individuals with BED when compared to individuals with obesity, but this finding is the result of only four studies that used

two tasks (Digit Span and NIH Toolbox Test) (Gisbert Cury et al., 2020). Only one study has reported the effects of LDX on attention: LDX improved performance of patients with BED in a visual oddball task that engages the attentional sytem (Fleck et al., 2019). Further, a single study has found that menopausal women given LDX had fewer self-reported symptoms of executive dysfunction (e.g., attention, processing speed, alertness) and experienced increased activation in the insula and dorsolateral prefrontal cortex (dlPFC) on a visual-spatial working memory task but no associated effect on working memory performance was found (Shanmugan et al., 2017). Hence, further investigation is required to establish whether the effects of LDX to reduce binge-eating symptoms may be due to improvements in attention and memory.

Finally, given that serotonin plays an important role in the control of eating, particularly in the mediation of satiety, (Dourish, 1995; Dourish et al., 2008) and LDX increases the release of serotonin (Kuroki et al. 1996; Rowley et al. 2012, 2014), it is plausible the effects of LDX on binge eating may be mediated by enhancement of satiety processes that are disrupted in BED (Sysko et al., 2007). In RCTs of the effects of LDX on binge eating, reductions in body weight were reported alongside reports of reduced appetite as an adverse event (Guerdjikova et al., 2016; Hudson et al., 2017; McElroy et al., 2015b; McElroy et al., 2016a). However, the effects of LDX on hunger and satiety responses has not been systematically examined in humans. The current study investigated the specific homeostatic, reward, and cognitive mechanisms that may underlie the effects of LDX on binge eating by testing the acute effects of the drug in participants with above threshold scores on a measure of binge-eating symptomatology. This approach is in line with the Research Domain Criteria Initiative (RDoC) established by the US National Institute of Mental Health (NIMH) which encourages research on dimensions of observable behaviour rather than a categorical, symptom-based approach to the study of mental

health (Insel et al., 2010). Binge-like eating was modelled using an eating in the absence of hunger paradigm in which participants first consumed a pasta meal to satiety and were then offered palatable cookies to consume *ad libitum* (Thomas et al., 2018). Satiety and reward processes were assessed by examining specific components of eating behaviour using a universal eating monitor that measures the timing of individual bouts of eating (Kissileff et al. 1980; Yeomans, 1996). Previous studies have established that an increase in satiety is reflected in a decrease in eating rate whereas reduced reward is reflected in decreased palatability responses at the start of a meal (Thomas et al., 2014; Yeomans & Gray, 1997). Impulsivity was assessed using a delay discounting and a stop-signal task (Logan, 1994; Mazur, 1987) and responses on a continuous performance task. Responses to emotional stimuli were assessed using the P1vital® Oxford Emotional Test Battery (Harmer et al., 2009; Thomas et al., 2016). Attentional processing was assessed using a sustained attention task and working memory was indexed via performance on an n-back task (Kirchner, 1958). Participants also underwent functional imaging using fMRI scanning but the fMRI portion of this study is omitted in this chapter, as it is not the focus of this thesis. We hypothesised that participants would consume less of the pasta meal and the cookies in the LDX condition than the placebo condition and that eating rate and palatability ratings would also decrease in the LDX condition compared to the placebo condition. We further hypothesized that LDX would improve performance on cognitive tasks compared to placebo.

4.2 Materials and Methods

4.2.1 Participants

Twenty-three participants took part in this study. Sample size was based on the results of a similar study that assessed the effects of the 5-HT_{2C} receptor agonist meta-chlorophenylpiperazine (mCPP) on food intake in women (effect size of 0.67) (Thomas et al.,

2018). A power analysis performed using G*power 3.1.9.7 (Faul et al., 2009) indicated a sample size of 20 participants was needed to obtain 80% power. To allow for a smaller effect size and for dropouts, we aimed to recruit 35 participants. However, due to the global pandemic caused by the novel coronavirus SARS-CoV-2, all in-person data collection was halted, and the resulting sample size was 22. Therefore, effect sizes are presented with all statistical outcomes. One participant withdrew from the study due to vomiting. Unblinding revealed the participant had received LDX on this test day. Therefore, the final sample size consisted of twenty-two females (*M* age = 24.41 ± 6.87, *M* BMI = 26.35 ± 4.98).

Participants were invited to take part if they met all of the inclusion criteria: aged 18-55; female; fluent English speaking; minimum BMI of 18.5 and maximum weight of 152.4kg (fMRI weight capacity); binge-eating symptoms as determined by the Binge Eating Scale (Gormally et al., 1982) (see below); and medical clearance from a physician. Participants were excluded if they had symptoms or current diagnosis of Bulimia Nervosa or Anorexia Nervosa, treatment (i.e., psychotherapy or pharmacotherapy) for BED in the last 3 months, metabolic disorder, current psychological disorder, substance use disorder, neurological disorder, intake of any medication that interferes with LDX, current smoking, current pregnancy or breastfeeding, a positive breathalyser test on the morning of testing, food allergies related to the study, vegan or vegetarian diet, disliking of the test foods, and MRI-related exclusion criteria. Fifty-seven participants underwent screening, but thirty-four participants were ineligible to attend a test day due to the following reasons: left-handed (n=2), not responding to scheduling requests (n=6), food restriction habits more indicative of Bulimia Nervosa (n=1), currently taking anxiety medication (n=1), vegetarian diet (n=1), class schedule conflicted with test days (n=1), < 18 score on BES (n=1), withdrew from university (n=1), not attending the test day (n=5), current psychological

symptoms/disorder (n=2), unable to attend scheduled session due to onset of COVID-19 pandemic restrictions (n=3), and the remaining participants exhibited abnormal cardiac readings (n=10), but this could have been due to a faulty electrocardiogram or reading of the results.

Participants were recruited from the West Midlands area via posters and social media platforms. The study was advertised under the guise 'Lisdexamfetamine dimesylate, taste, and brain activity' to avoid demand characteristics. Participants received £125 compensation for completion of the study. This study was approved by the University of Birmingham Research Ethics Committee and the National Research Ethics Service and was conducted in accordance with the principles outlined in the 1964 Declaration of Helsinki. All participants gave written informed consent to participate.

This study was pre-registered on ClinicalTrials.gov (Identifier: NCT04181957).

4.2.2 Design and Dosing

This study used a double-blind, placebo-controlled, crossover, design. Participants were randomised immediately after the screening days to receive oral LDX (50 mg) in a single morning dose, or placebo, in a counterbalanced order. The LDX and placebo were prepared by Guy's and St Thomas' NHS Foundation Trust Pharmacy Manufacturing Unit. Both LDX and placebo were prepared in identical capsules to maintain blinding. Previous research indicates that 50mg LDX is a clinically effective dose with few side effects (McElroy, Hudson, et al., 2016; McElroy, Mitchell, et al., 2016). Pharmacokinetic studies with LDX have demonstrated variable maximum d-amphetamine plasma concentrations in humans following oral administration. When a sample of older adults was given 50mg of LDX, peak d-amphetamine plasma levels were reached at 3.5-5.5 hours for men and women (Ermer et al., 2013). Similar results were found after single doses of 50-250mg of LDX, in which median d-amphetamine max concentration occurred at 4 to 6 hours post-

dosing (Ermer et al., 2010). Additional research also suggests a gradual concentration rise of d-amphetamine with observed peak levels at 3.5 hours post-dosing (Krishnan & Stark, 2008; Najib, 2009). For this study, peak d-amphetamine concentration was anticipated to be approximately 3.5 hours post-dose and blood samples were taken to confirm drug levels. Participants had a two-hour wait following drug administration so that peak plasma levels were achieved during the fMRI scan (not presented in this thesis) and the intake measures. All participants underwent two sessions on two separate days at least 7 days apart to allow for drug washout.

4.2.3 Questionnaires

4.3.3.1 Screening Questionnaires

The Structured Clinical Interview for DSM-5, Clinical Version (SCID-CV)*:* See Chapter 2 methods section for a full description of the questionnaire.

Binge Eating Scale (BES): The Binge Eating Scale (BES) is a 16-item questionnaire that indicates severity of binge-eating symptoms (Gormally et al., 1982). The BES has been shown to be a reliable tool for identifying women with clinically significant binge-eating symptoms within a community sample (Duarte et al., 2015). The BES was used to determine the presence of binge-eating symptoms. Participants were eligible to take part if they had a Moderate score (18-26) or Severe score (27-46). The BES has good test-retest reliability ($r = 0.87$, $p < .001$) and moderate associations with binge-eating severity measured subjectively and objectively (≥ 1,000 kilocalories) via food records ($r = 0.20\text{-}0.40$, $p < 0.05$) (Timmerman, 1999).

4.2.3.2 Test Day Questionnaires

The following questionnaires were used to characterize the sample:

The Dutch Eating Behaviour Questionnaire (DEBQ): See Chapter 2 methods section for a full description of the questionnaire.

Beck Depression Inventory – II (BDI-II): See Chapter 2 methods section for a full description of the questionnaire.

Barratt's Impulsiveness Scale (BIS-11): The BIS is a 30-item questionnaire that assesses trait impulsiveness and comprises three factors: attention impulsiveness, motor impulsiveness, and non-planning impulsiveness (Patton et al., 1995). After one-month follow-up, total score Cronbach's alpha was 0.83 ($r = 0.83$, $p < .001$) indicating good internal consistency and test-retest reliability (Stanford et al., 2009).

Visual Analogue Scales (VAS) assessing mood and physical state: See Chapter 2 methods section for a full description of the questionnaire. VAS were administered nine times throughout the test day.

4.2.4 Tasks/Instruments

4.2.4.1 P1vital® Oxford Emotional Test Battery (ETB)

The ETB (see www.p1vital.com) is a computerised battery that comprises validated cognitive tasks to determine emotional bias (Murphy et al., 2008; Thomas et al., 2016). It has been validated in previous drug studies to measure emotional changes in response to acute drug dosing (Harmer et al., 2009).

Facial expression recognition task (FERT): Faces with one of six emotional expressions (happiness, fear, anger, disgust, sadness, and surprise) or a neutral expression appeared on a black background screen. The faces were morphed from neutral to full expressions in 10% increments to foster ambiguity about the expression being displayed. Each intensity was represented 4 times, along with 10 presentations of neutral expressions totaling 250 stimuli. Each stimulus was presented for 500ms, followed by a blank screen. The participant was instructed to classify each expression as quickly and as accurately as

possible by clicking on the appropriate emotion adjective in the dialogue box. Percentage accuracy is reported for correctly classifying the facial expression, and RT for correct responses were recorded by valence. Commission errors (incorrectly classifying a facial expression) are reported as percentage incorrectly recognised by valence.

Emotional categorisation task (ECAT); *Emotional recall task (EREC)*; *Emotional recognition memory task (EMEM)*: See Chapter 2 methods section for a full description of these tasks.

4.2.4.2 Stop Signal Task (SST)

The SST is a measure of response inhibition (Verbruggen et al., 2008). This task was adapted from the STOP-IT software programmed by Verbruggen et al. (2008). During the no-signal trials, a white arrow is presented on a black background pointing either left or right until the participant responds or until the maximum presentation of 1,250 milliseconds. The participant is instructed to indicate the direction of the arrow using the left and right keys on the keyboard. When the arrow turned blue in colour (stop-signal trial), the participant was instructed not to respond. The blue arrow in stop-signal trials is initially presented for 250 milliseconds and this delay is then adjusted continuously using the staircase tracking procedure whereby the personalised adjusted score is the stop signal delay (SSD). The experiment consists of 3 blocks of 64 trials in which 75% of the trials are no-signal trials. An estimation of the RT on stop-signal trials (SSRT) is calculated by subtracting mean SSD from mean RT. Omission and commission errors, and RT for no-signal and stop-signal trials (SSRT), and SSD were calculated.

4.2.4.3 N-back

See Chapter 2 methods section for a full description of the task.

4.2.4.4 Continuous Performance Test

This task, which is modelled after the Conner's Continuous Performance Task, involves a series of white letters being presented on a grey background in random order (Advokat et al., 2007; Mesquita et al., 2016). Participants were instructed to press the space bar for every letter (target) except 'X' (non-target). Letters were presented for 900ms. The 'X'/non-target trials appeared in 42 (5%) of the 830 trials. The task duration was 14 minutes. An average of the RT standard deviations was calculated to measure response time variability (RTV). Increased RTV is considered to reflect poorer ability to sustain attention (Barkley, 1997). Analysis of commission errors in this task also provide a measure of impulsive responding, while omission errors provide a measure of inattention (Conners, 2014). Errors (omission and commission) and RT for target and non-target trials and RTV were calculated.

4.2.4.5 Universal Eating Monitor (UEM)

The universal eating monitor procedure was previously described (see Chapter 2 Methods section). For this study, participants consumed pasta with VAS similarly appearing after every 30g of pasta was consumed. The cookie snack followed the same procedure as that reported in Chapter 2.

4.2.5 Test Meals

Lunch consisted of pasta shells in a tomato and herb sauce (both Sainsbury's brand) served at 55-60 ºC. This meal was previously described by Thomas et al. (2014) and comprises 233 kilocalories per 200g. After 150 g had been consumed, the participants were interrupted, and the plate was replaced with a fresh 200 g plate of pasta. Participants were instructed to continue

to eat as many plates as they wished until they were comfortably full. The participants also completed computerised visual analogue scale (VAS) ratings (hunger, fullness and pleasantness of the pasta).

Maryland brand chocolate chip cookies were offered *ad libitum* 15 minutes after the pasta meal. Participants were served a bowl containing 80 grams (approximately 407 kilocalories) of cookies broken into bite-size amounts to avoid participants tracking the amount consumed. When 60 grams of cookies were consumed, participants were provided with a fresh bowl containing 80g and could continue in this manner until they wished to stop eating. Computerised visual analogue scale (VAS) ratings were also completed as described above. For both pasta and cookie intake, participants were informed that the intake was a taste test, but that they could eat as much as they would like.

4.2.6 Blood levels of d-amphetamine

Three 3 mL blood samples (see timings in procedure) were collected via venipuncture for assessment of d-amphetamine concentration (mg/L). Samples were centrifuged at 1500g for 15 minutes and were then stored at -20˚C until analysis by Analytical Services International Ltd. Samples were analysed by liquid chromatography tandem mass spectrometry (LC-MS/MS). The results confirmed no presence of d-amphetamine in baseline blood samples.

