NEUROCOGNITIVE AND PSYCHOPHARMACOLOGICAL MECHANISMS UNDERLYING DISORDERED EATING

by

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A thesis submitted to the University of Birmingham for the degree of
DOCTOR OF PHILOSOPHY

School of Psychology
University of Birmingham
January 2022

Abstract

The aim of this thesis was to investigate the neurocognitive and psychopharmacological mechanisms underlying disordered eating. Chapter One provides an introduction to the research area. In Chapter Two, inattentive and impulsive ADHD symptoms in a population sample predicted disordered eating, and negative mood fully accounted for the relationship between impulsivity and disordered eating, while partially accounting for the relationship between inattention and disordered eating. In Chapter Three, the effects of Lisdexamfetamine Dimesylate (LDX) on neural processing of food cues in women with binge eating symptoms was assessed, to understand the mechanisms underlying the efficacy of LDX as the only approved treatment for binge eating disorder. The results demonstrated an LDX-induced reduction of thalamic responses to food cues, suggesting that this is one mechanism through which LDX reduces binge eating symptoms. A systematic review of existing literature in Chapter Four revealed that deficits in interoception are consistently associated with disordered eating. Chapter Five examined the possibility that such deficits in interoception may explain the association between cognitive processes and disordered eating identified in Chapter Two. The results from Chapter Five revealed that interoceptive accuracy specifically mediated the relationship between inattention and binge eating. The theoretical and clinical implications of these studies are discussed in Chapter Six. Briefly, the research presented in this thesis highlights the contribution of processes including attention, impulsivity, and interoception to disordered eating. These processes may prove to be efficacious targets in the future development of novel tools for screening and prevention of eating disorders and for the discovery of improved therapies.

Acknowledgements

Firstly, I would like to thank my supervisors, Professor Suzanne Higgs, Dr Pia Rotshtein and Dr Colin Dourish for supporting me throughout my PhD. Without your combination of seemingly infinite knowledge, encouragement, and compassion, none of this would have been possible. I would also like to thank Dr Maartje Spetter for taking me under her wing and teaching me the skills and confidence that I needed in the beginning.

I am indebted to all of the participants who gave their time for these studies. Without them I could not have had the privilege of researching the topics I am so interested in.

Elizabeth, Madhronica and Rachel thank you for being the most inspiring and uplifting group of friends I could ask for. Being in the office with you could always transform a difficult day into a great one. I would particularly like to thank Elizabeth, who has been beside me since the first day, and without whom I simply cannot imagine this process. There are countless others who have helped me greatly over the last four years. Thank you to Ross for always being the first to offer help, no matter what the problem was; to Sam for all of the advice, laughter and coffee breaks; to Ruth for the much-needed evenings climbing; to Stephen for the helpful discussions and to Emily for endless laughs, even after long months of lockdowns together.

Lastly I would like to thank my brilliant mum, for encouraging me and believing in me even when I didn't believe in myself.

This PhD was funded by the Biotechnology and Biological Sciences Research Council (BBSRC) in partnership with P1vital.

Published Work

Peer Reviewed Journal Articles

Martin, E., Dourish, C. T., Rotshtein, P., Spetter, M. S., & Higgs, S. (2019). Interoception and disordered eating: A systematic review. *Neuroscience & Biobehavioral Reviews*, *107*, 166-191.

Martin, E., Dourish, C. T., Hook, R., Chamberlain, S. R., & Higgs, S. (2020). Associations between inattention and impulsivity ADHD symptoms and disordered eating risk in a community sample of young adults. *Psychological Medicine*, 1-10.

Schneider, E*., **Martin, E***., Rotshtein, P., Qureshi, K. L., Chamberlain, S. R., Spetter, M. S., ... & Higgs, S. (2022). The effects of lisdexamfetamine dimesylate on eating behaviour and homeostatic, reward and cognitive processes in women with binge-eating symptoms: an experimental medicine study. *Translational psychiatry*, *12*(1), 1-8.

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Martin, E., Kaisari, P., Dourish, C., Rotshtein, P., Higgs, S., & Spetter, M. (2020, February). ADHD symptoms are associated with binge eating and enhanced reward-related neural activation to food stimuli. In *European Neuropsychopharmacology*, 31, S58-S58

Schneider, E., **Martin, E**., Dourish, C., Thomas, J., Hallschmid, M., Lee, M., ... & Spetter, M. (2020). P. 203 Intranasal insulin decreases palatable food intake, increases satiety and enhances positive mood in women with obesity. *European Neuropsychopharmacology*, *31*, S20-S21.

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* Published chapters are presented with pagination from the journal in which they are published

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Statement of authorship

This research was funded by the Biotechnology and Biological Sciences Research Council (BBSRC) in partnership with P1vital. Chapters Two, Three and Four contain material that is published in peer-reviewed journals and each chapter has been presented as a standalone paper. All authors were involved in study design and planning. I collected the data presented in all chapters except Chapter Two, which utilised data from an existing cohort. I analysed the data in all chapters under the supervision of Suzanne Higgs, Pia Rotshtein and Colin Dourish. I wrote all chapters, with feedback and editing provided by Suzanne Higgs, Colin Dourish and Pia Rotshtein.

Chapter One: General Introduction

1.1 Eating Disorders

There are three main eating disorders defined in the Diagnostic and Statistical Manual of Mental Disorders DSM-V (APA, 2013): Anorexia Nervosa (AN), Bulimia Nervosa (BN) and Binge Eating Disorder (BED). The typical presentation of AN involves restriction of food intake, an intense fear of gaining weight despite being underweight, and a disturbance in perception of one's own weight. BN is characterised by recurrent episodes of binge eating that are accompanied by repeated compensatory behaviours, such as vomiting, use of laxatives and fasting, to prevent weight gain. A binge eating episode is defined as eating in a discrete period an amount of food that is much larger than most people would consider normal. Binge episodes may be associated with a lack of control overeating during the eating episode; eating more quickly than usual; feeling uncomfortably full and feeling guilt, embarrassment and distress about the binge eating behaviour. BED is also characterised by recurrent binge eating but unlike BN, BED is not associated with compensatory behaviours. In addition to these three defined eating disorders the DSM-V, includes the category of Other Specified Feeding or Eating Disorders (OSFED) which refers to presentation of symptoms not meeting typical diagnostic criteria for AN, BN or BED. For example, symptoms meeting the criteria for AN but maintaining normal range weight, or meeting the criteria for BED or BN and exhibiting binge eating/compensatory behaviours less frequently than required for diagnosis of either disorder.

The worldwide lifetime prevalence of eating disorders is estimated at 8.4% for women and 2.2% for men (Galmiche, Déchelotte, Lambert & Tavolacci, 2019). The estimated lifetime prevalence rate for AN, BN and BED is 1.4% for women and 0.2% for

men, 1.9% for women and 0.6% for men and 2.8% for women and 1% for men respectively (Galmiche, Déchelotte, Lambert & Tavolacci, 2019).

Eating disorders are associated with impairments of psychological and physical function. For example, a diagnosis of AN requires a patient to have significantly low body weight (APA, 2013), complications of which can include osteoporosis, endocrine and cardiovascular problems (Sachs, Harnke, Mehler & Krantz, 2015; Westmoreland, Krants & Mehler, 2016) the latter being a potential cause of death in patients with the disorder (Westmoreland, Krants & Mehler, 2016). Physical health complications are also present in BN, particularly as a consequence of purging behaviours (Westmoreland, Krants & Mehler, 2016) which can lead to oral and oesophageal damage and irritation and cardiac arrhythmias (Sachs & Mehler, 2016).

Binge episodes in BED are not associated with any compensatory behaviours and so in approximately 67% of patients BED is associated with overweight (Body Mass Index (BMI, kilogram/metre^2) $\geq$ 25) and obesity (BMI $\geq$ 30) potentially due to excess energy intake (Dingemans, Bruna & Furth, 2002). However, the relationship between BED and body weight is complex. Patients with BED can present as underweight, healthy weight, overweight, or having obesity (Fairburn et al., 2000; Hudson et al., 2007). A WHO World Mental Health Survey on the prevalence of BED reported that, while 30.7% of patients had overweight and 36.2% had obesity, 31.7% were healthy weight and 1.3% of patients were underweight (Kessler et al., 2013). Further, it has been proposed that underweight and healthy weight individuals may be a distinct subset of BED patients who exhibit greater usage of healthy and unhealthy weight control behaviours compared to BED patients with overweight and obesity (Goldschmidt et al., 2011). Overweight and obesity are of concern worldwide due to increasing prevalence. Obesity prevalence has recently been estimated at 19.5-37% in Europe and 38.5% in the USA (Janssen, Bardoutsos & Vidra, 2020), with

these figures predicted to rise to 24-37% in Europe and 44% in the USA between 2030 and 2052 (Janssen, Bardoutsos & Vidra, 2020). Overweight and obesity are associated with an increased likelihood of developing a range of health conditions including type-2 diabetes, cardiovascular disease and cancers, and globally pose a large economic burden, as well as a burden on healthcare systems (Chu et al., 2018).

1.2 Risk factors for Eating Disorders

Several risk factors associated with eating disorders have been identified. For example, research into genetic predisposition to AN has so far revealed eight genetic loci for the condition, and research is ongoing to determine candidate genes for BN and BED (Treasure et al., 2020). One potential heritable risk factor for eating disorders is a personality endophenotype that increases susceptibility to eating disorders such as body dissatisfaction, thin-ideal internalisation, ineffectiveness (e.g. feelings of worthlessness and inadequacy) and body dissatisfaction (Wilksch & Wade, 2009). Stice and Desjardins (2018) found that an interaction between low body weight and body dissatisfaction predicted future onset of AN, whereas overeating and thin-ideal internalisation predicted BN, and body dissatisfaction and overeating predicted BED. Negative affect and functional impairment (e.g. impairment in daily functioning) increases the risk for future onset of all eating disorders (Stice, Gau, Rohde & Shaw, 2017). There are several possible routes through which negative affect may contribute towards disordered eating, for example both binge and restrictive eating may provide a coping mechanism for individuals to cope with negative affect (e.g. Goossens, Braetm Vlierberghe & Mels, 2009). Alternatively, negative mood can increase the tendency to act impulsively, which may increase likelihood of binge eating (Fischer, Wonderlich, Breithaupt, Byrne & Engel, 2018). Stice et al. (2017) suggest that functional impairment contributes to negative affect, which may in turn contribute further towards eating disorders. Moreover, a recent meta-

analysis assessing the relationship between negative affect and disordered eating revealed a bidirectional association (Puccio, Fuller-Tyszkiewicz, Ong & Krug, 2016) suggesting that negative affect and disordered eating both increase the risk of the other.

AN, BN and BED have also been associated with behavioural traits which potentially predispose individuals to the disorders. For example, patients with AN have been demonstrated to show reduced automatic approach responses (reflecting automatic tendencies to orient motivation towards stimuli) to food cues (Veenstra & Jong, 2011; Paslakis, Kühn, Schaubschläger, Schieber, Röder, Rauh, & Erim, 2016) which may reflect a susceptibility to restrict food intake. Conversely, reduction of approach biases in individuals with symptoms of BN and BED shows some promise for reducing symptoms (Brockmeyer et al., 2019; Gordon, Williamson, Gkofa, Schmidt, Brockmeyer & Campbell, 2021), suggesting that approach biases towards food may be a risk factor contributing to binge eating in both BED and BN.

1.3 Current treatment for Eating Disorders

Currently psychological treatments such as cognitive behavioural therapy (CBT) and focal psychodynamic psychotherapy (FPT) are most common for AN, at times combined with nutritional intervention to aid weight gain (Brockmeyer, Friederich Schmidt, 2018). Additionally, for adolescents, family-based therapy appears to be of particular value (Couturier, Isserlin & Lock, 2010). To date there are no pharmacological treatments approved specifically for AN. In adults AN is associated with high relapse rates and low recovery rates (Khalsa, Portnoff, McCurdy-McKinnon & Feusner, 2017; Berends, Boonstra & Van Elburg, 2018). These poor disease outcomes highlight the importance of further research into effective treatments for AN.

Psychological treatments are also common for BN, with CBT showing some effectiveness (Linardon et al., 2017). Similarly to AN, adolescent patients with BN may benefit from family-based therapy (Le Grange, Lock, Agras, Bryson, Jo, 2015). Relapse is also common after treatment for BN. For example Halmi, Agras, Mitchell, Wilson, Crow, Bryson & Kraemer (2002) found that 44% of their sample experienced symptom relapse within 4 months of treatment, despite displaying absence of symptoms at the termination of treatment. Currently the only approved pharmacological treatment for BN is the antidepressant fluoxetine, which is of potential benefit to patients who relapse following psychotherapy (Walsh et al., 2000).

Currently CBT is the most frequently used psychotherapy to address mechanisms supporting BED (e.g. body image concerns) and shows efficacy when compared to being on a waitlist and to other psychotherapies (Hay, Bacaltchuk, Stefano & Kashyap, 2009; Hilbert, Petroff, Herpertz, Pietrowsky, Tuschen-Caffier, Vocks & Schmidt, 2019). There is evidence that antidepressant medications, including selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, show some efficacy in reducing symptoms of BED (Appolinario, Nardi & McElroy, 2019), although this symptomatic change is not accompanied by weight loss. There is also some limited evidence of potential for anticonvulsants to reduce symptoms of BED (Appolinario, Nardi & McElroy, 2019), the mechanisms underlying which are largely unknown, but may result from suppression of appetite or enhancement of satiety due to their effects on monoamine release (Schiffer et al., 2001) and/or on glutamate receptors (McElory et al., 2007). However, neither antidepressant nor anticonvulsant medications are approved to treat BED, due to lack of evidence for long-term efficacy and potential adverse effects (McElroy et al., 2015). Lisdexamfetamine dimesylate (LDX), a pro-drug of d-amphetamine, it is not pharmacologically active when ingested, but is metabolised following ingestion into l-

lysine and active d-amphetamine. LDX is the only marketed pharmacological treatment for BED and the drug is only approved in a limited number of countries (such as the US, Australia and Canada) and is not approved in most European countries. LDX shows efficacy in reducing both symptoms and relapse rates in BED (Hudson, McElroy, Ferreira-Cornwell, Radewonuk & Gasior, 2017). Despite the efficacy of LDX in treating symptoms of BED, the neural and cognitive mechanisms that mediate its effects are unknown. In addition, LDX is a stimulant and a Schedule 2 controlled drug in the US and the UK. A recent review of drug therapy for BED highlighted the urgent need for further research into improved drugs to treat BED (Levitan, Papelbaum, Carta, Appolinario & Nardi, 2021). Treatments for BED also target overweight and obesity although as noted above only approximately two thirds of BED patients are overweight or obese. These treatments include lifestyle changes (e.g. dietary changes and increased physical activity), pharmacological therapies and surgical approaches (such as gastric banding/bypassing). However, a recent review revealed that BED negatively impacts the ability to maintain weight loss (Kantilafti, Chrysostomou, Yannakoulia & Giannakou, 2021). Overall, the currently available treatments for BED show mixed effectiveness (Hilbert, Petroff, Herpertz, Pietrowsky, Tuschen-Caffier, Vocks & Schmidt, 2020) and many weight management interventions show limited efficacy for long-term weight loss (Ruban, Stoenchev, Ashrafian, & Teare, 2019) with weight regain common following a range of weight-control interventions (Anderson, Konz, Frederich,& Wood, 2001; Magro, Gelonez, Delfini Pareja, Callejas & Pareja, 2008).

1.4 Mechanisms Underlying Eating and Disordered Eating

The burden of eating disorders, disordered eating and obesity, and the lack of existing effective treatments clearly warrants further research. Identifying the mechanisms that may lead to the development of disordered eating could highlight worthwhile targets

for treatment and prevention of eating disorders and disordered eating. To understand the mechanisms that underlie disordered eating, it is useful to first discuss the mechanisms that underlie eating. The control of appetite has been proposed to be underpinned by interactions between metabolic, cognitive and reward systems (Higgs, Thomas, Rotshtein, Lee, Hallschmid, & Dourish, 2017).

1.4.1 Homeostatic/Metabolic Control of Appetite

Food intake is crucial for survival and as a result a homeostatic system ensures sufficient intake of energy, through signals of energy depletion (e.g. hunger). In addition, to maintain a relatively constant internal bodily state there is also an interacting system to discourage overconsumption, through signals of short-term satiety and of existing energy storage. Information about nutritive state is received from the gastrointestinal tract by the brainstem and hypothalamus. The hypothalamus is a key brain area involved in the homeostatic control of appetite, in particular the arcuate nucleus (ARC). Distinct nuclei involved in food intake control in the ARC are the orexigenic (appetite promoting) Neuropeptide Y (NPY)/agouti-related protein (AgRP) neurones and the anorexigenic (appetite suppressing) proopiomelanocortin (POMC) neurones. These nuclei receive and integrate inputs from numerous hormones, neuropeptides and neurotransmitters known to be involved in regulation of energy intake.

The neuropeptide hormones peptide YY (PYY), cholecystokinin (CCK) and Glucagon-like peptide-1 (GLP-1) are secreted from intestinal cells post-ingestion in proportion to the number of calories consumed, to promote satiety and reduce food intake (Strader & Woods, 2005; Raybould, 2007; Woods & D'Alessio, 2008; Ahima & Antwi, 2008; Perry & Wang, 2012). Information is then relayed to the hypothalamus via the brainstem, and contributes to the detection of ingested nutrients and subsequent termination of an eating episode through activating POMC neurones and suppressing

NPY/AgRP neurones (Ueno & Nakazato, 2016; Beutler, Chen, Ahn, Lin, Essner & Knight, 2017; He et al., 2019). Due to the role of these hormones in reducing food intake, their potential in weight management treatments has been assessed (Zac-Varghese, De Silva & Bloom, 2011; Pathak, Flatt, & Irwin, 2018) and GLP-1 agonists have been approved as weight management therapies (Crane & McGowan, 2015) and show potential efficacy in assessment of use as a potential novel therapy for binge eating (Robert, Rohana, Shah, Chinna, Modamud & Kamaruddin, 2015).

In addition to the aforementioned short-term signals to reduce intake, the hormones insulin and leptin are involved in the hypothalamic control of appetite. Insulin and leptin are secreted in proportion to adiposity, serving as longer-term signals of energetic state by reflecting existing energy stores in the body (Considine et al., 1996; Schwartz, Peskind, Raskind, Boyko & Porte Jr, 1996; Staiger et al., 2003; Benoit, Clegg, Seeley & Woods, 2004). Leptin is produced primarily from adipose cells (Klein, Coppack, Mohamed-Ali & Landt, 1996), but also in small amounts by the stomach (Sobhani et al., 2000) and insulin is released from the pancreas. Insulin and leptin cross the blood-brain barrier to contribute to hypothalamic control of appetite by activating POMC neurones and inhibiting NPY/AgRP neurones, leading to a reduction in appetite (Ghamari-Langroudi, Srisai & Cone, 2011; Mercer, Chee, Colmers & Colmers, 2011; Qiu et al., 2014; Shadel & Horvath, 2015; Timper & Brüning, 2017).

The hormone ghrelin is produced mainly in the gastrointestinal tract and has long been considered a major orexigenic hormone (Atalayer, Gibson, Konopacka & Geliebter, 2013) as it has a short-term effect of encouraging meal initiation (Cummings, 2006). When an individual is in a nutrient depleted state (e.g. during hypoglycemia), circulating levels of ghrelin elicit feeding. Conversely, when an individual is in a satiated state circulating levels of ghrelin decrease (Cummings, 2006). Ghrelin is the only known circulating

hormone to stimulate NPY/AgRP neurones, and inhibit POMC neurones (Horvath, Diano, Sotonyi, Heiman & Tschöp, 2001; Ferrini, Salio, Lossi & Merighi, 2009). In addition to eliciting eating, ghrelin also has a slower-acting role in energetic homeostasis through increasing adiposity (Al Massadi, López, Tschöp, Diéguez & Nogueiras, 2017; Cummings, 2006).

In addition to hormonal and neuropeptide influences on appetite, several neurotransmitters, including serotonin and noradrenaline, are involved in the hypothalamic control of appetite. Serotonin 5-HT_{2C} receptors are expressed on the anorexigenic POMC neurones of the ARC, and activation of these receptors excites the POMC neurones (Heisler et al., 2002; Sohn, Xu, Jones, Wickman, Williams & Elmquist, 2011). Drugs that stimulate 5-HT_{2C} receptors are known to reduce appetite and the 5-HT_{2C} receptor agonist lorcaserin was approved for the treatment of obesity but subsequently withdrawn due to safety concerns expressed by the FDA (Halford, Harrold, Boyland, Lawton & Blundell, 2007; Brashier, Sharma, Dahiya, Sing & Khadka, 2014). The primary site of noradrenergic action in the control of appetite is the paraventricular nucleus (PVN) of the hypothalamus. Noradrenaline in the PVN has been shown to both increase and decrease food intake, for example drugs that inhibit the reuptake of noradrenaline have been shown to both suppress and stimulate appetite (Wellman, 2005), an effect thought to be a result of specific receptor subtype influences on eating (Wellman, 2000). In addition to direct action, there is also evidence for an interaction between neurotransmitter and hormonal influence on appetite, for example, ghrelin has been shown to inhibit serotonin release, contributing to the effects of ghrelin to enhance appetite (Brunetti, Recinella, Orlando, Michelotto, Di Nisio & Vacca, 2002) and leptin has been shown to inhibit noradrenaline neuronal firing and neurotransmitter release (Brunetti, Michelotto, Orlando & Vacca, 1999).

1.4.2 Reward Mechanisms

Initiation of eating in humans often occurs in the absence of signals of energy depletion and individuals frequently eat for enjoyment (Berthoud, 2012). This demonstrates that eating is not the result of a purely homeostatic drive for nutrients and that there is also a hedonic drive to eat. Rewarding responses following eating high-sugar and high-fat foods particularly (generally considered to be more palatable food types) may once have been of evolutionary benefit, to motivate consumption and decrease likelihood of energy depletion (Berthoud, 2012). In modern society, abundance of these highly palatable foods may encourage overeating with a consequence of overweight and obesity.

Reward does not simply refer to experiences of conscious pleasure. Berridge (1996) defined two components of food reward: liking and wanting. Using this definition of distinct reward components, 'liking' can be considered to reflect the palatability of and hedonic responses to food, whereas 'wanting' refers to incentive salience: motivation to seek out and consume food (Berridge, 1996). Through repeated exposure to a liked food, motivational value of food cues is ascribed through incentive salience attribution (Berridge, 2009), once this salience is ascribed, cues associated with food (e.g. visual or olfactory cues) become learned attractive motivational targets, e.g. 'wanted'. Learning refers to predictive associations between cues associated with foods (e.g. visual or olfactory cues) and the expected associated rewarding outcome (Berridge, Robinson & Aldridge, 2009).

'Liking and 'wanting' are supported by distinct neural pathways. 'Liking' is thought to be underpinned by endocannabinoid, opioid and orexin signalling particularly in the nucleus accumbens and the ventral pallidum which receives output from the nucleus accumbens and the parabrachial nucleus of the brainstem (Berridge, Robinson & Aldridge, 2009; Morales & Berridge, 2020; Smith, Tindell, Aldridge & Berridge, 2009). Other brain regions associated with the hedonic properties of food are the orbitofrontal cortex and the

insula (Morales & Berridge, 2020). In animal studies, subregions of the aforementioned brain regions seem to have distinct localised roles in liking, for example although the rostrodorsal medial shell of the nucleus accumbens has been identified as a 'hotspot' for liking, stimulation of other areas of the nucleus accumbens shell are associated with decreasing liking (Morales & Berridge, 2020).

The main neurotransmitter that mediates the 'wanting' of food is dopamine (Berridge & Robinson, 2016). Dopamine is produced in neurones of the hypothalamus, substantia nigra and ventral tegmental area (VTA). The cell bodies of dopamine neurones in the VTA are part of a key mesolimbic food reward pathway, which projects to innervate areas such as the nucleus accumbens and the prefrontal cortex (Alonso-Alonso et al., 2015). The prefrontal cortex in turn innervates both the VTA and the nucleus accumbens (Alonso-Alonso et al., 2015). Dopamine appears to have a wanting-specific role, demonstrated through the observation that suppression of dopamine reduces wanting but not liking (Morales & Berridge, 2020). This can be demonstrated in animal models, for example Berridge, Venier & Robinson (1989) found that lesions of the nigrostriatal pathway in rats led to aphagia, but perseverance of positive hedonic facial expressions in response to sucrose tasting (e.g. tongue protrusions, paw licking). In humans, activation of the mesolimbic dopamine circuit is associated with food reward, which has been demonstrated using both Positron Emission Tomography (PET) and functional magnetic resonance imaging (fMRI). For example, a meta-analysis of fMRI studies revealed that regions of the ventral striatum consistently show increased blood oxygen level dependent (BOLD) responses during attention to food (Tang, Fellows, Small & Dagher, 2012). Increased dopamine agonist binding in the ventral striatum has been associated with elevated BMI (Caravaggio et al., 2015) and activation in the nucleus accumbens and VTA while attending to food stimuli has been associated with elevated BMI and increased snack

consumption (Lawrence, Hinton, Parkinson & Lawrence, 2012; Carnell, Benson, Pantazatos, Hirsch & Geliebter, 2014) suggesting that alterations in reward responses can shape eating behaviours.

1.4.3 Cognitive Mechanisms

To identify an object as food we must direct attention towards it and recognise that it is food. Given the importance of food in the maintenance of energy homeostasis it is beneficial that attention is preferentially directed towards food and there is some evidence for this being the case. For example, Nijs, Muris, Euser & Franken (2010) found an attentional bias towards food stimuli (compared to non-food stimuli), by showing that food items (compared to pictures of office items) elicited enhanced P300 amplitude (reflective of selective attention), faster visual probe task responses, a higher proportion of first gaze fixations, and longer gaze duration. This enhanced attention may not solely be a product of metabolic or reward-driven responses to food, as there is also evidence for top-down influence. Higgs, Rutters, Thomas, Naish & Humphreys (2012) found that holding food items in working memory (maintaining information in memory while updating and manipulating this information) increased attention towards food cues. The findings of Higgs et al. (2012) suggest that thinking of food items may increase attention given to food, which is a potential mechanism that leads to increased eating. Accordingly, there is evidence to suggest heightened initial attention towards food items in individuals with overweight/obesity. For example, Werthmann et al. (2011) found that, (compared to lean women) women with overweight/obesity were more likely to initially fix their gaze on a food image than a non-food item, suggesting an attentional bias towards food cues. Interestingly, Werthmann et al. (2011) also found that participants with overweight/obesity showed a reduced maintenance of food cues in attention (e.g. reduced gaze fixation), suggesting that attention may have a complex relationship with eating. Attention may also

predict future weight gain, for example Groppe et al. (2017) found that childrens' ability to shift attention predicted BMI over a 1-year interval . Despite this evidence, results from a recent meta-analysis (Hagan, Alasmar, Exum, Chinn & Forbush, 2020) suggest that individuals with overweight/obesity do not differ in their attentional biases towards food, as measured by dot-probe tasks, emotional Stroop tasks and eye gaze measurements. The sole difference between overweight/obesity and healthy weight individuals highlighted by Hagan et al. (2020) was in automatic attention ERP measurements. Hagan et al. (2020) suggest that differences in methodology as well as a lack of consideration of potential moderating influences (e.g. binge eating) may contribute to these null findings. In summary, it is clear that attention is preferentially given to food items compared to non-food items, however the impact of increased attention towards food cues on eating behaviour is unclear.

Following attentional focus towards food, a decision to approach and eat the food may or may not be made. Making a decision about what food to eat, and how much of it to eat can be considered as a neurocomputation that depends on the outcome of three systems: Pavolvian, habitual and goal-directed (Rangel, 2013). The Pavlovian system refers to the learned 'wanting' described previously, resulting from the paired associations between food stimuli (e.g. the sight of an appetising food) and the reward response resulting from consumption. Habitual control is the consequence of repeated exposure to a rewarding stimulus within a certain context, which leads to the context eliciting behaviour (e.g. eating certain food) regardless of the outcome. Unlike the habitual control system which considers only stimulus-action associations, the goal-directed system incorporates longer-term 'future-looking' (Rangel, 2013) outcomes, such as health outcomes. As longer-term goals may be in conflict with Pavlovian/habitual responses, the decision to, for example, inhibit eating a food that undermines future health goals is therefore dependent

on the goal-directed system accurately ascribing value to certain food choices and inhibiting the habitual and Pavlovian systems (Rangel, 2013), which may otherwise encourage overeating.

Working memory appears to be a key cognitive process underpinning the computations described above and adherence to long-term dietary goals may require maintenance of these long-term goals in working memory (Higgs & Spetter, 2018). Long-term goals are recruited from long term memory into working memory to create active representation of these goals, and this may contribute towards self-regulation (Hoffmann, Schmeichel & Baddeley, 2012). Behaviourally the relationship between working memory and food intake has been demonstrated in a study by Whitelock, Nouwen, van den Akker & Higgs (2018), who found that better visuospatial memory performance was associated with lower intake of high energy dense foods in a taste-test.

In addition to working memory, research suggests that episodic memory is a key cognitive mechanism for influencing food intake through supporting satiation (Higgs & Spetter, 2018). Notably, patients with amnesia show a propensity to overeat and report difficulties in determining internal signals such as fullness (Higgs, 2005). Distraction during eating (preventing attention and encoding of memories of the eating episode) can increase the amount eaten at subsequent meals, whereas enhancing memory (e.g. through cued recall of previous meals) can decrease eating at subsequent meals (Robinson, Aveyard, Daley, Holly, Lewis, Lycett & Higgs, 2013). Martin, Davidson & McCrory (2018) demonstrated that performance in an episodic memory task was positively associated with dietary restraint, avoidance of fatty foods and strategic dieting, and negatively associated with uncontrolled eating and emotional eating. These associations between attention, memory and overeating provide some insight into how cognitive processes may influence binge eating. It is unclear whether increased propensity of binge

eating/overweight and obesity in individuals with deficits in attentional processes (e.g. in attention deficit hyperactivity disorder, ADHD) occur as a direct result of trait inattention and associated cognitive deficits.

The role of memory as described above is to support adherence to health goals, and this can encourage inhibitory control of impulsive responses to food. Impulsivity can broadly be considered as the inability to exert inhibitory control over prepotent thoughts or behaviours (Logan, Schachar & Tannock, 1997), and higher trait impulsivity may influence food intake. Increased impulsivity and poorer inhibitory control have been associated with increased BMI and obesity (Batterink, Yokum & Stice, 2010; Rydén, Sullivan, Torgerson, Karlsson, Lindroos & Taft, 2003). The mechanism through which impulsivity increases body weight may be through a positive association with overeating in response to external and emotional cues, as well as basing food choices on taste as opposed to health (Jasinska, Asuda, Burant, Gregor, Khatri, Sweet & Falk, 2012). Accordingly, heightened impulsivity/ less inhibitory control is also associated with an increased likelihood of binge eating (Kessler, Hutson, Herman & Potenza, 2016; Schag, Schonleber, Teufel, Zipfel & Giel, 2013). Deficits in inhibitory control related to food have been associated with decreased activity in the dorsolateral prefrontal cortex (Gluck, Viswanath & Stinson, 2017). Together, this evidence suggests that inhibition, impulsivity and the neural systems that underpin them may contribute towards overeating and disordered eating.

1.4.4 Altered Homeostatic, Reward and Cognitive Systems in Eating Disorders

There is evidence to suggest that disruption to the homeostatic, reward and cognitive systems is associated with eating disorders and disordered eating. In a recent genome-wide association study, Watson et al. (2019) found genetic correlations between AN and a range of metabolic phenotypes including fasting insulin and leptin, suggesting

that metabolic dysregulation may be a risk factor for AN. Recently, a study assessing polygenic associations with eating disorders (Hübel et al., 2021) found positive associations between anthropometric polygenic scores (such as waist circumference, overweight and obesity) and BED and BN, but negative relationships with AN. These results suggests that genomic differences in regulation of body weight may underlie differences in eating disorder symptomatology. Further, genetic studies have highlighted a potential role for polymorphisms in genes responsible for ghrelin in AN (e.g. Müller et al., 2011) suggesting disruption in the ghrelinergic system may lead to an increased risk of AN. There is also evidence for a reduced suppression of ghrelin post-meal (Kojima et al., 2005) and reduced circulating leptin (Jimerson, Mantzoros, Wolfe & Metzger, 2000) in patients with BN, suggesting alterations in levels of these hormones may be contributing factors to overeating in BN.

Alterations in reward processing have also been documented in individuals with eating disorders. There is consistent evidence (Amlung et al., 2019) that patients with AN display a tendency to delay reward more readily than healthy controls (e.g. Steinglass, Figner, Berkowitz, Simpson, Weber, Walsh, 2012), whereas patients with eating disorders involving binge eating (e.g. BN and BED) may be more likely to accept a sooner reward, even if this reward is smaller (McClelland, Dalton, Kekic, Bartholdy, Campbell & Schmidt, 2016). There is also neural evidence for altered reward processing in eating disorders, for example Wagner et al. (2008) found that women recovered from AN showed lower BOLD activation in reward-related areas (e.g. ventral striatum) in response to sweet taste, compared to healthy controls. Following administration of the dopamine transporter blocker methylphenidate, participants with BED and obesity show enhanced striatal extracellular dopamine levels compared to participants with obesity but not BED, suggesting that alterations in dopaminergic reward processing may contribute towards

binge eating (Wang et al., 2012). Although the evidence is somewhat inconsistent (Ritschel et al., 2015), if these alterations in reward processes are present, they may contribute to the restriction of food in AN, and overeating in BN and BED.

Cognitive process may also be implicated in eating disorders. For example, deficits in a range of memory components have been observed in active and weight-restored AN (e.g. Nikendei et al., 2011), as well as reductions in hippocampal (a region involved in learning and memory) volume, although evidence is inconsistent (e.g. Lao-Kaim, Giampietro, Williams, Simmons & Tchanturia, 2020). It is unclear whether the presence of memory deficits in both active and weight-restored AN suggests that memory deficits contribute to the development of AN, or vice versa. Memory deficits have also been observed in a range of facets of memory in BN, for example Bosanac et al. (2007) demonstrated poorer immediate and delayed word recall in participants with BN compared to healthy controls. Alterations in memory performance have also been observed in BED, for example Eneva, Murray & Chen (2017) found reduced immediate and delayed visuospatial memory performance in women with BED compared to healthy controls. Given the previously discussed role of memory in the control of eating, the memory deficits present in individuals with eating disorders may reflect a role for memory deficits in the development of disordered eating and eating disorders.

There may also be a role for attention in eating disorders. Halevy-Yosef et al. (2019) found increased self-reported attention deficits in patients with eating disorders compared to healthy controls. In addition, there is experimental evidence for attentional differences related to eating disorders, for example Jonker, Glashouwer, Hoekzema, Ostafin & Jong (2019) found that patients with AN showed less attentional engagement to food pictures (assessed using a measure of spatial attention allocation) compared to healthy controls, which suggests reduced attention to food cues may play a role in

restrictive eating seen in AN. Conversely, participants with BED have been demonstrated to show enhanced engagement with food words compared to participants without BED (Schmitz, Naumann, Biehl & Svaldi, 2015), suggesting attentional bias towards food may contribute towards BED. Despite this apparent increased attention towards food in BED, self-report measures of attention deficits suggest that BED is associated with higher levels inattention (e.g. Bleck, DeBate & Oliviardia, 2015). Overall, it seems that attention, both towards food and in general may contribute to disordered eating.

