Mapping and modulation of brain homeostatic and self-control systems for appetitive behaviour

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Abstract

Obesity is a multifactorial neurobehavioural disease, which is currently a leading risk factor for mortality worldwide. Weight gain is attributed primarily to overconsumption of foods that are cheap and abundant in the modern environment. The neural processes leading to optimal food intake need to be understood in order to estimate abnormalities in obesity. It is thought that there are three interrelated neural systems that interact with the environment to influence dietary decisions and food intake in humans. The first one is the homeostatic system, where peripheral peptides such as ghrelin interact with the hypothalamus to communicate energy balance information. However, homeostatic hunger does not alone drive food craving and intake, and can be overridden by hedonic aspects of foods and their related cues that activate the appetitive system. This second system is thought to encode and update value of cues associated with food reward, largely via dopamine. The third, or self-control system engages processes including inhibitory control and value modulation to regulate food craving and intake to meet health-related goals, habits and other factors. Overeating and weight gain are partly attributed to overreactive appetitive system and blunted self-control system, which is reflected in a personality trait, Uncontrolled Eating that predicts body mass index and food intake.

This thesis primarily aimed to modulate the homeostatic and self-control networks to test directly how the systems interact with one another to influence eating-related behaviours in healthy humans. In the first study, participants were administered ghrelin, a homeostatic orexigenic signal known to stimulate dopamine, to test the role of the hormone on food-odour learning in the brain. We observed behaviourally that ghrelin enhanced conditioning specific to food cues, which was associated with activation in dopaminergic brain regions. The second study took a meta-analytic approach to identify brain regions consistently involved in eating-specific self-control, and their

relation to body mass index. It was revealed that neuroimaging tasks of dietary self-control mainly tap into value modulation and/or inhibitory control, which engage both common and distinctive neural networks. The third study used transcranial magnetic stimulation to modulate the dorsolateral prefrontal cortex, a brain region engaged during food-craving regulation, to examine its role in food decision making in individuals with high and low scores on a questionnaire assessing Uncontrolled Eating. We found that the high Uncontrolled-Eating group compared to the low exhibited greater activation during food-craving regulation in some brain regions (including the stimulation target) and networks known to subserve self-control. Moreover, stimulation effects on food decisions were present only in the high Uncontrolled-Eating group.

The thesis utilized modulation approaches to observe interactions among the neural systems involved in appetite control. By doing so, it complemented findings of modulatory animal research and correlational studies that are most commonly performed in humans. The results confirm the impacts of the homeostatic and self-control systems on food cue learning and computation via the appetitive system. However, the extent of influence of the self-control system on the appetitive system appears to depend on a personality trait related to obesity, which may suggest that individuals at risk for obesity may be characterized by differential responsivity of their appetite control networks to stimulation and during food value modulation. The work presented in this thesis furthers our knowledge of how the homeostatic, appetitive and self-control systems may interact with one another to influence eating-related behaviours.

Résumé

L'Obésité est une maladie neurocomportementale multifactorielle, dont le risque de mortalité est planétaire. La prise de poids est principalement attribuée à une surconsommation de nourriture bon marché, en abondance dans un environnement moderne. Les procédés neuronaux qui guident à une consommation optimale d'aliments méritent d'être compris afin d'évaluer les anormalités liées à l'obésité. Chez l'humain, trois systèmes semblent interagir avec l'environnement afin d'influencer les décisions en matière de diète et d'alimentation. Le premier est le système homéostatique, dans lequel les peptides périphériques tels que la ghréline interagissent avec l'hypothalamus pour transmettre la balance énergétique. En revanche, la faim homéostatique n'est pas seule responsable du désir et de l'ingestion d'aliments, et peut être surpassée par des aspects hédoniques de ceux-ci, et l'élément déclencheur du système d'appétit. Ce second système est connu pour coder et mettre à jour la valeur des signaux déclenchant la récompense procurée par l'aliment, principalement par le biais de la dopamine. Le troisième, le système de la maîtrise de soi fait appel à des procédés incluant le contrôle inhibitoire et la modulation de la valeur capables de réguler l'envie et la consommation alimentaire à des fins saines et pour d'autres objectifs. La suralimentation et la prise de poids sont en partie attribuées à un système d'appétit plus réactif et une maîtrise de soi altérée, reflet d'un trait de personnalité, alors que l'alimentation dîte non contrôlée (« Uncontrolled Eating ») permet de prédire l'indice de masse corporelle et la consommation alimentaire.

Cette thèse s'intéresse dans un premier temps à la modulation des réseaux homéostatique et de la maîtrise de soi afin d'évaluer comment les systèmes interagissent entre eux pour influencer le comportement alimentaire chez l'humain. Dans la première étude, les participants reçoivent de la ghréline, dont le signal homéostatique orexigène stimule la dopamine, afin de tester le rôle de l'hormone dans l'association par le cerveau de l'aliment avec l'odeur. La seconde étude utilise une

approche méta-analytique pour identifier les régions du cerveau impliquées de manière consistante dans la maîtrise de soi face à l'alimentation, et leur corrélation avec l'indice de masse corporelle. Des investigations en neuro-imagerie sur la maîtrise diététique de soi mettent en évidence la modulation de la valeur et/ou le contrôle inhibitoire, tous deux engagés dans des réseaux neuronaux aussi communs que distinctes. La troisième étude utilise la simulation magnétique transcranienne afin de moduler le cortex préfrontal dorsolatéral, une région cérébrale impliquée dans la régulation de l'envie alimentaire, et d'évaluer son rôle dans la prise de décision chez les individus avec un fort et faible score dans l'évaluation de leur alimentation dîte non contrôlée (« Uncontrolled Eating »). Nous avons trouvé que le groupe avec une forte « Uncontrolled Eating », contrairement au groupe avec un faible score, montre une plus haute activation dans certaines régions (incluant la zone sujette à la stimulation) et réseaux du cerveau engagés dans la maîtrise de soi. De plus, les effets de la stimulation sur les décisions dans l'alimentation sont seulement présents dans ce même groupe.

Cette thèse s'appuie sur les approches modulatoires pour observer les interactions au sein des systèmes neuronaux impliqués dans le contrôle de l'appétit. Ceci complète ainsi les découvertes dans la recherche modulatoire chez l'animal, et les études de corrélation, plus courantes chez l'humain. Les résultats confirment les impacts des systèmes homéostatiques et de la maîtrise de soi dans l'apprentissage des signaux stimulants alimentaires et l'évaluation par le biais du système qui régule l'appétit. Cependant, l'étendue de l'influence du système de la maîtrise de soi sur celui de l'appétit semble dépendre d'un trait de la personnalité lié à l'obésité. Cela suggérait que les individus présentant un risque d'obésité pourraient être caractérisés par une différente réactivité de leurs réseaux de maîtrise de l'appétit aux stimulations et pendant la modulation de la valeur alimentaire. Le travail présenté dans cette thèse aspire à faire avancer nos connaissances sur la manière dont les systèmes homéostatique, de l'appétit, et de la maîtrise de soi peuvent interagir entre eux pour influencer les comportements liés à l'alimentation.

Contributions of Authors

The work presented in this thesis is original scholarship and a distinct contribution of knowledge.

Chapter 1

The general introduction was completed by Jung Eun Han with the supervision of Dr. Alain Dagher and Dr. Robert J. Zatorre.

Chapter 2:

Han, J. E., Frasnelli, J. A., Zeighami, Y., Larcher, K., Boyle, J. A., McConnell, T., Malik, S., Jones-Gotman, M., & Dagher, A. (2018). Ghrelin enhances food odor conditioning in healthy humans: an fMRI study. *Cell Reports*, *25*, 2643-2652.e4.

Jung Eun Han completed the majority of work involved in this experiment, including study design, data collection and analysis, and preparation of the manuscript. Dr. Johannes Frasnelli, Julie Boyle, Dr. Marilyn Jones-Gotman and Dr. Saima Malik contributed to study design, Julie Boyle and Ted McConnell helped with data collection, and Dr. Johannes Frasnelli, Dr. Yashar Zeighami and Kevin Larcher provided assistance in data analysis. Dr. Alain Dagher provided guidance and feedback throughout the experiment and helped revise the manuscript.

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Han, J. E., Boachie, N., Garcia-Garcia, I., Michaud, A., & Dagher, A. (2018). Neural correlates of dietary self-control in healthy adults: A meta-analysis of functional brain imaging studies. *Physiology & behavior*. *192,* 98-108.

Jung Eun Han was involved in all aspects of this study, namely experimental design, data collection,

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Jung Eun Han planned and conducted the experiment, analyzed data, and prepared the manuscript. Dr. Uku Vainik and Dr. Travis Baker contributed to study design, Jennifer Guan, Dr. Travis Baker and Jose C.G. Alanis helped with data collection, and Dr. Thomas Hinault and Kevin Larcher provided assistance in data analysis. Dr. Alain Dagher provided guidance and feedback throughout the study and helped revise the manuscript.

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Other contributions (not elaborated in the thesis)

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Dagher, A., Neseliler, S., & Han, J. E. (2017). Appetite as Motivated Choice: Hormonal and Environmental Influences. In *Decision Neuroscience* (pp. 397-409).

Vainik, U., Han, J. E., Epel, E., Tomiyama, J., Dagher, A., & Mason, A. (2018). Rapid Assessment of Reward-Related Eating: The RED-X5. Accepted in *Obesity*

Chapter 1 - Introduction

1.1 Overview

Overweight and obesity are now leading risk factors for mortality as it has increasingly contributed to deaths by many severe illnesses such as cardiovascular disease, diabetes and musculoskeletal disorders (Foreman et al., 2018). The World Health Organization (WHO) estimated in 2016 that globally about 39% of adults were overweight (body mass index (BMI) between 25 and 29) and 13% were obese (BMI of 30 or above). Canada is one of the most overweight countries with 43% of males and 31% of females being overweight, and 20% of men and 21% of women living with obesity (GBD 2015 Obesity Collaborators et al., 2017). Understandably, therefore much effort has been dedicated to elucidating underlying mechanisms of obesity.

Weight gain results from an imbalance of energy consumption and expenditure, which has numerous causes, including genetic, neurobiological, environmental, behavioural and cognitive factors. Overeating or consumption beyond homeostatic need is facilitated by the contemporary environment that is replete with easily accessible and energy-dense foods. In such a context, humans frequently need to refrain from or limit consumption of calorie-dense foods, which are innately preferred, in order to prevent overeating and weight gain (Drewnowski, 1997; Mennella & Bobowski, 2015). The neural processes leading to optimal food decisions need to be understood, in order to understand the neurocognitive factors that lead to obesity. It is thought that there are three interrelated neural systems that interact with the environment to influence dietary decisions and food intake in humans (Neseliler, Han, & Dagher, 2017). As illustrated in Figure 1.1, the systems are 1) the homeostatic system, in which the peripheral peptides interact with the hypothalamus to

communicate energy balance information, 2) the appetitive network, which encodes and updates value of food-related cues, and 3) an executive system centred on the prefrontal brain regions suggested to modulate activity in the appetitive network and exert control over eating. Here I will refer to this 3rd system as the self-control system.

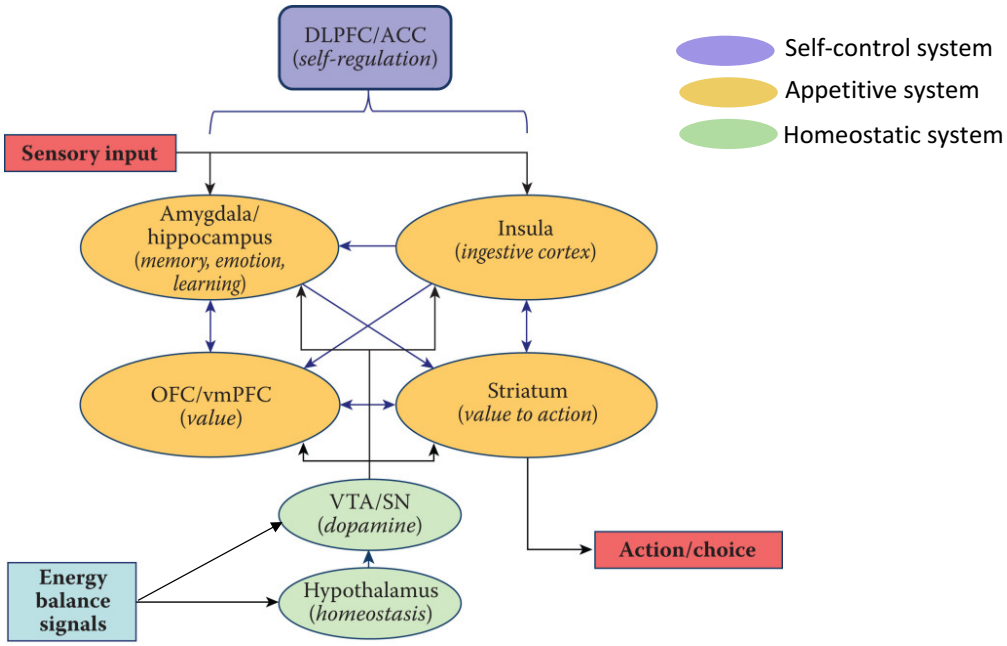

Figure 1.1. The neural systems of appetite control: Three interrelated circuits in the brain influence eating, which are 1) the homeostatic system involving the interaction between energy balance signals and the hypothalamus (green circle in the diagram), 2) the appetitive system that responds to food cues (yellow circle), and 3) the self-control system that regulates reward responses in the appetitive system and action selection (purple circle) (Neseliler et al., 2017).

1.2 Homeostatic system

Energy homeostasis is a process that regulates feeding and energy expenditure to ensure stability of body weight over time and constant availability of stored energy needed for cellular function. Homeostasis is theorized to detect negative feedback that arises whenever an internal regulated variable is deviated from its optimal value and to elicit corrective responses to restore the variable to its optimal level (Cannon, 1929). Readers should keep in mind an alternative model, referred to as allostasis, that is less reactive compared to homeostasis, and aimed at promoting reproduction and

survival (Sterling, 2012). Allostasis is thought to elicit anticipatory responses to prevent potential perturbations based on learned errors, and relies on brain regions involved in learning and control. The allostatic model therefore seems to better explain eating behaviours in humans that depend on a variety of factors such as habits, cues and stress. Nevertheless, the brain also regulates feeding in response to information conveyed through peripheral homeostatic signals. The hypothalamus is a critical region that enables this process, as it interacts with the key energy-balance hormones (Timper & Brüning, 2017; Waterson & Horvath, 2015).

1.2.1 Hypothalamus

The hypothalamus is the key regulator of energy homeostasis. Owing to its small size and its location, the hypothalamus is hard to study in humans with currently available neuroimaging techniques, and thus much of our knowledge of this region comes from animal research. Among about a dozen nuclei in the hypothalamus, the arcuate nucleus (ARC) is considered the key controller of feeding and metabolism (Myers & Olson, 2012). ARC is located adjacent to a circumventricular organ (median eminence) lacking blood-brain barrier, and contains neurons that are receptive to the blood-borne hormones and other molecules, which facilitate peripheral signalling to the brain (Rodríguez, Blázquez, & Guerra, 2010). The two relevant neuron groups in the ARC are the AgRP/NPY neurons that express neuropeptide Y (NPY) and agouti-related peptide (AgRP), and pro-opiomelanocortin (POMC)-expressing neurons (Balthasar et al., 2005; Gropp et al., 2005). The AgRP/NPY neurons are considered to stimulate appetite as they are activated upon fasting, and release NPY and AgRP to trigger food intake and reduce energy expenditure (Clark, Kalra, Crowley, & Kalra, 1984; Stanley & Leibowitz, 1984). On the other hand, POMC neurons have appetite-suppressing effects by acting on second-order neurons in the other parts of the hypothalamus such as the paraventricular hypothalamic nucleus (Kleinridders, Könner, & Brüning, 2009; Leibowitz, Hammer, & Chang, 1981; Waterson & Horvath, 2015). Furthermore, the AgRP/NPY neurons appear to directly inhibit POMC neurons to influence feeding and metabolism (Cowley et al., 2001).

1.2.2 Peripheral signals

To regulate homeostatic food intake, the hypothalamus receives information about energy balance from peripheral peptides such as leptin, insulin and ghrelin. In anticipation of a meal or following eating, insulin is released from pancreatic β cells (Ramsay & Woods, 2016). It can bind to insulin receptors on the POMC neurons to modulate their firing and increase POMC mRNA expression (Benoit et al., 2002; Könner et al., 2007; Prentki, Matschinsky, & Madiraju, 2013; Williams et al., 2010), or act on the AgRP/NPY neurons to decrease neuronal firing (Könner et al., 2007). Insulin also induces leptin that is derived from adipose tissue in proportion to whole-body fat mass (Myers & Olson, 2012; Russell, Ricci, Brolin, Magill, & Fried, 2001). Leptin, a marker of body adiposity and energy stores, binds to its receptors on the POMC and AgRP/NPY neurons to increase firing of the former and inhibit activity of the latter, through which it reduces food intake and heightens energy expenditure (Sohn et al., 2013). While leptin and insulin have satiety effects, another hormone, ghrelin, promotes eating. A study presented in this thesis explores ghrelin as a peptide hormone that regulates food intake, in order to further investigate findings of a previous study conducted in our laboratory (Malik, McGlone, Bedrossian, & Dagher, 2008), and thus here I elaborate on the function of ghrelin.

1.2.2.1 Ghrelin's role in homeostatic feeding

In contrast to insulin and leptin, the gut-derived ghrelin exerts appetite-stimulating effects. Since its discovery in 1999, ghrelin has remained the only known orexigenic hormone produced in the periphery (Muller et al., 2002). Its levels rise prior to scheduled mealtimes and after fasting, and fall postprandially (Cummings, 2004; Cummings et al., 2001; Muller et al., 2002). Ghrelin injection triggers hunger and food intake in the short term while long-term administration can promote fat accumulation (Druce et al., 2005; Nakazato et al., 2001a; Tschöp, Smiley, & Heiman, 2000; Wren et al., 2001). This 28-amino acid peptide, which is synthesized in the stomach, is proposed to communicate with the central nervous system through two pathways: the vagus nerve and the blood. Blood-borne ghrelin is known to reach the brain where it can bind to its unique receptor, the growth hormone secretagogue receptor type 1a (GHSR1a), to stimulate secretion of growth hormone (Yanagi, Sato, Kangawa, & Nakazato, 2018). In order to bind to GHSR1a, ghrelin needs to be

acylated through GOAT, the only known enzyme responsible for the acylation process (Yanagi et al., 2018). It is notable that in rats, about 67% (stomach) and 90% (blood) of total ghrelin represents desacyl ghrelin that does not bind to GHSR1a and may have its own receptors that remain unidentified (Hosoda, Kojima, Matsuo, & Kangawa, 2000). In the ARC of the hypothalamus, about 94% AgRP/NPY neurons and about 8% of POMC neurons contain GHSRs (Willesen, Kristensen, & Rømer, 1999). Ghrelin stimulates feeding by activating AgRP/NPY neurons while suppressing POMC neurons (Andrews et al., 2008; Tong, Ye, Jones, Elmquist, & Lowell, 2008). In influencing homeostatic feeding, ghrelin's actions extend to other parts of the hypothalamus including the lateral hypothalamus (LH) that generates appetite-stimulating neuropeptides such as orexin. It appears that ghrelin activates orexin in the LH to induce feeding (Hsu et al., 2015).

1.3 Appetitive system

Even in the absence of energy deficits, food craving and eating can be induced by cues that trigger memories of eating-derived pleasure (Boswell & Kober, 2016). This reflects that the homeostatic system involving the hypothalamus and metabolic signals does not alone govern food decisions and consumption. The hypothalamus is directly connected to the ventral tegmental area (VTA) that releases dopamine (DA) to compute rewarding aspects of food, allowing homeostatic and hedonic signals to interact. For instance, activation of neurons in the LH leads to stimulation of VTA dopaminergic neurons (Sheng, Santiago, Thomas, & Routh, 2014). Increased food motivation is observed following activation of GABAergic projection from the LH to the VTA, which may increase DA firing neuron rate via inhibition of VTA GABAergic interneurons (Barbano, Wang, Morales, & Wise, 2016; Jennings et al., 2015; Nieh et al., 2016). The hedonic system can also influence homeostasic signals, as shown by the finding that food-related cues that promote eating can induce release of metabolic hormones such as ghrelin (Schüssler et al., 2012).

The hedonic system can be more readily studied in humans using techniques such as functional magnetic resonance imaging (fMRI). FMRI essentially measures task-induced changes in blood oxygenation levels that are thought to reflect changes in neural activity (please see the Thesis Methodology section for more details about fMRI). Results of fMRI studies are interpreted as

measures of task-related activity in brain regions and their interactions. In support of above-mentioned animal research demonstrating the interaction between the homeostatic and hedonic systems, a human resting-state fMRI study demonstrated functional coupling between the hypothalamus and the brain regions that are receptive to dopaminergic input from the midbrain (Kullmann et al., 2014). These brain regions include the striatum, amygdala, insula, orbitofrontal cortex (OFC)/ventromedial prefrontal cortex (vmPFC) and collectively can be considered to make up the "appetitive" network (Dagher, 2012).

1.3.1 Food cues and dopamine

Food-associated cues (e.g., sight, smell and flavour of food) have the ability to override homeostatic hunger. Even in the absence of energy deficits, the cues can induce behavioural, physiological and neural responses associated with eating (Boswell & Kober, 2016). They trigger hunger and food craving while increasing salivation and raise the levels of hormones such as ghrelin and insulin. Food-related cues are therefore excellent stimuli to study food reward in the MRI environment. The cues are initially neutral stimuli that acquire incentive value of food through Pavlovian conditioning whereby the stimuli are repeatedly associated with food (Petrovich & Gallagher, 2007). For example, when a person sees the McDonald's logo "M" for the first time, it is merely an alphabet M without any reward value. However, after repeated consumptions of Bic Macs during which the person sees the logo on its packages, the menu and napkins, an association between the logo and the burger is established. At this point, the logo has acquired motivational value of the burger and can alone trigger food craving. The logo-burger association further strengthens as the person frequently consumes the burger to satisfy the logo-induced craving. In the same way, food properties like the sight, smell, and taste of actual foods can also become conditioned cues.

DA is a neurotransmitter that has a central role in food motivation and cue-reward associative learning. "Wanting" or incentive salience for food, reflected in preference, desire to eat and willingness to work for the reward, is modulated by DA (Berridge & Robinson, 2016). In animals, food motivation is abolished following depletion of striatal DA induced by 6-hydroxy-DA lesion in the substantia nigra (Berridge, Venier, & Robinson, 1989) and heightened upon stimulation of the LH that increases DA levels, without affecting how much animals like food

(Berridge & Valenstein, 1991). In a human positron emission tomography study, blocking DA transporters in combination with oral, olfactory and visual food stimulation yields increased extracellular DA in the striatum and stronger desire for food (Volkow et al., 2002). Moreover, "wanting" ratings correlate with fMRI response to food images and odours in dopaminergic brain regions, which is modulated by hunger levels (Born et al., 2011; Jiang, Soussignan, Schaal, & Royet, 2015).

DA not only encodes or represents incentive salience of food but it also enables cues to gain the salience of the naturally rewarding food. Recording of midbrain DA neurons to study cue-reward learning reveals that initially phasic DA firing is present during reception of juice in monkeys (Schultz, Tremblay, & Hollerman, 2000). Upon acquisition of the cue-juice association, DA neurons respond to the cue that predicts delivery of the reward, but not the reward itself. However, when juice is unexpectedly omitted, there is a depression in DA firing and a subsequent decrease in tonic DA release. Taken together, these findings and others show that DA appears to drive conditioning by encoding the discrepancy between the expected value assigned to the cue and the value of the actual reward outcome, known as the reward prediction error (RPE) (Glimcher, 2011; Schultz, 2016).

In humans, food-cue learning has been explored using variations of a task where participants learn to associate abstract cues with delivery of food or food-related images or odours (i.e., which have already become reward signals) (e.g., Gottfried, O'Doherty, & Dolan, 2002; Valentin, Dickinson, & O'Doherty, 2007). Previously researchers typically focused on brain response to cues over time to assess learning-related activity. In more recent studies, learning-related signals are estimated using learning models and regressed onto brain activity to more precisely identify RPE-related brain response. For example, researchers have used the Rescorla-Wagner reinforcement learning model, which calculates the RPE signal δ by subtracting the expected cue value V from the actual reward value R for each trial ($\delta_t=R_t-V_t$), and the expected cue value is updated (from that of a previous trial) by adding δ weighted by a learning rate α ($V_t=V_{(t-1)}+\alpha\delta_t$) (Bray & O'Doherty, 2007; Rescorla, & Wagner, 1972). The RPE signal can subsequently be correlated with fMRI activity.

The above-mentioned learning model also allows exploration of activity related to cue value, which includes DA's anticipatory response to conditioned stimuli (Hamid et al., 2016). The

conditioned cue value is more commonly captured using other paradigms such as a food decision making task and a food cue reactivity task. During a typical food decision making task using a Becker-DeGroot-Marschak (BDM) procedure, individuals are asked to bid a monetary amount for each food image they are presented with (e.g., Hare, Camerer, & Rangel, 2009; Hare, Malmaud, & Rangel, 2011; Harris, Hare, & Rangel, 2013). This approach has been validated as measuring true "wanting". Regressing the bids onto brain activity allows for identification of subjective value-related activity. Another way to capture cue value is to use a food cue reactivity task during which participants perceive food-related stimuli such as food images and odours in the absence of specific instructions (Huerta, Sarkar, Duong, Laird, & Fox, 2014). It is the most utilized food reward task that consistently activates, across studies, the striatum, amygdala, insula, hippocampus, and OFC/vmPFC, and that may reflect the central appetitive state. In line with this idea, activity in this appetitive network relates to psychological and physiological responses to food cues such as peripheral energy balance signals, levels of hunger and future food intake (Neseliler et al., 2017). Perception of food cues is a multifaceted process, which is reflected in different functions subserved by the brain regions of the appetitive network.

1.3.2 Insula

In response to taste stimuli, the mid-insula seems to process their features including quality and intensity, while the anterior insula and its adjacent fronto-operculum encode their incentive value (Bender, Veldhuizen, Meltzer, Gitelman, & Small, 2009; Small, 2010). The insula also processes textural and olfactory information of food (de Araujo, 2004). Convergence of different properties of foods may take place in the mid and anterior insula to influence dietary decisions (de Araujo, Geha, & Small, 2012). In support of these observations, the insula was revealed by a meta-analysis to be the only brain area that showed increased activation to food cues, regardless of the sensory modality (i.e., images, odours, and actual food) (Huerta et al., 2014).