4.2.7 Procedure

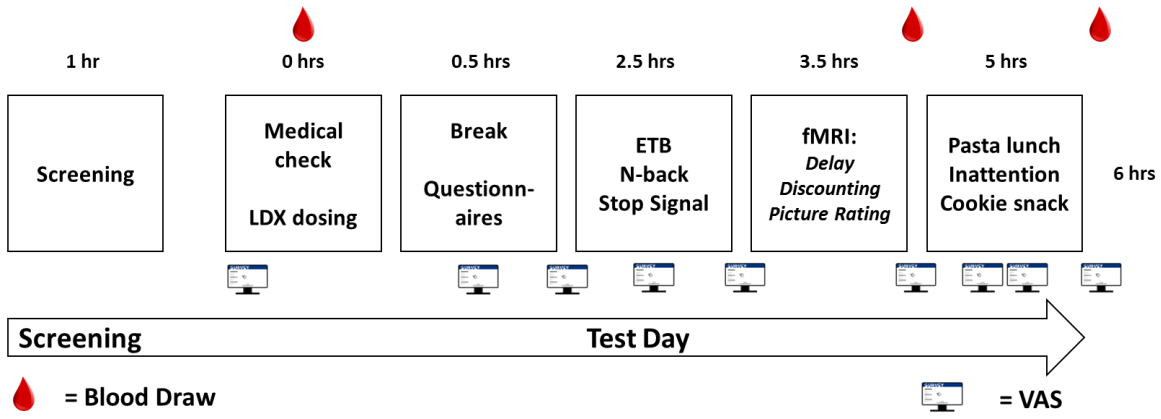
Prior to the study, all participants attended a screening session to ensure eligibility. The screening session included collection of height and weight (to calculate BMI) and completion of the SCID-CV. Participants were assessed by a physician to determine medical fitness.

Participants arrived at the testing site at 8:30 or 9:00. To standardise hunger levels, participants were instructed to eat their usual breakfast prior to arriving. A urine-sample was

collected for the pregnancy test and a breathalyser test was taken to ensure alcohol abstinence. A baseline blood sample was taken. Participants completed the first VAS and then the LDX or placebo capsule was self-administered. After administration, participants waited in a designated area for two hours for drug absorption before beginning cognitive tasks. During the break, participants completed the following questionnaires: DEBQ, BIS, and second VAS.

After the two-hour wait, participants completed the following tasks in order: third VAS, ETB, fourth VAS, SST, n-back, and a fifth VAS. Participants then underwent an fMRI scan for 1.5 hours. During the scan, participants completed a delay discounting task and a picture rating task. After the fMRI scan, a second blood draw was taken and a sixth VAS was completed. Participants then consumed lunch on the UEM and completed a seventh VAS. Then participants completed the inattention task and an eighth VAS before consuming the cookie snack on the UEM. A final blood sample and VAS (VAS 9) was taken before the participant was debriefed (see Figure 13 for a summary of the test day).

Figure 13: Timeline of the test day



4.2.8 Data and Statistical Analysis

Performance based exclusion criteria were determined prior to data analysis. Cognitive data with RTs below 200ms and ≥ 6000ms were removed. For the cognitive tasks, outliers within 3*interquartile range of the lower and upper grand mean values were removed. Because there is a 50% chance for accuracy on the EMEM and N-back tasks, scores at or below 50% on each task were removed for unreliable responding, which resulted in smaller degrees of freedom for these tasks. All data were analysed using IBM SPSS 26 software. Unless noted otherwise, the data were analysed using paired samples t-tests and repeated measures ANOVA. In cases where time or stimuli were factors, data were analysed using factorial repeated measures ANOVA where drug condition (LDX or placebo) was factor one and time or stimuli was factor two. Main effects and interactions that did not involve drug condition are not reported or analysed further. Violations of sphericity were addressed using the Greenhouse-Geisser correction. A test was deemed statistically significant if $p < 0.05$. *Post-hoc* paired samples *t*-tests were computed if an interaction was significant. After missing VAS responses were determined to be random, regression imputations were used to replace missing data. Using the factor structure calculated by Thomas et al. (2014), VAS factors consisted of 'Arousal' (alertness, drowsiness, and happiness), 'Appetite' (hunger, fullness, and desire to eat), 'Negative Effects' (disgust, anxiety, sadness, and withdrawn), 'Physical Effects' (lightheaded, nausea, and faint) (Thomas et al., 2014). Though thirst was reported as a negative effect by Thomas et al. (2014), thirst was treated as a separate factor in this study, as thirst does not always theoretically indicate a negative effect. VAS factors were converted to AUC using the trapezoid method. Due to the unintended smaller sample size obtained, the preplanned mediation analysis to statistically determine the mechanism(s) of action for the effects of LDX on food intake was unfeasible. Therefore,

exploratory correlation analyses on significant outcomes presumed to underlie food intake effects were performed in place of a mediation analysis to determine LDX mechanism of action. Where these analyses are performed, the variables are placebo minus LDX to determine LDX-specific effects on each measure.

4.3 Results

3.1 Demographics

Participant demographics included age, BMI, and scores on the BES, DEBQ, BDI, and BIS (see Table 6). The majority (59%) of the sample scored Severe on the BES.

Table 6. Participant characteristics

Characteristic ($N = 22$)	$M(\pm SD)$	Min & Max Score
Age	24.41(6.87)	18-49
BMI	26.35(4.98)	19.5-41
BES (0-46)	28.36(6.59)	18-40
DEBQ (1-5)		
Restraint	2.99(0.55)	1.6-3.7
External Eating	3.92(0.44)	2.8-4.6
Emotional Eating	3.52(0.71)	2-4.62
BDI (0-63)	11.80(6.24)	1-26
BIS		
Total (30-120)	68.7(10.05)	44-86
Attention (8-32)	17.70(4.32)	10-26
Motor (11-44)	24.55(4.36)	15-36
Non-planning (11-44)	26.45(4.06)	15-32

Table 6. Factors expressed with measure's range in parentheses. Mean and ± standard deviation of the data presented alongside each measure's minimum and maximum score obtained. BMI: Body Mass Index; BES: Binge Eating Scale; DEBQ: Dutch Eating Behaviour Questionnaire; BDI: Beck Depression Inventory; BIS: Barratt Impulsiveness Scale

4.3.2 Food Intake

The main effect of drug condition on food intake was significant ($F(1, 21) = 11.65$, $p < 0.01$, $\eta_p^2 = 0.36$), and the interaction between drug condition and food type (pasta and cookies) was also significant ($F(1, 21) = 4.42$, $p = 0.048$, $\eta_p^2 = 0.17$). Follow-up t-tests showed that LDX reduced intake of both the pasta ($t(21) = -2.83$, $p = 0.01$, $d = 0.52$) and the cookies ($t(21) = -4.28$,

$p < 0.01$, $d = 0.65$). The difference in percentage decrease between pasta and cookie intake was not statistically significant ($t(20) = -1.51$, $p = 0.15$), but the effect size was larger for cookies ($d = 0.65$) than for pasta intake ($d = 0.52$) (see Figure 14).

Figure 14: Food Intake Results

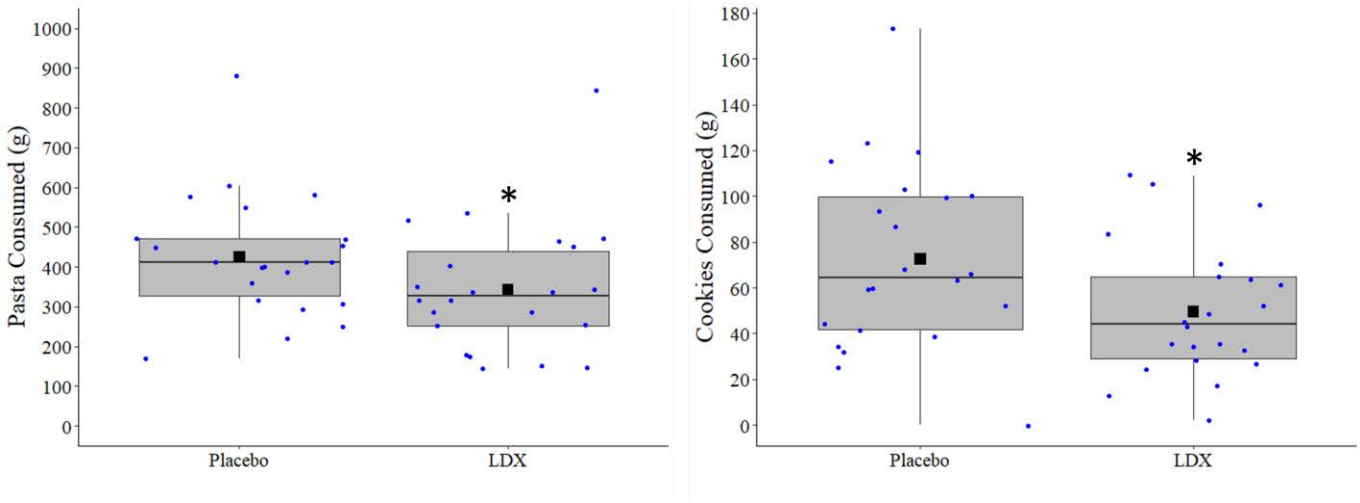


Figure 14. Intake (grams) data presented with squares denoting means and dots representing individual data points. Asterisks denote significance at $p < 0.05$ level.

4.3.2.1 Liking Ratings

The main effect of drug condition on liking ratings was not significant ($F(1, 21) = 1.67$, $p = 0.21$, $\eta_p^2 = 0.07$) and neither was the interaction between drug condition and food type ($F(1, 21) = 2.39$, $p = 0.14$, $\eta_p^2 = 0.10$), nor the interaction between drug condition and time (beginning of meal and end of meal) ($F(1, 21) = .43$, $p = 0.52$, $\eta_p^2 = 0 .02$). The interaction between drug condition, food type, and time was near-significant ($F(1, 21) = 4.24$, $p = 0.05$, $\eta_p^2 = 0.17$).

Follow-up tests revealed that pasta was rated as less pleasant at the end of the meal after LDX ($t(21) = -2.57$, $p = 0.018$) but not at the start of the meal (see Figure 15).

Figure 15: Liking Ratings for Pasta and Cookies

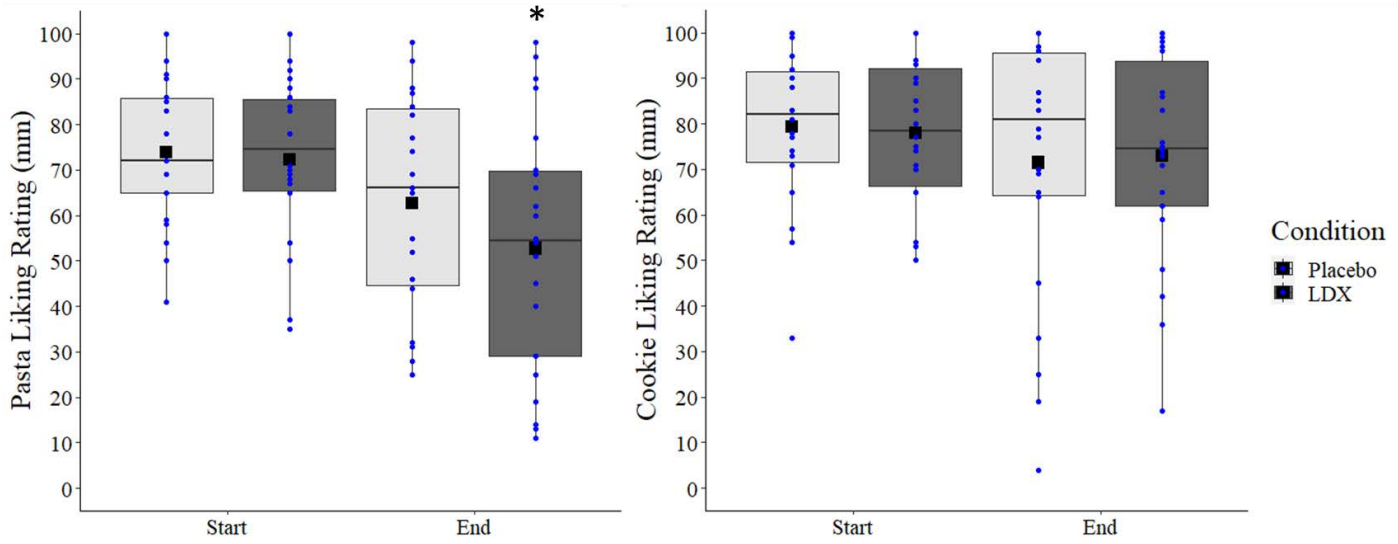


Figure 15. Liking ratings (mm) for pasta and cookies with squares denoting means and dots representing individual data. Light grey fill indicates the placebo condition while dark grey fill indicates the LDX condition. Asterisks denote significance at $p < 0.05$ level.

4.3.2.2 Eating Rate

The main effect of drug condition on eating rate was significant ($F(1, 20) = 16.53$, $p < 0.01$, $\eta_p^2 = 0.45$) as was the interaction between drug condition and food type ($F(1, 20) = 5.80$, $p = 0.03$, $\eta_p^2 = 0.23$). Follow-up tests indicated participants ate fewer grams per minute after LDX for pasta only ($t(21) = -3.14$, $p = 0.01$, $d = 0.46$) (see Figure 16).

Figure 16: Eating Rate for Pasta and Cookies

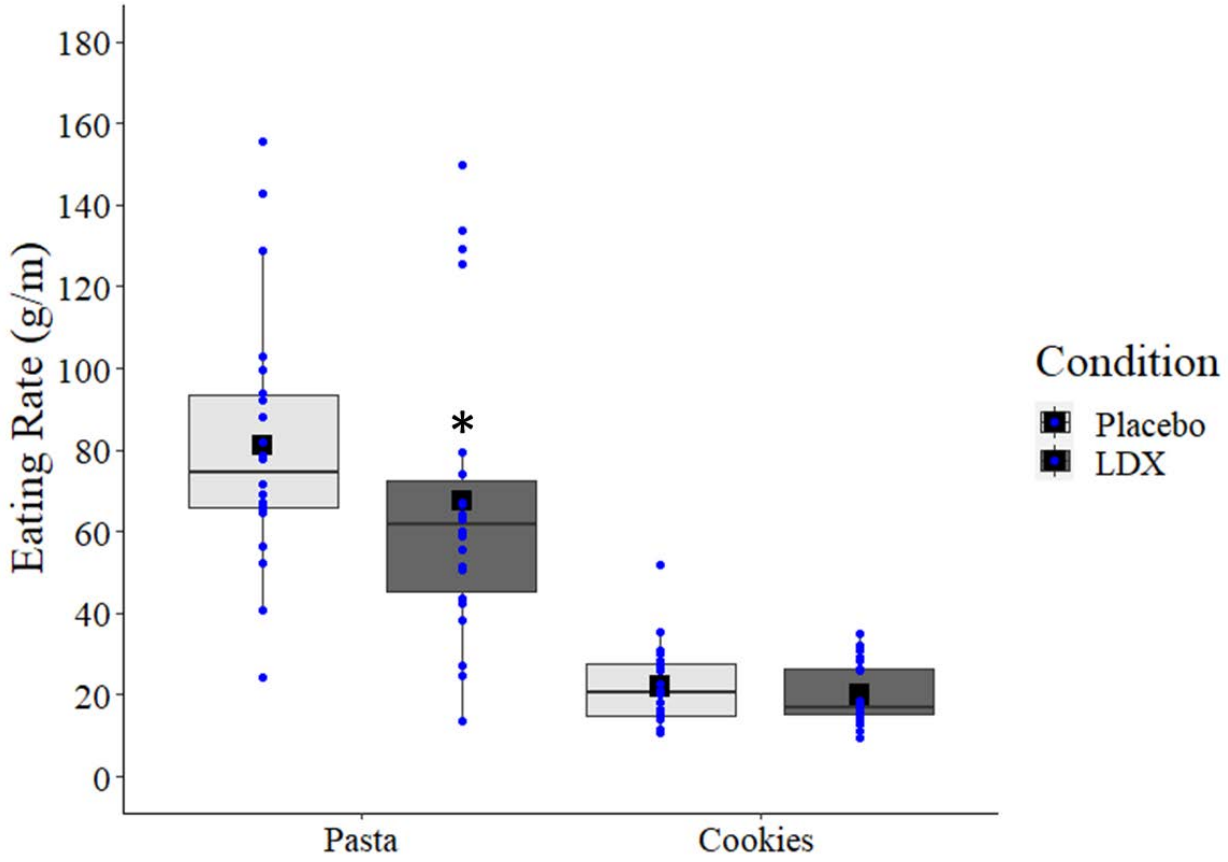


Figure 16. Eating rate (grams/minutes) for pasta and cookies with squares denoting means and dots representing individual data. Light grey fill indicates the placebo condition while dark grey fill indicates the LDX condition. Asterisks denote significance at $p < 0.05$ level.