1.4.5 Interaction between homeostatic, reward and cognitive control of appetite

Although thus far, homeostatic, reward and cognitive systems have been discussed independently, in reality the three systems interact to influence appetite. The interaction between homeostatic and reward process has been widely documented in both animal and human research. Leptin receptors are found on the dopaminergic neurones of the VTA which project to the nucleus accumbens (Figlewicz, Evans, Murphy, Hoen & Baskin, 2003). Animal studies reveal that administration of leptin appears to inhibit dopaminergic activity in the VTA and reduces food intake (Hommel et al., 2006). This suggests a role for leptin in decreasing the reward value of food when satiated which will discourage intake. Stimulation of insulin receptors in the brain have been shown to decrease activity of dopaminergic reward circuits (Figlewicz, 2003; Mebel et al., 2012). GLP-1 receptors are expressed in areas of the mesolimbic reward pathway, activation of which is thought to contribute towards reduced food reward when satiated (Dickson, Shirazi, Hansson, Bergquist, Nissbrandt & Skibicka, 2012). Ghrelin has been found to increase ‘wanting’ but not ‘liking’ of food (Figlewicz & Sipols, 2010) through stimulating dopamine release in the mesolimbic system (Abizaid et al., 2006; Abizaid, 2009), and therefore increasing motivation to eat when in a non-satiated state.

Recently attention has been given to evidence that cognition also interacts with homeostatic and reward processes to control appetite (Higgs, Spetter, Thomas, Rotshtein, Lee, Hallschmid & Dourish, 2017). Many of the aforementioned metabolic signals influence cognitive processes. For example ghrelin administration increases activity (e.g. fMRI BOLD response) in the hippocampus in healthy adults when attending to food pictures, and has been shown to increase memory for food items but not non-food items, whereas there is evidence in animals and humans to suggest that leptin may improve cognitive function, potentially related to inhibitory control of intake (Higgs et al., 2017).

Thomas, Higgs, Dourish, Hansen, Harmer and McCabe (2015) found that, compared to when hungry, satiated participants show reduced fMRI BOLD response to food cues in areas associated with food reward, including the nucleus accumbens, ventromedial prefrontal cortex and hypothalamus, whereas satiation was associated with increased activation in the dorsolateral prefrontal cortex (an area typically associated with cognitive control). This demonstrates how both cognitive and reward system activation responds to changes in metabolic state.

Attentional bias towards a food cue present when hungry decreases significantly following satiation to that food (di Pellegrino, Magarelli & Mengarelli, 2011) reflecting how changes in energy balance influence cognitive processes. Di Pellegrino, Magarelli and Mengarelli (2011) found that this effect was specific to the type of food eaten and was accompanied by a decrease in the subjective pleasantness of the food, an example of sensory-specific satiety. This study, showing how satiation decreases both reward and cognitive responses to food, demonstrates how homeostatic, reward and cognitive systems interact.

For homeostatic, cognitive and reward systems to interact to control food intake, information about the current state of the body must be monitored and interpreted. This process must also allow predictions about how eating will change the current nutritional state. Interoception is defined as "the process by which the nervous system senses, interprets, and integrates signals originating from within the body, providing a moment-by-moment mapping of the body's internal landscape across conscious and unconscious levels" (Khalsa et al., 2018). Interoception is intricately linked with homeostasis (Craig, 2002) due its role in monitoring of the body's internal condition. Theoretical models of interoception detail several facets involved in the ongoing monitoring of internal signals, and the propensity to use these signals to guide behaviour (Khalsa et al., 2018). For example, interoceptive sensibility refers to the trait tendency to notice sensations such as heart rate, itch or bloatedness, whereas interoceptive accuracy refers to how accurately one is able to perceive these signals (e.g. correctly interpreting the locus and magnitude of signals) (Garfinkel, Seth, Barrett, Suzuki & Critchley, 2015). Theoretical models of interoception also detail the possibility of an internal generative model (Barrett & Simmons, 2015), which represents a predicted internal state based on previous experiences. Sensory input from the viscera will either match or mismatch expectations. Mismatches are reflected as prediction errors, which are then used to update future expectations, to ensure accurate future predictions (Barrett & Simmons, 2015; Khalsa et al., 2018). In the context of eating, interoception encompasses the detection of hunger and fullness and when combined with appropriate interpretation of signals, learned experiences and necessary sensory input (e.g. available food), it aids in guiding meal initiation and termination (Quigley, Kanoski, Grill, Barrett & Tsakiris, 2021). As a result, interoception is fundamental to the control of both eating and disordered eating (Simmons & DeVille, 2017; Quadt, Critchley & Garfinkel, 2018).

The integrated model of appetite control proposed by Higgs et al. (2017) provides a framework from which further research into the causes of and treatments for disordered eating and eating disorders can be developed. For example, recognition of the important role of cognitive influences on reward processes presents an opportunity for novel research into treatments, as cognitive processes such as attention and memory are observable processes which can be manipulated (Higgs et al., 2017).

1.5 Attention Deficit Hyperactivity Disorder (ADHD): A model for studying neurocognitive processes in disordered eating

The study of conditions that involve dysregulation in cognitive, metabolic and reward systems may provide insight into the role of these systems in disordered eating. Attention Deficit Hyperactivity Disorder (ADHD) is one such condition. ADHD is a common neuropsychological disorder with an estimated worldwide prevalence of 5.3% in children and 4.4% in adults (Polanczyk & Rohde, 2007). ADHD is characterised by a persistent pattern of inattentive and/or hyperactive and impulsive behaviours, which are inappropriate to the stage of development in children and can be disruptive to functioning and performance of daily tasks including academic performance in children and occupational performance in adults (DSM-5, APA 2013). ADHD is typically initially diagnosed in childhood and has historically been considered to be a childhood disorder, however adult diagnosis is possible, and there is growing appreciation of ADHD as a lifelong disorder (Zalsman & Shilton, 2016). In individuals with a childhood diagnosis, ADHD persists into adulthood in 65% of cases (Faraone, Biederman & Mick, 2006), and is associated with ongoing impairment of functioning (Biederman, Mick & Faraone, 2000). In the transition from childhood to adulthood, inattentive symptoms of ADHD typically predominantly persist, as opposed to hyperactive and impulsive symptoms, which show higher rates of remission (Biederman, Mick & Faraone, 2000).

1.5.1 Eating Disorders and Disordered Eating in ADHD

Individuals with ADHD have an increased risk of developing disordered eating and eating disorders (Kaisari et al., 2017). Results from a large community sample revealed that individuals with ADHD symptoms had a possible eating disorder prevalence of 19.2% compared to those without ADHD symptoms (5.7% possible eating disorder prevalence). Girls with ADHD were 3.6 times more likely to develop an eating disorder than were girls without ADHD (Biederman, Ball, Monuteaux, Surman, Johnson & Zeitlin, 2007). In addition, it has been reported that as many as 31% of eating disorder patients screen positive for ADHD (Svedlund, Norring, Ginsberg & Hausswolff-Juhlin, 2017).

Specific eating disorders that have been linked to ADHD include BED (Steadman & Knouse, 2014), BN (Mikami et al., 2009) and AN (Kaisari et al., 2017). The relationship between ADHD and anorexia has been less consistently reported and may be stronger for men (Kaisari et al., 2017). In addition to clinically diagnosed eating disorders, increased risk of disordered eating behaviour is observed in individuals with high levels of ADHD symptoms (e.g. Jacob, Haro & Koyangi, 2018). The most consistent relationship appears to be between ADHD and disordered eating involving loss-of-control type eating and binge/overeating (Kaisari et al., 2017), with the consequence that adults with ADHD are also at an increased risk of overweight and obesity (Nigg, Johnstone, Musser, Long, Willoughby & Shannon, 2016).

1.5.2 Impulsivity and Inattention ADHD Symptoms and Disordered Eating

Within the interactive model of appetite control outlined previously (Higgs et al. 2017), both attention and control of impulsive behaviours (i.e. inhibitory control) are cognitive processes that underpin appetite. Given the heightened risk of disordered eating in individuals with ADHD, it is worthwhile to assess whether inattentive, hyperactive and/or impulsive symptoms of ADHD predict disordered eating risk.

Most studies assessing disordered eating in ADHD have not attempted to disaggregate the contributions of specific symptoms (Kaisari et al., 2017) but where this has been done, the results suggest that both inattentive and impulsive symptoms of ADHD are associated with disordered eating, particularly binge eating symptoms (Kaisari et al., 2017). In addition, there is more limited evidence for an association between hyperactivity symptoms of ADHD and restrictive eating in males but not females (Kaisari et al., 2017). Data from studies of large community samples suggest an indirect relationship between impulsivity and disordered eating that is mediated by negative affect (Jacob, Haro & Koyangi, 2018; Kaisari et al., 2018), which is heightened in both ADHD (Sobanski, 2006) and BED (Grilo, White & Masheb, 2009; Yanovski, Nelson, Dubbert & Spitzer, 1993). Further research is necessary to confirm whether comorbidities such as depression and anxiety explain the association between impulsive symptoms of ADHD and disordered eating or whether specific ADHD symptoms (e.g. impulsive behaviour around food) predispose an individual towards binge eating.

Research into disordered eating in ADHD has provided mixed results regarding the relationship between inattentive symptoms and disordered eating (Kaisari et al., 2017). Some studies suggest that subclinical levels of inattentive symptoms of ADHD predict disordered eating behaviours, particularly binge-type behaviours (e.g. Bleck, DeBate & Olivardia, 2015; Kaisari et al., 2018). The relationship between inattentive symptoms and disordered eating may also be mediated by negative affect (Kaisari et al., 2018; Nazar et al., 2014). In addition, Kaisari et al. (2018) found that reliance on internal cues of hunger and satiety partially mediated the relationship between inattentive symptoms and binge/disinhibited eating. This result suggests that deficits in interoceptive processes could be associated with inattention, and that this relationship increases the likelihood of binge/disinhibited eating.

Accordingly, experimental manipulations of attentional processes appear to disrupt interoception. For example, Morris, Vi, Obrist, Forster and Yeomans (2020) found that performance of a high perceptual load task (creating distraction) disrupted cues of satiety following ingestion of a beverage designed to induce satiety, providing evidence that processing interoceptive information is dependent on attention. In light of this finding, one route through which ADHD symptoms may foster disordered eating is through the impact of disrupted attentional processes on interoception.

Interestingly, LDX the only currently approved pharmacological treatment for binge eating disorder was initially marketed to treat ADHD (Najib, Wimer, Zeng, Lam, Romanyak, Morgan & Thadavila, 2017). As LDX improves the cognitive symptoms associated with ADHD, one possible mechanism by which it improves symptoms of BED is through its enhancement of cognitive processes such as attention and inhibitory control which, as previously discussed, are important processes for appetite regulation. However currently, despite its proven efficacy, it is currently unknown how LDX reduces symptoms of BED.

Research targeting the specific contribution of inattentive and impulsive symptoms to the likelihood of developing disordered eating, as well as the common/mediating mechanisms will further understanding of the role of cognitive processes in the development of disordered eating. This knowledge will aid development of preventative therapies and treatments focussing on these processes. Research should first focus on whether inattention and impulsivity predispose individuals to disordered eating, or simply co-occur. For example, this question could be addressed by conducting longitudinal studies, that subsequently may help to identify underlying mechanisms by assessing mediating variables of the relationship.

1.6 Thesis Aims

This thesis aims to further our understanding of the neurocognitive mechanisms that underlie disordered eating. Firstly, through assessing the possibility that cognitive symptoms associated with ADHD may predict disordered eating over time, and secondly through focussing on the mechanisms which may underlie the relationship between these cognitive symptoms and disordered eating, by assessing mediators of this relationship and how they are affected by the only approved pharmacological therapy for both ADHD and BED. Figure 1 illustrates the conceptual model underlying the research in this thesis.

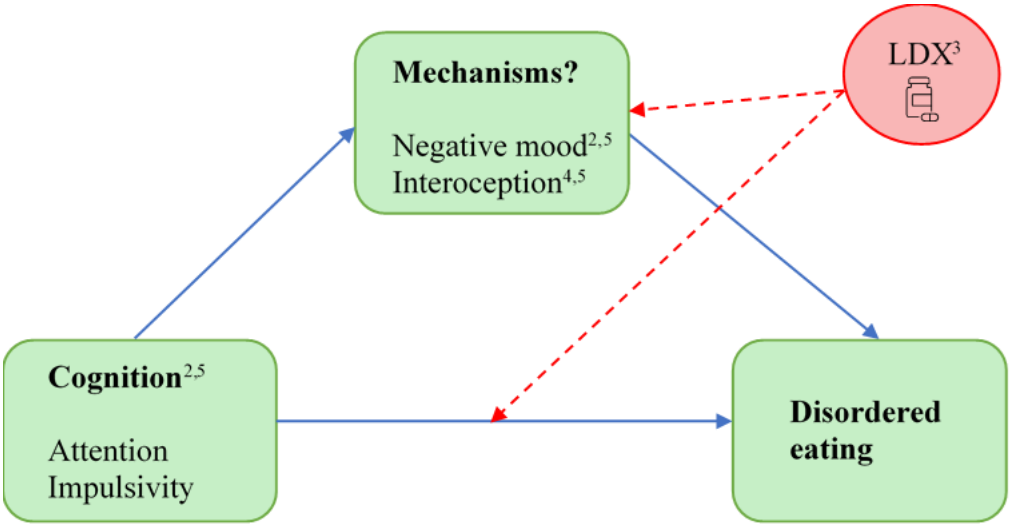

Figure 1. Conceptual model underlying research presented in this thesis. Superscript numbers reflect chapters in which ideas are addressed. LDX = Lisdexamfetamine Dimesylate

1.7 Thesis Overview

Chapter 2 presents data from a cohort study that investigated the relationship between ADHD symptoms and disordered eating risk both cross-sectionally and longitudinally. Specifically, this study investigated whether ADHD symptoms predicted disordered eating risk over a two-year period in young adults, and whether the relationship was mediated by measures of negative mood.

Chapter 3 presents data from a neuropsychopharmacological study using fMRI to investigate neural mechanisms associated with the reduction of binge eating following administration of LDX. This study assessed the effects of LDX (versus placebo) on brain responses to food stimuli in women with moderate and severe binge eating symptoms. The aim of this study was to further understanding of the mechanisms that underlie binge eating and its amelioration by LDX.

Chapter 4 presents a systematic review of 104 studies assessing the link between disordered eating and interoception. Based on previous findings, interoception was considered as a potential mediator of the relationship between ADHD symptoms (particularly inattentive-type symptoms) and disordered eating. Prior to investigating this relationship, it was necessary to assess the strength of the evidence for a link between interoception and disordered eating. The systematic review also aimed to assess whether general deficits in interoception are linked to disordered eating, or whether only specific domains of interoception (e.g. related to gastric information) are associated with disordered eating.

Chapter 5 presents longitudinal data obtained online from a community sample across two timepoints 6 months apart assessing the potential mediating role of interoception in the relationship between ADHD symptoms and disordered eating. Firstly, this study aimed to replicate cross-sectional findings that reliance on internal cues of

hunger and satiety mediate the relationship between ADHD symptoms and disordered eating and assess whether this relationship also exists longitudinally. Secondly, based on results from Chapter 4, this study aimed to assess the potential mediating role of interoceptive awareness and interoceptive accuracy.

Chapter 6 is a summary of the key findings from the thesis, and a discussion of how the research has added to the existing literature and the implications of the results in the context of further research and clinical considerations. The strengths and limitations of the research conducted in this thesis are also discussed.

Chapter Two:

Martin, E., Dourish, C. T., Hook, R., Chamberlain, S. R., & Higgs, S. (2020).

Associations between inattention and impulsivity ADHD symptoms and disordered eating risk in a community sample of young adults. *Psychological Medicine,* 1-10. *

2.1 Introduction

Children and adults with symptoms of Attention Deficit Hyperactivity Disorder (ADHD) appear to be at higher risk of developing disordered eating (Kaisari, Dourish, & Higgs, 2017; Nazar et al., 2016). Evidence from longitudinal studies suggests that symptoms associated with ADHD may predict the onset of several types of eating disorders (Biederman et al., 2007; Rojo-Moreno et al., 2015; Viborg, Wångby-Lundh, & Lundh, 2014). For example, Sonneville et al., (2015) found that ADHD symptoms in childhood predicted binge eating behaviour during adolescence. Thus, these results suggest that features of ADHD may foster disordered eating behaviour.

To date, few studies have examined the relationship between specific ADHD symptoms and types of disordered eating. In addition, little is known about the underlying mechanisms and whether the relationship can be accounted for by variables known to be associated with both ADHD and disordered eating e.g. negative mood. Seitz and colleagues (2013) reported that in females seeking treatment for bulimia nervosa (BN), the severity of BN was best predicted by inattentive symptoms, rather than impulsivity or hyperactivity symptoms of ADHD. On the other hand, data from a cross-sectional study of two independent adult samples suggested that both inattentive and hyperactive/impulsive ADHD symptoms are positively related to binge/disinhibited and restrictive eating, even when controlling for factors such as alcohol and drug use, other comorbid psychiatric disorders and medication (Kaisari, Dourish, Rotshtein, & Higgs, 2018). Negative mood was a mediator of several of these relationships, but in both studies there was also a direct relationship between inattentive symptoms of ADHD and binge/disinhibited eating that was not fully accounted for by negative mood. Evidence from longitudinal studies is more limited, but Yilmaz and colleagues (2017) reported that a combination of inattentive and

hyperactive/impulsive symptoms in children predicted higher eating disorder symptomatology during late adolescence, even when adjusting for levels of anxiety and depression. A study of younger children found that attention problems and hyperactivity were positively associated with prospective changes in food-related responses that may precede disordered eating (emotional overeating and satiety responsiveness) and that attention problems were also positively associated with changes in food responsiveness, (Fuemmeler et al., 2020). These results linking ADHD symptoms to increases in both emotional eating (suggesting a tendency to overeat) and satiety responsiveness (suggesting a food-avoidant behaviour) reflect that ADHD symptoms are associated with a range of traits that may underlie both restrictive eating (e.g. through increased satiety responsiveness) and overeating (e.g. through emotional eating). Importantly, the reverse relationship between ADHD symptoms and eating measures were not significant (e.g. eating behaviours at timepoint one did not predict later ADHD symptoms).

Further research is required to clarify the relationship between inattentive and hyperactive/impulsive symptoms and disordered eating. In particular, because some types of disordered eating e.g. binge eating disorder are more likely to emerge in later adolescence/early adulthood (Udo & Grilo, 2018) studies in young adults may shed more light on the potential significance of ADHD symptoms as risk factors. Peaks in the onset of eating disorders occur from teens to young adulthood, especially for BN and binge eating disorder where the average onset is later than that for anorexia nervosa (AN) but an eating disorder can emerge at any age (Christian et al. 2019). Young adulthood represents a major transition period as young adults launch into independence. Peer opinion becomes more important, and lifestyles are less structured and supervised and there is evidence for the emergence of eating disorders during this period (Pearson, et al., 2017).

In addition, the broader concept of 'trait' self-report impulsivity is also highly relevant in this context. For example, a recent, large cross-sectional population based study reported that trait impulsivity on the Barratt Impulsivity Scale (BIS) was associated with disordered eating (Bénard et al., 2019). In a systematic review, there was evidence from a range of studies that eating disorders were associated with significantly elevated impulsivity on self-report questionnaires (such as the, BIS) compared to controls (Waxman, 2009). This review highlighted several limitations in the corpus of literature: (i) the vast majority of research had been conducted only in women; (ii) studies using dimensional measures in more normative (population type) cohorts were lacking; and (iii) longitudinal studies were absent.

The current study had two primary aims. First, in a general population of young adults, we examined the cross-sectional relationship between inattentive and hyperactive/impulsive symptoms of ADHD and disordered eating behaviour (as assessed by the SCOFF eating disorder screening tool) while adjusting for factors which have been associated with both ADHD and disordered eating (e.g., alcohol or drug abuse, self-esteem). Based on previous work (e.g. Kaisari et al. 2017, 2018; Yilmaz et al., 2017), we predicted that both inattentive and hyperactive/impulsive symptoms would be positively associated with eating disorder risk. Second, we investigated the longitudinal relationships between trait impulsivity on the BIS, and subsequent disordered eating using data from baseline and follow up in the same data set. We hypothesized that trait impulsivity would be positively associated with subsequent risk of eating disorder. Given our previous observations from cross sectional studies (Kaisari et al. 2018) we also hypothesised that depression scores would mediate the predicted relationships between inattentive and hyperactive/impulsive ADHD symptoms and eating disorder risk.

2.2 Methods

2.2.1 Participants

This study used data from 642 young adults from the original cohort of the Neuroscience in Psychiatry Network (NSPN) and who subsequently completed a follow up survey in 2018-2019. NSPN is a previously established accelerated longitudinal study examining brain development in young people, which was designed to be representative of the general population; i.e. constitutes a normative cohort (Kiddle et al. (2018). The accelerated longitudinal design involves recruitment of multiple, age-adjacent cohorts who are followed for a limited period. Each participant completed a Home Questionnaire Pack (HQP) and Sociodemographic Questionnaire that focused on assessing participants' mood, behaviour and wellbeing along with demographic characteristics. Recruitment to the cohort was via General Practitioners who were asked to recruit young people using their sex-age registers, Schools and Further Education colleges and purposive advertisement. The Home Questionnaire Pack was sent to 3726 participants and returned by 65% of them (N = 2402, marking the baseline assessment stage of the NSPN 2400 Cohort). All the original participants who had previously provided baseline questionnaires via post (2012–2014) were contacted by email in 2018-2019 and asked to complete a follow up online survey implemented in SurveyMonkey (Chamberlain et al. 2019; Romero-Garcia et al., 2020). The time between baseline and follow-up assessments was Mean: 3.85 SD: 0.41, Range: 1-5. This survey examined a broader range of impulsivity/compulsivity measures than were included in the original study, some of which were not available at the time the NSPN cohort was conceived. Participants were excluded if they had a current or past history of clinical treatment for a psychiatric disorder, drug or alcohol dependence, neurological disorder including epilepsy, head injury causing loss of consciousness, or

learning disability. Individuals taking psychotropic medication (including ADHD drugs) were also excluded from the study at the point of the cohort being established.

2.2.2 Participant characteristics

Participants answered questions relating to socio demographic characteristics (age, sex and ethnicity) and other variables known to be associated with both ADHD and disordered eating: alcohol and drug use, depression and self-esteem.

2.2.3 Measures of interest

The present study analysed measures from the baseline questionnaire and follow-up survey specifically relating to eating disorder risk and impulsivity and ADHD. Based on prior work we also selected specific variables known to be associated with both ADHD and eating disorders for inclusion as covariates: alcohol and drug use and depression and self-esteem measures.

2.2.3.1 Alcohol use and drug use

Alcohol use was assessed using the Fast alcohol screening test (FAST), which consists of four questions from the full alcohol use disorders identification test (AUDIT) (Hodgson et al. 2003; Saunders, Aasland, Babor, De la Fuente, & Grant, 1993). Nicotine dependence was estimated using the Fagerström Test for Nicotine Dependence (FTND) (Heatherton, Kozlowski, Frecker, & Fagerstom, 1991). The FTND has been used to test for nicotine dependence in both research and clinical settings and has good psychometric reliability (Pomerleau, Carton, Lutzke, Flessland, & Pomerleau, 1994). Illicit drug use was assessed using additional questions regarding type of illicit drug(s) used and frequency in the last month.

2.2.3.2 Self esteem

Self-esteem was assessed using the 10-item Rosenberg Self-Esteem Scale (RSE; Rosenberg 1965). Items are rated on a four-point Likert scale, ranging from (1) strongly disagree to (4) strongly agree, where higher sum score on the scale indicates higher levels of global self-esteem (range 10–40).

2.2.3.3 Depression

Depression was assessed using the Moods and Feelings Questionnaire (MFQ; Costello & Angold, 1988). The MFQ is a 33-item scale used as a screening tool for depression in children and young people. It has demonstrated good validity and reliability in both clinical and non-clinical samples (Thabrew, Stasiak, Bavin, Frampton, & Merry, 2018).

2.2.3.4 ADHD

ADHD symptoms were assessed with the Adult ADHD Self-Report Scale (ASRS) Part A Screener (Kessler et al., 2007). This is a six item questionnaire that includes questions on inattention (four items) and hyperactivity symptoms (two items) in the previous 6 months. Participants responded using a 5-point response scale with answer options ranging from “never”—scored 0, to “very often”—scored 4. Responding ‘sometimes’, ‘often’ or ‘very often’ to at least four questions reflects the presence of symptoms consistent with ADHD (Kessler et al., 2007). Based on previous work (Blanco et al., 2009), factor analysis was conducted using varimax rotation to extract scores for inattention and for hyperactivity-impulsivity on the instrument.

2.2.3.5 Trait Impulsivity

The Barratt Impulsivity Scale, Brief Version (BIS-Brief) was used to measure unidimensional trait impulsivity. The BIS-Brief is an 8-item self-report questionnaire with

good reliability and validity in both healthy young people and patients (Mathias et al., 2018).

2.2.3.6 Trait Impulsivity (Measured Previously)

The Barratt Impulsivity Scale, Version 11 (BIS-11), 25 was used to measure trait impulsivity: attentional impulsivity, motor impulsivity, and non-planning impulsivity. The BIS-11 is a 30-item self-report questionnaire shown to have good reliability and validity in both clinical and non-clinical subjects (Stanford et al. 2009). This questionnaire was collected on average 2.8 years prior to the above measures, in a preceding data round.

2.2.3.7 Disordered eating

The SCOFF questionnaire was used to assess disordered eating behaviour (Hill, Reid, Morgan, & Lacey, 2010). It comprises 5 questions (yes/no response format) asking whether in the past year the participant 1) had lost more than one stone (6.35 kg) in 3 months (weight loss); 2) had made him/herself be sick because he/she felt uncomfortably full (self-sick for feeling full); 3) worried that he/she had lost control over how much he/she eats (uncontrolled eating); 4) believed him/herself to be fat when others said that he/she was too thin (self-perceived fatness); and 5) thought that food dominated his/her life (food dominance). Responding yes to at least two items was considered a positive screen for possible ED (Morgan, Reid & Lacey, 1999). The SCOFF is not a diagnostic instrument but has been found to have high specificity and sensitivity for detecting AN and BN (Luck et al., 2002). However it may be less effective in identifying binge eating disorder (Solmi et al. 2015). It has high negative predictive validity but more moderate positive predictive validity, which is common for low prevalence conditions (Luck et al., 2002; Solmi et al. 2015). A recent meta-analysis of 25 studies reported the validity of the SCOFF to be high across samples with a pooled sensitivity of 0.86 (95% CI, 0.78–0.91) and specificity of

0.83 (95% CI, 0.77–0.88). The test re-test reliability has been shown to be high (Garcia-Campayo et al 2005; Garcia et al. 2011).

2.2.4 Data processing and Analysis

High and low symptom groups were compared on demographic variables and potential covariates using t-tests. Groups of participants were assigned to high (n = 167) or low ADHD (n = 475) symptoms based on the recommended cut-off for symptom scoring consistent with ADHD in adults provided in the ASRS (described above).

Three hierarchical regressions (two for the cross-sectional and one for the longitudinal relationship) were conducted. Both the cross-sectional and longitudinal model consisted of three hierarchical model steps. The outcome variable was eating disorder risk score. Participants were assigned to either a 'high' or 'low' risk for eating disorders group, based on responses to the SCOFF questionnaire. Guidelines for using the SCOFF (Hill et al. 2010) suggest that a score ≥ 2 reflects potential eating disorder risk. In the first step of the first cross-sectional model BIS-brief scores were entered, and in the second cross-sectional regression model ASRS inattentive and hyperactive/impulsive scores were entered simultaneously. In the first step of the longitudinal regression model, the three BIS subscales (attentional impulsivity, motor impulsivity and non-planning impulsivity) were entered simultaneously. In the second step of all models age, sex and ethnicity were entered. In the third step for all models, MFQ scores, RSE scores, FAST scores, FTND scores, and illicit drug use scores were entered. Based on results from logistic regression analyses, mediation models were tested to assess the potential mediating influence of significant predictor variables.

Further exploratory analyses were conducted, consisting of hierarchical regression models, with each SCOFF subscale as the outcome variable in a separate regression model,

and separate model steps described as above. These models were run only for predictor ASRS scores/BIS subscales that significantly predicted SCOFF risk status in the first regression. Bonferroni correction was applied to these models to account for multiple comparisons (α =0.01).

2.3 Results

2.3.1 Participant Characteristics

The sample consisted of 642 participants (Mean age 23 years (± 3.1), 65% female). See Table 1 for participant characteristics. The prevalence of possible eating disorder in the sample was 21.5%, 76% of whom were female. The prevalence of possible ADHD in the sample was 26%, 56% of whom were female. Participants scoring higher for disordered eating had higher: FTND, ASRS Inattention and Hyperactivity/Impulsivity and higher BIS Attentional Impulsivity and Non-planning Impulsivity (see Table 1 for descriptive statistics).

Table 1. Group (ED risk/ no ED risk) differences in questionnaire measures of alcohol use, smoking, illicit drug use and disordered eating. ED risk = responding 'yes' to at least two SCOFF questions

	All (n= 642)	**SCOFF no risk** (n= 504)	**SCOFF ED risk** (n= 138)			
Sex	416:223:3 (female:male:other)	311:191:2 (female:male:other)	105:32:1 (female:male:other)			
Ethnicity	74.6% White 7.5% Asian/British Asian 6.9% Multiracial 4.4% Black/African/Caribbean 0.9% Other 5.7% Not Recorded					
		Mean (SD)		**F**	**P**	**np^2**
Age (years)	23.4 (3.1)	23.4 (3.1)	23.2 (3.0)	0.7	0.41	0.001
Alcohol use (FAST score)	6.3 (2.3)	6.3 (2.2)	6.6 (2.5)	1.8	0.18	0.003
Smoking (FTND score)	0.95 (2.8)	0.8 (2.6)	1.4 (3.3)	5.0	0.03	0.008
Illicit Drug Use	1.8 (0.4)	1.9 (0.4)	1.8 (0.4)	3.0	0.09	0.005
ASRS Inattention Score	5.2 (2.7)	4.7 (2.5)	6.7 (2.5)	68.7	<0.001	0.97
ASRS Hyperactivity/Impulsivity Score	3.15 (1.8)	3.0 (1.7)	3.9 (1.9)	30.1	<0.001	0.05
BIS Attentional Impulsivity	15.2 (4.1)	14.8 (3.9)	16.9 (4.2)	24.8	<0.001	0.044
BIS Motor Impulsivity	20.6 (4.2)	20.5 (4.3)	21.1 (4.0)	1.5	0.22	0.003
BIS Non-planning Impulsivity	23.9 (5.2)	23.6 (5.2)	25.0 (4.9)	7.2	0.008	0.013
Mood and Feelings Questionnaire	17.8 (13.4)	15.7 (11.7)	25.8 (16.4)	61	<0.001	0.09

2.3.2 Cross-sectional Analysis

2.3.2.1 Cross-sectional Logistic Regression: BIS-brief

The first model including BIS-brief score only was statistically significant, $\chi 2$ (1) = 22.9, $p < 0.001$ and explained 6% (Nagelkerke R square) of the variance associated with being classified as 'at risk' and 80% of cases were classified correctly. The second model step (additionally including age, sex and ethnicity) significantly improved model fit $\chi 2$ (3) = 10.39, p = 0.02. BIS-brief score remained a significant predictor in this model (β= 1.4, $p < 0.001$, Exp(B) = 1.15) and sex also significantly contributed to the model (β= 0.7, p = 0.002, Exp(B) = 2.1). This model explained 9% (Nagelkerke R square) of the variance associated with being classified as 'at risk' and 80% of the cases were correctly classified. The third model step (additionally including MFQ, RSE, FAST, FTND, and Illicit Drug Use) significantly improved model fit $\chi 2$ (5) = 32.1, $p < 0.001$. BIS-brief score (β= 0.1, p = 0.001, Exp(B) = 1.1) and sex (β= 0.7, p = 0.005, Exp(B) = 2.0) remained significant predictors in the model, and MFQ significantly contributed to the model (β= 0.4, $p < 0.001$, Exp(B) = 1.0). The final model was statistically significant $\chi 2$ (9) = 65.3, $p < 0.001$, explained 17% (Nagelkerke R square) of the variance associated with being classified as 'at risk' and 81% of cases were classified correctly.

2.3.2.2 Cross-sectional Logistic Regression: ASRS

The first model including ASRS factors (hyperactive/impulsive and inattentive symptoms) was statistically significant, $\chi 2$ (2) = 47.7, $p < 0.001$ and explained 13% (Nagelkerke R square) of the variance associated with being classified as 'at risk' and 79% of cases were classified correctly. Both of the two ASRS factors individually significantly contributed to the model: inattentive symptoms (β= 0.233, $p < 0.001$, Exp(B) = 1.3), hyperactive/impulsive symptoms: β= 0.13, p = 0.05, Exp(B) = 1.1. The second model step

(additionally including age, sex and ethnicity) significantly improved model fit $\chi 2$ (3) = 10.42, p = 0.02. This model explained 15% (Nagelkerke R square) of the variance associated with being classified as 'at risk' and 80% of the cases were correctly classified. The third model step (additionally including MFQ, RSE, FAST, FTND, and Illicit Drug Use) significantly improved model fit $\chi 2$ (5) = 20.0, p = 0.001. The contribution of inattentive symptoms and sex remained significant in the model, and MFQ scores significantly contributed to the model. Hyperactive/Impulsive symptoms no longer significantly contributed to the model (see Table 2). Inattentive symptoms of ADHD were associated with all individual ED symptoms with the risks apart from weight loss: self-sick for feeling full (β= 0.327, p < 0.001, Exp(B) = 1.387); uncontrolled eating (β= 1.46, p = 0.003, Exp(B) = 1.15); self-perceived fatness (β=0.177, p = 0.004, Exp(B) =1.19); food dominance (β=0.163, p = 0.002, Exp(B) =1.17) weight loss (β= 0.012, p = 0.96, Exp(B) = 0.99). In contrast, hyperactive/impulsive symptoms were associated with uncontrolled eating only (β= 1.58, p =0.03, Exp(B) =1.17).

2.3.2.3 Mediation

Inattentive symptoms (controlling for hyperactive symptoms) predicted SCOFF risk category both directly (Effect = 0.22, se = 0.05, Z= 4.5, p<0.001 CI= 0.12:0.313) and indirectly through MFQ scores (Effect = 0.051, Bootstrapped CI= 0.027:0.82) (see Figure 1A). Hyperactive/impulsive symptoms (controlling for inattentive symptoms) did not predict SCOFF risk category directly (Effect = 0.01, se = 0.07, Z= 1.4, p=0.17 CI= -0.042: 0.24) but did predict SCOFF risk category indirectly through negative mood (Effect = 0.04, Bootstrapped CI= 0.013:0.07) (see Figure 1B). Because women were more likely than men to be at risk for disordered eating we examined sex as a moderating variable. Sex did not moderate the relationship between ADHD symptoms and mood and feelings scores nor the relationship between MFQ and SCOFF risk category (Inattention: Index = 0.04,

Bootstrapped CI = 0.00: 0.096, Hyperactivity/Impulsivity: Index = -0.0004, Bootstrapped CI = -0.035:0.034).