The insula appears to be involved in different aspects of food cue processing. First, this brain region participates in acquisition of the association between taste and nutritional aspects of ingested food, referred to as flavour-nutrient learning (de Araujo, Lin, Veldhuizen, & Small, 2013). In rats, bilateral lesions in the insula lead to diminished sensitivity to outcome devaluation, with animals

showing similar performance for both devalued and valued actions (Balleine & Dickinson, 2000), while electrical stimulation of the insula increases acquired value of a flavour (Cubero & Puerto, 2000). In support of these findings from animal studies, the insular fMRI activity induced by perception of food images in humans is associated with levels of peripheral glucose and insulin (Simmons et al., 2013), and macronutrient intake influences insular activity (Li, An, Zhang, Li, & Wang, 2012). In addition, there is evidence that insular activity is related to value-reflecting functions such as pleasantness (Small et al., 2003; Sun et al., 2015), and to plasma ghrelin concentration (Malik et al., 2008). Finally, expectancy (a higher-order cognitive function) appears to engage the insula. For instance, in animals, expectation of sucrose on a trial in which it has been omitted induces sucrose-like responses in the insula (Gardner & Fontanini, 2014). In humans, expecting that a taste stimulus would be less distasteful reduced insular activity (Nitschke et al., 2006), while greater insular activity is related to attempts to detect a taste in a tasteless solution (Veldhuizen, Bender, Constable, & Small, 2007; Veldhuizen, Douglas, Aschenbrenner, Gitelman, & Small, 2011).

In obese individuals compared to those with healthy weight, satiation reduces insular activity to a greater extent (Gautier et al., 2001) and is associated with altered connectivity between the insula and the OFC (Avery et al., 2017). In the absence of satiety, obese individuals, compared to the normal weight, show heightened insula activity in response to palatable foods (Yokum, Ng, & Stice, 2011), which is stronger in those who are worse at weight loss (Murdaugh, Cox, Cook, & Weller, 2012). These findings may suggest the presence of abnormalities in interoceptive awareness and processing of food cues as well as the interaction between the two in obesity.

1.3.3 Amygdala

Sensory and homeostatic information is received in the amygdala, which enables this region to play an important role in acquisition and assignment of incentive salience of food cues. A meta-analysis revealed association between RPE during food-cue associative learning and amygdala activity (Chase, Kumar, Eickhoff, & Dombrovski, 2015). In addition to its involvement in acquisition of reward-cue contingencies, the amygdala appears to represent incentive value of food as food cues consistently activate the amygdala in human fMRI studies, and its activity is further related to the amount of

intake of energy-dense foods, and hunger levels (Farr et al., 2016; Mehta et al., 2012). In addition, amygdala activity in response to images of energy-dense foods tends to be stronger in obese humans (Stoeckel et al., 2008), and amygdalar activity to food odours or taste can predict weight change (Sun et al., 2015).

1.3.4 Hippocampus

Consistent with the key role of the hippocampus in learning and memory, lesions in this region can lead to greater food intake and weight gain in rats (Davidson, Kanoski, Walls, & Jarrard, 2005), and consumption of a second full meal shortly after completing a full meal in humans (Hebben, Corkin, Eichenbaum, & Shedlack, 1985; Rozin, Dow, Moscovitch, & Rajaram, 1998). Animal studies investigating precise anatomy and functions of the hippocampus appear to collectively suggest that this region influences dietary decisions by linking external cues (e.g., food cues), internal context (e.g., energy status) and learned information (Kanoski & Grill, 2017). This speculation finds some support from human studies. In line with the findings that the hippocampal neurons house receptors for metabolic hormones such as ghrelin and leptin (Scott et al., 2009; Zigman, Jones, Lee, Saper, & Elmquist, 2006), healthy volunteers show hippocampal activity in response to food cues that is modulated by metabolic hormones such as ghrelin and hunger (Malik et al., 2008). Imagining craved foods also activates the hippocampus (Pelchat, Johnson, Chan, Valdez, & Ragland, 2004). Moreover, there is some evidence that the hippocampus may store and retrieve reward values of cues, which may be used to guide value-based decisions in interaction with the striatum (Wimmer & Shohamy, 2012). In obese humans, compared to the lean, the hippocampus exhibits heightened activation in response to appetitive foods and liked food odours (Bragulat et al., 2010; Stoeckel et al., 2008). On the other hand, in response to a satiating meal, hippocampal activity is observed to be lower in obese individuals compared to the normal weight (DelParigi et al., 2004).

1.3.5 Orbitofrontal cortex/Ventromedial prefrontal cortex

The OFC, primarily the lateral part of this structure, is considered as the secondary olfactory and gustatory cortex. The lateral OFC is connected to sensory and associative cortex, enabling it to receive sensory inputs from diverse modalities such as olfaction, vision, taste and somatic sensation

(Haber & Behrens, 2014; Ongür & Price, 2000). There is some recent evidence that the lateral OFC may be involved in initial representation of subjective nutritive attributes of food, while the medial OFC/vmPFC may compare and integrate the attributes, more directly guiding dietary decisions (Suzuki, Cross, & O'Doherty, 2017). The OFC appears to track anticipated reward value, and be recruited during cue-reward associative learning (Gottfried, 2003). Medial OFC activity to images of high-fat food predicts post-scan selection of fatty foods and is related to self-reported hunger (Mehta et al., 2012). A meta-analysis showed that fMRI activity in the lateral OFC in response to food compared to non-food images is stronger in hungry versus satiated state (van der Laan, de Ridder, Viergever, & Smeets, 2011). OFC response to liquid food is also related to self-reported ratings of pleasantness (Kringelbach, O'Doherty, Rolls, & Andrews, 2003). Moreover, obese individuals compared to the normal-weight exhibit greater OFC activation in response to images of high calorie foods (Dimitropoulos, Tkach, Ho, & Kennedy, 2012), and its activity related to anticipation of eating predicts weight gain (Stice, Burger, & Yokum, 2015).

Subjective value of different rewards including food is most consistently related to activity in the vmPFC (including part of the medial OFC) (Bartra, McGuire, & Kable, 2013). The caudal parts of the vmPFC are interconnected with the homeostatic system and other regions in the appetitive network, and its rostral parts are connected to dorsal prefrontal areas implicated in self-control (Haber & Behrens, 2014). Therefore, the vmPFC can receive and integrate relevant information (e.g., sensory attributes, memories, energy balance state, diet goals) to compute the overall value of available food stimuli that guide food decisions. Consistent with this, the vmPFC shows increased fMRI activity in response to food cues that is related to absolute caloric density of foods (Tang, Fellows, & Dagher, 2014), hunger levels (Thomas et al., 2015), the amount of postscan food intake (Mehta et al., 2012) and future weight gain (Yokum et al., 2011). The vmPFC is functionally coupled with the striatum during food decision making (Tang et al., 2014; Thomas et al., 2015), and the coupling between the two structures at rest is increased in obese individuals (Coveleskie et al., 2015).

1.3.6 Striatum

Midbrain DA neurons heavily project to the striatum, which consists of the putamen, caudate

nucleus and nucleus accumbens. As discussed above, DA neurons respond to cues associated with food, and encode RPE to guide conditioning, as well as motivation and incentive salience. The striatum receives information not only from the other regions of the appetitive system (e.g., amygdala, hippocampus, insula, OFC, vmPFC), but also from the other two relevant systems for feeding (namely the hypothalamus and lateral prefrontal cortex (PFC)) (Haber & Behrens, 2014). Such interconnections allow the striatum to combine information about food stimuli (e.g. caloric density, healthiness), with which it contributes to motivated behaviour, and acquiring and updating food-cue associations.

The role of the striatum in food cue salience is reflected in fMRI studies that consistently show its increased activation in response to appetitive food cues (Tang et al., 2014; van der Laan et al., 2011), which correlates with subjective levels of food craving and tastiness (Hollmann et al., 2012; Pelchat et al., 2004), and is greater in the fasted state (Goldstone et al., 2009). Increased striatal activity to food cues is seen in individuals affected by obesity (DelParigi et al., 2004; Stoeckel et al., 2008) or those that exhibit greater in-laboratory food intake (Frankort et al., 2015), and can predict future weight gain (Demos, Heatherton, & Kelley, 2012; Stice, Yokum, Burger, Epstein, & Small, 2011) or less success in weight loss (Murdaugh et al., 2012). These findings may reflect blunted regulation of striatal activity by the lateral PFC (Kober et al., 2010). While striatal activity in the obese is greater in response to food cues, it is reduced upon receipt of a high-calorie food such as a milkshake (Babbs et al., 2013). These results can be interpreted in light of DA's role in encoding RPE, which has been demonstrated in several human fMRI studies (Bray & O'Doherty, 2007; Chase et al., 2015). It is plausible that altered striatal activity in obesity reflects greater food anticipation (and lack of inhibition of reactivity) and reduced reward-cue associative learning (Kroemer & Small, 2016).

1.4 Self-control system

Sometimes, our desire to eat (driven by the two above-mentioned systems) needs to be overridden, for various reasons including our habits, social and cultural factors, and health-related goals. Mental processes that allow an individual to forego temptations to select goal-consistent actions are referred to as self-control or self-regulation (Hofmann & Dillen, 2012). This ability plays a particularly

important role in our modern environment loaded with cheap and palatable foods and their cues. Indeed, individuals with higher BMI appear deficient in self-control ability, which can be assessed using behavioural tasks and personality questionnaires. More specifically, those with greater BMI show greater food-specific delay discounting, and poorer inhibitory and attentional control and cognitive flexibility (Amlung, Petker, Jackson, Balodis, & MacKillop, 2016; Bartholdy, Dalton, O'Daly, Campbell, & Schmidt, 2016; Fitzpatrick, Gilbert, & Serpell, 2013). Personality research has linked high BMI with low Conscientiousness and perseverance, and high disinhibition (Gerlach, Herpertz, & Loeber, 2015; Vainik, Dagher, Dubé, & Fellows, 2013). It should, however, be noted that a recent study failed to find an effect of Conscientiousness, thought to be a measure of self-control ability, in a large sample (Vainik et al., 2018). These findings may indicate a small effect size of the BMI-Conscientiousness relationship.

Self-control can be framed in terms of models of emotion-regulation and value-based decision making (Figure 3.1). When a food-related cue is perceived (cue perception), its value is assessed (valuation), based on which an action is chosen (action) (Etkin, Büchel, & Gross, 2015; Giuliani & Berkman, 2015). In this decision-making chain, self-control can be exerted to modulate the valuation process and/or to override the urge to pursue the reward. The former can be labeled as "value modulation" and the latter as "inhibitory control". Currently available fMRI tasks that tap into dietary self-control appear to target the two processes to varying degrees. An intentional food craving regulation task is the most utilized dietary self-control task that seems to assess both processes (e.g., Hollmann et al., 2012). This task instructs participants to decrease craving of food presented in images, and depending on the downregulation strategy they rely on, the task may target more predominantly inhibitory control (e.g., when they are diverting their attention away from the perceived cues) or value modulation (e.g., when they are devaluing the food). Inhibitory control is more predominantly targeted by some other tasks, which include food-specific Go/No-go and Stroop tasks. In the Go/No-go task, participants press a button for food stimuli paired with "go" cues and inhibit the button response to those associated with "no-go" cues (He et al., 2014). The "no-go" trials assess inhibitory motor control and food attention bias. The food-specific Stroop task instructs participants to name the color of food and non-food words, thereby assessing interference control and food attention bias (Janssen et al., 2017). On the other hand, the BDM task described

above (e.g., Hare et al., 2009) predominantly taps into value modulation. This task is often modified to better capture self-control. Added components include requesting participants be on a diet and compensating for successful diet implementation, and asking them to focus on health aspects (as opposed to taste aspects) of food stimuli (Hare et al., 2011; Hutcherson, Plassmann, Gross, & Rangel, 2012).

Across different appetite self-regulation tasks, fMRI researchers most frequently observe activation of the lateral PFC, particularly the dorsolateral PFC (DLPFC) and inferior frontal gyrus (IFG) (Michaud, Vainik, Garcia-Garcia, & Dagher, 2017) during voluntary self-regulation. Both of these regions show increased activity associated with suppression of desire for food or inhibition of prepotent response to palatable foods. Response inhibition-related activity in the IFG is correlated negatively with levels of food desire and daily food intake, and positively with ability to resist food temptations (Lopez, Hofmann, Wagner, Kelley, & Heatherton, 2014). DLPFC activity in response to food-related cues is reduced in people with high BMI, and greater in those who consider dieting as important (Smeets, Kroese, Evers, & de Ridder, 2013). The DLPFC activity can also predict subsequent weight loss success (Murdaugh et al., 2012), and is increased when people select healthier foods (Hare et al., 2011, 2011; Harris et al., 2013; Hutcherson et al., 2012) and eat a lesser amount of food post-scan (Frankort et al., 2015). Reduced postprandial activity in the left DLPFC is detected in obese people compared to those with normal weight, and the activity correlates with percentage adiposity (Le et al., 2009), implicating the DLPFC in satiety.

To complement correlational findings derived from fMRI studies, researchers can apply brain stimulation techniques such as transcranial magnetic stimulation (TMS) in healthy volunteers, which allows one to infer brain-behaviour causal relationships. TMS temporarily excites or inhibits activity in the target area, depending on the protocol used, eliciting changes in emotional and cognitive processes and behaviours subserved by the target region and its connected networks (Dayan, Censor, Buch, Sandrini, & Cohen, 2013). The technique is detailed in the Thesis Methodology section. Most of the regions that make up the self-control network are located on the surface of the brain, which make them ideal target sites for TMS. The majority of previous stimulation studies exploring eating-related behaviours targeted the DLPFC, and detected increased food craving after inhibiting DLPFC activity as well as decreased craving upon excitatory TMS

(Hall, Lowe, & Vincent, 2017; Lowe, Vincent, & Hall, 2017). Considering that DLPFC is recruited during dietary self-control according to fMRI data, and that TMS to the PFC modulates executive functioning (Lowe, Manocchio, Safati, & Hall, 2018), these researchers interpret that DLPFC-TMS alters self-control to influence food craving and intake.

1.5 Interaction between the systems

As discussed above, the homeostatic, appetitive and self-control networks have distinct roles, however it is ultimately their interactions that shape and produce dietary decisions. In humans, these interactions are most commonly explored using fMRI connectivity techniques that identify brain regions showing coherent changes in activity either at rest or associated with task performance. For example, Kullmann and colleagues have detected resting state functional coupling of the hypothalamus with the appetitive and self-control systems (Kullmann et al., 2014). In another study, the coupling between hypothalamus and the medial PFC at rest was observed to be enhanced following intranasal administration of insulin (Kullmann et al., 2017). Other studies do not report the hypothalamus but have shown correlations between homeostatic peptides such as ghrelin, insulin and leptin and fMRI response to food cues in the region of the appetitive network such as the medial PFC, amygdala and insula (Zanchi et al., 2017). Given the above-mentioned difficulty mapping the hypothalamus with fMRI, it can be interpreted that the brain activity in response to hormones could be the result of the hypothalamic effects mediated by known connectivity patterns.

Connectivity between prefrontal and appetitive systems may yield insights about their interplay during self-control. Making healthier decisions (i.e., choosing healthy foods and/or rejecting tasty unhealthy ones) was associated with greater DLPFC-IFG-vmPFC coupling, which may reflect the influence of the self-control system on the appetitive network in modulating the reward value (Hare et al., 2009, 2011). Moreover, successful dieters showed stronger functional coupling between vmPFC and DLPFC during food decision making (Neseliler et al., 2018; Weygandt et al., 2013).

The above-mentioned studies offer insight into the potential interactions between the neural systems of appetite control. However, their findings are correlational in nature. A more powerful way to capture the interactions among the networks is to modulate a system and observe its effects in

the brain. Some non-invasive techniques that can be utilized in humans include increasing the levels of homeostatic hormones, and using brain stimulation tools (e.g. TMS) to modulate neural activity. As non-invasive application of TMS is typically limited to superficial brain regions, only some regions of the self-control system are common candidate stimulation targets. With currently available tools, it remains a challenge to directly alter the appetitive system. Here, I review some modulation studies.

1.5.1 Ghrelin's influence on the appetitive network

The interaction between the homeostatic system and the appetitive system has been tested by modulating levels of peripheral signals such as ghrelin. The hormone not only acts on the homeostatic hypothalamic circuit (as detailed above) but it also binds to GHSR expressed in the VTA, striatum and hippocampus to act directly on the appetitive system involved in learning and motivation (Perello & Dickson, 2015). Animal studies have tested ghrelin's ability to enhance the motivational salience of food cues and its potential underlying mechanisms. Following ghrelin administration into the VTA, there is stronger activity of DA neurons, release of DA in the nucleus accumbens, and greater willingness to work to obtain food rewards (Abizaid et al., 2006; Jerlhag et al., 2007; Skibicka, Hansson, Alvarez-Crespo, Friberg, & Dickson, 2011; Skibicka et al., 2013). Such food motivated behaviour is abolished upon administration of a ghrelin or DA antagonist (Skibicka et al., 2013). These findings from animal research were partly corroborated by fMRI studies in humans. High levels of ghrelin in healthy volunteers, as a result of fasting or intravenous ghrelin injection, led to greater activity in perception of food images in brain regions such as the OFC, striatum and hippocampus, and greater subsequent recall of the food images (Goldstone et al., 2014; Malik et al., 2008). These results may reflect ghrelin's ability to heighten incentive salience and memory of food cues.

As discussed above, DA is not only a motivational signal but it also plays a key role in cue-reward associative learning through encoding RPE. Therefore, it is reasonable to hypothesize that ghrelin, with its ability to stimulate phasic DA signalling, may also influence food cue conditioning. Indeed, ghrelin injection was shown to augment DA phasic signalling in response to food cues (Cone, Roitman, & Roitman, 2015), whereas GHSR knockout mice do not show release of

accumbens DA upon exposure to food (Egecioglu et al., 2010). The hippocampus is another candidate region through which ghrelin may influence food-cue related associative learning. GHSR are densely expressed in the hippocampus where ghrelin can increase spine density, improve learning and memory, and provoke conditioned feeding, possibly by modulating DA signalling (Diano et al., 2006; Hsu, Suarez, & Kanoski, 2016; Kanoski, Fortin, Ricks, & Grill, 2013; Li et al., 2013; Ribeiro et al., 2014). To date, direct evidence for ghrelin's influence on food-related conditioning exists only in animals. More specifically, GHSR null-mice did not show conditioned place preference to high-fat food that is typically observed following ghrelin injection (Perello et al., 2010). Moreover, caloric restriction associated with high levels of endogenous ghrelin failed to induce conditioned place preference in GHSR-null mice or those treated with a GHSR-antagonist during the conditioning phase. Ghrelin's role in food cue associative learning remains untested in humans.

1.5.2 Influence of self-control system on the appetitive system

As mentioned above, the interaction between the self-control and the appetitive systems can be non-invasively explored using brain stimulation techniques to manipulate activity in the self-control system, most commonly the DLPFC. Previous stimulation studies have shown that inhibiting or exciting activity in the DLPFC leads to increased or decreased food craving respectively (Hall et al., 2017; Lowe et al., 2017). To date, its underlying mechanisms have been directly investigated in only one TMS study using electroencephalography (EEG) (Lowe, Staines, Manocchio, & Hall, 2018). In line with previous study results, Lowe and colleagues reported that inhibiting the left DLPFC using TMS increased consumption of energy-dense foods after viewing images of high and low calorie foods (Lowe, Staines, et al., 2018). EEG data revealed that inhibitory TMS, compared to sham, increased the amplitude of the P3a in response to high versus low calorie food images. The P3 component is assumed to reflect brain networks related to motivational salience and attention deployment (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Gable & Harmon-Jones, 2010), and shows greater amplitude in response to high caloric food stimuli (Asmaro et al., 2012; Gable & Harmon-Jones, 2010; Meule, Kübler, & Blechert, 2013; Nijs, Franken, & Muris, 2009; Werthmann, Field, Roefs, Nederkoorn, & Jansen, 2014).

1.6 Altered neural systems in obesity and impulsivity

Neuroimaging studies offer some insight into how the homeostatic, appetitive and self-control systems may be altered in obesity. Some have associated gut hormones with food cue-related activity during fMRI. For instance, individuals at genetic risk for obesity compared to controls show altered relationship between plasma ghrelin levels and activity in the hypothalamus, nucleus accumbens and OFC (Karra et al., 2013). BMI was observed to be related to plasma levels of leptin, which was correlated with ventral striatal activity (Vollmert, 2012). These findings, however need to be interpreted with caution given altered hormonal functioning in obese individuals involving reduced plasma ghrelin levels, and elevated levels of leptin and leptin resistance (as reviewed in Smith, 2018). As reviewed above, the most consistent fMRI response to food cues in obesity is increased activity in the insula, amygdala, hippocampus, OFG and striatum and decreased activity in the DLPFC.

The heightened activity in the appetitive network (greater reward sensitivity) and the blunted activity in the self-control network (diminished self-control) observed in obesity may be reflected in a personality trait, impulsivity, which characterizes a tendency to act without thorough consideration of consequences (see Figure 1.2 taken from Dagher, Neseliler, & Han, 2017; Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001).

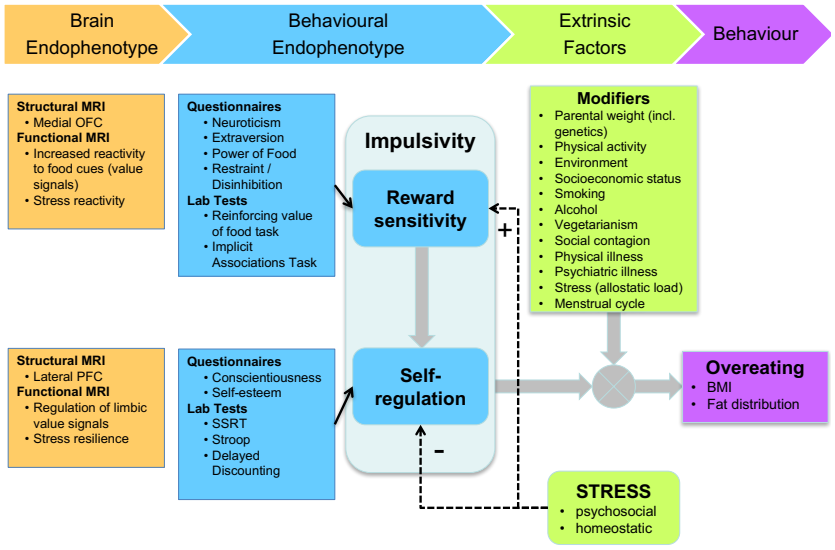

Figure 1.2. An endophenotype model of vulnerability to obesity

Impulsivity, reflecting increased reward sensitivity and diminished self-control, is related to obesity as shown in neuroimaging, personality and behavioural investigations (Dagher, Neseliler, & Han, 2017).

Impulsivity is a composite trait that appears to entail Neuroticism, disinhibition (or low Conscientiousness) and Extraversion, which are concepts derived from the five-factor personality model (Sharma, Markon, & Clark, 2014), and can be measured in humans using the NEO-PI questionnaire (Costa & McRae, 1992). All three traits are related to BMI and obesity. Neuroticism is a tendency to feel negative emotions (Sharma et al., 2014). Higher scores in Neuroticism are related to smaller DLPFC volume in healthy individuals, and are observed in those with DLPFC damage (Bjørnebekk et al., 2013; Forbes et al., 2014; Kapogiannis, Sutin, Davatzikos, Costa, & Resnick, 2013). Some studies also relate Neuroticism with hippocampal activity and volume as well as amygdalar volume (Barrós-Loscertales et al., 2006; Holmes et al., 2012; Koelsch, Skouras, & Jentschke, 2013; Omura, Todd Constable, & Canli, 2005). In the field of obesity, some facets of Neuroticism seem most relevant that include "impulsiveness" and "negative urgency", which are correlated with adiposity and BMI (Mobbs, Crépin, Thiéry, Golay, & Van der Linden, 2010; Murphy, Stojek, & MacKillop, 2014; Sutin, Ferrucci, Zonderman, & Terracciano, 2011; Terracciano et al., 2009). Conscientiousness is an inclination to be organized, purposeful and disciplined (Roberts, Lejuez, Krueger, Richards, & Hill, 2014), and appears to be positively related

to DLPFC volume in healthy people and lesion studies (DeYoung et al., 2010; Forbes et al., 2014; Kapogiannis et al., 2013). This trait shows a negative relationship with BMI (Terracciano et al., 2009). Finally, Extraversion measures sensation and novelty seeking and reward sensitivity (Sharma et al., 2014). Higher sensation seeking is related to lower volume in the medial PFC and greater striatal activity (Cremers et al., 2011; DeYoung et al., 2010; Holmes et al., 2012). Structural connectivity between ventral striatum and hippocampus/amygdala is related to novelty seeking (Cohen, Schoene-Bake, Elger, & Weber, 2009). Individuals with high BMI or at greater risk for weight gain tend to score high on Extraversion (Sutin et al., 2011; Terracciano et al., 2009). However, there is also some evidence that the relationship between BMI and reward sensitivity is inverted U-shaped, which has led some researchers to propose that both hypo- and hyper-sensitivity to (food) reward may predict one's predisposition to obesity (Davis & Fox, 2008; Dietrich, Federbusch, Grellmann, Villringer, & Horstmann, 2014; Verbeken, Braet, Lammertyn, Goossens, & Moens, 2012).

The above-mentioned relationships between general impulsivity traits and BMI are not unanimously detected across different studies. Indeed a recent large meta-analysis revealed that the strength of the relationship between general impulsivity traits and BMI was rather low (effect size of 0.07) (Emery & Levine, 2017). Moreover, there is evidence that eating-specific impulsivity traits or uncontrolled eating more strongly predict BMI than general ones (Vainik, Neseliler, Konstabel, Fellows, & Dagher, 2015). These findings collectively point to the importance of specificity in characterization of eating-related behaviours and obesity.

1.7 Thesis methodology

The thesis will use the following tools to address research questions: fMRI and TMS.

