Neural Features of Obesity and Intervention: A Food-Cue fMRI Study

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Legend

BMI	Body Mass Index
CNS	Central Nervous System
GI	Gastrointestinal
PYY	Peptide Tyrosine Tyrosine
GLP-1	Glucagon-like peptide-1
ARC	Arcuate Nucleus
PVN	Paraventricular Nucleus
VMH	Ventromedial Nucleus
DMH	Dorsomedial Nucleus
LHA	Lateral Hypothalamic Area
BBB	Blood Brain Barrier
NPY	Neuropeptide Y
AgRP	Agouti-related Peptide
POMC	Proopiomelanocortin
aMSH	Alpha Melanocyte Stimulating Hormone
DA	Dopamine
VTA	Ventral Tegmental Area
NAc	Nucleus Accumbens

OFC	Orbitofrontal Cortex
PFC	Prefrontal Cortex
VS	Ventral Striatum
fMRI	Functional Magnetic Resonance Imaging
BOLD	Blood Oxygen-Level Dependant
BIS	Behavioural Inhibition System
BAS	Behavioural Approach System
BAS-R	Behavioural Approach System – Reward Responsiveness
BAS-D	Behavioural Approach System - Drive
BAS-F	Behavioural Approach System – Fun Seeking
ACC	Anterior Cingulate Cortex
MOP-R	μ-Opioid Receptor
HC	High Calorie
LC	Low Calorie
NC	Neutral Control
ROI	Region Of Interest
FC	Food Cues
ROMHC	Royal Ottawa Mental Health Centre
EEG	Electroencephalography

CeeN	Clinical EEG and Neuroimaging
NIH	National Institute of Health
BIC	Brain Imaging Centre
MEMPRAGE	Multi-echo MPRAGE
MNI	Montreal Neurological Institute
GLM	General Linear Model
FWE	Family-Wise Error
dACC	Dorsal Anterior Cingulate Cortex
dlPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
FIT	Frontal Inferior Triangularis

Abstract

Obesity is a global epidemic associated with alterations in reward processing and inhibitory control. Pharmacological interventions, such as Contrave® (naltrexone/bupropion), combined with dietary modification, may influence these neural processes; however, the short-term neural effects of such interventions remain unknown. This is a double-blind, placebo-controlled, and randomized phase four clinical trial investigating neural responses to food cues before and after a 4-week Contrave® and diet intervention (total N=15 at baseline and N=11 pre/post). At baseline, we identified activity in several regions (notably the insula) across different food-viewing conditions. Baseline brain responses to food cues were also associated with in-scanner food cue ratings in the Rolandic operculum, as well as reward motivation traits in the dorsolateral prefrontal cortex, and more. The 4-week intervention induced changes in brain activity in the hippocampus and precuneus, among other regions. Changes in brain activity were also associated with reward motivation traits in several regions, including the insula and frontal cortex. This study contributes evidence regarding the neural correlates of obesity and the potential impact of a short-term drug/diet intervention. To our knowledge, it is the only study to combine fMRI with a pharmacological *and* dietary weight-loss intervention in men and women with obesity. Overall, we hope that this research will improve obesity-related patient care and the clinical use of Contrave®.

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Chapter 1: Introduction

1.1 Overview

1.1.1 Obesity: A Complex Disorder

Obesity is an increasing worldwide epidemic with serious implications for individual and public health (Balasundaram et al., 2025). Defined as a body mass index (BMI) of over 30 kg/m^2 by the World Health Organization, obesity is a systemic disorder that presents with an abnormal accumulation of subcutaneous and visceral adipose tissue and considerably increases secondary health risks across all main organ systems (WHO, 2025; Mitchell et al., 2011; Boutari et al., 2022). These risks include, but are not limited to, cardiovascular disease, sleep apnea and respiratory disorders, metabolic diseases, intracranial hypertension, arthritis, fatty liver disease, chronic kidney disease, reproductive system disruptions, psychiatric disorders, cancer, and more (Apovian et al., 2022). Importantly, the risk of comorbidity is positively associated with increases in weight and BMI (Apovian et al., 2022). For example, the prevalence of hyperlipidemia is more than doubled in individuals with a BMI of >40 kg/m^2 compared to individuals with a BMI of 25-40 kg/m^2 (Apovian et al., 2022). This is also true for several other comorbidities, such as hypertension, diabetes, and metabolic syndromes, among others (Apovian et al., 2022). Furthermore, obesity is associated with increased incidences of mental health issues; it is estimated that 20%-60% of obese individuals suffer from a psychiatric illness (Sarwer & Polonsky, 2016). Not only does obesity increase risk for comorbidities, but it also decreases life expectancy and quality of life, reduces employment rates, and poses a serious threat to the economy (Balasundaram et al., 2025). These observations are of extreme concern, considering that in 2022, the World Health Organization

estimated that 2.5 billion adults were overweight (BMI 25 kg/m^2), with 890 million of these being clinically obese (WHO, 2025).

Ultimately, obesity arises from an imbalance between food intake and energy expenditure, leading to weight gain. However, its etiology involves a complex interplay between a myriad of genetic, epigenetic, and lifestyle factors. Genetic causes of obesity can be categorized into three main types: syndromic obesity, monogenic obesity, and polygenic obesity (Tirthani et al., 2025). Syndromic obesity involves chromosomal rearrangements which lead to the development of well-known syndromes, such as Fragile X syndrome, which are often characterized by neurodevelopmental delay among many other clinical features, including obesity (Tirthani et al., 2025). Monogenic obesity involves a mutation in a single gene responsible for relaying satiety signals (Tirthani et al., 2025). Mutations of this kind are inherited as autosomal dominant or recessive mutations and cause obesity early in life (Tirthani et al., 2025). Polygenic obesity is a multifactorial condition that results from the cumulative effect of genetic mutations or variants interacting with behaviour and the environment (Tirthani et al., 2025). This form of obesity can manifest at any age (Tirthani et al., 2025). Epigenetic factors also play an important role in the etiology of obesity (Tirthani et al., 2025). For example, maternal exposure to toxins, stress, malnutrition, and diabetes, nutritional disturbances in early childhood, use of antibiotics in the first year of life, and many more, are all known to induce epigenetic DNA changes which contribute to obesity (Tirthani et al., 2025). Lifestyle contributors to obesity include reduced physical activity and a Western diet (Clement-Suárez et al. 2023), which includes readily available fast-food and processed food options; 72.1% of foods consumed by everyone in the United States include refined sugars and vegetable oils, dairy products, cereal, and alcohol (Clement-Suárez et al. 2023). The Western diet is thought to negatively impact inflammation, gut flora, mitochondrial fitness,

cardiovascular health, mental health, metabolism, and more (Clement-Suárez et al., 2023), all of which contribute to obesity.

1.2 Mechanisms of Control of Food Intake

1.2.1 Overview

Energy balance is maintained by a complex physiological system. Afferent signals from the periphery inform the system about energy stores and food in the body, while efferent signals from the central nervous system (CNS) produce the senses of hunger and satiety, driving energy intake and expenditure (Abdalla, 2017). All peripheral and CNS signals in the body that promote a state of hunger and food-seeking behaviours are considered orexigenic, while signals that promote satiety and energy expenditure are anorexigenic. The following sections will briefly outline the proposed interactions between the gastrointestinal tract, adipose tissue, and brain regions involved in regulating food intake in healthy individuals, providing a foundation for understanding the central focus of this thesis: the brain in the context of obesity.

1.2.2 Peripheral Control of Food Intake

The gastrointestinal (GI) tract produces many hormones and peptides that play key roles in modulating satiation and satiety. Further, gastric distention, which follows food consumption, has a satiating effect by activating gastric mechanoreceptors, relaying stomach size and digestive state to the brain via the va gus nerve (Hargrave & Kinzig, 2012). The pancreas produces many appetite-controlling hormones and peptides, including insulin and amylin, glucagon, enterostatin, and pancreatic polypeptide (Abdalla, 2017). First, insulin is produced by pancreatic beta cells to promote the absorption of circulating glucose into tissues, regulate adipocyte metabolism, and bind to insulin receptors in the brain to promote satiation (Shin et al., 2017). Amylin is co-

secreted with insulin and acts on the gut and the brain to reduce food intake, slow down gastric emptying and gastric acid formation, and prevent glucagon secretion (Abdalla, 2017). Glucagon is produced by pancreatic islet alpha cells and has opposing effects to insulin (Abdalla, 2017); its primary role is to increase blood sugar by initiating glycogenolysis in the liver (Abdalla, 2017). It also promotes satiation and satiety by directly targeting the brain, as well as decreases weight by promoting lipid metabolism (Al-Massadi et al., 2019). Next, enterostatin is released from the exocrine pancreas in response to fat intake to help its digestion; it peripherally and centrally targets serotonergic and opioid pathways to help decrease fat intake (Erlanson-Albertsson & York, 1997). Last, pancreatic polypeptide is produced by gamma cells in the pancreas in response to food intake and exerts many anorexigenic effects, including promoting satiation (Abdalla, 2017).

Meanwhile, the stomach and intestinal tract also produce appetite-regulating hormones and peptides in response to food consumption. Cholecystokinin is released by I-cells of the small intestine into the bloodstream following food consumption and promotes satiation (Abdalla, 2017). Next, ileal and colonic L-cells produce peptide tyrosine tyrosine (PYY), which is released into the bloodstream following food consumption and binds to receptors in the brain to promote satiety (Chaudhri et al., 2006; Abdalla, 2017). Glucagon-like peptide-1 (GLP-1) and oxyntomodulin are also anorexigenic peptides produced by the L-cells of the intestines in response to food consumption (Abdalla, 2017), by promoting satiation and insulin production (Abdalla, 2017). Lastly, ghrelin is a peptide produced by the stomach and is the only orexigenic peptide produced from the GI tract (Abdalla, 2017). Ghrelin production is stimulated when the stomach is empty and inhibited with gastric distention (Young & Jialal, 2023). This peptide travels directly to the brain to exert its orexigenic effects (Abdalla, 2017).

Finally, leptin is an adipokine created by adipocytes in adipose tissue and released into the bloodstream in concentrations that are proportionate to the amount of adipose tissue present in the body (Abdalla, 2017). Leptin secretion increases following food consumption and decreases during fasting (Abdalla, 2017). Together, all the above hormones and peptides play important roles in regulating the control of food intake through central and peripheral mechanisms.

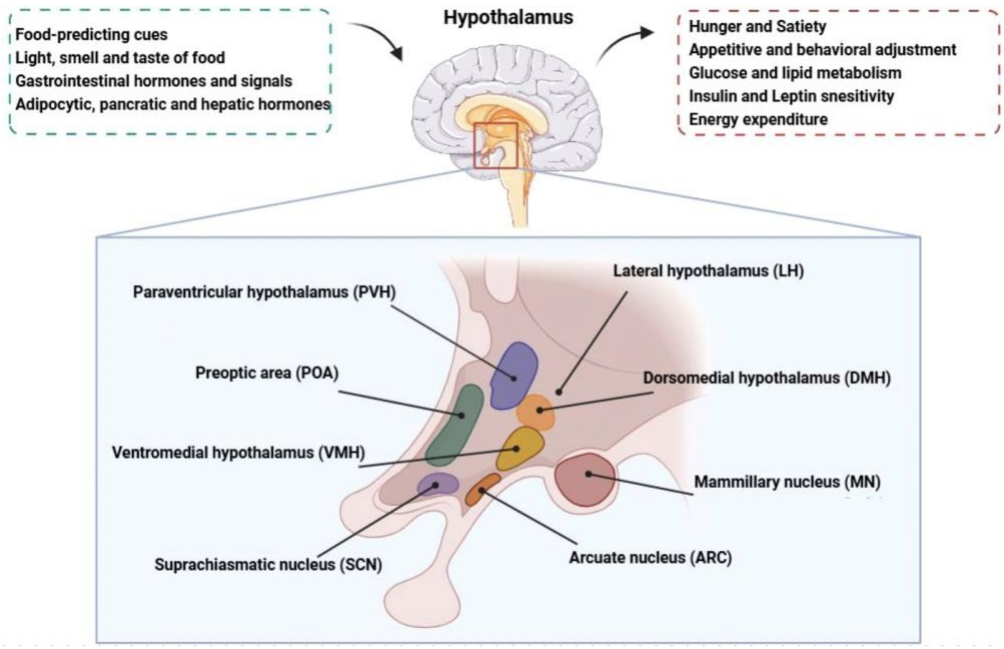
1.2.3 Homeostatic Control of Food Intake

The hypothalamus is the primary brain region responsible for regulating the homeostatic control of food intake, i.e., assessment of energy stores (Pop et al., 2021). It receives and processes peripheral signals reflecting hunger/satiety, as well as central signals from reward and cognitive control systems (Pop et al., 2021), including from limbic, reward, and autonomic brain regions. The arcuate nucleus (ARC) of the hypothalamus is considered the primary nucleus responsible for regulating appetite and metabolism. It is located near the median eminence, a capillary-rich structure with a leaky blood–brain barrier (BBB) that facilitates the access of circulating hormonal and nutrient signals to the ARC (Primeaux et al., 2021). The ARC contains two important nuclei, the first is exclusively orexigenic and expresses neuropeptide Y (NPY) and agouti-related peptide (AgRP), and the second is exclusively anorexigenic and expresses proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (Primeaux et al., 2021). POMC neurons are particularly significant given their clinical relevance, which will be discussed in detail in section 1.4.3. POMC, a precursor protein, is primarily cleaved into alpha-melanocyte-stimulating hormone (aMSH), which activates its post-synaptic targets and produces anorexigenic effects like satiation and increased energy expenditure (Abdalla, 2017). POMC can also be cleaved into beta-endorphins, which self-regulate POMC neuron activity by

activating post-synaptic neurons responsible for generating inhibitory feedback signals to the POMC neurons (Abdalla, 2017); an inhibitory feedback loop.

Other hypothalamic nuclei also play important roles in controlling food intake. For example, the paraventricular nucleus (PVN)_ is an anorexigenic hypothalamic nucleus which regulates the autonomic nervous system and neuroendocrine system by controlling hormone release from the anterior and posterior pituitary gland (Hill et al., 2012). The ventromedial hypothalamus (VMH) is anorexigenic and regulates food-seeking/avoiding behaviours by regulating the sympathetic nervous system (Khodai et al., 2021; Viskaitis et al., 2017). The dorsomedial hypothalamus (DMH) is thought to promote orexigenic states, as it has several inhibitory projections to POMC neurons (Bi et al., 2012; Rau et al., 2019). Lastly, the lateral hypothalamic area (LHA) plays both anorexigenic and orexigenic roles (Lee et al., 2021). It contains two subsets of neurons, melanin concentrating hormone neurons and orexin neurons, which are important in prolonging food intake/initiating food metabolism and generating responses relevant to acquiring food, respectively (Lee et al., 2021). The LHA is heavily connected to reward systems, which will be explored in section 1.2.4 (Stuber & Wise, 2016). See **Figure 1** for a schematic representation of the hypothalamic nuclei.

Figure 1. *Hypothalamic Nuclei*



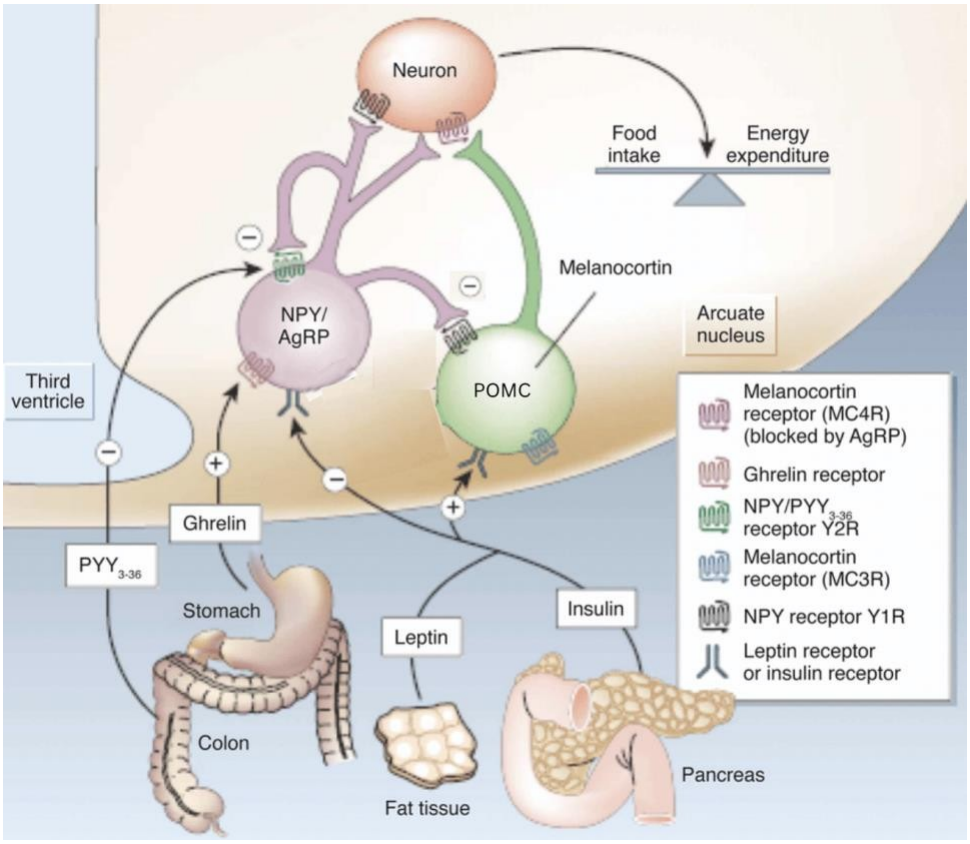
Note. Edited image taken from Wang et al. (2025)

During food consumption/satiated states, circulating insulin, leptin, and GI hormones, like GLP-1 and PYY, inhibit NPY/AgRP neurons and activate POMC neurons (Abdalla, 2017). Additionally, the nucleus of the solitary tract, a nucleus in the brainstem, receives vagal input from the GI tract, which carries information about luminal/gastric distension, nutritional content, and more, to activate POMC neurons (Schneeberger et al., 2021). POMC neurons then project primarily to the PVN, VMH, and LHA to promote an anorexigenic state: satiation and increased energy expenditure (Primeaux et al., 2021).

In fasting conditions, when energy is limited, circulating levels of insulin, leptin, and gastrointestinal hormones decrease. Since these signals normally exert inhibitory effects on NPY neurons, their reduction leads to disinhibition of NPY activity (Timper & Brüning, 2017). Simultaneously, ghrelin levels rise in response to the absence of food intake, directly stimulating NPY neurons (Austin & Marks, 2009). Once engaged, NPY/AgRP neurons suppress anorexigenic

POMC neurons in the ARC and extend projections to multiple hypothalamic nuclei, including the PVN as the primary target, along with the VMH, DMH, and LHA, mediating hunger and food-seeking behaviours (Primeaux et al., 2021; Timper & Brüning, 2017). A simplified depiction of the NPY/POMC dynamic in the homeostatic control of food intake is presented in **Figure 2**.

Figure 2. *Hypothalamic Control of Food Intake*



Note. Edited image from Lizarbe et al., 2013. NPY: Neuropeptide Y; AgRP: Agouti-related Peptide; POMC: Proopiomelanocortin; PYY: Peptide Tyrosine Tyrosine

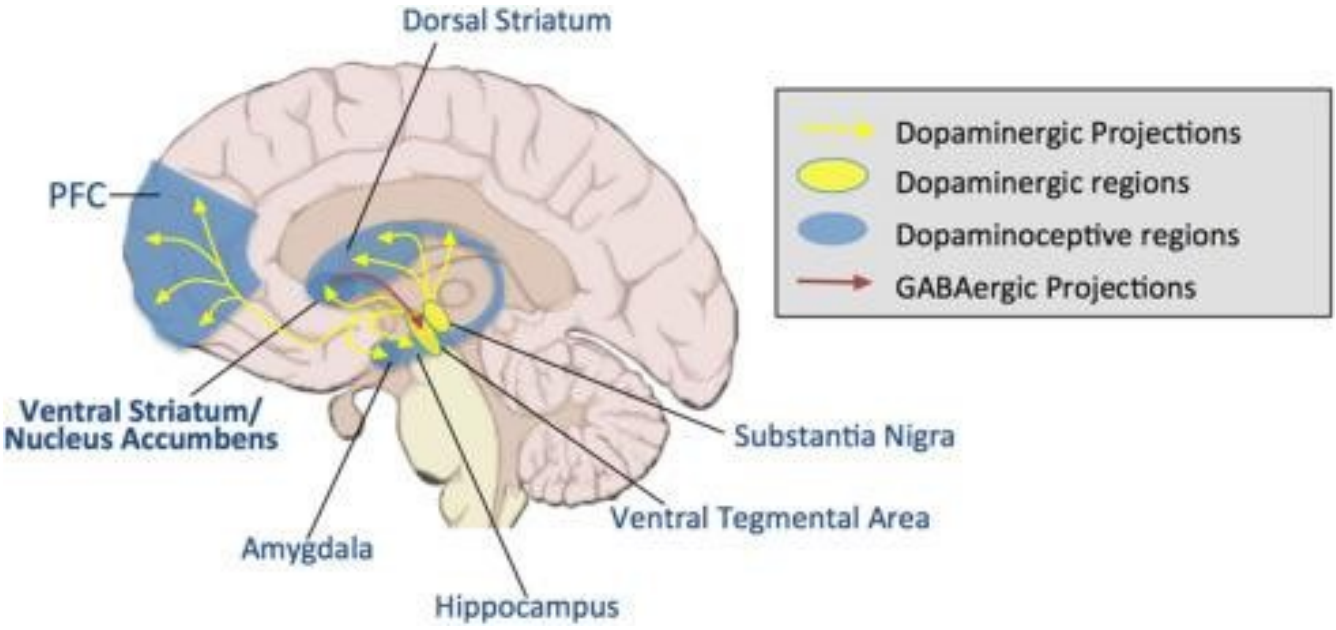
1.2.4 Hedonic Control of Food Intake

Hedonic control of food intake is driven by pleasure and reward, relying heavily on mesolimbic systems in the brain, which can drive food intake even in the absence of an energetic requirement (Volkow et al., 2011). Ultimately, it begins with sensory mechanisms, particularly sight, taste, and smell (Saper et al., 2002). Preclinical work has found that animals will consume sweet and salty foods past homeostatic requirements, while a food-deprived animal will avoid sour or bitter foods as they might indicate toxicity or spoilage (Saper et al., 2002). Food-related conditioning is highly adaptive, where strong associations can be formed between stimulus (food) and reward (as an experience), suggesting potent and plastic neural circuitry encoding sensory systems and hedonic value of food (Saper et al., 2002; Volkow et al., 2011). Once conditioning has taken place, the sight of food alone can provide information about flavour and palatability, and cues can activate brain areas related to reward, facilitating the desire to eat (Wadhera et al., 2014).