Table 2. Summary of binary logistic regression statistics for the cross-sectional analysis (model 3). Control variables/covariates are shaded grey, and variables of interest are white.

	B	**Sig.**	**Exp(B)**	**95% CI Lower for Exp(B)**	**95% CI Upper for Exp(B)**
ASRS att.	0.194	<0.001	1.2	1.1	1.3
ASRS hyp/imp.	0.088	0.23	1.09	0.95	1.3
Age	-0.5	0.22	0.95	0.88	1.03
Sex	0.71	0.006	2.03	1.2	3.4
Ethnicity	0.031	0.81	1.03	0.81	1.3
Mood and Feelings	0.033	<0.001	1.03	1.02	1.05
Rosenberg	0.077	0.22	1.08	0.96	1.2
FAST	0.45	0.4	1.05	0.94	1.2
FSTROM	-0.2	0.63	0.98	0.91	1.06
ILLICIT DRUG	-0.24	0.40	0.78	0.45	1.4

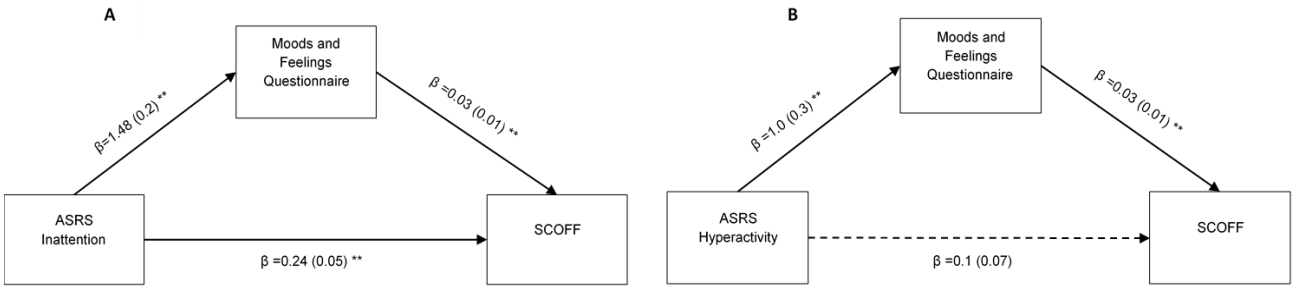

Figure 1. Cross-sectional mediation models. Model A shows the relationship between ASRS inattentive symptoms and SCOFF risk. Model B shows the relationship between ASRS hyperactive/impulsive symptoms and SCOFF risk. Solid lines reflect significant pathways. Estimates (β) are unstandardized regression coefficients, numbers in parentheses show bootstrapped standard error. All analyses controlled for sex, alcohol use, smoking, illicit drug use, age. **p < 0.001

2.3.3 Longitudinal Analysis

2.3.3.1 Longitudinal Logistic Regression: BIS subscales

The first model including BIS subscales (attentional impulsivity, motor impulsivity and non-planning impulsivity) was statistically significant, $\chi 2$ (3) = 21.97, p < 0.001 and explained 7% (Nagelkerke R square) of the variance associated with being classified as 'at risk' and 82% of cases were classified correctly. Attentional impulsivity was the only BIS subscale to significantly contribute to the model (β= 1.4, p < 0.001, Exp(B) =1.15). The second model step (additionally including age, sex and ethnicity) did not significantly improve model fit $\chi 2$ (3) = 5.0, p = 0.172. This model explained 9% (Nagelkerke R square) of the variance associated with being classified as 'at risk' and 82% of the cases were correctly classified. The third model step (additionally including MFQ, RSE, FAST, FTND, and Illicit Drug Use) significantly improved model fit $\chi 2$ (5) = 20.0, p = 0.001. The contribution of attentional impulsivity and sex remained significant in the model, and MFQ scores significantly contributed to the model (see Table 3). The motor impulsivity and non-planning impulsivity subscales were not associated with disordered eating risk (p = 0.58 and p = 0.99 respectively). Attentional impulsivity associated specifically with:

uncontrolled eating (β =0.124, p=0.001, Exp(B) = 1.132) and self-perceived fatness (β =0.11, p=0.008, Exp(B) = 1.123) but not self-sick for feeling full (β = 0.120, p=0.032, Exp(B) = 1.127); weight loss (β =-0.013, p=0.825, Exp(B) = 0.938) or food dominance (β =0.048, p=0.2 Exp(B) = 1.05).

Table 3. Summary of binary logistic regression statistics for the longitudinal analysis (model 3). Control variables/covariates are shaded grey, and variables of interest are white.

	B	**Sig.**	**Exp(B)**	**95% CI Lower for Exp(B)**	**95% CI Upper for Exp(B)**
BIS attention	0.078	0.045	1.1	1.0	1.2
BIS motor	-0.02	0.58	0.98	0.92	1.05
BIS non-planning	0.00	0.99	1.0	0.94	1.06
Age	-0.004	0.93	1.0	0.92	1.08
Sex	0.64	0.024	1.9	1.09	3.3
Ethnicity	-0.01	0.93	0.99	0.75	1.3
Mood and Feelings	0.038	<0.001	1.04	1.02	1.06
Rosenberg	0.087	0.20	1.1	0.95	1.2
FAST	0.089	0.14	1.1	0.97	1.2
FSTROM	-0.002	0.96	1.0	0.91	1.09
ILLICIT DRUG	-0.25	0.45	0.78	0.42	1.5

2.3.3.2 Mediation

Because there was no relationship between BIS motor impulsivity and non-planning impulsivity and disordered eating risk the mediation analysis focused only on BIS attentional impulsivity. Attentional impulsivity did not predict SCOFF risk category directly (Effect = 0.07, se = 0.04, Z= 1.8, p=0.06 CI= -0.003: 0.15) but did predict SCOFF risk category indirectly through scores on the MFQ (Effect = 0.07, Bootstrapped CI= 0.038 : 0.1) (See Figure 2). Because women were more likely than men to be at risk for disordered eating we examined sex as a moderating variable. Sex did not moderate the relationship between ADHD symptoms and MFQ scores nor the relationship between MFQ scores and SCOFF risk category (Index = -0.01, Bootstrapped CI = -0.04: 0.012).

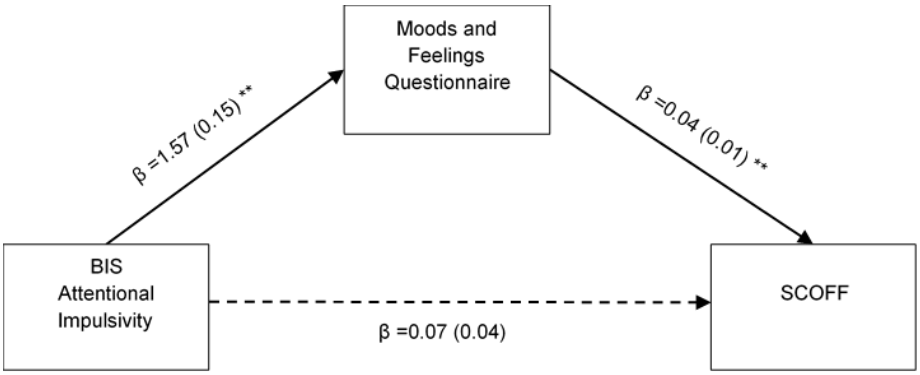

Figure 2. Longitudinal mediation model. Solid lines reflect significant pathways. Estimates (β) are unstandardized regression coefficients, numbers in parentheses show bootstrapped standard error. All analyses controlled for sex, alcohol use, smoking, illicit drug use, age. **p < 0.001

2.4 Discussion

We observed a positive cross-sectional relationship between inattentive symptoms of ADHD and overall risk of disordered eating in a community sample of young adults, even when controlling for a range of covariates. We also observed a prospective relationship between trait impulsivity and risk of disordered eating in the same sample. The association between trait impulsivity and eating disorder risk was fully mediated by depression scores, whereas the association between inattentive symptoms and eating disorder risk was only partially mediated by depression. None of the relationships between ADHD symptoms and trait impulsivity were moderated by sex, suggesting that they hold for both young men and women.

In the cross sectional analysis, inattentive symptoms of ADHD were associated directly both with overall eating disorder risk and all individual risk categories of the SCOFF (self-sick, self-perceived fatness, food dominance and uncontrolled eating) apart from weight loss. Hyperactive/impulsive symptoms were not associated with overall risk in the final model but did predict uncontrolled eating. Whereas depression scores fully mediated the association between hyperactive/impulsive symptoms and uncontrolled eating risk, the relationship between inattentive symptoms and overall eating disorder risk was only partially mediated by depression scores. These findings are in agreement with the results of Kaisari and colleagues (2018) who found that inattentive symptoms of ADHD (as assessed by the Conners Adult Rating Scale – CARS; Conners et al. 1999) were directly and indirectly associated with both binge-disinhibited and restrictive eating, whereas hyperactive/impulsive symptoms were more consistently associated with binge-disinhibited eating and this relationship was mediated by negative mood. Taken together, these data suggest that inattentive symptoms are directly associated with a range of

disordered eating symptoms independent of negative mood whereas hyperactive impulsive symptoms appear to be mainly indirectly associated with binge/uncontrolled eating via depressive symptoms.

It is possible that binge/uncontrolled eating provides a mechanism for coping with negative affect that is associated with experiencing ADHD symptoms. Depression and mood disorders are often co-morbid with ADHD (Friedrichs, Larsson & Larsson, 2012) and depressive symptoms have been reported to predict binge eating (Spoor et al. 2006), which is consistent with the suggestion from the present data that the association between ADHD symptoms (particularly hyperactive/impulsive symptoms) and uncontrolled eating is likely to be explained by depressive symptoms. However, the finding that depression scores did not fully mediate the association between inattentive symptoms of ADHD and eating disorder risk suggests that there are additional underlying mechanisms that could account for this relationship. Indeed, our regression models only explained around 20% of variance in disordered eating risk. Jacob, Haro, and Koyanagi (2018) observed a positive cross-sectional relationship between ADHD scores and disordered eating risk in a nationally representative sample and found that between 28–42% of the association between ADHD symptoms and possible eating disorder was explained by stressful life events, anxiety, and borderline-personality traits, which we did not measure in this study but could have similarly accounted for at least some of the additional variance. In addition, there could be a distinct contribution of factors related specifically to inattentive symptoms of ADHD that act independently of co-morbidities.

For example, inattentive symptoms (which include forgetfulness and difficulty in organising tasks) are linked to impaired perception of and/or utilisation of interoceptive

signals to guide appetitive behaviour, which in turn is related to increased risk of disordered eating (Martin, Dourish, Rotshtein, Spetter, & Higgs, 2019). In support of this suggestion, Kaisari et al. (2018) reported that inattentive symptoms of ADHD were associated with decreased awareness of internal signals of hunger and satiety, and in turn these deficits were positively associated with disordered eating. Another alternative mechanism is that inattentive symptoms may be associated with impaired encoding of episodic food memories, which has been shown to influence subsequent responses to food cues (see Higgs, 2016 and Higgs et al., 2017 for a review). For example, distraction while eating (e.g., watching TV) has been shown to impair the memory encoding of a meal and result in an increase in subsequent snack intake. It is, therefore, possible that individuals with pronounced inattentive symptoms of ADHD may be easily distracted when eating, resulting in impaired memory for recent eating, leading to subsequent overeating, especially in the presence of highly palatable foods. Interestingly, problems with episodic memory more generally have been associated with overeating and obesity (Cheke, Simons, & Clayton, 2016; Higgs, Williamson, Rotshtein, & Humphreys, 2008; Higgs & Spetter 2018). While the role of depression and anxiety in the emergence of disordered eating has been appreciated for some time, how cognitive problems related to attention might contribute has received far less attention. Future research should investigate further the role of interoception and memory/attention processes as mediators of the association between inattentive symptoms of ADHD and eating disorder risk.

Longitudinally we observed that trait attentional impulsivity (as assessed by the BIS) predicted risk of eating disorder indirectly through negative mood. This finding is consistent with the results of previous cross-sectional studies that have reported an association between impulsivity and eating disorders (e.g. Lee-Winn, Townsend,

Reinblatt, & Mendelson, 2016) and with our cross sectional finding that hyperactive/impulsive symptoms were associated with risk of eating disorder via depression. Few studies to date have examined the longitudinal association between trait impulsivity and eating disorder risk in general populations (especially young adult populations) and most studies have not distinguished between different facets of impulsivity nor examined the mediating mechanisms (Bodell, Joiner, & Ialango, 2012; Pearson, Combs, Zapolski, & Smith 2010; Mikami et al., 2010; Evans et al., 2019; Bénard et al. 2019). Here, we find that attentional impulsivity, but not non-planning nor motor impulsivity predicted eating disorder risk longitudinally via depression scores. From the present data it is not clear why the association between trait impulsivity and eating disorder risk should be specific to attentional impulsivity but one possibility is that an underlying factor relating to both trait attentional impulsivity and inattentive symptoms of ADHD explains the relationship. Questions from the BIS assessing trait impulsivity ask about difficulty concentrating and having extraneous thoughts as well as ability to "pay attention", which could affect eating behaviours via the effects of distractibility on interoception and memory processes outlined above and reported previously (Kaisari et al., 2018). Hence, our findings are suggestive of an important role for attentional mechanisms generally in the development of disordered eating.

Attentional impulsivity may also enhance appetitive responses to food cues which could promote binge/overeating tendencies. In support of this suggestion, a review of the relationship between BIS subscales and measures of eating behaviour suggested that attentional impulsivity was most consistently related to tendency towards overeating, whereas the relationship with motor impulsivity was less consistent and was very weak for non-planning impulsivity (Meule, 2013). Moreover, attentional impulsivity in Binge Eating Disorder patients has been shown to be related to poorer response inhibition to food

cues and hypoactivity in the prefrontal cognitive control network that regulates responsiveness to food cues (Hege et al., 2015).

We found that impulsivity as assessed by the ASRS was not associated with overall eating disorder risk (although it was associated with uncontrolled eating) in the cross sectional analysis whereas impulsivity as assessed by the BIS predicted overall risk in the longitudinal analysis. The reason for this probably relates to the fact that the ASRS measure captures both impulsiveness and hyperactivity whereas the BIS focuses in more detail on impulsivity rather than hyperactivity. Further work is required to assess the specific contribution (if any) of hyperactive symptoms to eating disorder risk, and to tease out which components of impulsive behaviour are important.

Particular strengths of the present study are that the sample size is relatively large and represents a normative cohort including young women and men, who are generally representative of the UK populations (Kiddle et al., 2018), from which conclusions are broadly generalisable. In line with previous studies we did not find that sex was a moderating influence on any of the relationships between ADHD symptoms and eating disorder risk (Brewerton & Duncan, 2016; Kaisari et al. 2018). We also controlled for several co-variates in our analyses to account for the potential confounding effects of factors such as age and co-morbid drug use. Along with these strengths the findings should also be interpreted within the context of some limitations. Because the ASRS was only included in the follow-up assessment period we were unable to conduct a longitudinal analysis on these data. In addition, the longitudinal analysis involved only two assessment points which means that causal inferences from the mediational findings cannot be made. Further studies using at least 3 assessment points are required to tease out the temporal associations between impulsivity and depression in predicting disordered eating risk. We

also note that it has been suggested that hyperactive-impulsive symptoms change at different rates over time in ADHD (for discussion see Martel et al., 2016), and this may have differentially impacted the statistical ability to detect longitudinal relationships with other variables. In addition, the prevalence of possible ADHD in our sample was much higher than the reported prevalence of ADHD in the general population when estimated based on clinical diagnosis. In this context it is important to consider that the ASRS was developed as a screener for ADHD and is not a diagnostic tool. Thus, while it has good negative predictive value, the positive predictive value is more moderate and therefore could over identify ADHD. However, over-identifying ADHD would not explain the association between ADHD symptoms and possible eating disorder and indeed might be expected to mask any group differences that exist. Finally, the SCOFF screener only identifies participants with a possible eating disorder rather than a clinical diagnosis. However, disordered eating patterns which do not meet clinical criteria are, nevertheless, often associated with psychopathology (Tanofsky-Kraff, Engel, Yanovski, Pine, & Nelson, 2013). Despite efforts being made to recruit a nationally-representative sample, there are possible limitations of the sample. For example, participants are noted to have higher parental educational attainment than the general population (Kiddle et al., 2018), which may reflect that the sample comes from a higher socioeconomic status background than the general UK population. Additionally, it is possible that the use of GPs to recruit participants may have resulted in those with existing relationships with their GP to be more likely to participate.

In conclusion, in a normative cohort of young men and women we found that inattentive symptoms of ADHD were directly associated with increased risk of an eating disorder and measures of impulsivity were associated indirectly via depression with risk of an eating disorder both cross-sectionally and longitudinally. These data highlight the need

for further investigation of the specific role that inattentive symptoms play in the development of eating disorders. Our findings also suggest that future research should be directed towards unravelling the relationships between depression and impulsivity in predicting the emergence of eating disorders. A better understanding of the role that ADHD-related symptoms have in the risk for developing eating disorders will inform future prevention, detection and treatment strategies. For example, the presence of inattentive and impulsive symptoms as well as depression could be assessed as indicators of enhanced risk of the development of eating disorders. In addition, clinical management for individuals with ADHD and eating disorders might benefit particularly from treatment of psychiatric comorbidities such as depression. Finally, future research should assess whether treatments and behavioural therapies that directly target attentional deficits may prove effective in the management of both ADHD and eating disorders.

Chapter Three: The effects of Lisdexamfetamine Dimesylate on fMRI BOLD responses to food pictures in women with binge eating symptoms

3.1 Introduction

Binge Eating Disorder (BED) is the most common specific eating disorder and the estimated lifetime global prevalence is between 0.9-1.9.% (Qian et al., 2013; Erskine & Whiteford, 2018). Individuals with BED report significantly reduced quality of life compared with individuals without BED (Rieger, Wilfley, Stein, Marino & Crow, 2005; Hay, Mitchison, Lopez Callado, Gonzalez-Chica, Stocks & Touyz, 2017). Current drug treatments for BED are limited but in 2015, the United States Food and Drug Association (FDA) approved lisdexamfetamine dimesylate (LDX) (Vyvanse®, Takeda) as the first and, to date, only drug for the treatment of BED.

LDX is a pro-drug of dextroamphetamine (d-amphetamine) which is a psychostimulant and was originally developed to treat symptoms of ADHD. As a pro-drug, LDX is not pharmacologically active when ingested, but is metabolised by red blood cells into l-lysine and active d-amphetamine, an indirect catecholamine agonist (Pennick, 2010). Once LDX is converted into d-amphetamine, it acts to increase presynaptic availability of dopamine, noradrenaline and serotonin by inhibiting reuptake, increasing release into the synaptic cleft, and preventing breakdown of cellular dopamine through inhibition of monoamine oxidase A (Solanto, 1998; Blick & Keating, 2007; Weber & Siddiqui, 2009). Animal studies of LDX and d-amphetamine have documented increased release of catecholamines and serotonin in the prefrontal cortex and striatum (Heal, Cheetham & Smith, 2009; Rowley et al., 2012, 2014).

McElroy et al. (2015) performed the first randomised clinical trial (RCT) assessing the potential of LDX in reducing symptoms of BED. Over 12 weeks of administration of 50-70mg of LDX, participants reported fewer days with a binge eating episode compared to placebo, and significantly more participants in the LDX group reported 4-week cessation from binge eating. In a further study, Hudson et al. (2017) found that, following

26-weeks withdrawal from LDX, relapse rates were significantly lower for patients on LDX compared to placebo suggesting long-term efficacy of LDX treatment. LDX also appears to consistently reduce body weight in patients with BED (e.g. McElroy et al., 2015; Guerdjikova et al., 2016; Hudson et al., 2017).

A recent systematic review and meta-analysis (Schneider et al., 2021) summarised the effects of LDX on binge eating in both preclinical and clinical studies. Schneider et al. (2021) report consistent reductions in binge eating associated with LDX. Interestingly, both hedonic and homeostatic eating appears to be reduced by LDX compared to placebo. From this, the authors conclude that LDX likely reduces food intake by way of multiple mechanisms, acting on both homeostatic and hedonic systems. Additionally, Schneider et al. (2021) highlight the lack of studies into the cognitive and neural mechanisms that might underlie the therapeutic effects of LDX. Thus, the mechanism(s) through which LDX leads to the reduction of binge eating are unknown.

Despite the general absence of studies detailing mechanisms through which LDX may cause a reduction in binge eating, there is some evidence that LDX impacts cognitive processes in BED, which may be one contributing factor to decreases in binge eating. McElroy et al. (2015) reported an LDX-induced reduction in binge eating after an 11-week placebo-controlled trial which was accompanied by improvements in self-reported motor impulsivity and non-planning impulsivity (McElroy et al. 2016). McElroy et al. (2016) also reported improvements in binge-eating related obsessive thoughts and compulsive behaviours associated with the 11-week LDX dosing. This study suggests that one mechanism through which LDX leads to improvements in symptoms of BED is by a reduction in impulsivity and compulsivity. This interpretation is supported by findings from Griffiths et al. (2021) who found that LDX reduced self-reported food related and non-planning impulsivity (as measured by the Brief Loss of Control over Eating Scale,

Latner et al., 2014) and this was correlated with a reduction in frequency of binge eating episodes. Despite initial evidence that LDX reduces impulsive behaviours, the effects of LDX on task-based measures of impulsivity, which may be one cognitive mechanism supporting binge eating, have yet to be assessed.

In addition to impulsivity, the overlap between ADHD symptoms and binge eating suggests an effect on attentional mechanisms may also explain the ability of LDX to reduce binge eating. LDX improves measures of attention in individuals with ADHD (Findling et al., 2011) and given that inattention to food while eating has been associated with increased consumption (Robinson, Aveyard, Daley, Jolly, Lewis, Lycett & Higgs, 2013), the LDX-induced reduction in binge eating could occur through enhanced attention. However, the role that attention-enhancing effects of LDX play in the reduction of binge eating symptoms has not yet been explored.

Aside from cognitive effects of LDX administration, it is plausible that LDX influences reward processing in individuals with binge eating symptoms. There is evidence to support altered reward processing in individuals with BED (Schienle et al., 2009; Lee et al., 2017), and reward-related neurotransmission that is influenced by LDX has been implicated in the pathophysiology of BED (Kessler, Hutson, Herman & Potenza, 2016). Additionally, overlapping abnormalities in reward circuitry in ADHD and binge eating (Seymour, Reinblatt, Benson & Carnell, 2015) may at least partially explain the comorbidity between the two conditions. Given the aforementioned influence of LDX on hedonic eating (Schneider et al., 2021), it is possible that LDX blunts reward responses to food, which may be heightened in BED compared to healthy controls and contribute towards binge eating.

To investigate the neural mechanisms impacted by LDX, several studies have measured the effect of LDX administration on neural responses using functional magnetic resonance imaging (fMRI) paradigms. For example, Schulz et al. (2018) tested adults with ADHD who completed an emotional go/no-go task during a fMRI scan after 3 weeks of placebo administration, and 3-4 weeks of LDX. Compared to placebo, LDX increased activation in the right amygdala and decreased connectivity between the amygdala and left inferior frontal gyrus when responding to sad faces. The authors concluded that LDX increases amygdala-dependent processing of emotional stimuli while reducing the influence of emotional cues on cognitive control, resulting in enhanced cognitive control.

In a study into the effects of LDX-induced improvements in executive functioning in menopausal women, Shanmugan et al. (2017) compared BOLD signal during performance of an n-back task following 4 weeks of LDX and placebo administration (separated by a 2-week washout period). Shanmugan et al. (2017) reported that LDX increased activation in the insula and dorsolateral prefrontal cortex (dlPFC), and that these changes were associated with improvements in symptom severity. The authors concluded that LDX-induced improvements in executive functioning in menopausal women may be modulated by insula and dlPFC recruitment. The dlPFC is an area associated with cognitive control, and the increases in activation following LDX administration observed by Shanmugan et al. (2017) suggest that LDX increases cognitive control. Although this is in line with the conclusions of Schulz et al. (2018), the two studies suggest different mechanisms through which LDX-induced enhancement of cognitive control may arise. In individuals with BED, an LDX-induced increase in cognitive control may reduce impulsive responses towards food, which may be one mechanism through which BED is supported. However, based on the inconsistent changes in local activation following LDX administration reported in the aforementioned studies, the neural effects of LDX are

unclear. The differing results from these studies may be due to the different populations tested and different tasks used during scanning, suggesting that studies of participants with binge eating symptoms on food-related responding are required to fully understand the mechanisms underlying the ability of LDX to improve BED symptoms.

Only one study has assessed LDX-induced neural changes in participants with symptoms of BED. Fleck et al. (2019) recruited 20 women with BED onto a 12-week trial of LDX, involving an fMRI scan at baseline and at 12 weeks. During the fMRI scan at baseline and 12 weeks participants completed a visual oddball task consisting of food and non-food pictures. Fleck et al. (2019) reported a reduction in activation in the globus pallidus in BED patients after 12 weeks on LDX. Additionally, changes in activation of VMPFC between baseline and 12 weeks were positively correlated with changes in binge eating scale (BES) scores, and changes in thalamus activation were positively correlated with changes in score on the Y-BOCS-BE (an obsessive compulsive disorder questionnaire, modified to capture obsessive thoughts and compulsive behaviours towards binge eating) scores. Conclusions from this pilot study are limited as although it included a baseline vs treatment comparison, there was no placebo condition.

To date, no placebo-controlled study of the neural effects of LDX in women with binge eating symptoms has been conducted. As a result, the acute effects of LDX administration on neural processes in individuals with binge eating symptoms are unknown. Increased knowledge of the binge eating processes impacted by administration of LDX is important for a number of reasons. Firstly, knowledge of these processes could contribute to development of improved treatments for BED with increased efficacy and reduced stimulant-related side-effects and abuse potential. Secondly, observation of the mechanisms that are affected by administration of LDX, which mediate the decrease in symptoms of BED induced by the drug, will increase understanding of mechanisms that

underlie BED. Thirdly, given that LDX treats both ADHD and BED symptoms, assessing the processes impacted by administration of the drug may help elucidate the nature of the comorbidity between the two disorders, and perhaps transdiagnostic processes more broadly. These processes can then be considered as targets for novel treatments.

We sought to address these gaps in the literature regarding the effect of LDX on neural responses to food cues in individuals with binge eating symptoms. We measured the impact of LDX administration on binge-like eating measured using an ad-libitum food intake paradigm, comprising a pasta lunch (which participants ate until satiated), and a cookie snack (to measure eating in the absence of hunger). We measured the effect of LDX on neural responses to food cues in women with binge eating symptoms, using a picture-rating task during an fMRI scanning session.

3.2 Hypotheses

We hypothesised that administration of LDX would reduce food intake, and that this would coincide with reductions in BOLD responses to viewing food pictures in areas associated with appetitive/reward responses to food (e.g. striatum, orbitofrontal cortex, insula) and increases in BOLD responses in areas associated with cognitive control (e.g. dorsolateral prefrontal cortex).

3.3 Methods

3.3.1 Participants

22 women (*M* age = 24.41 ± 6.87 years, *M* BMI = 26.35 ± 4.98 kg/m^2) with moderate-to-severe binge eating symptoms were recruited via posters and social media posts. Exclusively women were recruited due to a higher prevalence of BED symptoms in women compared to men (Erskine & Whiteford, 2018), as well as to avoid possible sex-related effects on responses to food (e.g. Geliebter et al., 2013; Atalayer et al., 2014) which would otherwise require a larger sample to be recruited. The study was advertised as investigating 'The effects of LDX on taste and brain activity' to mask the true objectives. Participants were reimbursed £125 for full completion of one screening session and two test days. Incomplete participation was reimbursed pro rata at £10/per hour.

3.3.2 Design

A double-blind placebo-controlled design was used. Following confirmation of meeting inclusion criteria (see below for details), the order of participants' visits was randomised by an independent researcher, to first receive 50mg of LDX or an identically encapsulated placebo containing lactose. A 50mg dose was chosen as it is sufficient to produce clinical changes while minimising risk of side effects (McElroy et al., 2016). Test days were separated by one week minimum to ensure washout of LDX. The study was approved by the National Research Ethics Service and was pre-registered on clinicaltrials.gov as NCT04181957.

3.3.3 Exclusion/Inclusion Criteria

Participants were required to self-report moderate-to-severe binge eating symptoms. Binge eating symptoms were measured using the Binge Eating Scale (BES, Gormally, Black, Daston & Rardin, 1982) and participants scoring ≥ 18 were recruited, as scores between 18 and 26 are considered to indicate moderate binge eating symptoms, and

scores of 27 or above are considered to indicate severe binge eating symptoms. Additionally, participants were required to have a minimum BMI of 18.5 kg/m^2, be aged between 18 and 55 years, speak fluent English, and pass the medical checks described below. Exclusion criteria included current diagnosis of AN or BN, recent treatment for BED, metabolic disorder, current diagnosis of a mental health disorder excluding BED (determined using the Structured Clinical Interview for DSM-5), current substance use disorder, smoking, pregnant or breastfeeding, allergies or dietary restrictions (e.g. vegan diet), alcohol mg/l > 0 (tested via breathalyser) on test day, and contraindications to MRI scanning (e.g. non-removable metal, claustrophobia).

3.3.4 Questionnaire Measures

The Dutch Eating Behaviour Questionnaire (DEBQ) (Van Strien, Frijters, Bergers, & Defares, 1986) was used to characterise eating behaviours in the sample. The DEBQ is a 33-item questionnaire and measures three dimensions of eating behaviour: emotional eating, external eating and restrained eating. Good reliability and validity have been demonstrated in the DEBQ (e.g. Ohara et al., 2020; Malesza & Kaczmarek, 2021).

The Conners' Adult ADHD Rating Scales–Self Report: Screening Version (CAARS-S:SV) (Conners, Edhart & Sparrow, 1999) was used to determine self-reported ADHD symptoms in the sample. The CAARS-S:SV consists of 30 items, each relating to inattentive or hyperactive/impulsive symptoms. Responses are scored on a 4-point scale ranging from Not at all/Never to Very much/Very frequently which are totalled to give a score for each symptom type. Standardised scores (T-scores) > 60 indicate elevated levels of any symptom subscale, and indicate an at-risk ADHD index score. The CAARS-S:SV shows good validity and reliability (Sadeghi-Bazargani, Amiri, Hamraz, Malek, Abdi & Shahrokhi, 2014).

The Barratt's Impulsiveness Scale (BIS) (Patton, Stanford & Barratt, 1995) was used to determine trait impulsivity in the sample. This BIS consists of 30 items, scored on a 4-point scale ranging from Rarely/Never to Almost always/Always. Impulsivity is split into three subscales: Motor Impulsivity; Non-planning Impulsivity and Attentional Impulsivity. Good reliability and validity have been demonstrated for the BIS (Stanford, Mathias, Dougherty, Lake, Anderson & Patton, 2009).

The Intuitive Eating Scale (IES) (Tylka & Kroon Van Diest, 2013) subscale Reliance on Internal Cues of Hunger and Satiety (IES-RHSC) was used to measure gastric interoceptive awareness, as this scale has previously been found to be related to binge eating and ADHD (Kaisari et al., 2018). The IES-RHSC subscale consists of 6 items, scored on a 5-point scale ranging from Strongly disagree to Strongly agree. Reliability and validity have been demonstrated for the IES (e.g. Tylka & Kroon Van Diest, 2013; Duarte, Gouveia & Mendes, 2016).

3.3.5 Food intake

Participants were served a lunch of pasta shells with tomato and herb sauce, and a snack of Maryland chocolate chip cookies, served 15 minutes after the pasta lunch. All food was served using the Sussex Ingestion Pattern Monitor (SIPM) which consists of a digital scale placed underneath the surface of a table covered by a placemat (as described in Thomas, Dourish, Tomlinson, Hassan-Smith & Higgs, 2014). Pasta was served in bowls containing 200g and cookies were served in bowls containing 80g. Cookies were broken into pieces to avoid participants monitoring the amount consumed. When 150g of pasta was consumed or 60g of cookies were consumed, participants were interrupted via a computer screen and provided with a fresh bowl of food. Participants were instructed to eat as many bowls of food as they would like and had unlimited water available during the meal and snack. Although participants were aware of the presence of the scale (to avoid

measurement errors occurring e.g. through leaning on the scale), the study was advertised as measuring taste, rather than intake.

3.3.6 fMRI Scanning Session

3.3.6.1 Image Acquisition

Images were acquired using a Siemens MAGNETOM Prisma 3T MRI system at the University of Birmingham Centre for Human Brain Health. Functional images were acquired during the task (3 runs x 300 volumes) using an echo-planar imaging (EPI) sequence with the following parameters: repetition time (TR = 1500 ms), flip angle = 71°, echo time (TE = 35 ms), and 57 slices (voxel size = 2.5 × 2.5 × 2.5 mm^3). Structural T1-weighted images were acquired with the following parameters: repetition time (TR = 2000 ms), flip angle = 8° 208 slices (voxel size = 1 x 1 x 1 mm). Additionally, a field map was acquired with the following parameters: echo time (short = 4.92 ms, long = 7.38 ms), slice thickness = 3mm.

3.3.6.2 Picture Rating Task

The task comprised an event-related design in which participants were presented with 120 standardised pictures of food items and 120 pictures of visually-matched non-food items in 3 task runs, each lasting approximately 7 minutes. Food items were categorised as high/low sugar and high/low fat, resulting in four stimulus categories. Food and non-food items were selected from a standardised photo set and were previously shown to successfully detect food-specific BOLD responses (Chechlacz et al., 2009). Items were presented for 1500ms each in a randomised order, separated by a variable fixation period of 1.5-12.0 seconds. During viewing participants were asked to rate how appealing they found the pictures on a scale of 1-5 (1 = not appealing at all, 5= very appealing).

3.3.7 Procedure

3.3.7.1 Eligibility screening session

Participants attended a screening session to determine presence of binge-eating symptoms. The screening session was also used to exclude participants with contraindications to MRI scanning (e.g. non-removable metal, possible pregnancy), determined using a standardised screening form. Eligibility to safely ingest LDX was determined during the screening session by a physician via medical background checks and an ECG recording (e.g. to detect the presence of arrythmia). During the screening session, test days were scheduled to occur outside of the luteal or menstrual phase of participants' menstrual cycle, to control for potential influences of menstrual stage on intake.

3.3.7.2 Test days

Prior to the test sessions, participants were asked to eat their normal breakfast to minimise individual variation in baseline hunger levels, and upon arrival completed an alcohol breathalyser test and urine pregnancy test to ensure they were safe to participate. Following confirmation of eligibility, a baseline blood draw via venepuncture was taken, and either LDX or placebo was administered. Following LDX or placebo administration participants rested in a waiting room for 2.5 hours to allow for peak plasma levels of d-amphetamine to be reached (Ermer, Pennick, & Frick, 2016). Participants were instructed not to eat during this time and to drink only water. Following the 2.5 hour waiting period participants completed several cognitive tasks not presented in this thesis. At 3.5 hours after administration participants underwent an MRI scanning session (details of scanning session are reported below). Following the MRI scanning session participants had a second blood draw and then ate ad-libitum a pasta meal followed, 15 minutes after meal

completion, by a cookie snack. Details of additional tasks completed by participants (not reported in this thesis) can be found in Schneider et al. (2022).