1.7.1 Magnetic resonance imaging

Magnetic Resonance Imaging (MRI) is a non-invasive tool that produces images of anatomy of inner body structures such as the brain. The technique utilizes properties of hydrogen nuclei of water, a major component (~60%) of the human body including the brain of which 75% is water. An MRI scanner contains a large superconducting magnet (typically 1.5 or 3 Tesla) that induces a strong

magnetic field (Pooley, 2005). When a person is placed in a scanner, the strong magnetic field forces a small proportion of protons in water molecules in his/her body to align parallel to the magnetic field (Hendee & Morgan, 1984; Pooley, 2005). During the scan, radio frequency pulses are introduced through coils at a frequency that specifically targets hydrogen protons, and this additional energy disturbs the alignment of the water molecules along the magnetic field (Pooley, 2005). When the radio transmitter is turned off, the water molecules return to their original position along the static magnetic field. The time it takes for the water molecules to realign is captured by the scanner head coil and referred to as T1 relaxation time (Hendee & Morgan, 1984; Pooley, 2005). As T1 depends on the interaction between water contents and the composition of surrounding tissue, which differs for the grey matter, white matter and cerebrospinal fluid, they can be differentiated with MRI (Gracien & Deichmann, 2018). For instance, MRI provides distinctive images of cerebrospinal fluid, white matter and grey matter, whose T1's are relatively long, short and intermediate respectively. The resolution of T1-weighted images can be enhanced by decreasing the time between radio frequency pulses administered as well as the time between the pulse and signal detection.

1.7.2 Functional magnetic resonance imaging

In addition to providing structural images of the brain, an MR scanner is used to explore brain activity, a technique referred to as fMRI. FMRI is also known as blood oxygenation level dependent (BOLD) imaging as it aims to detect changes in oxygenation of cerebral blood that may correlate with neural activity (Huettel, Song, & McCarthy, 2004). BOLD is shown to be strongly related to the local field potentials that are signals of excitatory and inhibitory dendritic potentials from a collection of neurons reflecting information flow across neural networks (Goense & Logothetis, 2008; Shmuel, Augath, Oeltermann, & Logothetis, 2006). When neurons are active (e.g., during task performance, at rest), their oxygen consumption increases, which is provided via blood hemoglobin. However, with neuronal activation the increase in cerebral blood flow is greater than oxygen utilization, generating a surplus of oxyhemoglobin (Kim & Ogawa, 2012). The surplus produces an increase in BOLD signal in the engaged brain regions, because the magnetic properties of oxy- and deoxyhemoglobin induce local changes in magnetic homogeneity, resulting in changes in

T2-weigthed signal (referred to as T2*). Changes in BOLD are interpreted as reflecting greater neural activity. The BOLD response is convolved with the hemodynamic response function, which accounts for the delay between neural firing and blood flow increase, and entered into design matrix along with information about experimental condition (e.g., onsets, duration) to generate statistical parametric maps (Lindquist, 2008; Lindquist, Meng Loh, Atlas, & Wager, 2009). Subsequently, BOLD response in different brain regions can be compared between different conditions and/or groups.

1.7.3 Transcranial magnetic stimulation

TMS is one of the most commonly used non-invasive brain stimulation techniques that temporarily modulates cortical activity. Its use is becoming widespread both in clinical settings (e.g., for treatment of depression) and in research as it uniquely allows testing causal relations between brain regions and specific behaviours in cognitively intact volunteers.

A typical TMS apparatus is a figure eight coil made with two circular coils that permits focal stimulation (George & Aston-Jones, 2010; Wassermann & Zimmermann, 2012). The coil produces a small, short-lasting magnetic field (1.5-2T) that induces electrical current below the skull, leading to neuronal depolarization and an action potential. Stimulation only affects the brain regions that are within 2 cm below the surface of the skull, and cannot directly target subcortical regions. However, many studies have shown that TMS effects are not limited to the stimulation target site but its connected regions and networks (To, De Ridder, Hart Jr., & Vanneste, 2018). The direction and strength of TMS effects depend on length, form and intensity of stimulation. TMS can be administered as a single pulse of less than 1ms or repetitively (repetitive TMS) (George & Aston-Jones, 2010; Wassermann & Zimmermann, 2012). The effects of single pulse – TMS last about 40-60 ms, and thus stimulation and task performance should be administered simultaneously. This protocol is suitable for measuring motor responses, for example. On the other hand, repetitive TMS (rTMS) during which pulses are administered repetitively can induce more sustained changes in brain activity beyond the stimulation period (George & Aston-Jones, 2010; Wassermann & Zimmermann, 2012).

1.7.3.1 Theta burst stimulation

Theta Burst Stimulation (TBS) is a form of TMS that is gaining popularity, mainly because of its speed of application and duration of action. While other forms of rTMS require at least 10 minutes of administration, typical TBS protocols used in humans take a maximum of 3.5 minutes to apply effective stimulation.

TBS originates from the observation that explorative behaviour in rats is associated with burst discharge of hippocampal neurons at 4-7 Hz (Diamond, Dunwiddie, & Rose, 1988; Huang, Rothwell, Chen, Lu, & Chuang, 2011). Stimulation at this frequency, which lies in the theta range in EEG, induces plasticity in animal brain slices. The TBS protocol used for humans entails three 50Hz-pulses administered at 5Hz (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). There are two types of TBS protocols that are most widely utilized. Continuous TBS (cTBS) is applied continuously for 20s (300 pulses) or 40s (600 pulses) and is observed to inhibit brain activity for approximately 20 minutes or 60 minutes respectively after stimulation (Wischnewski & Schutter, 2015). On the other hand, intermittent TBS (iTBS) sends a 2 second-train of 10 bursts every 10 seconds and is observed to enhance neural activity (Wischnewski & Schutter, 2015).

The mechanisms underlying post-TBS effects remain unclear. TBS is thought to stimulate axons rather than neuronal cell bodies (Suppa et al., 2016). The changes observed during and shortly after stimulation are assumed to reflect changes in neural excitability. The lasting effects observed beyond the stimulation period seem to reflect to changes in long-term potentiation (LTP) or long-term depression (LTD), through which synaptic efficiency is increased or reduced respectively. Influx of Ca^{2+} to postsynaptic neuron is assumed to induce LTP and LTD, and TBS is believed to trigger the influx of Ca^{2+}. TBS effects require activation of Ca^{2+} channels, and a Ca^{2+} channel blocker reduces effects of cTBS in a dose-dependent manner. Administration of NMDA receptor antagonists blocks TBS effects and the excitatory effects of iTBS are reversed by a partial NMDAR agonist. The different types of TBS protocols influence the amount and the rate of the TBS-triggered Ca^{2+} influx, which determines which of LTP and LTD is more dominant, and ultimately the direction and amount of change in synaptic strength. A single train of TBS tends to induce a facilitatory effect in the first 2 seconds while suppression is more dominant when stimulation lasts longer (Huang et al., 2005). Therefore, in the iTBS protocol, dominance of the excitatory effect is maintained by giving

short TBS trains intermittently, whereas continuous administration of pulses (as in cTBS) ensures the suppression effect to dominate.

One of the challenges in TBS experiments arises from high interindividual variability in the response to stimulation (Hinder, Reissig, & Fujiyama, 2014; López-Alonso, Cheeran, Río-Rodríguez, & Fernández-del-Olmo, 2014; Suppa et al., 2016). Although underlying mechanisms of the variability remain unclear, some potentially relevant factors include local gene expression (Cheeran et al., 2008) and the electrical response of intracortical networks to each TMS pulse (Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2013).

1.8 Thesis questions and hypothesis

The literature review provided above described the homeostatic, appetitive and self-control networks that work together to generate food decisions. In humans, correlational studies have been most frequently used to test the interactions among the three systems. There is a need for the use of modulation approach to validate the presence of these interactions. To fill this gap, the thesis will describe experiments to modulate homeostatic signals and self-control circuitry and observe their effects to more precisely map the communications among the appetite control networks. Moreover, individual differences in the obesity-related trait, Uncontrolled Eating, will be considered in the investigation.

More specifically, in the first study we will increase the levels of a homeostatic signal, ghrelin, through injection and observe behavioral and neural changes in the context of food cue learning using fMRI, with a broad aim to examine the interaction between the homeostatic and appetitive systems. Ghrelin's influence on food cue reactivity has been studied in both animals and humans. However, the hormone's role in food-cue associative learning, another process subserved mainly by the appetitive system, has only been tested in animals. Therefore, this study will use fMRI to test in humans how infused ghrelin may modulate food cue conditioning in the brain and behaviour. Based on previous findings, we hypothesize that ghrelin will stimulate the dopaminergic system through which it enhances food cue conditioning. The second and the third studies will explore and manipulate the self-control network. As discussed above, eating-specific impulsivity or Uncontrolled Eating in comparison to general impulsivity appears to more strongly predict BMI. Moreover, brain

stimulation studies targeting the DLPFC (typically the F3 in the EEG 10-20 system) to study eating-related behaviours revealed inconsistent findings. It is therefore possible that an eating-specific self-control network exists in the brain. To date, no meta-analyses have identified brain regions that may subserve domain-specific self-control predicting eating and weight gain. Therefore, in the second study, we will conduct a meta-analysis on only the fMRI studies that examined brain activity related to dietary self-control. Finally, the last study will involve modulating the dietary self-control network using TMS to see changes in food decisions in individuals who score high or low in Uncontrolled Eating. This study aims to map the potential interaction between the self-control and appetitive systems. Most previous brain stimulation studies on eating-related responses used food craving and consumption as dependent variables, without investigating the processes through which the self-control system might influence eating-related behvaiours. One recent study examined the influence of DLPFC-TMS on food cue reactivity (Lowe, Staines, et al., 2018). However, the passive viewing task they utilized do not elicit responses that can be indices of self control-related processes potentially modulated by TMS. Moreover, despite the role of Uncontrolled Eating in predicting BMI and brain activity, no previous studies have controlled for this trait in examining the effects of DLPFC-TMS. To fill these gaps, our TMS study will utilize a food decision-making task with high and low calorie food images that may allow observation of TMS-induced changes in self-control implementation. Moreover, unlike previous studies that stimulated the DLPFC identified in the previous literature or the standard EEG system, we will stimulate individually determined locations within the DLPFC revealed in fMRI data collected prior to TMS. We will test if stimulating the DLPFC affects self-control to influence the appetitive network and dietary decisions, and how the outcomes differ in the high and low Uncontrolled-Eating groups. Based on the literature, we hypothesize that inhibition of DLPFC activity will increase selection of unhealthy food items while excitatory TMS will promote healthier decision making. In addition, sensitivity to TMS-related modulations may differ between the two impulsivity groups.

The work from this thesis attempts to further delineate, in healthy volunteers, the interactions among the brain networks of appetite control that shape our response to food-related stimuli and dietary decisions, and how they may be influenced by an obesity-related trait. This knowledge will help map more precisely abnormalities present in the obese brain. The use of brain

modulation techniques additionally offers a glimpse into potential brain-based interventions for obesity or other disorders presenting impaired self-control.

Chapter 2 - Ghrelin enhances food odor conditioning in healthy humans: an fMRI study

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2.1 Preface

Ghrelin is a homeostatic peptide that stimulates appetite (Müller et al., 2015). The hormone has been shown to enhance DA signalling through which it may promote food cue conditioning (Perello & Dickson, 2015; Perello et al., 2010). The first study, published in *Cell Reports*, used fMRI to explore the interaction between the homeostatic and appetitive systems by testing if ghrelin injection to healthy humans modulates food odour learning. We observed that ghrelin accelerated participants' response time to cues associated with food, but not non-food, odours. In line with this finding, stronger learning-related activity was observed during food-related conditioning in the striatum, hippocampus and vmPFC following ghrelin administration. Furthermore, ghrelin induced stronger coupling between the striatum and hippocampus on food trials. The above-mentioned brain regions are DA-responsive appetitive areas thought to subserve reward-cue associative learning. Therefore, our results provide behavioural and neural evidence that a homeostatic signal, ghrelin heightens food odour conditioning possibly via stimulating the DA system. This work offers insight into how the homeostatic system interacts with the appetitive circuit to drive eating-related behaviours.

2.2 Summary

Vulnerability to obesity includes eating in response to food cues, which acquire incentive value through conditioning. The conditioning process is largely subserved by dopamine, theorized to encode the discrepancy between expected and actual rewards, known as the reward prediction error (RPE). Ghrelin is a gut-derived homeostatic hormone that triggers hunger and eating. Despite extensive evidence that ghrelin stimulates dopamine, it remains unknown in humans if ghrelin modulates food cue learning. Here we show using functional magnetic resonance imaging that intravenously administered ghrelin increased RPE-related activity in dopamine-responsive areas during food odor conditioning in healthy volunteers. Participants responded faster to food odor-associated cues and perceived them to be more pleasant following ghrelin injection. Ghrelin also increased functional connectivity between hippocampus and ventral striatum. Our work demonstrates that ghrelin promotes the ability of food cues to acquire incentive salience and has implications for the development of vulnerability to obesity.

Key words: ghrelin, fMRI, olfactory conditioning, reward prediction error, food

2.3 Introduction

Accumulating evidence from psychology, cognitive neuroscience, genetics, and neuroimaging has established the role of higher-level cognitive and emotional brain systems in the maintenance of energy balance in humans. Homeostatic peptides from the periphery convey energy balance information to the brain. In order for this information to affect food intake it must influence brain circuitry involved in decision-making and motivation.

Exposure to cues associated with palatable food can evoke motivation to eat, and eventually lead to weight gain (Boswell & Kober, 2016). The cue-potentiated feeding response results from conditioning whereby neutral cues acquire incentive value after being repeatedly paired with ingestion of food. Such cues include the sight, smell and flavour of food. The ability of food cues to become conditioned as well as their subsequent potency to elicit feeding is greater in the hungry state (Balleine, 1992). A likely candidate mediating the interaction of hunger and food cue conditioning is the hormone ghrelin.

Ghrelin is a stomach-derived peptide hormone that elicits hunger and feeding by acting on the brain (Müller et al., 2015). It binds to a unique receptor, the growth hormone secretagogue receptor (GHSR), expressed densely in brain areas involved in feeding and energy balance, such as the hypothalamus and nucleus of the solitary tract (Mason, Wang, & Zigman, 2014). Ghrelin levels rise prior to scheduled mealtimes and after fasting, and fall postprandially (Cummings et al., 2001). Moreover, administration of ghrelin induces hunger and food consumption (Nakazato et al., 2001; Wren et al., 2001). Ghrelin signals several different types of information that affect the motivation to eat, notably the immediate availability of food, the timing of an expected meal, and both short and long-term energy balance status (Müller et al., 2015). There is much evidence that ghrelin acts not only on the homeostatic hypothalamic-brainstem circuits that regulate energy balance but also on systems involved in learning and motivation, notably the ventral tegmental area (VTA), striatum and hippocampus, to influence food cue reactivity. More specifically, ghrelin may increase the motivational salience of food cues by stimulating dopaminergic neurons in the VTA where GHSR are also found (Mason et al., 2014; Perello & Dickson, 2015). Ghrelin injection into the VTA increases activity of dopamine (DA) neurons and triggers DA release in the nucleus accumbens while motivating animals to work harder to obtain food rewards (Abizaid et al., 2006; Skibicka et al.,

2013). On the other hand, administration of a ghrelin or DA antagonist abolishes the ghrelin-induced increase in food motivated behavior (Skibicka et al., 2013). These findings from animal studies are corroborated by fMRI studies in humans. High levels of ghrelin in healthy volunteers, as a result of fasting or intravenous ghrelin injection, appear to enhance the incentive salience of food cues, as reflected by stronger activity in response to food images in brain regions such as the orbitofrontal cortex (OFC), striatum and hippocampus, and greater subsequent recall of the food images (Kroemer et al., 2013; Malik, McGlone, Bedrossian, & Dagher, 2008).

Ghrelin's ability to stimulate DA has implications not only for its influence on responses to learned cues associated with food but also for the food cue conditioning process. Associative learning is theorized to be driven by the discrepancy between the expected value assigned to the cue and the value of the actual reward outcome, known as the reward prediction error (RPE) (Schultz, 2016). Phasic firing of DA neurons in the VTA is thought to encode the RPE, through which the DA system contributes to acquisition and update of reward-cue associations. DA phasic signaling in response to food cues is augmented by central ghrelin injection (Cone, Roitman, & Roitman, 2015). GHSR knockout mice, on the other hand, do not demonstrate release of accumbens DA upon exposure to food (Egecioglu et al., 2010). These findings collectively suggest that ghrelin may promote food-cue associative learning by enhancing the phasic RPE signal.

Another region implicated in food-cue related associative learning is the hippocampus (Kanoski & Grill, 2017). There is also a high concentration of GHSR in the hippocampus, where ghrelin can increase spine density and improve learning and memory, possibly by modulating DA signaling (Diano et al., 2006; Li et al., 2013). Conditioned feeding, which occurs in response to learned food-cue associations, is increased in rats upon ghrelin injection into the ventral hippocampus (Kanoski, Fortin, Ricks, & Grill, 2013). To date, the influence of ghrelin on food-related conditioning has only been tested in animals. Ghrelin injection enabled conditioned place preference to high fat food in wild-type mice but not in GHSR knockouts (Perello et al., 2010). Moreover, caloric restriction associated with high levels of endogenous ghrelin failed to induce conditioned place preference in GHSR-null mice or those treated with a GHSR-antagonist during the conditioning phase.

Whether ghrelin also modulates food-cue associative learning in humans remains

unexplored. In the midst of an escalating global obesity epidemic, this is an important question to address given the role of excessive food cue learning and reactivity in weight gain and food intake (Boswell & Kober, 2016) and evidence of impaired ghrelin signaling in obesity (Zigman, Bouret, & Andrews, 2016). Here we test the ability of the orexigenic peptide ghrelin to promote Pavlovian conditioning to food odors by increasing neural reward prediction error activity in dopaminergic projection sites such as ventral striatum (VStr) and hippocampus. This work attempts to make a link between homeostatic signaling and learning systems that help shape food behavior.

Following intravenous administration of ghrelin (1μg/kg) or saline on two separate days, thirty-eight subjects underwent functional magnetic resonance imaging (fMRI) while they learned to associate neutral abstract images with food or non-food odors. Participants rated pleasantness of the images throughout the scan and again 24 hours after each scan session. It was hypothesized that ghrelin would enhance conditioning of cues paired with food, but not non-food, odor via an effect on dopaminergic brain regions.

2.4 Experimental model and subject details

2.4.1 Participants

Forty young healthy right-handed individuals (age: 22.46±2.60, body mass index: 23.33±2.98, 17 women) were recruited by advertisements. Of those, 38 completed the study. Exclusion criteria included psychiatric or neurological illness, body mass index > 25.9 (men) and >27.0 (women) or <19, gastrointestinal or eating disorders, current use of medications (other than oral contraceptives), tobacco or other drugs of abuse, food allergies, hay fever, deviated nasal septum, a cold or sinus infection, vegetarianism, and/or contraindications for MRI scanning. In order to exclude individuals with abnormal olfactory thresholds, we administered a brief olfactory test where participants were presented with 10 sets of three bottles (one with an odorant and the other two containing no odorant) and instructed to identify the bottle from each set that smells strongest. We also excluded individuals with abnormal eating behaviours who scored above 20 on the Eating Attitude Test (Garner & Garfinkel, 1979), and/or answered "Yes" to any of the two questions on the eating-related section of the Structured Clinical Interview for the Diagnostic and Statistical Manual of

Mental Disorders-IV Screening Module (APA, 1998). Female participants were scanned during the luteal phase. All participants provided written informed consent as approved by the Montreal Neurological Institute Research Ethics Board and received monetary compensation for their time and effort.

2.4.2 METHOD DETAILS

2.4.2.1 Ghrelin and task stimuli

Human ghrelin acetate was obtained from Clinalfa (Bachem Distribution Services GmbH, Weil am Rhein, Germany). The hormone was manufactured according to GMP regulations and was sterile and pyrogen free. The peptide was delivered lyophilized in individual 100µg glass vials, and intended for intravenous injection to humans. Ghrelin was reconstituted with saline (1 ml).

Food odors (strawberries and cream, caramel, guava, and orange) and non-food odors (rose, olibanum, freesia, and muguet) used in the study were matched for intensity, familiarity and pleasantness based on a pilot study using 28 different commercially available odorants conducted in a separate group of 15 volunteers. Odors (25ml each, undiluted odorants) were delivered through a computer-controlled, 8-channel olfactometer (Dancer Designs, Merseyside UK), which ensures accurate odor onset and a steep odor rise-time. The visual stimulus set, taken from the Abstract Design List learning task (Jones-Gotman, 1986), consisted of 12 abstract line drawings, 6 made of straight lines and 6 of curved lines .

2.4.2.2 Testing sessions

Each participant underwent two fMRI sessions following saline or ghrelin injection, scheduled at least one week apart at the same hour of the day. The order of ghrelin and saline injection was counterbalanced. Participants received saline or 1µg/kg of ghrelin intravenously, in single-blinded fashion. No side effects were reported.

As illustrated in Figure 2.1A, on testing day, participants arrived at the laboratory between 7:30AM and 11AM and were provided with a standard breakfast following a 12-hour overnight fast.

The breakfast menu was designed to be moderately low in glycemic index and protein, to minimize their influence on brain function. The meal included 2 slices of toasted bread (1 white and 1 whole wheat), 42g of cheddar cheese, 10ml of butter, 125ml of orange juice and 1 cup of coffee or tea with 20ml of 2% milk and 1 sachet of white sugar. Participants were instructed to consume the provided meal in its entirety and nothing else until the end of the session. Immediately before and after breakfast, subjects were asked to rate their levels of hunger, boredom and irritability on a visual analog scale (VAS), ranging from -5 (not at all) to 5 (extremely).

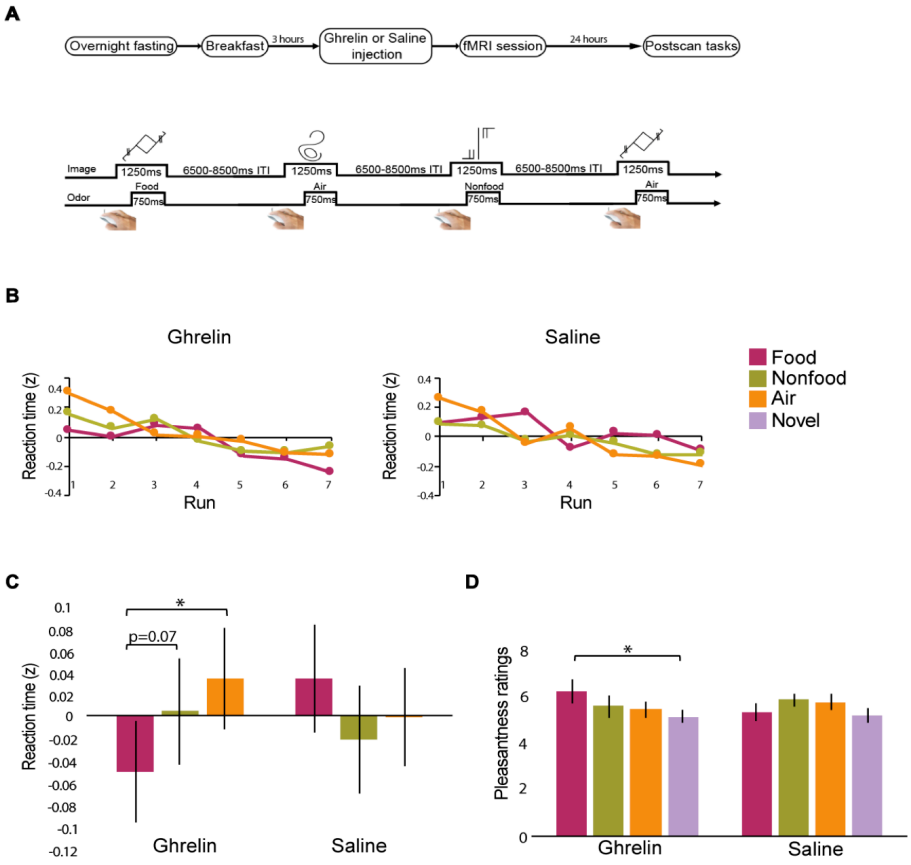

Figure 2.1. Olfactory Conditioning protocol and behavioural results.

(A) Subjects underwent two sessions, ghrelin or saline, counterbalanced and single-blind, at least 7 days apart. The ghrelin or saline administration and the subsequent fMRI session took place 3 hour post-breakfast. The fMRI conditioning task began with the presentation of an abstract image followed by its corresponding odor or air, ending with an inter-trial blank screen. There were 7 fMRI runs, each of which consisted of 36 image-odor/air trials. (B) In both ghrelin and saline conditions, participants' reaction times in response to abstract images decreased over the course of the task ($F(2.74, 76.72)=6.63$, $p<0.005$). (C) The difference in reaction time between food and non-food trials and that between food and air trials significantly differed between ghrelin and saline conditions ($t(28)=-2.47$, $p<0.05$; $t(28)=-2.20$, $p<0.05$). Following ghrelin administration, participants responded faster toward food-related images compared to those paired with non-food odors (($t(28)=-1.87$, $p=0.07$) and air ($t(28)=-2.63$, $p<0.05$). On the other hand, in the saline condition, food-associated images induced greater response time compared to non-food odor-paired images ($t(28)=1.70$, $p=0.1$). (D) The only significant result observed on the hedonic rating task administered after a 24-hour delay was greater pleasantness ratings for food odor-associated images compared to novel ones following the ghrelin session ($t(17)=2.14$, $p<0.05$). Error bars represent the SEM.

Neuroimaging took place 3 hours after the breakfast when the circulating ghrelin levels are expected to be at nadir (Cummings et al., 2001). Prior to scanning, subjects completed the Profile of Mood States questionnaire (McNair, Lorr, & Droppleman, 1971) and again reported their hunger, boredom and irritability levels. Subsequently, we collected participants' saliva and blood samples in order to measure levels of cortisol (saliva), and insulin, growth hormone and glucose (blood). Ghrelin or saline was then administered by infusion into the antecubital vein over 60 seconds, after which another saliva sample and the VAS ratings (hunger, boredom and irritability) were collected. Participants were then placed in the MRI scanner. The session began with a 5-minute structural scan, followed by seven functional scans (7 minutes each) during which subjects performed the odor conditioning task detailed below.

Upon completion of the imaging part of the study, we again administered the VAS scales to quantify participants' hunger, irritability and boredom and collected their saliva and blood samples. In a subset of participants (n=18), we also assessed odor detection thresholds for n-Butanol (Fisher Scientific Pittsburgh, PA) using a staircase, triple-forced choice procedure (Kobal et al., 2000).

Approximately 24 hours following the scan session, participants returned to the laboratory for a behavioral session where they provided pleasantness and familiarity ratings for the conditioning images and two novel images, and pleasantness, familiarity and intensity ratings for the odors used during the scan as well as two new odors.

The fMRI and behavioral sessions took place 7 to 30 days apart. Participants completed the same tasks with different sets of visual and olfactory stimuli.

2.4.2.3 Blood and cortisol sampling

Blood samples were collected from the antecubital vein (approximately 2ml) before injection of ghrelin or saline and after the scan in order to quantify the serum levels of growth hormone, glucose and insulin. Blood was collected in gold-top serum separation tubes (bd.com) and placed on ice immediately. Tubes were then sent to the McGill University Health Centre biochemical laboratory for analysis.