Reward and motivation have predominantly been studied in drug addiction, i.e. rewards with no homeostatic benefit (Saper et al., 2002). However, several studies have suggested that foods and drugs may share similar reward-based neural substrates, namely, the mesolimbic reward pathways (Lutter et al., 2009; Saper et al., 2002). This pathway involves the release and projection of dopamine (DA) from the ventral tegmental area (VTA) and striatum to the hypothalamus, orbitofrontal cortex (OFC), prefrontal cortex (PFC), amygdala, hippocampus, dorsal striatum (DS), and more (**Figure 3**; Serafini et al., 2021; Lutter et al., 2009; Volkow et al., 2011). When exposed to the taste of a new or unexpected food reward, DA is released in the DS (in proportion to self-reported pleasure from consuming the food), ventral striatum/nucleus accumbens (NAc), and VTA (Volkow et al., 2011). With repeated exposure to the same cue, DA

release habituates and shifts from taste to other sensory features associated with the cue, like smell or sight (Lutter et al., 2009; Volkow et al., 2011). As such, DA release can be a predictor of reward (a conditioned response) (Schultz, 2016) and has been associated with motivational saliency towards food cues, i.e. "wanting food" (Scczypka et al., 1999). Glutamatergic afferents to DA neurons from sensory (insula, operculum), homeostasis (hypothalamus), reward (NAc, OFC), and memory/emotion-related regions (hippocampus, amygdala) all contribute to the formation of these condition responses, leading to large-scale network-based responses to rewards (Volkow et al., 2011). Opioid signalling through the basolateral amygdala has also been shown to encode (but not retrieve) short-term and long-term incentive value, or "wanting" of rewarding foods in mice (Wassum et al., 2009). The "liking" of food, however, has been suggested to depend on opioid and GABAergic systems involving the ventral pallidum (Volkow et al., 2011). Further, peripheral peptides involved in homeostatic regulation can also mediate reward effects. For example, leptin, insulin, ghrelin, PYY, and more, can interact with DA neurons/signalling across the VTA, NAc, PFC, amygdala, and hippocampus, i.e., mesolimbic regions (Volkow et al., 2011). Additionally, insulin and leptin, elevated during fed/high-energy states, have been shown to attenuate reward responses to food stimuli in healthy individuals, potentially reducing hedonic drives to consume food (Volkow et al., 2011). Overall, dopamine and opioid signalling through the mesolimbic system mediates reward responses to food cues, including encoding "wanting" and "liking" of food cues.

Figure 3. *Mesolimbic Reward System*



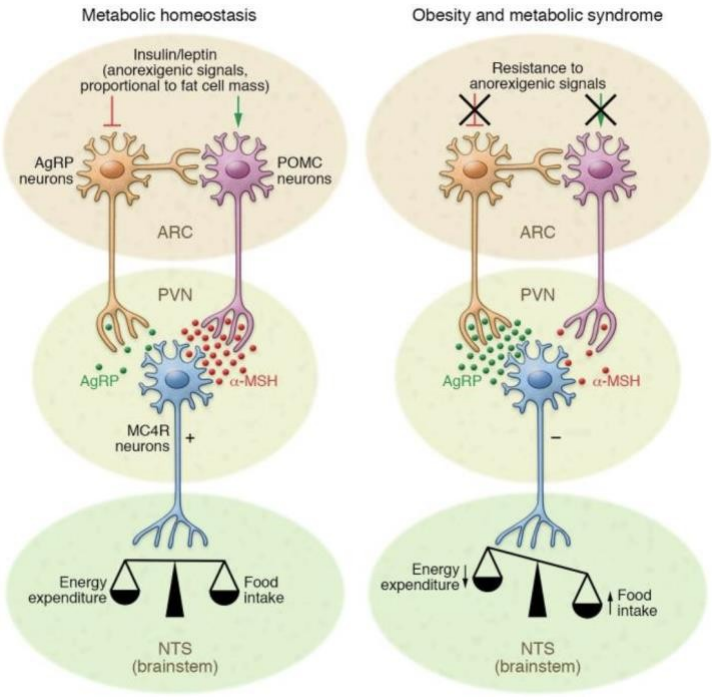
Note. Image taken from Telzer (2016)

1.2.5 Control of Food Intake and Obesity

Brain and body systems controlling food intake become considerably dysregulated in obesity. First, there is a disruption in peripheral signalling to the brain. For example, increased amounts of adipose tissue (associated with obesity) increase circulating leptin (Abdalla et al., 2017); in turn, leptin resistance develops, and its transport across the BBB becomes less efficient (Abdalla et al., 2017). Excessive amounts of adipose tissue also stimulate adipocyte release of inflammatory cytokines, including interleukin and tumour necrosis factor-α (Ellulu et al., 2016). These cytokines promote a pro-inflammatory state, which can alter lipid and glucose metabolism, promote insulin resistance, and affect brain structure and function (Ellulu et al., 2016; Jais & Brüning, 2017). Indeed, preclinical work indicates that high-fat diets can also activate hypothalamic microglia to produce pro-inflammatory cytokines, which can dysregulate metabolic homeostasis and hypothalamic signalling (Jais & Brüning, 2017). Resistance to both

leptin and insulin in obesity is thought to increase the activation of orexigenic neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons in the hypothalamus, which, in turn, is associated with hunger and food-seeking behaviours (**Figure 4**).

Figure 4. *Homeostatic Control of Food Intake in Metabolic Homeostasis and Obesity*



Note. Image taken from Jais & Brüning, 2017. AgRP: Agouti-related Peptide; POMC: Proopiomelanocortin; ARC: Arcuate nucleus; PVN: Paraventricular Nucleus; a-MSH: Alpha Melanocyte Stimulating Hormone; MC4R: Melanocortin Receptor 4; NTS: Nucleus of the Solitary Tract

Brain Effects of Obesity

As described, exposure to excess nutrients and fat/calorie-dense foods over long-term periods considerably impairs the proper functioning of the hypothalamus. Hypothalamic disruption and whole-brain neuroinflammation are thought to contribute to brain-wide neural atrophy. Several neuroimaging studies have identified negative correlations between BMI and

white matter/grey matter volume in various regions (e.g. insula, middle frontal gyri, amygdala, precuneus, brain stem, and corpus callosum; Gómez-Apo et al., 2021). Aspects of the reward system are also disrupted in individuals with obesity. Specifically, reductions in striatal DA receptors have been noted and might contribute to a disruption of reward processing (Volkow et al., 2008). Details on brain activity alterations in obesity (likely due to these structural and neurochemical changes) are discussed below (Moyse et al., 2022).

1.3 Obesity and Brain Activity

1.3.1 Overview

Functional magnetic resonance imaging (fMRI) has aided us in understanding brain features in obesity (Drelich-Zbroja et al., 2022). fMRI relies on the blood oxygen level-dependent (BOLD) signal, which uses strong magnets to detect changes in diamagnetic oxygenated blood from paramagnetic deoxygenated blood. This reflects localized changes in blood flow, coupled to underlying neuronal activity (neurovascular coupling) (Hillman, 2014). In-scanner tasks can target specific reward and cognitive processes known to rely on activity in specific regions; such tasks can be used to compare brain activity between different task conditions (e.g., different types of cues) or between different population groups (like healthy weight vs. obese) to gain insight into food reward processing and obesity brain activity correlates.

Dopaminergic-mediated habituation to reward shifts sensations of pleasure derived from taste to smell and sight alone (Volkow et al., 2011; Schultz, 2016). When a rewarding food is consumed for the first time, its taste acts as an unconditioned stimulus that naturally elicits reward responses; however, with repeated exposure, cues such as the sight and smell of the food become conditioned stimuli that can trigger anticipatory reward responses, potentially driving

overconsumption (Volkow et al., 2011). Passive viewing of a food cue alone is sufficient in generating physiological and neurological responses, facilitating food consumption (see section 1.2.4; Wadhera et al., 2014). Therefore, food cues serve as a suitable fMRI task stimulus for examining how obesity might influence brain activity and whether these effects are altered during weight-loss interventions.

1.3.2 fMRI Neural Reward Responses

A primary focus of this thesis is to measure reward-related brain activity responses to food cues in participants with obesity. As outlined, passively viewing food cues induces physiological arousal (increased salivation), anticipated pleasure of consuming food, and motivation to consume food (Boswell, et al. 2016; Berridge, et al. 2009; Morewedge, et al., 2010). Brain areas involved in these reward-based processes include the ventral striatum/NAc, OFC, VTA, insula, amygdala, gustatory cortex, and somatosensory cortex (Giuliani et al., 2018). More specifically, the ventral striatum has been shown to encode food-related reward value and hedonic aspects of food consumption (Giuliani et al., 2018). The OFC plays a critical role in integrating sensory information, evaluating predicted vs. received reward, and modulating reward-related behaviours (Giuliani et al., 2018). Other areas, like the VTA, insula, and amygdala, are also important structures in the mesolimbic reward system, which play an important role in food-cue reactivity (Giuliani et al., 2018).

In healthy-weight individuals, many of these regions are activated in response to food cues. For example, Schur et al. (2009) noted that the insula, hypothalamus, and striatum were significantly more active when viewing fattening food cues vs. non-fattening or non-food images. Further, in Yang et al.'s (2021) meta-analysis, they identified that across 39 studies,

viewing high-calorie food cues elicited activity in the bilateral insula and OFC, among other regions. Interestingly, another group identified that activity in the OFC, insula, amygdala, and NAc when viewing fattening foods was associated with increased carbohydrate consumption post-scan in an ad libitum buffet (Mehta et al., 2012). Activity in the amygdala and OFC was positively correlated with hunger (i.e. increased hunger led to more activity and greater carbohydrate consumption; Mehta et al., 2012). Overall, reward regions are active in healthy individuals when viewing food cues, promoting food consumption.

The effects of obesity on fMRI-indexed neural activity during the viewing of food cues are mixed. For example, a meta-analysis including 60 studies by Pursey et al. (2014) identified increased activity in the OFC, insula, and amygdala, among others, in obese vs. healthy-weight participants when viewing food cues. However, this group failed to identify the contrasts in which these results were obtained (food vs. neutral cue or vice versa), and they did not include results where activity was greater in lean individuals or equal between the two. Regardless, several other studies have also identified similar results, with greater activity to food cues in the insula (Stoeckel et al., 2008; Martin et al., 2010; Oltmanns et al., 2012, Luo et al.'s 2013), caudate (Rothemund et al., 2007; Stoeckel et al., 2008; Nummenmaa et al., 2012), OFC, amygdala, NAcc, anterior cingulate cortex (ACC), pallidum, putamen, hippocampus and more (Rothemund et al., 2007; Stoeckel et al., 2008; Martin et al., 2010; Oltmanns et al., 2012), in obese vs. lean individuals. Next, some studies have identified blunted responses to rewards in obese vs. lean individuals. Decreased activity in the anterior cingulate, lingual and superior occipital gyri (Heni et al., 2014), superior frontal gyrus (Nummenmaa et al., 2012), precentral gyrus, cingulate gyrus, dlPFC (Dimitropoulos et al., 2012) and more was observed in obese vs. lean individuals when viewing food cues. Additionally, Stice et al. (2008) identified decreased activity in the dorsal striatum in

obese vs. lean individuals upon receipt of a chocolate milkshake (vs. a tasteless solution), perhaps reflecting blunted reward processing. Lastly, in their meta-analysis, Morys et al. (2020) highlighted these inconsistencies and examined differences in brain activity between obese and lean individuals during passive food viewing; they did not identify any evidence for altered cue processing in obesity. A few theories exist to support the existing (albeit mixed) literature, suggesting that varying degrees of reward sensitivity may be relevant to understanding differences in brain activity between people with and without obesity.

Reward Sensitivity

As discussed in section 1.2.4, DA responses in the mesolimbic reward system are initially pronounced when tasting a novel rewarding food. With repeated exposure, DA release shifts from the taste itself to anticipatory cues such as sight and smell, a process known as reward conditioning. Once conditioning occurs, these cues can independently trigger DA release, driving reward-seeking behaviour. Stice & Burger (2019) have developed several theories of obesity, each supporting existing literature. First, their *incentive sensitization model* of obesity argues that as overweight/obesity progresses, the DA shift becomes exaggerated: taste-induced DA responses are blunted due to habituation, while cue-induced responses remain strong, creating an imbalance that promotes overeating (Stice & Burger, 2019; Sutton et al., 2022). Next, their *reward surfeit theory* of obesity instead suggests that individuals prone to obesity may simply be more sensitized to food cues, such that these cues evoke an unusually strong DA response regardless of changes in taste processing (Stice & Burger, 2019; Sutton et al., 2022). It is feasible that increased reward sensitivity might be true as a risk factor for obesity and that blunted reward processing may evolve with time and continued exposure to rewarding cues. The behavioural approach system (BAS) is

a neuropsychological theory of personality measuring motivation/approach behaviours towards biological reinforcers and rewards, reflecting reward sensitivity. High BAS individuals may be more motivated to seek out palatable foods and related cues in their environment, potentially leading to greater consumption of such foods and excess energy intake (Sutton et al., 2022), i.e., they might be at a greater risk for obesity.

Carver et al. (1994) developed the Behavioural Inhibition System and Behavioural Approach System (BIS/BAS) scales to capture reward sensitivity (BAS) and punishment sensitivity (BIS). The scale also consists of three BAS subscales to help encompass different behaviours mediated by reward sensitivity: BAS-**Reward Responsiveness (**BAS-R), BAS-**Drive** (BAS-D), and BAS-**Fun Seeking** (BAS-F). BAS-R reflects the anticipation of receiving a reward and how much pleasure one would feel from receiving the reward. BAS-D represents motivation to approach familiar rewarding stimuli, and BAS-F reflects motivation and impulsivity in seeking novel rewards and experiences. Increased reward sensitivity, measured through these scales, has correlated with increased activity in reward regions. For example, Beaver et al. (2006) identified that BAS-D scores were positively correlated to activity in the ventral striatum, NAc, amygdala, and OFC in 12 healthy individuals when viewing appetizing food cues vs. non-food control cues. Self-reported reward sensitivity has been positively correlated with body weight in humans, with obese individuals generally displaying greater reward sensitivity than lean individuals (Davis et al., 2004; Franken and Muris, 2005). In obesity, increased reward sensitivity may reflect increased activity in reward regions like the insula or OFC, but a decrease in activity in the dorsal striatum. For example, women who gained weight over 6 months had decreased activity in the dorsal striatum when viewing palatable food cues compared to women who did not gain weight (Stice et al., 2010).

Overall, one unifying framework reconciling some of the discrepant findings is Stice & Burger's (2019) *dynamic vulnerability theory of obesity*, which combines aspects of the previously mentioned theories. Here, Stice & Burger (2019) propose that both baseline and conditioned reward responses (reward surfeit theory and incentive sensitization theory) predispose individuals to overweight and obesity. In individuals with obesity (with increased reward sensitivity), corticolimbic regions involved in anticipating and seeking familiar food rewards (e.g., insula and OFC) may become hyperactive, while striatal regions mediating the hedonic experience of eating may become progressively less responsive due to blunted DA receptors/release in this region (reward desensitization; Kenny, 2011). This shift, characterized by heightened motivational value but diminished hedonic value of palatable food, may synergistically drive persistent overconsumption. While further research is required, Carver et al.'s (1994) BAS scales might provide greater insight into the effects of different motivation systems and relations with brain activity in healthy-weight vs. obese individuals.

1.3.3 fMRI Inhibitory Control Responses

Impulsivity and inhibitory control are also thought to be altered in obesity. Impulsivity involves rapid and unplanned reactions to desired stimuli, without consideration of potential consequences for oneself or others (Jasinska et al., 2012). Impulsivity can arise from decreased inhibitory control, which refers to the capacity to inhibit or suppress responses that are unnecessary, inappropriate, or incompatible with current goals (Jasinska et al., 2012). Reduced inhibitory control and heightened impulsivity are correlated with overeating and binge eating; further, individuals with these traits are more prone to being overweight and obese (Jasinska et al., 2012). fMRI research has explored the role that regions involved in cognitive/inhibitory

control play in obesity (Giuliani et al. 2018). The dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), inferior frontal gyrus (IFG), posterior parietal cortex (PPC), and dorsal anterior cingulate cortex (dACC) all contributed to regulating cognitive control of food intake (Giuliani et al. 2018). For example, obese adults have been shown to have blunted activity in the dlPFC when viewing food cues compared to lean men and women (Le et al., 2007; Le et al., 2006). Another study showed decreased activity to food cues in the IFG in first-year university students not coached on eating habits and physical exercise, compared to students who were (Stice et al., 2015). Thus, there is some evidence suggesting that increased activity in these regions to food cues might be associated with increased ability to regulate cravings and impulses towards food consumption (Stice et al., 2015; Farr et al., 2016; Giuliani et al. 2018).

1.4 Treatments for Obesity

1.4.1 Overview

Several intervention options are available for managing obesity, including dietary restriction, increased physical activity, weight-loss medications, bariatric surgery, and cognitive behavioural therapy (or a combination of all of these) (Baker et al., 2022). Lifestyle modifications, including dietary and exercise adjustments, are often the first-line treatment option for people with obesity (Kloock et al., 2023). While this strategy is effective in the short-term, in the long-term, lifestyle modification interventions often lead to weight regain, even if the patient remains on the intervention (Hall et al., 2018; Baker et al., 2022). Behavioural changes and cognitive therapy can supplement lifestyle interventions, encouraging patients to focus on behaviour and cognitive aspects of food consumption (e.g., stress/emotional eating, negative body image, low self-esteem,

etc.; Baker et al., 2022). Several pharmaceutical options also exist, which will be detailed below (section 1.4.3). Bariatric surgery is generally a last-resort option for obesity treatment (Gulinac et al., 2023). However, patients who received bariatric surgery often continue to experience weight regain, some regaining over 70% of the weight lost (King et al., 202; Lauti et al, 2016). As such, better treatment options for obesity continue to be a priority.

1.4.2 Dietary Interventions

While there is no universal diet that suits everyone, a balanced diet will target macronutrient (fat, carbohydrates, and protein are the three primary macronutrients) intake to regulate energy balance, satiety, appetite, and insulin resistance (Parmar & Can, 2023). For example, low-fat diets suggest that low-fat intake may prevent cardiovascular risk (Parmar & Can, 2023); though many other diets/nutrient management strategies exist (e.g., intermittent fasting or meal replacement options). Generally, obese individuals are often advised to follow a low-calorie and low-carbohydrate diet, and to increase energy expenditure through exercise (Kloock, et al., 2023). Low-calorie diets are personalized but often range from daily caloric intakes of 1000 to 1500 kcal/day (Parmar & Can, 2023). Very low-calorie diets (800 to 1000 kcal/day, or lower) are designed to target extreme weight loss but are generally not recommended (Parmar & Can, 2023). As mentioned, most studies suggest that a majority of weight lost will be regained within five years following dietary interventions, which has been explained by decreases in metabolic activity during caloric restriction (Hall et al., 2018; Baker et al., 2022). After the desired weight has been lost and the individual resumes normal eating habits, metabolic activity remains low, resulting in weight regain (Baker et al. 2022). As a result, weight management can be extremely discouraging (Hall et al., 2018).