3.3.8 Data processing and Analysis

3.3.8.1 Behavioural and Questionnaire Data

All behavioural and questionnaire data were analysed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA).

Average scores for questionnaire measures were calculated. Additionally, measures relating to ADHD symptomatology, and interoception were correlated with the BES, to test the previously documented relationship between ADHD symptoms, interoception and disordered eating (Kaisari et al., 2018).

Food intake was analysed using a 2-way ANOVA (pasta/cookies, drug/placebo). Ratings for food items were analysed using a 2-way ANOVA (stimulus type, drug/placebo). Follow-up T-tests were used to analyse significant interactions. Bonferroni corrections were applied for all follow-up tests. Additionally, picture ratings were correlated with parameter estimates extracted from clusters significantly influenced by LDX when viewing food images.

3.3.8.2 fMRI Pre-processing

All pre-processing and statistical analysis was conducted using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK) run with MATLAB 2016 (Mathworks Inc, Natick, MA). Pre-processing steps included: slice-timing correction, functional image realignment to the mean functional image from both scanning sessions, calculation of a voxel displacement map using the fieldmap which was used to unwarp functional images, and structural T1-weighted images were coregistered to the mean functional image. The T1-weighted images were then segmented into white and grey matter and this was inputted

into the DARTEL toolbox (Ashburner, 2007) to create a group template, which was normalised to MNI space. Images were smoothed using a Gaussian kernel of 8 mm. Task runs that included head movement >3mm (equivalent to > 1 voxel) were excluded from further analysis. One participant was excluded from analysis due to excessive movement in all task runs. Eight participants had one task run excluded from analysis (3 LDX runs, 5 placebo). Two participants had two task runs removed (All placebo).

3.3.8.3 General Linear Model Analysis

For each participant a model was defined containing 8 regressors: four food stimulus categories (as detailed above) and four matched non-food stimulus categories. Six motion parameters were also included. The response to events was modelled by a canonical hemodynamic response function. This resulted in four different contrast images: food items (four food categories) vs. matched non-food items. These contrast images were entered into a second-level two-way ANOVA with condition (drug and placebo) and food type (high fat high/low sugar, low fat high/low sugar). As there were no specific hypotheses relating to effect of LDX on responses to foods of differing sugar and fat content, the contrast of interest used to compare the drug effect included all food items vs all non-food items.

Main effects and interactions were considered significant at $p < 0.05$ family-wise error (FWE) correction using a primary uncorrected threshold of $p < 0.001$. Small-volume correction was applied to *a priori* defined regions of interest.

3.3.8.3 Psycho-physiological Interaction (PPI)

Regions (if any) showing a main effect of drug were used as seed regions for PPI analysis to assess connectivity changes associated with LDX administration. 4mm spheres around the peak of these areas were defined and the first eigenvariate for this volume of

interest extracted. PPI analysis was run to determine the interaction between the time-series and food/non-food stimuli and the results of this model were entered as a regressor into a group level GLM with one factor (drug and placebo). Small volume correction was applied to regions determined to be involved in processing of food rewards (from food > non-food contrast and meta-analysis).

3.4 Results

3.4.1 Participant Characteristics

On average, scores on the BES of the sample reflected presence of severe binge eating symptoms. The mean BMI of the sample was overweight. See Table 1 for mean values and further participant characteristics.

3.4.2 Questionnaire Measures

Average scores on the CAARS inattention and hyperactive/impulse subscales, and the CAARS combined score were not within an elevated range (see Table 1).

Participants showed increased mean scores on all three DEBQ subscales, particularly emotional eating and external eating, compared to reports from general populations (e.g. van Strien, Frijters, Bergers & Defares, 1986; Bailly, Maitre, Amanda, Hervé & Alaphillippe, 2012; Nagl, Hilbert, de Zwaan, Braehler & Kersting, 2016). See Table 1 for mean scores for all questionnaires.

Table 1. Participant characteristics.

	Mean (±SD)	**Range**
Age	24.4 (± 6.9)	18 - 49
BMI	26.4 (± 1.1)	19.5 - 41.3
BES (0-46)	28.4 (± 1.4)	18 - 40
DEBQ (1-5)		
Restrained Eating	3.0 (±0.5)	1.6 - 3.7
External Eating	3.9 (±0.4)	2.8 - 4.6
Emotional Eating	3.5 (±0.7)	2.0 - 4.6
CAARS		
Impulsive/Hyperactive (0-27)	8.6 (± 3.8)	2 - 14
Inattentive (0-27)	9.6 (± 4.6)	1 - 20
Combined (0-54)	18.2 (± 7.4)	4 - 33
BIS		
Attentional (8-32)	17.7 (± 4.3)	10 - 26
Nonplanning (11-44)	26.5 (± 4.1)	15 - 32
Motor (11-44)	24.6 (± 4.4)	15 - 36
IES RHSC (1-5)	2.3 (± 0.8)	1 - 3.4

BES = Binge Eating Scale; DEBQ = Dutch Eating Behaviour Questionnaire; CAARS = Conners' Adult ADHD Rating Scale (short screening version); BIS = Barratt's Impulsiveness Scale, IES RHSC = Intuitive Eating Scale, Reliance on Hunger and Satiety Cues subscale.

3.4.3 Food Intake

A two-way ANOVA revealed an interaction between food type (pasta vs cookies) and condition (drug vs placebo) $F(1,21) = 4.4$, $p = 0.048$, $np^2 = 0.185$. Post-hoc paired t-tests revealed reduced intake of both pasta ($t(21) = 2.8$, $p = 0.01$, $d = 0.52$) and cookies ($t(21) = 4.3$, $p < 0.001$, $d = 0.65$) when on LDX compared to placebo, although the effect was larger for cookies than for pasta (bonferroni-corrected $\alpha = 0.025$) (Figure 1).

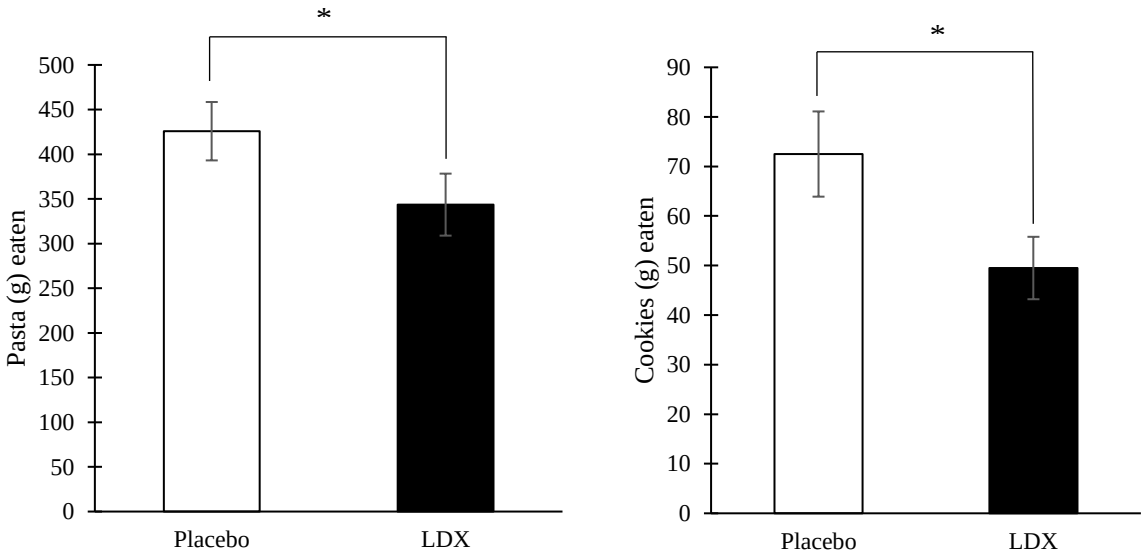

Figure 1. Mean intake of pasta (left) and cookies (right) after placebo (white) and LDX (black). * = p < 0.01.

3.4.4 Picture Rating Task

3.4.4.1 Behavioural Task

A two-way ANOVA revealed an interaction between condition (drug vs placebo) and stimulus type (fat and sugar content of stimulus foods) $F(3) = 4.76$, $p = 0.005$, $np^2 = 0.185$. Post-hoc paired t-tests revealed lower ratings of high-fat, low sugar foods only after drug (*mean* = 3.73) compared to placebo (*mean* = 4.07), $t(20)=2.61$, $p=0.009$, $d = 0.58$ (bonferroni-corrected $\alpha = 0.0125$) (Figure 2).

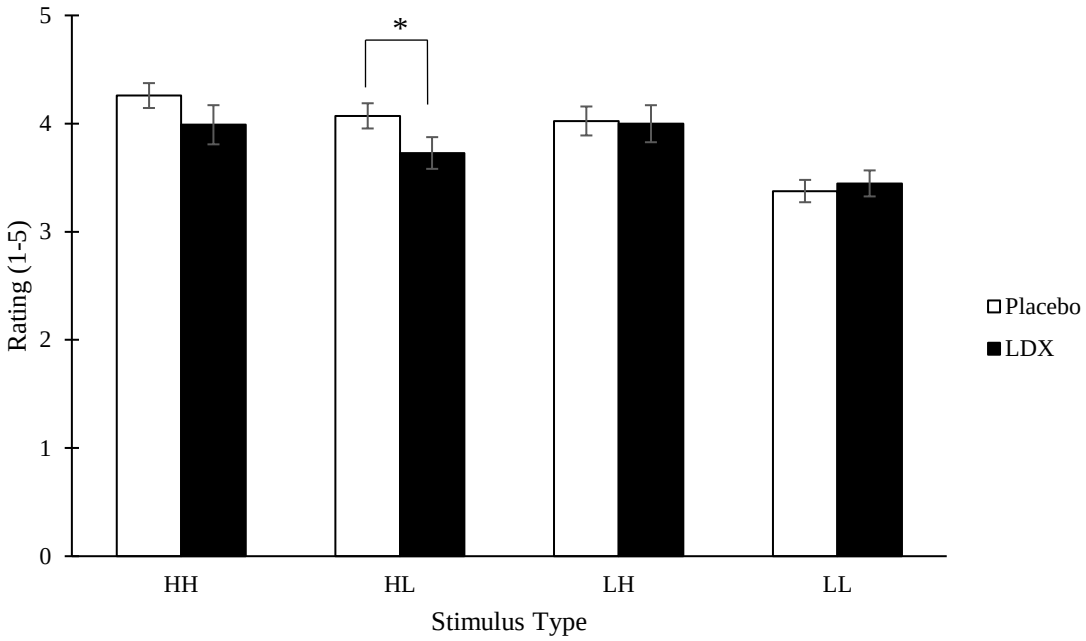

Figure 2. Mean appealing rating for each four food stimuli after placebo (white) or LDX (black). HH = high fat, high sugar; HL = high fat, low sugar; LH = low fat, high sugar; LL = low fat, low sugar. * = $p < 0.01$.

3.4.4.2 fMRI Results

3.4.4.2.1 Main effect of task (food versus non-food)

Statistically significantly greater (whole-brain FWE-corrected) BOLD responses to food compared to non-food images were observed in the bilateral insula, bilateral midfrontal, left precuneus, left inferior orbitofrontal cortex, left inferior temporal, left middle occipital gyrus, left superior frontal, left thalamus, left midcingulate, left precentral, left angular gyrus, right superior frontal gyrus. See Table 2 for details.

Table 2. Clusters significant for contrast Food > Non-food.

Area	**K**	**X**	**Y**	**Z**	**Z-score**	**FWE-corrected p**
Insula (L)	349	-37.5	-5	7.5	7.68	<0.001
Midfrontal (L)	117	-35	35	20	7.26	<0.001
Precuneus (L)	348	-5	-50	17.5	6.94	<0.001
Inferior Orbitofrontal (L)	10	-30	32.5	-5	6.15	0.008
Inferior Temporal (L)	55	-47.5	-47.5	-20	6.11	<0.001
Mid Occipital (L)	89	-25	-65	37.5	6.1	<0.001
Insula (R)	97	37.5	0	7.5	5.95	<0.001
Superior Frontal (L)	322	-15	30	52.5	5.94	<0.001
Thalamus (L)	33	-2.5	-10	7.5	5.33	<0.001
Mid Cingulate (L)	27	-2.5	0	32.5	5.29	0.002
Precentral (L)	46	-47.5	10	35	5.27	<0.001
Angular Gyrus (L)	13	-45	-65	37.5	4.91	0.006
Superior Frontal (R)	10	17.5	40	42.5	4.89	0.009
Midfrontal (R)	11	37.5	37.5	17.5	4.8	0.008

Values reported at FWE-corrected $p < 0.05$. L = left, R = right.

3.4.4.2.2 Placebo versus LDX

Figure 3 shows the regions where activity was attenuated by LDX only for food stimuli (cyan -green) and the areas showing a main effect of food > non-food (red-orange). Under a whole-brain FWE-corrected significance threshold the only contrast that remained significant was for the right thalamus. A cluster in the left thalamus was significant (*#voxels* = 26, *Z = 3.8*, small volume FWE-corrected $p = 0.001$, $d = 0.85$) when using small volume correction, of a 6mm sphere around the food > non-food peak. No above threshold increases in activity resulting from LDX administration were observed. See Table 3 for details.

Table 3. Clusters detected for contrast placebo > LDX (for food > non-food).

Area	**K**	**x**	**y**	**z**	**Z-score**	**FWE-corrected p**
R thalamus	228	10	-8	3	4.26	0.01
Fusiform Gyrus/ Parahippocampal Gyrus	106	-35	-48	-10	4.03	0.12
L thalamus	33	-10	-10	8	3.9	0.59
R Inferior Frontal Gyrus /Anterior Insula	46	30	35	3	3.8	0.45

Values reported at initial uncorrected detection threshold p<0.001. L = left, R = right.

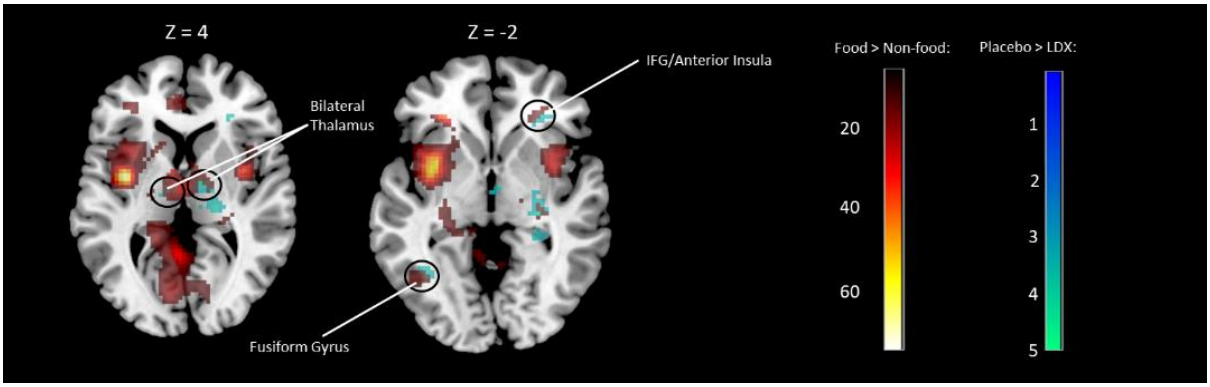

Figure 3. Regions showing greater responses to food (red) compared to non-food overlaid with regions showing greater responses to food after placebo compared to LDX (blue). Image clusters thresholded at p < 0.001 uncorrected.

3.4.4.2.3 Psycho-physiological Interaction Analysis

A trend towards attenuated functional connectivity (for food > non-food) between the left thalamus and left middle insula (*#voxels* = 9) in the LDX condition was found relative to placebo (Z = 2.17, small volume corrected p = 0.069, d = 0.50) using small volume correction from the food > non-food peak, and meta-analysis coordinates (Tang et al., 2012). There were no above threshold changes to functional connectivity of the right thalamus after LDX.

3.4.4.2.4 Correlation between thalamus response and ratings

Appealing ratings for high fat low sugar items only were correlated with thalamus parameter estimates due to the stimulus-specific reduction in ratings for high fat low sugar items. Appealing ratings for high fat low sugar items did not correlate with right thalamus parameter estimates in the placebo condition (r_s = -0.14, p = 0.95) and there was a trend towards a negative correlation in the LDX condition (r_s = -0.42, p = 0.055).

3.5 Discussion

The aim of this study was to determine the effect of LDX administration on neural responses to food pictures in women with binge eating symptoms, to further understand the neural mechanisms underlying the efficacy of LDX in treating BED. To the best of our knowledge, this is the first placebo-controlled study of the effects of an acute dose of LDX on neural responses to food stimuli in women with binge eating symptoms.

Compared to placebo, LDX administration decreased intake of both a lunch meal (given to model homeostatic-driven eating) and a palatable snack (given to model hedonically-driven eating). In addition, compared to placebo, LDX attenuated activity in the bilateral thalamus when looking at food images. There was also a trend towards decreased functional connectivity between the thalamus and the insula after LDX compared to placebo. When given LDX, participants rated images of savoury, high fat food as less appealing than after placebo. Although these ratings did not significantly correlate with activation in the thalamus, there was a trend towards a negative relationship between ratings of savoury high fat food and thalamic activation when given LDX.

3.5.1 Effect of LDX on food intake

The finding that LDX reduced both homeostatic eating (e.g. eating pasta when hungry) and hedonic eating (eating cookies when satiated) is consistent with findings from a recent meta-analysis (Schneider et al. 2021) which reported LDX consistently reduces food consumption in general and not intake of palatable food specifically. This global effect on food intake suggests that the improvement in BED symptoms seen after LDX administration may be a result of multiple mechanisms being impacted by the drug. For example, individuals with BED show reduced satiety (Sysko, Devlin, Walsh, Zimmerli & Kissileff, 2007), which may contribute towards the intake of large quantities of food in BED. Therefore, the observed reduction in intake of the pasta lunch when hungry may be

indicative of LDX increasing satiety. Additionally, the observed reduction of eating in the absence of hunger (e.g. eating despite satiety) may suggest that LDX not only influences satiety, but also decreases intake through blunting reward responses, which otherwise motivate overeating of attractive foods. Ratings for attractiveness of food were reduced after LDX compared to placebo, in particular for savoury, high fat food items. This possibly reflects a reduction in perceived rewarding properties of food after LDX, particularly for highly rewarding (e.g. high fat) foods.

3.5.2 Effect of LDX on BOLD fMRI responses to food

The only area affected by LDX while attending to food pictures was the thalamus bilaterally. This result is consistent with results from the only previous study to assess the effects of LDX on fMRI responses in women with binge eating symptoms (Fleck et al., 2019). This study found that 12-week dosing of LDX improved binge eating symptoms, and that (non-significant) changes in thalamus activity when attending to food stimuli correlated with a reduction in obsessive thoughts about binge eating and compulsive binge eating behaviours. Findings from our study add to this evidence that alterations in thalamic activity in response to food cues following LDX administration may contribute to improvements in binge eating.

3.5.3 Thalamus and Salience for Rewarding Cues

Dopamine is a key neurotransmitter considered to control incentive salience, the motivational value attributed to rewarding cues (Berridge, 1996). The thalamus receives widespread dopamine innervation (García-Cabezas, Rico, Sánchez-González & Cavada, 2007) and in animals, nuclei in the thalamus have been suggested to supply neurones in the striatum with information about motivationally salient events (Matsumoto et al., 2001). Similarly, in humans the thalamus is considered, along with the insula, anterior cingulate cortex and the amygdala, to be part of the salience network (Uddin, 2015; Seeley, 2019), a

series of brain regions detecting behaviourally significant stimuli, connectivity between which is related to dopaminergic transmission (McCutcheon et al., 2019). In line with the significant attenuation of thalamus activation and the trend towards attenuation of thalamic connectivity in the current study, Schrantee et al. (2015) reported decreased functional connectivity between the thalamus and other structures in the cortico-striatal-thalamic loop associated with dopamine release induced by d-amphetamine administration. Although Schrantee et al. (2015) scanned in the absence of a task, given the role of this loop in detection of rewarding cues, attenuation of activation in this loop may impact processing of otherwise salient cues.

One such cue which is attributed incentive salience is food. Accordingly, an example of one reward stimulus that the thalamus is thought to be involved in processing is the rewarding aspects of food, for example there is evidence from animal models that obesity is associated with heightened thalamus reactivity to food cues (e.g. Thanos et al., 2008). There is also evidence from human neuroimaging studies that the thalamus is involved in valuation of food reward (Small, Zatorre, Dagher, Evans & Jones-Gotman, 2001; DiFeliceantonio et al., 2018) and in reward-related processes more generally (Kühn & Gallinat, 2012; Liu, Hairston, Schrier & Fan, 2011). In the present study, motivationally salient information may be sensory information such as the visual food cues presented during scanning. The observed reductions in activation of the thalamus, in addition to a disruption in the relationship between thalamus activation and pasta intake, may reflect a reduction of an otherwise over-active response to food cues which, after placebo, contributes towards overeating. Previous research has shown that adolescents at-risk for obesity show increased thalamic responses to reward compared to those not at-risk (Stice, Yokum, Burger, Epstein & Small, 2011), suggesting that heightened reward-related activity in the thalamus may contribute to overeating such as that characteristic of BED.

However, given that additional regions of the salience network did not appear to be impacted by LDX administration, future research is required to determine whether attenuation of thalamic responses to food are indeed indicative of a reduction of salience processing. Similarly, it is unclear why areas more classically associated with reward processing were not affected by LDX administration and therefore the suggested impact of LDX on reward requires further investigation. It therefore remains unclear whether the processes reflected by the attenuated thalamic response are in fact related to saliency. One potential way to pinpoint specific processes would be to determine LDX-induced alterations in BOLD response within specific subregions associated with specific functions. Using anatomical tracing to determine subregions connectivity of each participant would allow to account for individual differences in thalamus anatomy, and subsequent determination of LDX effects in specific subregions. An additional method for future research to assess whether the BOLD response results of the current study reflect an attenuation of saliency processing could be to compare BOLD responses on LDX and placebo during processing of some other salient stimulus (e.g. money).

3.5.4 Integration of information in the thalamus

LDX-induced attenuation of thalamic activation to food pictures in our study may correspond to a reduction in aberrant saliency of food cues, which in women with symptoms of BED drives overeating. Eating guided by external factors has been linked to a tendency towards overeating and loss-of-control style eating, such as is seen in BED (Mason & Lewis, 2014). Accordingly, in the current sample, the external eating measure on the DEBQ was relatively high (mean = 3.9) compared to reports from general populations (e.g. van Strien, Frijters, Bergers & Defares, 1986; Bailly, Maitre, Amanda, Hervé & Alaphillippe, 2012; Nagl, Hilbert, de Zwaan, Braehler & Kersting, 2016). The thalamus plays a role in processing of exteroceptive information, and exhibits resting state

functional connectivity (Cauda, D'agata, Sacco, Duca, Geminiani & Vercelli, 2011) and structural connectivity (Ghaziri et al., 2018) with the insula. Exteroceptive information from the thalamus is integrated with interoceptive information in the insula (Craig, 2009; Simmons et al., 2013). Deficits in the accuracy of interoceptive processing have been noted in BED (e.g. Aloi et al., 2017; Ramacciotti et al., 2008; Vinai et al., 2015). A possible interpretation of results from the present study is that LDX-induced reductions in thalamic responding to external food information may reduce an existing imbalance that otherwise favours exteroceptive cues to guide eating, which may in turn enable a relative increase in interoceptive signals in guiding eating. However, in the absence of a comparator sample of participants without symptoms of BED, and without a task to specifically measure integration of interoceptive and exteroceptive information, this conclusion is speculative and requires further investigation.

Contrary to one of the hypotheses, we observed no impact of LDX on areas typically associated with ADHD symptomatology, such as those involved in control of impulsivity (e.g. dorsolateral prefrontal cortex). As suggested by Schneider et al. (2021) it is likely that LDX influences multiple processes relating to food, and the task used during the scanning session may not have measured the neural correlates of all of these processes. Therefore, the lack of effect in the aforementioned areas does not necessarily mean these areas and the associated cognitive processes are not impacted by LDX administration, but may be the result of the picture rating task used during the scanning session being best suited to test appetitive responses to food cues, whereas tasks such as a go/no-go task may be better suited to measuring processes such as impulsivity. In addition, participants in the current study did not score highly on self-report measures of impulsivity such as the BIS and the CAARS, suggesting that this particular sample was low in trait impulsivity, which may not be reflective of individuals with symptoms of BED generally.

3.5.5 Study Strengths and Limitations

The current study is the first double-blind placebo-controlled study to investigate the acute effects of LDX on neural responses to food in women with binge eating symptoms. Double-blind placebo-controlled study designs are beneficial as they mitigate the influence of researcher and participant expectations on the effect of a drug.

Prior to the current study, there had been no investigation of the effect of LDX on response to visual food cues in participants with binge eating symptoms. The picture rating task contrast (food > non-food) was successful in specifically detecting responses to food cues in areas such as the bilateral insula, precuneus, and orbitofrontal cortex (Tang et al., 2012). The paradigm used in the current study is therefore highly specific in assessing how neural response to BED-relevant stimuli is impacted by LDX administration.

From the results presented it is not possible to conclude whether the reduction in thalamic activation associated with LDX administration reflects the existence of a heightened thalamic response to food in women with binge eating symptoms compared to healthy control participants and whether this contributes to BED symptomatology. Future studies to address this question should recruit women with and without binge eating symptoms to assess baseline response to food cues, and the relative impact of LDX on thalamic activity in response to food cues between the two groups.

Given that the BOLD signal may be influenced by a range of physiological processes including cerebral blood flow (CBF) and neurovascular coupling, it cannot be completely excluded that changes measured by fMRI are secondary to LDX-induced effects on the cerebrovasculature. However, this appears very unlikely for several reasons. Firstly, although the influence of CBF on BOLD response cannot be removed, by using subtractive contrasts (e.g. food > non-food), the only subject-level stimulus-related difference carried forward into group level analysis should minimise any global effects on

variables. Additionally, fitted responses to food and non-food stimuli from individual participants were visually inspected to confirm that drug administration had not caused the response to deviate from expected shape. Secondly, there is no evidence that oral d-amphetamine administration decreases blood flow in the thalamus. In contrast, Devous, Trivedi & Rush (2001) found that, while oral d-amphetamine administration reduced CBF in areas including the motor cortex, visual cortex and fusiform gyrus, it increased CBF in the thalamus (and mesial prefrontal cortex, inferior frontal cortex and amygdala), suggesting that an attenuation of the fMRI BOLD signal, such as that observed in our study was not a result of LDX-induced reduced CBF to the thalamus. Nevertheless, a limitation of interpretation of results from the current study is the inability to definitively exclude the possibility that changes in BOLD response are not solely a result of LDX-induced vascular changes. To confirm that this is not the case, future research may wish to account for several additional measurements. For example, analysis of data on perfusion (e.g. MRI arterial spin labelling, Wang, Chen, Fernández-Seara & Detre, 2011) would allow future research to rule out the possibility that changes in the BOLD signal reflect LDX induced changes in baseline perfusion only. Additionally, data relating to peripheral changes that may impact signal of neurovascular origin (e.g. blood pressure) could be recorded and included as covariate measurements. Finally, LDX-induced alterations in cerebrovascular reactivity can be assessed using a hypercapnia paradigm such as a breathing-holding paradigm (Pillai & Mikulis, 2015) to determine changes in BOLD signal in response to hypercapnia, to rule out the possibility that cerebrovascular reactivity is affected locally in regions also displaying changes in the BOLD signal in response to tested contrasts.

Despite the study aims being concealed, it is possible that participants' consumption was reduced as a result of awareness of their eating being observed (e.g.

Robinson, Kersbergen, Brunstrom, & Field, 2014). There is evidence that awareness of the presence of the Universal Eating Monitor does not impact food intake in healthy participants (Thomas, Dourish & Higgs, 2015). The potential impact of feeling observed may be of particular concern when measuring intake in individuals with symptoms of BED, given that one characteristic of BED is eating alone due to embarrassment concerning how much one is eating (APA, 2013). Despite this, the expected LDX-induced reductions in intake were observed, suggesting that it is unlikely that the effects of being observed caused any meaningful impact on results.

3.5.6 Conclusions

In conclusion, this is the first study to document neural responses to food pictures in women with binge eating symptoms when administered a single dose of 50mg LDX compared to placebo. A single dose of 50mg LDX reduced intake of both a pasta meal and a palatable cookie snack, suggesting that the drug reduces both homeostatic and hedonic food intake. LDX also decreased activity in the thalamus, suggesting that the thalamus is a key target for the reduction of binge eating symptoms by the drug, and may play a role in the pathophysiology of binge eating. One mechanism of action of LDX may be to decrease relative salience of external food cues, enabling increased influence of interoceptive signals. This possibility was not addressed in the current study and requires further investigation, for example through manipulation of internal state (via consumption) and measurement of the subsequent impact on integration of exteroceptive and interoceptive information.

Chapter Four:

Martin, E., Dourish, C. T., Rotshtein, P., Spetter, M. S., & Higgs, S. (2019). Interoception and disordered eating: A systematic review. *Neuroscience & Biobehavioral Reviews, 107,* 166-191. *

4.1 Introduction

A recent consensus statement defined interoception as "the process by which the nervous system senses, interprets, and integrates signals originating from within the body, providing a moment-by-moment mapping of the body's internal landscape across conscious and unconscious levels" (Khalsa et al. 2018). Traditionally, interoception was considered to relate to signals with internal origin (e.g. visceral signals, heartbeat, breathing rate) but more recent conceptualizations of interoception include representations of the skin and body temperature, pain, itch and sensual touch (Craig 2002; Ceunen et al., 2016). Interoception is important for the maintenance of stable internal states and for motivating behaviour and guiding decision making. For example, sensing of a depleted nutritional state of the body guides food seeking behaviours and consumption (for a recent review Maniscalco & Rinaman, 2018).

Dysfunctional interoceptive processing has been implicated in a number of mental health disorders including anxiety, panic disorder, depression and eating disorders (Ehlers & Breuer, 1996; Khalsa et al., 2018; Pollatos, Traut-Mattausch & Schandry, 2009; Simmons & Deville, 2017). Impaired interoception has long been considered to be a key feature of eating disorders (Silverstone & Russell, 1967). Bruch (1962) documented a disturbance in the perception of stimuli arising in the body of patients with anorexia that was subsequently labelled as a deficit in interoception (Garfinkel et al., 1978). Research into interoception and disordered eating has since employed a range of physiological, behavioural and imaging methods to assess the ability to detect and utilise cues from bodily systems to direct behaviour.

The widely-used Eating Disorders Inventory is a questionnaire designed to assess common traits of anorexia and bulimia (Garner, Olmstead & Polivy, 1983) and it includes 'interoceptive awareness' as a factor. Using this questionnaire, interoceptive impairments

have been noted in patients with anorexia and bulimia (Klabunde et al., 2013; Pollatos et al., 2008) and in subclinical populations with disordered eating behaviour (Brown et al., 2010; Koch & Pollatos 2014; Young et al., 2017). Another method to measure interoception that has been used to study participants with disordered eating is heartbeat counting (e.g. Eshkevari et al., 2014; Fischer et al., 2016). Sensitivity to painful stimuli has also been used to measure interoceptive sensitivity in eating disorders (e.g. Raymond et al., 1999a,b; Schmahl et al. 2010; Strigo et al., 2013). In addition, neuroimaging has been used to measure neural activity in interoception-related areas of the brain during performance of tasks that require monitoring the state of the body (e.g. Kerr et al., 2016; Strigo et al., 2013). The brain area most commonly associated with interoception is the insula (Critchley, Wiens, Rotshtein, Ohman & Dolan, 2004; Schulz, 2016; Stephan et al., 2003) and functional neuroimaging studies have identified differences in neural responses in the insula in healthy controls and individuals with eating disorders (Holsen et al., 2012; Wierenga et al., 2015,2017). Additional brain regions that have been associated with interoceptive dysfunction in disordered eating are the anterior cingulate cortex (Wierenga et al., 2015, 2017), and the somatosensory cortex (Lavagnino et al., 2014).

A search for existing reviews relevant to the role of interoception in eating disorders identified a recent narrative review (Simmons & DeVille, 2017) and two systematic reviews that assessed 1) the link between interoception and eating disorders using a questionnaire measure focused on the perception of hunger and satiety signals (Jenkinson, Taylor & Laws, 2018) and 2) the specific link between interoception and bulimia nervosa (Klabunde, Collado & Bohon, 2017). The results of these reviews provide evidence that interoceptive dysfunction is present in eating disorders but to date there has been no systematic review of the association between different types of eating disorders/disordered eating and interoception. This is significant because evidence that

impairments in interoception occur across different types of eating disorder and are observable in sub-clinical populations at risk for the development of eating disorders would suggest that interoception constitutes a transdiagnostic feature of eating disorders (Fairburn, Cooper, & Shafran, 2003). In addition, there has been no systematic examination of interoception in disordered eating according to the modality of the signal (type of sensory channel involved). Establishing whether interoceptive disturbances in people with disordered eating is specific to visceral signals relating to the processing of food or whether there are deficits in interoception regardless of the origin of the signals has implications for understanding the nature of the interoceptive deficits in disordered eating. Finally, there has been no evaluation of the evidence for a specific role of interoception in the development and/or maintenance of disordered eating. Poor interoception could be a factor that predisposes an individual to develop eating disorder symptoms but might also be related to conditions that are co-morbid with eating disorders, such as anxiety and depression. Interoceptive problems may also be a consequence of prolonged exposure to a starved or disordered eating state. Evidence that interoceptive deficits are present in individuals who go on to develop an eating disorder, and in individuals recovered from current eating disorder symptoms or their relatives would suggest that poor interoception constitutes a potential endophenotype.

Here, we present the results of the first systematic review of studies that have investigated interoceptive functioning across the spectrum of disordered eating behaviour, ranging from diagnosed anorexia and bulimia nervosa, to subclinical disordered eating behaviours such as emotional eating. We aim to synthesize evidence from studies that used a range of methods to assess interoception related to visceral signals and to signals related to pain, itch, temperature and sensual touch. To provide insight into the possible role of poor interoception as a predisposing factor in the development of eating disorders we also

assess potential associations between interoception and disordered eating in longitudinal studies and in the relatives of affected individuals. We also aim to assess the current evidence on potential moderators and mediators of the relationship between disordered eating and interoception. Hence, our aim is to answer four questions: 1) Is dysfunctional interoception present across the spectrum of disordered eating from subclinical to clinical and across eating disorder subtypes? 2) Is dysfunctional interoception associated with disordered eating present across interoceptive modalities? 3) What is the role of interoception in the onset versus maintenance of disordered eating? 4) Have moderators/mediators of the relationship between disordered eating and interoception been identified? Our evaluation of the current state of this research provides a guiding framework for future studies on the role of interoception in the development and maintenance of disordered eating.

4.2 Methods

4.2.1 Literature Search

A search for original research articles was performed in September 2018 by a single investigator. Databases used in the search were Web of Science (collection), PubMed Central (all databases) and Ovid databases. A full list of search terms used can be found in the supplementary material. The search included only papers written in English and using human participants. The Preferred Reporting items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart was used to guide the search and selection of articles. Results were supplemented by searching reference lists of related articles and reviews.