Salivary cortisol was sampled using the salivette collection device (Sarstedt Inc., Quebec City,

QC, Canada) at three different time points, before and after saline or ghrelin injection and after the scan. Participants were required to place the salivettes in their mouths for approximately one minute. The samples were stored at -20C until analysis. Cortisol (nmol/l) was quantified using a time-resolved fluorescence immunoassay as described by Dressendorfer and colleagues (Dressendörfer, Kirschbaum, Rohde, Stahl, & Strasburger, 1992).

2.4.2.4 fMRI olfactory conditioning task

The fMRI task design was based on Gottfried et al. (Gottfried, O'Doherty, & Dolan, 2003). Four odors (2 food, 2 non-food) were paired with 4 abstract images (CS+) on a 50% positive reinforcement schedule. The remaining two images (CS-) were paired with odorless air. Stimuli, their pairings and the presentation sequence varied between the two sessions and across the participants. Stimuli were presented in a pseudo-random order such that no two identical images or odors appeared consecutively. In addition, no more than five air-paired events were presented in a row (Figure 2.1A).

Each trial began with the 1250ms-presentation of a visual stimulus. Its corresponding odor was delivered 500ms after the image onset and disappeared together with the image. Each trial was followed by an inter-trial blank screen with a jittered interval ranging from 6500ms to 8500ms. Upon viewing each image, subjects indicated whether the image was made of curvy or straight lines using a MRI-compatible mouse-like device. There were 7 fMRI runs in each session, each of which was composed of 36 trials (12 CS+paired, 12 CS+ unpaired, &12 CS-). At the end of each functional run, a subset of participants (n=21) rated pleasantness of the 6 images on a Likert scale, ranging from 0 (not pleasant at all) to 10 (highly pleasant).

2.4.2.5 fMRI data acquisition

Imaging data were acquired using a 3T Siemens (Erlangen, Germany) Magnetom Trio MRI scanner with a 32-channel head coil. Following a MPRAGE, T1-weighted anatomical scan (Voxel size = 1x1x1 mm), functional T2*-weighted echoplanar images were acquired using blood oxygenation level dependent (BOLD) contrast (7 sessions of 140 volumes each, 38 axial slices, TR = 2300ms, TE = 30ms, Flip angle = 90°, Voxel size = 3.5x3.5x3.5ms, FoV = 224mm). E-Prime (Psychology Software Tools, Pittsburgh, PA) running on a PC laptop was used to trigger the olfactometer and to present visual stimuli, projected onto a screen in the fMRI scanner visible to subjects through a mirror system, and to record subjects' button responses.

2.4.3 QUANTIFICATION AND STATISTICAL ANALYSIS

2.4.3.1 Modeling of RPE signals

We used the Rescorla-Wagner reinforcement learning model to generate trial-by-trial prediction signals, namely expected value assigned to CS (referred to as "CS Value") and RPE (Rescorla & Wagner, 1972). The RPE signal, δ, is defined as the difference between the value of the actual outcome on a given trial, R, at time t, and that of the expected outcome on that trial, V.

$$\delta_t = R_t - V_t$$

We modeled the presentation of an odor with R=10, and the omission of an odor with R=0, for both food and non-food odors. The CS Value (V) was updated by adding δ weighted by a learning rate α:

$$V_t = V_{(t-1)} + \alpha\, \delta_t.$$

The learning rate α is dependent on the specific features of the learning paradigm used (O'Doherty, Buchanan, Seymour, & Dolan, 2006). Here we estimated α from participants' reaction times (RT), which were used as trial-by-trial measures of conditioning. It has been previously shown that learning systematically modulates RT, which can reflect changes in the coded value of each stimulus, and can be used to generate a reinforcement learning model (Bray & O'Doherty, 2007; Gottfried, O'Doherty, & Dolan, 2002). Because α is difficult to estimate on an individual basis, we followed the practice of Bray and O'Doherty to use average RT change to estimate a group learning rate (Bray

& O'Doherty, 2007). We estimated trial-by-trial values for the entire range of learning rates (0 to 1) and regressed RT onto each of the value curves. The learning rate that minimized the error was 0.17. While individual variability in α is possible, it has been shown that fMRI results for RPE and Value obtained in this way are quite robust to the use of different learning rates (Wilson & Niv, 2015).

2.4.3.2 Behavioural analysis

Participant RTs and pleasantness ratings were used as indices of learning (Bray & O'Doherty, 2007). We speculated that the images associated with food odors following ghrelin injection would induce faster RTs and greater pleasantness. RTs were z-score normalized, after which odor type-specific RTs for each participant were averaged for each conditioning run. A three-way ANOVA was conducted to observe the effects of odor type, time and treatment on RT using SPSS (version 23, SPSS Inc., Chicago, IL). RT data was analyzed in 29 participants whose fMRI dataset was deemed valid (see below).

Owing to a size-related error in the images presented during the hedonic rating tasks administered to seven participants, the hedonic rating data were analyzed in 14 participants who were shown properly-sized images. Event type-specific in-scanner hedonic ratings for each subject were averaged for each conditioning run and were then analyzed using a three-way ANOVA. Additionally, we performed a two-way ANOVA on the pleasantness rating data collected following a 24-hour delay to investigate the effects of event type and treatment.

2.4.3.3 fMRI data analysis

Neuroimaging analyses were conducted in 29 participants as nine were excluded due to missing responses during the conditioning task and/or excessive head movements (n=8), and lack of growth hormone response to ghrelin injection (n=1).

SPM 8 software (Wellcome Department of Imaging Neuroscience, London, UK) was used for preprocessing and statistical analysis of the fMRI data. The images were slice-time corrected, realigned to the first volume, and normalized into MNI space (final voxel size = 2 x 2 x 2 mm). Spatial smoothing (isotropic Gaussian kernel of 6mm FWHM) was then performed to improve the signal-to-noise ratio. Low frequency temporal drifts were removed using a high pass filter with a cut-

off of 1/128s. The event-related general linear model (GLM) implemented by SPM was used for statistical analysis.

The first analysis was conducted to examine brain activity related to odor processing. We defined five event types: (1) air, (2) images paired with air, (3) odors (both food and non-food), (4) images paired with odors, and (5) button press. To investigate BOLD response during processing of different types of odors, we built another model with the following event types: (1) air, (2) images paired with air, (3) food odors, (4) images paired with food odors, (5) non-food odors, (6) images paired with non-food odors, and (7) button press.

Several parametric analyses were additionally conducted to examine CS Value- and RPE-associated brain activity. First, we defined three event types: (1) images, (2) odors (including odorless air), and (3) button press. In order to identify brain areas whose fMRI activity is modulated by stimulus values regardless of the type of odor, we entered CS Values (estimated by the reinforcement learning model) as parametric regressors for each trial at the time of the presentation of the image. In another GLM, RPE signals were entered as parametric regressors for each trial at the time of the delivery of the odor.

With an aim to observe CS Value- and RPE-related brain activity in different conditions, we defined the following event types: food odor-paired abstract images (CS+), food odors, non-food odor-paired abstract images (CS+), non-food odors, air-paired images (CS-) never paired with an odor, air, and button press. In one GLM, CS Value was entered as a parametric regressor for each conditioning trial at the time of the presentation of an image. In the second GLM, RPE was entered as a parametric regressor for each corresponding trial at the time of the delivery of the odor or air.

For each of the analyses mentioned above, regressors of interest for the BOLD response were generated by convolving the modulated stimulus functions with a standard synthetic hemodynamic response function. The single-subject models also included the six movement parameters obtained from the realignment procedure. For each participant, linear contrasts of parameter estimates for conditions of interest were generated and subsequently submitted to a whole-brain second-level random effects analysis. We present whole-brain results for RPE, CS Values, Odor contrasts with a False Discovery Rate correction of $p<0.05$ at the voxel level. All maps are also available at https://neurovault.org/collections/4131/. Additionally, we conducted region of interest (ROI)

analyses on regions previously identified to be associated with subjective value (Bartra, McGuire, & Kable, 2013) and RPE (Chase, Kumar, Eickhoff, & Dombrovski, 2015), based on published meta-analyses. The subjective value ROI was taken from the positive > negative map from Bartra et al. (2013) and encompasses vmPFC and ventral stiratum, while the RPE ROI consists of ventral striatum, amygdala, midbrain, thalamus, frontal operculum and insula. The analyses were performed using the MarsBaR toolbox (http://marsbar.sourceforge.net/). We obtained, for each session and for each participant, effect sizes for the contrasts of interest for each ROI, which were further analyzed using one-sample t-tests and paired t-tests in SPSS. An additional ROI analysis with small volume correction (SVC) was performed on the hippocampus defined by the AAL atlas implemented in SPM8 (http://www.gin.cnrs.fr/en/tools/aal-aal2/).

Furthermore, to test if ghrelin modulated task-dependent connectivity between learning-related brain regions, we used a generalized form of psychophysiological interaction analysis (gPPI) (McLaren, Ries, Xu, & Johnson, 2012). As per our hypothesis, the regions of interest chosen for this analysis were activation clusters within the hippocampus and ventral striatum (VStr) that exhibited a significant modulation by overall RPE in both ghrelin and saline conditions at the group level (FDR corrected $p<0.05$). First, the physiological variable was derived by extracting de-convolved time series from the VStr seed for each subject. The psychological regressors were created by convolving the canonical hemodynamic response function with the onset times for food odor-paired images, food odor-unpaired images, non-food odor-paired images, non-food odor-unpaired images, air-paired images, and button press. Subsequently the time series from the psychological regressor were multiplied with the physiological regressor, creating the interaction terms (PPIs). We were interested in functional connectivity between the two regions revealed in our activation analysis to be associated with RPE. Therefore, we took a ROI approach where the mean contrast estimates of the PPI regressor were extracted from the target ROI, namely the hippocampus. Repeated ANOVAs and paired t tests were then conducted on the contrast estimates.

2.5 Results and discussion

2.5.1 Ghrelin increases subjective hunger and elevates growth hormone and cortisol

Subjective hunger ratings were collected using a visual analogue scale (VAS) throughout the experiment. We observed significant main effects of condition and time ($F(1,33)=11.32$, $p<0.01$ and $F(3,99)=108.88$, $p<0.001$ respectively) as well as a significant interaction between the two factors ($F(3,99)=4.26$, $p<0.01$; see Figure S2.1A). Participants were least hungry after eating breakfast, which was provided 3 hours before ghrelin or saline administration (ps<0.001). Their pre-scan (post-injection) hunger ratings were also lower compared to pre-breakfast and post-scan ratings (ps<0.001). Consistent with the role of ghrelin, post-injection and post-scan hunger ratings were higher in the ghrelin versus saline condition ($t(33)=4.83$, $p<0.001$ and $t(33)=2.16$, $p<0.05$ respectively). VAS ratings of boredom and irritability did not differ between conditions (Figure S2.1B-C).

Given that ghrelin binding to central nervous system GHSR triggers growth hormone (GH) secretion (Takaya et al., 2000), another way to measure a brain effect of ghrelin is to examine associated changes in GH levels. Blood samples were withdrawn before ghrelin injection (before the MRI scan) and after the scan to quantify levels of GH. As illustrated in Figure S2.2A, we observed significant main effects of condition ($F(1,25)=31.90$, $p<0.001$) and time ($F(1,25)=34.26$, $p<0.001$) and a significant interaction between the two variables ($F(1,25)=35.38$, $p<0.001$). As expected, post-scan growth hormone levels were significantly higher following ghrelin compared to saline administration ($t(25)=5.91$, $p<0.001$). One participant did not show the expected growth hormone response to ghrelin injection (pre-scan: 3ug/L, post-scan: 2.12ug/L) and was excluded from further analyses.

In line with previous findings (Takaya et al., 2000), ghrelin also increased levels of salivary cortisol (Figure S2.3). We observed significant main effects of condition and time ($F(1,32)=12.63$, $p<0.01$ and $F(2,64)=3.50$, $p<0.05$ respectively) as well as a significant interaction between the two variables ($F(1.32, 42.22)=20.08$, $p<0.001$). At post-scan, cortisol levels were significantly greater following ghrelin than saline infusion ($t(32)=5.88$, $p<0.001$).

2.5.2 Ghrelin reduces response time to food odor-paired cues and intensifies their pleasantness

We administered a food odor conditioning task during fMRI (Figure 2.1A) on two different days, following ghrelin or saline intravenous injection (single-blind and counterbalanced). During the task, participants were presented with a series of trials in which one of four abstract images was followed, 50% of the time, by one of two food or two non-food odors (with odorless air being delivered in the remaining trials), or one of two abstract images that invariably cued delivery of odorless air. In all, there were six images and four odors. Participants were instructed to indicate using a MRI-compatible mouse-like device whether each image was composed of straight or curvy lines. This allowed us to examine reaction time, frequently used as an index of learning during classical conditioning. As illustrated in Figure 2.1B, z-transformed reaction time decreased over the course of the task, regardless of odor type and condition ($F(2.74, 76.72)=6.63$, $p<0.005$). We also observed significant interactions between time and odor type ($F(12, 336)=3.35$, $p<0.001$) and between condition and odor type ($F(2, 56)=3.48$), $p<0.05$; see Figure 2.1C). Post-hoc paired t tests revealed that the difference in response time between the food and non-food trials differed significantly between the ghrelin and saline conditions ($t(28)=-2.47$, $p<0.05$): following ghrelin infusion, subjects responded faster toward food-related images compared to those paired with non-food odors ($t(28)=-1.87$, $p=0.07$) while in the saline condition the response time was (not significantly) lower for the non-food odor-paired images ($t(28)=1.70$, $p=0.1$). Furthermore, the reaction time difference between food and air trials differentiated the ghrelin and saline conditions ($t(28)=-2.20$, $p<0.05$) such that ghrelin induced faster reaction time on the food compared to air trials ($t(28)=-2.63$, $p<0.05$) while no such difference was observed following saline administration ($t(28)=0.91$, $p=0.37$).

We also used hedonic ratings of the abstract images to measure conditioning. Repeated measures ANOVAs conducted on the hedonic ratings collected during the scans and 24 hours after each scan did not yield any significant results (interaction between condition, time and odor type on in-scanner ratings: $F(4.24, 67.87)=0.56$; interaction between condition and odor type on delayed ratings: $F(2, 32.03)=0.94$). However, paired t tests revealed that after a 24-hour delay, abstract images associated with food odors following ghrelin administration were perceived to be more pleasant than novel images ($t(17)=2.14$, $p<0.05$; see Figure 2.1D). The effect was not significantly

different between ghrelin and saline conditions (t(17)=1.20, p=0.25). Taken collectively, faster reaction times and increased liking toward food-associated cues following ghrelin administration suggest that the hormone may enhance conditioning to food-related stimuli.

2.5.3 Ghrelin increases RPE-associated activity during food odor conditioning

To induce RPE and reward learning, the fMRI task implemented a 50% reinforcement schedule. In order to map brain activity related to RPE, a group learning rate was first estimated by fitting a Rescorla-Wagner learning model to participant reaction times. We then used the derived learning rate and the model to calculate the trial-by-trial RPE, which was subsequently regressed with brain activation (O'Doherty, Hampton, & Kim, 2007). In each of the ghrelin and saline conditions (analyzed independently), RPE was positively correlated with activity in a large number of regions including the piriform cortex, amygdala, VStr, putamen, globus pallidus, insula, substantia nigra/VTA, OFC, and anterior and posterior cingulate cortex (Figure 2.2A, Table S2.1).

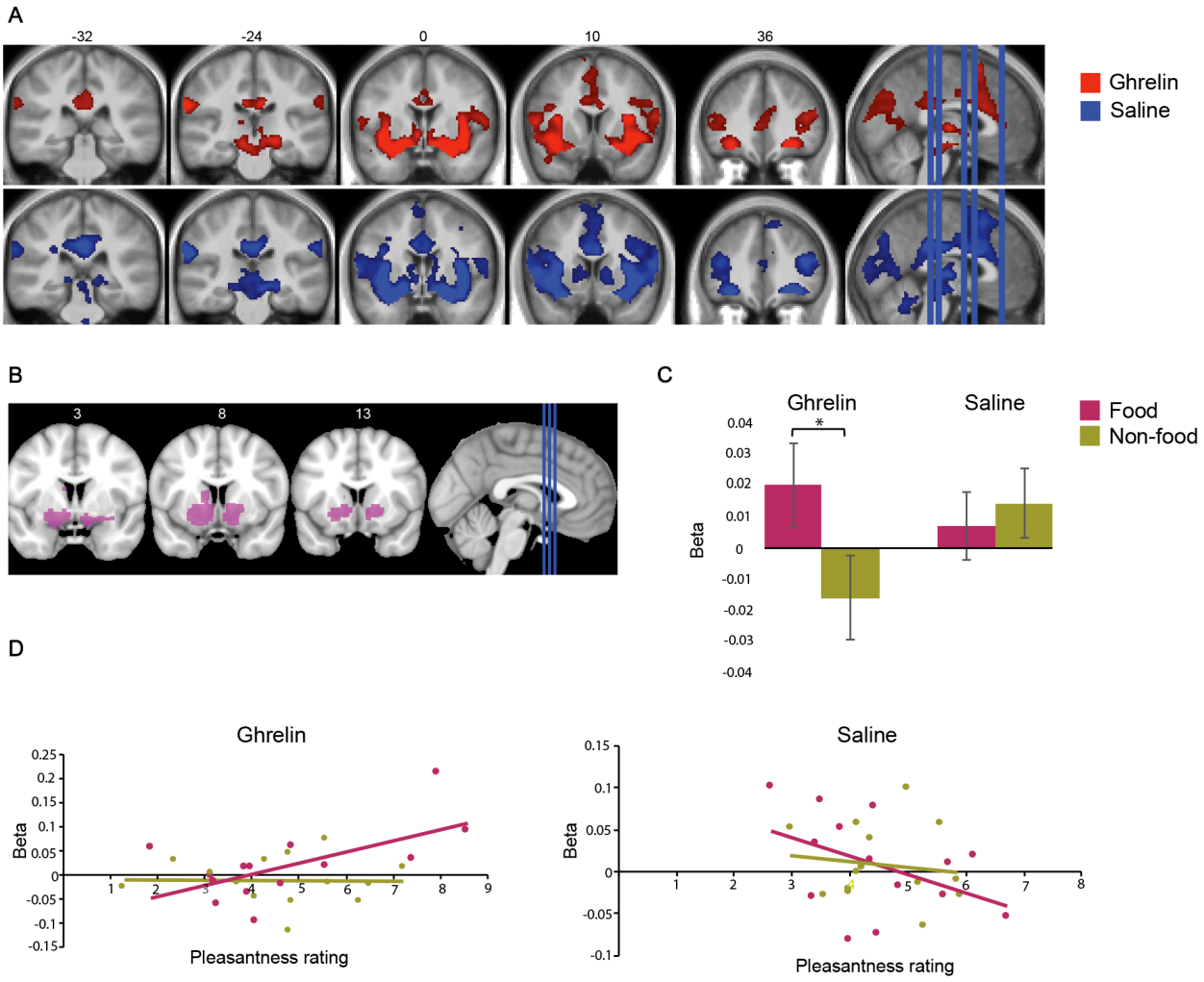

Figure 2.2. Ghrelin increases RPE-associated activity during food odor conditioning

(A) The whole brain analysis revealed RPE-related activity in a large number of brain regions including the piriform cortex, VStr, putamen, OFC and substantia nigra/VTA in both ghrelin and saline conditions (FDR corrected $p<0.05$). (B) A mask of the brain regions that were previously identified by a meta-analysis to subserve RPE (Chase et al., 2015). We conducted an ROI analysis using the mask and compared RPE-related activity between ghrelin and saline conditions. (C) The ROI analysis revealed that only in the ghrelin condition, RPE-related activity was stronger on food trials compared to non-food trials ($t(28)=2.41$, $p<0.05$). Error bars represent the SEM. (D) In-scanner pleasantness ratings of the abstract images correlated positively with RPE-related activity on food trials following ghrelin infusion ($r=0.61$). No other significant correlations were revealed.

To test the effect of ghrelin on RPE-related activity, we limited the analysis to a group of brain regions previously identified by meta-analysis to subserve RPE (Chase et al., 2015) including the bilateral VStr as well as portions of the anterior insula, midbrain and thalamus (Figure 2.2 B). We observed a significant interaction between condition and event type in the region of interest defined by the meta-analysis ($F(1,28)=4.60$, $p<0.05$; Figure 2.2 C). More specifically, RPE-associated activity following ghrelin injection was greater on food compared to non-food trials ($t(28)=2.41$, $p<0.05$). Such a difference was absent in the saline condition ($t(28)=-0.55$, $p=0.59$). Furthermore, we observed, only in the ghrelin condition, a positive correlation between RPE-associated activity during food-related learning and in-scanner pleasantness ratings of the images associated with food odors ($r=0.61$; $n=14$; Figure 2.2 D). An additional analysis demonstrated that condition significantly moderated the relationship between the pleasantness ratings and RPE-related activity on food trials (B: 24.93, β: 0.82, $p<0.01$). Finally, in a separate analysis focusing on the hippocampus, we observed stronger RPE-related activity in the right hippocampus during food-odor conditioning following ghrelin compared to saline administration (Montreal Neurological Institute [MNI] coordinates: 32 -12 -16, $t=4.45$, $p=0.015$, family-wise error [FEW] after small volume correction using the hippocampus mask derived from the automated anatomical labeling [AAL] atlas provided in SPM8).

Cue-reward associations are thought to be shaped by DA-generated RPE signals (Schultz, 2016). In human fMRI studies, RPE signals are related to activity in DA-sensitive brain regions such as the striatum, and typically reflect learning (Schonberg, Daw, Joel, & O'Doherty, 2007). Ghrelin binds to GHSR expressed in the VTA, where it can stimulate DA signaling to promote food cue conditioning (Mason et al., 2014; Perello & Dickson, 2015). Considerable evidence suggests that phasic DA encodes the RPE (Schultz, 2016). Ghrelin injection is shown to increase phasic DA signaling in response to food cues and to heighten activity in DA-responsive brain regions in humans (Cone et al., 2015; Malik et al., 2008). Furthermore, flavour-nutrient conditioning, a process that mostly implicates olfaction, necessitates D1 receptor-dependent phasic DA signaling (Sclafani, Touzani, & Bodnar, 2011). Our neuroimaging results extend these findings and provide more direct evidence that ghrelin enhances activity associated with prediction errors for food reward in dopaminergic projection sites, while also enhancing food cue-related learning.

2.5.4 Ghrelin heightens the brain response associated with expected value assigned to food cues

Successful associative learning is also reflected in the degree to which cues acquire the incentive salience of their associated reward. The reinforcement learning model described in the previous section also provides an estimate of expected value assigned to conditioned stimuli (CS) on each trial, hereafter referred to as "CS Value". The trial-by-trial CS Values were regressed onto fMRI responses, providing another measure of learning-related brain activity. As illustrated in Figure 2.3A, both conditions were associated with CS Value-related activity during exposure to the visual cues in several brain regions including the piriform cortex, insula, globus pallidus, anterior and posterior cingulate cortex and OFC (Table S2.2). The analysis testing ghrelin's effects was limited to the two regions of interest previously shown to encode subjective value by meta-analysis, namely the vmPFC and VStr (Bartra et al., 2013). As seen in Figure 2.3B, CS Value-related activity in the vmPFC was only significant on food-odor trials in the ghrelin condition ($t(28)=2.16$, $p<0.05$), which was greater than that revealed in the saline session ($t(28)=1.99$, $p=0.06$). The analyses on the VStr revealed significant food value-related activity in both the ghrelin and saline conditions ($p's<0.05$; $n=29$; Figure 2.3C). Moreover, in the right VStr, the CS Value-associated activity was stronger during food versus non-food odor conditioning ($t(28)=2.01$, $p=0.05$, ghrelin; $t(28)=1.87$, $p=0.07$, saline). However, only in the ghrelin condition, food CS Value-associated activity correlated with in-scanner hedonic scores in both the right and left VStr (for both correlations, $r=0.51$, $p=0.06$; $n=14$; Figure 2.3D).

In line with these neuroimaging findings, the delayed rating task revealed that the abstract images paired with food odors following ghrelin injection were perceived to be more pleasant. Considering our RT and RPE-related results, this supports ghrelin-induced enhancement of conditioning to food odors, leading to increased incentive value of the conditioned stimuli paired with food odors.

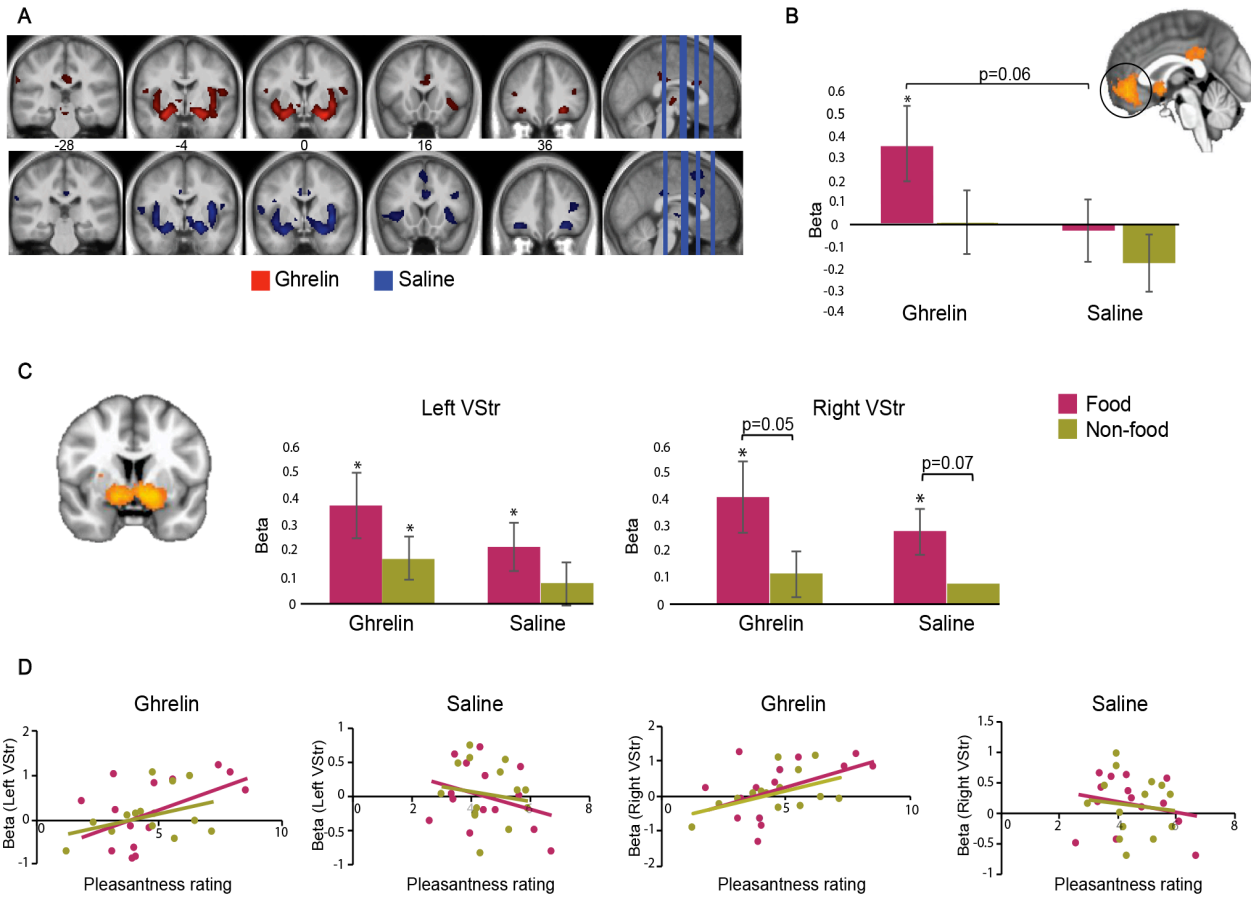

Figure 2.3. Ghrelin heightens brain response associated with expected value assigned to food cues.
(A) Expected value assigned to cues (CS Value) correlated with activity in many brain regions including the piriform cortex, insula, anterior and posterior cingulate cortex and OFC in both ghrelin and saline conditions. (B) In the analysis focusing on the part of the vmPFC previously associated with subjective value, we observed greater CS Value-related activity during food conditioning in the ghrelin versus saline condition ($t(28)=1.99$, $p=0.06$). (C) Another analysis focused on the clusters previously identified to encode subjective value that largely include the VStr. We observed increased CS Value-related activity on food trials following ghrelin and saline administration in both the left and right VStr (p's<0.05). (D) Only in the ghrelin condition, food CS Value-related activity in the VStr was correlated with in-scanner pleasantness ratings (r's$=0.51$, $p=0.06$). Error bars represent the SEM.