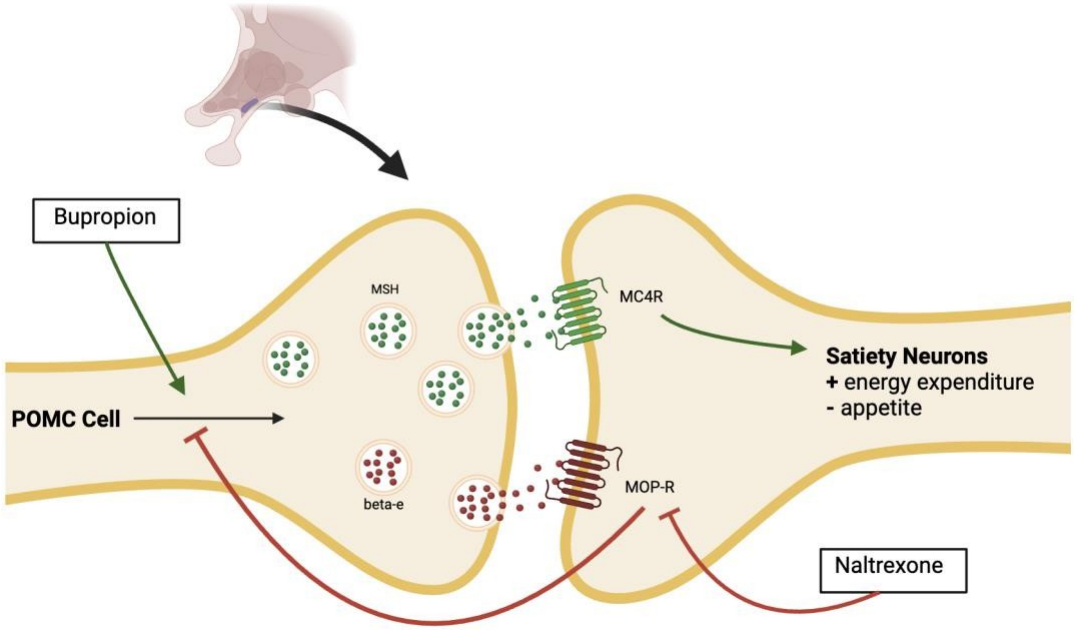
Briefly, brain reactivity to food cues can predict dietary and lifestyle intervention success. In their meta-analysis, Pursey et al. (2014) reviewed three studies which included nutrition/lifestyle weight-loss interventions. They observed that those with increased baseline activity in areas associated with reward processing (insula, OFC, NAc, and anterior cingulate cortex (ACC)) were least successful in losing weight (Pursey et al., 2014). McCaffery et al. (2009) compared differences in brain activity to food cues between normal-weight, obese individuals, and individuals who had successfully lost weight through lifestyle intervention (and maintained the loss over 3 years). They identified increased activity in the superior and middle frontal gyri, insula, and cuneus, among others, when viewing food cues in those who lost weight compared to obese individuals (McCaffery et al., 2009). The ACC was the only region with greater activity in obese vs. those who lost weight (when viewing food cues). Normal-weight individuals displayed greater activity in the cingulate and superior parietal region when viewing food cues compared to those who lost weight, and in the precuneus, superior frontal, and superior temporal regions compared to obese participants (McCaffery et al., 2009). These results suggest that baseline brain activity to viewing food cues might provide insight into intervention outcomes.

1.4.3 Pharmacological Interventions

Pharmacological interventions for obesity are an increasingly popular option, with four Health Canada-approved options approved to date (Olivieri et al., 2024): semaglutide, liraglutide, naltrexone/bupropion, and orlistat. Weight-loss drugs generally aim to promote satiety via different mechanisms. Orlistat, for example, is an intestinal lipase inhibitor, reducing fat absorption by up to 30% (Tchang et al., 2021). Others, like semaglutide and liraglutide, are GLP-1 receptor agonists (see section 1.2.2) which promote anorexigenic neural activity and satiety.

Since its approval by the FDA in 2014, **Contrave® (Naltrexone 32mg/Bupropion 360mg)** has become one of the first-line pharmacological interventions for obesity. *Contrave* ® contains two active components: naltrexone, a μ-opioid receptor antagonist, and bupropion, a weak dopamine and norepinephrine reuptake inhibitor (Sherman et al., 2016). *In vitro*, bupropion was found to enhance the activity of the anorexigenic proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus, thus increasing the production of alpha melanocyte-stimulating hormone (aMSH) and beta-endorphins (Sherman et al., 2016). aMSH binds to post-synaptic targets to decrease food intake and increase energy expenditure. As such, bupropion is thought to produce desired satiation effects via increased aMSH production. However, increased POMC activity also promotes inhibitory feedback via increased beta-endorphin production. As such, naltrexone complements bupropion's action by blocking the beta-endorphin postsynaptic targets, mu-opioid receptors (MOP-R), preventing beta-endorphin-induced inhibitory feedback on POMC cells (Sherman et al., 2016). A combination of these active ingredients was thus proposed to reduce food intake and increase weight loss *in vivo*, which was indeed observed in preclinical studies and in human clinical trials (Sherman et al., 2016; Greenway et al., 2010). Please refer to **Figure 5** below.

Figure 5. *Contrave ®Mechanism of Action*



Note. POMC: Proopiomelanocortin; MSH: Melanocyte Stimulating Hormone; Beta-e: Beta-endorphin; MC4R: Melanocortin Receptor 4; MOP-R: Mu-Opioid Receptor

The hypothalamus is heavily connected with regions involved in reward processing, including the VTA, striatum/NAc, and amygdala, which help mediate hedonic aspects of food consumption (Lee et al., 2021; Schneeberger et al., 2014). In turn, these reward areas also send and receive signals to cognitive/inhibitory control areas (i.e., dlPFC, vlPFC, IFC, PPC, dACC; Timper & Brüning, 2017; Kober et al., 2010). Since Contrave® acts by altering hypothalamic activity in individuals with obesity (by promoting POMC activity), it is feasible that this may affect brain regions downstream of hypothalamic targets. Research in rodents has suggested that weight-lowering drugs may increase activation across areas and circuits involved in the homeostatic control of eating and feeding reward, including the hypothalamus, brainstem, cortex,

striatum/NAcc, amygdala, and others (Hansen et al., 2021; Gabery et al., 2020). One meta-analysis explored the effects of anti-obesity drugs on food cue reactivity across 24 studies and identified that anti-obesity medications (as a whole) reduced activity in the right claustrum and insula (Yeung, 2021). However, most of these studies were conducted with healthy-weight individuals, and they included 20 different anti-obesity drugs (Yeung, 2021). Only one study included in the meta-analysis, and the only study to our knowledge to explore the effects of Contrave® on brain activity, administered Contrave® or placebo to obese women for 4 weeks and compared brain activity before and after the intervention (Wang et al., 2014). This group revealed that a 4-week Contrave® intervention increased activity in the superior parietal, posterior insular, superior frontal, dACC, hippocampal regions and decreased activity in the hypothalamus when viewing a food-video paradigm compared to placebo-treated controls (Wang et al., 2014). This is in contrast to the effects of lorcaserin, another weight loss medication, where decreased activity in brain areas related to attention (parietal and visual cortices) and emotion processing (insula and amygdala) when looking at food-cues was observed, suggesting that lorcaserin may induce its weight-loss effects by decreasing emotional and attentional activity when looking at food (Farr al., 2016). Apart from these studies, there has been very little work assessing the effects of pharmacological interventions in obese people when viewing food cues; existing data suggest potentially different consequences on neural profiles in obesity based on drug intervention.

To our knowledge, no study has explored the effects of Contrave® with a dietary intervention on brain activity in obese individuals. Considering that this medication has been on the market in Canada for over 10 years, a better understanding of this drug's effects on brain

activity might aid in improving patient care and its clinical use, as well as provide greater insight into the neural consequences of obesity.

1.5 Objectives and Hypotheses

1.5.1 Study Objectives

The overarching objective of this study was to assess brain activity in individuals with obesity before and after a weight-loss intervention. This study used a food-cue task to assess BOLD responses, i.e. brain activity, in participants with obesity, before and after a 4-week Contrave® (or placebo) coupled with a dietary intervention. During baseline and post-intervention fMRI scans, participants were shown images of high-calorie (HC), low-calorie (LC), and neutral-control (NC) non-food items and were asked to rate the appeal of each image on a scale of 1-8 (see Chapter 2 for more details).

The primary objective of this study was to assess neural responses to HC, LC, and NC food cues prior to the intervention. Neural responses to food cues were analyzed at the whole-brain level and in predetermined regions of interest (ROI): the bilateral insula and orbitofrontal cortex (OFC). Analyses were also run to determine potential associations between baseline neural responses to food cues and cue ratings as well as Behavioural Approach System (BAS) scores.

This study's exploratory objectives were to assess changes in neural responses to food cues following a diet/drug intervention, across the whole brain, as well as in our predetermined ROIs. Analyses were also run to determine potential associations between change in brain activity pre vs. post intervention with changes in food cue ratings/BAS scores.

1.5.2 Primary Hypotheses

First, we assessed different cue types (HC, LC, and NC) on BOLD responses across the brain, and within predetermined ROIs, in people with obesity. ROIs were taken from Luo et al.'s

(2013) study, which employed a comparable food-cue task in which females with obesity viewed images of high-calorie, low-calorie, and neutral control foods. We expected whole-brain analyses to reveal increased activity in reward (e.g., amygdala, hippocampus, VTA) when viewing HC or all FC vs. NC cues. Additionally, due to potentially blunted activity in obese individuals when viewing food cues in superior frontal as well as superior parietal regions, we predicted no difference in activity for HC vs. LC, or FC vs. NC cues. Finally, while data are mixed, we expected participants to show increased BOLD responses in the OFC and insula (our pre-selected regions of interest [ROIs]) when viewing HC or all food cues (FC) vs. NC cues

Next, we explored potential relationships between BOLD responses to food cues and conscious appraisal of appeal for these cues, measured through participant cue ratings (the 1-8 Likert scale). We expected that HC would be rated as being most appealing, and NC would be rated as having the least appeal. Second, we assessed the association between BOLD activity and behavioural/appeal rating. Generally, whole-brain analyses were conducted to explore potential associations in brain regions related to reward-processing (amygdala, hippocampus, VTA) and inhibitory control (dlPFC, vmPFC). We then expected to see positive associations in brain activity in our predetermined ROIs (bilateral OFC and insula) and appeal ratings for the HC/FC>NC conditions.

Lastly, we assessed relations between BOLD responses (HC/FC > NC cues) to food cues and BAS scale sub-scores (BAS-R, BAS-D, BAS-F), which tap into reward sensitivity. Whole-brain analyses were first conducted to assess potential associations between BAS scores and activity in reward regions across the brain (including amygdala, VTA, striatum, hippocampus, etc.), where we expected to identify positive associations. Next, we expected positive associations between brain activity in our predetermined ROIs and BAS-D/BAS-R scores since

our task paradigm is most relevant to these two scales (receiving and seeking reward). In contrast, we did not anticipate associations with BAS-F, as this scale reflects impulsivity and novel rewards.

1.5.3 Exploratory Hypotheses

Exploratory objectives explored BOLD responses in participants with obesity, after a 4-week Contrave® (or placebo) and dietary intervention; considering our small sample, subgroup analyses (i.e., Contrave® vs. placebo) were not conducted. Considering that all participants completed a dietary intervention, we expected to see changes in post-intervention data compared to baseline.

First, we explored BOLD responses to food cues between baseline and post-intervention fMRI scans. Performing whole-brain analyses, we expected decreased activity in reward-related regions, like the amygdala and hippocampus. Here, we also predicted that the intervention might lead to increases in BOLD responses in regions including the superior frontal and superior parietal cortex, as well as the dorsolateral prefrontal cortex (dlPFC). When viewing HC/FC vs. NC cues, we also expected to see a decrease in activity in our ROIs (insula and OFC).

Second, we explored appeal ratings and whether changes in these ratings were related to changes in BOLD activity. First, we expected decreased HC ratings and potentially higher LC ratings post- vs. pre-intervention (i.e., diminished difference between HC vs. LC). Second, we expected that people with larger decreases in ratings of HC or FC cues (relative to neutral) would show greater decreases in activation in our ROIs and other reward regions (i.e., positive correlation). Conversely, we expected a negative association in areas related to cognitive control (like the dlPFC).

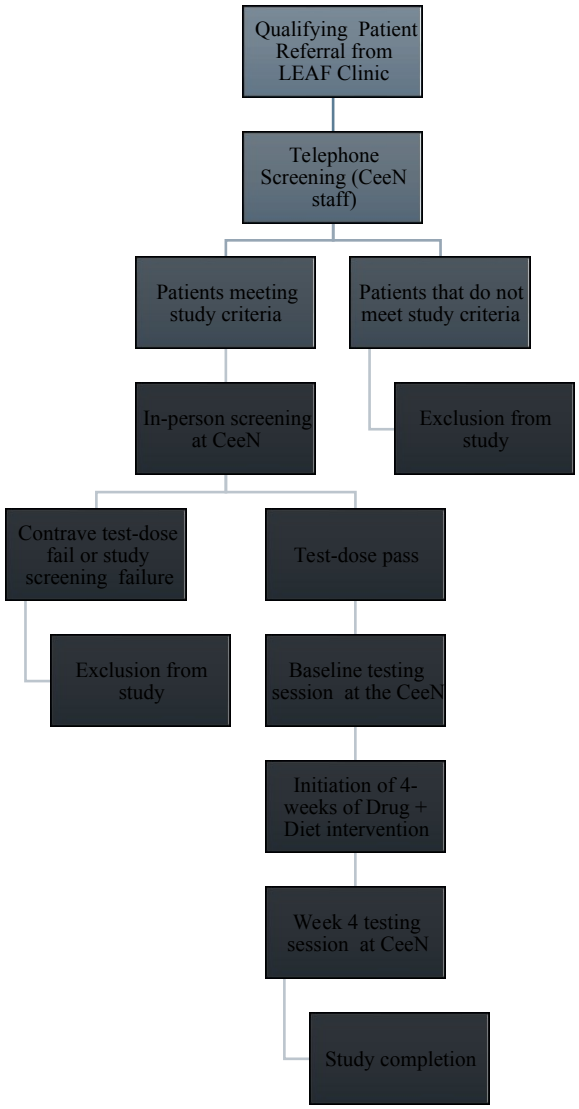
Lastly, we explored potential associations between BAS scores and changes in BOLD responses (post vs. pre-intervention). For reward-related regions such as the OFC and insula, we expected overall decreases in activity from pre- to post-intervention. We hypothesized that individuals with higher reward sensitivity (those scoring high on BAS-R and BAS-D) would show larger activity decreases in these regions, resulting in a negative correlation between BAS-R/D scores and BOLD change (as our fMRI contrast was defined as post vs pre). For BAS-F, we predicted a positive association with dlPFC and superior frontal activity: individuals with higher BAS-F scores might exhibit increased recruitment of these regions post-intervention (vs. pre-), reflecting enhanced cognitive control in those with greater food-related impulsivity.

Chapter 2: Methods

2.1 Study Overview

This thesis is part of a larger study assessing the effects of Contrave® vs. placebo (coupled with a dietary intervention) on the body and the brain. Brain-related measures were collected at The Royal Ottawa Mental Health Centre (ROMHC), including MRI, fMRI, and electroencephalography (EEG). Body-related measures (e.g., dual-energy X-ray absorptiometry) were collected in the Doucet Lab at the University of Ottawa campus. This thesis focuses on fMRI data and accompanying behavioural responses (detailed below). The broader study was approved by ROMHC Research Ethics Board (REB#2023004) (**Appendix I**) and the University of Ottawa REB (H-06-23-9364) (**Appendix II**); this study is also registered on clinicaltrials.gov (ID: NCT06809166). In brief, this was a two-arm, randomized, double-blind, placebo-controlled clinical trial (**Supplementary Table 1, Figure 6**).

Figure 6. *Study Flow Chart*



Note. CeeN: Clinical EEG & Neuroimaging Laboratory at the Royal Ottawa Mental Health Centre

2.1.1 Participants

Participants were recruited from the LEAF Weight Management clinic in Ottawa, Ontario. Interested participants were subsequently screened by phone for inclusion and exclusion criteria (**Appendix III**) by members of the CeeN (Clinical EEG & Neuroimaging) laboratory, where testing procedures took place.

2.1.2 Inclusion Criteria & Exclusion Criteria

Participant inclusion criteria included having been approved for weight loss by a clinician at the LEAF clinic, being 18-64 years old, having a body mass index (BMI)>30 kg/m^2, having normal/corrected vision, understanding and speaking English, being able to participate in the study protocol, and having access to a stable internet connection (for dietary consultation and online questionnaire assessments sent via REDCap database; Harris R et al. 2009, Harris R et al. 2019)

Exclusion criteria were having severe depression or history of bipolar disorder or psychotic spectrum disorder (operationalized as having a positive diagnostic on the Mini International Neuropsychiatric Interview version 7.0.0); currently using antidepressants, thyroid medication, or medication that could affect appetite; hypertension; history of cardiac defects or known cardiac condition; diabetes; current or past substance use disorder; history of eating disorder; history of glaucoma; seizure disorders; use of monoamine oxidase inhibitors (within 14 days), pressor agents, coumadin, anticonvulsants, or phenylbutazone, or other bupropion-containing products or CYP2B6 inhibitors; history of thyroid, liver, or renal disease; use of opioids, opioid agonists or partial agonists; currently or planning on becoming pregnant; a known allergy to Contrave® ingredients (lactose); hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption; current use of obesity medication; current attention deficit hyperactive disorder medication use; claustrophobia; inability to lie still; metal in body that cannot be removed. These criteria were used to ascertain that there were no contraindications to the study medication and no contraindications to the biological variables collected (including imaging).

2.1.3 Randomization, Blinding, and Allocation

Eligible participants were invited to participate in an in-person screening at the ROMHC. Group randomization (placebo/Contrave®) was performed before in-person screening by a pharmacist at the ROMHC (using the sealedenvelope.com site on a Windows 11 computer; 2 Contrave®: 1 placebo, as a greater number of dropouts from the Contrave ®-receiving group was expected, due to side effects). Following randomization, participants received their 4-week medication (Contrave® or placebo) from the ROMHC's pharmacy (delivered in blister packs). Weekly dosing increased following titration up to a therapeutic dose of 32mg of naltrexone and 360mg of bupropion (**Table 1**).

Table 1. *Contrave ®Titration Schedule*

Daily Dose	Morning Dose	Evening Dose
Week 1 (8mg Naltrexone/90 mg Bupropion)	1 tablet	None
Week 2 (16mg Naltrexone/180 mg Bupropion)	1 tablet (8mg/90mg)	1 tablet (8mg/90mg)
Week 3 (24mg Naltrexone/270 mg Bupropion)	2 tablets (16mg/180mg)	1 tablet (8mg/90mg)
Week 4 (32mg Naltrexone/360 mg Bupropion)	2 tablets (16mg/180mg)	2 tablets (16mg/180mg)

During the 4-week intervention, registered dieticians at the LEAF clinic were responsible for implementing their BUDS® program, which was the dietary intervention portion of this study. The BUDS® program was a special program offered by the LEAF clinic, which included personalized meal planning and coaching, meal replacements with commercial shakes, and weekly check-ups with a registered dietitian via Zoom. Briefly, the BUDS® program emphasizes a moderate caloric deficit (200–500 kcal) and a focus on whole, minimally processed foods.

2.2 Study Procedures

2.2.1 In-person Screening Session Overview

During this session, participants first completed the informed consent form, MRI safety form, and the National Institute of Health's (NIH) neurocognitive battery toolbox (Denboer J. et al., 2014). If any neuropsychiatric concerns were brought up during the telephone screening, we also administered relevant sections of the Mini International Neuropsychiatric Interview during the in-person screening session. Following consenting procedures, participants were brought to the mock scanner at the Brain Imaging Centre (BIC) to ensure that they could fit into the bore of the scanner, and to assess for potential claustrophobia/discomfort that was debilitating and/or interfered with the completion of the study.

Test Dose: The test dose of either Contrave® or placebo was administered before the intervention to ensure tolerability and minimize dropout. The test dose was administered in the CeeN lab along with a light, low-fat snack; subsequently, the participant was free to watch movies/work in the room for 3 hours. During this time, the participants were closely monitored. Specifically, the study clinician monitored side-effects using the Adverse Events Questionnaire (**Appendix IV**) at T=0, T+1h, and T+3h of the test dose administration. Participants who could not tolerate the test dose would be removed from the study. If they could tolerate the test dose, they were provided with their medication (blister packs). Test dose tolerability was determined by the study clinician using the Adverse Events Questionnaire, as well as with patient observation and discussion. 24 hours following the test dose administration, research staff at the CeeN lab contacted participants by phone to ensure no moderate to severe side effects were experienced in that period, and to confirm the participant's interest in study enrollment. Before

baseline testing, participants were required to wait a one-week washout period following test-dose administration.

2.2.2 Testing Sessions and Intervention Overview

Testing procedures for baseline and post-intervention were identical. Participants first arrived at the BIC at the ROMHC for their fMRI scans (see section 2.3.2). Weight and height was collected at the BIC. Once completed, participants completed an EEG session in the CEEN lab (not included in this thesis). During EEG set-up, participants were asked to complete the behavioural inhibition system/behavioural activation system (BIS/BAS) questionnaire (Carver C. et al. 1994), which was used as part of the analyses in this thesis (**Appendix V**); details on analyses are provided in section 2.4. Please refer to (**Supplementary Table 1, Figure 6**) for more information regarding study procedures.

2.3 Measures

2.3.1 Clinical Measures

Weight and height were collected during the in-person screening session, baseline testing session, and post-intervention testing session. BMI was calculated using baseline and post-intervention weight and height, independently. The BIS/BAS questionnaire was administered during the baseline testing session and contains four sections: BAS-Reward Responsiveness (BAS-R), BAS-Drive (BAS-D), BAS-Fun Seeking (BAS-F), and BIS. Each section is scored separately.

2.3.2 fMRI Task Paradigm

For the fMRI component, we used a 3T PET-MR Siemens scanner and a 30-channel head coil. All MRI sessions were run in the morning, between 8 am – 11 am; participants were fasted. The MRI session lasted 45 minutes and contained four sequences: an 8-minute resting state fMRI scan, followed by a 6-minute high-resolution structural multi-echo MPRAGE (MEMPRAGE) scan (van der Kouwe, A. et al. 2008; parameters below), a 12-minute fMRI with an event-design task (detailed below), and, last, an 8-minute neuromelanin scan. For the purposes of this thesis, the fMRI task is the focus; however, the MEMPRAGE images were also used for analyses.