4.3.3 Mood

Analysis of pre-dose VAS ratings revealed no statistical differences ($p > 0.05$) between drug conditions. LDX increased post-dose ratings of arousal ($t(21) = 3.11$, $p = 0.01$, $d = 0.46$) and physical effects ($t(21) = 3.11$, $p = 0.01$, $d = 0.28$). LDX reduced appetite compared to placebo ($t(21) = -6.62$, $p < 0.01$, $d = 1.18$). LDX near-significantly increased ratings of negative effects ($t(21) = 2.07$, $p = 0.05$, $d = 0.38$). The difference between LDX and placebo on ratings of thirst was not statistically different ($t(21) = 3.11$, $p = 0.17$, $d = 0.27$) (See Figure 17).

Figure 17: VAS Ratings

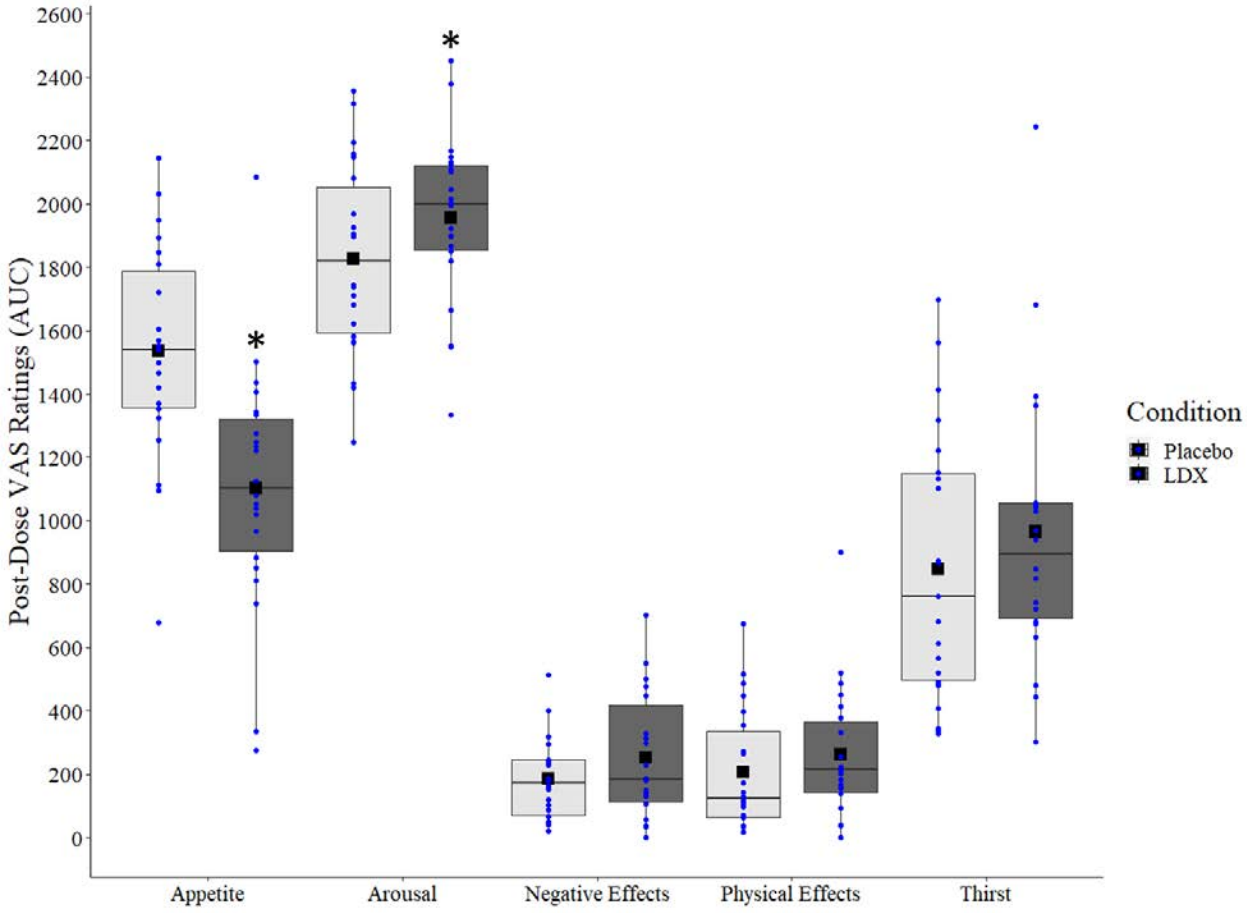


Figure 17. Visual Analogue Scales (VAS) ratings with squares denoting means and dots representing individual data for area under the curve (AUC). Light grey fill indicates the placebo condition while dark grey fill indicates the LDX condition. Asterisks denote significance at $p < 0.05$ level. The main effect of drug condition was statistically significant.

4.3.4 Cognition

4.3.4.1 ETB

ETB – FERT: Neither the main effect of drug condition on accuracy ($F(1, 18) = 0.95$, $p = 0.34$, $\eta_p^2 = 0.05$), commission errors ($F(1, 19) = 0.43$, $p = 0.52$, $\eta_p^2 = 0.02$), and RT ($F(1, 18) = 2.21$, $p = 0.15$, $\eta_p^2 = 0.11$) was statistically significant, nor were the interactions between drug

condition and valence for accuracy ($F(4, 65) = 1.81$, $p = 0.14$, $\eta_p^2 = 0.09$), commission errors ($F(2, 42) = 0.13$, $p = 0.90$, $\eta_p^2 = 0.01$), and RT ($F(4, 70) = 0.98$, $p = 0.43$, $\eta_p^2 = 0.05$) (see Table 7).

ETB – ECAT: There was no main effect of drug condition on accuracy ($F(1, 21) = 0.48$, $p = 0.50$, $\eta_p^2 = 0.02$), nor an interaction between drug condition and stimulus valence (positive and negative) ($F(1, 21) = 0.48$, $p = 0.50$, $\eta_p^2 = 0.02$). LDX reduced RT ($F(1, 20) = 10.42$, $p < 0.01$, $\eta_p^2 = 0.34$). The interaction between drug condition and valence on RT was not statistically significant ($F(1, 20) = 1.70$, $p = 0.21$, $\eta_p^2 = 0.08$).

ETB – EREC: The main effect of drug condition ($F(1, 21) = 0.03$, $p = 0.86$, $\eta_p^2 < 0.01$) and the interaction between drug condition and valence ($F(1, 21) = 0.95$, $p = 0.34$, $\eta_p^2 = 0.04$) were not statistically significant. The main effect of drug condition ($F(1, 21) = 0.01$, $p = 0.92$, $\eta_p^2 < 0.01$) and the interaction between drug condition and valence on commission errors ($F(1, 21) = 0.54$, $p = 0.47$, $\eta_p^2 = 0.03$) were not statistically significant (see Table 7).

ETB – EMEM: The main effect of drug condition on accuracy was not statistically significant ($F(1, 16) = 1.88$, $p = 0.19$, $\eta_p^2 = 0.11$), nor was the interaction between drug condition and valence ($F(1, 16) = 0.002$, $p = 0.96$, $\eta_p^2 < 0.01$). The main effect of drug condition ($F(1, 21) = 0.01$, $p = 0.92$, $\eta_p^2 < 0.01$) and interaction between drug condition and valence ($F(1, 21) = 2.42$, $p = 0.14$, $\eta_p^2 = 0.10$) on RT was not statistically significant. The main effect ($F(1, 20) = 0.42$, $p = 0.53$, $\eta_p^2 = 0.02$) and interaction between drug condition and valence ($F(1, 17) = 0.20$, $p = 0.89$, $\eta_p^2 < 0.01$) on commission errors was not statistically significant (see Table 7).

Table 7: ETB Tasks Results

		Negative Valence		Positive Valence	
ETB Task	Measure	Placebo	LDX	Placebo	LDX
Emotional Categorisation (ECAT)	Accuracy (%)	96.82 (4.77)	95.45 (8.00)	94.32 (5.63)	94.55 (5.75)
	Reaction time (ms)	1476.38 (271.73)	1317.43 (157.77)	1353.95 (207.15)	1239.52 (148.83)
Emotional Recall (EREC)	Correct words	3.45 (1.92)	3.91 (1.77)	6.68 (3.17)	6.10 (2.39)
	Commission	1.23 (1.57)	1.41 (1.76)	2.50 (2.11)	2.23 (2.18)
Emotional Recognition	Accuracy (%)	80.44 (8.26)	83.09 (3.81)	83.24 (7.33)	86.03 (6.85)
Memory (EMEM)	Commission (%)	18.89 (8.50)	17.64 (4.81)	16.39 (7.29)	14.72 (7.37)
	Reaction time (ms)	1401.18 (324.68)	1442.10 (339.11)	1401.27 (336.87)	1372.73 (311.32)

Facial Expression Recognition Task (FERT)

	Accuracy (%)		Commission Errors (%)		Reaction Time (ms)	
Valence	Placebo	LDX	Placebo	LDX	Placebo	LDX
Neutral	87.57 (7.13)	81.12 (11.01)	27.44 (4.49)	27.90 (5.67)	1545.48 (220.90)	1622.27 (324.28)
Sad	67.26 (9.54)	71.69 (8.53)	3.89 (2.16)	3.93 (3.34)	1471.17 (135.83)	1565.48 (170.06)
Anger	61.20 (10.58)	63.31 (10.58)	1.92 (1.64)	2.02 (2.22)	1828.00 (256.12)	1876.18 (261.95)
Disgust	70.00 (10.82)	70.28 (7.34)	1.54 (1.63)	1.61 (1.19)	1797.05 (325.49)	1781.15 (283.52)
Fear	52.89 (14.10)	50.87 (15.68)	1.20 (0.93)	1.07 (0.88)	2103.84 (328.22)	2231.83 (386.78)
Surprise	69.08 (6.48)	68.99 (7.43)	3.09 (3.04)	3.53 (2.99)	1621.35 (236.09)	1738.98 (415.28)
Happy	54.18 (10.46)	49.47 (9.24)	0.86 (0.90)	0.77 (0.73)	1607.28 (150.84)	1688.25 (222.87)

Table 7. Mean and ± standard deviation presented for Emotional Test Battery (ETB) results. LDX reduced reaction time for negatively and positively valenced words in the ECAT.

4.3.4.2 N-back

The difference between the 2 and 3-back stimuli on accuracy was significant ($F(1, 15) = 11.55$, $p < 0.01$, $\eta_p^2 = 0.44$). As expected, participants were more accurate at responding to the 2-back stimuli than the 3-back stimuli. The main effect of condition on n-back accuracy was not statistically significant ($F(1, 15) = 0.11$, $p = 0.75$, $\eta_p^2 = 0.01$), nor was the interaction between drug condition and stimulus type (2-back versus 3-back) ($F(1, 15) = 0.50$, $p = 0.49$, $\eta_p^2 = 0.03$).The main effect of LDX on reaction time was not statistically significant ($F(1, 21) = 0.14$,

$p = 0.71$, $\eta_p^2 = 0.01$), nor was the interaction between drug condition and stimulus type ($F(1, 21) = 0.69$, $p = 0.42$, $\eta_p^2 = 0.03$) (see Table 8).

Table 8: N-Back Accuracy and Reaction Time Results

	Placebo ($N = 22$)		LDX ($N = 22$)	
Stimulus	Accuracy (%)	RT (ms)	Accuracy (%)	RT (ms)
2-Back	83.88(10.83)	712.55(219.76)	84.63(10.26)	689.83(208.61)
3-Back	76.63(13.96)	726.16(246.00)	74.25(12.67)	725.55(237.97)

Table 8. Means and ± standard deviations of 2-back and 3-back accuracy (%) and reaction time (RT; ms) results.

4.3.4.3 Stop Signal Task

LDX had no statistical effect on no-signal omission errors ($t(19) = 0.67$, $p = 0.51$, $d = 0.15$), nor no-signal RT ($t(20) = 1.59$, $p = 0.13$, $d = 0.35$). The effect of LDX on stop-signal commission errors ($t(20) = -1.97$, $p = 0.06$, $d = 0.43$) was near-significant, in which LDX reduced commission errors. LDX had no statistical effect on SSD ($t(20) = 1.20$ $p = 0.24$, $d = 0.26$), nor SSRT ($t(19) = -0.15$, $p = 0.88$, $d = -0.03$) (see Table 9).

Table 9: Stop Signal Task Results

Measure	Placebo *Mean* (±SD)	LDX *Mean* (±SD)
No-signal omission error (%)	5.66(6.70)	6.58 (5.56)
No-signal RT (ms)	919.66(263.97)	989.26 (255.73)
Stop-signal commission error (%)	47.11 (2.73)	45.88 (2.54)
Stop-signal RT (SSRT; ms)	194.71 (31.58)	192.33 (60.18)
Stop-signal delay (SSD; ms)	723.56 (281.04)	786.31 (270.69)

Table 9. Stop-signal task (SST) results presented as means and ± standard deviation. RT: reaction time.

4.3.4.4 Continuous Performance Task

LDX had no effect on target (non-X trials) omission errors ($t(18) = -0.52$, $p = 0.61$, $d = -0.12$) nor target RT ($t(19) = 1.46$, $p = 0.16$, $d = 0.33$). For non-target trials (X trials), LDX reduced commission errors ($t(19) = -2.11$, $p = 0.048$, $d = -0.47$). LDX also reduced RTV ($t(19) = -2.23$, $p = 0.04$, $d = -0.50$) (see Table 10). In an exploratory correlation analysis, neither pasta intake ($r(20) = -0.28$, $p = 0.23$) nor cookie intake ($r(20) = -0.04$, $p = 0.86$) correlated with commission errors. For RTV, pasta intake did not correlate ($r(20) = 0.20$, $p = 0.36$), but the correlation between cookie intake and RTV was near-significant ($r(20) = 0.43$, $p = 0.06$) whereby improved sustained attention after LDX was associated with lower consumption of cookies after LDX.