2.5.5 Ghrelin strengthens hippocampus-Vstr coupling during food conditioning

Complex cognitive processes such as learning tend to recruit networks of spatially separate brain regions rather than engaging them independently. Indeed, connectivity between the hippocampus and VStr has been shown to support value-related learning by linking stored memories of value in

the hippocampus to reinforcement processes in the striatum (Wimmer & Shohamy, 2012). We therefore conducted a generalized psychophysiological interaction (gPPI) analysis (McLaren et al., 2012) to determine whether ghrelin modulated task-dependent connectivity between the hippocampus and VStr regions that were revealed in the activation analysis to be associated with RPE. We observed in trials in which odors were delivered a significantly greater coupling between the left VStr (seed) and the left hippocampus on food-odor trials in the ghrelin versus saline condition ($t(28)=2.14$, $p=0.04$; Figure 2.4). In the saline condition, the left VStr was more strongly associated with the right hippocampus on non-food trials compared to food trials ($t(28)=3.03$, $p=0.005$).

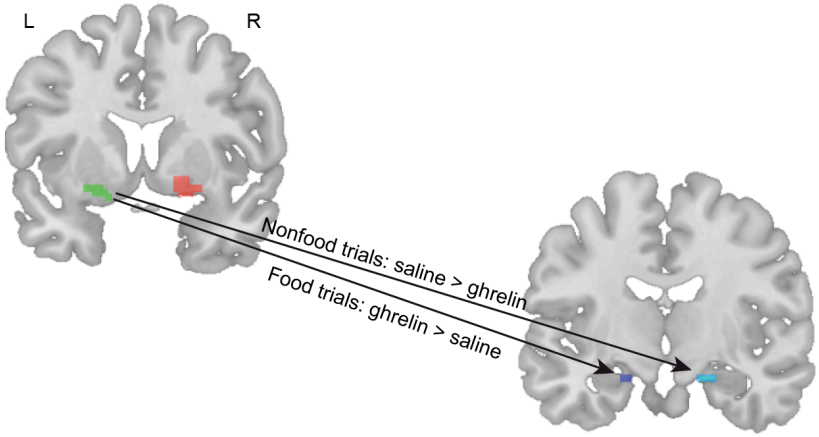

Figure 2.4. Ghrelin strengthens hippocampus-ventral striatum coupling during food conditioning.
The gPPI analysis with the VStr as the seed region and the hippocampus as the target revealed a greater functional coupling between the left VStr and the left hippocampus during food conditioning in the ghrelin versus saline condition ($t(28)=2.14$, $p=0.04$). In the saline condition, the left VStr showed greater functional coupling with the right hippocampus on non-food compared to food trials ($t(28)=3.03$, $p=0.005$).

The above-mentioned brain regions thought to generate learning-related RPE signals are heavily connected to the hippocampus. The hippocampus is speculated to provide input into the VStr to modulate learning-related signals and participate in encoding and retrieving of cue-reward associations (Pennartz, Ito, Verschure, Battaglia, & Robbins, 2011). For instance, in reinforcement learning tasks that rely on episodic memory for cues, associations have been found between learning performance and both stronger hippocampal activity and hippocampus-striatum coupling (Wimmer

& Shohamy, 2012). Ghrelin also acts on the hippocampus, where GHSR are densely expressed (Mason et al., 2014). Thus, the learning- and value-promoting effects of ghrelin also appear to be exerted via the hippocampus. Our study involved second order conditioning, which is thought to necessitate recruitment of the hippocampus (Wimmer & Shohamy, 2012). We observed greater RPE-related activity in the hippocampus during food conditioning following ghrelin compared to saline injection. Furthermore, functional connectivity between the two regions associated with RPE, namely the hippocampus and VStr, was stronger on food trials versus non-food trials following ghrelin infusion while the reverse pattern was seen in the saline condition. Finally, the food trial-induced coupling between the two regions was significantly stronger following ghrelin compared to saline treatment.

The hippocampus is implicated in cue-potentiated feeding, in which a food-paired conditioned stimulus drives feeding behavior (Kanoski et al., 2013). It is also necessary when contextual information must be used for the learning or expression of an association between a food cue and feeding behavior (Kanoski & Grill, 2017). Both phenomena depend on ghrelin signaling in the hippocampus. For example, ghrelin, as a meal anticipatory signal, promotes cue-driven feeding via actions on the hippocampus: in animals trained on a fixed meal schedule, hippocampal GHSR blockade reduces food consumption at the anticipated mealtimes (Hsu et al., 2015), presumably by decoupling the temporal context from cue reactivity. There is also evidence from animal experiments that ghrelin acts during the formation of food-cue reward associations (Hsu et al., 2018). Thus, the hippocampus incorporates information about familiar food cues, the current context, and circadian and energy balance information to control feeding behavior. Animal studies implicate connections between hippocampus and mesolimbic DA structures including the VStr in these processes (Kanoski & Grill, 2017). Our results support this model, whereby ghrelin promotes the formation of context-specific cue-reward associations by augmenting hippocampal signaling and connectivity to VStr.

2.5.6 The actions of ghrelin are food-specific

An intriguing finding revealed consistently across the dataset is that only the responses to food odors were modulated by ghrelin injection. As argued above, the effects on RPE and value appear to be plausibly exerted via DA signaling, which is known to be stimulated by ghrelin. However, given the

responsivity of DA to a wide variety of rewards, it might be assumed that the actions of ghrelin could generalizable to non-food stimuli. Indeed, a few studies have demonstrated ghrelin-induced modulation of responses to drug rewards such as cocaine and alcohol (Jerlhag et al., 2009; Wellman, Davis, & Nation, 2005). In the present work, however, ghrelin injection enhanced learning with food, but not non-food, odors despite their similar pleasantness, intensity ratings and evoked brain responses. The ability of ghrelin to selectively facilitate associative learning with food reward was revealed in reaction times, RPE and Value-related activity in dopaminergic brain regions, and in hippocampal-striatal connectivity. It is possible that ghrelin preferentially targets food-specific pathways within the DA system and other regions such as the lateral hypothalamus, which contains the highest density of GHSR and regulates appetite and energy balance (Olszewski et al., 2003). Lateral hypothalamic projections to VTA DA neurons (Nakamura et al., 2000) could then mediate this food-specific learning effect of ghrelin.

Alternatively, hippocampal involvement may also explain the food-specificity of our findings. Food odors are learned contextual cues that rely on hippocampal memory systems. Ghrelin may activate hippocampal memory traces of food-specific cues to promote associative learning via hippocampal-striatal connectivity (Kanoski & Grill, 2017). However, the precise neuronal mechanisms underlying the selective effects of ghrelin on food stimuli cannot be addressed here given the low spatial resolution of fMRI and our study design.

2.5.7 Ghrelin does not alter odor perception

There is some evidence that ghrelin can increase olfactory sensitivity and sniffing as it binds to GHSR present in the olfactory bulb and other odor-processing brain regions (Tong et al., 2011). To determine whether the effects of ghrelin on food-related learning are attributed to its influence on sensory signaling, neural activation associated with odor perception was examined by contrasting odor and air trials. Exposure to odors increased activity in the piriform cortex, insula, OFC, middle and inferior frontal gyri, VStr and posterior cingulate cortex in both ghrelin and saline conditions, which did not differ from each other (Figure S2.4A, Table S2.3). Moreover, odor detection thresholds taken after scan did not differ between the ghrelin and saline conditions ($t(17)=1.02$, $p=0.32$). Finally, when fMRI response to different types of odors was investigated, food odors

compared to air evoked activity in the piriform cortex, OFC, insula, ventral striatum, and middle frontal gyrus in both ghrelin and saline conditions (Figure S2.4B, Table S2.4). Only following saline injection, did non-food odors lead to increased activation in the middle frontal gyrus. We may conclude, therefore, that the effects of ghrelin on food-related conditioning observed using our task cannot be attributed to increased sensory signaling.

In this paradigm, RPE and odor sensation covary. Positive RPEs only occur when there is odor presentation, and negative RPEs only following the air stimulus. The absence of an effect of ghrelin on odor perception suggests that our RPE results (above) are truly a measure of RPE signaling, and not merely an effect of response to odor minus air. However, to test this further we applied an axiomatic approach (Rutledge, Dean, Caplin, & Glimcher, 2010) to further confirm that the RPE-related blood oxygen level-dependent (BOLD) signals truly reflect a putative biological RPE signal. The RPE contrast tests Rutledge et al.'s Axiom 1 ("with equal expectation, greater activation to high value versus low value outcome"). To test Axiom 2 ("with equal outcome, there will be greater activation when the reward expectation was lower") we generated a contrast of air events following odor cues vs air cues. Axiom 2 would predict reduced activation following odor cues. The contrast of air stimulus -air cue minus air stimulus-odor cue identified a peak in the VStr (MNI coordinates: 10 4 -10; t=4.68) in the ghrelin condition, and in the overall condition (MNI coordinates: 10 10 -8; t= 3.91).

2.5.8 Limitation

We propose that greater DA signaling explains enhanced food-related learning following ghrelin treatment. Our interpretation is based on substantial evidence that ghrelin stimulates the DA system that is thought to encode RPE-related activity associated with reinforcement learning. However, DA signaling was not directly assessed in this study. Moreover, there is some evidence that ghrelin also modulates opioid and the endocannabinoid signaling, which also interact with DA and may influence food motivation (Edwards & Abizaid, 2016; Kawahara et al., 2013). Therefore, the possibility for the involvement of non-dopaminergic systems in ghrelin-induced facilitation in learning should not be ruled out. On a related note, while ghrelin is known to stimulate release of other hormones such as GH, cortisol and adrenocorticotropic hormone, we attribute our findings to the effects of ghrelin, as pharmacological levels of the hormone were injected. Nevertheless, readers should keep in mind the potential indirect influences of the other hormones on our results.

We did not measure sniff responses. It is known that the somatosensory activity related to sniffing can activate the piriform cortex (Mainland & Sobel, 2006), and it plausible that sniff timing or intensity may have been affected by ghrelin or by the conditioning process. However, we note that there was no difference between ghrelin and saline conditions on the odor minus air contrast, nor was there an effect of ghrelin on olfactory detection thresholds. It is therefore unlikely that the ghrelin effects described here are only due to effects on sniffing.

2.5.9 Clinical relevance

Our results support the animal literature in highlighting the role of ghrelin in the motivational and learned aspects of feeding. They may explain the consistent observation that, while chronic ghrelin administration causes weight gain, ghrelin or GHSR null mice are the same weight as wild-type animals when chow-fed (Müller et al., 2015). However, lack of ghrelin signaling appears to protect these animals against diet-induced obesity when they have access to appetizing high-fat foods. Ghrelin deficient mice may simply lack the ability to condition to high-calorie foods, despite having seemingly normal energy homeostasis.

Obesity is characterized by abnormal reactivity to food-related cues abundant in our environment (Boswell & Kober, 2016). Here we show that ghrelin enhances food-odor conditioning

and its related BOLD response in mesolimbic projection sites. This provides a mechanistic link between energy signaling and learning about the food environment.

The ghrelin-responsive regions identified here have been implicated in a neural endophenotype that confers vulnerability to obesity. Cue reactivity in the vmPFC and VStr has been shown to encode the learned value of food cues based on their energy content (Tang et al., 2014) and this response in turns appears to correlate with obesity and prospective weight gain (Boswell & Kober, 2016; Stoeckel et al., 2008b). In summary, conditioning to the hedonic, and typically caloric, aspects of food cues modifies the neural response to these cues in ways that appear to predispose to future weight gain. Our results show that homeostatic or circadian signals like ghrelin play a role in the neural plasticity processes that predispose to obesity. By providing further support for the role of ghrelin as a link between energy balance and motivation and learning, the present work unravels potential mechanisms through which ghrelin may contribute to both normal and maladaptive eating behaviors.

2.6 Acknowledgements

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2.7 Author contributions

Conceptualization, J.E.H., J.F., J.B., S.M., M.J.G., A.D.; Methodology J.E.H., J.F., S.M., M.J.G., K.L., and A.D.; Investigation, J.E.H., J.B., T.M., Y.Z. and J.F.; Writing, J.E.H., J.F., Y.Z., and A.D.; Acquisition, S.C.P. and S.Y.W.; Resources, M.J.G. and A.D.; Supervision, J.F., M.J.G., and A.D.; Funding, A.D.

2.8 Declaration of interests

The authors declare no competing interests.

2.9 Data and software

All statistical maps have been deposited at Neurovault (https://neurovault.org/collections/4131/) under ID code 4131.

2.10 Supplementary material

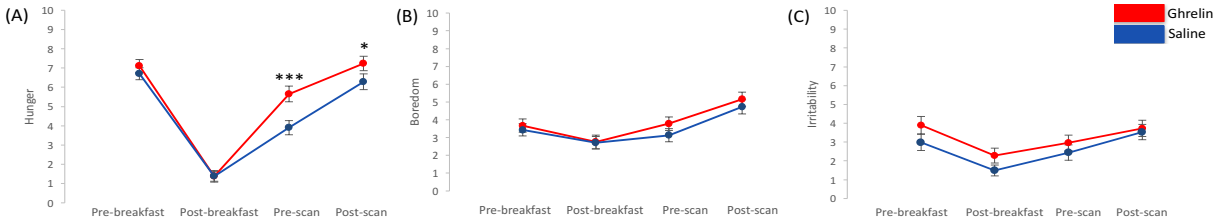


Figure S2.1. Subjective ratings of hunger, boredom and irritability throughout the experiment (n=34; * p<0.05, *** p<0.001). (A) The analysis on hunger levels revealed significant main effects of condition and time ($F(1,33)=11.32$, $p<0.01$ and $F(3,99)=108.88$, $p<0.001$ respectively) as well as a significant interaction between the two factors ($F(3,99)=4.26$, $p<0.01$). Posthoc paired t test revealed that both pre-scan and post-scan hunger ratings were greater in the ghrelin versus saline condition ($t(33)=4.83$, $p<0.001$ and $t(33)=2.16$, $p<0.05$ respectively). (B)(C) There was a significant main effect of time on both boredom and irritability ratings ($F(2.80, 92.46)=13.08$, $p<0.001$ and $F(2.94, 97)=13.03$, $p<0.001$ respectively). Error bars represent the SEM.

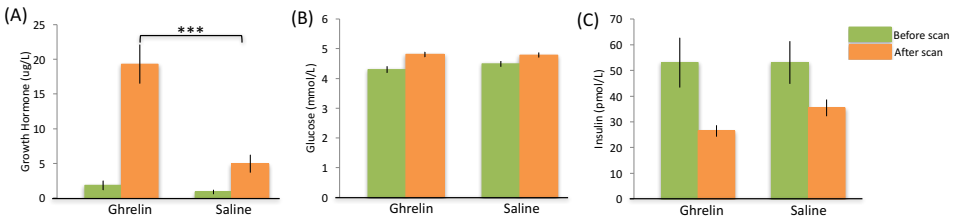


Figure S2.2. Changes in levels of plasma growth hormone (GH), glucose and insulin between pre- and post-scan **(*** p<0.001)** (A) The analysis on GH levels revealed significant main effects of condition and time ($F(1,25)=31.90$, $p<0.001$ and $F(1,25)=34.26$, $p<0.001$ respectively) as well as a significant interaction between the two factors ($F(1,25)=35.38$, $p<0.001$). Greater post-scan GH levels were detected in the ghrelin compared to saline condition ($t(25)=5.91$, $p<0.001$). (B) In both conditions, the post-scan levels of glucose were significantly higher than the pre-scan levels ($F(1,28)=22.42$, $p<0.001$). (C) Regardless of condition, the insulin levels dropped significantly from pre- to post-scan ($F(1,28)=13.58$, $p<0.005$). Error bars represent the SEM.

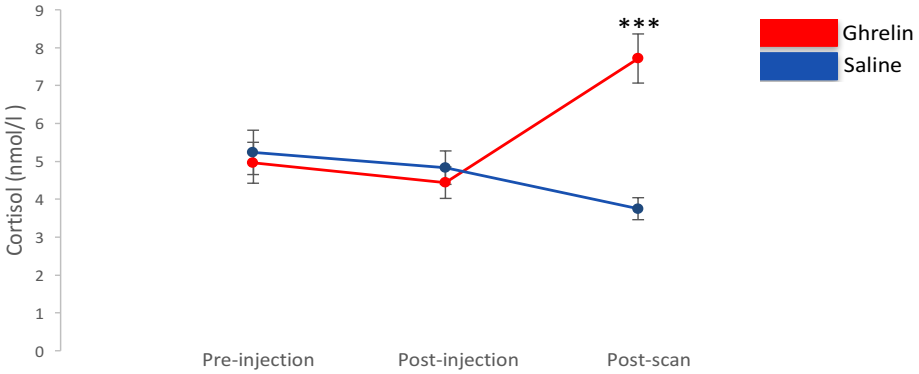
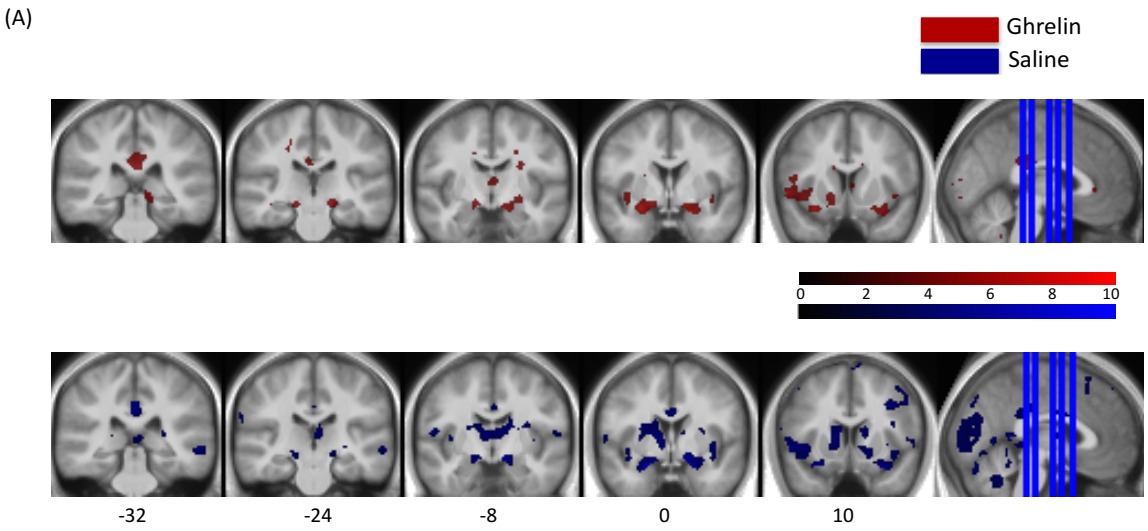


Figure S 2.3. Changes in cortisol levels during the experiment **(n=33; *** p<0.001).** In addition to significant main effects of condition and time ($F(1,32)=12.63$, $p<0.01$ and $F(2,64)=3.50$, $p<0.05$ respectively), we observed a significant interaction between the two variables ($F(1.32, 42.22)=20.08$, $p<0.001$). Posthoc paired t tests showed that post-scan cortisol levels were significantly higher following ghrelin compared to saline injection ($t(32)=5.88$, $p<0.001$). Error bars represent the SEM.



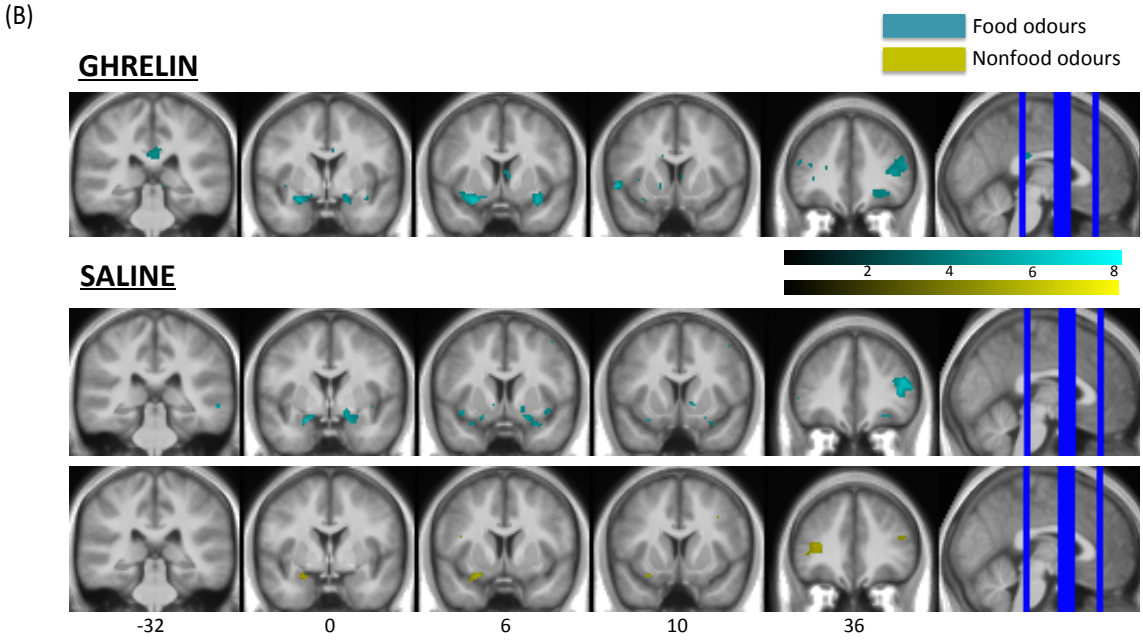


Figure S2.4. Brain responses to odors following ghrelin and saline infusions **(FDR-corrected p<0.05).** (A) The analysis for neural activation to all odours combined revealed no significant differences between the ghrelin and saline sessions, both showing increased activity in brain regions including the piriform cortex, OFC, insula and posterior cingulate cortex. (B) Brain activity patterns in response to different types of odours were similar between the two sessions. Food odour-evoked activity was detected in the piriform cortex, OFC, insula, ventral striatum, and DLPFC in both ghrelin and saline conditions. Upon saline injection, perception of non-food odours was associated with increased activity in the piriform cortex, DLPFC, and OFC.