4.2.2 Study selection

All original, peer reviewed research articles (e.g. no reviews/meta-analyses) assessing interoception/interoceptive processes in relation to disordered eating behaviour were included. The inclusive definition of interoception used here was based on the sensations suggested by Craig (2002) and therefore, studies assessing sensations of hunger, fullness, heartbeat, pain, itch, temperature and sensual touch were included. Studies of taste processing were excluded because taste is classically considered an exteroceptive sense that relates to sensing of the environment rather than the internal milieu. In addition, many studies of taste processing in disordered eating have focussed on hedonic/reward related responses rather than taste sensation/perception. For fMRI studies, articles that reported neural activation as an outcome measure were included, provided the neural activation occurred during the performance of an interoception-related task or in relation to changes in interoceptive state. Studies assessing interoception in individuals recovered from eating disorders and their relatives were included. There was no exclusion based on the age of the study participants and the selected studies included children, adolescents and/or adults. Articles assessing the mediating effect of interoception on treatment outcome were also included.

4.2.3 Data Extraction

Data extraction was performed using standardized forms created for the review and each article was evaluated by two reviewers. The second reviewer (SH) confirmed the first reviewer's (EM) data extraction for completeness and accuracy The information extracted from each study was sample size; age and gender; eating disorder/disordered eating type; comorbidities; exclusion criteria; measure of interoception; measure of disordered eating; covariates/control measures; findings on differences in interoception between disordered eating groups. The quality of each study was assessed by two reviewers using a tailored quality assessment tool (Kmet, Cook & Lee, 2004). Items in the tool included assessment

of the validity of the measurement methods, sample size and control for confounders. Reporting on the methodological aspects of the studies rather than relying on a numerical score for quality is considered more appropriate for systematic reviews and meta-analyses (Jüni, Witschi, Bloch, & Egger, 1999). Therefore, we rated individual components of the checklist (criteria met, criteria not met, not reported) and provided an overall rating for the quality of the study (low, moderate or high). The second reviewer (EM) confirmed the first reviewer's (SH) quality assessment.

4.3 Results

4.3.1 Inclusion of Articles

Figure 1 shows the PRISMA flowchart used to guide selection of articles. Searches using the keywords (see Appendix A) generated 7316 results. 527 of these were from Web of Science, 1936 were from Ovid databases, and 4853 were from PubMed Central. After the removal of duplicates, initial screening based on relevance of the paper title and abstract to the research question was conducted. Following this step, and the removal of papers that were not original research articles or articles that were not written in English (4), 114 full-text articles remained to be assessed for eligibility for inclusion in the review. Further screening, based on full-text articles led to the exclusion of 19 articles that were not relevant to the research question. Five further papers were found through a search of reference lists of related articles. This left 100 research articles for consideration in the systematic review. Two articles presented two studies relevant to the association between disordered eating and interoception (Maïano et al., 2016; Young et al., 2017) and one article presented three relevant studies (Lattimore et al., 2017). Therefore, the final number of studies included was 104.

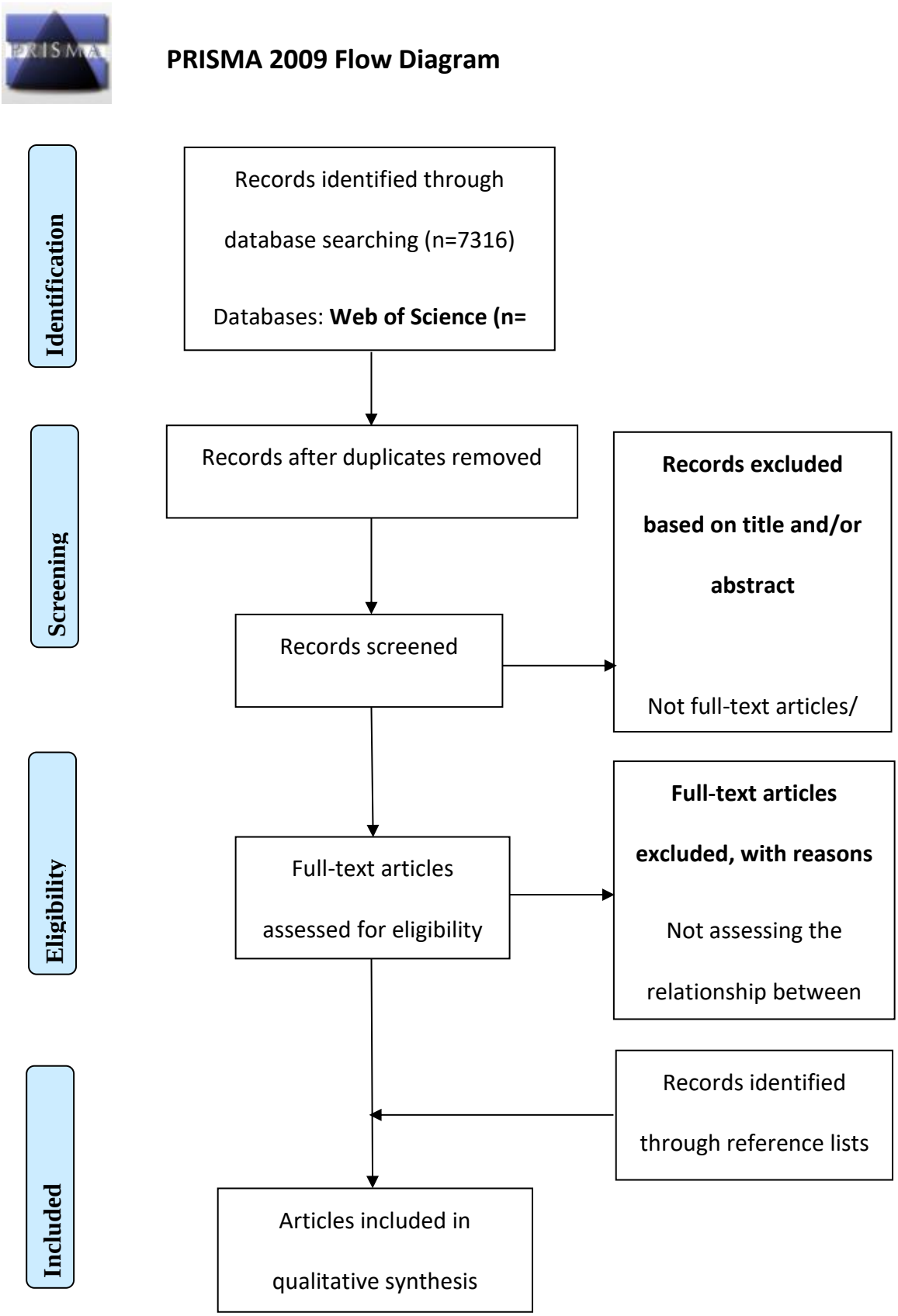

Figure 1. PRISMA flow diagram, showing process of article search and selection
*Number of records accurate for search conducted 26/09/2018

4.3.2 Characteristics of included articles

Across the 104 studies included, the total number of participants was 32883 with a minimum number of eight participants (Matsumo et al., 2006) and a maximum number of 5139 participants (Kim, Annunziato & Olatunji, 2018). The majority of studies (n =77, 74%) recruited women participants only. The remaining studies comprised 26 studies that included both men and women, and one study that recruited men only (Ussery & Prentice-Dunn -Dunn, 1992). Of the 26 studies that recruited both men and women, the percentage of women participants ranged from 50-93%. The majority of studies (n = 93) recruited adult participants (mean age of participants = > 18). Ages of the participants across all samples ranged from 9 years (Koch & Pollatos, 2014) to 60 years (Fassino et al., 2004). Publication dates of the articles ranged from 1974 (Garfinkel et al., 1974) to 2018 (e.g. Berner et al., 2018; Romano et al., 2018). The majority of studies used a cross-sectional design (n=78), eleven used longitudinal observational designs, five used quasi-experimental pretest-posttest designs (one of which only ran a cross-sectional comparison of interoception), seven used an experimental design, and two used a cross-sectional family-based design.

The majority of the studies assessed interoception using questionnaire measures (n = 66). Other methods employed were heartbeat perception tasks (n = 9), pain detection and threshold paradigms (n = 15), and neuroimaging, with tasks and conditions including comparisons of hungry/full, pain perception, and trials consisting of focussing on internal sensations (n = 11). One study used a drug to elicit interoceptive state changes, one compared the sensation of gastric fullness with gastric volume, and one compared pre- and post-meal aversion to glucose.

Thirty-one studies in this systematic review presented data relevant to the association between anorexia nervosa and interoception; 17 studies presented data relevant to the association between bulimia nervosa and interoception; 6 studies measured interoception in participants with clinical binge eating disorder; 26 studies collected data from participants with anorexia and participants with bulimia as part of a mixed 'eating disorder group' and 24 studies presented data relevant to the association between subclinical disordered eating behaviours and interoception.

To answer the questions posed by this review, in the following sections we first present data according to the type of eating disorder/disordered eating focusing on cross sectional studies that do not speak to the issue of whether dysfunctional interoception is a cause or consequence of disordered eating. Where relevant, these studies are organised according to whether the recruited participants had active or remitted illness. Neuroimaging studies are presented separately from studies using other methods. We then stratify the data according to the interoceptive modality studied (gastric, cardiac, pain, touch and other modalities) and finally we present the data from studies relevant to the potential role of interoception in onset versus maintenance of disordered eating. We found no studies that formally analysed potential moderators or mediators of the relationship between disordered eating and interoception. A summary of the studies included in this review are included in Appendix 2. A summary of the data from the cross sectional studies is presented in Figure 2.

4.3.3. Interoception in Anorexia Nervosa

4.3.3.1 Active Illness

Twelve cross sectional studies included in this systematic review presented data relevant to an association between active anorexia nervosa and interoception using

measures other than neuroimaging. Of the 12 studies assessing interoception in active anorexia, 2 studied participants with restricting-type only (Ambrosecchia et al., 2017; Goldzak-Kunik et al., 2011) 7 studied a combination of restricting and purging-type (e.g. Aguera et al., 2015; Amianto et al., 2017) and 3 did not specify the subtype (Brytek-Matera & Schiltz, 2009; Garfinkel et al., 1979; Maïano et al., 2016).

In 11 out of the 12 studies impairments were reported on at least one measure of interoception. The methods used to assess interoception in these studies included self-report (n = 5), heartbeat counting (n = 1), pain perception (n =1), aversion to glucose following satiety (n = 1), comparisons of gastric volume to self-reported fullness (n = 1), changes in gastric sensations over an eating period (n = 1) and drug-induced changes in interoceptive state (n = 1). One study (Ambrosecchia et al., 2017) found mixed results: participants with AN did not differ from controls in heartbeat perception but on self-reported measures they had poorer interoception. One study (Goldzak-Kunik, 2011) found no impairment in interoception in anorexia, and this study used a pain paradigm to assess interoception.

4.3.1.2 Recovered/remitted

Four cross sectional studies reported data relevant to the association between interoception and anorexia nervosa in a sample of participants recovered from anorexia (using measures other than neuroimaging). The methods employed in these studies were self-report (Casper et al., 1990; Srinivasagam et al., 1995), heartbeat counting (Pollatos et al., 2008) and pain perception (Krieg et al., 1993). Three of these studies found significant impairments in interoceptive processing in participants recovered/remitted from anorexia (Casper et al., 1990; Pollatos et al., 2008; Srinivasagam et al., 1995). The study that found no difference (Krieg et al., 1993) used a pain paradigm to assess interoception, and showed

that participants with intermediate outcome from anorexia, good outcome, restrained eaters and unrestrained eaters did not differ in pain threshold.

4.3.1.3 Neuroimaging of active illness

Three cross-sectional studies used brain imaging and heat pain thresholds to assess interoceptive processing in participants with active anorexia (Bär et al., 2013; 2014; Holsen et al. (2012). One of these studies (Holsen et al. 2012) included both a recovered and remitted group of patients with AN. Bär et al., (2013) found that in participants with anorexia, pain evoked an increased activation in the left posterior insula compared with healthy controls. Bär et al. (2014) reported a positive correlation between pain threshold and dorsal posterior cingulate cortex (PCC) activation in participants with anorexia, but there was no correlation between pain threshold and PCC activation in healthy controls. Holsen et al. (2012) examined that effect of a meal on appetite ratings and found a negative correlation between right insula activation and hunger ratings in individuals with anorexia, whereas a positive correlation was observed in the control group.

4.3.1.4 Neuroimaging of recovered/remitted anorexia

Eight cross-sectional studies used brain imaging to assess interoceptive processing in participants recovered/remitted from anorexia. All measured various interoception processes, and reported differences in neural activation in relation to the task or manipulation in individuals remitted/recovered from anorexia. The most common measure of interoception was an indirect approach; the manipulation of internal state by food intake. Holsen et al (2012) found a greater activation in healthy controls when hungry versus full in the hypothalamus, amygdala and insula when viewing high caloric food pictures. Moreover while performing a delay discounting task, hunger increased neural activation in reward

areas, whereas satiety evoked a greater response in cognitive control networks in healthy women. In addition, cerebral blood flow (CBF) measures showed an effect of nutritional state in striatum, anterior cingulate cortex (ACC), and left posterior insula, which was reduced in remitted patients when hungry. The other studies showed an altered insula response in remitted anorexia patients in relation to visceral and cardio interception (Kerr et al 2016 & 2017), touch (Bischoff et al 2018), pain (Strigo et al 2013), and aversive breathing load (Berner et al 2018). However, activation in other limbic areas also appeared to be dysfunctional in anorexia (Kerr et al. 2017, Berner et al. 2018, Strigo et al 2013).

4.3.2 Interoception in Bulimia Nervosa

4.3.2.1 Active Illness

Ten cross sectional studies (e.g. Heilburn & Worobow, 1991; Pollatos & Georgiou, 2016) presented data relevant to interoceptive processing in participants with active bulimia nervosa. Seven studies found significant impairments in at least one measure of interoception. The methods used included measurement of pain detection and threshold (n = 4) and self-report (n = 3). One study (Faris et al., 1992) found mixed results: participants with BN had higher pain threshold than did healthy controls in pain perception, but there were no difference in tactile threshold perception. Three studies showed no impairment in interoception in participants with bulimia, of which two used self-report methods (Heilburn & Worobow, 1991; Schmahl et al., 2010) and one used heartbeat perception (Pollatos & Georgiou, 2016).

3.2.2. Recovered/Remitted

Three studies reported recruiting participants remitted/recovered from bulimia (Kaye et al., 1998; Klabunde et al., 2013; Stein et al., 2003) and all three of these studies reported significant impairments in interoception in participants recovered from bulimia.

The methods employed in these studies were heartbeat counting (n = 1), pain perception (n = 1) and self-report (n = 1).

4.3.2.3 Neuroimaging of active illness

One study (Lavagnino et al., 2014) used resting-state fMRI to assess interoceptive processing in participants with active bulimia nervosa and correlated BOLD activity with self-report measures of interoception. Significantly weaker functional connectivity in interoception-related areas was found in bulimia nervosa, and a significant negative correlation between interoceptive dysfunction and functional connectivity was reported.

4.3.2.4 Neuroimaging of recovered/remitted

No studies in this systematic review assessed neural correlates of interoceptive processing in participants recovered from bulimia nervosa.

4.3.3 Interoception in Binge Eating Disorder

The results of four cross sectional studies on patients with active illness are reported here. No studies in this systematic review measured interoception in participants recovered from binge eating disorder and there were no studies using neuroimaging.

4.3.3.1. Active Illness

All four cross sectional studies assessing interoception in binge eating disorder recruited participants with active binge eating disorder and found significant impairments in interoception. Three of these studies (Aloi et al., 2017; Ramaciotti et al., 2008; Vinai et al., 2015) used self-report measures and one measured pain threshold (Raymond et al., 1995).

4.3.4. Interoception in Mixed Diagnosis Groups

There were twenty-four cross sectional studies. The majority of these studies collected data from groups including participants with both anorexia and bulimia (e.g. Ciccolo et al., 2002; Halmi & Sunday, 1991), with the exception of Rossiter, Wilson & Goldstein (1989) and Laessle et al. (1989) who included participants with bulimia and 'restrained' participants. In studies with participants with bulimia and participants with anorexia, 8 studies also reported on additional eating disorder groups including binge eating disorder or eating disorder not otherwise specified (EDNOS) (Eshkevari et al., 2014; Fassino et al., 2004; Kim, Annunziato & Olatunji, 2018; Nevonen et al., 2006; Nyman-Carlsson et al., 2014; Preyde et al., 2016; Solmi et al., 2018; Van Dyck et al., 2016).There were no studies in participants recovered from eating disorders and no neuroimaging studies.

Overall, of the 24 cross sectional studies reporting data relevant to the association between a mixed eating disorder sample and interoception, 22 showed impairments in at least one measure of interoception. The methods employed in these studies included self-report (n = 18), pain perception (n = 3) and reporting of gastric sensations across eating episodes (n = 1). One study assessed differences in acceptance and clarity of interoceptive processing in eating disorders (Merwin et al., 2010) and found mixed results, with neither the acceptance nor clarity interoception subscales predicting bulimia and only 'lack of clarity' predicting restraint. One study (Eskevari et al., 2014) found no difference in interoceptive processing in an eating disorder sample using a heartbeat detection paradigm, however 83% of participants were 'poor' detectors of heartbeat, which may explain the null results.

4.3.5 Interoception in Subclinical Disordered Eating Behaviours/non-clinical samples

Twenty studies were cross sectional and none used neuroimaging techniques. The range of disordered eating behaviours in studies included in the current systematic review were emotional eating (e.g. Koch & Pollatos, 2014; Young et al., 2017), external eating (e.g. Koch & Pollatos, 2014), subclinical binge eating (e.g. Brown et al., 2010), restraint (e.g. Tylka & Wilcox, 2006) and mixed/composite measures from questionnaires (e.g. Anderson et al., 2016; Myers & Crowther, 2008).

All of the twenty cross sectional studies reporting data relevant to the association between disordered eating behaviour and interoception, found impairments in at least one measure of interoception. The majority of these studies (n = 18) used self-report methods and the two remaining studies used heartbeat counting and detection tasks. One study found results which were somewhat mixed: once anxiety and depression were controlled for, a significant relationship remained for only two measurements out of four: confidence in heartbeat counting, and the relationship between heartbeat perception and self-reported interoceptive impairments (Young et al. 2017, Study 1).

4.3.6 Interoceptive Modalities

A range of interoceptive modalities were investigated in the studies included in this systematic review including cardiac, respiratory, gastric, pain and touch interoception. The most commonly measured interoceptive modalities were gastric, cardiac and pain, with measurements of these modalities comprising 101 out of the 104 studies.

4.3.6 Gastric Interoception

Gastric interoception was the most common modality measured in studies assessing interoception in disordered eating. Seventy-four studies included in the

systematic review measured gastric interoception, 19 of these studied gastric interoception in anorexia, 7 in bulimia, 4 in binge eating disorder, 20 in mixed eating disorder groups and 24 in subclinical disordered eating. Of these studies, 72 found significant differences in gastric interoception associated with disordered eating. The most commonly used methods to measure gastric interoception (n=68) were self-report questionnaire measures. These included the Interoceptive Awareness subscale of the Eating Disorders Inventory (Garner, Olmstead & Polivy, 1983) and the Intuitive Eating Scale (Tylka 2006). One study (Bluemel et al., 2017) compared gastric volume with self-reported hunger and fullness and found at each given stomach volume. Participants with anorexia reported higher fullness and lower hunger than control participants, however participants with anorexia had a slower gastric emptying rate, which may account for this difference. Five studies used neuroimaging methods and found altered neural activation during gastric interoceptive processing associated with disordered eating. Two studies (De Caro & Di Blasm 2016; Heilburn & Worobow, 1991) did not find that gastric interoception was associated with disordered eating.

4.3.6.2 Cardiac Interoception

Twelve studies measured detection of cardiac interoceptive signals. Six of these studies assessed cardiac interoception in participants with AN, 2 in participants with BN, 1 in a mixed eating disorder sample, and 3 in subclinical/ disordered eating behaviour. The most common method used to measure cardiac interoceptive signals was heartbeat detection which was used in 9 studies with significant impairments found in 7 studies. Of the two studies that did not show a significant association between cardiac interoception and disordered eating, one used a straightforward heartbeat counting paradigm

(Ambrosecchia et al., 2017) and one used a heartbeat-detection paradigm, which required participants to discriminate their heartbeat from an auditory tone (Eshkevari et al., 2014). Eshkevari et al. (2014) reported that 83% of their participants were poor at detecting their heartbeat, which may explain this null result.

Two studies (Kerr et al., 2106; Kerr et al., 2017) used fMRI to assess interoceptive processing of cardiac signals and both found differences in neural processing of interoception in patients recovered from AN and healthy controls One study (Khalsa et al., 2015) used infusions of isoproterenol (a non-selective β adrenoceptor agonist) to elicit changes in cardiac activity and found that participants with anorexia reported increased cardiac sensations under low arousal states.

4.3.6.3 Pain Interoception

Seventeen studies measured pain-related responses. Seven of these studies measured pain interoception in participants with AN, five in BN, one in binge eating disorder, four in a mixed eating disorder sample and one in binge eating disorder. The majority of methods used to elicit pain were either temperature-based (utilising the application of either cold or hot stimuli to cause pain n = 11), or mechanical (utilising pressure to cause pain, n = 4). Two studies (Girdler et al., 1998; Stein et al., 2003) used submaximal effort tourniquet tests to measure ischemic pain. Fourteen out of the 17 studies found dysfunctional pain processing in participants with disordered eating.

Methods of quantifying pain included both the measurement of pain threshold (e.g. time taken for a stimulus to first cause a painful sensation) and the measurement of pain tolerance (e.g. time taken for a participant to withdraw from a painful stimulus). Three studies combined pain measurement with neuroimaging measures (Strigo et al., 2013; Bär

et al., 2013; Bär et al., 2015) and all three of these studies found dysfunctional pain processing associated with disordered eating. Three studies that assessed pain threshold and tolerance did not find a difference in pain in disordered eating (Goldzak-Kunik et al., 2011; Krieg et al., 1993; Schmahl et al., 2010). In the study by Goldzak-Kunik et al., 2011, neither threshold nor tolerance was assessed, instead participants completed Visual Analogue Scales of cold, unpleasantness and pain during application of an ice pack, which may explain the null effects since application of an ice pack is a non-standard test. Both the studies by Schmahl et al. 2010 and Krieg et al. 1993 used a thermal pain stimulus which suggests that the type of pain stimulus used may be important.

4.3.6.4 Other Interoceptive Modalities

Two studies measured other interoceptive modalities using fMRI, and both were in participants recovered from anorexia. One measured respiratory interoception (Berner et al., 2018) and the other measured touch (Bischoff-Grethe et al., 2018) and found significant differences in interoceptive processing between participants recovered from anorexia and healthy controls. The study Khalsa and colleagues (2015) that involved infusions of isoproterenol showed that participants with anorexia reported increased breathing sensations under states of low arousal.

4.3.7 Onset/maintenance

We found only ten studies that used longitudinal observational designs and only x of these used prospective design that included a premorbid baseline and thus may provide insight in then role of interoception is the onset of disordered eating. Two studies measured interoception in the relatives of individuals with disordered eating. These studies provide insight into whether disturbed interoception is a heritable feature that might

predispose someone towards developing an eating disorder. Finally we found six studies that used quasi-experimental pretest-posttest designs that provide data relevant to the question of whether interoceptive dysfunction is a feature of the active illness that resolves with treatment.

Of the 10 longitudinal studies, eight presented data to support a longitudinal relationship between disordered eating and interoceptive processing. De Caro & Di Blas (2016) found no significant relationship between interoception and bulimic tendencies over a seven month period. Fischer et al. (2016) found a cross-sectional influence of interoception on disordered eating, but no interaction between interoception and time on disordered eating.

One study assessed interoception in family members of women with bulimia (Lilenfield et al., 2000). This study found higher interoceptive impairments in first-degree relatives who had also experienced an eating disorder, but no significant difference between interoceptive impairments in never-ill relatives of bulimia patients and relatives of healthy controls. The second study that assessed interoception in family members recruited a sample of women recovered from anorexia and their relatives (Casper, 1990). There was no significant difference in interoceptive impairments between relatives of recovered patients and either recovered patients or healthy controls. Six studies in this systematic review used a quasi-experimental pretest-posttest design to assess changes in interoceptive processing over the course of therapy. All six studies reported improvements in interoceptive processing over the course of treatment.

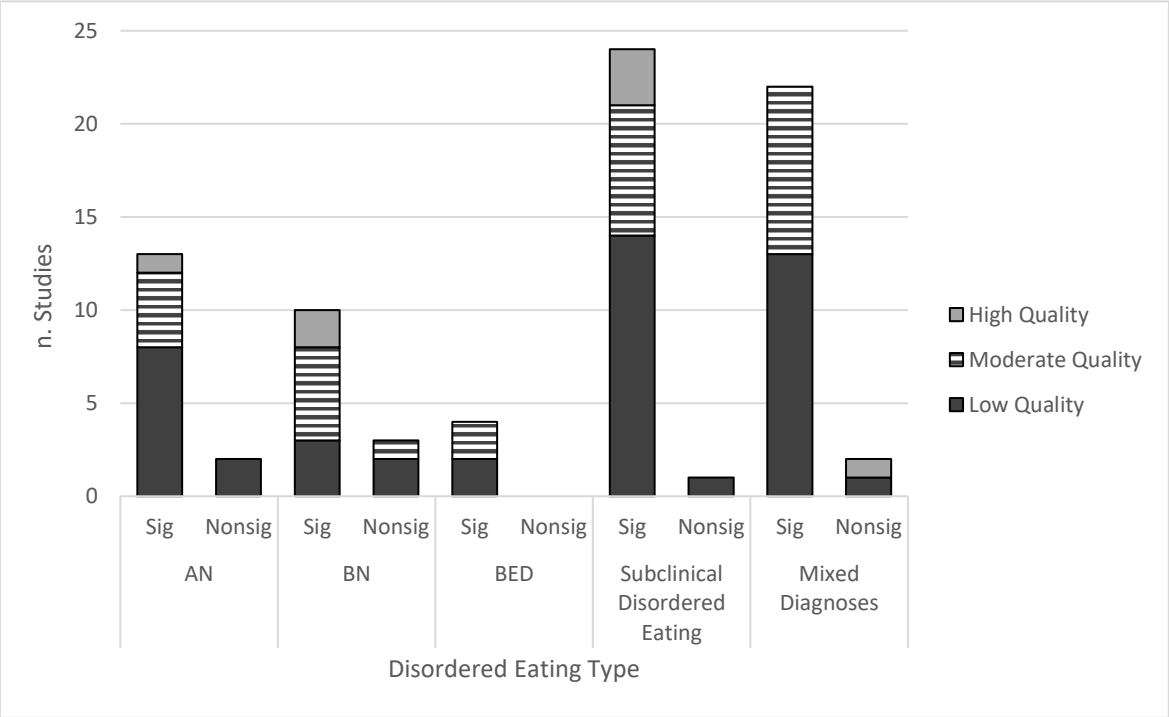

Figure 2. Summary of evidence on the association between interoception and disordered eating behaviour. Bars represent the number of (non-imaging) studies presenting data relevant to disordered eating behaviour types showing significant differences (labelled Sig) or nonsignificant results (labelled Nonsig). Bars are split into number of low, moderate and high quality studies. AN Anorexia Nervosa, BN Bulimia Nervosa, BED Binge Eating Disorder.

4.3.8 Quality of included studies

Inter-rater agreement for quality assessment was good (kappa: 0.64, SE of kappa: 0.156, 95% CI: 0.34 to 0.947). Quality ratings varied significantly across studies. Most of

the studies included were of either moderate (n = 44) or low (n = 48) quality. The remaining twelve studies were high quality (see Figure 2 for a summary). Small sample sizes and poor or no control for potential confounds were the main limitations. Most of the questionnaire studies were not designed specifically to assess interoception but rather were validation studies of specific measures that happened to include a subscale relevant to interoception.

4.4. Discussion

To the best of our knowledge this is the first paper to systematically review the literature on interoception across the broad spectrum of disordered eating behaviours and interoceptive modalities. One hundred and four studies were included in the review and we find that all types of disordered eating behaviour are associated with impairments in interoceptive function across several modalities.

There was consistent evidence for a relationship between dysfunctional interoception and AN, with 92% of studies finding impaired interoceptive function in AN. Similarly, 93% of studies measuring interoception in a mixed group of eating disorders (e.g. AN, BN and BED/EDNOS) reported impairments in interoception relative to controls. Ninety-five percent of studies assessing a variety of disordered eating behaviours reported impaired interoception on at least one measure. The evidence to support the relationship between bulimia and interoceptive abilities was more mixed but still supportive of dysfunctional interoception associated with bulimia, with just over 80% of studies showing significant impairment in interoception. The strength of evidence is moderate because the majority of studies were limited by methodological issues, in particular the use of small sample sizes and poor control for confounds.

It is difficult to rule out that the association between interoceptive functioning and disordered eating is due to the confounding influence of comorbid psychiatric disorders such as anxiety and depression, which are known to influence interoceptive capabilities (Pollatos, Traut-Mattausch & Schandry, 2009) and are found in the majority of individuals with eating disorders (Kaye et al. 2004; Bulik, et al (1997). Indeed, for many of the studies reviewed, the eating disorder group had comorbid psychiatric disorders whereas the presence of psychiatric conditions was an exclusion criterion for the control groups. In studies that did control for potential confounds of comorbid disorders (Ambrosecchia et al., 2017; Lavagnino et al., 2014; Pollatos et al., 2008; Pollatos & Georgiou, 2016; Matsumo et al., 2006; Young et al., 2017), or that reported no significant differences in depression scores between participant groups (Strigo et al., 2013), the results were mixed. In some cases, where anxiety and depression were controlled for, no significant differences were found between disordered eating groups and controls (e.g. Ambrossechia et al., 2017; Young et al., 2017). However, in other studies (e.g. Pollatos et al., 2008) when controlling for anxiety and depression, the association between eating disorders and interoception remained significant, suggesting that the relationship between interoception and disordered eating is not fully accounted for by depression/anxiety. This conclusion is supported by the finding that depression was not a significant predictor of effect size in the meta-analysis conducted by Jenkinson and colleagues (2018). Future research might employ a propensity score matching approach that involves including additional control groups matched for levels of comorbidities. Alternatively, studying the relationship between interoception and disordered eating in non-clinical samples that have reduced prevalence of co-morbidities would also be informative.

4.4.1. Disordered eating/eating disorder types

In line with the findings from a recent meta-analysis of the data on self-reported interoceptive impairments in eating disorders using the Eating Disorder Inventory (Jenkinson, Taylor & Laws, 2018), we find that interoceptive impairments exist across the spectrum of disordered eating from subclinical populations with emotional eating and binge eating to individuals with clinically diagnosed eating disorders including anorexia (AN) and bulimia (AN) and binge eating disorder (BED). The finding that interoceptive impairments occur in different types of eating disorders/disordered eating suggests interoception may constitute a transdiagnostic feature of eating disorders (Fairburn, Cooper, & Shafran, 2003).

The role of interoception in disordered eating could be investigated further by adopting a dimensional research framework, such as that advocated by the National Institute of Mental Health Research Domain Criteria (RDoC) initiative which argues for the study of fundamental components of behaviour (domains) using different units of analysis that link brain and behaviour (Insel et al. 2010). Studies of interoceptive processes in both clinical and subclinical populations using validated instruments that assess self-report, behaviour, physiology, neural circuits and genetics could provide novel insights into the nature of the relationship between interoception and disordered eating and identify potential biomarkers relevant to the diagnosis and treatment of eating disorders.

4.4.2. Interoceptive Modalities

To assess the specificity of interoceptive impairments in disordered eating, we stratified our findings by the interoceptive modality that was measured. The modality in which impairments were most consistently associated with disordered eating was gastric interoception, with 96% of studies measuring gastric interoception reporting impairments associated with disordered eating. This finding may be a result of the characteristics of

disordered eating itself, as gastric interoception is strongly associated with eating. However, it is also important to note that gastric interoception was measured using self-report methods more often than any other modality. Hence, it is possible that the association between gastric interoception and disordered eating reflects a specific problem in conscious processing of interoceptive signals measured using self-report tools.

A number of studies assessed pain and cardiac interoception in disordered eating. In both of these modalities, just over 80% of studies reported aberrant processing associated with disordered eating, suggesting that these modalities are also affected. Although heartbeat counting tasks are commonly used to assess interoception due the ease of measurement it should be noted that there are methodological limitations to this approach (Brener and Ring Ring, 2016). For example, knowledge of one's resting heart rate influences the accuracy on heat beat counting tasks (Murphy et al. 2018). In addition, only around a third of participants can accurately count their own heat beat at rest, which opens up the possibility that floor effects may explain some null findings (Khalsa & Lapidus 2016). In relation to pain processing, variability of the results might be explained by a lack of consistency of measures across studies e.g. the use of heat vs. cold stimuli.

The finding that impaired interoception is seen across different modalities could be explained by aberrant signalling within an afferent neural system that represents all aspects of interoception (Craig 2009). Indeed, for cardiac and gastric signalling there are partially overlapping cortical representations within the mid insula and so it is possible that aberrant insula activity and functional connectivity may contribute to interoceptive dysfunction across modalities in eating disorders. The extent to which interoception is served by a unitary system remains unclear at present, although most models emphasize the role of functionally coupled circuits rather than modular processing in specialised domain specific systems (e.g. Craig, 2009; Quattrocki and Friston, 2014). Further investigation of the

neurobiological mechanisms that underpin interoceptive dysfunction in disordered eating could shed further light on this issue.

4.4.3. Onset/maintenance

Our review found evidence that impairments in interoception are present in individuals who have recovered from an eating disorder (e.g. Khalsa et al., 2015; Klabunde et al., 2013), which suggests that problems with interoception are not solely explained by features associated with an active illness, such as severe calorie restriction or binge-purge behaviours. These data imply that dysfunctional interoception might be a predisposing factor for the onset of disordered eating. This proposal is supported by data from prospective longitudinal studies indicating that problems with interoception precede the onset of disordered eating (e.g. although see De Caro & Di Blas, 2016). The suggestion that problems with interoception might predispose an individual to develop an eating disorder is also supported by data from studies that have linked dysfunctional interoception to specific genetic variants (Frieling et al., 2006). However, there are also reports that impaired interoception is reversed as a result of successful therapy (e.g. Matsumoto et al., 2006), which implies that at least some of the problems with interoception might be a complication of the eating disorder that resolves with treatment rather than constituting a causal factor. In fact, it is possible the problems with interoception that are observed in recovered patients might reflect an enduring change in interoception or a scarring effect of having experienced an eating disorder (e.g. Klabunde et al., 2013; Stein et al., 2003). Such an interpretation is supported by evidence, albeit currently limited, from family studies (Lilenfield et al., 2000; Casper 1990), which have found that family members of patients, without a history of eating disorders, do not show impairments in interoception. These data suggest that interoceptive dysfunction does not constitute a heritable trait or

endophenotype that is observable in non-affected first degree relatives of people with eating disorders.