Table 10: Inattention Task Results

Measure	Placebo *Mean* (±SD)	LDX *Mean* (±SD)
Target omission errors (%)	3.75(1.48)	3.58(0.69)
Target reaction time (ms)	340.91(43.85)	349.32(36.23)
Non-target commission errors (%)	39.29(17.37)	31.31(14.35)*
RTV (ms)	123.03(28.53)	108.09(28.30)*

Table 10. Inattention data presented as means and ± standard deviation. RTV: response time variability. Asterisks denote significance at $p < .05$ level.

4.3.5 Plasma D-amphetamine Concentration

The concentration of d-amphetamine was 0.05 (SD = 0.01) mg/L at 275 minutes post-dose and 0.06 (SD = 0.01) mg/L at 325 minutes post-dose. This is within the reference d-

amphetamine concentration for clinical efficacy of 0.044-0.08 in healthy adults dosed with 50-70mg LDX (Ermer et al., 2016).

4.4 Discussion

LDX has been found to be effective in treating binge-eating symptoms in adolescents and adults (Guerdjikova et al., 2019; McElroy, Hudson, et al., 2016; Srivastava et al., 2019), but the mechanisms underlying the efficacy of the drug are largely unknown. Determination of the mechanism of action of LDX may aid in the development of improved BED pharmacotherapies. To this end, we investigated the effects of acute administration of 50mg LDX to women with binge-eating symptomatology on food intake and measures of reward, cognition, and emotion. LDX reduced intake of both pasta and cookies. Participants ate fewer grams per minute of pasta in the LDX condition than in the placebo condition and ratings of palatability for pasta were significantly reduced in the LDX condition at the end of the meal. There were no effects of LDX on eating rate or palatability for cookies. Appetite ratings were reduced after LDX and ratings of arousal and physical effects (lightheaded, nausea, and faint) were increased. LDX did not affect performance on the n-back task but did improve sustained attention and reduced impulsive responding.

The finding that LDX reduced both the pasta meal and the cookie snack eaten in the absence of hunger suggests that the drug may have a dual effect to enhance satiety as well as reduce reward-driven eating. This conclusion is also supported by the effects of LDX on specific components of eating. The action of LDX to reduce the rate at which the pasta meal was consumed is consistent with a drug induced enhancement of satiety (Halford et al., 2010; Thomas et al., 2018). LDX did not reduce the initial rated palatability of pasta but did reduce rated palatability at the end of the meal, which suggests that it may have accelerated satiety-induced reductions in the pleasantness of food (Cabanac, 1971). In addition, LDX reduced intake of cookies that were offered after participants had become satiated and this effect was not

associated with a decrease in eating rate. These data suggest that LDX also decreases hedonically-motivated consumption of a highly palatable food eaten in the absence of hunger. A review and meta-analysis of the effects of LDX on feeding in rodents similarly found that the drug reduces the intake of both standard lab chow and palatable food in binge-eating models (see Chapter 3). Taken together, these data suggest that LDX may be effective in reducing binge eating because the motivation to consume highly palatable binge foods is reduced but also because the drug enhances satiety.

It is unlikely that the effects of LDX to reduce food intake are explained by adverse effects on mood and physical state. LDX increased ratings of arousal and physical symptoms, which is consistent with previous reports from clinical studies (Dolder et al., 2018; Guerdjikova et al., 2016; Hudson et al., 2017b; McElroy, Hudson, et al., 2015, 2016). However, the relatively low occurrence reported in RCTs and the relatively low reporting of physical symptoms in the current study indicates that physical symptoms are not a primary cause for the reduction in food intake observed in this study. In addition, the lack of effect of LDX on the ETB measures suggests that the drug was not inducing any anxiety or depression-like responses that could account for the changes in intake.

It is possible that the effects of LDX on cookie intake may be explained at least in part by a drug-induced reduction in impulsivity/improvement in attention. In this study, impulsivity and sustained attention were assessed using the Stop Signal Task (SST) and Conners' Continuous Performance Task (CPT). On the CPT, LDX significantly reduced commission errors that are indicative of impulsive responding, suggesting that LDX improves response inhibition. This is significant given that response inhibition deficits are related to greater severity in eating pathology in BED (Svaldi et al., 2014). Conceptually, response inhibition could translate to an

increased ability to resist the action to binge eat once an urge is experienced. These findings mirror LDX-induced reductions in impulsivity reported in preclinical models of binge eating (Vickers et al., 2017) and clinical studies of participants with binge-eating symptoms (McElroy, Hudson, et al., 2015; McElroy, Mitchell, et al., 2016). LDX also improved sustained attention on the CPT, which may be linked to reduced binge-eating symptoms through attentive eating that has been linked to reduced consumption in healthy individuals (Alberts et al., 2012; Warren et al., 2017). Additionally, LDX might reduce intake through interoceptive changes. In individuals with ADHD symptoms, inattentive, but not hyperactive, symptoms correlated with lower levels of awareness and reliance on hunger/satiety cues and these interoceptive deficits mediated the relationship between inattentive symptoms and binge eating (Kaisari et al., 2018). Increased satiety on measures of pasta intake and eating rate may therefore reflect improved awareness of interoceptive signals. It is possible that LDX improves the ability to inhibit distractions thereby leading to more attentive eating and greater attention to internal satiety signals, but further research is needed to test this hypothesis.

In this study, LDX did not improve performance on a working memory task. A recent meta-analysis found conflicting results on working memory impairments in BED and attributed these inconsistent findings to underpowered sample sizes and heterogeneity in tasks and outcome measures (Gisbert Cury et al., 2020). LDX has been reported to improve working memory performance in non-binge-eating samples (Dupaul et al., 2012; Epperson et al., 2015), but these improvements were observed on subjective self-report measures. Dupaul et al. (2012) included a letter version of the n-back task ranging from 0-3 back and observed no effects of LDX on performance. Similarly, Shanmugan et al. (2017) reported working memory improvements following LDX treatment on self-report measures but not on a letter n-back task in menopausal

women with executive function difficulties. It is possible that the questionnaires incorporated by Dupaul et al. (2012) and Epperson et al. (2015) measure multiple cognitive facets (e.g., episodic memory) in addition to working memory and thus may measure a broader range of cognition compared to the n-back task.

On the ETB, LDX reduced RT for negatively and positively valenced words during the ECAT. This finding is in line with ample evidence that stimulants reduce processing speed (Marraccini et al., 2016). Importantly, this effect confirms that the drug was active at this point of the test day during completion of other cognitive tasks (i.e., n-back and SST). LDX had no effect on classification of emotional expressions. These results mirror those reported by Dolder et al. (2018), in which neither LDX nor d-amphetamine affected classification of neutral, happy, sad, angry, or fearful expressions in healthy subjects. LDX also had no effect on measures of emotional memory (EREC and EMEM), which likely reflects the drug's limited actions on mood, as mood changes were also not observed on the VAS. When these results are considered together, it appears that LDX does not significantly alter social cognition or emotional memory in women with binge-eating symptoms.

The current study sought to experimentally determine potential indicators to the mechanism action of LDX for treating of BED. The combined effects of LDX on food intake, self-report measures, and cognitive measures suggest a multi-faceted mechanism involving appetite, satiety, reward, and cognitive processes that are likely to be mediated by the drug's catecholaminergic and serotoninergic actions (see Chapter 3). Indeed, LDX increases the neurotransmission of dopamine, noradrenaline, and serotonin in rat prefrontal cortex (PFC) and striatum (Rowley et al., 2012; Rowley et al., 2014), areas of the brain associated with cognitive impairments and reward dysfunction respectively in BED (Kessler et al., 2016; Wang et al.,

2011). These results help to elucidate the mechanisms underlying BED, specifically the role of executive functioning in the onset and maintenance of the disorder. Improved understanding of BED mechanisms could lead to important advances in pharmacological and behavioural interventions that reduce symptoms with minimal adverse effects.

A significant strength of this study is the incorporation of multimodal measures, including detailed measures of appetite, that enabled insight into mechanisms of action. Another strength is the assessment of LDX in women with above threshold scores on a measure of binge-eating symptomatology in accordance with the RDoC initiative. The current study is not without limitations, however. We tested only one dose of LDX and given the reported inverted U-shaped dose-response curve for amphetamine and performance (Cools & D'Esposito, 2011), different effects might be seen at different doses. Additionally, the study included only women who comprise the majority of BED diagnoses, and it is unclear if men would exhibit the same pattern of results. Lastly, it is unclear if the timing of certain tasks in relation to drug peak affected the results. Blood samples were taken at only three time points during the study, so we do not have data on the plasma d-amphetamine levels when the ETB, n-back, and stop signal task were completed. We did find significant effects of LDX on performance in the ETB, but it is possible that the null effects of the drug on the n-back and SST could be explained by the drug not being at sufficient levels at the point the tasks were completed. Thus, future studies should consider more frequent blood sampling to exclude the possibility that any null effects are explained by insufficient drug levels. Future studies should also include a matched control group to determine if LDX has differential effects on individuals with above and below threshold scores on a measure of binge-eating symptomatology, as this has not been compared in humans. Formal mediation analyses should also be conducted on a larger sample size to determine if attentive

and/or impulsive processes explain the reduction in food intake by LDX. The correlation observed between cookie intake and sustained attention was near significant with a medium to large effect size, but future studies with larger sample sizes are needed to replicate these findings.

In summary, the results provide the first detailed behavioural profile of the effects of an acute dose of 50mg LDX in women with binge-eating symptomatology. LDX had multiple effects to enhance satiety and reduce food-reward related responding and to improve cognitive control. These data provide novel mechanistic insights into LDX in the context of binge eating and suggest that novel drugs to treat binge eating disorder might be most effective if they combine effects on appetite/satiety, reward, and cognitive processes.

Chapter 5: General Discussion

5.1 Introduction

The overall aim of this thesis was to better understand the neuropsychopharmacological, cognitive, and behavioural mechanisms that underlie eating and disordered eating, particularly in women who overeat. The specific aims of this research were to (1) To examine interactions between metabolic, hedonic, and cognitive processes in appetite and their relevance to obesity and BED. (2) To understand the potential role of weight in moderating the effects of insulin on eating. (3) To assess the evidence for the efficacy of LDX in the treatment of BED. (4) To explore the mechanisms underlying the actions of LDX in the treatment of BED. The achievements of these aims along with summaries of the major findings, strengths and limitations, and suggestions for future research are considered in this chapter. Finally, the wider theoretical and clinical implications for this research is discussed.

5.2 Overview of Findings

The study presented in Chapter 2 examined the effects of an acute dose of 160 IU insulin delivered IN to women with and without obesity on appetite, cognition, and reward processes. Previous reports have shown appetite reducing effects after acute IN insulin administration in lean individuals (Benedict et al., 2008; Jauch-Chara et al., 2012; Santiago & Hallschmid, 2017), but no study has measured IN insulin effects on food intake in women with obesity. Further, previous reports have suggested differential effects of IN insulin on men and women with women being less responsive to the anorexigenic effects on insulin (Benedict et al., 2008; Hallschmid et al., 2004), although acute 160 IU IN insulin delivered to lean women in a postprandial state decreased rated palatability and intake of a cookie snack (Hallschmid et al., 2012). To help clarify the conflicting findings on the effects of insulin on appetite and food

intake in women and to determine if these actions are BMI-dependent, the effects of IN insulin were measured in women with and without obesity after a fixed lunch. Moreover, to determine if IN insulin-induced changes in appetite are due to effects on cognition, measures of inhibition, working memory, and long-term memory were collected. IN insulin reduced cookie snack intake, initial snack ratings of palatability, and self-reported appetite in women with obesity but not in lean women, and had no effect on cookie eating rate. In women with obesity, IN insulin increased ratings of positive affect. This augmentation of positive affect in women with obesity is particularly significant, as women are more likely to be overweight/obese and to have depression (Kanter & Caballero, 2012; Zender & Olshansky, 2009). IN insulin improved performance for selecting positive self-referent adjectives and for rejecting negative self-referent adjectives. IN insulin had no effect on inhibition, working memory, and delayed recall. The anorexigenic effects observed are not likely due to decreases in blood glucose, as blood glucose before the snack did not differ between the placebo and insulin condition. The lack of effect of IN insulin observed in lean women contrast those of Hallschmid et al. (2012), and this could be due to methodological factors, such as the lack of cookie varieties offered during the cookie snack. These results suggest that women with obesity may be more sensitive to the effects of IN insulin a finding that contrasts with previous reports of hyposensitivity in individuals with obesity in response to exogenous insulin administration (Guthoff et al., 2011; Hallschmid et al., 2008; Tiedemann et al., 2017).

In Chapter 3, the efficacy and behavioural and neuropharmacological mechanisms of action of the only drug approved to treat BED, LDX, was assessed in a systematic review and meta-analysis. The most recent meta-analysis to assess the efficacy of LDX for the treatment of BED was conducted in 2016 with data from only three RCTs (Fornaro et al., 2016). Further, little

is known about the underlying mechanisms of LDX to treat BED. To this end, preclinical and clinical data were included in a systematic review and meta-analysis of 21 articles measuring effects of LDX on food intake or BED-related symptoms. The inclusion of preclinical data allowed for insight into potential mechanisms of the drug that could not be gleaned from human data. The meta-analysis of clinical studies found LDX consistently reduces binge-eating symptoms. The results of the preclinical meta-analysis revealed that LDX reduces both chow and palatable food intake in rodents. Vickers et al. (2015) suggested that LDX preferentially decreases palatable food intake with no effect on chow intake, thus implying LDX decreases hedonic intake while sparing effects on homeostatic intake. Importantly, a subgroup analysis presented in Chapter 3 indicated equivalent effects of LDX on chow and palatable food intake. Given the reduction in both homeostatic and hedonic intake observed in rodents, the results indicated that LDX likely acts on both reward and homeostatic (appetite and satiety) systems in humans. Additionally, a qualitative analysis of only one study tentatively found that LDX improved cognitive performance using a self-report measure. Combined evidence from the review presented in Chapter 3 suggests that the effects of LDX on appetite are likely mediated by serotoninergic and dopaminergic signaling to alter satiety and reward processes while effects on cognition may be mediated by dopaminergic and noradrenergic actions in the brain. Thus, LDX appears to treat BED through combined effects on appetite, reward, and cognitive processes that are mediated by actions on catecholaminergic and serotonergic pathways in the brain. However, there is a need for more studies investigating behavioural and neural effects of LDX to systematically test this conclusion.

In Chapter 4, the effects of 50mg LDX on appetite, reward, and cognition were measured in women with binge-eating symptomatology. Behavioural studies investigating the effects of

LDX on food intake in participants with binge-eating symptomatology had not previously been conducted, which limits our understanding of potential mechanisms of action of the drug in treating BED. To model eating in the absence of hunger that is typically observed in BED (American Psychiatric Association, 2013), a cookie snack was served shortly after a pasta meal eaten to satiety by the participants. LDX reduced pasta and cookie intake and self-reported appetite in women with binge-eating symptomatology. LDX had no effect on eating rate or liking for cookies but decreased eating rate and liking for pasta at the end of the meal. LDX improved sustained attention and inhibition, suggesting that reductions in hedonic appetite could be related to improvements in cognitive control. The reductions in food intake observed are not likely due to adverse effects, as the results of the systematic review reported in Chapter 3 found relatively low rates of adverse events across several RCTs and the self-reported physical and negative symptoms reported throughout the test day were also relatively low. The results of this behavioural study provides further support for the hypothesis that LDX treats BED through combined actions on satiety, reward, and cognitive control as posited in the systematic review (Chapter 3).