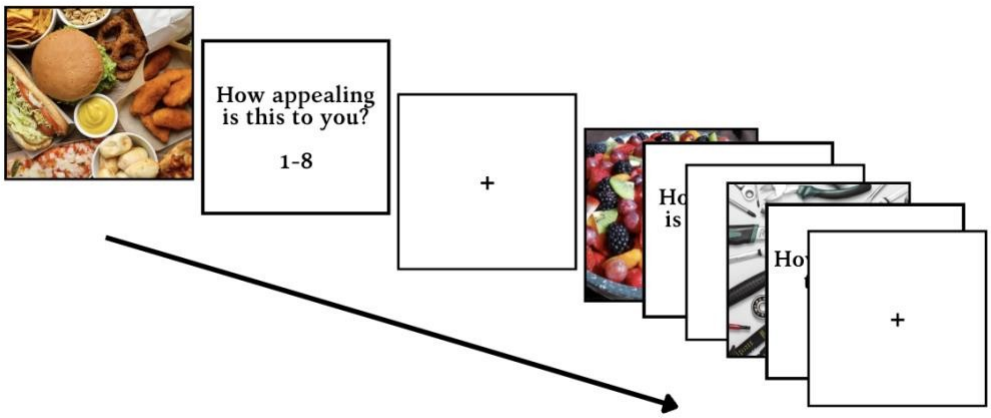
The parameters for the fMRI task were as follows: a T2-weighted echo planar imaging sequence, TR = 1500 ms, TE = 30 ms, 51 slices interleaved, voxel size = $2.5 \times 2.5 \times 2.5mm^3$, multiband acceleration factor=3, 2.5mm slice thickness. The parameters for the MEMPRAGE image were as follows: TE 1 = 1.69ms, TE 2 = 3.55ms, TE 3 = 5.41ms, TE 4 = 7.27ms, TR = 2500 ms, 192 slices interleaved, voxel size = $1 \times 1 \times 1mm^3$, 1mm slice thickness.

The fMRI task included: 1. images of high-calorie (HC) foods, 2. low-calorie (LC) foods, and 3. neutral control (NC) non-food items taken from the food.pics database (Blechert et al., 2019). This task was adapted from work by Weygandt et al. 2019, Chin et al. 2018, and Spetter et al. 2018. The food.pics database contains images of foods with simple figure-ground composition, including high and low-calorie foods, and 315 comparable non-food images. It also contains a master Excel sheet indicating which images are high-calorie and which are low-calorie. Images were chosen based on their high-calorie/low-calorie content. Additionally, we attempted to balance sweet/salty foods and avoid repetition of foods. Non-food items were chosen randomly. See **Appendix VI** for selected images. The task also included a behavioural measure wherein participants were asked to rate how *appealing* they found each image. This

food-cue task was created using E-Prime (version 3.0) software on a Windows 11 Enterprise computer (version 23H2). The task was run at the Brain Imaging Centre on a Windows 10 Pro (version 22H2). Using MR-compatible button response boxes (Current Designs), the participants answered on a Likert scale from 1-8 (1 = not at all appealing, 8 = extremely appealing).

One trial consisted of an image being presented for 2.5s, followed by the question prompt, which lasted 2s. Each trial was separated by an interstimulus interval with a variable duration ranging from 1s to 1.2s (mean of 1.1s) during which time they looked at a fixation cross. There were 40 images per category, for a total of 120 images. See **Figure 7**.

Figure 7. *Event-Design Food-Cue fMRI Task*



2.3.3 Data Preprocessing

Raw task and structural images (i.e., DICOM files) were first downloaded onto a Windows 11 Pro (version 24H2) computer from the Brain Imaging Centre's data portal. Using Statistical Parametric Mapping 12 (SPM12; Wellcome Department of Imaging Neuroscience;

Institute of Neurology, University College of London, London UK) software, which runs on MATLAB (version R2021a Update 8; The MathWorks Inc. (2021)) on a Windows 11 Pro computer, the raw data was converted from .dicom to .nii files, a format compatible with SPM12. An initial quality check was performed where the structural and functional images were manually re-oriented to 0, 0, 0 Montreal Neurological Institute (MNI) coordinates (the anterior commissure – posterior commissure) and assessed for extreme motion, presented as visible striations/distortions in the structural image. Next, preprocessing batches were created and included the following steps: slice timing, realignment, coregistration, segmentation, normalization, and smoothing. First, slice timing ensured that the data was corrected for differences in image acquisition time between each slice. Here, we used the slice count of 51, TR of 1.5, TA of 1.47 (as calculated by TR-(TR/# of slices)), an interleaved (top→down/descending) slice order matrix of [51:-2:1, 51-1:-2:1], and lastly, used slide 25 as the reference image. Next, we realigned the data (estimation and reslice) to remove motion artifacts. Minimizing the number of interpolations, we chose to reslice only the mean image. This step also generated motion/realignment parameters, which were saved as a text file and used for quality control (outlined below). The data was then coregistered (estimation) to combine structural and functional data, using the mean image from the previous step as the reference image, and the structural MEMPRAGE as the "source" image. Following that step, the data was segmented into six different tissue types (grey matter, white matter, cerebrospinal fluid, soft tissue, skull, and other (air or tumours)) to reduce the confounding effects of non-brain (e.g. scalp) structural variability on the registration. This step used the co-registered MEMPRAGE file from the previous step, with the "save bias corrected" and "forward" deformation fields parameters selected. Next, functional scans were normalized, i.e. the scans were aligned to a standard MNI

space using a [2 2 2] mm voxel size. This step used the deformation fields from the previous step to normalize the functional images from the realignment step. Last, the data was smoothed with a default [8 8 8]mm Gaussian kernel, ensuring normal distribution. The structural MEMPRAGE image was then normalized using the deformation field generated above. This step allowed us to perform a second quality check, ensuring that data preprocessing was executed correctly. Specifically, the normalized structural image and a randomly chosen preprocessed functional image were aligned in space and visually inspected (i.e., by comparing the normalized structural image and a preprocessed functional image). If not well aligned, preprocessing was re-run. Additionally, a motion artifact quality check was performed by graphing the translation and rotation motion correction plots (generated from the realignment step); for inclusion in data analyses, translational motion must have been <3mm, and rotational motion <5 degrees. Data that did not meet these criteria were either excluded or preprocessed using fMRIPrep Software (version 24.0.0; Esteban O et al. 2018). This software identifies outlier slices (due to elevated movement artifacts) and creates a confounding file with those outliers. This file will be used in subsequent analyses to remove the outlier slices from the dataset.

Next, 1st first-level general linear model (GLM) analyses were performed to prepare the scans for group-level analysis. Here, the exact onset time of each stimulus was taken from the E-Prime output file to create three averaged conditions per participant per scan. These conditions were the viewing of high-calorie (HC), low-calorie (LC) and neutral control cues (NC). Motion parameters generated during the realignment preprocessing step were also included as a regressor in the model. If applicable, the outlier file generated from fMRIPrep was also included as a regressor in the model (to regress out outlier slices). Next, statistical parametric maps were created to compare the different conditions within one participant at one time point. We created 4

different contrast conditions in SPM for each participant: HC>LC, HC>NC, LC>NC, HC+LC>NC. These contrasts correspond to the 1st level GLM (within participant variability).

2.4 Statistical Analyses

2.4.1 Clinical and Behavioural Analyses

Microsoft® Excel for Mac (Version 16.98) on a MacBook Air was used for analyses in this subsection. Paired t-tests were used to compare whether weight and BMI changed after the intervention.

Paired t-tests were also used to compare participants' ratings of HC, LC, and NC cues. Specifically, an average rating for each HC, LC, and NC cue was generated for each participant at each session. Next, paired t-tests between the average ratings for each participant were performed for HC vs. LC, HC vs. NC, and LC vs. NC to assess differences in how participants rated different food cues. Paired t-tests were also used in exploratory post-intervention analyses to examine pre-to-post changes in cue ratings within each stimulus category. A difference with a $p<0.05$ for all paired t-tests was considered significant.

Correlations were used in Excel to assess for potential similarities between BAS subcategories: BAS-R, BAS-D, and BAS-F scores.

2.4.2 fMRI Whole-Brain Analyses

The same SPM12 and Matlab software on the Windows 11 computer used for fMRI preprocessing were also used for fMRI analyses.

To explore blood oxygen level dependent (BOLD) responses to different cue types at baseline, we used the respective 1st-level GLM-generated contrasts to generate a 2nd-level GLM model to assess group effects. Specifically, the following contrasts were independently assessed

across all participants at baseline: HC>LC, HC>NC, LC>NC, HC+LC>NC. Within each contrast, activation and deactivation (e.g., HC>LC, and LC>HC) were also assessed. An initial threshold at the whole-brain level was set to cluster-level uncorrected $p<0.01$ and voxel threshold of >10 voxels, to form the activation map. While this threshold is relatively liberal, it was deemed appropriate given the pilot nature of this work. Only clusters that then survived a family-wise error rate correction (FWE-corrected) of $p<0.05$ were considered significant (Dimitropoulos et al. 2012; Yeung, 2021). BMI and sex were tested as covariates of interest in the model but were ultimately not included in any final analyses as their inclusion decreased statistical power, likely due to small sample sizes.

Second, we explored whole-brain effects of the drug (i.e., 4-week Contrave® or placebo), and dietary intervention (i.e., all participants obtained the dietary intervention). As the study is ongoing, we remained blinded to drug allocation. In SPM, the same 2nd-level GLM contrasts conditions (HC>LC, HC>NC, LC>NC, HC+LC>NC) were created from post-intervention scans. Using the baseline and post-intervention 2nd-level GLM contrasts, paired t-tests were built for each contrast type. Here, we assessed pre- vs. post-intervention effects, and vice versa, for each contrast. These analyses used the same cluster-level thresholding and p-values as above

2.4.3 fMRI ROI Analyses

Region of interest (ROI) analyses were conducted to assess BOLD responses to food cues in specific regions. ROIs were predetermined from Luo et al.'s (2013) work as they used a similar food-cue task paradigm as used in the current work, wherein females with obesity were presented with images of high-calorie, low-calorie, and neutral control cues. Focus was on the bilateral insula and orbitofrontal cortex (OFC). The exact functional coordinates were (x, y, z): -40, -4, 2 (left insula), 40 -4 0 (insula right), -30 34 -16 (OFC left), and 26 34 -10 (OFC right).

Using the MarsBar toolbox (Brett et al., 2002), which runs on SPM12, a 5mm sphere mask (i.e., centre of sphere: coordinates) was applied to the above contrasts. ROI analyses were only conducted for whole-brain contrasts that showed at least subthreshold activity (cluster-level $p < 0.01$ uncorrected) within the predefined ROIs. Contrasts showing no visible activity within the ROIs on the uncorrected whole-brain maps ($p < 0.01$) were not examined further, as it is highly unlikely that such regions would survive ROI analysis (small volume correction) cluster-level FWE correction at $p < 0.01$. If an a priori ROI showed activation at a subthreshold level in the whole-brain analysis, we conducted a small volume correction (SVC) using the "ROI analysis" function in SPM. A 5mm radius spherical mask centred on the ROI coordinate was created, and statistical inference was performed within this restricted search space using an initial uncorrected $p<0.01$ and then a family-wise error (FWE) correction ($p < 0.05$), correcting for multiple comparisons within the ROI. However, BAS-F FC>NC ROI regressions used an initial whole-brain level thresholding uncorrected $p<0.005$, and BAS-F LC>NC ROI regressions used an initial uncorrected $p<0.001$. Due to the small size of the spherical ROI, a minimum cluster extent threshold (k) was not applied.

2.4.4 fMRI Regression Analyses

Next, multiple linear regression analyses were conducted to assess whether in-scanner behavioural responses or BAS scores predict baseline BOLD responses to food cues. All regression models were generated in the "multiple regression" function in SPM. First, baseline BOLD responses, i.e. activation maps for each contrast generated above, were modelled with the corresponding behavioural responses. For instance, for the HC>LC BOLD contrast, regressions were run with the HC-LC behaviour values for each participant (i.e., if the average 'appeal' rating was 8 for HC, and 4 for LC, the behavioural value was 4). Again, an initial threshold was

set at the whole-brain level, uncorrected $p<0.01$ and voxel size of >10 voxels, to form the activation map. For all regression analyses, final significance values were adjusted to $p<.01$ to correct for multiple comparisons (trends were reported and considered to be $p=.01$-$.p<.02$).

Next, we ran regression analyses between baseline BOLD responses to food cue contrasts and baseline BAS scores. Regressions were run separately for each category of the BAS (BAS-R, BAS-D, and BAS-F) and contrast type. These regressions used the same thresholding and p-values as above.

Exploratory regression analyses were conducted to examine whether changes in cue ratings and baseline BAS sub-scores predicted BOLD responses to food cue contrasts following the intervention. First, for each contrast condition (HC > LC, HC > NC, LC > NC, and FC > NC), a difference image (ΔBOLD) was created by subtracting the pre-intervention contrast map from the post-intervention contrast map. In parallel, behavioural change scores (ΔBehaviour) were calculated by taking the difference in cue ratings between pre- and post-intervention sessions, relative to control cues. For example, (HC – NC)post – (HC – NC)pre behavioural was regressed with [HC>NC]post>[HC>NC]pre. These behavioural scores were entered as covariates of interest in second-level multiple regression analyses to identify brain regions where changes in activation to food-related cues were associated with cue-specific behavioural change. These regressions used the same statistical thresholds and correction parameters as described above. Lastly, associations between ΔBOLD images and baseline BAS-R, BAS-D, and BAS-F scores, respectively, were analyzed using the same multiple regression model in SPM. BAS-F FC>NC regressions used an initial whole-brain level thresholding, uncorrected $p<0.005$, BAS-F LC>NC used an initial uncorrected $p<0.001$, and BAS-D FC>NC used an initial uncorrected $p<0.005$. Voxel threshold was set to >10 voxels.

Chapter 3: Results

3.1 Participant Characteristics

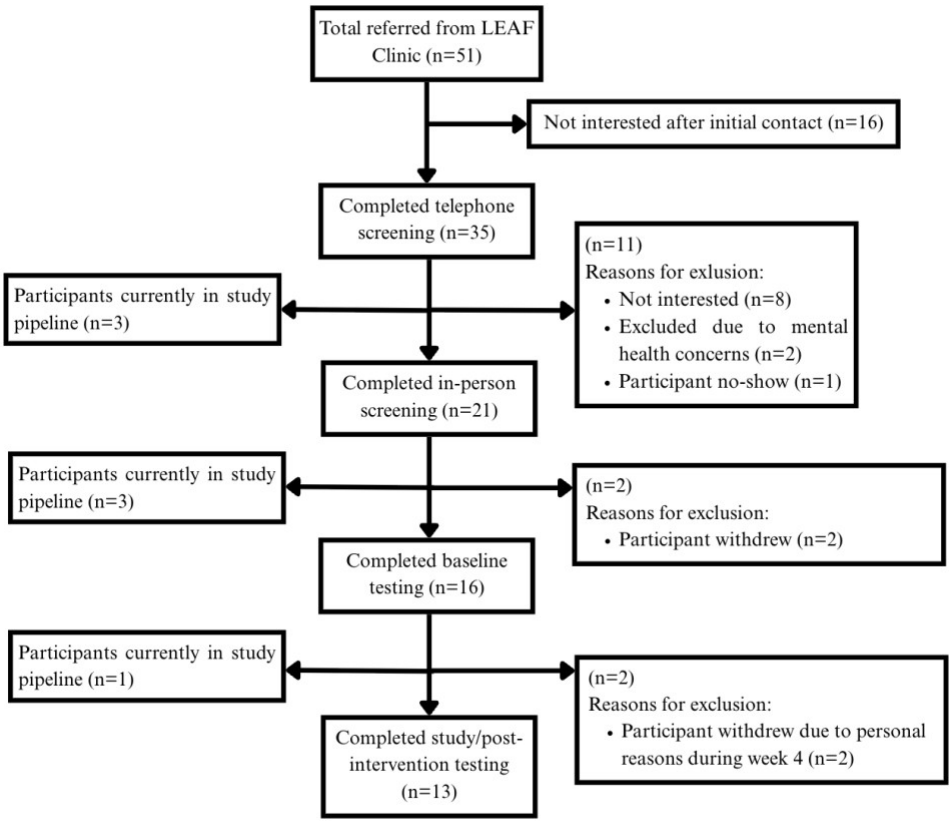
Recruitment commenced in April 2024; in total, N=52 participants with obesity were referred for this study by the LEAF Weight Management Clinic as of June 2026. Of these, N=35 completed the telephone screening session, and N=21 completed the in-person screening session (i.e., drug test session) and were enrolled in the study. A total of N=2 participants withdrew before completing baseline testing. N=16 completed baseline testing, and N=13 participants completed post-intervention testing (**Figure 8**).

For the neuroimaging analyses (i.e., for the purposes of this thesis), N=1 participant was excluded from all analyses due to technical issues (i.e., asynchrony between scanner start and task start). As such, N=15 scans were available for baseline assessments. One participant had moderate motion effects, with translational motion over 4mm (threshold of <3mm). As such, fMRIPrep (version 24.0.0; Esteban O et al. 2018), a preprocessing software, was used to detect outlier slices from the functional data, where they were subsequently regressed out of the dataset. After this additional processing, analyses were run with and without this participant, and no differences were observed; thus, they were included in the final analyses.

An additional N=1 participant was excluded from analyses involving cue ratings (i.e., behavioural data due to data collection error); behavioural analyses (i.e. cue ratings) at baseline included a total of N=14 participants. In the baseline analyses involving BAS scores, another N=1 participant was excluded because no BAS scores were available (i.e. N=14 participants available). A final sample of N=12 participants was available for post-intervention analyses; however, N=1 participant was excluded from post-intervention analyses involving cue ratings

due to data collection error with E-Prime; analyses using behavioural results (i.e. cue ratings) at post-intervention had a total of N=11 participants. Additionally, post-intervention analyses using BAS scores also had N=1 participant excluded due to a lack of BAS score collection; analyses using BAS scores at post-intervention had a total of N=11 participants. Demographic and baseline clinical information are presented in **Table 2**. Post-intervention demographic, clinical information, and change in clinical information from baseline are presented in **Table 3**.

Figure 8. *Flow Diagram for Recruitment and Enrollment Numbers*



Note. Enrollment commenced in April 2024 and ended in June 2025.

Table 2. *Baseline Participant Characteristics*

	Baseline		
Characteristic	**N**	**Mean ± s.d.**	**Range**
Age (yr)	15	44.3 ± 11.8	21-60
Sex	11 F 4 M	73% F 27% M	N/A
Weight (lbs)	15	258.1 ± 32.8	215-317.4
BMI	15	41 ± 4.3	34.4-48.8
BAS-R	14	16.6 ± 1.6	14-19
BAS-D	14	10.4 ± 2.1	6-14
BAS-F	14	11.1 ± 2.1	6-14

Note. BMI: Body Mass Index; BAS-R: Behavioural Approach System - Reward Responsiveness; BAS-D: Behavioural Approach System – Drive; BAS-F: Behavioural Approach System – Fun; BIS: Behavioural Inhibition System.

Table 3. *Participant Characteristics at Post-Intervention Testing and Change Over Time*

	Pre-Intervention			**Post-Intervention**		**Change over time (post-baseline)**		
Characteristic	**N**	**Mean ± s.d.**	**Range**	**Mean ± s.d.**	**Range**	**N**	**Mean difference ± s.d.**	**p-value**
Age (yr)	12	46.4 ± 10.6	29-60	(Unchanged)		(Unchanged)		
Sex	9 F 3 M	75%F 25%M	N/A	(Unchanged)		(Unchanged)		
Weight (lbs)	12	252.1± 27.0	215 – 301	242.2 ± 25.4	209.4 - 301.2	12	-9.9 ± 8.1	p=0.001*
BMI	12	40.9 ± 4.8	34.4 – 48.8	39.3 ± 4.8	33.1 – 47.3	12	-1.55 ± 1.3	p=0.001*

Note. BMI: Body Mass Index; "" Indicates statistically significant difference.*

3.2 Primary Analyses

3.2.1 Baseline effect of cue type on neural responses

We assessed how different types of food/neutral visual cues affect the BOLD response before intervention (i.e., in obese people). Analyses were conducted at the whole-brain level and in *a priori* ROIs for N=15 participants.

Whole-Brain Analyses: Baseline whole-brain results are presented in **Table 4**. Notably, the contrast of high-calorie vs. low-calorie (HC>LC) elicited no significant activation; however, this contrast was associated with deactivation of the left hippocampus (i.e., increased left hippocampal activity for HC<LC).

When viewing high-calorie vs. neutral control cues (HC>NC), there was significant activation of the left occipital middle area, right calcarine, and left superior parietal lobule. Further, there was significant deactivation of the right superior temporal gyrus, left middle temporal gyrus, and right superior occipital gyrus for HC<NC.

The left occipital inferior area, lingual area, and superior parietal lobule were more active during the viewing of low-calorie vs. neutral-control cues (LC>NC), whereas the superior occipital gyrus, supramarginal gyrus, cingulate region, and middle temporal gyrus were less active.

Lastly, when viewing all food cues vs. neutral cues (FC>NC), the left occipital pole, right calcarine, and left superior parietal lobule were more active; the right supramarginal gyrus, supplementary motor area, superior occipital gyrus, and left middle occipital gyrus were less active.