One interpretation that could explain the existing data is that dysfunctional interoception might predispose an individual towards the development of disordered eating but once disordered eating behaviour patterns become established, problems with interoception are accentuated. Prospective longitudinal studies provide the most rigorous test of whether or not dysfunction in interoception predisposes an individual to the development of disordered eating but these are costly and difficult to implement. However, very large sample sizes would be required due to the relatively small number of individuals who go on to develop an eating disorder. An alternative is to use a high-risk design in which the incidence of a diagnosis at follow-up is increased by following individuals already deemed high-risk for future eating disorders (Stice & Desjardins, 2018).

4.4.4 Gaps in knowledge and directions for future research

This review has highlighted a lack of research on the moderators and mediators of the relationship between interoception and disordered eating. Not all individuals with dysfunction in interoceptive processing will develop disordered eating and so identifying potential moderators will be an important avenue for future research. For example, there may be personality factors such as impulsivity or obsessive–compulsive traits that interact with interoceptive dysfunction, and the presence or absence of these traits may determine the likelihood of interoceptive dysfunction leading to disordered eating.

Future research should also address the mechanisms mediating the relationship between interoception and disordered eating behaviours/eating disorders. Interoceptive states may

influence eating behaviours via changes in the reward value of food. Information about the state of the body is passed to areas of the brain involved in computing the incentive salience of a food so that its motivational value is increased when in a state of food deprivation and decreased in a replete state (Cabanac 1971). Dysfunction in interoceptive signalling might reduce the motivating effect of food deprivation on behaviour as has been observed in women who are in remission from AN (Wierenga et al. 2015). Furthermore, a failure to downregulate food reward with food consumption might promote overeating once eating has begun, which could facilitate binge like eating as has been observed in bulimia (Ely et al. 2017). Thus, future studies could examine the potential mediating role of reward responsiveness in the relationship between interoception and disordered eating. In addition, problems with interoceptive processes could result in bodily signals related to nutrient ingestion or nutrient deficits not being factored into more complex decision making processes that mediate food consumption and food choices (Higgs 2008). In this case, decisions are more likely to be influenced by other inputs e.g. external cues. Thus, overeating or undereating might occur depending on the predominant influences on the food-related decision making at any one time for an individual, which might be weight concerns, emotional concerns or hedonic goals. Such links between interoceptive capabilities and responses to different types of external cues have yet to be fully explored. Finally, problems with interoception might also promote disordered patterns of eating via dysfunctional body perception/evaluation which could lead to disordered eating through body dissatisfaction (Badoud, & Tsakiris, 2017).

There have also been fewer studies to date on the role of interoception in binge eating disorder than in AN and AN. BED was introduced as an eating disorder category in the Diagnostic and Statistical Manual of Disorders, Fifth Edition (DSM-5) in 2013 (APA, 2013). It is the most prevalent form of eating disorder and one of the primary chronic

illnesses among adolescents (Nicholls and Barrett 2015). Hence further investigation of the role of interoception in in binge eating disorder is advised.

The current systematic review considered 'interoception' in general due to the broad focus of research to date, but a number of separate facets of interoceptive insight have been described (Khalsa et al. 2018). In order to further understand of the role of interoception in disordered eating it will be necessary delineate different aspects of interoception (Khalsa et al. 2018). Interoception encompasses functioning at many different levels including physical responses in the body, the neural representations of these responses and their perception, as well as insight and conscious awareness of these responses. Three psychological dimensions of interoception that relate to the perception of interoceptive responses have been distinguished: interoceptive accuracy, sensibility, and awareness (Garfinkel et al. 2015). Interoceptive accuracy refers to the process of detecting and counting internal bodily sensations and is measured using methods such as heartbeat counting. Interoceptive sensibility refers to self-evaluated interoceptive capability and is usually assessed by questionnaire measures. Interoceptive awareness refers to the correspondence between interoceptive accuracy and insight into one's own interoceptive performance and so represents a metacognitive aspect of interoception. An additional dimension of interoceptive awareness has been suggested recently which describes a person's ability to flexibly attend to, and utilize, interoceptive information or to adaptively switch between interoceptive and exteroceptive representations (Quadt et al. 2018).

At present it is unknown whether dysfunctional interoception associated with disordered eating is due to dysfunctional afferent signalling, central sensory processing of interoceptive stimuli or perception or insight into interoceptive performance. It is possible that there is no dysfunction in afferent interoceptive signalling (e.g. the presence and magnitude of signals is detected), but there may be dysfunction in signal monitoring

(accuracy) and/or the tendency to focus on signals (sensibility). A small number of studies in this systematic review measured more than one dimension of interoception (e.g. Ambrosecchia et al., 2017; Young et al., 2017), and some of these assessed the association between dimensions (e.g. Pollatos et al., 2008). Interestingly, some studies found impairment in one dimension of interoception (e.g. sensibility), but no impairment in another dimension (e.g. accuracy). For example Ambrossechia et al. (2017) found that participants self-reported poorer interoceptive sensibility, but had interoceptive accuracy that was comparable to healthy controls. Similarly, Pollatos et al. (2008) found no association between interoceptive awareness and sensitivity. However, it should be noted that these studies assessed interoceptive accuracy in the cardiac domain and sensibility using the Interoceptive subscale of the Eating Disorders Inventory (EDI) rather than assessing accuracy and sensibility within the same modality. In addition, while the EDI has been shown to discriminate between individuals with eating disorders and healthy controls, it is not a measure that was designed specifically to assess visceral interoceptive sensibility. Future systematic studies that assess interoception across a range of modalities and include measures of neural signalling, behavioural performance, and self-evaluated interoceptive capability, alongside metacognitive measures both within and between modalities, are required to uncover the specific nature of the interoceptive dysfunction associated with disordered eating.

The evidence reviewed here from studies that assessed neuronal activation using fMRI suggests that disordered eating is associated with dysfunction in the neural processing of interoception compared with individuals without disordered eating. The majority of the studies linked differences in neural responses in the insula to dysfunctional interoception. However, it should be noted that an issue with the fMRI methods used in a number of studies in this systematic review is the reliance on reverse inference, which is

using specific patterns of activation to infer the engagement of specific mental processes e.g. inferring that activation of the insula is related to interoceptive processing because the insula has been previously implicated in such processes. The reliance of a study's conclusion on reverse inference depends on the paradigm used (Poldrack, 2011). For example several studies (Wierenga et al 2015, 2017 and Holsen 2012) altered the fullness of the stomach and inferred that the differences in brain responses between a AN group and the control group was due to differences in interoception. However, interoception defined as accuracy in sensing the internal state of the body was not measured directly and so these studies rely on reverse inference. To address the issue of reverse inference, predicative modelling techniques (Varoquaux & Poldrack, 2019) to identify a neural signature for interoception that predicts interoceptive capability and hence could be used a biomarker in future studies. In addition, the interpretation of the relationship of the reported neural activity to interoceptive abilities is not straightforward since reduced activity in the insula for example could represent more efficient processing of interoceptive signals or reduced inputs. Nevertheless, the fMRI data reviewed here suggest that neural signalling in the insula depends upon the specific context in which that activity is assessed (e.g. Berner et al., 2018; Bischoff-Grethe et al., 2018). In particular, there is evidence that patients recovered from AN show increased neural activation in insula in anticipation of interoceptive events but decreased activation during an aversive interoceptive event (e.g. Berner et al., 2018; Strigo et al., 2013). For example, during anticipation of pain, patients recovered from AN showed greater activation in right anterior insula than did healthy controls but showed significantly decreased posterior insula activation during pain processing (Strigo et al., 2013). This pattern of responses may indicate heightened interoceptive responses in anticipation of pain but poorer processing of interoceptive stimuli. However, other studies have reported an opposite pattern of results,

whereby recovered AN patients had a reduced activation in right mid-insula in the anticipatory period but increased bilateral, anterior, mid-, posterior insula activation during and after an aversive breathing load task (Berner et al. 2018). One possibility is that some interoceptive problems in AN arise from a mismatch between predictions about how the body should feel and the information coming from the body, which has been referred to as an interoceptive prediction error. Such prediction errors have also been hypothesized to account for aberrant interoceptive functioning in anxiety disorders (Paulus & Stein 2010) and are a core feature of predictive coding accounts of interoception (Barrett & Simmons 2013; Seth & Critchley 2013).

Predictive processing is a theoretical model of neural functioning (Friston, 2010) that has recently been applied to the study of interoception. Rather than assuming that interoceptive perceptions are linked directly to internal bodily sensations, predictive processing accounts suggest that perceptions arise from a comparison between representations of anticipated sensations and current interoceptive signals. Interoceptive perceptions are thought to mainly reflect the anticipated state of the body based on what is predicted given past experience, but, incoming sensory information about the actual state of the body provides a check on the accuracy of these prediction (Barrett & Simmons 2013; Seth & Critchley 2013). If a mismatch between actual and predicted states, or a prediction error, is detected then this error may be used to update the predictions, and possibly change perceptions, or trigger changes in the body that fulfil those predictions. This account is similar to that proposed by Higgs (2005) who has argued that feelings of satiety are cognitively constructed in the brain; a process that involves integrating current internal state cues with information in memory about recent eating to predict the effects of further consumption.

Within a predictive/constructive interoceptive framework, dysfunctional interoception could arise if the incoming sensory signals are noisy or unreliable (see Paulus, et al. 2019 for a recent review). In such circumstances, predictions (and perceptions) might be strongly influenced by external sources of information or beliefs that are not updated by prediction error. For example, the perception of the body as it relates to food deprivation or repletion in patients with eating disorders might be influenced by beliefs that are not updated by incoming interoceptive signals. A similar situation might arise from a failure to integrate incoming sensory signals with anticipated states. Further research guided by the predictive/constructive framework is needed to test these hypotheses.

4.4.5 Strengths and limitations of the current systematic review

We conceptualised disordered eating as a continuum ranging from normal eating to eating disorders and considered studies using a range of interoceptive modalities which enabled a large number of studies to be systematically reviewed. However, there may be a language and a publication bias, as the search was limited to studies written and published in the English language. However, the number of non-English language studies identified was only four. The majority (77%) of studies in the current systematic review recruited women only. Therefore, the results should be applied to males with caution, particularly as one longitudinal study suggested that sex may moderate the relationship between interoception and disordered eating. This finding highlights the need for more research into interoception and disordered eating behaviour in males. In addition, many studies published in this area were not designed to explore an association between interoception and disordered eating. For example, most studies comparing self-rated interoceptive sensibility were designed as questionnaire validation studies, which resulted in suboptimal

study designs and the potential for biased results. It is possible that the literature search and selection strategy introduced bias in the reviewed neuroimaging studies, with regard particularly to those studies using comparisons of hungry/full. The search terms used did not include any words (e.g. hungry, full) specifically relating to this contrast, and therefore neuroimaging studies using this paradigm would likely only appear in the initial search if regions identified in the results were identified by authors as being implicated in interoception, whereas if such regions had not been detected in analysis, interoception would not necessarily be a focal discussion point of the paper, and therefore may not appear in the initial literature search. The result of such a possibility could increase the detection of positive results, while excluding those papers which did not find differences in interoception-related areas. Finally, due to the heterogeneity of the studies, particularly with respect to the methodologies and outcomes used a meta-analysis was not considered feasible.

4.4.6 Clinical implications

If further research confirms that interoceptive dysfunction predisposes individuals to the development of eating disorders then assessment of interoception may be useful in identifying those at risk of developing eating disorders and hence could be valuable for prevention programmes. There is evidence that interoceptive function can change over time and be modified by treatment (Khalsa et al. 2018) and so interoceptive dysfunction could also be a useful focus for the treatment of eating disorders and other conditions with comorbid eating disturbances such as Attention Deficit Hyperactivity Disorder (ADHD) (Kaisari, Dourish and Higgs 2017, 2018) and depression (Simmons and Deville 2017). There are opportunities for treatments based on stimulating afferent interoceptive signalling e.g. vagus nerve stimulation (De Couck et al. 2017) or flotation therapies that

reduce exteroceptive signals allowing enhanced exposure to interoceptive signals (Feinstein et al. 2018). Future work could also examine the potential for using drug therapies to target interoceptive dysfunction in patients with eating disorders. There is growing interest in the role of the hormone oxytocin in interoception (Betka et al. 2018; Quattrocki and Friston, 2014) and given that oxytocin has already been found to improve some of the symptoms of AN (e.g. Kim et al. 2014), future studies could examine whether intranasal administration of oxytocin improves interoception in disordered eating.

4.4.7 Conclusions

The majority of studies included in the current systematic review reported significant impairments in interoceptive processes associated with disordered eating behaviour and eating disorders. Impairments were observed across eating disorder types and interoceptive modalities suggesting that interoception may constitute a transdiagnostic feature of eating disorders that is related to dysfunction in a common neural system which underpins the processing of different types of interoceptive signals. There is currently limited evidence on the potential causal role of interoception in the development of disordered eating and on the moderating and mediating mechanisms. Future research that examines specific dimensions of interoception in both clinical and subclinical populations at different levels of analysis may provide novel insights into the underlying dysfunction in interoception associated with disordered eating and which could potentially lead to the development of improved therapies for eating disorders.

Chapter Five: Interoceptive accuracy mediates the longitudinal relationship between ADHD inattentive symptoms and disordered eating in a community sample

5.1 Introduction

Symptoms of Attention Deficit Hyperactivity Disorder (ADHD) are consistently associated with an increased risk of disordered eating, particularly binge and disinhibited eating (Kaisari et al., 2017). This relationship may suggest that the cognitive symptoms which are central to ADHD (e.g. inattention and impulsivity) foster disordered eating behaviour. To date, it is unclear how exactly ADHD symptoms may contribute towards disordered eating, as few studies have investigated the contribution of specific symptoms of ADHD to disordered eating, or explored potential mediators of this relationship.

Kaisari and colleagues (2018) analysed self-report data on ADHD symptoms, disordered eating and several related variables from two large non-clinical independent samples and found that negative mood mediated the relationship between both inattentive and impulsive symptoms of ADHD and disordered eating. This mediating influence of negative mood is also supported by longitudinal evidence (Martin et al., 2020). Symptoms of depression and anxiety are elevated in ADHD (Kessler et al., 2006) and disordered eating (Santos, Richards & Bleckley, 2007; Puccio et al., 2017), and Kaisari et al. (2018)'s findings suggest that depression and anxiety may explain why disordered eating is enhanced in association with symptoms of ADHD, even when present at subclinical levels. For example, experiencing ADHD symptoms may increase depression and anxiety, for which disordered eating behaviours become a coping mechanism (Goossens, Braetm Vlierberghe & Mels, 2009).

In addition to negative mood, Kaisari et al. (2018) found that a reduced reliance on hunger and satiety cues to guide eating (as measured by the intuitive eating scale) specifically mediated the relationship between inattentive symptoms of ADHD and disordered eating. Reliance on hunger and satiety cues may reflect the interpretation and use of gastric interoceptive information. There is consistent evidence that interoceptive

processing is altered in individuals with eating disorders and with disordered eating (e.g. Van Dyck et al., 2016; Nyman-Carlsson et al., 2015; Pollatos et al., 2008, Martin et al., 2019). The results of Kaisari et al. (2018) suggest that trait inattention may negatively impact interoceptive processing, which in turn could contribute towards disordered eating.

Although at present it is unclear how inattentive ADHD symptoms may affect interoceptive processing, there is consistent evidence for a role of attention in eating. For example, Bellisle, Dalix & Slama (2004) found that food intake was increased when participants' attention to the food was reduced, either by listening to a story or watching television during the meal. Similarly, Blass et al. (2006) reported that participants ate significantly more calories during a meal when watching television, compared to when there was no distraction. In addition, da Mata Gonçalves et al. (2019) found that participants increased intake of a snack when reading either a smartphone or printed text, compared to when no distraction was present. These effects of attention manipulation also extend to subsequent intake, for example, Higgs (2015) found that reduced attention paid to food during eating, either by playing a video game or by watching television, increased later snack intake compared to when there was no distraction present. Enhancement of attention can create the opposite effect, for example Robinson, Kersbergen and Higgs (2014) found that when participants with overweight and obesity ate a meal while listening to an audio which encouraged them to pay attention to their food, they ate fewer snacks at a later taste test compared with participants who listened to an audio unrelated to eating. Trait inattention may have a similar effect, leading to lessened attention allocation towards interoceptive signals and in turn, an increase in propensity to overeat. In line with this hypothesis, there is evidence that individuals with ADHD perform poorly on an interoception task involving attending to their heartbeat (Kutscheidt et al., 2019), although there is also evidence to suggest comparable performance with non-ADHD controls

(Wiersema & Godefroid, 2018). These contradictory results may be the result of the task used, as the utility of classic heartbeat detection tests in measuring interoceptive abilities has been criticised (Brener & Ring, 2016). The association between trait inattention and interoception therefore requires further investigation, using alternative measures.

Interoception represents the sensing of signals from several modalities including information about the viscera, temperature, pain and heart-rate. Deficits in the processing of signals from a range of interoceptive modalities have been associated with disordered eating (Martin et al., 2019). The measure used by Kaisari et al. (2018) relates specifically to gastric interoceptive processing, capturing the respondent's trust in signals of hunger and satiety, and their propensity to use these as cues to guide behaviour. There is evidence that sensitivity to interoceptive signals is global, and not restricted to specific modalities (e.g. Herbert, Muth, Pollatos & Herbert, 2012), and therefore it is possible that a global deficit in interoceptive processing mediates the relationship between ADHD symptoms and disordered eating. Given that interoceptive deficits are evident across a range of psychiatric conditions (Khalsa et al., 2018), a global deficit in interoceptive abilities may reflect a transdiagnostic feature of psychiatric conditions, rather than a specific relationship between gastric interoceptive abilities and disordered eating.

In addition to different modalities of interoception, recent research suggests that measurements can be categorised depending on the facet of interoception measured. For example, Murphy et al. (2019) distinguish between interoceptive attention (herein referred to as interoceptive sensibility: the trait tendency to attend to interoceptive signals) and interoceptive accuracy (how accurately one detects internal state). Indeed, there is evidence that interoceptive accuracy and interoceptive sensibility are distinct (Garfinkel et al., 2015; Murphy et al., 2019), suggesting that use of measurement tools that do not conflate the two is beneficial. Using measures to specifically target different facets of

interoception may enable determination of whether interoceptive deficits associated with disordered eating occur specifically in one facet (e.g. sensibility *or* accuracy), or in multiple facets. To date, there has been limited research into the relationship between specific facets of interoception and disordered eating. Preliminary evidence for dissociable effects of different facets of interoception on eating behaviours is mixed. For example, Young et al. (2017) found that although external eating (eating in response to the sight and smell of food) was associated with lower interoceptive accuracy, emotional eating tendencies were associated with higher interoceptive accuracy. In contrast, it has been suggested that emotional eating is associated with poorer interoceptive accuracy, but is not related to interoceptive sensibility (Robinson et al., 2021). It is therefore unclear how specific facets of interoception may contribute to disordered eating, and to date the influence of attention on different facets of interoception on how this may contribute towards disordered eating has not been assessed.

Despite some evidence for an association between ADHD symptoms and disordered eating, the presence of a causal relationship is unknown. Longitudinal studies investigating the relationship between ADHD symptoms and disordered eating are limited in number, but do provide some evidence that ADHD symptoms can predict disordered eating. For example, Yilmaz et al. (2017) found that both inattentive and hyperactive/impulsive symptoms of ADHD during childhood predicted disordered eating in adolescence. Due to the general lack of studies investigating the longitudinal relationship between ADHD symptoms and disordered eating, only one study (Martin et al., 2020) has assessed longitudinal mediating mechanisms. Therefore, while cross-sectional evidence exists that interoception may explain the association between inattentive symptoms of ADHD and disordered eating (Kaisari et al., 2018), there are no studies to date which investigate the potential longitudinal mediating influence of

interoceptive deficits on ADHD symptoms and disordered eating. In contrast with cross-sectional studies, longitudinal studies have the ability to determine whether a changes in disordered eating (e.g. increases in symptomatology) are preceded by deficits in interoceptive processing. Addressing this question will contribute towards knowledge of the potential causal role of ADHD symptoms and interoceptive deficits in disordered eating.

Research to support a causal role of interoception in the development of disordered eating may provide novel targets for prevention/treatment of disordered eating. It is possible to train individuals to improve interoceptive accuracy (e.g. Fischer, Messner & Pollatos, 2017; Meyerholz, Irzinger, Witthöft, Gerlach, & Pohl, 2019) and there is preliminary evidence that interventions aimed at increasing awareness of bodily sensations can be beneficial in eating disorders (Catalan-Matamoros, Helvik-Skjaerven, Labajos-Manzanares, Martínez-de-Salazar-Arboleas, & Sánchez-Guerrero, 2011). Increasing interoceptive sensibility through mindfulness interventions is another approach which may be a promising avenue for interventions (Weng, Feldman, Leggio, Napadow, Park & Price, 2021), although the association between mindfulness and interoception is unclear (Khalsa, Rudrauf, Hassanpour, Davidson & Tranel, 2020).

5.1.1 Study Aims

The current study aimed to address the gaps in the literature regarding the potential longitudinal mediating mechanisms between inattention and impulsivity/hyperactivity symptoms of ADHD, and disordered eating. The relationship between self-reported ADHD symptoms and disordered eating over six months was assessed using mediation models testing the mediating influence of negative mood, reliance on hunger and satiety cues, interoceptive accuracy and interoceptive sensibility.

5.2 Hypotheses

We hypothesised that ADHD symptoms and interoception would predict disordered eating at 6-month follow-up. Further, we hypothesised that the data would confirm previous evidence of a mediating influence of reliance on cues of hunger and satiety, and negative mood on the relationship between inattentive ADHD symptoms and disordered eating. We predicted that the mediating influence of cues of hunger and satiety could be explained by at least one facet of interoception: interoceptive accuracy as measured by the interoceptive accuracy scale and/or interoceptive sensibility, as measured by the body perception questionnaire.

5.3 Methods

5.3.1 Participants

504 participants were recruited at baseline using Prolific (https://prolific.co/). To detect a mediated effect (power = 0.8), a sample size of between 398 and 412 was required, assuming a small effect on the predictor-to-mediator pathway (Fritz & MacKinnon, 2007), as was apparent in previous similar research (Kaisari et al., 2018). To account for potential data loss due to incomplete responding, poor quality data, and participant attrition, we aimed to recruit 500 participants at baseline. Inclusion criteria were: a minimum age of 18 years and a maximum age of 60 years, and English as a first language. Although it is not possible to create a customised screening questionnaire within Prolific, the participant information sheet included an exclusion criterion of those currently taking anxiety, depression, ADHD or antipsychotic medication.

5.3.2 Procedure

Two data collection rounds took place in November 2020 and May 2021. In the study consent form completed at baseline, participants agreed to be re-contacted through Prolific 6 months after initial participation. The survey took around 30 minutes to complete and participants were paid £3.75 at each data collection round (equivalent to £7.50 per hour). The study was advertised under the title ‘Cognitive Factors Influencing Eating Behaviours’ to conceal details of the study aims. Questionnaires were presented in the order in which they are described below. The study was approved by the University of Birmingham Science, Technology, Engineering and Mathematics Ethical Review Committee (reference number ERN_19-1237).

5.3.3 Measures

Demographic information including age, sex and ethnicity were recorded to characterise the sample. Height and weight were self-reported by participants to calculate body mass index (BMI, kg/m^2). Participants were asked to report if they had been treated for an eating disorder or for ADHD.

5.3.3.1 Measurement of interoception

The Intuitive eating scale (IES) (Tylka, 2006) comprises 23 items measuring trait tendency to use cues of hunger and satiety to guide eating, scored on a 5-point scale ranging from Strongly disagree to Strongly agree. Four subscale scores can be calculated using the IES: Unconditional permission to eat; Eating for physical rather than emotional reasons; Reliance on hunger and satiety cues; body-food choice congruence scale. In addition, an overall IES can be calculated using all items. The 'reliance on internal cues of hunger/satiety' subscale of the IES has previously been found to mediate the relationship between ADHD and disordered eating behaviour (Kaisari et al., 2018). Reliability and validity have been demonstrated for the IES (e.g. Tylka and Kroon Van Diest, 2013; Duarte, Gouveia & Mendes, 2016).

The interoceptive accuracy scale (IAS) (Murphy et al., 2020) is a 21- item questionnaire which measures self-reported interoceptive accuracy across a range of interoceptive domains including hunger, thirst, heartbeat and itch. The IAS shows good reliability and validity (Murphy et al., 2020). Items consist of the stem questions 'I can always accurately perceive when', followed by a bodily sensation e.g. hunger, breathing rate. Items are scored on a 5-point scale ranging from 1 = Disagree Strongly to 5 = Strongly Agree. Self-reported interoceptive accuracy as measured by the IAS has been shown to correlate with objective measurement (heartbeat counting) of interoceptive accuracy (Murphy et al., 2020).

Body Perception Questionnaire – Very Short Form (BPQ-VSF) (Porges, 1993) is a 12-item questionnaire used to measure body awareness, thought to reflect interoceptive sensibility as opposed to interoceptive accuracy, such as is measured by the IAS. Respondents are asked 'During most situations I am aware of:' followed by 12 bodily sensations e.g. bloating and heartbeat. Items are scored on a 5-point scale ranging from 1 = Never to 5 = Always.

5.3.3.2 Measurement of ADHD symptoms

The Conners' Adult ADHD Rating Scale: Short Version (CAARS:SV) (Conners, Erdhart & Sparrow, 1999) was used to measure ADHD symptoms in participants. The CAARS:SV comprises 30 items, which can be used to score participants on a continuous measurement of ADHD symptoms (inattention, impulsive/hyperactive, and combined). It can also be used to determine a possible diagnosis of ADHD, based on age and sex of the respondent. Standardised scores (T-scores) > 60 indicate elevated levels of any symptom subscale, and indicate an at-risk ADHD index score. Responses are scored on a 4-point scale ranging from Not at all/Never to Very much/Very frequently. The CAARS-S:SV shows good validity and reliability (Sadeghi-Bazargani, Amiri, Hamraz, Malek, Abdi & Shahrokhi, 2014).

5.3.3.3 Measurement of Disordered Eating

The Dutch Eating Behaviour Questionnaire (DEBQ) (Van Strien, Frijters, Bergers, & Defares, 1986) was used measure specific characteristics of eating behaviour in the sample. The DEBQ consists of 33-items which relate to three dimensions of eating behaviour: restrained, emotional and external eating. Items are scored on a 5-point scale ranging from Never to Very Often. The DEBQ has been reported to have good reliability and validity (e.g. Ohara et al., 2020; Malesza & Kaczmarek, 2021).

The Eating Attitudes Test (EAT-26) (Garner et al., 1982) was used to measure disordered eating behaviour. EAT-26 is a 26-item questionnaire consisting of three subscales: dieting, bulimia and oral control. Items are scored on a 6-point scale ranging from Always to Never. Acceptable to good reliability has been reported for the EAT-26 (Ocker, Lam, Jensen & Zhang, 2007; Siervo, Boschi, Papa, Bellini & Falconi, 2005).

The Binge Eating Scale (BES) (Gormally et al., 1982) was used to measure symptoms of binge eating in participants. The BES consists of 16 questions relating to frequency and severity of binge eating behaviours. Each question includes 3 - 4 statements on behaviours and thoughts associated with binge eating, increasing in severity. Participants are asked to select the statement that best describes themselves. Each response is assigned a numerical value from 0 (least severe) to 4 (most severe). Good reliability and validity has been reported for the BES (Duarte, Pinto-Gouveia & Ferreira, 2015).

The SCOFF (Morgan, Reid & Lacey, 1999) was used to characterise risk of eating disorders in the sample. The SCOFF is a screening tool for detecting eating disorders. It comprises 5 yes/no questions asking whether in the past year the participant 1) has lost more than one stone in 3 months (weight loss); 2) had made him/herself be sick because he/she felt uncomfortably full (self-sick for feeling full); 3) worried that he/she had lost control over how much he/she eats (uncontrolled eating); 4) believed him/herself to be fat when others said that he/she was too thin (self-perceived fatness); and 5) thought that food dominated his/her life (food dominance). Endorsement of $\geq$2 items suggests a possible eating disorder. Good reliability and validity have been reported for the SCOFF (Garcia, Grigioni, Allais, Houy-Durand, Thubaut, Déchelotte, 2011; Kutz, Marsh, Gunderson, Maguen & Masheb, 2020).

5.3.3.4 Measurement of Negative Mood

The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) consists of 14 questions relating to anxiety and depression symptoms (7 depression, 7 anxiety). Responses are scored from 0 (least severe/frequent symptoms) - 3 (most severe/frequent symptoms) to give a total score for anxiety and depression ranging from 0 – 21. The HADS is consistently reported to show good reliability and validity (Bjelland, Dahl, Haug & Neckelmann, 2002).

The Perceived Stress Scale (PSS) (Cohen et al., 1983) is a 10-item questionnaire to measure how frequently the respondent has experienced feelings of stress in the last month. Items are scored on a 5-point scale ranging from Never to Very Often. The PSS is a reliable and valid measurement of perceived stress (Roberti, Harrington & Storch, 2006).

5.3.3.5 Covariate Measures

The Fast Alcohol Screening Test (FAST) (Hodgson, Alwyn, John, Thom, and Smith, 2002) is a four item screening tool used to assess alcohol use. The FAST consists of four questions taken from the full alcohol use disorders identification test (AUDIT) scored on a 5-point scale ranging from Never/No to Daily or Almost Daily/Yes (during the last year). The FAST has good sensitivity and specificity in identifying hazardous drinkers (Hodgson, Alwyn, John, Thom, and Smith, 2002) shows good reliability (Meneses-Gaya et al., 2010).

The Drug Abuse Screening Test (DAST) (Skinner, 1982) was used to assess illicit drug use. The DAST consists of 28 items asking the respondent about problematic drug usage, each with a binary yes/no response. The DAST consistently demonstrates satisfactory reliability and validity (Yudko, Lozhkina & Fouts, 2007).

5.3.4 Data processing and Analysis

5.3.4.1 Attention check

Three attention check questions were inserted between true questionnaire items to assess if participants were reading questions, to ensure data quality. Attention check questions asked participants to select a specific response, for example ‘Please Select ‘Never’ for this question’.

5.3.4.2 Composite Scores

Using scores from the EAT-26, DEBQ and BES, composite scores were calculated for binge/disinhibited eating and restrictive eating, based on factor loadings from Kaisari et al. (2018). Kaisari et al. (2018) reported that emotional eating and external eating subscales of the DEBQ, and the bulimia subscale of the EAT-26 load onto a Binge/Disinhibited eating factor. The restrained eating subscale of the DEBQ and the Dieting and Oral Control subscales of the EAT-26 were found to load onto a restrictive eating factor. Composite scores for binge/disinhibited eating and restrictive eating were calculated accordingly, by totalling subscale scores that corresponded to each factor in Kaisari et al. (2018).

Composite scores were also calculated for negative mood using scores from the HADS and the PSS. Composite scores were calculated by totalling the HADS anxiety subscale, HADS depression subscale, and the PSS score.

5.3.4.3 Mediation models

Mediation was analysed using PROCESS for SPSS (Hayes, 2017). Age, sex, BMI, alcohol and drug use were covariates in the mediation models. Three models for both disordered eating type (binge/disinhibited and restrictive) were defined. The first included IES-RHSC as the mediating variable, to test the relationship reported in Kaisari et al.

(2018). The second model included both BPQ and IAS scores as mediators to assess specific contributions of interoceptive sensibility and self-reported interoceptive accuracy. The final model included negative mood as the mediating variable. Predictor and mediator variables were from baseline measurement. Two outcome variables for each disordered eating type were tested: change in disordered eating score between baseline and follow-up, and disordered eating score at follow-up only.

5.4 Results

5.4.1 Baseline Participant Characteristics

At baseline, 493 participants were included after removing participants with incomplete datasets, and participants who did not pass the attention checks (n = 11). At follow-up 70% of participants completed the second data round, resulting in a final sample size of 345 participants (*M* age = 33.9 ± 10.9), *M* BMI = 26.3, 72.5% women). Forty-two participants (12% of total sample) scored ≥ 2 on the SCOFF screening tool, suggesting a possible risk of eating disorder in those participants. Eight participants (2%) reported having previously been treated for an eating disorder. Seventy-eight participants reported inattentive ADHD symptoms within an elevated range (26% of total sample). Thirty-three participants reported hyperactive/impulsive symptoms of ADHD within an elevated range (10% of total sample). Fifty-two participants reported combined symptoms of ADHD within an elevated range (15% of total sample). Fifty-seven participants reported symptoms indicating an 'at-risk' ADHD index (T-score > 60) (17% of total sample). One participant reported currently taking ADHD medication. See Table 1 for baseline characteristics of the sample.

5.4.2 Differences between completers and non-completers

T-tests revealed differences in baseline characteristics between those participants who did (completers) and did not complete (non-completers) the follow-up data collection round. Completers were significantly older (M = 33.9) compared to non-completers (*M* = 29.9) $t(491) = 4.0$, $p < 0.001$. Completers had significantly lower combined ADHD symptoms (*M* = 17.2) than non-completers (*M* = 20.1), $t(491) = 3.7$, $p < 0.001$. There were no differences between completers and non-completers in measures of negative mood, interoception or disordered eating. A chi-square test revealed that fewer men completed

both timepoints than expected, whereas more women completed than expected, $X^2(1) = 4.1$, $p = 0.04$.

5.4.3 Change in Disordered Eating

There was a significant increase in mean restrictive eating between baseline ($M = 11.0$) and follow-up ($M = 12.3$), $t(344) = 3.7$, $p < 0.001$. There was a non-significant trend increase in mean binge/disinhibited eating between baseline ($M = 20.5$) and follow-up ($M = 21.1$), $t(342) = 1.3$, $p = 0.078$.

5.4.4 Associations between ADHD symptoms

Bivariate correlations revealed that inattentive ADHD symptoms were associated with hyperactive/impulsive ADHD symptoms ($r = 0.42$, $p < 0.001$).

Table 1. Baseline participant characteristics.

	Mean (±SD)	**Range**
Age	33.9 (±10.9)	18 - 60
BMI	26.3 (±6.6)	15.8 - 56.3
BES (0-46)	12.7 (±9.2)	0 - 42
DEBQ (1-5)		
Restrained Eating	2.7 (±0.9)	0.8 - 5.0
External Eating	3.2 (±0.6)	1.5 - 4.8
Emotional Eating	2.4 (±1.0)	0.2 - 5.0
EAT-26		
Dieting (0-39)	5.7 (±6.3)	0 - 34
Bulimia and Food Preoccupation (0-18)	1.6 (±2.6)	0 - 12
Oral Control (0-21)	2.1 (±2.8)	0 - 21
SCOFF (0-5)	0.9 (±1.1)	0 - 5
CAARS		
Impulsive/Hyperactive (0-27)	8.0 (±4.2)	0 - 25
Inattentive (0-27)	9.2 (±5.0)	0 - 25
Combined (0-54)	17.2 (±7.8)	0 - 49
IES RHSC (1-5)	3.3 (±0.9)	1 - 5
IAS (21-105)	76.5 (±10.5)	34 - 100
BPQ-VSF (12-60)	40.8 (±9.6)	14 - 60
HADS (0-21)		
Anxiety	8.76 (±4.4)	0 - 21
Depression	5.92 (±5.9)	0 - 21
PSS (0 - 40)	20.0 (±7.7)	0 - 40

BES = Binge Eating Scale; DEBQ = Dutch Eating Behaviour Questionnaire; EAT-26 = Eating Attitudes Test; CAARS = Conners' Adult ADHD Rating Scale (short screening version; IES RHSC = Intuitive Eating Scale; Reliance on Hunger and Satiety Cues subscale; IAS = Interoceptive Accuracy Scale; BPQ-VSF = Body Perception Questionnaire-Very Short Form; HADS = Hospital Anxiety and Depression Scale; PSS = Perceived Stress Scale

5.4.4 Associations between interoception measures

Bivariate correlations revealed that IES-RHSC was associated with interoceptive accuracy as measured by the IAS ($r = 0.19$, $p < 0.001$), but not interoceptive sensibility as measured by the BPQ ($r = -0.12$, $p = 0.83$). Interoceptive accuracy and sensibility were significantly positively associated ($r = .33$, $p < 0.001$).