5.3 Theoretical and Practical Implications

5.3.1 Theoretical Implications

The findings presented in this thesis have implications for conceptualisation of eating behaviour. This thesis has largely focused on a model of eating whereby cognition, homeostatic, and reward systems interact in the control of eating. A commentary on the relevant theoretical findings of this model are presented below.

Evidence for an interactive model of appetite. Previous research has shown cognitive improvements following IN insulin in individuals with (Benedict & Grillo, 2018; Kullmann et

al., 2016) and without memory impairments (Hallschmid, 2021). Given the bidirectional relationship between appetite and memory (Higgs & Spetter, 2018), it was hypothesised that IN insulin might decrease appetite, at least in part, through improvements in cognitive performance. However, acute IN insulin reduced palatable snack intake but did not improve performance on measures of delayed recall, inhibition, and working memory in women with and without obesity. Instead, we observed improvements in positive affect for women with obesity (but not lean women), which suggests that elevated positive affect could be related to the anorectic effects of IN insulin. Additionally, the reduction in snack intake in a satiated state is indicative of changes in reward signalling. The results of acute dosing of IN insulin support an interactive role of homeostatic, hedonic, and emotional processes in regulating appetite.

Cognitive deficits have been reported in individuals with BED (Gisbert Cury et al., 2020). The increased risk of individuals with ADHD for developing disordered eating supports a relationship between cognition and disordered eating (Kaisiri et al., 2017, 2018; Ptacek et al., 2016). Moreover, the robust efficacy of LDX in treating both ADHD and BED further suggests cognitive processes play an important role in mediating the onset and maintenance of eating and disordered eating. The results of a systematic review and meta-analysis presented in Chapter 3 of this thesis of the available preclinical and clinical evidence found that LDX reduces both standard chow intake and palatable food intake and may improve cognition. To determine if cognitive improvement is related to appetite in BED and its treatment, 50mg LDX was administered acutely to women with binge-eating symptoms. LDX reduced both pasta and cookie intake. LDX had no augmenting effect on working memory performance or socioemotional processing, but improved sustained attention/inhibition. This suggests that

inattention may prompt intake of highly palatable foods and that improvements in attention could be, at least partially, the basis of the drug's efficacy to treat BED.

The results of the two experimental studies and the systematic review and meta-analysis provide support for the interactive model of eating outlined in Chapter 1. Reductions in palatable snack intake were observed in two experimental studies of acute dosing of drugs known to affect appetite in women with obesity and women with binge-eating symptoms but this appeared to be brought about by different underlying mechanisms. In women with obesity, the metabolic signal, insulin, was found to reduce intake via a reduction in food reward, which is consistent with cross talk between homeostatic and reward mechanisms. In women with binge eating, LDX also decreased food intake, but evidence from the eating rate and cognitive control measures suggested that this may be due to interactions between homeostatic, reward, and cognitive processes. Finally, the finding that insulin heightens positive affect in women with obesity indicates that the interactive model of appetite proposed in this thesis should be expanded to include emotional processes whereby emotion acts as a mediating and/or moderating factor to control appetite in eating and disordered eating.

Unique and overlapping underlying mechanisms. An overview of the results from the experimental studies on each domain related to appetite is presented in Table 11. A satiating meal was offered before administration of IN insulin precluding a direct investigation of homeostatic mechanisms. However, LDX reduced intake and eating rate of a satiating meal, and this reduction may be due to effects of the drug on serotonin mechanisms. Serotonergic activity in the hypothalamus, specifically the ARC, is implicated in the control of homeostatic intake (Timper & Brüning, 2017) and likely led to the reduction of pasta intake observed in Chapter 4.

Importantly, both LDX and insulin reduced palatable food intake in the absence of hunger, but only insulin decreased initial liking of the cookie snack. IN insulin has previously been shown to reduce subjective ratings of palatability of food cues, and this accompanied inhibited functional connectivity from the VTA to the NAc of the striatum (Tiedemann et al., 2017). This divergent response in reward may be due to actions on different components of reward. For instance, insulin appears to reduce wanting as evidenced by reduced palatable food intake as well as liking as reflected by reduced initial ratings of cookie palatability. The wanting system of reward comprises much of the mesocorticolimbic system, while the liking regions consist of only a subset of the reward system that includes the OFC, ACC, insula, ventral pallidum, NAc, and amygdala (Morales & Berridge, 2020). IN insulin has also been found to act on areas associated with wanting and liking, such as the insula, PFC, caudate, putamen, NAc, amygdala, and the VTA (Kullmann et al., 2020). Conversely, it is possible that LDX predominantly alters the wanting system, as evidence by reduced intake of a palatable cookie snack without effects on liking. LDX is thought to primarily exert its therapeutic action through increased neurotransmission of the catecholamines, noradrenaline and DA, and DA activates the wanting system (Morales & Berridge, 2020). More systematic evidence is needed to test this theory, however. Liking and wanting has been discriminated through validated computerised tasks in women with binge-eating symptoms (i.e., Leeds Food Preference Questionnaire) and this approach could be applied to determine if LDX has differential effects on food reward (Dalton & Finlayson, 2014). Neuroimaging studies investigating the effects of LDX on appetite/BED are limited to only one study. In this study, LDX had a marginal effect on responses of the ACC and striatum to viewing food images, but a significant effect on responses of the PFC (Fleck et al., 2019). The PFC is an area of the brain involved in cognitive control (Miller, 2000) and increased

cognitive control has been associated with reduced food intake (Lawrence et al., 2015). Thus, LDX could decrease food intake through actions on cognitive processes.

Across the two experimental chapters, there was a greater effect of LDX on cognitive processes compared to insulin. While IN insulin has been found to improve cognition including memory (Benedict et al., 2004), these effects appear to be more limited than the effects of LDX on cognition. IN receptors are located within the hippocampus, an area of the brain associated with memory, and IN insulin dosing has been found to enhance functional connectivity between the hippocampus and PFC (Zhang et al., 2015). Thus, it is likely that the cognitive effects of insulin may largely be due to actions on the hippocampus, which might explain why many of the cognitive enhancing results reported in previous studies are predominantly memory related (Benedict et al., 2004; Hallschmid et al., 2008). Conversely, LDX did not improve memory in our study and appears to mainly modulate cognitive control, including attentional and inhibitory processes. This modulation is likely due to dual actions of LDX on dopaminergic and noradrenergic pathways. DA and noradrenaline processes have both been found to influence attention (Borodovitsyna et al., 2017; Nieoullon, 2002).

Table 11: Overview of Results

Domain and Measures	Insulin	LDX
Homeostatic: 1. Satiating meal intake 2. Eating rate 3. Self-reported appetite	 1. NA 2. No effect 3. Reduced – obese only	 1. Reduced 2. Reduced – pasta only 3. Reduced
Reward: 1. Palatable food intake 2. Palatability ratings 3. Delayed discounting	 1. Reduced – obese only 2. Reduced – start of meal obese only 3. No effect	 1. Reduced 2. Reduced – end of meal for pasta only 3. NA
Cognition: 1. Inhibition/attention 2. Working memory 3. Social cognition (i.e. facial expression recognition task)	 1. NA 2. No effect on accuracy 3. NA 4. No effect 5. Improved self-reference accuracy	 1. Improved 2. No effect 3. No effect 4. NA 5. Reduced self-reference reaction time

4. Immediate and delayed verbal memory recall 5. Emotional memory		
Mood: 1. Self-reported arousal 2. Self-reported negative affect 3. Self-reported positive affect 4. Self-reported physical symptoms	1. No effect 2. No effect 3. Increased 4. No effect	1. Increased 2. Near-significant increase 3. NA 4. Increased

* NA = not applicable

5.3.2 Practical Implications

The psychopharmacological methods used in this study were employed for the purpose of understanding mechanisms that mediate eating and disordered eating, however, the results have important implications for future laboratory work and interventions. The practical implications of these results are presented below.

IN insulin as an intervention for obesity. Approved weight management drugs are limited, and adverse side effects are barriers to treatment (Bessesen & Van Gaal, 2018). IN insulin shows promise for weight management pharmacotherapy. The non-invasive, rapid, and safe profile of the IN route in conjunction with the appetite reducing effects of insulin for palatable foods indicates IN insulin could be a viable therapy for weight loss. Additionally, IN insulin has a unique advantage compared to extant drugs in that it improves mood, rather than worsens it. This is especially significant given that negative mood has been linked to disordered eating (Davis-Becker et al., 2014) and individuals with obesity often have comorbid depression (Luppino et al., 2010). For some individuals, weight loss after IN insulin could potentially be achieved through mood improvements alone. Researchers should conduct clinical trials investigating the effects of prolonged IN insulin dosing in individuals with obesity and/or dysthymia to determine long-term viability of this potential therapy.

Validation of a new model for testing novel compounds to treat BED. With several new compounds to treat BED in development (Heal & Smith, 2021), validated experimental medicine models to assess their efficacy are needed prior to undertaking large scale studies in patients. In Chapter 4, women with above threshold scores on a measure of binge-eating symptomatology were offered a palatable snack 20 minutes after consuming a satiating meal. In the placebo condition, the women consumed an average of approximately 70 grams (~ 392 kilocalories) of chocolate chip cookies in a satiated state. Importantly, this measure is sensitive to drug manipulation, as LDX, the only approved drug to treat BED, significantly reduced cookie intake compared to placebo. These results suggest the eating in the absence of hunger model used in this thesis is a reliable means of assessing the efficacy of novel compounds to treat BED.

Cognition as a target for treatment. Deficits in inhibition have been observed in obesity and disordered eating (Giel et al., 2017). The results of Chapter 4 provide support for inhibitory processes as a target for treatment. Behavioural go/no-go tasks in which a participant responds to 'go' stimuli and withholds for 'no-go' stimuli can be readily employed for inhibitory training. It is common for no-go stimuli to be highly palatable food (e.g., Turton et al., 2018), but avoidance (no-go) of high-calorie food items can contribute to the 'forbidden foods' phenomenon that is associated with an increased risk for binge eating (Guertin & Conger, 1999; Tuschl, 1990) thereby exacerbating disordered eating symptoms. Therefore, it is recommended that inhibitory tasks such as the go/no-go incorporate non-food stimuli, as this will likely translate into inhibition of cravings in daily living without increasing pathological symptoms. Further, because sustained attention is key to inhibiting distractions and has shown to be implicated in BED (see Chapter 4), future interventions should focus on augmenting attention. Computerised tasks, mindfulness, and exercise have shown promise in improving attentive processes for individuals

with ADHD and are relatively easy to implement (Lambez et al., 2020; Lee et al., 2017; Ng et al., 2017). However, because some evidence suggests that training programs have limited effects (Rapport et al., 2013), pharmacotherapies may be advantageous. Pharmacologically, drugs that target the noradrenergic system in the brain enhance response inhibition, while drugs that target the cholinergic system, such as nicotine, enhance attention in rodents (Floresco & Jentsch, 2011). Thus, drugs that target acetylcholine or noradrenaline receptors could be effective alternatives to behavioural interventions or LDX to improve cognitive processes.

5.4 Strengths, Limitations, and Future Research

A strength of the experimental studies in this thesis is the focus on testing women as women have higher rates of obesity and comprise a majority of BED diagnoses (Erskine & Whiteford, 2018). This is in line with methodological calls to power studies based on the gender representation in the disorder of interest (Dickinson et al., 2012). Additionally, there are recent appeals to include more women in research, as they have been historically underrepresented (Jit Singh Bajwa & Kurdi, 2020). Similarly, a proposed initiative of investigating dimensions of behaviour rather than categorical diagnoses established in the RDoC research framework (Insel et al., 2010) was addressed via the inclusion of women with above threshold scores on a measure of binge-eating symptomatology.

Studies investigating the effects of IN insulin on eating across a range of different BMI status are sparse, which limits insights into both mechanisms and developments for optimised weight management pharmaceutics. A strength of this thesis was to directly compare women with and without obesity. Additionally, future studies should include a healthy control group to assess differences between placebo and LDX on appetite and food intake, as this has yet to be examined in humans.

A strength of this thesis was the pre-registration of hypotheses for all measures in the experimental chapters and the pre-registration of the protocol for the systematic review and meta-analysis. The psychopharmacology studies in this thesis utilised the gold standard randomised placebo controlled design. Further, placebos in each of the studies were identical in appearance, texture, taste, and odour to the investigational compound and were administered double blind. This was especially important for the IN insulin study, as IN insulin has a distinctive odour that could have been detected by participants if not sufficiently disguised. Another methodological strength of the two experimental studies were the detailed microstructural measures of appetite used (i.e., intake, appetite ratings, eating rate, palatability ratings) and the multiple measures of cognition included (e.g., working memory, attention, inhibition) that enabled more precision in mechanistic insights. Future studies should also include a measure of set shifting to determine mechanisms of action of LDX for the treatment BED, as impairments in set shifting have been observed in both ADHD and BED (Dingemans et al., 2015; Kofler et al., 2019). Finally, the inclusion of preclinical and clinical data sets in the systematic review and meta-analyses presented in Chapter 2 enabled insight into mechanisms of LDX that could not have been gleaned from clinical studies alone. Future reviews aimed at understanding mechanisms of action should strongly consider including these methodologies.

This thesis is not without limitations. The paradigm in the experimental studies relied upon laboratory measurement of food intake as opposed to assessing food intake in a naturalistic setting. Criticisms of laboratory food intake measurement include the suggestion that participants restrain intake which leads to underestimates of actual consumption, and that the environment is less comfortable than participants would feel eating at home (Gough et al., 2021; Robinson et al., 2015). However, a recent systematic review and meta-analysis found that calorie intake was

higher in laboratory settings than intake reported through food diaries or food recall across diagnoses of bulimia nervosa and BED, and there was no difference between laboratory intake and self-reported intake for those with BED (Mourilhe et al., 2021). These results suggest, at least in those with disordered eating, intake can be captured accurately in an experimental setting. Although participants knew their food intake was being measured, they were unaware that this was the main objective of the study, which has been previously observed to attenuate demand characteristics (Robinson et al., 2015). Moreover, even if participants were aware that measurement of food intake was the main objective of the study, previous results using this paradigm showed that participants' awareness of their food intake being monitored did not affect food consumption (Thomas et al., 2015). Similarly, the food stimuli selected for intake measurement was based on previous psychopharmacology experiments (Thomas et al., 2014; Thomas et al., 2018). A model in which the participant selects the food items to be consumed during the test day could potentially reflect more realistic intake. It is possible that some participants did not enjoy the study foods, which created a floor effect. Though liking of study foods was included in the eligibility criteria, the natural stratification of food liking means some participants may not have liked the foods enough to detect differences between conditions. Future studies should consider customising food items in within participant designs or having quantitative cutoffs (i.e., self-report palatability ratings of 75/100) as opposed to categorical verbal statements (i.e. 'I like the food' versus 'I do not like the food') for palatability ratings to ensure adequate liking. Finally, the prolonged test days (minimum 5 hours) could have induced fatigue in the participants that affected performance. Importantly, several of these experimental limitations were mitigated through the use of a within participants design.