Table 4. *Whole-Brain Coordinates of Active Clusters at Baseline Across Different Contrasts*

Contrast Type	Coordinates			BA	k	p(FWE)
	x	y	z			
HC<LC						
Hippocampus	-30	-22	-12	Hippocampus	1266	0.021
HC>NC						
Occipital middle	-20	-98	-4	N/A	1920	0.003
Calcarine	26	-96	2	N/A	2432	0.001
Superior parietal lobule	-24	-64	36	N/A	3625	0.000
HC<NC						
Superior temporal gyrus	62	-32	10	N/A	9486	0.000
Middle temporal gyrus	-54	-40	6	N/A	4720	0.000
Superior occipital gyrus	10	-90	28	N/A	2439	0.001
LC>NC						
Occipital inferior	-20	-96	-8	16	1495	0.010
Lingual	18	-90	-4	N/A	1299	0.020
Superior parietal lobule	-34	-52	52	N/A	4178	0.000
LC<NC						
Superior occipital gyrus	22	-88	34	19	1764	0.004
Supramarginal gyrus	50	-32	24	40	4038	0.000
Cingulate region	6	-2	44	N/A	4301	0.000
Middle temporal gyrus	-50	-66	22	39	1530	0.009
FC>NC						
Occipital pole/calcarine	-18	-98	-6	N/A	1549	0.011
Calcarine	26	-96	2	N/A	2408	0.001
Superior parietal lobule	-34	-54	52	N/A	3838	0.000
FC<NC						
Supramarginal gyrus	48	-30	24	N/A	3453	0.000
Supp motor area	14	-14	58	6	4669	0.000
Superior occipital gyrus	10	-90	28	N/A	1816	0.004
Middle occipital gyrus	-42	-82	22	N/A	3835	0.000

Note. HC, High-calorie; LC, low-calorie; NC, neutral control; FC, all food cues; BA, Brodmann area; k, cluster size (in voxels); p(FWE), p-value including family-wise error correction.

ROI analyses: At baseline, left insula ROI analyses revealed significant activation clusters for FC>NC and LC>NC (**Table 5**).

Table 5. *ROI-Specific Coordinates of Active Clusters at Baseline Across Different Contrasts*

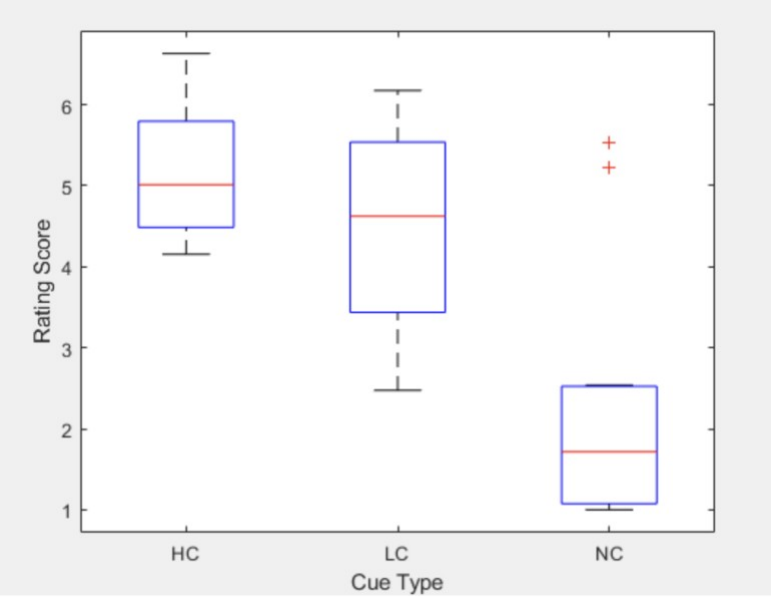
Contrast Type	**Coordinates**			**k**	**p(FWE)**
	x	y	z		
FC>NC					
Insula	-38	-6	6	11	0.048
LC>NC					
Insula	-38	-6	6	14	0.046

Note. LC, low-calorie; NC, neutral control; FC, all food cues; k, cluster size (in voxels); p(FWE), p-value including family-wise error correction.

3.2.2 Associations between baseline brain activity and cue ratings

Among the 14 participants included, at baseline, high-calorie (HC) foods were rated as having a higher appeal than both low-calorie (LC) foods (HC: m=5.18, sd=0.81; LC: m=4.48, sd=1.24; p=0.047, t=2.20) and neutral cues (NC; m=2.18, sd=1.47; p<0.001, t=5.83) (**Figure 9**). LC foods had increased self-reported appeal ratings vs. NC (p=0.002, t=3.84) (**Figure 9**).

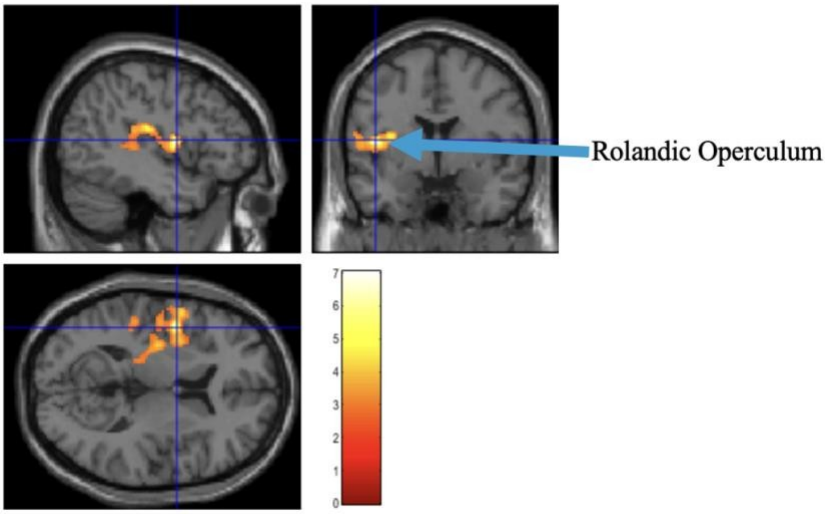
Figure 9. *Box Plot Representing Baseline Cue Rating Scores for High-Calorie, Low-Calorie, and Neutral Control Cues*



Note. HC, High-calorie; LC, low-calorie; NC, neutral control

Whole brain analyses: At baseline, the difference in HC vs. LC-calorie appeal ratings (i.e., HC-LC ratings) was associated with increased activity in the left Rolandic operculum to HC>LC contrasts (p(FWE)=0.009, k=1470, MNI: -44 0 10; **Figure 10**).

Figure 10. *Contrast Map Depicting Association Between High-Calorie vs. Low-Calorie Cue Ratings and Activity in the Rolandic Operculum*



ROI analyses: At baseline, both HC-LC and LC-NC cue appeal ratings were associated with clusters of activity in the left insula for HC>LC and LC>NC contrasts, respectively (**Table 6**).

Table 6*. ROI-Specific Coordinates of Active Clusters Associated with Cue-Ratings at Baseline Across Different Contrasts*

Contrast Type	**Coordinates**			**k**	**p(FWE)**
	x	y	z		
HC>LC					
Insula	-42	-2	6	22	0.041
LC>NC					
Insula	-42	-2	4	44	0.031

Note. HC, high-calorie; LC, low-calorie; NC, neutral control; k, cluster size (in voxels); p(FWE), p-value including family-wise error correction.

3.2.3 Associations Between Baseline Brain Activity & BAS Scores

Next, we assessed associations between BOLD responses to food cue contrasts and BAS scores at baseline. Among the 14 participants included, several negative associations were identified between BAS scores and baseline BOLD responses (**Table 7, Figure 11**). BAS-R, BAS-D, and BAS-F scores were not correlated with one another (**Supplementary Table 2**).

Whole-brain analyses: First, for HC<NC at baseline, BAS-R scores were associated with BOLD deactivation of the right cerebellum (i.e., greater BAS-R scores, lower right cerebellum activation). Second, for LC<NC, BAS-R scores were associated with deactivation of the right pons and anterior cingulum. BAS-R scores were also associated with deactivation of the right pons, left middle frontal gyrus, right caudate, left superior parietal lobule, and left superior frontal gyrus for FC<NC contrasts. BAS-D scores were associated with deactivation of the right putamen for LC<NC contrasts. Lastly, BAS-F scores were associated with deactivation in the right pons and left putamen in that same contrast condition.

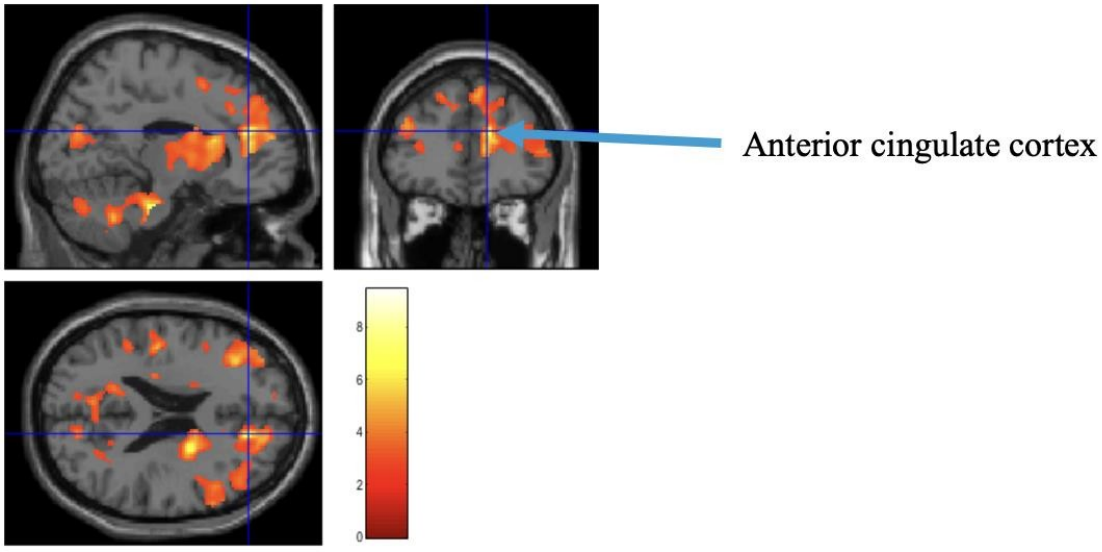
Table 7. *Coordinates of Active Clusters Associated With BAS Scores at Baseline Across Different Contrasts*

BAS Scale	Contrast Type	Coordinates			BA	k	p(FWE) p<0.01
		x	y	z			
BAS-R	**HC<NC**						
	Cerebellum	16	-76	-44	N/A	2537	0.000
	LC<NC						
	Pons	16	-26	-30	N/A	3765	0.000
	Anterior cingulate	14	40	22	9	12677	0.000
	FC<NC						

	Pons	16	-26	-30	N/A	3065	0.000
	Middle frontal gyrus	-42	34	30	N/A	1777	0.002
	Caudate	22	12	20	N/A	1777	0.002
	Superior parietal lobule	-36	-58	44	40	1457	0.007
	Superior frontal gyrus	-20	20	58	N/A	2306	0.000
BAS-D	**LC<NC**						
	Putamen	26	6	-10	N/A	6399	0.000
BAS-F	**LC<NC**						
	Pons	6	-44	-42	N/A	1591	0.003
	Putamen	-30	-10	8	N/A	1205	0.013

Note. HC, High-calorie; LC, low-calorie; NC, neutral control; FC, all food cues; BA, Brodmann area; BAS-R: Behavioural Approach System - Reward Responsiveness; BAS-D: Behavioural Approach System – Drive; BAS-F: Behavioural Approach System – Fun; k, cluster size (in voxels); p(FWE), p-value including family-wise error correction.

Figure 11. *Contrast Map Depicting Positive Association Between BAS-R Scores and Activity in the Anterior Cingulate Cortex for Low Calorie vs. Neutral Cue Contrasts*



ROI analyses: Using our predetermined ROIs, no significant regressions between BOLD responses to any of the contrasts in the bilateral insula or OFC and BAS emerged.

3.3 Exploratory Analyses

3.3.1 Effect of intervention on BOLD responses to food cues

N=12 participants are included in the exploratory pre/post intervention fMRI analyses (as outlined in section 3.1).

As shown in **Table 8**, the intervention led to a decrease in weight and BMI. With respect to BOLD activity, there was increased activity at post-intervention (vs. pre-intervention) in the left occipital inferior cortex for HC>NC. Additionally, BOLD responses increased post-intervention (vs. pre-intervention) in the left lingual gyrus/calcarine, right precuneus, and right hippocampus when viewing FC>NC. No changes pre/post were noted for any of the contrasts in the *a priori* ROIs.

Table 8. *Coordinates of Active Clusters Post-Intervention vs. Pre-Intervention Across Different Cue Conditions*

Contrast	Coordinates			BA	k	p(FWE)
	x	y	z			
$[HC>NC]_{post} > [HC>NC]_{pre}$						
Occipital inferior	-26	-82	-4	N/A	1182	0.026
$[FC>NC]_{post} > [FC>NC]_{pre}$						
Lingual gyrus/calcarine	-6	-90	-8	N/A	5495	0.000
Precuneus	14	-66	32	N/A	971	0.033
Hippocampus	18	-34	6	N/A	971	0.033
$[LC>NC]_{post} > [LC>NC]_{pre}$						
Cuneus	18	-66	32	N/A	1123	0.026
Posterior cingulum	-6	-40	24	N/A	1123	0.026

Note. HC, High-calorie; LC, low-calorie; NC, neutral control; FC, all food cues; BA, Brodmann area; k, cluster size (in voxels); p(FWE), p-value including family-wise error correction. "Post" signifies post-intervention, and "Pre" signifies baseline.

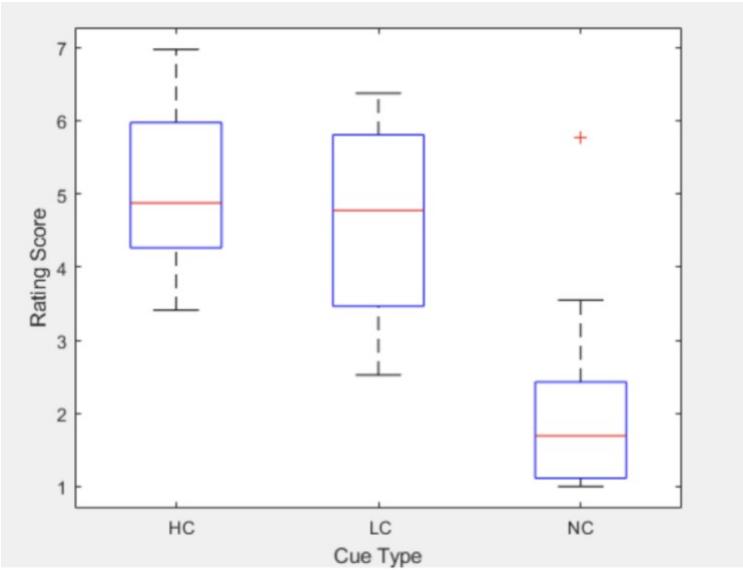
3.3.2 Association between post-intervention BOLD responses and cue appeal

Next, we explored regressions between change in BOLD responses and change in self-reported cue appeal over the intervention (post-pre). A total of N=11 participants were available for these analyses (see section 3.1 for more details).

At post-intervention, high-calorie food ratings were not significantly different from low-calorie food ratings (high-calorie: m=5.07, sd=1.09; low-calorie: m=4.66, sd=1.30; p=0.342, t=0.99) but were significantly different from neutral cues (m=2.15, sd=1.43; $p<0.001$, t=5.03) (**Figure 12**). Low-calorie foods also showed increased self-reported appeal ratings compared to neutral cues (p=0.004, t=3.59) (**Figure 12**).

Paired t-tests were performed to compare differences in type-specific cue ratings between post- vs. pre-intervention. We found no significant differences in high-calorie ratings ($HC_{baseline}$: m=1.67, sd=0.91; p=0.644, t=-0.48), low-calorie ratings ($LC_{baseline}$: m=4.56, sd= 1.33; p=0.413, t=0.85), and neutral control ratings ($NC_{baseline}$: m=2.43, sd= 1.56; p=0.096, t=-1.84) between post vs. pre intervention.

Figure 12. *Box Plot Representing Post-Intervention Cue Rating Scores for High-Calorie, Low-Calorie, and Neutral Control Cues*



Note. HC, High-calorie; LC, low-calorie; NC, neutral control

Next, we conducted exploratory regressions between change in post vs. pre-BOLD signals and change (difference) in post vs. pre cue responses (e.g., $[HC\text{-}LC]_{post}$-$[HC\text{-}LC]_{pre}$). No significant associations between BOLD responses and cue ratings were identified at the whole-brain or ROI level.

3.3.3 Association between post-intervention BOLD responses and BAS scores

Last, we explored regressions between change in post vs. pre-BOLD responses and baseline BAS scores in N=11 participants (see section 3.1) at the whole-brain level (**Table 9**), and within our *a priori* ROIs (**Table 10**). BAS scores were only measured at baseline.

Whole brain analyses: Change in BOLD responses post- vs. pre-intervention revealed significant associations with BAS-D scores in the superior parietal for the FC>NC contrast. Significant associations with BAS-F scores were evident in the precuneus, insula, cuneus, medial frontal gyrus, and middle frontal gyrus for the FC>NC contrast. Changes in BOLD responses for LC>NC were also significantly associated with BAS-F scores in the cerebellum, Rolandic operculum, postcentral gyrus, precuneus, middle cingulum, cerebellum, frontal inferior triangularis, and supramarginal gyrus.

Table 9. *Whole-Brain Coordinates of Change in BOLD Response Post-Intervention vs. Pre-Intervention Across Different Contrasts That are Significantly Associated With BAS Questionnaire Scores*

Scores	Contrast Type	Coordinates			BA	k	p(FWE)
		x	y	z			
BAS-D	**$[FC>NC]_{post} > [FC>NC]_{pre}$**						
	Superior parietal lobule	30	-52	46	N/A	759	0.008
BAS-F	**$[FC>NC]_{post} > [FC>NC]_{pre}$**						
	Precuneus	10	40	4	N/A	3338	0.000
	Insula	40	-18	12	N/A	8549	0.000
	Cuneus	8	-80	40	7	765	0.002
	Medial frontal gyrus	4	52	38	9	840	0.001
	Middle temporal gyrus	-58	-62	8	39	1479	0.000
	$[LC>NC]_{post} > [LC>NC]_{pre}$						
	Cerebellum (lobule VI)	-2	-50	-2	N/A	2675	0.000
	Rolandic operculum	44	-16	16	13	2192	0.000
	Postcentral gyrus	20	-38	74	2	959	0.000
	Precuneus	-6	-80	36	19	416	0.000
	Middle cingulum	2	-10	36	N/A	330	0.000
	Cerebellum (lobule IX)	24	-78	-44	N/A	544	0.000
	Frontal inferior triangularis	62	24	14	45	283	0.001
	Supramarginal gyrus	-60	-56	22	40	194	0.007

Note. HC, High-calorie; LC, low-calorie; NC, neutral control; FC, all food cues; BA, Brodmann area; k, cluster size (in voxels); p(FWE), p-value including family-wise error correction; BAS-D: Behavioural Approach System – Drive; BAS-F: Behavioural Approach System – Fun. "Post" signifies post-intervention, and "Pre" signifies baseline.

ROI analyses: The change in BOLD response post- vs. pre-intervention for FC>NC were significantly associated with BAS-F scores in the bilateral insula. Additionally, BAS-F scores were significantly associated with changes in BOLD responses in the right insula for LC>NC.

Table 10. *ROI-Specific Coordinates of Change in BOLD Response Post-Intervention vs. Pre-Intervention Across Different Contrasts That are Significantly Associated With BAS Questionnaire Scores*

Scores	Contrast Type	Coordinates			k	p(FWE)
		x	y	z		
BAS-F	**$[FC>NC]_{post} > [FC>NC]_{pre}$**					
	Insula	-40	-6	2	1	0.045
	Insula	42	0	2	12	0.028
	Insula	40	-8	2	5	0.036
	Insula	38	-2	-4	4	0.038
	$[FC>NC]_{post} > [FC>NC]_{pre}$					
	Insula	42	-2	2	23	0.003

Note. FC, all food cues; NC, neutral control; BA, Brodmann area; k, cluster size (in voxels); p(FWE), p-value including family-wise error correction; BAS-F: Behavioural Approach System – Fun. "Post" signifies post-intervention, and "Pre" signifies baseline.

Chapter 4: Discussion

4.1 Summary

The goal of this thesis was to assess neural activity in participants with obesity when viewing high-calorie (HC), low-calorie (LC), all food (FC; combining HC and LC) and neutral non-food/control (NC) cue contrasts. Additionally, we assessed associations between brain activity and in-scanner ratings of food cues based on appeal. We also assessed relations between BOLD responses to food cues and reward-based trait motivation/behaviour, as measured through the Behavioural Approach System (BAS) questionnaire. Exploratory analyses involved examining changes in BOLD to food cue contrasts following a 4-week dietary and drug intervention (Contrave® or placebo). Changes in neural responses following intervention were also associated with changes in in-scanner appeal ratings to the food stimulus cues and baseline BAS scores.

To our knowledge, this is the first study comparing neural responses to food cues before and after a 4-week dietary intervention coupled with Contrave® (or placebo) in men and women; it is also the first to examine self-reported motivation towards rewarding stimuli (as assessed using the BAS) in relation to brain activity to food cues in people with obesity following an anti-obesity intervention.