Table S2.1. Reward Prediction Error - related activity. Related to Figure 2.2A

		Ghrelin				Saline			
Region	L/R	t stat	x	y	z	t stat	x	y	z
Cerebellum	R	4.94	14	-72	-46	5.64	20	-70	-50
	L					5.17	-14	-68	-50
Piriform	R	12.04	26	2	-16	13.1	26	8	-20
	L	11.01	-22	0	-12	10.88	-28	2	-20
Amygdala	R	11.51	22	-4	-12	10.27	24	2	-20
	L	10.12	-22	-4	-12	9.39	-24	0	-20
Substantia nigra	R					6.1	12	-16	-12
	L	5.79	-8	-20	-16	4.72	-6	-12	-10
Oribitofrontal	R	8.14	26	34	-12	9.43	28	36	-14
	L	8.07	-28	32	-14	7.92	-26	30	-18
Ventral Striatum	R	7.11	20	4	-10	8.14	20	4	-12
	L	9.63	-16	0	-10	5.16	-16	4	-8
Putamen	R	5.92	22	6	-10	6.54	20	4	-10
	L					6.19	-20	4	-10
Insula	R	12.95	36	6	-8	11.17	40	6	-6
		7.63	38	-2	8	9.5	38	-4	8
	L	10.76	-36	2	-10	10.74	-36	6	-8
		8.89	-36	-6	8	10.59	-36	-8	10
Globus Pallidus	R	6.99	18	-2	-8	5.15	20	4	-6
	L	9.15	-16	-2	-8	6.78	-18	0	-6
Thalamus	R	6.17	4	-14	4	7.56	4	-14	2
	L	5.66	-4	-16	2	7.22	-4	-16	4
Inferior Frontal Gyrus	R					6.5	42	36	16
						6.98	58	10	12
	L	5.18	-56	10	10	5.56	-38	32	16
Middle Frontal Gyrus	R	4.83	42	40	12	6.22	40	38	14
Parietal operculum	R	5.44	60	-10	12	7.56	58	-12	18
Postcentral gyrus	R	4.89	60	-18	26	8.18	62	-18	26
	L	4.79	-56	-14	18	5.56	-60	4	14
						7.38	-62	-22	28
Frontal operculum	L					7.77	-52	10	4
						6.88	-54	-10	10

Anterior Cingulate	R					6.02	4	10	26
Posterior Cingulate	R					6.2	4	-22	28
	L					5.8	-6	-24	30
Posterior Cingulate	R					7.52	2	-34	30
Supplementary Motor	R					5.3	2	18	54
Anterior Cingulate	R	6.33	12	22	26	6.15	6	20	26
	L					6.36	-4	12	26
Cuneus/precuneus	R	5.04	12	-72	14				

Table S2.2. Value-associated activity. Related to Figure 2.3A

		Ghrelin				Saline			
Region	**L/R**	**t stat**	**x**	**y**	**z**	**t stat**	**x**	**y**	**z**
Piriform	R	11.49	28	0	-18	6.01	22	2	-14
		9.08	18	-4	-14				
		8.49	24	4	-14				
Amygdala	R	8.08	24	-4	-20	7.14	24	-4	18
Insula	R	8.64	38	0	-4	9.27	38	8	-8
		6.31	36	-6	14	8.92	38	0	-2
						9.27	38	8	-8
						8.05	36	-2	12
Sublenticular Area	R	5.49	18	0	-8	9.29	20	-4	-10
Frontal Operculum	R	7.02	46	-8	12				
		5.27	54	4	16				
Hypothalamus	R					6.39	8	-4	-4
Amygdala	L	9	-24	-4	-18	8.44	-22	-8	-12
Piriform	L	10.61	-28	-2	-16	7.88	-28	0	-18
Ventral Striatum	R	7.9	16	-2	-12				
	L	6.49	-14	-2	-12	5.03	-20	-2	-10
		7.84	-20	-4	-8				
Insula	L	8.13	-36	2	-10	7.73	-36	6	-10
		6.53	-34	-8	12	7.02	-38	-6	2
Frontal Operculum	L	5.39	-50	-8	14	4.82	-54	-10	12
Precentral gyrus	L					4.95	-60	4	12

Orbitofrontal cortex	R	7.09	26	36	-10	6.44	24	34	-14
	L	6.75	-26	32	-12	5.8	-26	28	-16
						5.6	-34	36	-12
Thalamus	L	4.94	-2	-16	2				
Middle Frontal Gyrus	R					4.93	34	42	8
						4.89	40	28	18
Inferior Frontal Gyrus	R					4.24	42	12	26
Anterior Cingulate	R					4.93	4	16	28
Mid Cingulate	L					5.17	-6	0	32

Table S2.3. Odor-evoked brain responses. Related to Fig. S2.4a

		Ghrelin				**Saline**			
Region	**L/R**	**t stat**	**x**	**y**	**z**	**t stat**	**x**	**y**	**z**
Cerebellum	R					4.66	32	-74	-42
						3.7	20	-80	-42
						3.66	20	-72	-50
	L					5.32	-28	-74	-48
						5.05	-32	-64	-42
						4.86	-10	-86	-32
Piriform	R	6.31	18	-2	-16	6.63	14	-2	-12
Temporal pole	R	6.25	34	6	-18	5.65	32	10	-22
Orbitofrontal Cortex	R	5.56	24	34	-14	5.66	26	34	-14
Mid ventral insula	R	5.56	36	8	-16	4.44	38	6	-12
Middle frontal gyrus	R	6	38	30	12	7.99	44	40	10
		5.63	46	40	6				
Ventral Striatum	R					5.04	16	6	-8
Piriform	L	8.35	-24	4	-14	7.38	-24	4	-20
Temporal pole	L	6.5	-54	12	-2				
Ventral Striatum	L	5.57	-14	12	-6				
Ventral Insula	L	5.11	-38	6	-8	5.03	-40	6	-12
Inferior Frontal Gyrus	L	6.49	-48	40	4	6.8	-42	44	6
		4.73	-50	42	-6	5.98	-42	44	-10
Caudate	L					4.89	-12	8	6

Thalamus	R					4.72	6	-20	12
Thalamus	L					4.71	-10	-2	6
Posterior Cingulate	R	5.16	4	-30	22	5.15	2	-30	34
	R	4.82	6	-36	28				
	L	4.73	-6	-18	26				
Postcentral Gyrus	L					4.62	-66	-22	24
Dorsomedial Prefrontal	R					4.6	4	30	46
						3.94	4	36	54
						3.75	6	20	66
Angular gyrus	R					5.33	52	-54	48
						4.1	40	-56	50
						3.62	30	-72	50

Table S2.4. BOLD responses to food and non-food odors. Related to Figure S2.4b.

			Ghrelin				**Saline**			
	Region	**L/R**	**t stat**	**x**	**y**	**z**	**t stat**	**x**	**y**	**z**
Food odours	Ventral Insula	R	5.52	34	6	-18				
	Piriform	R	5.88	16	-4	-16				
	Globus Pallidus	R		26	-6	-8				
	Piriform	L	7.01	-26	2	-16	6.25	-20	2	-18
	Midbrain	L	4.61	-12	-10	-14				
	Globus Pallidus	L	4.28	-14	-4	-8				
	Temporal pole	L	6.28	-56	10	-4	4.56	-30	8	-20
	Medial Orbital Gyrus	R	5.22	22	32	-14				
			4.25	32	36	-10				
			3.93	22	40	-8				
	Inferior Frontal Gyrus	R					6.19	42	36	8
							5.17	44	44	6
	Middle Frontal Gyrus	R					5.98	46	36	16
	Cerebellum	L					5.36	-38	-60	-24
Nonfood odours	MFG/IFG	R					5.98	42	44	6
							4.48	46	38	16

Chapter 3 - Neural correlates of dietary self-control in healthy adults: A meta-analysis of functional brain imaging studies

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3.1 Preface

The desire to eat, driven by the homeostatic and appetitive systems, is regulated to meet an individual's health- and eating-related goals. This regulation is thought to be achieved by a set of brain regions known to subserve self-control (Hare et al., 2009). In our second study, published in *Physiology and Behavior,* we performed a meta-analysis of functional brain imaging studies to identify brain areas that are consistently recruited during implementation of eating-specific self-control. A range of brain regions were revealed to be responsive during different types of dietary self-control tasks, which included the DLPFC, IFG and pre-supplementary motor area. These areas have been demonstrated in task-related activity and connectivity studies to be involved in emotion regulation and cognitive control (Ardila, Bernal, & Rosselli, 2017; Gratton, Sun, & Petersen, 2017; Morawetz, Bode, Derntl, & Heekeren, 2017). We further observed that self-control-induced activation in the DLPFC and IFG inversely correlated with BMI. The contributions of this study include not only identification of the brain regions involved in dietary self-control regardless of the task type, elucidating its possible underlying processes, but also providing insight into the potential key regions such as the DLPFC that may link self-control and eating.

3.2 Abstract

Self-control is known to influence food intake and body weight. Neuroimaging studies have used tasks that tap into different aspects of self-control. Here we conducted a coordinate-based meta-analysis on functional magnetic resonance imaging studies to identify brain regions associated with dietary self-control. Additionally, we tested the effect of task by comparing two widely used paradigms that require either (1) voluntary suppression of an appetitive response to cues, predominantly assessing inhibitory control or (2) food decision-making, where cognitive value modulation is targeted. Core brain regions related to dietary self-control included the anterior insula, inferior and middle frontal gyrus, supplementary motor cortex and parietal cortices. Dorsolateral prefrontal cortex was among regions that showed reduced activation during self-control as a function of body mass index. In addition, the two types of dietary self-control tasks recruited common brain regions making up the core self-control network as well as distinctive regions belonging predominantly to cingulo-opercular or fronto-parietal network. Taken together, our findings provide evidence for the presence of core brain regions related to dietary self-control as well as the involvement of distinct areas depending on the target process of self-control.

Keywords: meta-analysis, dietary self-control, fMRI, DLPFC, IFG, Insula

3.3 Introduction

Eating behaviors and body weight are influenced by self-control, defined as mental processes that allow an individual to override temptations (e.g., for tasty unhealthy food) to select a goal-consistent action (e.g., healthy eating) (Loewenstein, 1996; Mischel et al., 1989; Myrseth & Fishbach, 2009). For example, studies have found an association between body mass index (BMI) and personality traits related to self-control assessed using questionnaires such as the NEO Personality Inventory (NEO-PI) (Costa & McCrae, 1992), UPPS (Urgency, Perseverance, Premeditation, Sensation-Seeking) scale (Whiteside & Lynam, 2001) and Three-Factor Eating Questionnaire (TFEQ) (Stunkard & Messick, 1985). High BMI was revealed to be related to low conscientiousness (NEO-PI) (Gerlach et al., 2015; Vainik et al., 2013) and perseverance (UPPS) (Mobbs, Crépin, Thiéry, Golay, & Van der Linden, 2010b; Murphy, Stojek, & MacKillop, 2014b), and high disinhibition (TFEQ) (Hays & Roberts, 2008). The link between obesity and self-control gains further support from behavioral studies which report greater food-specific delay discounting, and poorer inhibitory and attentional control and cognitive flexibility in individuals with greater BMI (Amlung et al., 2016; Bartholdy et al., 2016; Fitzpatrick, Gilbert, & Serpell, 2013b; Kulendran et al., 2014; Weygandt et al., 2013b; Wu et al., 2014).

Self-control can be framed in terms of models of emotion-regulation and value-based decision-making. A food (or other emotional) cue could lead to a behavioral response in a stepwise process of perception, valuation and action (Etkin et al., 2015; Giuliani & Berkman, 2015). For a visual cue, relevant computations are performed in visual areas for perception, ventromedial prefrontal cortex (vmPFC) and ventral striatum for valuation, and motor areas and dorsal striatum for action. Self-control, instantiated by prefrontal cortical areas, could act at different points in the chain, interrupting the sequence from valuation to action, and/or modulating valuation itself (Figure 3.1). Here we refer to these two self-control or cognitive reappraisal processes as "Inhibitory Control" and "Value Modulation", recognizing that both processes will often co-occur in typical settings. In the first process, self-control is aimed at overriding the urge to pursue the reward. Value-modulation could be deployed to reappraise or change the value of the reward, indirectly influencing the response that is made.

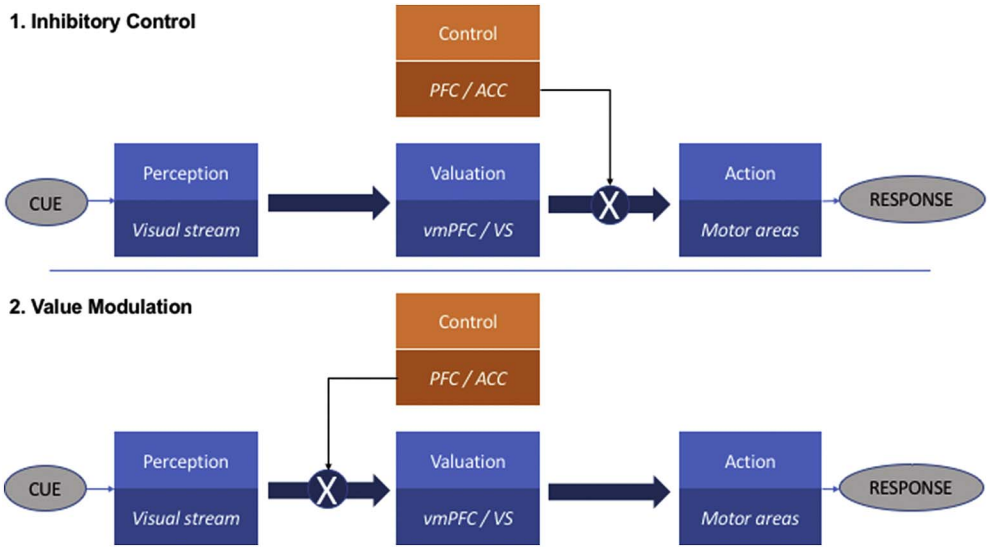

Figure 3.1. Dietary self-control framework. Dietary self-control placed within a three-step perception, valuation, action framework of emotional regulation.

Neural mechanisms underlying dietary self-control have been investigated using functional magnetic resonance imaging (fMRI) and tasks that appear to capture the two above-mentioned processes to varying degrees. For example, the most commonly used dietary self-control task in neuroimaging studies instructs participants to consciously decrease craving for the food items presented in pictures (experimental condition), or to passively view or imagine eating the pictured foods (control condition) (e.g.,(Hollmann et al., 2012)). Here we refer to this type of paradigm as an inhibitory control task; however, it is important to note that depending on the type of strategy participants use to suppress craving, additional processes may be involved, including top-down control of attention (e.g., diverting attention away from tempting food cues) and value-modulation (e.g., imagining the food to be rotten in order to de-value it). A few studies used different types of inhibitory control tasks that are fast-paced, namely the Go/No-go and the Stroop tasks designed with food-related stimuli. The food-specific Go/No-go task instructs participants to press a button for food images associated with "go" cues and to inhibit the response to food images paired with "no-go" cues (He et al., 2014). The No-go trials are therefore assumed to predominantly capture the exertion of inhibitory motor control and food attentional bias. On the food-specific Stroop task designed with food and non-food words, the amount of exerted dietary self-control is reflected in the

degree to which naming the word color is interfered with by processing of food versus non-food words (Janssen et al., 2017). Such tasks primarily assess interference control and food attentional bias. Finally, there are studies that focus mainly on value modulation using food-related decision-making paradigms (Hare, Malmaud, & Rangel, 2011). On these tasks, subjects are observed or instructed to modulate the reward value of food cues in order to select healthier food options or reject unhealthy ones. Similar to the other dietary self-control tasks discussed above, the decision-making tasks involve not only value modulation but additional processes such as attentional control when the task requires participants to focus on health aspects of food items (Hare et al., 2011).

Consistent with findings from studies of self-regulatory processes in other domains, fMRI studies on dietary self-control have frequently observed activation in brain regions such as the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), also sometimes referred to as inferior frontal gyrus (IFG), and supplementary motor area (SMA) (for a review see (Michaud et al., 2017)). Moreover, DLPFC activity in response to food-related cues was observed to be reduced in individuals with high BMI (Brooks, Cedernaes, & Schiöth, 2013), can predict subsequent weight loss success in dieters (Goldman et al., 2013; Jensen & Kirwan, 2015), and is increased when subjects make healthier food choices (Hare et al., 2011). Similarly, IFG response to food cues predicts future food intake (Lopez, Hofmann, Wagner, Kelley, & Heatherton, 2014), consistent with its role in inhibitory control.

The role of the DLPFC in dietary self-control has been further explored using transcranial magnetic stimulation (TMS), which may help to draw causal inferences by monitoring behavior following transient inhibition or stimulation of a small cortical region (Dayan et al., 2013). TMS studies have yielded mixed results, with only some observing significant effects of DLPFC stimulation on food craving or food intake (Hall, Lowe, & Vincent, 2017; Lowe et al., 2017). One potential reason for such inconsistent findings may be differences in the site of stimulation. Many neuromodulation studies target the F3 area of the 10-20 EEG system, which may not correspond precisely to the DLPFC (Hall et al., 2017; Lowe et al., 2017; Rusjan et al., 2010). Moreover, given the large size of the DLPFC and functional heterogeneity of the prefrontal cortex, it is plausible that different parts of the DLPFC are distinctively involved in different forms of self-control (e.g., inhibitory control, delay discounting) or self-control in different domains (e.g., food, drug).

Conducting a meta-analysis specifically on dietary self-control studies would allow us to localize the part of the DLPFC and connected regions more strongly associated with food-related self-control, which may ultimately help enhance consistency and effect sizes of neuromodulation on eating behavior. Another rationale for performing the meta-analysis arises from the fact that some brain regions are inconsistently activated across fMRI studies on dietary self-control. This may be due to the high between-study variability in terms of sample size, study design, the type of task used, and/or data processing. This meta-analysis may help identify core brain regions associated with dietary self-control while minimizing the effects of between-study differences in confounding factors.

The first aim of this meta-analysis was to identify brain regions that are most consistently activated in fMRI studies of dietary self-control. Furthermore, in order to explore the heterogeneous nature of self-control, we compared the two most widely used task types that predominantly recruit inhibitory control or value modulation, allowing us to identify potential neural circuitries subserving the two forms of self-control. The meta-analyses were conducted using Anisotropic Effect-Size Signed Differential Mapping (AES-SDM) software (Radua et al., 2012; Radua et al., 2014). AES-SDM borrows aspects from other coordinate-based meta-analysis tools such as Activation Likelihood Estimation and has novel features such as inclusion of effect sizes in the analysis. Based on previous findings, we hypothesized that the ventral and dorsal lateral prefrontal cortex, dorsal anterior cingulate cortex (ACC), and pre-SMA would be the most consistently observed cortical regions across the studies. In addition, we hypothesized that the two types of tasks that we compare would recruit both common and distinctive brain regions associated with general and task-specific processes.

3.4 Method

3.4.1 Literature search and study selection

The literature search and study selection were completed independently by two authors (J.H. & N.B.). The meta-analysis contained literature published between 1995 and 2017. PubMed, Neurosynth, ScienceDirect and OvidOnline were searched, in addition to examining the reference lists of retrieved review or meta-analytic articles (see Table 3.1). A follow-up search using Google

scholar did not result in any new studies. Searches were performed using combinations of key words related to neuroimaging and eating. Search terms consisted of an imaging word (fMRI), 'eating', 'food,' and a word associated with dietary self-control. The key words associated with dietary self-control used here were 'appetite control', 'cognitive control', 'self-control', 'suppression', and 'regulation'. All of the key words used are listed in Table 3.1. An example of a search term used is: 'fMRI AND eating AND food AND suppression.' The Neurosynth database only contains fMRI results, therefore key word searches only included single words or phrases (e.g., "cognitive control").

Table 3.1. Key word search for each data bases.

Data base	Searched key words	Total results
Neurosynth	1. "Appetite control" N = 1 2. "Cognitive control" N = 106 3. Self-control N = 7 4. Suppression N = 56 5. Regulation N = 107	N = 277
Ovid Online (includes PSYC INFO, Ovid MEDLINE, Global Health and Psychosocial Instruments)	1. fMRI AND eating AND food AND "appetite control" N = 9 2. fMRI AND eating AND food AND "cognitive control" N = 42 3. fMRI AND eating AND food AND self-control N = 24 4. fMRI AND eating AND food AND suppression N = 4 5. fMRI AND eating AND food AND regulation N = 84	N = 163
PubMED	1. fMRI AND eating AND food AND "appetite control" N = 6 2. fMRI AND eating AND food AND "cognitive control" N = 34 3. fMRI AND eating AND food AND self-control N = 14 4. fMRI AND eating AND food AND suppression N = 7 5. fMRI AND eating AND food AND regulation N = 90	N = 151
Science direct	(Original research articles only) 1. fMRI AND eating AND food AND "appetite control" N = 20 2. fMRI AND eating AND food AND "cognitive control" N = 138 3. fMRI AND eating AND food AND "self-control" N = 104 4. fMRI AND eating AND food AND suppression N = 124 5. fMRI AND eating AND food AND regulation N = 359	N = 745

Total papers searched = 1336.
After duplicates removed = 937.

We selected studies that met the following criteria: 1) were published in a peer-reviewed journal, 2) included healthy adults or adolescents, free of neurological or psychiatric illness, 3) used a task with food stimuli (e.g., food images, food words) 4) used fMRI, 5) examined the contrasts to identify brain activity related to the implementation of food-related self-control, 6) reported the results from whole brain analysis in Montreal Neurological Institute (MNI) space, and 7) used the same statistical thresholds across the contrasts of our interest (if there were more than one).

Figure 3.2 illustrates selection steps. The search identified 937 articles after removal of duplicates. Based on our inclusion and exclusion criteria, we further excluded 918 papers from reading their titles (711), abstracts (180) and full texts (27). A total of 19 studies (24 contrasts) were

included in the meta-analysis. Characteristics of these studies are summarized in Table 3.2a-c.

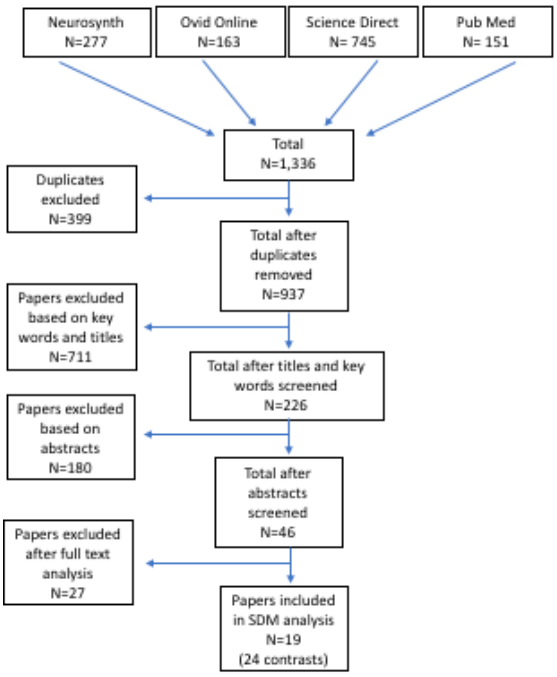

Figure 3.2. *Selection of papers for the meta-analysis*

Table 3.2a. Characteristics of studies using intentional food craving regulation tasks included in the meta-analysis.

Authors	Number of subjects	Sex ratio (f/m)	Mean age (SD)	Mean body mass index (SD)	Stimulus material	Contrasts	Fasting before scan	Included in the BMI analysis	Analysis software
Dietrich et al. [71]	43	43/0	26.7 (3.5)	27.5 (5.3)	Images of high-caloric, unhealthy food items classified as tasty or non-tasty	Regulate vs. Admit tasty food items	> 6 h	N	SPM8
Giuliani et al. [70]	48	33/17 (in all 50 participants)	21.77 (2.36) (in all 50)	21.71 (2.8) (in all 50)	Image of low- and high-energy foods	Regulate vs. Admit craved food items	> 2 h	Y	SPM8
Giuliani et al. [19]	60	60/0	16.66 (3.68)	Not indicated	Image of low- and high-energy foods	Regulate vs. Admit craved food items	Not indicated	N	SPM12
Hollman et al. [20]	17	17/0	25.3 (3.1)	25.1 (3.5)	Images of high-caloric foods	Regulate vs. Admit tasty food items	> 6 h	N	SPM5
Scharmuller et al. [69]	12 (obese)	12/0	26.6 (4.5)	31.5 (5.2)	Images of high-caloric foods and neutral foods	Regulate vs. passive viewing of food items	Overnight fast	N	SPM8
Scharmuller et al. [69]	14 (normal weight)	14/0	25.6 (6.7)	20.6 (1.3)	Images of high-caloric foods and neutral foods	Regulate vs. passive viewing of food items	Overnight fast	N	SPM8
Tuulari et al. [68]	41	41/0	obese:42.1 (9.3); healthy: 44.9 (11.9)	obese: 41.4 (3.9), healthy: 22.6 (2.7)	Images of food	Regulate vs. Passive viewing of food items	> 3 h	Y	SPM8
Yokum et al. [67]	21	13/8	15.2 (1.18)	27.9 (5.16)	Images of most appetizing and least appetizing foods	Costs of eating vs. Imaging eating	> 5 h	N	SPM8
Yokum et al. [67]	21	13/8	15.2 (1.18)	27.9 (5.16)	Images of most appetizing and least appetizing foods	Benefits of not eating vs. Imagine eating	> 5 h	N	SPM8
Yokum et al. [67]	21	13/8	15.2 (1.18)	27.9 (5.16)	Images of most appetizing and least appetizing foods	Suppress craving vs. Imagine eating	> 5 h	N	SPM8

Table 3.2b. Characteristics of studies using food decision-making tasks **included in the meta-analysis**

Authors	Number of subjects	Sex ratio (f/m)	Mean age (SD)	Mean body mass index (SD)	Stimulus material	Contrasts	Fasting before scan	Included in the BMI analysis	Analysis software
Harding et al. [66]	30	14/16	24.17 (5.98)	Range = 18–37.8	Images of healthy and unhealthy beverages	Healthy vs. Unhealthy food choice when fasted compared to sated	10 h	Y	SPM12
Hare et al. [65]	37	20/17	25 (range: 19–35)	successful self-controllers: 24.8 (5.2), non self-controllers: 23.2 (5.1)	Images of junk food and healthy snack items	Response in successful self-control trials in the SC group vs. NSC group	> 3 h	N	SPM5
Hare et al. [23]	33	23/10′	24.8 (5.1)	Not indicated	Images of junk food and healthy snack items	Response greater when paying attention to health vs. natural condition	> 3 h	N	SPM8
Hutcherson et al. [64]	26	9/17′	22 (range: 19–28)	Not indicated	Images of appetizing snacks	Response greater during the craving suppression condition vs. natural condition	> 4 h	N	SPM5
Petit et al. [63]	22	10/13 (in the total sample)	25.91 (3.85) in the total sample	23.47 (2.8) in the total sample	Images of tasty food, healthy or Unhealthy	Healthy food choice vs. healthy food reject in the control condition	> 4 h	Y	SPM8
Petit et al. [63]	22	10/13 (in the total sample)	25.91 (3.85) in the total sample	23.47 (2.8) in the total sample	Images of tasty food, healthy or unhealthy	Healthy food choices in the healthy diet condition vs. control condition	> 4 h	Y	SPM8
Petit et al. [63]	22	10/13 (in the total sample)	25.91 (3.85) in the total sample	23.47 (2.8) in the total sample	Images of tasty food, healthy or unhealthy	Healthy food choices in the tasty diet condition vs. control condition	> 4 h	Y	SPM8
Smith et al. [62]	20	10/10′	30.85 (6.3)	25.64 (3.46)	Images of healthy and unhealthy foods and activities	Food vs. activities	1 h	N	SPM8
van der Laan et al. [61]	20	20/0	21.2 (2.8)	21.3 (1.7)	Images of high and low energy snack foods	Activity related to the proportion of rejected high energy snacks	> 2 h	N	SPM8

Table 3.2c. Characteristics of studies using other dietary self-control tasks **included in the meta-analysis**

Authors	Number of subjects	Sex ratio (f/m)	Mean age (SD)	Mean body mass index (SD)	Stimulus material	Task	Contrasts	Fasting before scan	Included in the BMI analysis	Analysis software
Batterink et al. [60]	29	29/0	15.7 (0.93) (in all 39 participants)	Range = 17.3–38.9	Images of vegetables and high-calorie desserts	Food-specific go/no-go	No go vs. Go	> 4 h	Y	SPM5
He et al. [21]	30	17/13	19.7 (1.7)	23.1 (3)	Image of low- and high-energy foods	Food-specific go/no-go	High calorie food no-go vs. Go	Not indicated	N	FSL
Skunde et al. [59]	29	29/0	27.25 (6.68)	21.83 (1.82)	Images of high caloric foods	Food-specific go/no-go	No-go food vs. go nonfood	3 h	N	SPM8
Janssen et al. [22]	76	65/11′	31.5 (10.7)	26.4 (3.8)	Food, emotional and neutral words	Food-specific Stroop	Food vs. neutral words	> 4 h	Y	SPM8
Dong et al. [58]	27	27/0	21.56 (1.37)	20.35 (1.89)	Images of preferred chocolate	Chocolate delayed discounting	Difficult vs. Easy	> 3 h	N	SPM8

3.4.2 Meta-analytic methods

FMRI activation associated with implementation of dietary self-control was first explored. We extracted data from relevant contrasts in all identified studies (Table 3.2a, 3.2b & 3.2c) to conduct a meta-analysis using AES-SDM software, version 5.14 (https://www.sdmproject.com; (Radua et al., 2012; Radua et al., 2014)). The method uses peak coordinate statistics and effect sizes (i.e., t values) to recreate a map that reflects the difference between the conditions of interest (i.e., regulate vs. control and control vs. regulate) for each study. AES-SDM creates a map of effect sizes by converting the t values from the studies to Hedges effect size and modeling an anisotropic kernel in such a way that voxels that are close to the reported peak have an effect size that is similar but slightly smaller than that of the peak. All individual effect size maps are then combined in a voxel-wise random-effects meta-analysis that favors studies with larger samples and lower effect size variability (Radua et al., 2012; Radua et al., 2014). The meta-analysis included individual studies with considerable methodological heterogeneity. Thus, we examined the robustness of our results using jackknife sensitivity analysis (Radua & Mataix-Cols, 2009) to discard the possibility that some of the results are driven by a single study.