The samples used in this thesis also provided limitations. First, we only tested females in the United Kingdom (UK) who were mostly university students. UK university students are a privileged sample classified as WEIRD (Western, Educated, Industrialised, Rich, Democratic) participants who are often reported in scientific literature, but are estimated to comprise only 12% of the global population (Henrich et al., 2010). Though women do represent the majority of obesity and BED diagnoses, the results may not generalise to men. Future studies should look at the effects of IN insulin and LDX in male samples. In the second experimental study, the inclusion of women with above threshold scores on a measure of binge eating symptomatology (BES) meant eligibility was determined by a questionnaire. The BES has been found to reliably discern BED in undiagnosed community samples (Duarte et al., 2015), but there are always concerns with self-report measures. Finally, the relatively small sample sizes could have led to some Type 2 statistical errors, in which effects were undetected. Reporting of effect sizes and planned comparisons were included to mitigate Type 2 errors, but the results should be treated with some caution until replicated. Additionally, the sample sizes obtained in the experimental chapters were not sufficient to conduct a mediation analysis, which limited insights into the mechanisms of action of insulin and LDX on food intake. Future studies should ensure adequate sample sizes to replicate these findings and to statistically determine the mediating mechanisms.

To expand upon the findings of this thesis, future studies should assess the different etiologies and phenotypes of BED. For example, BED has been associated with past trauma (Grilo & Masheb, 2001), ADHD (Reinblatt et al., 2015), a dysregulated reward system (Davis, 2015), dieting (da Luz, Sainsbury, et al., 2018), negative affect (Schulz & Laessle, 2010), and diseases marked by elevated levels of testosterone such as polycystic ovary syndrome in women (Krug et al., 2019). Further, individuals with BED present with a range of BMIs (Mackenzie &

Harris, 2015), but the majority of compound efficacy trials for BED tend to focus on comorbid BED and obesity. Future studies should assess the effects of LDX in lean individuals with BED to determine a behavioural profile of eating behaviour and cognition for the development of new compounds that reduce binge-eating symptoms without substantially reducing weight. Generally, it is possible that the broad classification of BED fails to capture individual phenotypic differences and ultimately impedes treatment. A responder versus non-responder analysis of LDX effects on binge eating could reveal differential efficacy of the drug that is moderated by an individual's predisposing factors. This understanding could predict who will respond or not respond to specific treatments which has practical benefits for the community (e.g., monetary) and the patient (e.g., time to remission, avoidance of adverse events).

5.5 Conclusions

In summary, the results from this thesis provide new insights into the control of eating and the specific mechanisms underlying the effects of IN insulin and LDX on food intake. By using a range of measures that included self-report, microstructural measurement of food intake, and computerised cognitive tasks, it was found that 1) IN insulin likely reduces food intake in women with obesity through the reduction of food reward while satiated but also improves mood and 2) LDX likely reduces binge eating by enhancing satiety as well as reducing food reward and improving attention and inhibitory control. These results indicate that successful therapeutics for obesity will target reward-based eating while compounds that have some action on cognitive control are likely to reduce binge eating in BED. These results suggest that IN insulin may hold promise as a weight management option for women with obesity. They further indicate that novel compounds to treat BED should target multiple mechanisms including satiety, reward, and cognitive control. Finally, the experimental medicine approach described in this thesis also

provides a model for future studies to assess the psychopharmacology of eating and disordered eating and to examine the effects of novel therapeutics for weight management and the treatment of BED.

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Appendix A: Reducing Craving via Cognitive Load in Women with Binge-Eating Symptoms

Introduction

Food cravings are an intense desire to eat a particular food and occur in normal eating patterns (Weingarten & Elston, 1990). Food cravings can be transient and inconsequential, however results from a meta-analysis found that food cravings often lead to subsequent eating and weight gain (Boswell & Kober, 2016), suggesting cravings can transcend temporary desires and have lasting impacts. Food cravings also precipitate disordered eating (Mussell, Mitchell, Zwaan, Crosby, Seim, & Crow, 1996; Cartwright & Stritzke, 2008; Greeno, Wing, & Shiffman, 2000; Moreno, Rodríguez, Fernandez, Tamez, Cepeda-Benito, 2008) and are found to be more prevalent and persistent in individuals with disordered eating (Ng & Davis, 2013), indicating an important target for intervention.

Cravings initiate from many factors including neurological vulnerabilities, behavioural learning, and cognitive processes (Rodríguez-Martín & Meule, 2015; Sun & Kober, 2020). Many interventions focus on the cognitive aspect of cravings, however. For example, instructing participants to focus on long-term negative consequences of consuming the craved food engages future episodic thinking and reduces craving ratings (Kober et al., 2010). This intervention borrows from cognitive-behavioural treatments in which individuals with disordered eating are asked to engage cognitive strategies to regulate cravings (Stapleton et al., 2016). Further, redirection of attention from food cues to neutral cues in women with overweight reduced food attentional biases and subsequent food intake (E. Smith et al., 2020). Hence, cognitive interventions are common and effective means of reducing food craving.

A prominent cognitive theory of craving is elaborated intrusion (EI) theory (Kavanagh, Andrade, & May, 2005). In EI theory, a desire is experienced and then attention is directed to target-related information thereby giving the target more salience. Once attention is biased, long-term memory is used to construct sensory information largely through mental imagery about the desired target, thus creating a process of elaboration. These elaborative processes of search, retention, and manipulation of the target rely upon working memory (Kavanagh, Andrade, & May, 2005; May, Andrade, Panabokke, & Kavanagh, 2010). Theorists of EI argue that the elaboration step is key for enhancing motivation to obtain the target item and ultimately for craving activation, thus interrupting the elaborative process could be essential for craving extinction. Indeed, several studies have shown that interruption of elaboration reduces food cravings in healthy individuals. Intervening tasks include guided imagery (Hamilton, Fawson, May, Andrade, & Kavanagh, 2013), sensory imagery (i.e., visual and olfactory; Kemps & Tiggemann, 2007), olfactory interference (Kemps & Tiggemann, 2013), and playing the visuospatial game, Tetris (Skorka-Brown et al., 2014).

The effect of extinguishing cravings by disrupting the elaboration process can be explained by load theory. Load theory explains that cognitive processes such as attention are limited and can be exhausted (Lavie, 2005). Under this theory, external stimuli must compete to gain executive attention. In high-load tasks, task-irrelevant stimuli (distractors) are ignored as all of the attentional resources are directed toward the task-relevant stimuli. The opposite effect is found in low-load tasks, as attentional resources are not exhausted allowing the processing of task-irrelevant stimuli (distractors). In relation to craving, supplanting the resources allocated to elaborating the craved food item to a more taxing and challenging task leads to an attentional shift from the craving to the loaded task. Effectively, increasing perceptual load steals resources

available to elaborate the food desire reducing or eliminating cravings. Competing with load theory is distractor salience theory whereby distraction is the result of the distractor's salience and not limited attentional load capacity (Eltiti et al., 2005). In the context of cravings, craving temptation may perseverate with high load if the craved item is highly salient. This has implication for individuals with Binge Eating Disorder (BED), in which individuals excessively consume highly palatable foods with an accompanied loss of control despite adverse consequences (American Psychiatric Association, 2013a). It is unclear if individuals with binge-eating symptoms would benefit from load intervention or if the craved item's salience would supersede load capacity.

Applying load theory, Morris and colleagues (2020) measured intrusive appetite-related thoughts (cravings) after varying perceptual loads. Sixty healthy participants interacted with chocolate for two minutes to induce a craving state and were then instructed to suppress any chocolate-related thoughts and to focus on the task. Participants then completed either a low load or high load task. In the low load condition, participants searched for a target letter alongside five small homogenous non-target letters, while the high load condition consisted of the target letter among varying angular letters. Self-report intrusive/craving thoughts about chocolate were collected during and after the task. Intrusive thoughts about chocolate were reduced in the high load condition regardless of hunger state, chocolate liking, or initial chocolate craving (Morris, Keith Ngai, et al., 2020).

Though load theory primarily focuses on attention, cognitive load theory concerns finite working memory capacity (Sweller, 1988). In this theory, once working memory capacity is reached, attentional and working memory resources cannot easily be given to another stimulus. In applying cognitive load theory to cravings, cognitive resources cannot be directed to a craving

(distractor) if working memory capacity is allocated to another task. In a series of experiments, Van Dillen, Papies, and Hoffman (2013a) administered a low (rehearsal of a one-digit number) or high (rehearsal of an eight-digit number) cognitive load simultaneously with a speeded categorisation task of attractive and neutral food pictures and assessed subsequent food cravings. The authors hypothesised that high cognitive load would impede the participants' ability to assess the hedonic value of attractive food pictures due to unavailable cognitive resources, thus eliminating the food attention capture before elaboration can occur. Indeed, high cognitive load prevented attentional bias to attractive food cues and reduced self-reported craving ratings (Van Dillen et al., 2013a). In another study of the same article (2013c), the authors found that individual susceptibility to highly palatable food measured via the Power of Food Scale (PFS) increased subsequent unhealthy snack intake, but this effect was eliminated when these participants received a high cognitive load task (Van Dillen et al., 2013c). In a similar study, participants with low and high PFS scores selected foods from a menu to induce cravings and were then randomly allocated to a break condition (no distraction), a holiday selection condition (control), or a Tetris condition (distraction). Participants in the Tetris condition were less attracted to high-calorie foods, regardless of PFS scores (van Dillen & Andrade, 2016). This effect has also been replicated in neuroimaging. When participants viewed low and high-calorie foods with concurrent varying load on a digit span task, activation of areas of reward while viewing high-calorie foods was reduced in the high cognitive load task (van Dillen & van Steenbergen, 2018). Taken together, these results suggest that a high cognitive load blocks cognitive elaboration of food cravings before and after a craving has been established and reduces later unhealthy snack intake, even for those with greater vulnerability to palatable foods.

Current literature effectively demonstrates that taxing cognitive resources blocks initial cravings in addition to eliminating established cravings for those with low and high susceptibility to food cues. Little is known, however, how individuals with binge-eating symptoms might respond to cognitive load interventions, given their susceptibility to intense cravings (Chao et al., 2016). The current study seeks to investigate the interventional effects of a low and high cognitive load task in a craving state in a population with binge-eating symptoms. Recruitment of a sub-clinical sample is in line with the Research Domain Criteria Initiative (RDoC) established by the US National Institute of Mental Health (NIMH) which encourages research on dimensions of observable behaviour rather than a categorical, symptom-based approach to the study of mental health (Insel et al., 2010). Further, craving extinction will be measured using a lab-based *ad libitum* food task of the craved food item.

Objective

The main aim of this study is to investigate the effect of low and high cognitive load on self-reported cravings and food intake in females with binge-eating symptoms.

Hypotheses

- High cognitive load will reduce self-reported food craving.
- High cognitive load will reduce food intake.
- Low cognitive load will have little to no effect on self-reported food craving.
- Low cognitive load will not affect food intake.

Design

We will use a counterbalanced, randomised, within-participants experimental design. Participants will have a week between test days to allow for washout.

Method

Sample Size

Sample size was calculated using G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2009) power analysis software. Deriving the effect size (0.21) from Van Dillen, Papies, and Hoffman's (2013) first study with cognitive load as the independent variable and self-reported cravings as the dependent variable, an a priori repeated measures power analysis yielded a sample of 60 necessary to achieve 0.81 power. Similarly, Morris et al. (2020) observed an effect of varying loads on intrusive thoughts using a within-subject design with a sample of 60 participants. We will collect 65 participants to account for potential data loss and other issues that might arise.

Participants

We will recruit 65 female participants with self-reported binge-eating symptoms, as women have been found to experience food cravings more than men and are much more likely to binge eat than men (Erskine & Whiteford, 2018; Weingarten & Elston, 1991). Binge-eating symptoms will be measured via responses to a binge-eating questionnaire. Participants will include students and staff of University of Birmingham and the West Midlands community. Participants will be recruited via the University of Birmingham Research Participation Scheme (RPS), advertisements located around the university campus, word-of-mouth, posts on social media platforms (i.e., Facebook and Twitter), and/or advertisements in the local newspaper. Participants will have the option to choose 2 course credits for participation or £20.

This study has received ethical approval from University of Birmingham's Science, Technology, Engineering and Mathematics Ethical Review Committee.

Eligibility

Participants will be eligible for this study if they meet the following inclusion criteria and none of the exclusion criteria:

Inclusion criteria

- Aged 18-55
- Fluent English speakers
- Able to provide informed consent
- Minimum score of 18 on the Binge Eating Scale

Exclusion criteria

- Smokers
- Uncorrected vision
- Poor sleep the night before
- Diabetes or neurological (e.g. epilepsy, headache disorder, multiple sclerosis, traumatic brain injuries) diseases
- A score greater than 31 on the Beck Depression Inventory
- Symptoms or diagnosis of other eating disorders
- Current pregnancy and breastfeeding
- Food allergies (e.g. peanut allergy, lactose and gluten intolerance) related to the study food
- Vegan diet
- Disliking the selected foods available as the stimuli

- Women will be asked to participate only in weeks when they are not menstruating or on the pre-menstrual week to avoid hormonal disruption to appetite
- Consumption of alcohol in the past 24 hours

Materials

Questionnaires

Email Screening

Beck Depression Inventory (BDI): The BDI is a 21-item measure of depression severity (Beck, 1978). This will be used to remove participants who score 31 or above, as scores in this range indicate Severe or Extreme Depression.

Binge Eating Scale (BES): The Binge Eating Scale (BES) is a 16-item questionnaire that indicates severity of binge-eating symptoms (Gormally et al., 1982). The BES will be given to ensure the presence of binge-eating symptomatology. Participants who score Moderate and Severe on the Binge Eating Scale will be included for participation. Moderate severity is classified as a score ranging from 18-26, and Severe is a score of 27 or greater. Eligibility will only include Moderate and Severe, because the BES does not include a Mild classification. The other possible classification is Non-bingeing, which is a score less than 17.

The Eating Attitudes Test (EAT-26): The EAT-26 is an abbreviated version of the EAT-40 consisting of 26 questions of pathological eating behaviours (Garner et al., 1982). This will be used to ensure participants do not have symptoms of anorexia or bulimia nervosa. Any individuals with responses that indicate excessive engagement in compensatory behaviours (e.g. responses of Rarely, Sometimes, Often, Usually or Always on questionnaire items ‘Vomit after I have eaten’ and ‘Have the impulse to vomit after meals’) will be excluded as this is suggestive of Bulimia Nervosa rather than BED.

Test Day

The Dutch Eating Behaviour Questionnaire (DEBQ): The DEBQ is a 33-item self-report questionnaire. The DEBQ has dimensions of restrained, emotional, and external eating behaviour (van Strien et al., 1986). The DEBQ will provide population characteristics for both samples.