Briefly, at baseline, whole-brain analyses revealed significant activity in several clusters, including the hippocampus (LC>HC), and the superior parietal lobule (HC>NC, LC>NC, FC>NC), among others. Region of interest (ROI) analyses identified activity in the posterior insula to FC or LC vs. NC cues. Next, we found behavioural differences in terms of food cue ratings, in that high-calorie foods were rated as more appealing. We predicted positive

associations between cue ratings and brain activity; indeed, we identified positive associations at baseline in the posterior insula (HC>LC, LC>NC) and Rolandic operculum (HC>LC). Lastly, we expected positive associations between neural activity to food cues and traits measuring reward-motivation (through BAS), especially in BAS-R and BAS-D scores. However, we identified negative associations between BAS-R scores and brain activity in the cerebellum (NC<NC), pons (LC<NC), dorsolateral prefrontal cortex (dlPFC; LC<NC), middle and superior frontal gyri (FC<NC), caudate (FC<NC), and superior parietal lobule (FC<NC).

Exploratory analyses revealed significant increases in activity in the occipital inferior region (HC>NC), lingual gyrus (FC>NC), precuneus (FC>NC), hippocampus (FC>NC), cuneus (LC>NC) and posterior cingulum (LC>NC) post- vs. pre-intervention. Contrary to our hypotheses, there were no changes in activity in reward regions (our *a priori* ROIs) as a result of the intervention. Next, at post-intervention, expecting associations between change in BOLD activity and change in cue appeal (post- vs. pre-intervention), no such associations were identified. Lastly, we expected baseline BAS-R/D scores to be negatively correlated to increases in BOLD responses pre- vs. post-intervention in reward regions. However, we identified a positive association between BAS-D and change in BOLD in the superior parietal lobule (FC>NC). Positive associations were also identified between BAS-F and the precuneus (FC>NC, LC>NC), insula (FC>NC), cuneus (FC>NC), medial frontal gyrus (FC>NC), among other regions. Primary and exploratory results are discussed in greater detail below.

4.2 Primary Analyses

4.2.1 Baseline BOLD response to food cues

When examining HC>LC contrasts, we noted decreased activity of the hippocampus (or hippocampal activation when viewing low-calorie vs high-calorie) at baseline in people with obesity. The hippocampus is connected to the hypothalamus, insula, and ventral striatum; this network facilitates dopamine release, contributing to stimulus saliency and reward processing (Ventura et al., 2007). It is also connected to prefrontal areas and helps modulate cognitive control (Taepavarapruk et al., 2008). fMRI studies assessing gastric fullness (through gastric stimulators and balloon distension) have shown increased activity in the hippocampus, suggesting an association between hippocampal activity and the sensation of gastric fullness (Wang et al., 2006; Wang et al., 2008). In patients with obesity, the hippocampus has been shown to exhibit *decreased* activity in obese participants vs. non-obese people when tasting a liquid meal (DelParigi et al., 2004). Here, we show that the hippocampus is less active when viewing food cues associated with reward and increased palatability vs. LC foods. This may suggest an altered activation to high-calorie and palatable foods; this would be in line with a decreased sensitivity hypothesis of reward in chronically obese people.

Food (HC, LC, and FC) vs. NC cue contrasts elicited activity in the superior parietal lobule, occipital cortex, calcarine, and lingual area during baseline. The superior parietal lobule is associated with somatosensory processing and spatial attention (Scheperjans et al., 2005; Witting et al., 2001), suggesting that participants devoted increased attention and salience processing when viewing food vs. non-food cues. While the calcarine and occipital cortex are involved with visual processing, their activation to foods suggests that these cues are more visually engaging, which may contribute to their overconsumption.

In contrast, many regions were *deactivated* when viewing HC and/or LC vs. NC, including areas involved in visual search (superior temporal gyrus; Ellison et al., 2004), visual perception of motion (middle temporal gyrus; Blihar et al., 2020), basic visual processing and object recognition (superior/medial occipital gyri; Palejwala et al., 2021), phonological memory (supramarginal gyrus; Romero et al., 2006), and planning voluntary movement (supplementary motor area; Guida et al., 2023). Considering that other sensory/visual processing areas were active when viewing HC and/or LC vs. NC (opposite to the current condition), the deactivation in these areas may reflect sensory and motor processing of non-food cues (household items and plants).

Interestingly, the dACC was deactivated in the LC vs. NC contrast. The dACC is known to play a role in the cognitive guidance of reward-based decisions and to monitor conflicts between competing responses (Sheth et al., 2012). Excessive weight may impair the proper functioning of the dACC, as evidenced by a study that found negative correlations between BMI and dACC metabolism (measured through positron emission tomography; Volkow et al., 2009). Further, dACC metabolic activity was positively correlated to memory and executive functioning (Volkow et al., 2009). In obese participants, Volkow et al. (2008) found that diminished metabolic activity in the dACC correlated with reduced striatal dopamine D2 receptor levels, which may contribute to decreased self-regulation and increased compulsive food intake, a known feature of obesity. In our study, the dACC's decreased activity when viewing LC vs. NC cues may suggest an impaired capacity for food-related self-regulation.

Last, in line with our hypotheses, ROI analyses revealed increased activity in the posterior insula when comparing FC and LC vs. NC. The posterior insula is involved with interoceptive operations, receiving inputs from the hypothalamus, amygdala and limbic system

(Craig & Zhang, 2006). Prior research suggests that this area is activated by sensory processing, taste perception, and food cues (Craig, 2002). Hunger has been shown to increase blood flow in the posterior insula, an effect that is attenuated following food consumption (Gautier et al., 2001). As such, the posterior insula is thought to be involved in awareness of the body regarding hunger and food consumption via multisensory integration. It is feasible that activation of the posterior insula may reflect an internal "scan" of hunger signals when viewing food vs non-food cues. Contrary to our hypotheses, we found no orbitofrontal cortex (OFC) difference when viewing FC (HC and/or LC) vs. NC at baseline. This may in part be due to the small sample sizes/being underpowered (N=15).

4.2.2 Baseline BOLD Association with Behaviour

In line with our hypotheses, at baseline, participants rated HC cues higher than LC and NC cues, with NC cues being rated significantly lowest.

Our primary aim was to assess associations between BOLD activity and cue ratings across the brain. Wole-brain analyses revealed that higher ratings of HC > LC on appeal were associated with increased activity in the Rolandic operculum (HC > LC). The Rolandic operculum is part of the primary taste cortex (Rolls, 2005; O'Doherty et al. 2001); some (Rolls, 2005, de Araujo 2009, O'Doherty et al. 2001) have proposed that activity in this area reflects purely sensory features and does not reflect taste pleasantness or motivational states. Considering that participants in our study did not consume or taste any foods in-scanner, the relation between HC>LC appeal ratings and activity in the Rolandic operculum might, nevertheless, reflect a link of imagined taste. This result is supported by Ng et al.'s (2011) study, where the anticipation of a chocolate milkshake induced activity in the Rolandic operculum in obese vs. healthy weight

women, suggesting that imagining a palatable food cue can induce activity in the primary gustatory cortex, potentially reflecting imagined taste.

Next, we expected to see associations between brain activity in our *a priori* ROIs and the ratings of these cues. Indeed, higher HC vs. LC and LC vs. NC ratings were correlated with increased activity in the mid-posterior insula. As outlined, the mid-posterior insula is related to interoceptive processing and has been shown in previous work to activate in response to taste perception or the viewing of food cues (Craig, 2002). This activity decreases with satiation, suggesting its role in interoceptive signalling regarding hunger and satiety (Gautier et al., 2001). Individuals with obesity have been found to exhibit decreased activity in this area compared to healthy individuals, suggesting perhaps a blunted baseline satiety response (Luo et al., 2013). However, the relation between the posterior insula's activity and food appeal is positively associated in our obese cohort. Without a healthy weight comparison group, it is difficult to deduce whether this effect is pathological in nature. While this association may simply reflect a brain activation–behavioural link, we propose a potential reward-related sensitization in this cohort, wherein participants who rate HC higher than LC on appeal (or LC higher than NC) show greater hunger when viewing HC vs. LC (or LC vs. NC), as reflected in BOLD responses from the Rolandic operculum (HC vs. LC only) and insula, potentially driving overconsumption. A positive correlation was identified between insular activity when viewing HC vs. NC cues and HC vs. NC ratings; however, it did not pass our significance thresholds.

4.2.3 Baseline BOLD Association with BAS

Our final primary objective was to assess associations between baseline BOLD responses to food cues and BAS questionnaire scores (including BAS-R, BAS-D, and BAS-F). Carver and

White's (1994) Behavioural Approach System (BAS) and Behavioural Inhibition System (BIS) scales were designed to measure sensitivity to reward and punishment. To better account for the wide range of behaviours that could be mediated by reward sensitivity, they developed BAS subscales which would measure reward responsiveness (the degree to which one experiences positive responses to receiving rewards; BAS-R), drive (the degree to which one pursues a desired goal; BAS-D), and fun-seeking (the degree to which one seeks out new rewards and situations; BAS-F). While some studies have used a total BAS score, research has shown that a unitary score does not accurately measure appetitive motivation and that each scale reflects a unique construct (Ross et al., 2002; Taubitz et al., 2015). In our study, results from each scale were not correlated with one another, indicating that each scale reflects independent information.

Contrary to our predictions, baseline BOLD responses were not associated with BAS-R, BAS-D, or BAS-F in ROIs across any of the food-viewing contrasts. Beaver et al. 2006 explored associations between BAS-R/D/F scores and brain activity in N=12 healthy, non-obese participants when viewing different food cues, and observed positive associations between several reward-related regions, including the insula and OFC, and BAS-D scores. Overall, they concluded that BAS-D may be a better predictor of reward-related reactivity to food cues in healthy individuals. It is possible that we did not observe this relationship in our cohort because overexposure to highly palatable foods (common in obesity) may lead to dysregulation or desensitization in reward regions, reducing the neural distinction between highly rewarding and less rewarding foods. Desensitization to rewards may be a result of reduced dopamine signalling in participants with obesity, as a result of repeated exposure to and consumption of rewards (Sutton et al. 2022).

In line with a theory of desensitization to reward, whole-brain analyses revealed significant *negative* associations between BOLD responses to FC/LC/HC vs. NC contrasts in several regions and BAS scores at baseline. Concretely, we observed that when viewing FC vs. NC, activity in the pons, middle frontal gyrus, superior frontal gyrus, caudate, and superior parietal lobule was inversely associated with BAS-R scores. The pons houses many facial nerves, which relay sensory information regarding salivation and taste (Ackerman, 1992). The middle frontal gyrus is associated with working memory and attention; activity in this area has been previously shown to decrease with increases in waist circumference (Gonzales et al. 2015). The superior frontal gyrus plays a role in self-awareness, interoception, and sensory processing, and has also previously shown decreased BOLD activity in those with obesity (Wang et al., 2014). The caudate is implicated in coordinating reward-based decisions surrounding external cues and internal preferences (Doi et al. 2020). The superior parietal lobule is involved with somatosensory processing and spatial attention (Wang et al. 2014). Overall, when viewing all food vs. NC cues, participants with obesity with increased reward responsiveness traits (i.e. strong hedonic response to receiving rewards) may have a decreased capacity for sensory processing, working memory, self-awareness, and ability to make reward-related decisions. These regions are all interconnected (Lee et al. 2015, Burks et al. 2017, Yeterian & Pandya 1993) and may indicate dysfunction within neural networks that respond to food cues, whereby individuals who derive the most pleasure from receiving rewards may struggle to effectively process the sensory features of those cues and evaluate their appeal. BAS-R scores were also negatively associated with BOLD responses in the cerebellum's VII lobule when viewing HC vs NC. This part of the cerebellum plays important roles in cognitive and emotional processing, with strong connections to the prefrontal cortex (Beuriat et al. 2022; Stoodley & Schmahmann

2009). Last, activity in the pons and dACC (Broddman area 9) were also negatively associated to BAS-R scores when viewing LC vs. NC. Overall, and in line with the observations above, high BAS-R scores may be indicative of a decreased ability for cognitive processing (perhaps regarding the deciding of cue appeal) in the cerebellum's lobule VII and the dACC when viewing FC vs. NC (cerebellum) and LC vs. NC (dACC) cues in participants with obesity.

Next, BAS-D scores were negatively associated with activity in the putamen when viewing LC>NC cues. The putamen is known for its role in encoding reward value and directing related actions (Ghandili et al., 2023). Similarly to the BAS-R results obtained above, participants with obesity who go out of their way to acquire rewards (BAS-D) may have an impaired ability to evaluate rewards and make decisions surrounding the reward.

Lastly, BAS-F scores were also negatively associated with the pons when viewing LC>NC, potentially reflecting impaired taste sensory encoding.

Overall, our results suggest that in participants with obesity, BAS-R (i.e. measure of positive hedonic responses to rewards) negatively predicts BOLD responses to food cues. Additionally, in our study, BAS-R appears to be a better predictor of responses to food cues in people with obesity, rather than the BAS-D and BAS-F. The associations between BAS-R and neural responses in our cohort are likely influenced by both the nature of our task and the fact that our study population was comprised exclusively of individuals with obesity. Our task primarily engaged the affective component of reward processing—namely, the immediate positive hedonic response to viewing a reward. BAS-D and BAS-F, however, capture the motivational drive to obtain rewards or to seek novel rewards, respectively, which was less relevant in this context, as our task did not require effortful pursuit or exploration. Additionally, in participants with obesity, heightened BAS-R scores alongside reduced neural activity may

reflect reward desensitization from chronic overexposure to highly palatable foods, resulting in attenuated sensory/cognitive reward-related processing; this may be due to repeated exposure to food cues and reduced dopamine signalling. These findings diverge from Beaver et al. (2006), where BAS-D positively predicted neural responses in healthy-weight individuals. Their prediction and lack of associations between neural responses and BAS-R may reflect a more normalized response to rewarding cues in healthy individuals.

4.3 Exploratory Analyses

4.3.1 Pre vs. Post Intervention BOLD Responses

We found that the 4-week drug/diet intervention led to a significant decrease in weight (*m*=-9.9, *sd*=8.1, p=0.001) and BMI (*m*=-1.55, *sd*=1.3, p=0.001) in the N=12 participants who were included in these exploratory analyses. We performed paired t-tests to compare brain activity to food cues post- vs. pre-intervention. First, for the HC>NC contrasts, the inferior occipital cortex showed increased activity post-intervention (vs. pre-). This region is involved with visual processing, suggesting that participants might have been more attentive to HC cues after a 4-week diet/medication intervention. As high-calorie and highly palatable foods were limited during the dietary intervention, this might reflect increased salience to such cues. Next, the averaged BOLD response to food cues (vs. NC) elicited increased activity post vs. pre-intervention in the lingual gyrus, precuneus, and hippocampus. The lingual gyrus is associated with visual memory and processing (Palejwala et al., 2021); as such, increased activation may reflect increased attention to food cues due to dietary restriction during the intervention. The precuneus plays an important role in self-consciousness and self-related mental representation

during rest (Cavanna & Trimble, 2006); it is a central hub within the default mode network (DMN). Increased activity in this context suggests that the intervention might be leading participants to recruit more self-referential processing, potentially concerning food-related information/cues. Last, increased activity in the hippocampus post-intervention might reflect a "restoration" of proper hippocampus function. At baseline, we saw decreased hippocampal activity when viewing HC vs. LC cues. Further, a previous study exploring the effects of Contrave® on brain activity in people with obesity identified an increase in activity in the hippocampus throughout a 4-week intervention (Wang et al. 2014). As such, it is feasible that the intervention (and potentially Contrave®, in particular) might normalize hippocampal activity. In general, these data suggest a restoration in perhaps dampened (i.e., desensitized) reward-related processing in regions involved in salience and self-referential processing.

Contrary to our hypothesis, we did not observe any significant change in insular activity post- vs. pre-intervention. A 4-week intervention may not have allowed enough time to reveal alterations in activity in these regions; it is also possible that our sample sizes (N=12) were too low to detect significant changes in these regions.

4.3.2 BOLD Change Associations with Behaviour

Next, we explored how participants rated food cues on appeal following the intervention, and the relationship between changes in food cue ratings and changes in BOLD responses. In line with our hypotheses, at post-intervention, there were no significant differences between HC and LC cues; these differences were noted at baseline. As predicted, both HC and LC remained significantly higher than NC post-intervention. However, paired t-tests did not identify any significant differences in these ratings when comparing baseline and post-intervention, which might be due to limited power. Next, contrary to our hypotheses, we did not identify any

associations between change in cue rating and change in BOLD response across the whole brain or in our *a priori* ROIs pre-/post-intervention. Again, limited power and variability in the change in cue ratings may have limited our ability to assess significant results.

4.3.3 BOLD Change Associations with BAS

Last, we explored associations between baseline BAS scores and changes in BOLD responses (post- vs. pre-intervention). BAS scores were measured at a single time point, as they reflect relatively stable personality traits (Beaver et al. 2006; Kasch et al. 2002). First, we expected negative associations between BAS-R/D scores and change in BOLD response in reward regions (our ROIs and others), as we believed that a 4-week diet and Contrave® (or placebo) intervention would reduce reward activity most in those with increased reward-based traits. We also expected positive associations between BAS-F scores and BOLD activity in the dlPFC and superior frontal gyrus, representing an increase in activity post- vs. pre-intervention. As a reminder, BAS-R (Reward Responsiveness) represents the pleasure one feels in response to receiving a reward. BAS-D (Drive) describes the extent to which an individual goes out of their way to obtain familiar rewards, and BAS-F (Fun Seeking) represents impulsivity towards novel rewards/experiences. Our results identified several positive associations between an increase in neural activity post- vs. pre-intervention and BAS-D/F scores. First, ROI analyses revealed positive associations between BAS-F scores and change in BOLD responses in the bilateral insula to FC/LC>NC. This suggests that participants with greater impulsivity/impulsive tendency for seeking out new rewards displayed a greater increase in the activity of their posterior insula after a 4-week dietary and Contrave® (or placebo) intervention. This might reflect an increase in

appetitive interoceptive awareness in people with anti-obesity interventions, particularly in those with higher BAS-F.

Next, whole-brain analyses revealed that BAS-D scores were positively associated with increased BOLD activity (post- vs. pre-intervention) in the superior parietal lobule to FC>NC. As previously discussed, this area is important for somatosensory processing and spatial attention and was negatively associated with BAS-R scores at baseline. As such, those who strongly pursue appetitive rewards (high BAS-D) likely displayed increased attention and processing of food cues after a 4-week dietary/drug intervention. This effect may be due to the dietary restrictions participants experienced during the intervention, which likely prompted greater behavioural adjustments in high BAS-D individuals, resulting in increased attentional engagement to FC cues post-intervention.

When viewing all food cues (vs. control/non-food), increases in brain activity in areas involved with self-consciousness/awareness (precuneus; Cavanna & Trimble, 2006) between post- and pre-intervention were positively associated with participants' desire to seek novel rewards (BAS-F). This effect was also noted in areas related to hunger-related interoception (posterior insula; Wang et al., 2014), visual processing (cuneus; Nyatega et al., 2021), emotional intelligence (medial frontal gyrus/BA9; Snow et al., 2016), and object recognition/multimodal sensory integration (middle temporal gyrus; Chao et al., 1999, Onitsuka et al., 2009). When viewing low-calorie cues (compared to control), changes in brain activity in areas involved with self-consciousness (precuneus; Cavanna & Trimble, 2006), working memory and emotional processing (cerebellum, lobule VI; Sheth et al., 2012), cognition (cerebellum, lobule IX and dACC; Sheth et al., 2012, Beuriat et al. 2022), and sensory processing (Rolandic operculum, postcentral gyrus, and supramarginal gyrus; Rolls, 2005, Diguiseppi et al. 2023, Romero et al.,

2006) were also positively associated to BAS-F. We also observed this effect in the right frontal inferior triangularis (FIT). While this region is generally responsible for language comprehension and production, some studies have suggested that the right FIT may also be involved in cognitive/inhibitory control tasks (Aron et al., 2003; Choo et al., 2022). As such, this association may represent an increase in food-related inhibitory control as a result of the 4-week intervention. Overall, these results likely reflect changes in regions comprising networks involved in reward-related self-awareness, cognition, and sensory processing, wherein those with impulsive-like traits to seek rewards displayed greater malleability in the activity of these regions/networks.

We propose that individuals who may have initially exhibited reward-related impairments (demonstrated through negative associations between BAS-R and reward-based sensory and cognitive processing at baseline – section 4.2.3) may have experienced partial normalization or recovery of neural responsiveness to food cues. As such, BAS-R scores may be a better indicator of baseline reactivity to food cues in participants with obesity (compared to BAS-D in healthy controls; Beaver et al. 2006). Intervention-based neural changes may involve improved sensory processing, interoceptive awareness (e.g., satiety signals), working memory, and reward valuation, as evidenced by the positive associations between increases in brain activity (pre- vs. post-intervention) and BAS-D/F scores described above. These changes may be explained by the dietary component of the intervention, which specifically aimed to modify participants' food choices and reduce consumption of highly rewarding foods; the dietary restriction would represent a substantial change from their habitual behaviour. Consequently, the observed positive correlations between changes in neural activity and BAS-D/F scores (rather than BAS-R) are consistent with the idea that the intervention affected these individuals' reward-seeking,

producing a normalization of brain activity related to reward-based sensory and cognitive processing activity over time, wherein reduced exposure to hyperpalatable foods (via diet) may have restored the neural salience of food-related cues in high BAS-D/F individuals. As such, BAS-D/F scores may better predict obese participants' success with weight-loss interventions, while BAS-R may be better suited to predict their responses to food cues before intervention.