5.4.5 Mediation Analysis: Follow-up disordered eating

5.4.5.1 Mediation through Reliance on Hunger and Satiety Cues

Inattentive ADHD symptoms predicted binge eating scores both directly (Effect = 0.64, S.E. = 0.12, T = 7.3, $p < 0.001$, CI = 0.42 - 0.86) and indirectly through IES-RHSC (Effect = 0.27, Bootstrapped S.E. = 0.07, Bootstrapped CI = 0.15 - 0.41). (See Figure 1A).

Inattentive ADHD symptoms predicted restrictive eating scores both directly (Effect = 0.35, S.E. = 0.10, T = 3.4, $p < 0.001$, CI = 0.15 - 0.55) and indirectly through IES-RHSC (Effect = 0.09, Bootstrapped S.E. = 0.04, Bootstrapped CI = 0.03 - 0.17) (See Figure 1B).

Hyperactive/Impulsive ADHD symptoms predicted binge eating scores directly (Effect = 0.30, S.E. = 0.13, T = 2.3, $p = 0.025$, CI = 0.04 - 0.57) but not indirectly through IES-RHSC (Effect = 0.10, Bootstrapped S.E. = 0.09, Bootstrapped CI = -0.08 - 0.27). (See Figure 1C).

Hyperactive/Impulsive symptoms predicted restrictive eating scores directly (Effect = 0.33, S.E. = 0.12, T = 2.7, $p = 0.006$, CI = 0.09 - 0.56) but not indirectly through IES-RHSC (Effect = 0.003, Bootstrapped S.E. = 0.003, Bootstrapped CI = -0.03 - 0.10). (See Figure 1D).

5.4.5.2 Mediation through Interoceptive Accuracy and Interoceptive Sensibility

Inattentive ADHD symptoms predicted binge eating scores both directly (Effect = 0.85, S.E. = 0.13, T = 6.7, $p < 0.001$, CI = 0.60 - 1.09) and indirectly through IAS (Effect = 0.57, Bootstrapped S.E. = 0.29, Bootstrapped CI = 0.06 - 1.09) but not through BPQ (Effect = 0.007, Bootstrapped S.E. = 0.01, Bootstrapped CI = -0.016 - 0.03) (See Figure 2A).

Inattentive ADHD symptoms predicted restrictive eating scores directly (Effect = 0.30, S.E. = 0.10, T = 2.9, $p = 0.006$, CI = 0.15 - 0.55), but not indirectly through either IAS (Effect = 0.04, Bootstrapped S.E. = 0.26, Bootstrapped CI = -0.007 - 0.010) nor through BPQ (Effect = 0.008, Bootstrapped S.E. = 0.02, Bootstrapped CI = -0.03 - 0.05) (See Figure 2B).

Hyperactive/Impulsive ADHD symptoms predicted binge eating scores directly (Effect = 0.33, S.E. = 0.16, T = 2.1, $p = 0.04$, CI = 0.015 - 0.64), but not indirectly through either IAS (Effect = 0.04, Bootstrapped S.E. = 0.032, Bootstrapped CI = -0.01 - 0.12) or through BPQ (Effect = 0.03, Bootstrapped S.E. = 0.023, Bootstrapped CI = -0.07 - 0.08). (see Figure 3A).

Hyperactive/Impulsive symptoms predicted restrictive eating scores directly (Effect = 0.29, S.E. = 0.12, T = 2.4, $p = 0.017$, CI = 0.052 - 0.53) but not indirectly through IAS (Effect = 0.025, Bootstrapped S.E. = 0.021, Bootstrapped CI = -0.006 - 0.076) or through BPQ (Effect = 0.04, Bootstrapped S.E. = 0.024, Bootstrapped CI = -0.0003 - 0.092). (see Figure 3B).

5.4.5.3 Mediation through Negative Mood

Inattentive ADHD symptoms predicted binge eating scores both directly (Effect = 0.49, S.E. = 0.14, T = 3.5, $p = 0.0004$, CI = 0.22 - 0.76) and indirectly through negative

mood (Effect = 0.42, Bootstrapped S.E. = 0.090, Bootstrapped CI = 0.26 - 0.60). (see Figure 4A).

Inattentive ADHD symptoms did not predict restrictive eating scores directly (Effect = 0.12, S.E. = 0.12, T = 1.1, p = 0.29, CI = -0.104 - 0.35) but did predict restrictive eating indirectly through negative mood (Effect = 0.22, Bootstrapped S.E. = 0.07, Bootstrapped CI = 0.089 - 0.37). (see Figure 4B).

Hyperactive/Impulsive ADHD symptoms did not predict binge eating scores directly (Effect = 0.096, S.E. = 0.15, T =0.65, p = 0.52, CI = -0.19 - 0.39) but did predict binge eating indirectly through negative mood (Effect = 0.303, Bootstrapped S.E. = 0.08, Bootstrapped CI = 0.16 - 0.47). (See Figure 4C).

Hyperactive/Impulsive symptoms did not predict restrictive eating scores directly (Effect = 0.22, S.E. = 0.12, T = 1.8, p = 0.069, CI = 0.017 - 0.24) but did predict restrictive eating indirectly negative mood (Effect = 0.13, Bootstrapped S.E. = 0.047, Bootstrapped CI = 0.55 - 0.24). (See Figure 4D).

5.4.5.4 Mediation Analysis: Change in disordered eating

Neither the direct nor indirect pathways in any of the assessed mediation models predicted change in disordered eating scores.

5.4.5.5 Moderation by sex

The moderating influence of sex on all model pathways was assessed. Sex did not moderate direct or indirect pathways of any model.

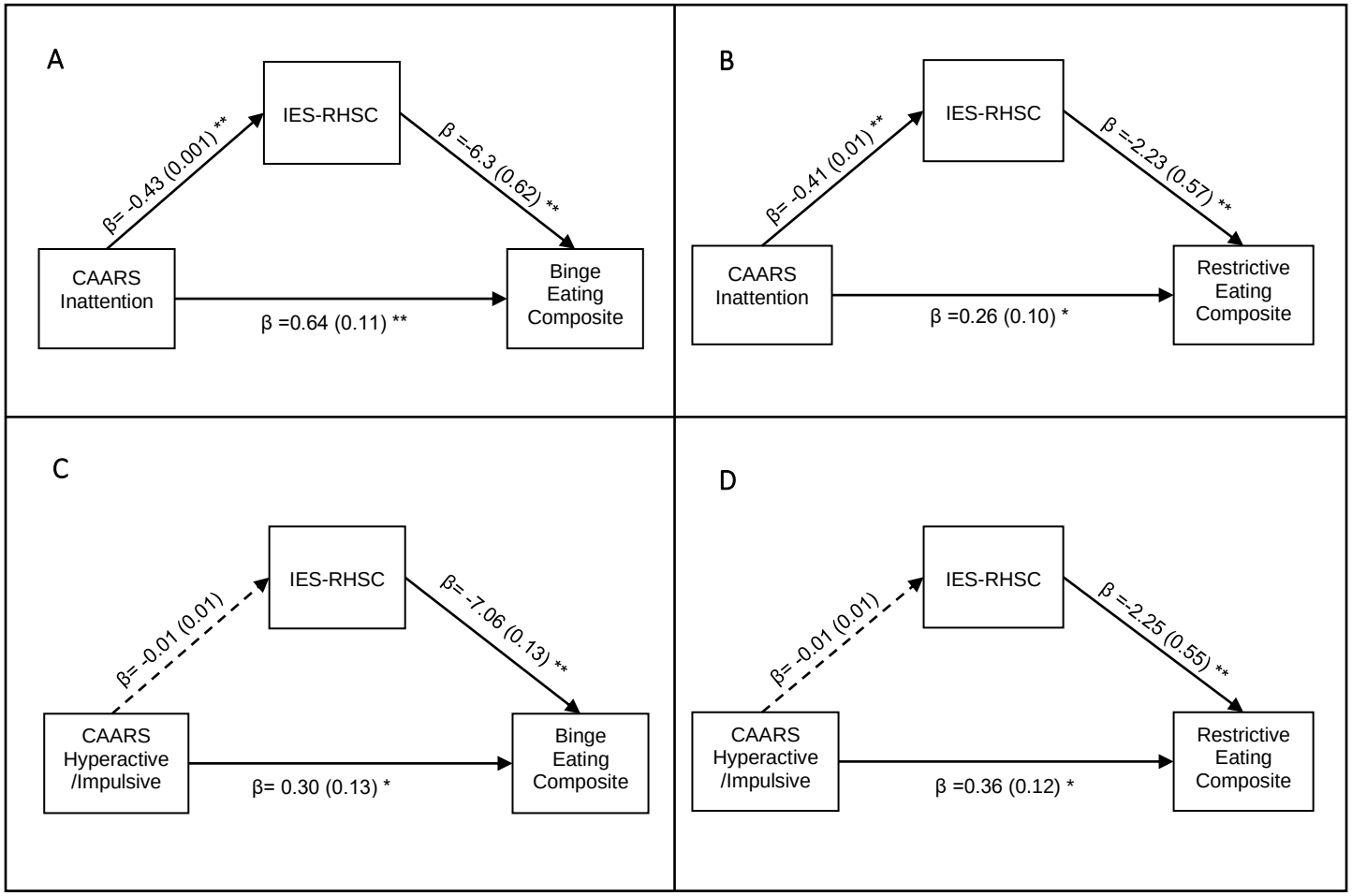

Figure 1. Mediation model showing the mediated relationship between inattentive symptoms and **A**: binge eating, **B:** restrictive eating, and the mediated relationship between hyperactive/impulsive symptoms and **C:** binge eating, **D:** restrictive eating.
Solid lines reflect significant pathways. Estimates (β) are unstandardized regression coefficients, numbers in parentheses show error (direct effects) and bootstrapped error (indirect effects). All analyses controlled for sex, age, BMI, alcohol use and illicit drug use. * = p < 0. 05, ** = p < 0.001

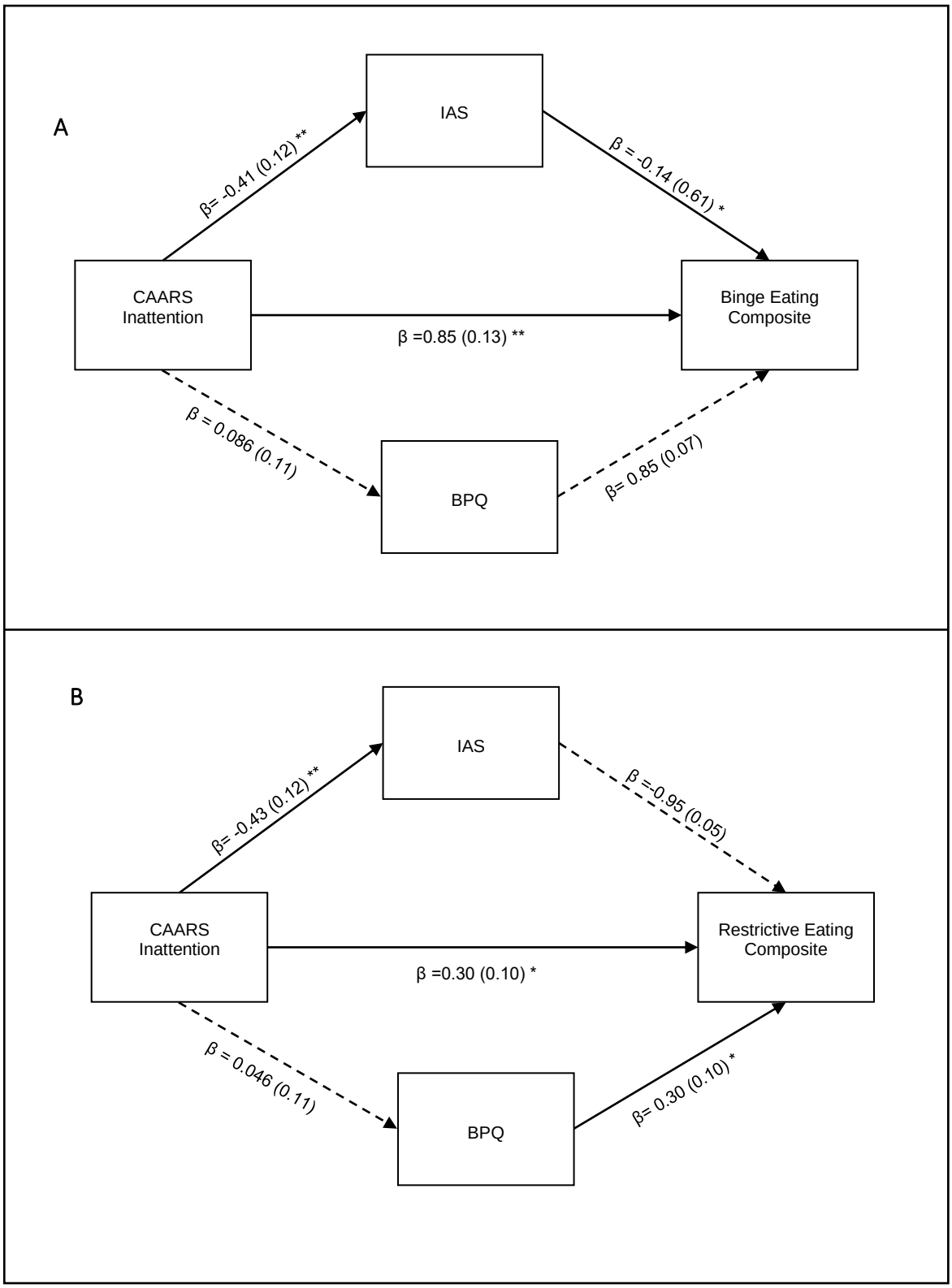

Figure 2. Mediation model showing the mediated relationship between inattentive symptoms and **A:** binge/disinhibited eating, **B:** restrictive eating. Solid lines reflect significant pathways.
Estimates (β) are unstandardized regression coefficients, numbers in parentheses show error (direct effects) and bootstrapped error (indirect effects). All analyses controlled for sex, age, BMI, alcohol use and illicit drug use. * = p < 0. 05, ** = p < 0.001

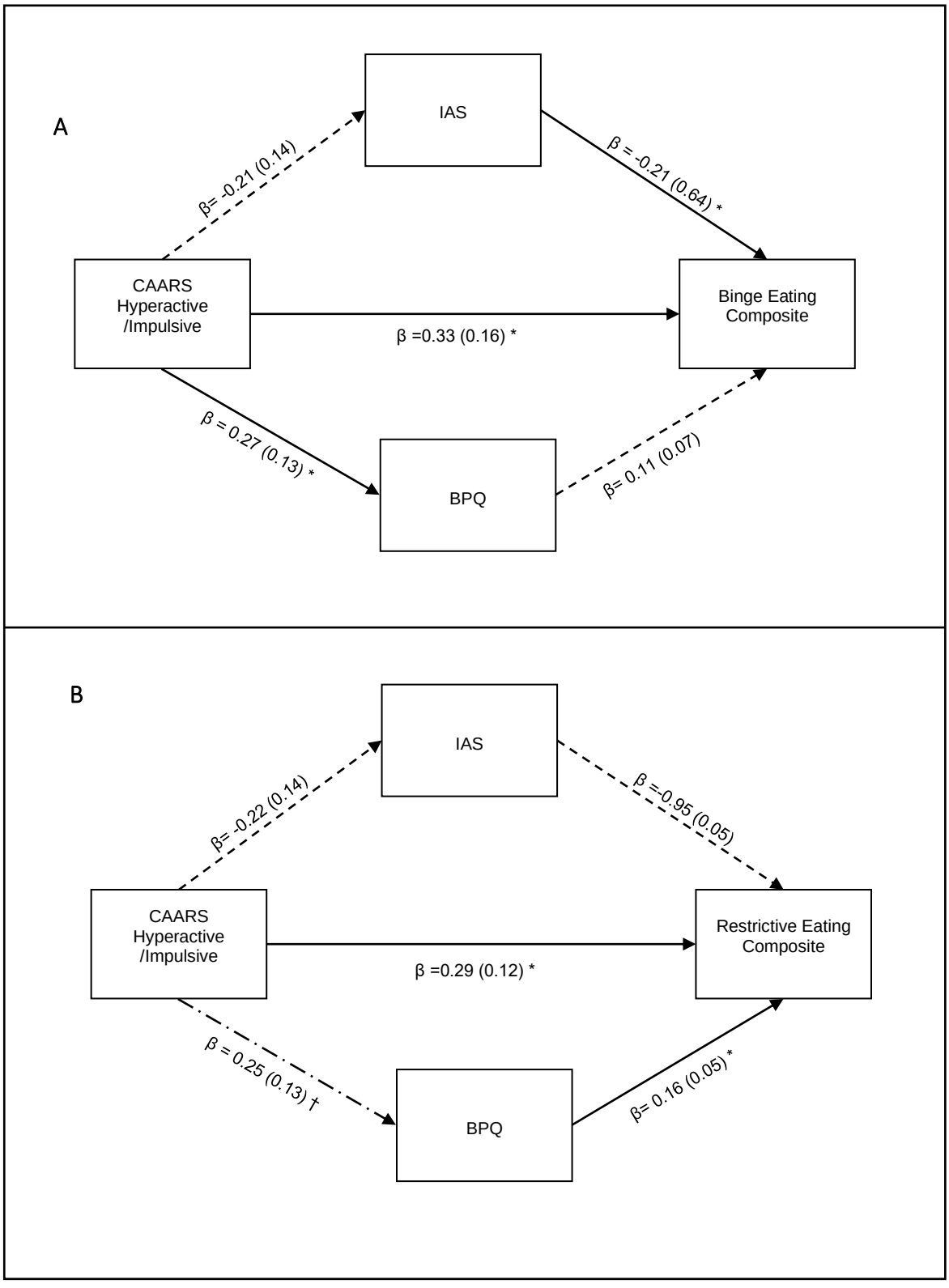

Figure 3. Mediation model showing the mediated relationship between hyperactive/impulsive symptoms and **A:** binge/disinhibited eating, **B:** restrictive eating. Solid lines reflect significant pathways.
Solid lines reflect significant pathways. Estimates (β) are unstandardized regression coefficients, numbers in parentheses show error (direct effects) and bootstrapped error (indirect effects). All analyses controlled for sex, age, BMI, alcohol use and illicit drug use. † = marginal significance (p = 0.05), * = p < 0. 05, ** = p < 0.001

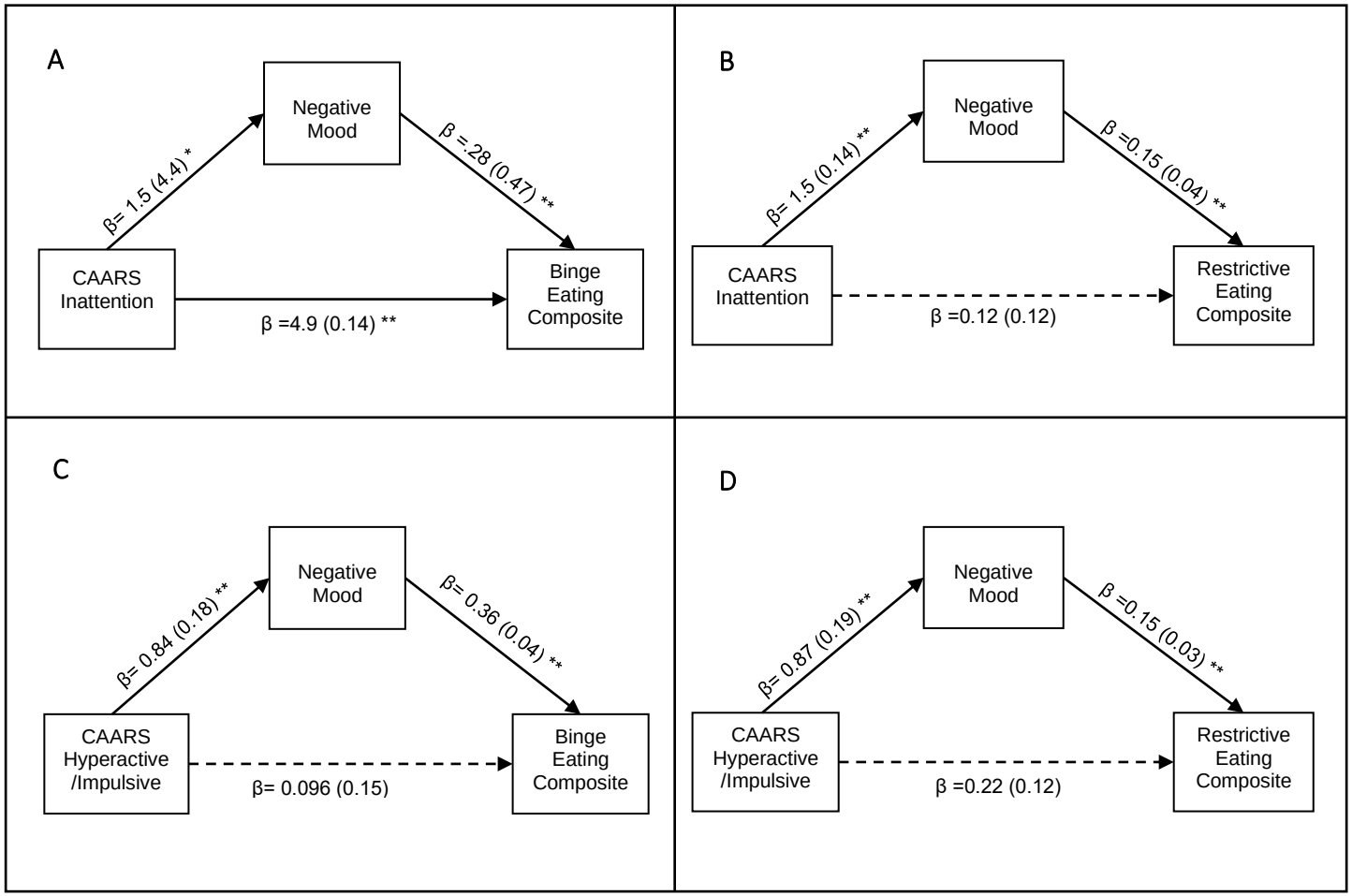

Figure 4. Mediation model showing the mediated relationship between inattentive symptoms and **A**: binge eating, **B:** restrictive eating, and the mediated relationship between hyperactive/impulsive symptoms and **C:** binge eating, **D:** restrictive eating.
Solid lines reflect significant pathways. Estimates (β) are unstandardized regression coefficients, numbers in parentheses show error (direct effects) and bootstrapped error (indirect effects). All analyses controlled for sex, age, BMI, alcohol use and illicit drug use. * = $p < 0.05$, ** = $p < 0.001$

5.5 Discussion

The aim of this study was to assess the mediating influence of separate facets of interoception, on the relationship between ADHD symptoms and disordered eating using a longitudinal study design. This was the first study to assess the mediating influence of specific interoceptive facets on the relationship between ADHD symptoms and disordered eating over a 6-month period. Although none of the predictor variables were able to predict change in disordered eating over 6 months, the relationship between inattentive symptoms of ADHD at baseline predicted both binge and restrictive eating behaviours at 6-month follow-up. Mediation models showed that self-reported interoceptive accuracy, rather than interoceptive sensibility mediates the relationship between inattention and binge eating symptoms, but not restrictive eating symptoms. As reported previously (Kaisari et al., 2018), reliance on hunger and satiety cues mediated the relationship between inattentive ADHD symptoms and disordered eating, and negative mood mediated the relationship between both ADHD symptom subtypes and both binge/disinhibited eating and restrictive eating. Sex did not moderate any of the mediation models tested.

The most consistent relationship demonstrated in the current study is that between inattentive symptoms of ADHD and symptoms of binge eating. This result highlights the role of inattention as a cognitive mechanism which may foster disordered eating. To date, it was unclear how (in)attention may impact disordered eating. Preliminary evidence suggested that interoception may be one mechanism underlying this relationship (Kaisari et al., 2018). The present results replicate this finding, and, for the first time, suggest that inattention specifically contributes towards disordered eating through an impact on interoceptive accuracy, rather than interoceptive sensibility. These results suggest that trait attention is necessary for supporting accurate interpretation of interoceptive signals, and that this accurate interpretation may specifically protect against binge eating. On the other

hand, attention does not appear to influence the trait tendency to notice interoceptive signals. This dissociable effect of attention may be explained through a predictive coding framework of interoception. Within the predictive coding framework of interoceptive processing, generative models about internal states are built, consisting of predictions about changes in internal state (priors), which are constantly updated based on prediction errors. Interoceptive accuracy has been suggested to reflect the ability to use attention to prioritise interoceptive signals (Ainley, Apps, Fotopoulou & Tsakiris, 2016), leading to increased precision (e.g. reduced variance and increased reliability) of priors and prediction errors, but not necessarily an enhancement in the saliency of signals (Ainley, Apps, Fotopoulou & Tsakiris, 2016). This suggested role of attention in interoceptive prediction is one explanation for how attention may relate specifically to accuracy, but not to sensibility. Further research guided by the predictive coding framework may elucidate why attention specifically relates to accuracy rather than sensibility, and the precise contribution of this relationship to binge eating.

Aside from the role of attention in interoceptive processing, attention has previously been implicated in the control of food intake. Increased attention towards food being eaten during an eating episode can decrease later intake, whereas distraction can increase later intake (Higgs, 2015). Interestingly, when distracted experimentally during eating, increased food intake is observed in the absence of any expected change in hunger and satiety ratings (Blass, Anderson, Kirorian, Pempek, Price & Koleini, 2006; Mittal, Stevenson, Oaten & Miller, 2010; Higgs, 2015). This suggests that even when attention to interoceptive signals is increased by explicitly asking participants to report internal state, interoceptive accuracy remains impacted by inattention during food intake. BED has been associated with impaired detection of hunger and fullness (Sysko, Devlin, Walsh, Zimmerli, Kissileff, 2007). Therefore, increased trait inattention could lead to inaccuracy

in detection of internal signals (including hunger, satiety and bloating) and this inaccurate representation may interrupt accurate detection of satiety, contributing towards excessive eating associated with binge eating episodes. In addition, inaccuracy in interoceptive signals may encourage binge/disinhibited eating through contributing towards an overreliance on salient external cues to guide behaviour, rather than interoceptive cues which are perceived as inaccurate. For example, eating in response to food-related stimuli has been associated with poorer interoceptive accuracy (Young et al., 2017) suggesting that individuals with poor interoceptive accuracy are prone to use external signals about available food to guide eating, rather than interoceptive signals. In the context of the modern obesogenic environment, this tendency could contribute towards overconsumption of highly palatable foods.

In addition to binge eating, results from the current study also suggest a relationship between both symptom subtypes of ADHD and restrictive eating. In comparison to binge/disinhibited eating, research into ADHD symptoms and restrictive eating has been less frequently studied, and results are less consistent (see Kaisari et al., 2017 for a review). The current study contributes further evidence that ADHD symptoms are associated with restrictive eating. The relationship between inattention and restrictive eating was mediated by reliance on hunger and satiety cues, but not through specific measures of interoceptive accuracy or interoceptive sensibility. It is plausible that, in individuals who engage in restrictive eating, attention to, and accuracy of interoceptive signals, as measured by the BPQ and IAS respectively are intact. However, with regard to trusting and using gastric interoceptive signals as measured by the IES-RHSC, mistrust in signals may give rise to a trait tendency to not use these signals. Accordingly, there is evidence that in individuals with anorexia nervosa mistrust in bodily sensations specifically connects interoceptive deficits to eating disorder symptomatology (Martini et

al., 2021). Similarly, Brown et al. (2020) found that mistrust in body sensations was the most relevant facet of interoception to disordered eating and was particularly associated with weight concerns. These results highlight that in individuals more prone to restrictive eating, trust in interoceptive signals may be more influential to symptomatology than sensibility or accuracy.

Unlike inattentive symptoms, hyperactive/impulsive symptoms of ADHD predicted restrictive and binge/disinhibited eating only through negative mood, not through any interoceptive measures. Given the aforementioned potential role of attention in interoception, this result highlights that inattentive symptoms of ADHD specifically influence interoception, and hyperactive/impulsive symptoms do not have the same impact. Negative mood mediated the relationship between both symptom subtypes of ADHD and both disordered eating behaviour types. The relationship between negative affect and eating has been well documented (e.g. Rosenbaum & White, 2015; Haynos, Watts, Loth, Pearson, Neumark-Stzainer, 2016; Schulz & Laessle, 2010), as has the relationship between ADHD symptoms and negative affect (Katzman, Bilkey, Chokka, Fallu, & Klassen, 2017). It is possible that there is a causal relationship between ADHD symptoms, negative mood and disordered eating. Thus, the experience of ADHD symptoms may contribute towards negative affect, and disordered eating behaviours may reflect a coping mechanism for this negative affect, for example through emotional eating. Additionally, there may be a common underlying factor influencing ADHD symptoms, negative mood and disordered eating, leading to their co-occurrence. For example, the serotonergic system has been implicated in ADHD, mood and disordered eating (Banerjee & Nandagopal, 2015; Reimold et al., 2011; Ruhé, Mason, & Schene, 2007; Bailer & Kaye, 2010; Wang et al., 2018), and in drug therapies used to treat these disorders (Schneider et al; 2021; Clevenger et al., 2018), however further research is necessary to determine the

existence of such a common substrate. It is worth noting that inattentive and impulsive symptom scores were correlated. Although this is not surprising as attention is known to be interrelated with impulsivity, evident through the existence of the 'attentional impulsivity' subscale of the Barratt Impulsiveness Scale (Patton, Stanford, & Barratt, 1995), it is possible therefore that the measurement of inattention and impulsivity as used in the current study are not measuring separable constructs. The implication of this on the results presented may mean that the apparent reduced relative influence of impulsivity on disordered eating may be exaggerated due to unique variance being shared between inattention and impulsivity. However, as the measures are not perfectly correlated ($r = 0.42$), it is likely that although they are interrelated, they are not measuring the same process. Future research assessing the specific contributions of impulsivity compared to attention on disordered eating may wish to employ more sophisticated measurement methods to disentangle the unique contribution of each construct.

There was a significant increase in restrictive eating reported over the 6-month period, but no statistically significant change in binge eating. No variables included in the current study were associated with a change in restrictive eating. Changes in restrictive eating over a similar time period in adolescents and young adults have been associated with variables such as body dissatisfaction and weight-related teasing (Wertheim, Koerner & Paxton, 2001; Haynos et al., 2016). Additionally, the differences in season during which responses were collected may interact with these factors. It is possible that a 'seasonal body image' variation exists (e.g. Griffiths, Austen & Blake, 2021), such that body dissatisfaction increases in warmer months, potentially as a result of factors such as the tendency to wear less clothing during warmer months, and media pressures to alter appearance in preparation for this seasonal change. It is unclear whether this may at least partially explain the increase in reported restrictive eating in our sample. Influences such

as body dissatisfaction may have contributed to the significant increase in restrictive eating in the current sample but were not variables of interest and were therefore not recorded in this study. As a result, the factors that contributed to the increase in restrictive eating in the current sample are unclear. Future research may explore further what factors predict an increase in restrictive eating in a community sample over a similar time period.

The results of this study have implications for the assessment of risk of disordered eating. Given that symptoms of ADHD, deficits in self-reported interoceptive accuracy, and negative mood appear to be associated with disordered eating, screening for negative mood and interoceptive accuracy may be useful in identifying individuals (e.g. those who present with symptoms of ADHD), who are at risk of developing disordered eating. Appropriate interventions can be applied based on this screening, and development of such interventions may also be guided by the current results. For example, targeting negative affect in individuals with ADHD symptoms may reduce the likelihood of subsequent disordered eating, and interventions aimed to improve interoceptive accuracy may specifically reduce binge eating in those individuals. Similarly, the early identification of individuals with ADHD symptoms who may be prone to restrictive eating could reveal cases where prescribing a drug therapy for ADHD that decreases eating, such as LDX, (Schneider et al., 2021) would be contraindicated.

5.5.1 Strengths and Limitations

This is the first study to assess the longitudinal mediating influence of interoception on the relationship between ADHD symptoms and disordered eating. The three interoception measures used, the IES-RHSC, the IAS and the BPQ-VSF, were specifically included to capture separate dimensions of interoception. Previous studies have conflated measurements of different facets of interoception, despite evidence that these are distinguishable (e.g. Murphy et al., 2019; Garfinkel et al., 2015). Interestingly,

despite displaying unique contributions to the relationship between inattention and disordered eating, interoceptive accuracy and sensibility were correlated, to a similar extent as has previously been reported (Robinson, Marty, Higgs & Jones., 2021). This suggests that although these measures reflect independent interoceptive processes, accuracy and sensibility may not be as dissociable as previously suggested (Murphy et al., 2020). The use of both measures in this study enabled the investigation of the distinct contribution of these interoceptive dimensions to disordered eating and demonstrated a unique contribution of self-reported interoceptive accuracy, rather than interoceptive sensibility, to the relationship between ADHD symptoms and disordered eating. More generally, the current results highlight the importance of measuring distinct facets of interoception to study the role of interoceptive processes in psychiatric conditions.

The study has some limitations. In planned mediation models, change in disordered eating scores was not predicted directly or indirectly by ADHD symptoms, through any mediator. Thus, it is impossible to conclude whether ADHD symptoms and/or deficits in interoceptive accuracy predispose an individual to disordered eating. One explanation for this apparent lack of explanatory power may be that the 6-month period chosen for the study was insufficient in duration to capture the variability expected during development of disordered eating behaviours. Although there was a significant increase in mean restrictive eating between the two timepoints, the absolute change was relatively small compared to the possible range of scores on the composite measures. Future studies may benefit from testing similar relationships over several timepoints to examine the trajectory of changes over a longer period of time between (e.g. 12 months) baseline and follow-up.

An additional extraneous influence on disordered eating which was not recorded in the current study was the impact of the COVID-19 pandemic on disordered eating. There is some evidence to suggest that the COVID-19 pandemic increased psychiatric problems

including disordered eating behaviours (Ramalho et al., 2021; Nutley et al., 2021), possibly as a result of factors such as increased distress, financial concerns, and social isolation (Rodgers et al., 2020). Thus, the variance in disordered eating behaviours in this study may be disproportionately explained by these factors, rather than the predictor variables included. Additionally, although the majority of participants were residents of the UK and Ireland (85%), the remaining participants were residents of several other countries (including the USA, Canada and South Africa), which will have been experiencing differing levels of COVID-19 restrictions. This means that the experience of COVID-19 restrictions will not be uniform across the sample and may therefore impact subgroups of the sample more than others.