Power of Food Scale (PFS): This is a 15-item measure of individual differences in appetite responsiveness to rewarding properties of the food environment (Lowe et al., 2009). This will be used to describe the population.

Urgency, Premeditation, Perseverance, and Sensation-Seeking Impulsive Behaviour Scale (UPPS): Impulsive Behaviour Scale. This is a 59-item measure of impulsivity and sensation seeking (Whiteside & Lynam, 2001). This will be used to determine trait impulsivity which may be used as a covariate in the analysis.

Craving Visual Analogue Scale (CVAS): This is a 4-item questionnaire that measures craving. Questions have been adapted from Van Dillen et al., 2013 to fit the current experimental design. This will be administered several times throughout the day to measure changes in craving.

Visual Analogue Scale (VAS): This is a 14-item questionnaire that measures appetite, arousal, mood, and physical symptoms using a visual analogue scale that the participant drags with a cursor from 1cm to 10cm. This will be given several times throughout the day to determine state feelings.

Tasks/Instruments

Food Items

Prior to coming to the lab, all participants will be sent an email asking to choose between a crisp and a cookie option. The flavours of each will be determined by the participant. The selection of food items is derived from the results of Schulte, Avena, & Gaerhardt's (2015) study. If the

participant does not like any of the food options, she will be excluded from the study. On the test day, cookies will be broken into smaller pieces. Consumed food amount will be measured in kilocalories.

Craving Induction

Consistent with the procedure reported by Smeets et al. (2009), participants will interact with their selected food item for 2 minutes and will be instructed to focus on the item and imagine eating it in as much detail as possible (E. Smeets et al., 2009). Additionally, participants will be asked to write down responses about the food item's smell, appearance, texture, and anticipated taste to ensure engagement.

Cognitive Load

In line with previous findings that visuospatial tasks reduced food cravings, a computerised visuospatial n-back will be used to (Kemps, Tiggemann, Woods & Soekev, 2004); Harvey, Kemps, & Tiggemann, 2005). The n-back is a working memory capacity task, which is often used as an operationalization of cognitive load and is successfully loaded with visual stimuli (Logan, 1978; Baddeley & Andrade, 2000; Wang & Duff, 2016). In this task, participants are presented a sequence of blue circles on a 3x3 grid. The participant is instructed to indicate whether the current circle location matches the location of the circle *n* trials earlier or if the circle appears in a pre-specified location. In this design, participants will identify if the circle appears in the top-right corner of the grid (0-back) in the low cognitive load task and if the circle matches the position presented three trials back (3-back) for the high cognitive load task. The n-back will take five minutes to complete.

Procedure

Before the Test Day

Once participants have expressed interest, the researcher will send the potential participant information about the study. Additionally, participants will be asked to complete the BES and choose between crisps or cookies and the preferred respective flavour and brand. The participant will indicate on a scale of 1-5 how much they like this item and their perceived loss of control for this food item on a scale of 1-5. Finally, the participant will complete the lifestyle questionnaire, BDI, and EAT. If the participant still wishes to participate and is eligible, the participant will be told to eat approximately one hour before coming to the lab.

Test Day

Upon arrival to the laboratory, participants will sign the consent form. Participants will be told that the purpose of the study is to sensory experiences, mood, and cognitive performance so as to not influence their behaviour. Participants will complete a baseline VAS and CVAS. To ensure understanding of the task, participants will practice the cognitive load task that the participant has been randomised to for that day.

Another VAS will be completed. Participants will be asked to rate the food that the participants selected prior to lab arrival. Participants will complete the craving induction task. Following responses, the food item will be removed from the participant's immediate visual field but will remain in the testing room. Participants will complete a CVAS and another VAS.

Another VAS will be completed. Participants will then either complete a low or high cognitive load task for five minutes. Following the task, participants will complete another VAS and another CVAS Next, participants will be given free access to the food item they selected for the study. Participants will be told the food is leftover and will be discarded if uneaten. Participants will have 20 minutes to consume the food. A final VAS and CVAS will be completed. To ensure there are no spillover negative effects on mood, participants will receive a relaxation session.

Participants will complete a word search for ten minutes. Participants must rate their mood as neutral or higher before they can leave.

On test day two, the day will be the same, but the participant will complete the alternative version of the cognitive load task and height and weight will be collected. Participants will also complete the DEBQ, PFS, and UPPS. The participants will then be asked about study purpose. Finally, the participant will be paid/compensated credits and debriefed. See Figure 18 for a schematic of the test day procedure.

Figure 18: Schematic of Test Day Procedure

0 mins	15 mins	25 mins	35 mins	55 mins	Test Day 2
Consent VAS CVAS Practice task	VAS Sensory rating task CVAS VAS	VAS Cognitive load task VAS CVAS	Ad libitum food intake VAS CVAS	Relaxation session	Question-naires Height Weight

Appendix B: Search Terms

Web of Science

(((((((Lisdexamfetamine OR "lisdexamfetamine dimesylate") OR "lisdexamfetamine dimesylate") OR "lisdexamfetamine") OR " SPD489") OR " Vyvanse") OR "Elvanse" OR "LDX") AND (((((((("binge" OR "binge-eating disorder") OR "binge eating disorder") OR "binge") OR "binging") OR "bingeing") OR "binge eating") OR "binge-eating") OR "binge disorder"))

PubMed Central

(((lisdexamfetamine) OR (lisdexamphetamine dimesylate) OR (lisdexamfetamine dimesylate) OR (lisdexamphetamine) OR (SPD489) OR (Vyvanse) OR (Elvanse) OR (LDX))) AND ((binge) OR (binge-eating disorder) OR (binge eating disorder) OR (binge) OR (binging) OR (bingeing) OR (binge eating) OR (binge-eating) OR (binge disorder))

OVID SP

((lisdexamfetamine or lisdexamphetamine dimesylate or lisdexamfetamine dimesylate or lisdexamphetamine or SPD489 or Vyvanse or Elvanse or LDX) and (binge or binge-eating disorder or binge eating disorder or binge or binging or bingeing or binge eating or binge-eating or binge disorder)).af.

PsycInfo

noft((lisdexamfetamine) OR (lisdexamphetamine dimesylate) OR (lisdexamfetamine dimesylate) OR (lisdexamphetamine) OR (SPD489) OR (LDX) OR (Vyvanse) OR (Elvanse)) AND noft((binge) OR (binge-eating disorder) OR (binge eating disorder) OR (binge) OR (binging) OR (bingeing) OR (binge eating) OR (binge disorder)

Appendix C: Characteristics of the Clinical Studies

Table 12. Characteristics of Clinical studies

Source	**Study Design/ clinical phase**	**Intervention**	**Study Duration**	**Eligibility**	**Comparator**	**Sample Size**	**Participant characteristics**	**Primary Outcome Measures**	**Secondary Outcome Measures**	**Adverse Effects (RCTs only)**	**Declaration of interests**
Author, year	**RCT Open label Case report Medical record review**	**Acute Chronic Dosing**	**Days, weeks, months**	**Inclusion criteria**	**Placebo SSRIs TCAs Bupropion Topiramate Dasotraline**		**Age, sex, BMI, co-morbidity**	**Binge eating**	**Physical health outcomes, mood improvement, cognitive changes**	**LDX dosages only**	**Funding source Author-industry ties**
Brucar et al.(2018)	Literature review and case report	Chronic Flexible dosing 30mg LDX (6 months) with potential to titrate to 50 or 70mg LDX Adjunctive 25mg Zoloft prescribed	6 months	45-year history of BED	None reported	N = 1	Age = 56 Sex = F BMI not reported No psychological co-morbidities reported	Cessation of BE episode and behaviours immediately after beginning LDX and continued treatment response at time of article publication Normalisation of EEG activity in insular cortex and prefrontal cortex pathways from pre-post treatment LDX reduced theta band power in right inferior frontal gyrus overlap with orbitofrontal cortex	NA	NA	Funding source not reported Authors declare no conflicts of interest
Fleck et al.(2019)	Open-label	Chronic Flexible dose 30mg (first	12 weeks treatment, 1	BED diagnosis	Control group: women with obesity	N = 40:	BED group M_{Age} = 38.6 Women only	Remission of BE episode and improvement in global BED symptoms (CGI-I)	Reduction in BED-related obsessive-compulsive symptoms	NA	Study partially funded by Shire

	Phase Post-approval	week only)-70mg LDX LDX titrations weeks 1-3, LDX maintenance weeks 4-12 Endpoint doses: 50mg (n= 4) 70mg (n=11)	week follow-up		and without BED		BED group M_{BMI} = 36.85 Co-morbidities: Major depressive disorder (n=2) and generalised anxiety disorder (n=1)	at endpoint for BED group Reduction in BE days/week, BE episodes/week, and self-reported BE scores (BES) for BED group BED group treated with LDX had reduced activation in globus pallidus at endpoint Reductions by LDX in vmPFC and thalamus activation correlated with BE and obsessive-compulsive symptom reduction	(YBOCS-BE), BMI, and reaction time on an emotional eating continuous performance task for BED group BED group did not differ in depression scores after treatment		Authors consult, co-investigate, hold membership on scientific advisory board, receive employment, and receive grant support from Shire
Gasior et al.(2017)	Open-label Phase III	Chronic Dose optimisation 30mg (first week only) Week 2 50mg LDX 70mg LDX titrated if tolerated 4 weeks dose optimisation and 48 weeks dose maintenance. At end of dose optimisation period, 179 (29.9%) participants had 50mg and 389 participants	12 months treatment, 1 week follow-up	Completion of McElroy, et al., 2016 or McElroy, et al., 2015 with no significant adverse effects	None reported	Safety analysis set N = 599, full analysis set N = 597	M_{Age} = 39.0 Sex F: 521 (87%) M_{BMI} = 33.75 No co-morbidities reported	Improvement in global BED symptoms (CGI-I) during the study and Reduction of BE days in the past 28 days (descriptive only)	A non-significant reduction in weight (greatest reduction at week 44) that stabilises toward end of treatment Reduction in self-reported eating psychopathology (EDE-Q)	NA	Study funded by Shire Authors are employees, consultants, stock holders, grant recipient, and scientific advisory board members of Shire

		(64.9%) had 70mg									
Guerdjikova et al.(2016)	RCT Phase I	Chronic Flexible dose 20mg-70mg dose at endpoint = 59.6mg	12 weeks treatment, 1 week follow-up	BED Diagnosis	Placebo	Total N = 50	M_{Age} total = 37.7 Sex total F: 46 (92%) M_{BMI} Total = 39.8 No co-morbidities reported	Over the study period, no reduction in BE episodes/week or BE symptoms (CGI-I) From baseline-endpoint, reduced BE days/week and BE episode/week From baseline-endpoint, improvements of reported BED symptoms (CGI-I) LDX did not differ from placebo in 4-week BE cessation rates	No improvement in: food cravings (FCI); BED-related obsessive-compulsive features (Y-BOCS-BE); or cognitive control of eating, disinhibition, or eating restraint (EI) Greater loss of weight/BMI and triglyceride levels No change in self-reported ADHD symptoms (CAARS), cholesterol, glucose, insulin, or HbA1c From baseline-endpoint, reduced weight/BMI From baseline to endpoint, no change in YBOCS-BE scores	Dry mouth: 48% Insomnia: 44% Jitteriness: 28% Headache: 20% Respiratory disorder: 20% Diarrhea: 16% Disturbance in attention: 12% Dizziness: 12% Increased talkativeness: 12% Anxiety: 8% Fatigue: 8% GI disturbance: 8% Hand tremor: 8% Influenza-like illness: 8% Nausea: 8% Sinus problems: 8% Back pain: 4% Increased dreaming: 4% Irritability: 4% Palpitations: 4% Paresthesias: 4% Constipation: 0%	Study funded by Shire Authors co-investigate, hold membership position on scientific advisory board, and consult for Shire Medication provided by Shire
Guerdjikova et al.(2019)	Retrospective medical record review	Chronic *M* dose = 58.0mg	*M* duration = 19.1 months	BED Diagnosis	None reported	25 records	M_{Age} = 16.5 Sex F: 18 (72%) M_{BMI} = 38.7	Reduced BED symptoms in a subset of the sample (15 cases) Complete remission of BED symptoms achieved (4 cases)	LDX did not reduce BMI A small number of participants reported less sneaking of food (1 case) and	NA	Funding source not reported Conflicts of interest not reported

	Phase Post-approval						Most common co-morbidity: depressive disorders and ADHD	Improved BE symptoms or reduced BE frequency in a subset of the sample (6 cases) A small number of participants reported likelihood to binge eat if LDX skipped (2 cases) Subset reported no improvement in BED symptoms (4 cases) and some reported worsening of BED (2 cases), while some reported no response (4 cases)	stress-triggered BE (2 cases)		
Hudson et al. (2017)	Open-label and RCT Phase III	Chronic Open-label phase: Dose optimisation 30mg (week 1 only), 50mg, or 70mg LDX 4 weeks dose optimisation (50 or 70mg), 8 weeks dose maintenance RCT phase: Dose optimisation of 50mg or 70mg LDX	Open-label phase: 12 weeks RCT phase: 26 weeks 1 week follow-up	BED diagnosis	Open-label phase: none reported RCT phase: Placebo	Open-label phase: N = 411 RCT phase: N = 270	Open-label phase and RCT phase: M_{Age} = 38.7 Sex = F: 234 (87.64%) M_{BMI} = 33.91 No co-morbidities reported	Open-label phase: Reduction of BE days/week Improvement in self-reported global BED scores (CGI-S) RCT phase: Increase in BED-related obsessive-compulsive features (Y-BOCS-BE) for placebo compared to LDX Increased time to BE relapse greater in LDX condition Reduction in BE days/week at weeks 37-38 greater for LDX	Open-label phase: Reduction in weight. RCT phase: Reduction in weight at week 38 in LDX condition	Any adverse event related to study drug: 23.5% Dry mouth: 5.1% Headache: 8.8% Insomnia: 0.7% Decreased appetite: 0% Nausea: 4.4% Anxiety: 1.5% Constipation: 2.9% Hyperhidrosis: 2.2% Feeling jittery: 0% Diarrhea: 1.5% Nasopharyngitis: 9.6% Fatigue: 2.9% Upper respiratory tract infection: 8.1%	Funding and conflicts of interest not reported