In addition, exploratory analyses were performed to test the potential effect of task paradigm. To do so, we conducted a multimodal meta-analysis and linear models in AES-SDM to detect common and distinctive brain activation between studies that used tasks that predominantly assess inhibitory control (Table 3.2a; 10 contrasts) and those that primarily target value modulation (Table 3.2b; 9 contrasts). To reduce variability, we did not include studies that chose infrequently used tasks, namely the Stroop, Go/No-go and delay discounting tasks (Table 3.2c). However, for completeness, we ran another contrast analysis after adding the studies using the Go/No-go task (3 contrasts) to the "inhibitory control" group. As the food-specific Stroop and food delay discounting tasks were each used in only one fMRI study, we did not include these studies in these contrast analyses.

A subset of the studies (n=12) additionally assessed the effect of obesity-related measures such as BMI on regulation-related brain activity. Of the nine studies that reported significant effects, we were able to conduct an exploratory meta-analysis on 6 studies (8 contrasts) that took a whole-

brain approach and reported the MNI coordinates. All included studies for this analysis used a simple BMI measure with the exception of one that calculated "obesity score" based on BMI, waist-to-hip ratio and waist circumference.

To test statistical significance, AES-SDM recommends using voxel-level $p<0.005$ uncorrected, peak SDM-Z>1, minimum 10 continuous voxels, which have been reported to provide an optimal balance between sensitivity and false-positive rate (Radua et al., 2012). We used a more stringent threshold, $p<0.001$, for the main analysis and the default thresholds for the exploratory analyses.

3.5 Results and discussion

We used a coordinate-based meta-analysis of fMRI studies to identify brain regions most consistently activated across all dietary self-control tasks, and to compare areas associated with two different types of widely used tasks that primarily tap into inhibitory control or value modulation. We additionally performed an exploratory analysis on the effects of obesity-related measures on self-control related activation.

3.5.1 Characteristics of included studies

The final sample consisted of nineteen studies with 24 contrasts including a total of 762 participants (593 women and 174 men before exclusion). Seven studies (10 contrasts) used an intentional food craving regulation task (Table 3.2a) while seven studies (9 contrasts) administered a food decision-making task (Table 3.2b). Other tasks used to capture dietary self-control were the food-specific go/no-go (n=3), chocolate delay discounting (n=1), and food-specific Stroop (n=1) tasks (Table 3.2c). All studies presented participants with images of food, with the exception of one that used food words. Seventeen out of the 19 studies instructed participants to refrain from eating for at least 1 hour prior to the scan in order to induce hunger. Neuroimaging results were analyzed using SPM (http://www.fil.ion.ucl.ac.uk/spm/) in all the selected studies except one that used FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/).

3.5.2 Core brain regions associated with dietary self-control

Our first aim was to identify brain regions most consistently associated with dietary self-control. We used contrasts that compared "regulate" to baseline conditions. Instructions during baseline conditions were to either allow oneself to crave tasty foods, or to passively view the food cues. In the regulate conditions, subjects were typically instructed to suppress food desires, choose healthy options, or reduce attention to interfering information (see Table 3.2 for details). As illustrated in Figure 3.3 and summarized in Table 3.3, the analysis performed on all of the dietary self-control studies revealed five clusters that largely include the anterior insula, IFG/VLPFC and SMA bilaterally. The clusters also include the left DLPFC and bilateral mid-cingulate cortex, and temporal parietal junction (TPJ). The regions that showed greater activation during the reverse contrast (i.e., Baseline – Regulate) include the left posterior insula extending to the postcentral gyrus and precuneus/cuneus.

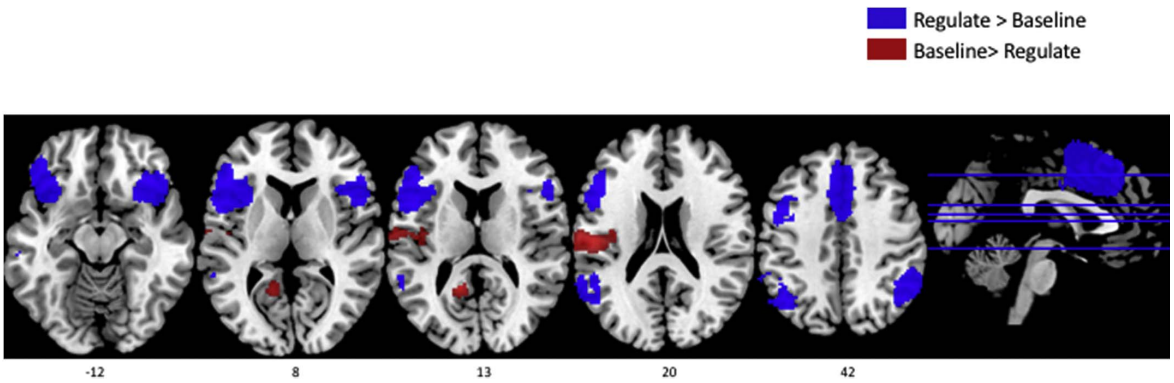

Figure 3.3. Significant brain functional activations during food-craving regulation: Regulate > Baseline (blue) and Baseline > Regulate (red) comparisons determined by meta-analysis. Results are displayed at p<0.001 (cluster size > 10 voxels).

Table 3.3. Results of meta-analysis for Regulate > Baseline and Regulate < Baseline contrasts: regional differences in activation at p<0.001, z>1 and cluster size>10 voxels.

Contrast	Cluster breakdown	R/L	Number of peaks	Number of voxels	MNI coordinates			SDM-Z	Voxel P	JK
					x	y	z			
Regulate > Baseline	IFG	L	16	3941	−44	22	0	4.978	~0	24/24
	Lateral OFG	L								
	MFG	L								
	Insula	L								
	Rolandic operculum	L								
	Precentral gyrus	L								
	SFG	L								
	(Pre-/)SMA	Both	10	3267	−4	22	52	4.581	~0	24/24
	SFG	Both								
	Anterior/Mid cingulate cortex	Both								
	IFG	R	9	2024	52	28	2	4.41	~0	24/24
	Lateral OFG	R								
	Insula	R								
	Rolandic operculum	R								
	Putamen	R								
	Angular gyrus	L	31	1159	−42	−64	42	4.492	~0	24/24
	Temporo-occipital junction	L								
	MTG	L								
	Supramarginal gyrus	L								
	Supramarginal gyrus	R	4	1044	46	−52	44	4.536	~0	24/24
	Angular gyrus	R								
	STG	R								
Baseline > Regulate	Postcentral Gyrus	L	12	884	−56	−16	16	1.373	0.000020623	23/24
	Supramarginal gyrus	L								
	Insula	L								
	Precuneus	L	1	105	−12	−52	10	1.295	0.000025809	22/24
	Occipital gyrus	L								

Cluster peak coordinate = MNI coordinates of the cluster peak in mm.
IFG, inferior frontal gyrus; OFG, orbitofrontal cortex; MFG, middle frontal gyrus; SFG, superior frontal gyrus; SMA, supplementary motor area; MTG, middle temporal gyrus; STG, superior temporal gyrus.

The brain regions revealed in the main analysis resemble those reported in meta-analyses on emotion regulation and cognitive control, reflecting overlapping processes between emotional regulation generally and domain-specific self-control of food craving (Ardila et al., 2017; Giuliani & Berkman, 2015; Morawetz et al., 2017). Cognitive processes, particularly complex ones like self-control, may not engage discrete brain regions independently but rather tend to recruit networks of spatially separate brain regions. Resting-state functional connectivity and lesion studies have revealed distinct networks that may subserve cognitive control, namely the cinguloopercular (CO) and frontoparietal (FP) networks (Gratton et al., 2017). The CO network centers around the anterior insula/frontal-operculum, dorsal ACC/pre-SMA and Inferior parietal lobule (IPL)/TPJ, and exhibits sustained activity related to maintaining cognitively demanding task sets. On the other hand, the FP network, which includes the DLPFC and inferior parietal sulcus, is associated with higher-level moment-to-moment adaptive control and error processing. There is a large overlap between the CO and FP regions and the areas identified in our meta-analysis. We observed activity in the

VLPFC/IFG, which is especially important in the inhibition of unwanted or irrelevant sensations, actions or desires (Aron, Robbins, & Poldrack, 2014; Cohen, Berkman, Lieberman, 2013). Regulation also elicited robust activation in the anterior insula, which subserves various functions including representation and integration of drive states (anterior ventral agranular insula), and working memory and response inhibition (dorsal anterior dysgranular insula and its adjacent frontal operculum) to facilitate physiological awareness of salient events (Cai, Ryali, Chen, Li, & Menon, 2014; Menon & Uddin, 2010; Wager & Barrett, 2017). Being positioned between the lateral PFC and the agranular insula, the dysgranular insula and frontal operculum may serve to translate drive states into action plans, which is necessary during tasks that require overriding temptations and food craving. Other regions we observed include the pre-SMA, which is involved in response inhibition (Limongi & Pérez, 2017; Nachev, Kennard, & Husain, 2008) and task initiation and maintenance (Dosenbach et al., 2007; Dosenbach et al., 2006). Regulation also elicited activity in the TPJ, associated with reorienting attention, strengthening the focus on one's future goals and reducing sensitivity to immediate rewards (Igelström & Graziano, 2017; Soutschek, Ruff, Strombach, Kalenscher, & Tobler, 2016). Taken together, these brain networks sustain diverse neurocomputational processes that enable the implementation of dietary self-control.

3.5.3 Effects of obesity-related measures on brain activity during dietary self-control

Our exploratory analysis revealed that BMI was positively correlated with activity in the mid/anterior insula and pre-cuneus but negatively correlated with response in the right VLPFC/IFG and left DLPFC during dietary self-control (see Figure 3.4, Table 3.4). This supports the extensive personality and behavioral literature linking BMI to impairments in self-control (Michaud et al., 2017). Interestingly, the left DLPFC, rather than the right, has been a frequent target of neuromodulation studies, which often report stimulation-induced changes in food craving and intake (Hall et al., 2017; Lowe et al., 2017). Our findings provide further support for the important role of the left DLPFC in the link between self-control and real-world eating-related behaviors.

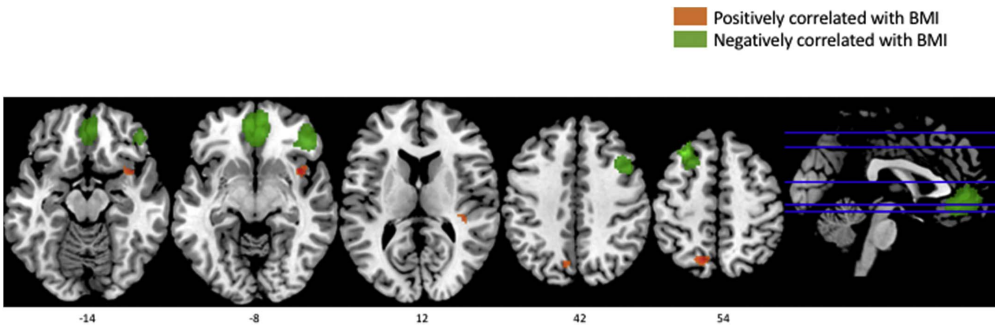

Figure 3.4. Significant brain functional activations for Regulate > Baseline modulated by body mass index. Results are displayed at p<0.005 (cluster size > 10 voxels).

Table 3.4. Results of meta-analysis for the Regulate > Baseline significantly modulated by body mass index **(p<0.005, z>1 and cluster size > 10 voxels).**

Contrast	Cluster breakdown	R/L	Number of peaks	Number of voxels	MNI coordinates			SDM-Z	Voxel P	JK
					x	y	z			
Positively correlated with BMI	Precuneus	L	1	128	−12	−64	56	1.123	0.002100468	6/8
	Superior parietal gyrus	L								
	Insula	R	2	116	38	12	−8	1.153	0.001795948	5/8
	Precuneus	L	1	21	−8	−70	40	1.012	0.003917038	6/8
Negatively correlated with BMI	Ventromedial PFC	R	3	1307	6	50	−4	1.467	0.000459313	6/8
	Ventromedial PFC	L								
	ACC	R								
	ACC	L								
	IFG	R	1	683	46	34	−4	1.433	0.000547051	7/8
	MFG	L	5	433	−28	24	50	1.889	0.000005186	7/8
	SFG	L								
	MFG	R	4	270	44	14	38	1.346	0.000830889	7/8

Cluster peak coordinate = MNI coordinates of the cluster peak in mm.
PFC, prefrontal cortex; ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; MFG, middle frontal gyrus.

In addition, our main analysis revealed greater activation in the posterior insula and cuneus when self-control was not instructed. These regions are thought to process interoceptive and visual signals, and include the gustatory cortex in humans (de Araujo, Geha, & Small, 2012). Their activation may reflect cue-induced appetitive responses. We may speculate that diminished lateral PFC activity and stronger activity in gustatory areas during performance of dietary self-control tasks in people with higher BMI could reflect or explain their lack of success in self-control implementation.

Given the nature of studies explored in the current work, our interpretation is focused on the involvement of the DLPFC in modulating food cue-elicited responses, and potentially BMI. However, a multitude of factors can influence body weight, and the DLPFC has been reported to

subserve processes related to executive control in many domains. Therefore, it is important to also consider the possibility that the DLPFC-BMI correlation may be attributed to other factors that affect BMI such as maintenance of physical exercise and quality of sleep habits, which are known to be associated with DLPFC function (Li et al., 2014; Martin et al., 2015).

3.5.4 Common and distinct brain regions involved in different forms of self-control

We compared the two most widely used types of task, namely intentional regulation tasks that predominantly assess inhibitory control (10 contrasts) and decision-making tasks that primarily target value-modulation or reappraisal (9 contrasts). The conjunction analysis revealed many overlapping brain regions engaged by the two types of tasks including the IFG, pre-SMA/SMA, insula and TPJ bilaterally, the left middle frontal gyrus, and the right putamen (see Figure 3.5, Table 3.5).

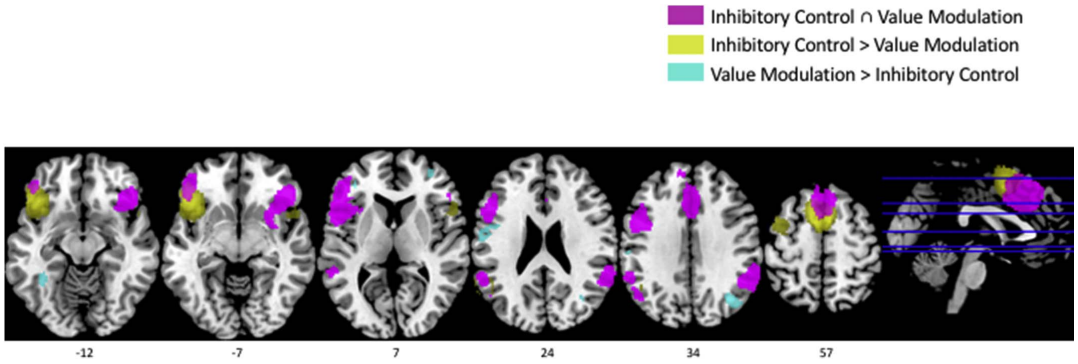

Figure 3.5. Comparison of significant brain functional activations depending on the task paradigm used. Results of overlapping activation are displayed at voxel p<0.0025, peak p<0.00025, and cluster size >10 voxels, and results of regional differences in activation are displayed at p<0.005, z>1, and cluster size >10 voxels.

Table 3.5. Results of meta-analysis for common and distinct brain regions involved in inhibitory control and value modulation: regional differences in activation at p<0.005, z>1 and cluster size >10 voxels.

Contrast	Cluster breakdown	R/L	Number of peaks	Number of voxels	MNI coordinates			SDM-Z	Voxel P
					x	y	z		
Food craving regulation ∧ Food decision making	IFG	L	76	3287	−52	22	18		
	MFG	L							
	Lateral OFG	L							
	Insula	L							
	Precentral gyrus	L							
	Rolandic operculum	L							
	Anterio/Middle cingulate cortex	Both	9	2246	0	28	34		
	SFG	Both							
	(Pre-/)SMA	Both							
	IFG	R	5	1143	50	30	−2		
	Lateral OFG	R							
	Insula	R							
	Rolandic operculum	R							
	Putamen	R							
	Angular gyrus	R	5	1254	46	−52	42		
	Supramarginal gyrus	R							
	STG	R							
	Angular gyrus	L	7	914	−44	−66	42		
	MTG	L							
	STG	L							
Food craving regulation > Food decision making	SMA	R	6	1777	6	8	54	3.499	~0
	SMA	L							
	SFG	Both							
	Lateral orbital gyrus	L	2	1588	−46	24	−8	3.065	~0
	IFG	L							
	Insula	L							
	Temporal pole	L							
	Precentral gyrus	L	4	608	−46	10	50	2.657	0.00003612
	MFG	L							
	IFG	R	5	323	56	22	0	2.134	0.000593483
	Insula	R							
	Rolandic operculum	R							
	STG	L	5	56	−48	−54	22	1.854	0.002188206
	Angular gyrus	L							
	Temporo-occipital junction	L	4	29	−58	−62	22	1.834	0.002399802
	MTG	L							
	Supramarginal gyrus	L							
	Angular gyrus	L							
Food decision making > Food craving regulation	Angular gyrus	R	1	220	36	−66	32	2.049	0.000603795
	Fusiform gyrus	L	1	129	−38	−50	−12	1.754	0.002260447
	Precentral gyrus	L	5	120	−48	0	22	1.914	0.001099229
	Postcentral gyrus	L							
	MFG	L	1	41	−36	40	8	2.07	0.000557363
	MFG	R	1	43	34	52	6	1.793	0.00187856
	MFG	L	1	47	−36	40	8	2.07	0.000505745
	Supramarginal gyrus	L	4	31	−58	−22	34	1.688	0.003153265

Cluster peak coordinate = MNI coordinates of the cluster peak in mm.
IFG, inferior frontal gyrus; MFG, middle frontal gyrus; OFG, orbitofrontal gyrus; SFG, superior frontal gyrus; SMA, supplementary motor area; STG, superior temporal gyrus; MTG, middle temporal gyrus.

The results reflect the presence of shared processes between the two types of tasks such as response inhibition, cognitive reappraisal, and attentional control that are largely discussed above. Nevertheless, we also observed that there appeared to be brain areas specific to each task paradigm. More specifically, the tasks that seem to predominantly assess inhibitory control induced greater activation bilaterally in the posterior parts of the SMA and VLPFC as well as the left lateral orbitofrontal cortex, anterior insula, and precentral gyrus. Activity in parts of the DLPFC were more strongly associated to the "value modulation" tasks. The analysis performed after including studies

that used the Go/No-go task revealed very similar results, with the exception of activity in the left precentral gyrus that seemed stronger in the analysis that does not include the Go/No-go studies.

The brain regions identified in the inhibitory control minus value modulation contrast generally make up the CO network, and could subserve functions such as inhibition of unwanted or irrelevant desires and task maintenance. A distinct feature of intentional inhibitory control tasks is that participants are asked to down-regulate food craving continuously for extended periods on each trial. Therefore, the greater engagement of these CO regions during intentional control compared to value modulation tasks may reflect a greater need for more prolonged and conscious inhibition of craving and hunger. The opposite contrast revealed the right DLPFC to be distinctively responsive to making healthy food decisions. Being part of the FP network, the right DLPFC is postulated to be recruited to maintain and manipulate information in working memory, control immediate impulses and reduce attentional conflicts (Knoch, Brugger, & Regard, 2005; Petrides, 2000; Vanderhasselt, De Raedt, & Baeken, 2009). There is also evidence that this area is important for computation of goal values during decision making. For example, when a part of the right DLPFC very close to where we observed activation in "value modulation" tasks was disrupted using TMS, previously determined liking ratings no longer predicted the amount of money that participants were willing to pay for food items (Camus et al., 2009), indicating disruption of online value computations. Taken together, the results may indicate that the tasks that primarily target value modulation more strongly involve brain areas associated with integration and computation of reward value, context, and error and conflict processing pre- and post-decision.

3.5.5 Limitations

A major limitation of the current work is the small number of studies included in the meta-analysis. It is therefore important to interpret with caution the findings from the two exploratory analyses performed on only a subset of studies. Given the insufficient number of studies using the food specific- delay discounting and Stroop tasks, we could not compare all of the dietary self-control tasks. As discussed above, the two types of tasks we compared should not be thought to capture mutually exclusive processes. Indeed, it is likely that all types of dietary self-control tasks tap into both common and distinct processes, which should be more precisely tested in future studies.

Moreover, we were not able to test the potential effects of sex, age and some personality traits, known to influence food cue processing in the brain and BMI. These variables need to be explored in future meta-analyses.

For our analysis exploring the effect of obesity-related measures on brain activity during dietary self-control, all but one study we included used BMI as a sole variable. Indeed, BMI has been widely used in epidemiological studies to conveniently estimate the prevalence of obesity in general populations. However, BMI is calculated using only height and weight and does not account for factors like muscle mass or insulin resistance, which further complicates the relationship between BMI and self-control ability (Tchernof & Després, 2013). For example, individuals who have high BMI due to their muscle mass may not exhibit difficulty controlling their food intake. Therefore, our results on the effect of BMI should be interpreted and applied with caution, and future studies exploring dietary self-control in the brain need to consider other physiological or personality factors in addition to BMI that correlate more strongly with self-control capacity.

Another limitation of the present study is the susceptibility of our coordinate-based meta-analytic approach to threshold bias. The studies included in our analyses reported only the coordinates that reached statistical significance, leaving other potentially relevant brain regions to appear uninvolved. This issue is further complicated by their reliance on different software, preprocessing routines and statistical criteria. Our study, like all meta-analyses, is also prone to publication bias, including the non-publication of negative results and experimenter degrees of freedom. Future studies may use image-based meta-analysis, less prone to the threshold bias, to help validate our results.

3.5.6 Conclusions and future directions

In summary, we identified core brain regions associated with dietary self-control. Our results overlap largely with findings from neuroimaging meta-analyses on cognitive control and emotion regulation. We also observed that two different task paradigms engage common brain regions that may make up the core dietary self-control network as well as distinct brain regions largely centred around the CO and FP networks, reflecting some differential processes involved.

Future meta-analytic studies on dietary self-control should test the potential effects of

variables such as sex, age and related personality traits that are known to modulate neural responses to food-related stimuli. Moreover, it would be important to identify neural networks involved in different forms of self-control in food and non-food domains.

3.6 Data availability

All the meta-analytic maps are publicly available at https://neurovault.org/collections/3401/.

3.7 Conflict of interest

All authors declare that there is no conflict of interest.

3.8 Funding sources

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Chapter 4 - The role of the dorsolateral prefrontal cortex in dietary self-control in relation to Uncontrolled Eating: an fMRI-TMS study

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4.1 Preface

The third study aimed to further investigate the causal role of the DLPFC, which was revealed in the second study to be a self control-processing region associated with obesity measures. By modulating activity in this region, we tested the influence of the self-control system on food decisions, partly subserved by the appetitive brain regions (Hare, Camerer, & Rangel, 2009). In addition, we recruited only individuals classified to be high or low in a personality trait, Uncontrolled Eating, documented to strongly predict BMI (Vainik, Neseliler, Konstabel, Fellows, & Dagher, 2015). We observed that the high Uncontrolled-Eating group, compared to the other group, had higher BMI, ate more snacks in the laboratory, and exhibited stronger activity in the DLPFC during food craving regulation. Furthermore, TMS of the DLPFC affected dietary decisions only in individuals high in Uncontrolled Eating, who may be more susceptible to obesity. The third study therefore suggests that individuals at risk for obesity may be characterized by a personality trait, Uncontrolled Eating, associated with responsivity of the DLPFC in response to food cues. High Uncontrolled Eating appears to be associated with enhanced food reward drive, requiring greater recruitment of DLPFC during self-control.

4.2 Abstract

Personality, behavioural and neuroimaging studies indicate that self-control is an important factor contributing to food intake and body mass index. Recent investigations have identified a personality trait that seems to more strongly predict eating-related measures, termed Uncontrolled Eating, that taps into dietary self-control and food reward sensitivity. Dietary self-control tasks have been observed to consistently activate the dorsolateral prefrontal cortex, and manipulating activity in this region was shown to modulate food craving. The current study aimed to explore the influence of Uncontrolled Eating on the response of the dietary self-control circuit and eating behaviours. We recruited individuals who scored high or low on the Reward-based Eating Drive Scale, a measure of Uncontrolled Eating. They underwent functional magnetic resonance imaging while performing a food craving regulation task. In a separate session, transcranial magnetic stimulation was administered to the dorsolateral prefrontal cortex, after which participants performed a food decision making task. We observed that individuals who scored high in Uncontrolled Eating compared to those with low scores had higher body mass index and exhibited greater food intake. The former group also showed stronger activity in the self-control circuit during food craving regulation. Furthermore, the two groups exhibited differential susceptibility to stimulation effects on dietary decisions. The present work provides potential neural mechanisms underlying the link between Uncontrolled Eating and eating-related behaviours and outcomes.