Chapter 5: Limitations and Conclusions

5.1 Limitations

While this research represents an important step toward understanding the effects of a weight-loss intervention on brain activity (particularly within the mesolimbic reward system), it is important to acknowledge limitations. First, the most substantial limitation was the small sample size, which constrained statistical power and necessitated a liberal threshold of $p < .01$ when assessing fMRI activation maps. Statistical power was especially reduced for the exploratory aims, comparing post- vs. pre-intervention results (i.e., $N = 12$ participants). Furthermore, due to both the small sample size and the ongoing status of the parent study, we were unable to differentiate the Contrave®-receiving group from the placebo group. A common alternative to unblinding is to have a separate researcher assign participants to coded groups (e.g., Group A and Group B), allowing investigators to analyze data without knowing treatment allocation. However, given that only $N = 12$ participants completed the study and had usable fMRI scans, the sample was underpowered, and further subdivision would not have been feasible.

Second, the short duration of the intervention limits the generalizability of our findings. While short-term interventions can produce measurable effects, these are often not sustained over time. Additionally, participants were titrating up to the full dose of Contrave® during the 4-week intervention; therefore, even if treatment groups had been distinguished, we would not have captured the full pharmacological effects of the medication. Although evaluating short-term

neural changes is valuable, a longer-term design may have provided greater insight into the sustained impact of Contrave® when combined with a dietary intervention.

Third, there were limitations related to the fMRI task. Inhibitory control, another key process implicated in obesity, was not directly assessed. Incorporating a complementary task targeting inhibitory control would have provided a more comprehensive understanding of intervention effects. Additionally, the extent to which participants found the reward task engaging remains unclear. Future studies could incorporate post-scan questionnaires assessing task engagement, attentiveness, and other factors, such as whether participants imagined taste during the stimuli. While we asked participants about satiety, this was done approximately one hour after the scan. Collecting this information immediately before/after scanning would have allowed us to assess potential associations between hunger state and brain activity.

Finally, the absence of a healthy-weight control group limits interpretation. No prior studies have used the same task and intervention paradigm as the present research; therefore, comparisons to healthy individuals (and associated inferences) relied on the literature rather than direct data. Including a healthy control cohort in future work would enable more robust within-study comparisons.

Future directions include expanding the dataset to address sample-size limitations, recruiting healthy-weight controls, incorporating additional analyses such as resting-state fMRI, and applying models such as the psychophysiological interaction model to examine connectivity patterns associated with task-related activity. Additionally, further exploration of the BAS scales could determine whether these measures correlate with other behavioural and neuroimaging variables collected in the study, and whether they may be able to predict intervention outcome.

5.2 Conclusions

In this study, we examined how viewing food cues influences brain activity in individuals with obesity, as well as potential changes following a four-week drug/diet intervention. Our primary analyses demonstrated that viewing food cues elicited activity in reward-related regions, including the insula. Furthermore, BAS–Reward Responsiveness scores were negatively associated with brain activity at baseline (in regions like the cerebellum, middle and superior frontal gyri, and more), potentially reflecting a habituation to reward cues in individuals with obesity who derive pleasure from receiving rewards. Exploratory analyses revealed that the drug/diet intervention induced changes in brain activity in several regions, including the precuneus, a region implicated in self-awareness. Given the small sample size, the observation of measurable changes suggests that a four-week intervention may be sufficient to alter brain activity. Additionally, pre- to post-intervention changes in brain activity were strongly associated with BAS–Fun Seeking scores in several regions, including the insula, precuneus, medial frontal gyri, etc., suggesting that individuals with higher BAS–F may experience greater behavioural change, and correspondingly, greater changes in brain activity.

Overall, this study contributes to the literature on neural responses to food cues in obesity and is among the few to investigate how brain activity may be modified by a pharmacological and dietary intervention. These findings may serve as a foundation for future work aimed at predicting intervention outcomes, with the broader goal of improving understanding of Contrave®'s effects on the brain and informing its clinical use in the treatment of obesity.

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Supplementary Tables

Supplementary Table 1. *Measures and Study Protocol*

Testing Variables and Location	**Phone Screening**	**In-Person Screening**	**Intervention**					
			Baseline	Week 1	Week 2	Week 3	Week 4	Post-Intervention
Basic inclusion/exclusion criteria	**X**							
Informed Consent Form		**X**						
Test Dose Tolerability		**X**						
BDI			**X**					**X**
GAD-7			**X**					**X**
Dietary Counseling			**X**	**X**	**X**	**X**	**X**	
fMRI Imaging			**X**					**X**
Medication Dispensing			**X**					
Adverse Side Effects			**X**	**X**	**X**	**X**	**X**	
Medication Adherence				**X**	**X**	**X**	**X**	
ISI				**X**	**X**	**X**	**X**	
Godin-Shephard			**X**	**X**	**X**	**X**	**X**	

Note. Blue= administered at the IMHR. Orange= administered at home via REDCap. Green= offered at the LEAF Clinic.

Supplementary Table 2. *BAS Sub-Score Correlations*

	BAS-R vs. BAS-D	**BAS-R vs. BAS-F**	**BAS-D vs. BAS-F**
Correlation Coefficient	0.1474359	0.43049832	0.03

Note. BAS-R: Behavioural Approach System - Reward Responsiveness; BAS-D: Behavioural Approach System – Drive; BAS-F: Behavioural Approach System – Fun Seeking

Appendices

Appendix I

The Royal's
Institute of Mental Health Research
affiliated with the University of Ottawa

RESEARCH ETHICS BOARD - APPROVAL

Date: 15 May 2023

Investigator Name: Natalia Jaworska and Pierre Blier

REB Number: **2023004**

Study Title: ***Identifying the Short-Term Neurobiological, Metabolic and Behavioural Effects of CONTRAVE® as Potential Mechanisms of Weight Loss in Adults with Obesity: A Randomized, Double-Blind, Placebo-Controlled Pilot Trial***

Submission Type: Initial Application

Review Type: ☒ Full Board Review ☐ Delegated Review

Date of Approval: 15 May 2023

Approval Expiry Date: **15 May 2024**

Dear Natalia Jaworska and Pierre Blier,

Thank you for submitting the above noted study to the Royal Ottawa Health Care Group (ROHCG) REB for review. The study has been reviewed by the REB and approval has been granted. This study is approved until the expiration date noted above.

The following documents are approved:

Document Name/Title	Version	Document Version Date
Protocol	1	28 February 2023
Informed Consent Form	1	6 March 2023
Consent to Contact – LEAF Staff	1	28 February 2023
Phone Screening Script	1	16 January 2023
Debrief Script	1	16 January 2023
Safety Protocol	1	23 February 2023
Study Questionnaire	1	3 March 2023
Research Poster – Simplified	1	8 May 2023
Research Poster	1	8 May 2023

No changes to, or deviations from, the approved documents should be initiated prior to submitting an appropriate amendment and obtaining written approval from the Research Ethics Board, except when necessary to eliminate immediate hazard(s) to study participants.

An Annual Progress Report must be submitted a minimum of 30 days prior to the date of study expiration if the study will continue beyond the expiration date.

The Royal's
Institute of Mental Health Research
affiliated with the University of Ottawa

If the study is completed by the expiry date noted above, a Study Closure/Termination report must be submitted to the REB.

Sincerely on behalf of the board,

Alexis Dorland, Interim REB Coordinator
Signing for:
Ann-Marie O'Brien
Chair, ROHCG REB

Research Ethics Board Attestation

REB members who are involved in a research project under review recuse themselves from the meeting and do not take part in the review, discussion or decision related to their respective projects.

The Royal Ottawa Health Care Group REB complies with the requirements of the Tri-Council Policy Statement (TCPS2): Ethical Conduct for Research Involving Humans; International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (ICH-GCP0; Part C, Division 5 of the food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Device Regulations and the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations.

You must retain a copy of this letter for your study file

Appendix II

12/07/2023

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

CERTIFICAT D'APPROBATION ÉTHIQUE | CERTIFICATE OF ETHICS APPROVAL

Numéro du dossier / Ethics File Number	H-06-23-9364
Titre du projet / Project Title	Identifying the Short-Term Neurobiological, Metabolic and Behavioural Effects of CONTRAVE® as Potential Mechanisms of Weight Loss in Adults with Obesity: A Randomized, Double-Blind, Placebo-Controlled
Type de projet / Project Type	Recherche de professeur / Professor's research project
Statut du projet / Project Status	Approuvé / Approved
Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)	12/07/2023
Date d'expiration (jj/mm/aaaa) / Expiry Date (dd/mm/yyyy)	15/05/2024

Équipe de recherche / Research Team

Chercheur / Researcher	Affiliation	Role
Éric DOUCET	École des sciences de l'activité physique / School of Human Kinetics	Chercheur Principal / Principal Investigator
Natalia JAWORSKA	Département de médecine cellulaire et moléculaire / Department of Cellular and Molecular Medicine	Co-chercheur principal / Co-principal investigator
Gary GOLDFIELD	CHEO Research Institute	Co-chercheur principal / Co-principal investigator
Andree-Anne LEDOUX	Département de médecine cellulaire et moléculaire / Department of Cellular and Molecular Medicine	Co-chercheur / Co-investigator
Pierre BLIER		Co-chercheur principal / Co-principal investigator

Conditions spéciales ou commentaires / Special conditions or comments

The expiry date is matched with the one on the ethics certificate from the Royal Ottawa Health Care Group (ROHCG) Research Ethics Board.

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12/07/2023

Université d'Ottawa

Bureau d'éthique et d'intégrité de la recherche

University of Ottawa

Office of Research Ethics and Integrity

Le Comité d'éthique de la recherche (CÉR) de l'Université d'Ottawa, opérant conformément à l'*Énoncé de politique des Trois conseils* (2014) et toutes autres lois et tous règlements applicables, a examiné et approuvé la demande d'éthique du projet de recherche ci-nommé.

L'approbation est valide pour la durée indiquée plus haut et est sujette aux conditions énumérées dans la section intitulée "Conditions Spéciales ou Commentaires". Le formulaire « Renouvellement ou Fermeture de Projet » doit être complété quatre semaines avant la date d'échéance indiquée ci-haut afin de demander un renouvellement de cette approbation éthique ou afin de fermer le dossier.

Toutes modifications apportées au projet doivent être approuvées par le CÉR avant leur mise en place, sauf si le participant doit être retiré en raison d'un danger immédiat ou s'il s'agit d'un changement ayant trait à des éléments administratifs ou logistiques du projet. Les chercheurs doivent aviser le CÉR dans les plus brefs délais de tout changement pouvant augmenter le niveau de risque aux participants ou pouvant affecter considérablement le déroulement du projet, rapporter tout évènement imprévu ou indésirable et soumettre toute nouvelle information pouvant nuire à la conduite du projet ou à la sécurité des participants.

The University of Ottawa Research Ethics Board, which operates in accordance with the *Tri-Council Policy Statement* (2014) and other applicable laws and regulations, has examined and approved the ethics application for the above-named research project.

Ethics approval is valid for the period indicated above and is subject to the conditions listed in the section entitled "Special Conditions or Comments". The "Renewal/Project Closure" form must be completedfour weeks before the above-referenced expiry date to request a renewal of this ethics approval or closure of the file.

Any changes made to the project must be approved by the REB before being implemented, except when necessary to remove participants from immediate endangerment or when the modification(s) only pertain to administrative or logistical components of the project. Investigators must also promptly alert the REB of any changes that increase the risk to participant(s), any changes that considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project or the safety of the participant(s).

Germain ZONGO
Responsable d'éthique en recherche / Protocol Officer
Pour/For **Daniel LAGAREC** Président(e) du/ Chair of the **Comité d'éthique de la recherche en sciences de la santé et sciences / Health Sciences and Sciences Research Ethics Board**

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Appendix III

SCREENING SCRIPT – Contrave Study (REB# 2023004)

Record ID: _____ Date of screening: _____
Person carrying out screening: _____

The following information may have been obtained before the screen (e.g. from e-mail or phone mssg. Or LEAF clinic staff). Demographic data are collected to characterize the cohort and ensure that there are no differences between placebo/CONTRAVE® groups.

Name: _____ Sex: M or F

Age & DOB: _____ (Must be **18-65 yr**)

Employment: _____

Highest Level of Education:_____

Height: _____ Weight: _____ **Confirm that BMI > 30kg/m^2** _____ Handedness: L R BOTH

Telephone:_____ Email:_____

The following is intended as a guide. You do not need to read it word-for-word.
Hello (INSERT INDIVIDUAL'S NAME)
My name is (FIRST NAME) and I am a(n) (POSITION) from the Clinical EEG Lab at the Royal Ottawa Hospital. I am calling about our study on the effects of Contrave on biological, behavioural and brain changes, which you had expressed an interest in participating in.

OR

Thank you for reaching out to us to find out more about our research.

Do you have a moment so that I can explain the study to you?

The purpose of our study is to examine the effects of 4-weeks of CONTRAVE® (+ diet program – the BUDS program offered as part of the LEAF clinic) vs. control (placebo pill + diet program) on various measures. Specifically, we will measure **(a)** changes in body weight/composition; **(b)** appetite sensations and food craving; **(c)** mood; **(d)** resting energy expenditure. Most novel, we also will assess the effects of CONTRAVE® vs. control on: **(e)** the brain using brain imaging and brain electrical activity recordings, called electroencephalography (EEG). We will also measure your stress/arousal through your heart rate and sweating, and **(f)** executive functioning using a computer program.

As part of this study, you will be randomly assigned to receive either Contrave or Placebo for 4-weeks. This study is double-blinded, meaning that you, and the research staff will not know if you are taking CONTRAVE® or Placebo. This can be identified if necessary.

If you meet all the screening criteria, you will be asked to come into the Clinical EEG & Neuroimaging Laboratory at the Royal for an in-person screening visit. If you qualify, you will be asked to attend 4 more in-person laboratory visits, two at the Royal and two at a laboratory at the University of Ottawa. Also, you will be asked to complete short online questionnaires on a daily or weekly basis.

During the in-person screening visit, you will undergo a brief clinical assessment, your height and weight and vital signs will be measured, you'll complete self-reported questionnaires, and perform a cognitive task on an iPad. You will try the mock or fake brain scanner. Importantly, you will also be administered a test-

dose that can be either Contrave or placebo, you will not know what you are receiving. All adverse events during the test dose will be tracked and monitored by the study physician. Based on how you feel, you and the study physician will decide on whether you can continue in this study. This in-person screening session will last ~3.5 hrs. During much of this time, you will be in a testing room and free to work, read or watch something. If you are eligible for the study, you will be given your study medication and scheduled for two baseline testing sessions and a first appointment with a dietician from the LEAF clinic. All of these will occur within the same week.

During the baseline visit at uOttawa, you will undergo assessments of body composition and resting energy expenditure. Food taste and appetite will be measured as will taste sensitivity and odor discrimination. You will be receiving a breakfast and lunch of choice at the lab. This visit will last ~5 hrs.

Within a week from that session, you will attend an in-person baseline visit at The Royal, we will take various brain measure using two methods. The first will is called magnetic resonance imaging (MRI), which uses a machine. The second is electroencephalography (EEG) which involves placing sensors on your head to measure brain electrical activity. You will also complete various questionnaires and we will measure your heart rate and sweating. This visit will last ~ 3.5 hrs.

These two visits will be repeated at the end of the 4 week drug and diet intervention.

During the 4-week intervention you will be asked to completed daily/weekly questionnaires regarding your daily experienced side effects/adverse events to the drug, physical activity, sleep, and diet adherence using an online platform.

You will receive an individualized dietary intervention from a registered dietitian involving weekly touch points and meal planning/coaching and includes a recommendation to take a partial meal replacement with a commercial shake – this is the BUDS program that you will be enrolled in with the LEAF Clinic. The start of the BUDS program will begin the same week as you start the study medication. You will be meeting with the dietician before the start of the intervention and weekly after.

Are you still interested in participating in this study and continuing with the screen? Do you have any questions?
[IF NO]: Thank you very much for your time.

[IF YES – still interested]:

Are you currently participating in any other studies?
[IF YES]: Thank you for your time.

[If NO]: Is this a good time to do the phone screen – it may take ~15-30 minutes?
[IF NO]: Set up a time to call back:

Date: _____ Time: _____

[IF YES]: "Before having you come into the lab, we need to ask you some questions to determine if you are eligible for the study. Any information collected during this call will be kept confidential and will be destroyed if you do not qualify for the study or choose not to participate. If you qualify, this information will be kept in a safe place. Do I have your consent to proceed?"
YES NO

[IF NO]: Thank you very much for your time.

1. SEX / GENDER

I'm going to start by asking you a series of questions about your sex and gender identity..

What sex were you assigned at birth (i.e. sex on your birth certificate)? ____Male ____Female

FOR FEMALES ONLY:
Are you currently pregnant or breastfeeding?____YES ____NO **[If YES: Exclude]**

How would you describe your current menstrual status?

Premenopause (before menopause; having regular periods)? ____YES ____NO

[IF YES] - Are your menstrual cycles relatively regular? ____YES ____NO

- What is the average duration of your menstrual cycle (i.e. from the 1st day of your period to the start of your next period)? _____ days; (we will be asking participants to track their period; please make sure they can/have a tool that they use for tracking; if not, suggest tracking by using a calendar or app such as Flo®):
- Are you currently taking any hormonal contraceptive? ____YES ____NO
- Have you previously taken a hormonal contraceptive? ____YES ____NO

Perimenopause/menopause transition (changes in periods, but have not gone 12 months in a row without a period)? ____YES ____NO;
[IF YES] How long have you been in this state?_____

Postmenopause (after menopause)? ____YES ____NO
[IF YES] How long have you been in this state?_____; are you taking any hormonal therapies? ____YES ____NO;

---

2. GENERAL MEDICAL

"I am going to start by asking you a series of questions about your medical history and physical health."

Have you been diagnosed with or are you currently being treated for any major medical problems?
YES NO
[IF YES]: Which ones?
_____

Are you currently on any antidepressants, thyroid medication, or any medication that could affect appetite, such as ADHD medication (e.g., Ritalin, Vyvanse, etc.), or seizure threshold (e.g., bupropion, tamoxifen, thioridazine)?
YES NO
[IF YES]: Which ones?
_____

Are you currently on any pain medication (chronic opioid or opiate agonist (eg, methadone) or partial agonist (eg, buprenorphine)) use, or acute opiate withdrawal?
YES NO
[IF YES]: Which ones?
_____

Are you currently on any obesity medication (liraglutide, semaglutide, orlistat, or other)?
YES NO
[IF YES]: Which ones?
_____

Are you currently taking MAO inhibitors (such as phenalzine, brand name Nardil), pressor agents, coumadin, anticonvulsants, or phenylbutazone, or other bupropion-containing products (such as Wellbutrin, Wellbutrin SR, Wellbutrin XL, Aplenzin or Zyban), or CYP2B6 inhibitors (e.g ticlopidine or clopidogrel)?
YES NO
[IF YES]: Which ones?
_____

Do you have a known allergy to lactose or to other ingredients in Contrave (Naltrexone/Bupropion)?
YES NO
[IF YES]: Which ones?
_____

Have you been diagnosed with or are you currently being treated for hypertension?
YES NO
[IF YES]: Which ones?
_____

Do you have problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption?
YES NO
[IF YES]: Which ones?
_____

Have you been diagnosed with or are you currently being treated for any cardiac conditions (coronary artery disease is not exclusionary)?
YES NO
[IF YES]: Which ones?
_____

Have you been diagnosed with or are you currently being treated for diabetes?
YES NO
[IF YES]: Which ones?
_____

Do you have a history of eating disorders? (Exclude if: history of/current Bulimia Nervosa or Anorexia Nervosa; current Binge Eating Disorder (no Binge Eating Disorder in the past year is OK for inclusion))
YES NO
[IF YES]: Which ones?
_____

Have you been diagnosed with or are you currently being treated for glaucoma?
YES NO
[IF YES]: Which ones?
_____

Do you have a history of thyroid disease, chronic liver, or renal disease?
YES NO
[IF YES]: Which ones?
_____

Have you been diagnosed with or are you currently being treated for or a family history of seizures?
YES NO

[IF YES]: Which ones?
_____

Do you have a history of any neurological or neuromuscular problems? (e.g., stroke, epilepsy, brain cysts, migraines, MS).
YES NO
[IF YES]: Which ones?
_____

Have you ever had a concussion?
YES NO
[IF YES]: Did you lose consciousness? How long? ***Exclude if >5 min**_____

Have you ever been diagnosed with a development problem? (e.g., autism)
YES NO
[IF YES]: Which ones?
_____

Have you ever been diagnosed with or struggled with major learning disabilities? (e.g. severe reading problems to the extent that reading is extremely challenging, dyslexia)
YES NO (only exclusionary if they cannot do the questionnaires/complete the consents)
[IF YES]: Which ones?
_____

Do you currently use any nicotine products, including cigarettes/cigars, e-cigarettes/vaporizers, chewing tobacco, gum, etc.?
YES NO
[IF YES]: Which ones? How often? _____
Can you abstain for nicotine/nicotine products for ~3hr, as this will be required before all EEG testing.
YES NO

Are you currently pregnant and/or breastfeeding, or plan on getting pregnant during the course of the intervention? Y / N
[IF YES]: EXCLUDE

Are you currently using any oral contraceptive or intrauterine device? Y / N
[IF YES]: Which kind / brand? _____
Participant may be excluded from the MRI if they have a metal IUD; ask the brand name.