		Open-label *M* LDX dose = 57.13mg RCT *M* LDX dose = 64.05mg									
Keshen et al.(2017)	Retrospective medical record review Phase Post-approval	Chronic Dose optimisation 30mg-70mg daily total Doses given in the morning and afternoon for most cases 5 cases received LDX and 1 case received extended-release amphetamine/ dextroamphetamine (titrated to 40mg/day) 3 weeks titration and then maintenance	Variable durations: Case 1 = 4 months Case 2 = 13 months Case 3 = 5 months Case 4 = 1 month Case 5 = 14 months Case 6 = 11 months	Bulimia Nervosa diagnosis	None reported	N = 6	M_{Age} = 26 Sex not reported Baseline BMI not numerically reported Co-morbidities: marijuana use disorder; dependent traits; avoidant, dependent, obsessive-compulsive personality traits; social anxiety disorder; persistent depressive disorder	Binge/purge days/month decreased at month 1 and remained consistent at follow-up in most cases Complete remission of symptoms (1 case)	Improvement of symptoms in most cases Weight gain (2 patients) following initiation of medicine and minimal weight loss (4 cases)	NA	Funding source not reported Author on advisory board for Shire
McElroy et al.(2015)	RCT Phase II	Chronic 30, 50, 70mg/d titration 3 weeks forced dose titration, 8	14 weeks total: 11 weeks treatment	BED diagnosis	Placebo	N=259	M_{Age} = 38.7 Sex = M: 48 (18.5%) F: 211 (81.5%) M_{BMI} = 34.9 Co-morbidities: not reported	Reduction in weekly BE days/week at week 11 for 50 and 70mg/d, but not 30mg/d Clinician-rated BED obsessive-compulsive features (Y-BOCS-BE) improved all doses	No significant changes in self-reported mood ratings (MADRS & HAM-A) Improvement of self-reported impulsivity	84.7% experienced some adverse event Dry mouth: 36.2% Decreased appetite: 21.4%	Partially funded by Shire Authors consult and co-investigate for Shire, receive research

		weeks dose maintenance						Reduction in BE episode at 11 weeks of treatment for 50 and 70mg/d Improvement of self-reported global BE symptoms (CGI-I) all doses At week 11, one-week cessation of BE observed in 50 and 70mg/d doses At week 11, 4-week cessation of BE observed in 50 and 70mg/d Improvement of self-reported BE symptoms (BES) at week 11 all doses	symptoms (BIS-11) at 30 and 70mg/d Improvement of self-reported physical health symptoms at 70mg/d only Improvement of self-reported disinhibition of eating and perceived hunger symptoms (TFEQ) with all doses Improvement in cognitive restraint of eating (TFEQ) at 30 and 70mg only Reduction in mean weight all doses	Insomnia: 13.3% Headache: 11.7% Nausea: 7.7% Constipation: 7.1% Nasopharyngitis : 6.1% Weight decrease: 6.1% Irritability: 5.6% Diarrhoea: 5.1% Anxiety: 4.6% Jittery: 4.6% Palpitations: 4.6% Respiratory tract infection: 4.6% Sleep disorder: 4.1%	support from Shire, and hold stock in Shire
McElroy et al.(2016) (extension study)								Greater improvement of self-reported BE symptoms (BES) during treatment for all doses	Reduction in BED obsessive-compulsive features (Y-BOCS-BE) throughout treatment for all doses During treatment, self-reported impulsivity symptoms (BIS-11) decreased all doses. Reductions from baseline to week 11 for impulsivity (BIS-11) with 70mg/d, but not with 30 or 50mg/d		

McElroy et al.(2016)	RCT Phase III	Chronic 30mg/d (first week only), 50 or 70mg/d titration 4 weeks dose optimisation; 8 weeks dose maintenance	12 weeks treatment 1-week follow-up	BED diagnosis	Placebo	Study 1: N = 379 Study 2: N = 366	Study 1 M_{Age} = 38.05 Study 2 M_{Age} = 37.90 Study 1 Sex = F: 328 (86.54%) Study 2 Sex = F: 312 (85.25%) Study 1 M_{BMI} = 33.45 Study 2 M_{BMI} = 33.53 Low proportion of co-morbidities, Major Depressive Disorder most prevalent	Reduction of BE days/week at weeks 11-12 4-week cessation of BE week 12 Reduction in self-reported BED-related obsessive-compulsive symptoms week 12 (YBOCS-BE) Improved self-reported global BED symptoms week 12 (CGI-I)	Reduction in body weight at week 12 Reduction in triglyceride levels at week 12	Combined adverse event related to study drug: 67.75% Dry mouth: 36.35% Insomnia: 14.1% Headache: 15.6% Decreased appetite: 7.5% Fatigue: 6.5% Nausea: 8.55% Irritability: 6.65% Diarrhoea: 6.1% Heart rate increased: 7.3% Anxiety: 6.8% Constipation: 5.6% Hyperhidrosis: 5.2% Jittery: 5.6% Blood pressure increased: 5.0% Respiratory tract infection: 4.2%	Funded by Shire. Authors consult, receive grant funding, employment, and hold stock shares in Shire

Kornstein et al.(2019) (extension study)						Age < 40: N = 398 Age ≥ 40: N = 347	Demographics for age < 40y M_{Age} = 29.82 Sex = F: 347 (87.2%) M_{BMI} = 33.45 Demographics for age ≥ 40y, Study 2 M_{Age} = 47.35 Sex = F: 293 (84.4%) LDX M_{BMI} = 33.52	Greater reduction of BE days/week 12 weeks, no difference between genders Greater improvement of global BED symptoms at 12 weeks no difference between genders Greater reduction of BE days/week at 12 weeks no difference between age subgroups Greater improvement of global BED symptoms at 12 weeks no difference between age subgroups	Greater improvement in BED- related obsessive-compulsive symptoms at weeks 11/12 no difference between genders Greater improvement in BED- related obsessive-compulsive symptoms at weeks 11/12 no difference between age subgroups		Funding by Shire Authors consult and hold stock in Shire Authors receive research support, and employment from Shire
McElroy et al.(2017) (extension study)								Greater change in BE days/week, and BE episodes/week decreased from week 1 through weeks 11/12 Greater improvement of self-reported global BE symptoms (CGI-I) Greater partial to full cessation of BE episode from week 1-week 12	Greater change in body weight from baseline to weeks 10 and 12 Improvement in BED- related obsessive-compulsive symptoms at weeks 4, 8, and 12 (YBOCS- BE)		Funding by Shire Authors consult, receive grant support, and hold scientific advisory board membership from Shire

McElroy, Martens et al.(2015)	RCT Phase I	Chronic Flexible-dose ranging from 20-70mg/d average daily dose LDX = 38.8mg final daily dose LDX = 52.7mg	8-week treatment, 4-week follow-up	Clinical Bipolar I and II Disorder and syndromal depression	Placebo	N = 25	M_{Age} = 43.0 Sex = F: 17 (68%) Total M_{BMI} = 34.5	Improved self-reported BE symptoms (BES) during treatment and at endpoint (8-weeks)	Reduced self-reported depression during treatment and at endpoint (IDS-SR) Reduced cholesterol during treatment and at endpoint and reduced triglycerides at endpoint Improved self-reported fatigue ratings at endpoint (FSS)	Headache: 45% Insomnia: 36% Decreased appetite: 18% Dry mouth: 36% Feeling jittery: 36% Fatigue: 9% Nausea: 18% Pyrexia: 18% Tremor: 27% Anxiety: 18% Diarrhea: 9% Irritability: 18% Palpitations: 9% Gastroenteritis: 0% Sinus congestion: 18% Strep throat: 9% Upper respiratory infection symptoms: 9%	Funded by Shire Authors are consultants, co-investigators, and members of Shire advisory boards
Srivastava et al.(2019)	Case report Phase Post-approval	Chronic Intensive lifestyle modification therapy and LDX 20-70mg titration: 20mg LDX from weeks 0-4 30mg from months 1-11 40mg from months 11-17 50mg from months 17-18	18 months	A score of 21 on the BES	None reported	N = 1	Age = 16 at treatment onset, 17 at treatment end Sex = F BMI at treatment onset = 48.89, 40.91 at treatment end Co-morbid ADHD symptoms Diagnosis of developmental delay/autism	Reduction of self-reported BED symptoms (BES) at 6 months of treatment	Reduction in BMI at 2 weeks and sustained until end of treatment Reduction of self-reported food cravings at 6 months and reduction reported again at 13 months Self-reported reduction in hunger at 13 months Improvement in focus reported at 2 weeks and sustained	NA	Received no external funding No conflicts of interest reported

							and milieu instability		until end of treatment with exception of LDX non-compliance periods Self-reported reduction in stress and anxiety at 16 months of treatment		

Table 12. Extension studies utilising the same data set are listed in bold and italics under the original study. Results of these studies that offer new findings beyond the original paper are listed in bold and italics under the results of the original study. Abbreviations: ADHD: Attention-Deficit Hyperactivity Disorder; BE: binge eating; BED: Binge Eating Disorder; BES: Binge Eating Scale; BIS-11: Barratt Impulsiveness Scale – Version 11; BMI: body mass index (kg/m^2); CAARS: Conners' Adult ADHD Rating Scales; CGI-I/S: Clinical Global Impressions – Improvement/Severity; EDE-Q: Eating Disorder Examination Questionnaire; EEG: electroencephalography; EI: Eating Inventory; F: female; FCI: Food Craving Inventory; FSS: Fatigue Severity Scale; HAM-A: Hamilton Rating Scale for Anxiety; HbA1c: Haemoglobin A1C; IDS-SR: Inventory of Depressive Symptomatology – Self Report; LDX: lisdexamfetamine dimesylate; M: male; *M*: mean; MADRS: Montgomery-Asberg Depression Rating Scale; RCT: randomised controlled trial; TFEQ: Three Factor Eating Questionnaire; YBOCS-BE: Yale-Brown Obsessive Compulsive Scale for Binge Eating.

Appendix D: Characteristics of the Preclinical Studies

Table 13. Characteristics of Preclinical studies

Source	Model	Species /Strain/ restriction	Dose/ route of Administration	Comparator	Sample Size	Behavioural Outcome measures	Declaration of interests
Ekstrand et al. (2019)	Ad-libitum water and food	Long-Evans male rats Non-food restricted	Chronic Oral 1.5mg/kg 20-day experimental period	Vehicle	N = 12	LDX-treated rats weighed less at the end of treatment than vehicle-treated rats LDX-treated rats had lower renal and mesenteric adiposity, as well as less epididymal fat mass than vehicle-treated rats No difference in running wheel activity, water intake, or food intake between vehicle and LDX-treated rats. No difference in anxiety between vehicle and LDX-treated rats LDX-treated rats were faster at performing a spatial working memory task (Water Maze)	Funding source and conflicts of interest not reported
Heal et al. (2016)	Food reward/punished responding conflict model for chocolate 24-hour home cage chow intake	Female Wistar rats Non-food restricted	Acute Oral 0.8mg/kg	Non-binge-eating rats and vehicle	N = 34	LDX reduced chocolate consumption in BE rats in 2-hour test session: LDX reduced 24-hour home cage chow intake in BE rats. LDX reduced 24-hour home cage chow intake in non-BE rats. LDX did not affect water intake or body weight over 24 hours in BE rats or non-BE rats Conflict task In BE rats LDX reduced: the number of escapes, time receiving foot shocks; the % of trials foot-shocks were received; time taken to respond to the warning tone/light and avoid a shock. LDX increased avoidances in BE rats	Funding provided by Shire Authors are employees and shareholders of Shire

Presby et al. (2020)	Chocolate exposure training (CE) group versus chow exposure (LChE) / versus empty dish Intake of chocolate and chow presented as choice (CE group) or chow intake only (LChE) Effort-related motivational choice model: Lever pressing for chocolate pellets versus concurrent chow access	Female Wistar rats Non-food restricted	Acute IP 0.1875, 0.375, 0.75, or 1.5 mg/kg	Vehicle and control chow-only exposure group (LChE)	N=30	LDX decreased free intake of chow and chocolate in CE group and tended to decrease chow intake in LChE group For operant sessions: LDX reduced lever pressing for chocolate pellets in CE group and control group (LChE group and the empty food dish group combined) and chow intake reduced in CE group. In control group no reduction in chow in intake	Funding provided by Shire Conflicts of interest not reported
Sachdeo et al. (2019)	Repeated limited access to palatable foods (sweetened hydrogenated vegetable shortening	*OPRM1 A112G* female mice – either AA or GG homozygous	Once/week acute oral dosing: 0.15, 0.5, and 1.5 mg/kg 14 days chronic oral administration 1.5 mg/kg	4 groups (restrict, restrict binge, binge, naïve) vehicle	N=254	No significant effects of either acute or chronic administration of LDX on intake or weight in any groups for either AA or GG mice	Funding provided by Shire Reported no conflicts of interest
Vickers et al. (2015)	Time-limited, intermittent, irregular access to a palatable food (ground milk chocolate) in addition to freely available standard powdered diet	Female Wistar rats Non-food restricted	Acute oral 0.1, 0.3, 0.6, 0.8, 1.0 and 1.5 mg/kg Alone and in combination with *SCH-23390, raclopride,*	Vehicle	Cohort 4 sample size N=75	LDX (doses ≥ 0.3 mg/kg) reduced chocolate but not chow intake during 2-hour binge session. LDX (doses ≥ 0.3 mg/kg) reduced total food intake (chocolate and chow) but had no effect on water intake or body weight over 24 hours *LDX and SCH-23390 / raclopride* SCH-23390 (0.1 mg/kg) attenuated LDX (0.1 mg/kg) reduction in chocolate intake in 2-hour binge session. SCH-23390 (0.1 mg/kg)/LDX (1.0 mg/kg) combination did not consume less chocolate than vehicle, but ate non-significantly more than LDX alone group. The LDX (1.0	Funding provided by Shire Authors are employees of Shire and hold stock in Shire

			prazosin and RX821002			mg/kg) reduction in chow intake in the 2-hour binge test was not modified by SCH-23390 (0.1 or 0.3 mg/kg). Raclopride (0.1 or 0.5 mg/kg) did not attenuate LDX (1.0 mg/kg) reduction of chocolate and chow intake in 2-hour binge test *LDX & prazosin / RX821002* Prazosin (0.3 and 1.0 mg/kg) attenuated the reduction in chocolate consumption induced by LDX. LDX (1.0 mg/kg) did not alter chow intake in 2-hour binge session, but prazosin (0.3 mg/kg)/LDX (1.0 mg/kg) reduced chow intake in 2-hour binge session compared to vehicle. RX821002 (0.1 or 0.3 mg/kg) did not attenuate LDX (1.0 mg/kg) reduction of chocolate in 2-hour binge session	
Vickers et al. (2017)	Two-lever, delay-discounting task: one lever delivered a single chocolate-flavoured pellet immediately and the other a three-pellet reward after increasing delay	Female Wistar rats Non-food restricted	Acute oral 0.3 and 0.8mg/kg	Non-binge-eating control group and vehicle	N = 28 19 BE rats and 9 controls	0.8mg/kg LDX reversed BE rats' reduced preference for a larger and more delayed reward.	Funding provided by Shire. Authors are employees and shareholders of Shire
Yohn et al. (2016)	Effort-related motivational choice model: Lever pressing for chocolate pellets versus concurrent chow access	Male Sprague Dawley rats Food restricted	Acute IP 0.09, 0.1875, 0.375, 0.75, and 1.5 mg/kg	Vehicle	Study 3: N = 16 Study 4: N= 12	Study 3: LDX (0.75 mg/kg) had no effect on chow intake nor lever pressing for pellets Study 4: LDX (0.75 and 1.5 mg/kg) increased lever pressing for pellets and reduced intake of concurrently available chow	Funding multi-grant supported (no funding from Shire). Author has received grants, employment, consultation work, and stock in Shire

Table 13. Abbreviations: BE: binge eating; IP: intraperitoneal injection; LDX: lisdexamfetamine dimesylate.