Possible biases exist in the participants recruited from Prolific. For example Prolific's participant pool appears to have a bias towards younger, more highly educated women (Prolific, 2018), which means that the sample is not necessarily generally representative of the population. Additionally, analysis of differences in baseline characteristics of 'completers' and 'non-completers' revealed that completers were more likely to be women, who were older and with lower ADHD symptoms than non-completers. These differences may introduce a source of bias in the sample. For example, given the known relationship between ADHD symptoms and disordered eating, it is possible that those with the highest ADHD symptoms at baseline experienced the greatest increase in disordered eating symptoms, which would not be reflected in the follow-up outcome measurements.

The prevalence of 'at-risk' levels of ADHD symptoms was higher (17%) than the prevalence of ADHD reported in the general population, which is consistently estimated below 5% (e.g. Kessler et al., 2006; Montejano, Sasané, Hodgkins, Rosso & Huse, 2011; de Zwaan et al., 2012; Fayyad et al., 2018). Similarly, the prevalence of possible eating

disorders measured by the SCOFF was relatively high (12%) compared to general population estimates (8.4% for women and 2.2% for men, Galmiche, Déchelotte, Lambert & Tavolacci, 2019). Although this could reflect low representativeness of the sample, it should be noted that both measures are screening tools, and neither are recommended to be solely used for diagnoses, rather to highlight those who are 'at risk', or who display behaviours consistent with the disorders which may require further clinical assessment. Importantly, despite these inflated estimates in this sample, the present results replicated previous findings (Kaisari et al., 2017), suggesting that the key relationships tested were not affected by possible high reported symptoms of ADHD or disordered eating in the current sample.

There was an increase in reporting of both binge and restrictive eating behaviours. It is possible that prior exposure to the same measurement could lead to a change in responding which could explain these results. However, test-retest reliability of the BES, DEBQ and EAT-26 has been reported as good (Banasiak, Wertheim, Koerner & Voudouris, 2000; Freitas, Lopes, Appolinario & Coutinho, 2006; Duarte, Pinto-Gouveia & Ferreira, 2015; Wu, Cai & Luo, 2017), and therefore prior exposure to measures is unlikely to underlie observed increases in reported disordered eating behaviours.

5.5.2 Conclusion

In conclusion, these results add to a growing body of evidence for a relationship between specific ADHD symptoms and disordered eating in the general population, particularly between inattentive symptoms and binge/disinhibited eating. The results also provide the first evidence that self-reported interoceptive accuracy, rather than sensibility, mediates the relationship between inattentive ADHD symptoms and binge/disinhibited eating. This suggests that interoceptive accuracy is dependent on trait attention and may contribute towards the development of binge/disinhibited eating. These results have

implications for the development of screening tools with a focus on negative mood and interoceptive accuracy for individuals with ADHD and individuals at-risk of eating disorders, as well as for the development of improved therapeutic interventions focused on these factors.

Chapter Six: General Discussion

The aim of this thesis was to address gaps in the literature regarding cognitive and neural mechanisms underlying disordered eating. Firstly, the relationship between inattentive and impulsive ADHD symptoms and the risk of eating disorder > 2 years later was assessed. Secondly, the neural mechanisms(s) impacted by a drug that improves symptoms of both ADHD and BED were assessed. Thirdly, the published literature on the relationship between disordered eating and interoception, a factor which may underlie the relationship between ADHD inattentive symptoms and disordered eating, was assessed in a systematic review. Finally, the mediating influence of interoception on the relationship between ADHD symptoms and disordered eating over a 6-month period was assessed, with a novel focus on how different facets of interoception may contribute to this relationship.

6.2 Overview of Results

In Chapter Two, the cross-sectional relationship between specific ADHD symptoms and the risk of developing an eating disorder, and the longitudinal relationship between trait impulsivity and the risk of developing an eating disorder were analysed. Despite consistent evidence for a relationship between ADHD and disordered eating, few studies have assessed the contribution of specific symptoms of ADHD, and studies have rarely assessed longitudinal relationships. Further, there had been no previous assessment of longitudinal mediating influences on this relationship. Analysis of cross-sectional data from a community sample of 642 participants revealed that inattentive symptoms of ADHD predicted the risk of developing an eating disorder, and this relationship was partially mediated by symptoms of depression. Analysis of longitudinal data revealed that attentional impulsivity, and not motor or non-planning impulsivity, predicted risk of eating disorder. This longitudinal relationship was fully mediated by symptoms of depression. These results expand on existing cross-sectional evidence suggesting that attentional

processes in particular are associated with risk of eating disorder in the general population, and that symptoms of depression, which are associated with impulsivity and inattention, may reflect one pathway through which inattention and impulsivity may lead to disordered eating.

In Chapter Three, the effect of LDX on food intake, and neural responses to food pictures in women with binge eating symptoms was assessed. LDX, which is a pro-drug of d-amphetamine, was originally used to treat ADHD but also has efficacy in reducing symptoms of BED, and is the only drug approved in the USA for treatment of BED. Few previous studies have assessed mechanisms through which LDX reduces binge eating symptoms. Analysis of food intake from 21 women with moderate-to-severe binge eating symptoms revealed LDX reduced intake of both a pasta lunch, and cookie snack and reduced the appeal of palatable foods. fMRI data revealed that LDX also attenuated BOLD responses to food pictures (compared to non-food pictures) in the thalamus. The behavioural results demonstrated that LDX reduces consumption of both a staple lunch meal and a palatable snack in women with binge eating symptoms through multiple mechanisms, including homeostatic and hedonic control systems. The fMRI results suggest that LDX may reduce the saliency of food as a rewarding stimulus, as thalamic responding has been implicated in reward and salience attribution. This reduction in the salience of external food cues could rebalance the relative contributions of exteroceptive and interoceptive cues to guide behaviour, enabling enhanced reliance on internal cues to guide eating.

In Chapter Four, existing evidence for an association between interoception and disordered eating was systematically reviewed. Although it has been argued that interoceptive deficits may be one mechanism through which symptoms of ADHD contribute towards disordered eating, there had been no comprehensive review of the

literature regarding the association between interoception and disordered eating. The results of 104 studies were reviewed. Interoceptive deficits were consistently reported to be associated with a range of eating disorders and disordered eating behaviours, across all interoceptive modalities. These findings suggest that interoceptive deficits may reflect a transdiagnostic feature of eating disorders and disordered eating. The review also revealed limited evidence for a longitudinal association between interoceptive deficits and disordered eating, and that no studies have assessed the mediating mechanisms of this potential relationship.

Chapter Five examined the longitudinal relationship between ADHD symptoms and disordered eating over 6-months, and the mediating factors of this relationship. Previous research suggests that reliance on cues of hunger and satiety to guide eating may mediate the relationship between inattention and disordered eating, but it is unclear whether this reflects a role for interoception in disordered eating. Two separate facets of interoception, self-reported interoceptive accuracy and interoceptive sensibility, were assessed as potential mediators of the relationship between ADHD symptoms and disordered eating. The results confirmed that reliance on hunger and satiety signals mediates the relationship between inattentive ADHD symptoms and disordered eating and revealed that interoceptive accuracy specifically mediated the relationship between inattentive symptoms and binge eating. These results confirm that inattentive symptoms in the general population are associated with disordered eating, through a reduced reliance on internal cues of hunger and satiety and provide novel evidence that this may reflect reduced perceived accuracy of interoceptive signals.

6.3 Theoretical implications of Findings

The research presented in this thesis has theoretical implications for the understanding of the mechanisms associated with disordered eating. In particular, the

results suggest that cognitive processes such as impulsivity and attention are associated with disordered eating, and elucidate how dysfunction in cognitive systems may contribute to disordered eating, for example through impacts on interoception.

6.4 Impulsivity, Attention and Disordered Eating

Historically, the influence of cognitive processes on eating have been afforded less attention than the influence of homeostatic and reward processes (Higgs et al., 2017). This thesis has assessed the contribution of specific cognitive processes to the development and maintenance of disordered eating. Impulsivity is one cognitive process commonly associated with disordered eating, particularly binge eating (Claes, Vandereycken, & Vertommen, 2005; Rosval et al., 2006). Impulsivity is a multifaceted process that can be measured using various methods. Self-reported impulsivity is commonly associated with binge eating (e.g. Meule & Platte, 2015; Lee-Winn, Townsend, Reinblatt & Mendelson, 2016; Solly, Chamberlain, Lust & Grant, 2021). However, the results of Chapter 2 showed that only attentional impulsivity (defined as the inability to focus attention, Stanford et al., 2009) predicted disordered eating, and that impulsive symptoms of ADHD were not associated with disordered eating when inattentive ADHD symptoms were also included in the model. These results suggest that impulsivity may be less influential on disordered eating than previously considered and is consistent with a recent systematic review which revealed an inconsistent relationship between behavioural measures of impulsivity and binge eating (Waltmann, Herzog, Horstmann & Deserno, 2021). LDX reduces symptoms of BED and impulsivity in BED patients (McElroy et al., 2016), however the results of Chapter 3 showed that LDX does not increase neural activation in regions associated with cognitive control (e.g. dorsolateral prefrontal cortex) when viewing food pictures. Although this result might suggest that LDX-induced improvements in cognitive control do not underlie the ability of the drug to reduce binge eating, the paradigm reported did not

include an impulsivity-related task (e.g. go/no-go). Future research assessing the mechanisms targeted by LDX in binge eating could use a food-based go/no-go task to determine whether impulsive responding to food is affected by LDX administration and thereby identify if impulsivity is an important mechanism in BED. Overall, the direct influence of impulsivity in binge eating requires further clarification. Further, impulsivity is less commonly associated with restrictive eating than with binge eating, and the relationship between restrictive eating and impulsivity is unclear (Howard, Gregertsen, Hindocha & Serpell, 2020). Further studies of various facets of self-reported impulsivity and restrictive eating, including assessing possible mediating influences are required to clarify this relationship.

It is possible that impulsivity contributes towards disordered eating specifically within the context of negative mood. In both Chapters Two and Five, the results showed that negative mood fully mediated the relationship between impulsivity and both restrictive and binge eating. The relationship between negative mood and disordered eating is well documented (e.g. Zaider, Johnson & Cockell, 2000; Blinder, Cumella & Sanathara, 2006; Santos, Richards, Bleckley, 2007; Touchette et al., 2011), and the research presented in this thesis has highlighted how alterations in cognitive processes may contribute towards this relationship. It is unclear how impulsivity and negative mood interact to elicit and maintain disordered eating. It is possible that impulsivity increases negative mood, for example the impact of ADHD symptoms on daily functioning, may contribute to stress, anxiety, and depression. Alternatively, the relationship between negative mood and impulsivity may reflect the influence of negative mood on the likelihood of impulsivity. Negative urgency refers to the trait tendency to act impulsively when experiencing negative mood (Cyders & Smith, 2008), and this specific facet of impulsivity has been associated with disordered eating, particularly binge eating (e.g. Davis & Fischer, 2013).

Negative urgency may therefore reflect a tendency to act impulsively towards food when experiencing negative emotions. On the other hand, it is possible that the associations observed between impulsivity and negative mood reflect the existence of a common biological substrate. For example, dysregulation in the monoaminergic system has been associated with both negative mood and impulsivity (Dalley & Roiser, 2012; Dean & Keshavan, 2017; Belujon & Grace, 2017). Additionally, there may be overarching behavioural influences that affect both impulsivity and mood. For example, poor sleep quality, associated with symptoms of ADHD (Hvolby, 2015) can increase both impulsivity and negative mood, and could therefore at least partially underlie the cooccurrence of negative mood and impulsivity. Future research should address the precise nature of the relationship between impulsivity and negative mood, investigate the genesis of this relationship and how treatment of both impulsivity and negative mood could improve symptoms of both binge and restrictive eating.

Unlike impulsivity, little research has reported on the role of attention in disordered eating. Attention has previously been implicated in the control of food intake, such that reduced attention to food during eating appears to increase food intake, in the absence of changes in hunger and satiety (Blass, Anderson, Kirorian, Pempek, Price & Koleini, 2006; Higgs & Woodward, 2009; da Mata Gonçalves et al., 2019). The role of trait attention in the development of disordered eating, however, has received little consideration, with the specific contribution of trait inattention to disordered eating being reported in only a few studies (e.g. Kaisari et al., 2017). Accordingly, previous reviews of the mechanisms underlying disordered eating have not emphasised the potential contribution of trait attention (e.g. Bakalar et al., 2015; Kober & Boswell, 2018). Evidence from Chapters Two and Five together highlights that inattentive symptoms of ADHD are specifically associated with disordered eating, particularly binge eating. These associations remained

when both hyperactive/impulsive symptoms of ADHD and confounding variables such as sex, age, alcohol, and drug use were accounted for. The direct relationship between inattentive symptoms of ADHD and disordered eating (binge eating in particular) reported in both Chapters Two and Five remained significant even when an indirect pathway through negative mood was accounted for, suggesting that inattention contributes uniquely towards disordered eating, via a mechanism(s) that is independent of negative mood. The results from Chapters Two and Five add further weight to the argument for a specific role of inattention in disordered eating (Rosval, Steigher, Bruce, Israël, Richardson, & Aubut, 2006; Kaisari et al., 2018).

In summary, the results presented in Chapters Two and Five extend existing evidence for the importance of cognitive processes in disordered eating. In particular, the results highlight a potential role of impulsivity specifically within the context of negative mood. Additionally, the results contribute further evidence towards the novel suggestion for an important role of attention in disordered eating.

6.5 Interoception

One way in which inattention has been suggested to contribute to disordered eating is via interoception (Kaisari et al., 2018). Chapters Four and Five examined the role of interoception in disordered eating. The suggestion that deficits in interoceptive processing are associated with eating disorders is not novel. Bruch (1962) reported that a 'disturbance in the accuracy of perception or cognitive interpretation of stimuli arising in the body' was a key characteristic in patients with anorexia nervosa (AN). This suggestion was experimentally investigated by Garfinkel et al. (1978), who found that patients with AN did not show the expected satiety-induced aversion to sucrose that healthy control participants did, from which they concluded that AN is associated with deficits in satiety regulation. Subsequently, the widely used eating disorder inventory (EDI) was developed

(Garner, Olmstead & Polivy, 1983), that includes an interoceptive awareness subscale, reported to 'reflect one's lack of confidence in recognising and accurately identifying emotions and sensations of hunger or satiety'. Despite this well-established association between interoception and disordered eating, and a recent resurgence in research interest in the role of interoception in psychiatric conditions (Simmons & DeVille, 2017; Khalsa et al., 2018), there had not been a comprehensive assessment of the influence of specific facets of interoception on disordered eating. Chapter Four revealed that the majority of studies assessing interoceptive deficits in association with disordered eating used the EDI, which does not dissociate between facets of interoception (Merwin, Zucker, Lacy & Elliot, 2010). Further, the underlying factors that may lead to differences in interoceptive processing, which could in turn contribute towards disordered eating, had not been addressed.

The research presented in this thesis provides the first in-depth examination of how interoceptive deficits in the general population may contribute towards disordered eating. The systematic review in Chapter Four revealed that interoceptive deficits related to disordered eating are observed in multiple modalities, supporting initial suggestions made by Bruch (1962). Further, these deficits occur in a range of eating disorders as well as in relation to disordered eating, which suggests that interoceptive deficits may represent a transdiagnostic feature of eating disorders. The results presented in Chapter Five support previous suggestions (Kaisari et al., 2018) that inattention may contribute to disordered eating through a reduced reliance on internal cues of hunger and satiety. Additionally, these results provide novel evidence that inattention may impact interoceptive accuracy, rather than sensibility, and this may specifically lead to binge eating. Through the research presented in Chapters Four and Five, our understanding of the role of interoceptive processes in disordered eating has been refined and extended, by a comprehensive review

of the literature, an assessment of the relationship between specific facets of interoception and specific disordered eating behaviours, and identification of cognitive processes which may underlie these interoceptive deficits. Future research may consider the origin of differences in interoceptive sensibility and accuracy. Interoception likely plays a key feature in survival (Craig, 2002). For example, accurate detection of fluctuations in nutritive state, accompanied by appropriate changes in behaviour dependent on external cues (e.g. availability of food) are crucial in maintaining health. As a result, accurate interoceptive processing is therefore likely to be subject to positive evolutionary pressure. It is possible that optimal levels of interoceptive sensibility and interoceptive accuracy reflect population traits which are protective against the development of eating disorders.

6.6 Measurement of Interoception

The research presented in this thesis has highlighted the necessity for more refined measurement of interoception. Until recently, much of the research into interoception has not made clear distinctions between interoceptive facets, with terms such as ‘awareness’ and ‘accuracy’ used indiscriminately. This is potentially problematic in the understanding of interoception as there is evidence that separate facets of interoceptive are dissociable. If interoceptive facets reflect dissociable processes, using indiscriminate measures of interoceptive processing may overlook or conflate the role of specific facets. At present however, the extent to which interoceptive facets can be considered as dissociable is unclear. For example, Murphy et al. (2020) reported that interoceptive sensibility and interoceptive accuracy were not correlated, whereas the results from Chapter Five showed a moderate correlation between the two measures. This correlation is consistent with the results of another recent study (Robinson et al., 2021). Therefore, although interoceptive sensibility and accuracy may reflect theoretically different processes, to date it is unclear whether they are truly dissociable.

A further potential result of the issues with measurement of interoception, is inconsistent evidence regarding the relationship between interoceptive accuracy and restrictive eating. Deficits in objective measurements of interoception (e.g. heartbeat counting) have been reported in AN patients (Pollatos et al., 2008), suggesting a link between AN and interoceptive accuracy. However, the results in Chapter 5 showed no association between restrictive eating and self-reported interoceptive accuracy. This apparent discrepancy could suggest that the process being measured by objective measures of interoceptive accuracy are different to those measured by subjective measures, despite previous reports that these two measures are correlated (Murphy et al., 2020). Alternatively, this could reflect issues surrounding the validity of commonly used objective measurements of interoception (Brener and Ring, 2016). Future research should continue to explore specific facets of interoception, to assess how these facets are related, and how specific facets may impact disordered eating.

6.7 Integration of Interoceptive and External Sensory Information

It is important to note that interoceptive information is not the sole source of information used to guide eating behaviour, and interoceptive information must be constantly integrated with sensory information (Craig, 2002). Through the process of 'positive alliesthesia', the motivational value of external food stimuli is altered, dependent on internal state (Simmons & DeVille, 2017), thus perception of external palatable food cues alone does not guarantee intake, as these cues are processed within the context of interoceptive state. Therefore, at any given time, the relative weighting of the contribution of internal information versus external information to guide eating behaviour varies. The results from Chapter Three revealed how the reduction of thalamic responses to food cues (possibly reflecting reduced saliency of external food cues) may be one mechanism through which LDX decreases binge eating. Integrating this finding with the deficits in

interoception in disordered eating highlighted in Chapters Four and Five, the efficacy of LDX in treating BED may in part rely on encouraging increased weighting of interoceptive information to guide eating, compared to external food cues, through reducing the relative salience of external food cues. Failure to accurately integrate interoceptive signals to alter responses to external food cues may underlie results from neuroimaging studies which show an absence of change in response to visual food cues following satiation in individuals with eating disorders. In healthy adults, satiation is associated with reduced fMRI BOLD activation of reward-related areas in response to food (Thomas et al., 2015), but this reduction in reward sensitivity following satiation does not appear to occur in individuals with AN and BN (Wierenga et al., 2015; Bischoff-Grethe, Wierenga, Bailer, McClure, & Kaye, 2021). This preliminary evidence suggests that responses to external food stimuli in eating disorders are not updated according to interoceptive information, and therefore consumption may become over-reliant on external food stimuli, as opposed to interoceptive information.

Future research should determine how the integration of interoceptive and exteroceptive information may be affected in eating disorders and disordered eating. Neuroimaging tasks can be used to assess neural activity during interoceptive versus exteroceptive processing. For example, Kerr et al. (2016; 2017) recorded BOLD fMRI responses while participants attended to the intensity of sensations in various organs and contrasted this with BOLD responses recorded while participants attended to the intensity of changes to various properties of presented text. Using this, or a similar task, it is possible to assess which brain regions preferentially respond to interoceptive or exteroceptive signals. Combining this approach with manipulation of internal state e.g. by eating, could provide a method to identify how processing of interoceptive and exteroceptive information varies depending on interoceptive state, and how this may differ

between individuals with and without disordered eating. At present, despite evidence for altered neural activity during interoception in participants with eating disorders (Kerr et al., 2016; 2017), it is unclear how this may be influenced by internal state. In addition to task-based fMRI measurements of interoception, there is evidence that connectivity networks observable during rest (e.g. the default mode network) may underlie interoceptive processing (Kleckner et al., 2017). Alterations in connectivity in such networks following changes in internal state may reflect an alternative approach to studying the neural bases of interoceptive processing in disordered eating.

6.8 Clinical Implications

The clinical implications of the findings presented in this thesis highlight opportunities for more effective screening of individuals who could be prone to developing an eating disorder. Based on results from Chapters Two and Five, individuals self-reporting high levels of attentional impairment, combined with negative mood, may be identified as at high risk of developing disordered eating. Similarly, results from Chapters Three and Five suggest deficits in interoception may be apparent in those at particular risk of eating disorders. Existing screening tools for disordered eating may therefore benefit from the addition of questions related to processes such as attention, impulsivity and interoception.

The results from this thesis also have implications for the identification of novel targets and the development of novel treatments for eating disorders. For example, given the role of negative mood highlighted in Chapters Two and Five, treatment of negative affect in those with eating disorders may synergise with treatments targeted at eating disorder symptoms. Indeed, antidepressants have been proposed to have potential for treating eating disorders, particularly in the prevention of relapse (Walsh, 2002; Marvanova & Gramith, 2018).

In addition to treatment of negative mood, there is preliminary evidence that interoceptive accuracy can be improved (Fischer, Messner & Pollatos, 2017). Treatments focussing on interoception are potentially efficacious in disordered eating although this approach is in its infancy and interoception-based treatments for eating disorders have thus far not targeted interoceptive accuracy. For example, 'interoceptive exposure' involves repeatedly invoking interoceptive sensations that may be associated with distress, and increasing tolerance to these sensations. This approach is traditionally used to treat anxiety disorders, but has potential to be applied to treating eating disorders (Boswell, Anderson & Anderson, 2015). However, it does not aim to improve interoceptive processing per se, but rather to enhance acceptance of interoceptive sensations. Interoceptive exposure may therefore be more suited to treating restrictive eating, given that the results from Chapter Five suggested that a trait tendency to mistrust interoceptive signals, rather than inaccuracy of the signals, may be related to restrictive eating. A randomised controlled trial using Body Awareness Therapy (Catalan-Matamoros et al., 2011), an approach suggested to be targeting interoceptive processes (Khoury, Lutz & Schuman-Olivier, 2018), showed efficacy in patients with eating disorders. However, it is unclear exactly how Body Awareness Therapy impacts interoception, and therefore this approach requires futher investigation to determine its viability as an interoception-based approach. These approaches have not targeted specific interoceptive facets, and the results presented in Chapter Five demonstrate that there may be differences between interoceptive processes that should be targeted for specific eating behaviours. For example, it is possible that treatment programmes for binge eating should focus on enhancing perceived accuracy of interoceptive signals, whereas treatment approaches for restrictive eating may benefit from a focus specifically on increasing trust in these signals.

The compelling evidence for a role of interoception in disordered eating and eating disorders presented in this thesis confirms that this sensory process is worthy of future research into potential interoceptive-based treatments, targeting specific interoceptive facets. For example, in addition to the aforementioned interoception-related treatments, biofeedback training may be a promising avenue for enhancing interoceptive accuracy in some domains (Meyerholz, Irzinger, Withöft, Gerlach, and Pohl, 2019) but using biofeedback specifically to improve interoceptive accuracy has thus far not been applied as a potential treatment for eating disorders. Additionally, treatments for BED targeted at interoceptive processes may be of particular use when used in tandem with LDX, given that the results from Chapter Four suggest a possible LDX-induced attenuation of saliency of external food cues, which may allow for enhanced relative ability to accurately detect interoceptive signals.

In addition to LDX, development of novel pharmacological therapies may be informed by the research presented in this thesis. Adverse effects of LDX include insomnia, headache, irritability and dry mouth and the drug is classified as a Schedule II controlled substance due to its potential for abuse. Given the ability of LDX to reduce binge eating, novel drug therapies for BED should possess comparable therapeutic efficacy as highlighted in Chapter Three, for example having similar effects on satiety, reward, and attention, but with an improved side effect profile and reduced potential for abuse. An additional point of consideration for development of novel drug therapies for BED is effects on body weight. LDX reduces body weight (McElroy et al., 2016), however given that around one-third (Kessler et al., 2013) of patients with BED are not overweight or obese, use of LDX may be contraindicated in these individuals. Therefore, development of a drug with similar effects to LDX on cognitive/reward processes, that does not induce significant weight loss would be valuable for treating BED. The research presented in this

thesis has highlighted several processes that may be targets for such novel therapies. Additionally, the experimental model used in Chapter Three, that comprises eating a test lunch meal and a palatable snack to assess satiety and reward, and assessing changes in neural responses to food cues, could be used in future to screen acute effects of novel drug therapies for BED. In addition to binge eating, restrictive eating is often comorbid with ADHD (Kaisari et al., 2017), but again LDX and other stimulants would be contraindicated for ADHD patients with restrictive eating due to their anorectic properties. Further research is required into drug therapy for restrictive eating (Cassioli, Sensi, Mannucci, Ricca, & Rotella, 2020), and the research presented in this thesis highlights processes such as negative mood that may be targets for the development of novel drug therapies to treat restrictive eating, particularly in individuals with comorbid ADHD symptoms.

6.9 Strengths and Limitations

The research presented in this thesis utilised multiple methodologies to provide an in-depth examination of the potential processes underlying disordered eating. Firstly, the association between ADHD symptoms and disordered eating was confirmed in Chapter Two. The potential mechanisms underlying disordered eating and the efficacy of LDX in treating BED were explored in Chapter Three, using a placebo-controlled double-blind design, considered to be the gold standard for experimental medicine studies. Further, the use of fMRI in Chapter Three enabled the measurement of otherwise unobservable processes (e.g. thalamic reactivity to food cues). The combination of self-report methods and experimental methods allows the limitations of one method to be addressed by the other approach. For example, one major limitation of self-report methods is that they are dependent on participants responding truthfully and accurately. In contrast, this type of response bias is unlikely to occur in a double-blind placebo-controlled design, in which

neural responses to food cues are recorded. Additionally, it is unrealistic to recruit large numbers of participants for psychopharmacological neuroimaging studies such as in Chapter Three, whereas it is possible to obtain large samples with relative ease via online questionnaire platforms. The systematic review of the literature presented in Chapter Four provided an overarching account of the relationship between disordered eating and various measures of interoception, and Chapter Five applied these results to extend findings from Chapter Two, highlighting for the first time that cognitive deficits may negatively impact interoceptive accuracy, and that this may contribute towards binge eating.

The approach to participant recruitment used in this thesis is in line with the Research Domain Criteria (RDoC) framework for studying psychiatric conditions (Insel et al., 2010), in which recruitment of participants who do not meet full diagnostic criteria for eating disorders is encouraged (Wildes & Marcus, 2015). In Chapters Two and Five, large community samples were studied, as opposed to clinical samples with diagnosed eating disorders, and in Chapter Three participants were recruited from the general population with moderate-to-severe symptoms of binge eating disorder. Additionally, diverse samples obtained from the general population as opposed to smaller samples of patient groups increases representativeness of the data and recruiting large numbers of participants in this way ensures that recruitment of the required number of participants to achieve the desired statistical power is achieved. The research presented in this thesis also supports the application of cognitive systems (e.g. attention, cognitive control) as RDoC domains to the study of eating disorders (Wildes & Marcus, 2015).

Nevertheless, limitations may exist in the representativeness of the samples used in this thesis. For example, although the NSPN sample in Chapter Two is thought to broadly match the general UK population, parents of the sample reported higher educational attainment than the general population (Kiddle et al., 2018). Additionally, English as a first

language was an inclusion criterion used to recruit the sample for Chapter Five. The purpose of this inclusion criterion was a straightforward way of trying to maximise understanding of the questionnaires, which contain complex or abstract concepts, however this criterion could potentially have affected the diversity of the sample. Data from samples consisting of homogeneous samples will not include considerations of cultural influences on eating behaviours (Anderson-Fye, 2018), or assess generalisability of results to non-English speakers.

An additional risk of bias is possible in studies with >1 data collection round, arising from participant retention/attrition. For example, the dataset used in Chapter Three reported 53% attrition (Kiddle et al., 2018), and in Chapter Five there was 30% attrition, despite participants agreeing to be contacted for follow-up participation. This has the potential to introduce bias into the sample if participants who complete both parts of the study have different characteristics to the original sample. Indeed, in Chapter Five there were several differences between individuals who completed both data collection rounds and those who completed the initial round only, including sex, age and ADHD symptoms. However, there is evidence that attrition alone is not sufficient to lead to meaningful differences in analyses of association (e.g. Gustavson, von Soest, Karevold & Røysamb, 2012; Saiepour, Najman, Ware, Baker, Clavarino & Williams, 2019), and therefore this rate of attrition, while potentially impacting how representative the sample is, may not be highly impactful on results.

The results reported in this thesis provide limited ability to draw conclusions about the direction of causality between cognitive deficits such as inattention and impulsivity, or processes such as interoception, and disordered eating. Although there are plausible pathways through which these mechanisms could contribute towards disordered eating, the reverse relationship may also be possible. For example, deficits in interoceptive processing

may lead to disordered eating, through an inability to accurately respond to signals of hunger and satiety, but on the other hand if an individual routinely ignores these signals, by restricting intake due to fear of weight gain, then disordered eating behaviours may contribute towards poorer interoception. Chapters Two and Five attempted to consider longitudinal relationships between these variables, which provides an opportunity to assess the trajectory of changes in behaviour or cognition, and potentially unravel the predisposing influence of interoception on disordered eating, or vice versa. However, the ability of results from these chapters to achieve this aim was limited. Chapter 2 utilised an existing dataset in which data regarding disordered eating was collected at timepoint 2 only, therefore in this chapter it was not possible to control for baseline disordered eating at timepoint 1, to assess whether baseline ADHD symptoms predict subsequent eating disorder risk above and beyond baseline risk. Chapter Five attempted to remedy this limitation, by collecting information on disordered eating at both timepoints and considering change in disordered eating as an outcome variable. However, using this approach led to no predictor variables being significantly associated with disordered eating change. As a result, absolute scores at follow-up were considered as outcome variables, which leaves unanswered the question of how ADHD symptoms/ interoceptive abilities may influence the trajectory of disordered eating.

6.10 Future Research Directions

A gap that remains in the literature regarding neurocognitive mechanisms underlying disordered eating is determination of the direction of causality. For example, although deficits in cognitive processes such as attention may underlie disordered eating, there is also evidence that eating patterns, such as those associated with disordered eating, may impact cognitive processing. Similarly, although deficits in interoceptive processing may contribute towards disordered eating, it is possible that a trait tendency to not use

interoceptive information to guide behaviour may impact interoceptive abilities. Aside from two timepoint studies such as those presented in this thesis, studies involving multiple timepoints over several years may enable the use of more sophisticated causal inference methods such as latent growth curve models (Locascio & Atri, 2011). Although studies following such protocols can be costly and impractical, efforts to create shared longitudinal datasets such as The National Longitudinal Study of Adolescent to Adult Health (Harris & Udry, 2018) are ongoing. In future, measures relating to the processes highlighted in this thesis (e.g. interoception) should be included in such datasets, allowing future research studies to assess longitudinal relationships between these processes and eating disorder symptom trajectory.

Longitudinal studies are just one method of testing causal relationships. Comparing cognitive processes highlighted in this thesis in individuals with eating disorders, and their relatives with and without eating disorders may highlight whether dysfunction in a particular process reflects an endophenotype that predisposes individuals to eating disorders. Additionally, experimental manipulations of processes thought to be involved in disordered eating, and the measurement of effects on subsequent eating could provide insight into the causal role of that process. As previously mentioned, this approach has been used to test how manipulations of attention impact eating and have helped to confirm a causal role of attention in eating. Similarly, the aforementioned potential for interoceptive training would highlight the potential causal role of interoceptive processes in disordered eating through observation of the impacts of improvements in interoception on disordered eating symptoms.

Future research could assess the impact of attentional dysfunction on disordered eating more broadly. For example, although there is now an emergent pattern of inattention relating to disordered eating, the contribution of specific facets of attention, such as

sustained or selective attention, has not been assessed. It is unclear whether specific facets of attention are particularly important in the relationship between inattention and disordered eating. Further, ADHD is not the only psychiatric disorder in which patients have attentional dysfunction, for example patients with schizophrenia demonstrate attentional dysfunction, and there is evidence for a high prevalence of comorbidity between schizophrenia and eating disorders (Kouidrat, Amad, Lalau & Loas, 2014). Investigation of comorbid eating disorders in psychiatric conditions with a focus on attentional dysfunction may further our understanding of how these processes could contribute towards disordered eating.

6.11 Conclusions

The research presented in this thesis used a broad range of methodologies to investigate neurocognitive mechanisms underlying disordered eating and a drug therapy for BED. The results contribute towards a greater understanding of the role of impulsivity in disordered eating, by highlighting the importance of considering impulsivity in the context of negative mood. The results also highlight the specific role of inattention in disordered eating, and reveal a novel association between inattention and interoceptive accuracy. Additionally, the results identified the thalamus as a key region implicated in the treatment of BED by LDX, potentially due to its role in reward and salience attribution, and rebalancing the relative contributions of exteroceptive and interoceptive cues to guide eating. The results suggest that inattention may be related to disordered eating by affecting the relative influence of interoceptive and exteroceptive processes in responses to food cues. The results have clinical implications for the development of improved screening tools and therapies for disordered eating.

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Appendix One: Search Terms used in Systematic Review

Figure 1. Search terms used in the systematic review. Within each search term category (interoception or disordered eating: presented here in separate columns), separate search terms were separated with the Boolean operator 'OR'. The two search term categories were separated with the Boolean operator 'AND'.

Interoception search terms		Disordered Eating search terms
interocept* interocept* awareness interocept* detection interocept* sensitivity interocep* process* interocep* deficit heartbeat detection heartbeat counting detection of pain* perception of pain* sensitivity to pain* pain threshold pain tolerance painful stimuli detection of temperature perception of temperature sensitivity to temperature detection of sati* sensitivity to sati* detection of hunger sensitivity to hunger detection of internal cues sensitivity to internal cues reliance on internal cues detection of internal state sensitivity to internal state internal cues of satiation somatosensory awareness perception of bodily signals bodily perception intuitive eating	**AND**	eating disorder feeding disorder* EDNOS OSFED disordered eat* body dysmorph* disorder* eating behav* eating patholog* eating psychopatholog* abnormal eating binge* binging binge-eating disorder grazing graze purging purge* vomiting chaotic eating bulimia bulimia nervosa bulimi* behav* anorexia anorexia nervosa restrictive eating restrictive food intake selective eating avoidant restrictive food intake disorder ARFID Pica night eating NES eating habit* eating pattern* eating attitude* eating problem* loss of control lack of control overeat* over eat* excessive eat* hyperphagia compulsive eat* compulsive food intake excessive appetite

Appendix Two: Characteristic of Studies Included in the Systematic Review

Table begins on following page