3. FURTHER MEDICAL – STUDY COMPATIBILITY - NEUROIMAGING

Have you ever had an EEG or participated in an EEG study? ___YES ___NO [IF YES]: What for/when?
_____

Have you ever had an MRI or participated in a MRI study? ___YES ___NO [IF YES]: What for/when?
_____

Do you wear eyeglasses/contacts? ___YES ___NO [IF YES]: Do you wear contact lenses/can wear them for testing?_____
[IF NO]: Inquire about glasses prescription (we have MR-compatible glasses) R:_____L:_____

OK, I'm now going to ask you some questions so that we can make sure it is safe for you to participate in brain imaging:
[ADMINISTER MRI SAFETY SCREEN – start on claustrophobia question/skip questions that were asked]

---

4. MENTAL HEALTH SECTION
Questions adapted from the Structured Clinical Interview for DSM-5 (SCID).

***Exclude patients with any current/concerning disorders (if unsure, ask PIs)**
"I am now going to ask you some questions about your mental health".

- Have you ever sought treatment or been treated for emotional or psychiatric problems? NO YES

If YES: What for? Treatment?_____

- Have you ever sought treatment or been treated for drug or alcohol use disorder? NO YES

If YES, details: _____

- Have you ever been hospitalized or visited the emergency room for emotional or psychiatric problems? NO YES

If YES: What for? Length? Location?_____

MOOD EPISODES
Depressive

- Has there been a period of time when you were feeling depressed or down most of the day nearly, every day?
  NO YES: _____
- …what about losing interest or pleasure in things you usually enjoy?
  NO YES: _____

(Skip the following if NO)
If YES: How long did this period last?
_____
If YES: When was the most recent time you felt this way?
_____
If YES: Just before this began were you: Physically ill? Drinking alcohol or using street drugs? Did this begin soon after someone close to you died?
NO YES: _____

Mania
Was there a period in your life when, for at least a continuous one week period:
-You were so happy/excited/energized that other people thought you were not your normal self and/or this was abnormal for you?
YES NO **[IF YES]**
Details?_____
-You were extremely irritable or angry for most of the time (for at least a week)? Did you fight or argue with people outside of your family? YES NO **[IF YES]**
Details?_____

[IF YES TO ABOVE] During this time:

Did you feel you had special talents or abilities?	Yes	No
[IF YES] What kinds talents/abilities_____		
Became impulsive in a way that was highly unusual for you (e.g. spent a lot of money, had sexual indiscretions)?	Yes	No
Needed significantly less sleep but did not feel tired?	Yes	No
[IF YES TO ANY OF ABOVE] Are you currently experiencing any of these feelings?	Yes	No

[IF YES] to any of above: INELIGIBLE (*please use discretion – ask about context*)

ANXIETY DISORDERS

Panic

- Have you ever had a panic attack, when you suddenly felt frightened or suddenly developed a lot of physical symptoms?

NO YES: _____

(Skip the following if NO)

If YES: Have these attacks ever come on completely out of the blue – in situations where you don't expect to be nervous or uncomfortable? NO YES: _____

If YES: Just before you began having panic attacks, were you taking any drugs, caffeine, diet pills, or any other medications? Physically ill? NO YES: _____

Do you think that participating in this study might evoke panic attacks (for those who experience them?)

NO YES: _____

Agoraphobia

- Were you ever afraid of going out of the house alone, being in crowds, standing in a line or traveling on buses or trains?

NO YES: _____

(Skip the following if NO)

If YES: What were you afraid would happen? _____

Does participant mention anxiety about being in places/situations in which escape may be difficult or embarrassing or in which help may not be available in the event of panic-like symptoms?

NO YES: _____

If YES: Just before you began having these fears, were you taking any drugs, caffeine, diet pills, or any other medications? Physically ill? NO YES: _____

Do you think that participating in this study/coming into the hospital and the University of Ottawa laboratory might evoke very pronounced anxiety (for those who report anxiety?)

NO YES: _____

Social Phobia

- Is there anything that you have been afraid to do/felt uncomfortable doing in front of other people eg. speaking, eating or writing?

NO YES: _____

(Skip the following if NO)

If YES to "Public Speaking": Do you think that you are much more uncomfortable than most people who are in a similar situation?

NO YES: _____

IF YES: What were you afraid would happen? _____

Does participant mention that exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic-attack?
NO YES:
If YES: Just before you began having these fears, were you taking any drugs, caffeine, diet pills, or any other medications? Physically ill? NO YES: _____

Do you think that participating in this study and performing certain tasks in front of research staff might evoke extreme anxiety (for those who report anxiety?)
NO YES: _____

PSYCHOTIC SYMPTOMS

Delusions

- Has it ever seemed like people were talking about you or taking special notice of you?

NO YES: _____
(Skip the following if NO)
If YES: Were you convinced they were talking about you or did you think it might have been your imagination?
NO YES: _____

- What about receiving special messages from the TV, radio, or newspaper, or from the way things were arranged around you?

NO YES: _____

- What about anyone going out of their way to give you a hard time, or trying to hurt you?

NO YES: _____

- Did you ever feel that you were especially important in some way, or that you had special powers to do things that other people couldn't do?

NO YES:
_____

- Did you ever feel that someone or something outside yourself was controlling your thoughts or actions against you will?

NO YES: _____

Auditory Hallucinations

- Did you ever hear things that other people couldn't hear, such as noises, or the voices of people whispering or talking? (were you awake at the time?)

NO YES: _____
(Skip the following if NO)
If YES: What did you hear? How often did you hear it?_____
If VOICES: Did they comment on what you were doing or thinking_____
How many voices did you hear? Were they talking to each other? _____

Visual Hallucinations

- Did you ever have visions or see things that other people couldn't see? (were you awake at the time?)

NO YES: _____

I'm now going to ask you some questions about your substance use. Can you let me know whether you consume the following?

Coffee/tea/energy drinks: ___YES ___NO _____times per day/week
Smoker: ___YES ___NO (exclude if smoker)
Do you use vaporizers or e-cigarettes? ___YES ___NO
[IF YES]: How frequently throughout the day/for how long (calculate approx. TOTAL LIFETIME cigarette use)? _____
[Exclude: if 1x/day use or -if unsure- discuss with PI/decide on case-by-case basis]
Have you ever been a smoker/regularly used e-cigarettes? ___YES ___NO [IF YES]: Details?__
_____
(calculate approx. TOTAL LIFETIME cigarette use)

ALCOHOL & DRUG USE

Alcohol use

- What are your drinking habits like? (How much do you drink?)_____
- Average per week or month?_____ When did you start drinking?_____
- Once you started drinking, was it the same as your current use?_____
- When in your life were you drinking the most? (How long did that period last?)

Record time of heaviest use and describe pattern:_____

During that time…

- How often were you drinking? _____
- What were you drinking? How much? _____
- Did your drinking cause problems for you? _____
- Did anyone object to your drinking?_____

*If PAST or CURRENT alcohol dependence seems likely, then participant likely **CANNOT** participate in this study. Use discretion (consider age etc.).*

DRUG & MEDICINE USE

*Any past or current substance use disorder is an exclusion criteria. Cannabis use may be okay, as long as they abstain 2 weeks prior to testing - use discretion.

- Have you ever become dependent on a prescribed medication or taken a lot more of it than you were supposed to? NO YES
- Have you **ever** used street drugs? NO YES

(Skip the following section if NO)

If YES: Have you ever used any of the following:

Circle the name of each drug ever used (or write in name if other)	Period of heaviest use (age or date, duration) & **describe pattern of use (THE MORE DETAILS THE BETTER)**	Level of use
Sedatives - hypnotics – anxiolytics:	_____ _____ _____	1 2 3

Quaalude, Seconal, Valium, Xanax, Librium, barbiturates, Miltown, Ativan, Dalmane, Halcion, Restoril, or other : _____		
Cannabis: marijuana, hashish , THC, or other: _____		1 2 3
Stimulants: amphetamine, "speed", crystal meth, dexadrine, Ritalin, "ice", or other: _____		1 2 3
Opioids: heroin, morphine, opium, Methadone, Darvon, codein, Percodan, Demerol, Dilaudid, unspecified or other: _____		1 2 3
Cocaine: intranasal, IV, freebase, crack, "speedball", unspecified or other: _____		1 2 3
Hallucinogens/PCP: LSD, mescaline, peyote, psilocybin, STP, mushrooms, PCP ("angel dust"), Ecstasy, MDMA, or other: _____		1 2 3
Other: steroids, "glue", paint, inhalants, nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers"), nonprescription sleep or diet pills, unknown, or other:		1 2 3

Family Interview for Genetic Studies (FIGS): Adapted General Screening Questions

In your immediate family – these include your parents, siblings, offspring/children and spouses does anyone have a developmental disability, depression, neurological/neurodevelopmental disorder, attempted or completed suicide?

YES NO [IF YES]
Details?_____

This study will require you to abstain from caffeine for 6hr before your test sessions (decaf is fine). Abstinence from alcohol and over-the-counter drugs (e.g. Benadryl, Nyquil etc.) is also required from midnight the night before your visit. We will also ask that you abstain from street drugs for 2-3wk prior to testing. We will ask you to provide a urine sample during the in-person screening session and potentially before the testing session to confirm abstinence. Do you think this would be a problem? ___YES ___NO

[FEMALE] In order to adequately schedule your testing, we require that you to keep track of your menstrual day. Do you think this would be a problem? ___YES ___NO *Suggest app, diary/calendar if needed*

As mentioned, our testing occurs at the Royal Hospital on 1145 Carling Ave – do you know where it is? Do you anticipate any difficulties in getting to/from the test sessions?_____

Will you require any reimbursement for bus tickets or parking? ___YES ___NO

"Just a few final questions before we wrap up."

As mentioned, this study will require that you attend 5 in-person sessions at the Royal Ottawa Hospital and at the University of Ottawa. We will be as flexible as possible in scheduling sessions to suit your schedule, and we know that occasionally you cannot attend. However, good attendance is important to this study. Do you foresee any issues with this commitment, or any scheduling conflicts that might prevent you from attending any of these sessions over the next 4-5 weeks?
NO YES:_____

If participant seems PERFECT for the study (i.e., no red flags):
Based on this preliminary screen, you seem like a great candidate for the study. Do you have any questions and are you still interested in participating?

[IF YES]: Great! I would like to tentatively schedule you to come in for your in-person screening session, although I must first review your file with my supervisor.

Is there a date/time that would work for your initial visit? ***Obtain more than 1 if possible to allow for flexibility***

_____
Alright, I will email or call you to confirm an appointment date as soon as possible. [Confirm phone email] Thank you.

If participant DOES NOT seem perfect for the study/there are some concerns:
Based on this preliminary screen, you seem like you may qualify for study participation. However, I will need to review this interview with one of the researchers to be sure. While I have you on the phone, why don't we tentatively schedule the first visit in the event that your file is approved? I will call/email you regardless to let you know the outcome.
Is there a date/time that would work for your initial visit? ***Obtain more than 1 if possible to allow for flexibility***

Do you have any further questions?

NOTES:

Appendix IV

Contrave Study – February 2024

Checklist of Adverse Events – Test-Dose Monitoring

Participant ID: CBS_____ **DATE: _____**

BASELINE adverse events **TIME: _____**

Please rate how you have felt **since taking the medication** by circling **one** of the following four options for each listed symptom.

1 – No symptoms at all; **2** – Mild symptoms; **3** – Moderate symptoms; **4** – Severe symptoms.

1.	Nausea	1	2	3	4
2.	Constipation	1	2	3	4
3.	Headache	1	2	3	4
4.	Vomiting	1	2	3	4
5.	Dizziness	1	2	3	4
6.	Insomnia	1	2	3	4
7.	Dry mouth	1	2	3	4
8.	Diarrhea	1	2	3	4
9.	Heart palpitations	1	2	3	4
10.	Tinnitus, Vertigo	1	2	3	4
11.	Tooth ache	1	2	3	4
12.	Abdominal pain	1	2	3	4
13.	Feeling jittery	1	2	3	4
14.	Tremor	1	2	3	4
15.	Changes in taste of food	1	2	3	4
16.	Disturbance in attention	1	2	3	4
17.	Lethargy	1	2	3	4
18.	Hot flush	1	2	3	4
19.	Hypertension	1	2	3	4
20.	Skin rash/itchy	1	2	3	4
21.	Excessive sweating	1	2	3	4
22.	Hair loss	1	2	3	4
23.	Agitation	1	2	3	4
24.	Anxiety	1	2	3	4

Blood pressure:_____; Heart rate:_____; SpO2:_____

Clinician's notes:

Clinician's signature: _____

1-hour post-administration adverse events **TIME: _____**

Please rate how you have felt **since taking the medication** by circling **one** of the following four options for each listed symptom.

1 – No symptoms at all; **2** – Mild symptoms; **3** – Moderate symptoms; **4** – Severe symptoms.

1.	Nausea	1	2	3	4
2.	Constipation	1	2	3	4
3.	Headache	1	2	3	4
4.	Vomiting	1	2	3	4
5.	Dizziness	1	2	3	4
6.	Insomnia	1	2	3	4
7.	Dry mouth	1	2	3	4
8.	Diarrhea	1	2	3	4
9.	Heart palpitations	1	2	3	4
10.	Tinnitus, Vertigo	1	2	3	4
11.	Tooth ache	1	2	3	4
12.	Abdominal pain	1	2	3	4
13.	Feeling jittery	1	2	3	4
14.	Tremor	1	2	3	4
15.	Changes in taste of food	1	2	3	4
16.	Disturbance in attention	1	2	3	4
17.	Lethargy	1	2	3	4
18.	Hot flush	1	2	3	4
19.	Hypertension	1	2	3	4
20.	Skin rash/itchy	1	2	3	4
21.	Excessive sweating	1	2	3	4
22.	Hair loss	1	2	3	4
23.	Agitation	1	2	3	4
24.	Anxiety	1	2	3	4

Blood pressure:_____; Heart rate:_____; SpO2:_____

Clinician's notes:

Clinician's signature: _____

3-hours post-administration adverse events **TIME: _____**

Please rate how you have felt **since taking the medication** by circling **one** of the following four options for each listed symptom.

1 – No symptoms at all; **2** – Mild symptoms; **3** – Moderate symptoms; **4** – Severe symptoms.

1.	Nausea	1	2	3	4
2.	Constipation	1	2	3	4
3.	Headache	1	2	3	4
4.	Vomiting	1	2	3	4
5.	Dizziness	1	2	3	4
6.	Insomnia	1	2	3	4
7.	Dry mouth	1	2	3	4
8.	Diarrhea	1	2	3	4
9.	Heart palpitations	1	2	3	4
10.	Tinnitus, Vertigo	1	2	3	4
11.	Tooth ache	1	2	3	4
12.	Abdominal pain	1	2	3	4
13.	Feeling jittery	1	2	3	4
14.	Tremor	1	2	3	4
15.	Changes in taste of food	1	2	3	4
16.	Disturbance in attention	1	2	3	4
17.	Lethargy	1	2	3	4
18.	Hot flush	1	2	3	4
19.	Hypertension	1	2	3	4
20.	Skin rash/itchy	1	2	3	4
21.	Excessive sweating	1	2	3	4
22.	Hair loss	1	2	3	4
23.	Agitation	1	2	3	4
24.	Anxiety	1	2	3	4

Blood pressure:_____; Heart rate:_____; SpO2:_____

Clinician's notes:

Participant release time: _____

Approved by clinician:

☐ YES
☐ NO

Clinician's signature: _____

Participant approval ___YES ___NO; and signature: _____

Appendix V

BIS/BAS

Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says. Please respond to all the items; do not leave any blank. Choose only one response to each statement. Please be as accurate and honest as you can be. Respond to each item as if it were the only item. That is, don't worry about being "consistent" in your responses. Choose from the following four response options:

1 = very true for me
2 = somewhat true for me
3 = somewhat false for me
4 = very false for me

1. A person's family is the most important thing in life. ____
2. Even if something bad is about to happen to me, I rarely experience fear or nervousness. ____
3. I go out of my way to get things I want. ____
4. When I'm doing well at something I love to keep at it. ____
5. I'm always willing to try something new if I think it will be fun. ____
6. How I dress is important to me. ____
7. When I get something I want, I feel excited and energized. ____
8. Criticism or scolding hurts me quite a bit. ____
9. When I want something I usually go all-out to get it. ____
10. I will often do things for no other reason than that they might be fun. ____
11. It's hard for me to find the time to do things such as get a haircut. ____
12. If I see a chance to get something I want I move on it right away. ____
13. I feel pretty worried or upset when I think or know somebody is angry at me. ____
14. When I see an opportunity for something I like I get excited right away. ____
15. I often act on the spur of the moment. ____
16. If I think something unpleasant is going to happen I usually get pretty "worked up." ____
17. I often wonder why people act the way they do. ____
18. When good things happen to me, it affects me strongly. ____
19. I feel worried when I think I have done poorly at something important. ____
20. I crave excitement and new sensations. ____
21. When I go after something I use a "no holds barred" approach. ____
22. I have very few fears compared to my friends. ____
23. It would excite me to win a contest. ____
24. I worry about making mistakes. ____

Appendix VI

Category	Filename	SubCategory
HighCal	0049.jpg	Sweet
HighCal	0041.jpg	Sweet
Neutral	1007.jpg	NA
LowCal	0576.jpg	Savoury
Neutral	1198.jpg	NA
Neutral	1149.jpg	NA
HighCal	0061.jpg	Savoury
LowCal	0429.jpg	Savoury
Neutral	1129.jpg	NA
Neutral	1086.jpg	NA
LowCal	0784.jpg	Sweet
HighCal	0053.jpg	Savoury
HighCal	0117.jpg	Savoury
HighCal	0022.jpg	Savoury
LowCal	0213.jpg	Savoury
HighCal	0004.jpg	Sweet
HighCal	0145.jpg	Savoury
LowCal	0267.jpg	Savoury
LowCal	0364.jpg	Savoury
Neutral	1210.jpg	NA
HighCal	0074.jpg	Sweet
Neutral	1060.jpg	NA
HighCal	0062.jpg	Savoury
Neutral	1013.jpg	NA
LowCal	0526.jpg	Savoury
Neutral	1011.jpg	NA
LowCal	0566.jpg	Savoury
LowCal	0659.jpg	Savoury
LowCal	0407.jpg	Sweet
HighCal	0144.jpg	Savoury
LowCal	0282.jpg	Sweet
HighCal	0109.jpg	Savoury
LowCal	0192.jpg	Sweet
Neutral	1135.jpg	NA
Neutral	1240.jpg	NA
LowCal	0275.jpg	Savoury
HighCal	0002.jpg	Savoury
Neutral	1278.jpg	NA
HighCal	0055.jpg	Sweet
LowCal	0396.jpg	Sweet
LowCal	0256.jpg	Sweet
Neutral	1004.jpg	NA

HighCal	0028.jpg	Sweet
LowCal	0382.jpg	Savoury
Neutral	1234.jpg	NA
HighCal	0016.jpg	Sweet
Neutral	1245.jpg	NA
HighCal	0063.jpg	Savoury
LowCal	0209.jpg	Sweet
Neutral	1033.jpg	NA
LowCal	0281.jpg	Sweet
Neutral	1226.jpg	NA
HighCal	0008.jpg	Savoury
Neutral	1144.jpg	NA
LowCal	0222.jpg	Sweet
LowCal	0206.jpg	Sweet
HighCal	0186.jpg	Savoury
LowCal	0805.jpg	Sweet
LowCal	0406.jpg	Savoury
HighCal	0025.jpg	Sweet
HighCal	0026.jpg	Savoury
Neutral	1251.jpg	NA
Neutral	1027.jpg	NA
LowCal	0200.jpg	Sweet
LowCal	0288.jpg	Savoury
Neutral	1146.jpg	NA
Neutral	1261.jpg	NA
HighCal	0031.jpg	Sweet
Neutral	1155.jpg	NA
HighCal	0056.jpg	Sweet
Neutral	1028.jpg	NA
LowCal	0244.jpg	Savoury
HighCal	0082.jpg	Savoury
HighCal	0048.jpg	Sweet
Neutral	1019.jpg	NA
HighCal	0128.jpg	Sweet
HighCal	0132.jpg	Savoury
LowCal	0528.jpg	Sweet
Neutral	1230.jpg	NA
Neutral	1036.jpg	NA
LowCal	0250.jpg	Savoury
LowCal	0811.jpg	Savoury
Neutral	1009.jpg	NA
LowCal	0201.jpg	Savoury
HighCal	0140.jpg	Sweet

HighCal	0149.jpg	Savoury
Neutral	1059.jpg	NA
LowCal	0389.jpg	Sweet
HighCal	0103.jpg	Sweet
LowCal	0226.jpg	Savoury
HighCal	0085.jpg	Savoury
Neutral	1262.jpg	NA
Neutral	1022.jpg	NA
Neutral	1274.jpg	NA
Neutral	1250.jpg	NA
HighCal	0079.jpg	Sweet
HighCal	0067.jpg	Sweet
HighCal	0066.jpg	Savoury
LowCal	0269.jpg	Sweet
LowCal	0229.jpg	Savoury
Neutral	1134.jpg	NA
Neutral	1140.jpg	NA
LowCal	0247.jpg	Savoury
Neutral	1046.jpg	NA
Neutral	1313.jpg	NA
LowCal	0560.jpg	Savoury
HighCal	0167.jpg	Sweet
LowCal	0398.jpg	Sweet
HighCal	0001.jpg	Sweet
LowCal	0263.jpg	Savoury
HighCal	0018.jpg	Sweet
LowCal	0255.jpg	Sweet
HighCal	0108.jpg	Savoury
Neutral	1256.jpg	NA
Neutral	1016.jpg	NA
LowCal	0199.jpg	Sweet
LowCal	0202.jpg	Sweet
HighCal	0110.jpg	Savoury
HighCal	0029.jpg	Sweet
Neutral	1277.jpg	NA