4.3 Introduction

Humans have innate preference for high caloric foods, which are easily accessible and abundant in the modern environment (Drewnowski, 1997; Mennella & Bobowski, 2015). Healthy eating in this environment frequently requires exertion of self-control to override dietary temptations. There is converging evidence that self-control is associated with food intake. Personality research has established links between self control-associated traits and body mass index (BMI). More specifically, individual with high BMI tend to score high on the Impulsiveness facet of Neuroticism and low on most facets of Conscientiousness (Vainik, Dagher, et al., 2018). In behavioural studies, high BMI was observed to be linked to greater food-specific delay discounting and poorer inhibitory and attentional control and cognitive flexibility (Amlung, Petker, Jackson, Balodis, & MacKillop, 2016; Bartholdy, Dalton, O'Daly, Campbell, & Schmidt, 2016; Fitzpatrick, Gilbert, & Serpell, 2013; Vainik, Dagher, Dubé, & Fellows, 2013).

Functional magnetic resonance imaging (fMRI) studies of dietary self-control consistently reveal recruitment of a number of brain regions including the dorsolateral prefrontal cortex (DLPFC), anterior insula/fronto-operculum, and dorsal anterior cingulate cortex (ACC)/pre-supplementary motor area (pre-SMA) (Han, Boachie, Garcia-Garcia, Michaud, & Dagher, 2018). These areas make up the neural networks that have been identified by resting-state fMRI and lesion studies to subserve cognitive control (Gratton, Sun, & Petersen, 2018). Of these brain regions, the DLPFC has particularly received much attention in the field. Intentional reduction of craving for foods presented in images was repeatedly shown to activate the DLPFC, which is thought to modulate food desire processed in dopaminergic brain regions such as the striatum (Ballard et al., 2011; Frankle, Laruelle, & Haber, 2006; Giuliani, Mann, Tomiyama, & Berkman, 2014; Hollmann et al., 2012; Kober et al., 2010). Individuals reporting greater weight loss success or higher weight-related concerns tend to show greater DLPFC activity in response to food pictures (Goldman et al., 2013; Murdaugh, Cox, Cook, & Weller, 2012; Smeets, Kroese, Evers, & de Ridder, 2013).

Food decision making tasks have also been used to capture dietary self-control. In these tasks, selection of untasty healthy food items and/or rejection of tasty unhealthy ones are assumed to reflect implementation of self-control. In several fMRI studies using a decision making paradigm, choosing healthier foods was related to greater activity in the DLPFC (Harding et al., 2017; Hare, Camerer,

& Rangel, 2009; Hare, Malmaud, & Rangel, 2011; Hutcherson, Plassmann, Gross, & Rangel, 2012). Electroencephalography (EEG) and functional connectivity estimated using fMRI were utilized to further observe that the DLPFC may be involved in attentional filtering and modulation of reward value of food encoded in the ventromedial prefrontal cortex (vmPFC) to elicit healthier decisions (Hare et al., 2009, 2011; Harris, Hare, & Rangel, 2013). Interestingly, functional coupling of vmPFC and DLPFC during food decision making is correlated positively with weight loss success and negatively with behavioural impulsivity (Neseliler et al., 2018; Weygandt et al., 2013).

The DLPFC is ideally located to be a target for transcranial magnetic stimulation (TMS). TMS can temporarily, focally, and non-invasively excite or inhibit activity in the target region, eliciting changes in emotional and cognitive processes subserved by this brain region and its networks. Therefore, TMS can be used to infer causal relations between brain and behaviour, and complement correlational findings of fMRI studies. Previous studies reported increased food craving upon inhibition of DLPFC activity and decreased craving following the use of an excitatory protocol (Hall, Lowe, & Vincent, 2017; Lowe, Vincent, & Hall, 2017). In an attempt to elucidate the underlying mechanisms of the link between DLPFC-TMS and eating-related behaviours, Lowe and colleagues (Lowe, Staines, Manocchio, & Hall, 2018) recorded EEG during passive viewing of food images following TMS inhibition of the left DLPFC. The group showed that the DLPFC-TMS induced greater P3a on high caloric food trials, which may reflect increased allocation of attention to energy dense foods upon down-regulation of DLPFC activity. While their results are consistent with the known role of the DLPFC in allocation of attentional resources (e.g., Harris, Hare, & Rangel, 2013), their use of the passive viewing task does not elicit other cognitive processes subserved by this region such as value modulation or inhibition (Han et al., 2018; Harris et al., 2013; Lowe, Manocchio, Safati, & Hall, 2018).

Both brain and personality research point to self-control as an important factor contributing to food intake and weight control. However, these observations are made in parallel, and it remains unclear how the relevant personality traits and brain responses may interact to influence appetitive behaviours. Similarly to the neuroimaging field, there has been much effort put into identifying personality traits that robustly and reliably predict eating and weight gain. Accumulating evidence suggests that eating-impulsivity traits compared to general ones more strongly predict BMI (Emery

& Levine, 2017; Vainik, Neseliler, Konstabel, Fellows, & Dagher, 2015). Moreover, frequently utilized questionnaires for eating-related behaviours appear to commonly capture different degrees of a latent factor referred to as Uncontrolled Eating (UE). UE entails elements contributing to loss of control over eating such as self-control ability, reward sensitivity and negative emotions. This trait is more directly and thoroughly assessed in a recently developed scale, called the Reward-based Eating Drive (RED) scale (Epel et al., 2014; Mason et al., 2017). Using the RED, a few studies were able to show that UE is strongly related to BMI and food intake. However, evidence for neural bases of dietary self-control in relation to UE remains indirect (Vainik, García-García, & Dagher, 2018).

To fill the gaps in the literature, the present study recruited young, healthy participants who scored high or low on the RED. They underwent fMRI while completing a food craving regulation task. Subsequently, the regulation-related part of the DLPFC detected with fMRI was targeted by inhibitory and excitatory TMS, following which participants performed a food decision making task. Based on the literature, we hypothesized that the two groups would show differential fMRI responses in the brain regions involved in dietary self-control. In addition, inhibitory TMS of the DLPFC is hypothesized to increase unhealthier decisions while upregulating DLPFC activity may promote healthier choices. The RED scores may further affect TMS's influence on food decision making. The findings will further specify the role of DLPFC in dietary self-control and offer insight into potential brain mechanisms underlying the link between UE and eating-related behaviours.

4.4 Materials and methods

4.4.1 Participants

Young, healthy men and women were recruited by online advertisements. Fifty-four participants (Age (n=53): 24.11±4.73 years; BMI:23.25±3.12 kg/m^2) completed the fMRI part of the study. Two (one man) were excluded prior to TMS sessions, one due to vegetarianism and one because of several missing responses during the Stroop task administered during fMRI. Forty-four participants completed 3 subsequent TMS sessions as eight individuals did not wish to continue. All participants underwent an initial screening process, which ensured exclusion of individuals presenting with psychiatric or neurological illness, gastrointestinal or eating disorders, current use of medications other than oral contraceptives, tobacco or other drugs, food allergies, vegetarianism and/or contraindications for MRI scanning. Vegetarians were excluded because many of the visual food stimuli used here contain meat. Most individuals who were invited to participate belonged to a high or low UE group, defined based on the 18 item-version of the RED scale (Epel et al., 2014; Mason et al., 2017) (Table S4.1). The RED scale captures different levels of UE by assessing lack of control, lack of satiation and preoccupation with food, and has been shown to be related to BMI and to predict risk of weight gain. Participants whose RED score fell 0.5 SD above and below the mean were referred to as individuals with high and low UE respectively. In order to gather further information about general and eating-related self-control, we additionally administered the Brief Self Control Scale (BSCS: Tangney, Baumeister, & Boone, 2004), the Three-Factor Eating Questionnaire (TFEQ: Stunkard & Messick, 1985) and the International Personality Item Pool – NEO – 120 (IPIP-NEO-120: Johnson, 2014). All participants provided written informed consent as approved by the Montreal Neurological Institute (MNI) Research Ethics Board and were provided monetary compensation for their time and effort.

4.4.2 TMS protocols

We selected theta burst stimulation (TBS), a form of TMS thought to mimic the hippocampal theta rhythm and induce long-term potentiation or long-term depression depending on frequency and duration of stimulation (Suppa et al., 2016). The typical TBS protocol entails a burst of 3-50Hz-stimuli repeated at 5Hz. Studies have shown that the intermittent TBS (iTBS) where a 2s train of

TBS is repeated every 10s for 190s (600 pulses) increases neuronal excitability in the target stimulation area whereas continuous stimulation for 40s (600 pulses), referred to as continuous TBS (cTBS), leads to suppression of neuronal activity lasting more than 30 minutes. TBS was applied at the fixed intensity of 40% of maximum stimulator output with a Magstim Super Rapid stimulator (Magstim Co., Whitland UK) and a 70mm figure-of-eight coil. The chosen protocol respected the safety recommendations proposed by Rossi and colleagues (Rossi, Hallett, Rossini, & Pascual-Leone, 2009).

The individually-targeted stimulation site was determined based on the results of a prior fMRI session involving performance of the food craving regulation task described below. The selected coordinates of TBS target were derived from the part of the DLPFC (and adjacent lateral premotor cortex) responsive to intentional regulation of food craving in each individual. We chose the individual peak coordinates that were closest to the group peak. We used the Brainsight frameless stereotactic system (Rogue Research Inc., Montreal QC) to localize and monitor coil position online.

4.4.3 Experimental procedure

Participants made four separate visits to the laboratory following a 3-hour fast (Figure 4.1). The first session was dedicated to MRI scanning while the subsequent 3 visits, at least one day apart, were TBS sessions.

On day 1, participants were first asked to practice the food craving regulation task and the Stroop task (see below for descriptions) that were to be administered during fMRI scanning. Once sufficiently familiarized with the tasks, participants were placed in the fMRI scanner and asked to indicate hunger levels using a visual analog scale (VAS). The session began with a 5-minute structural scan, followed by eight functional scans lasting about 50 minutes in total during which participants performed the food regulation and Stroop tasks. The order of the tasks was counterbalanced across participants such that half of them started with the food regulation task while the other half began with the Stroop task. Upon completion of the imaging part of the study, participants returned to the laboratory and provided once again their hunger ratings. They then completed a computerized rating task during which they provided VAS ratings of familiarity, liking

and caloric density of food items presented in pictures (that were to be used in the TBS task). Subsequently, they were left alone in a room with water and a bowl of their favourite Lays potato chips, which they were allowed to freely eat while filling out the IPIP-NEO-120 and the TFEQ questionnaires.

The subsequent three sessions were identical with the exception of the type of TBS protocol that was applied. In the active TBS conditions (i.e., iTBS and cTBS), the coil was placed parallel to the scalp while the coil in the sham condition was oriented perpendicular to the scalp. Unbeknownst to participants, the order of the conditions was counterbalanced. On each day, upon their arrival, participants first familiarized themselves with the food decision making task (described below) and re-practiced the Stroop task. TBS was then administered, following which participants rated unpleasantness of the stimulation from 1 (not at all unpleasant) to 10 (extremely unpleasant). Participants then completed the food decision making task followed by the Stroop task. At the end of session 4, subjects were debriefed and compensated for their time.

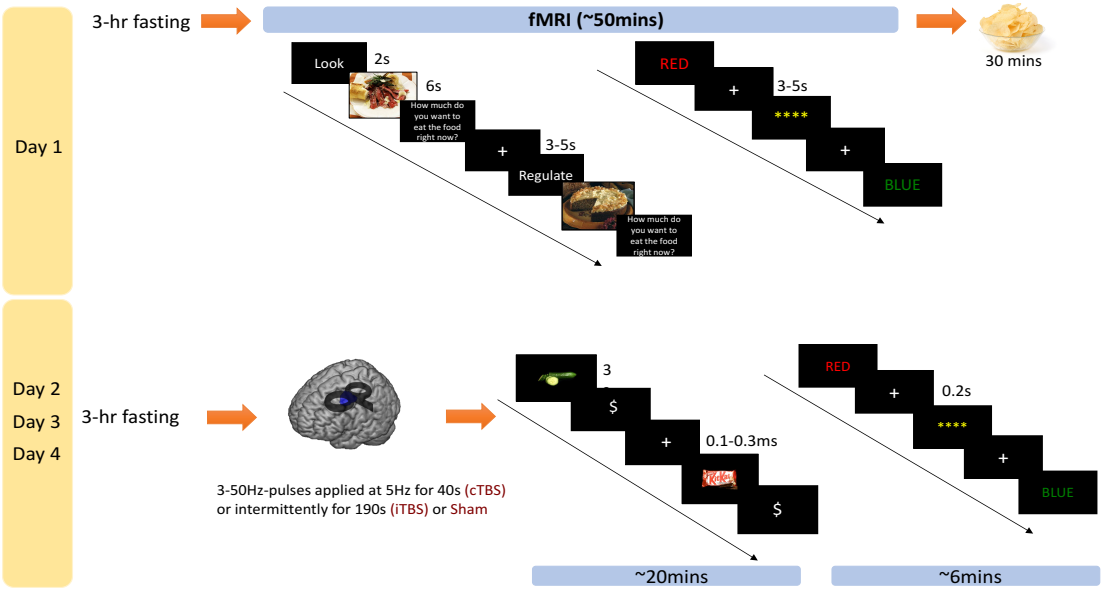

Figure 4.1. Study protocol. On day 1, participants visited our laboratory following a 3-hour fast. They subsequently underwent fMRI during which they performed a food craving regulation task and the Stroop task, counterbalanced in order. After scan, they freely consumed a bowl of their preferred potato chips. On days 2,3, and 4, following a 3-hour fast, iTBS, cTBS, or sham TBS were administered, counterbalanced in order. Participants then performed a food decision making task and the Stroop task.

4.4.4 Tasks

4.4.4.1 Volitional food craving regulation task

This is a commonly used task for fMRI investigation of dietary self-control (Han et al., 2018). In this study, the task presented, one at a time, a total of 48 images of appetitive food items, each of which was paired once or twice with the cue word "look" or "regulate". Stimuli were presented in a pseudo-random order such that no two identical images appeared consecutively and the same cue word did not appear more than twice in a row. As illustrated in Figure 4.1, each trial began with the 2s-presentation of a cue word, followed by presentation of its paired image for 6 s. Each trial ended with a question appeared on the screen, "how much do you want to eat the item you just saw right now" to which participants responded using a MRI-compatible mouse-like device on a Likert scale, ranging from 1 (not at all) to 4 (extremely). Upon each trial, an intertrial fixation cross was displayed on the screen with a jittered interval ranging from 3s to 5s. As trained prior to fMRI scanning,

participants suppressed craving for the food items paired with the cue word "regulate" using a cognitive strategy of their choice, and passively viewed the images associated with the "look" cue word. There were 4 fMRI runs dedicated to the food regulation task, each of which composed of 32 trials (16 "look" and 16 "regulate"). At the end of each functional run, participants indicated how successful they felt at regulating food craving using the button box on a Likert scale, ranging from 1 (not at all) to 4 (extremely).

4.4.4.2 Stroop task

We administered, in the fMRI and TBS, sessions the mostly-congruent version of the Stroop task, widely used to tap into attentional control (Grandjean et al., 2012; Stroop, 1992). In each trial, subjects were shown one of three stimuli: a string of asterisks printed in one of four colours (red, green, yellow or blue), a colour name in the same colour (congruent trial: e.g., "RED" in red colour) or a colour name in a different colour (incongruent trial: e.g., "GREEN" in red colour), and were instructed to indicate the ink colour as fast as possible using a button box (Figure 4.1). The stimulus disappeared from the screen as soon as the response was made and was replaced by an intertrial fixation cross, which stayed on the screen for 3-5s (fMRI) or 0.2s (TBS). Stimuli were presented in a pseudorandomized order such that no more than 3 congruent trials appeared consecutively, and neither the asterisk nor the incongruent trial was presented more than once in a row. There were 4 fMRI runs dedicated to the Stroop task, each of which consisted of 65 trials (11 asterisk, 11 incongruent and 43 congruent). In each TBS session, all 260 trials were presented in one run.

4.4.4.3 Food auction task (food decision making task)

Approximately 2 minutes (mean: 2.3, range 1-8) after TBS administration, participants first performed a food auction task (Figure 4.1). We used a typical food decision making task that uses a Becker-DeGroot-Marschak (BDM) procedure (Becker, DeGroot, & Marschak, 1964). The task has been widely used to probe processes involved in food decision making, including food valuation and self-control (Becker, DeGroot, & Marschak, 1964; e.g., Hare et al., 2009). The stimulus set was composed of the food images previously used by our group, for which participants in this study provided ratings of estimated caloric density, liking and familiarity. In the task, each trial began with

the 3s presentation of a food image, followed by a dollar sign which signaled participants to place a bid between $0 and $5 in $1 increments to indicate how much they were willing to pay to eat the item at the end of the experiment. There were three TBS runs where 61 food items (32 high-calorie and 26 low-calorie) were presented three times. After each run, participants indicated how hungry they were on a VAS scale. At the end of the experiment, the computer selected at random a food item with a price. If the participant's bid was higher than the computer's price, he or she bought the item at the computer's price and received the remainder of the $5 in cash. Otherwise, participants received the $5 in cash without getting an item.

4.4.5 MRI data acquisition

Imaging data were acquired using a 3T Siemens (Erlangen, Germany) Magnetom Trio MRI scanner with a 32-channel head coil. Following a MPRAGE, T1-weighted anatomical scan (voxel size = 1x1x1mm), functional T2* weighted echoplanar images were acquired using blood oxygenation level dependent (BOLD) contrast (8 sessions, 40 axial slices, TR=2110ms, TE=30ms, Flip angle = 90°, voxel size = 3x3x3mm, FoV = 224mm). E-Prime (Psychology Software Tools, Pittsburgh, PA) running on a PC laptop was used to present visual stimuli, projected onto a screen in the fMRI scanner visible to participants through a mirror mounted on the head coil, and to record their button responses.

4.4.6 Analysis

4.4.6.1 Behavioural data analysis

SPSS (version 23.0; SPSS Inc., Chicago, www.spss.com) was used to analyze behavioral data collected throughout the experiment. Independent samples t tests were used to compare the high and low UE groups on BMI, post-scan food intake, and their scores on the BSCS and TFEQ. For the BDM task data collected after TBS, we ran a mixed-design ANOVA to test the effects of stimulation and group on bid amounts placed for all food items, and another ANOVA after splitting the items into high and low-calorie ones. To explore the data further, percentage differences in bid amounts between the two real stimulation conditions and the sham were calculated, each of which was tested for its significance in each UE group using one sample t tests. Finally, correlational analyses were conducted to see if the amount of fMRI response in the TBS target, DLPFC, was related to differences in bid amounts across stimulation conditions.

4.4.6.2 FMR data analysis

SPM 8 software (Wellcome Department of Imaging Neuroscience, London, UK) was used for preprocessing and statistical analysis of the fMRI data. The images were slice-time corrected, realigned to the first volume, and normalized into MNI space (Evans et al., 1994). Spatial smoothing (isotropic Gaussian kernel of 6mm FWHM) was then performed to improve the signal-to-noise ratio of the images. Low frequency temporal drifts were removed using a high pass filter with a cut-off of 1/128s.

The first set of statistical analyses relied on the event-related general linear model implemented by SPM. In order to identify brain regions recruited during intentional regulation of food craving, we defined five event types: (1) “look” cue words, (2) images following the “look” words, (3) “regulate” cue words, (4) images following the “regulate” words, and (5) button response. For each of the analyses, regressors of interest for the BOLD response were generated by convolving the modulated stimulus functions with a standard synthetic hemodynamic response function. The single-subject model also included the six movement parameters obtained from the realignment procedure. For each participant, linear contrasts of parameter estimates for conditions of interest were generated and subsequently submitted to a whole-brain second-level random effects analysis.

We focused on the contrast of the images associated with "regulate" minus "look". We also entered BMI, scores on the BSCS and TFEQ and amount of snack consumption as covariates to test if any of these factors influenced regulation-related brain activity.

In addition to the whole-brain analysis, we conducted region of interest (ROI) analyses to test if the two UE groups differed in the degree to which the selected brain regions were engaged during implementation of food craving regulation. The analyses were performed on the part of the vmPFC, left DLPFC, IFG, and temporal-parietal junction and dorsomedial PFC/pre-SMA whose activity was modulated by the food regulation task in the present study. These regions were chosen as they have been previously implicated in self-control processes. The ROI analyses were performed using the MarsBaR toolbox (http://marsbar.sourceforge.net), which allowed us to extract from each participant effect sizes of activity for the contrasts of our interest for each function ROI. These effect sizes were then analyzed using two-samples t-tests in SPSS to test if brain activity differed between high and low UE groups.

Several past studies have shown that exertion of dietary self-control is reflected in the modulation of reward value encoded in the vmPFC by the DLPFC (Hare et al., 2009; Neseliler et al., 2018). In order to see if the two regions were functionally coupled in our task and if the connectivity strength differed between the two UE groups, we conducted a generalized form of psychological interaction analysis (gPPI). The chosen seeds were the clusters within the left DLPFC and vmPFC that exhibited different degrees of activation between the Look and Regulate conditions. First, the physiological variable was created using de-convolved time series extracted from both seed regions for each subject. The onset times for five event types stated above were then convolved with the canonical hemodynamic response function, which generated the psychological regressors. The interaction terms (PPIs) were then created by multiplying the psychological regress with the physiological regressor. As per our hypothesis, we took a ROI approach where the mean contrast estimates of the PPI regressor were extracted from the target ROI (i.e., DLPFC for the vmPFC seed). Contrast estimates were compared between the two groups.

In addition to the univariate analyses, we also ran an independent component analysis (ICA; McKeown & Sejnowski, 1998), a multivariate approach that allows examination of integrated activity of multiple brain regions associated with cognitive processes or resting state. To do so, we

used the Group ICA of fMRI toolbox (GIFT, icatb.sourceforge.net, version 4.0b) implemented in MATLAB. First, preprocessed data from all subjects were concatenated into a single dataset, which was reduced using principal component analysis and separated into 20 independent components using an infomax algorithm. Time courses and spatial maps for the components were then back-reconstructed for each participant. A linear regression was performed for each component with its time course and the time course of the events (i.e., "look" cue words, images followed by the "look" words, "regulate" cue words, images followed by the "regulate" words, and button response) and generated beta weight that reflects the degree to which a given component (network) was engaged in each event. We ran t tests on the beta weights to identify the components significantly associated with the Regulate versus Look contrast. In addition, we tested if and how activity in the regulation-related networks was influenced by trait UE, BMI, scores on the BSCS and TFEQ and amount of snack consumption.

4.5 Results

FMRI and TBS results of the Stroop task will be reported elsewhere. Only the results of the food tasks are included in this article.

4.5.1 Participants

We were able to use fMRI data of all 52 participants, which included 29 people who scored low in UE and 20 with high UE. Owing to excessive head movements present during TBS administration, 2 participants were excluded from TBS data analysis, and data of the remaining 42 participants (22 low UE and 19 high UE) was deemed valid.

4.5.2 The two groups differ in BMI and eating related – traits and behaviours

The group differences in eating-related measures are displayed in Figure 4.2. Individuals with low scores in UE, compared to those with high UE, were observed to have lower BMI ($t(47)=-2.04$, $p<0.05$) and consumed a smaller amount of potato chips post-scan ($t(46)=-2.04$, $p<0.05$). Moreover, the low UE group scored higher on the BSCS ($U=103.5$, $p<0.001$) and lower on all three aspects of eating behavior assessed in the TFEQ (Cognitive Restraint: $U=194.5$, $p=0.05$; Disinhibition: $U=38$, $p<0.001$; Hunger: $t(47)=-5.34$, $p<0.001$). Finally, participants' willingness to pay for food items, reflected in their bid amounts (following sham TBS) was significantly lower in the low UE group in comparison to the high UE ($t(41)=-4.07$, $p<0.0001$).

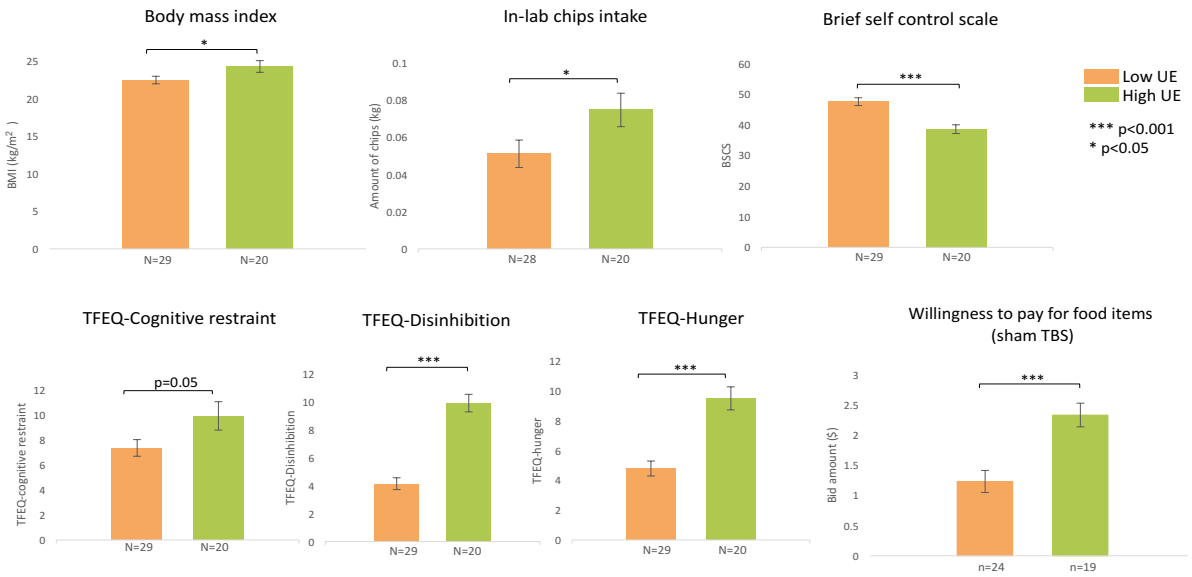

Figure 4.2. Group differences in eating-related measures. Individuals with low UE compared to high UE had lower body mass index, ate less potato chips, and scored higher on the Brief Self Control Scale, and lower on all three aspects assessed in the Three Factor Eating Questionnaire (TFEQ). Moreover, the high UE group, compared to the low UE, was willing to pay more money for food items on the task administered following sham stimulation.

4.5.3 Volitional regulation of food craving recruits a large number of brain regions

As seen in Figure 4.3A, the univariate analysis revealed increased activity in the left DLPFC and bilateral IFG, pre-SMA, and dorsal ACC in the Regulate minus Look contrast (FDR corrected p=0.05) (Table S4.2). It is important to note that the part of the brain region recruited in the Regulate condition, which we refer to as the left DLPFC, was more precisely located in the middle frontal gyrus and premotor cortex. However, we labelled this region as the left DLPFC in order to be consistent with the nomenclature in the dietary self-control literature (e.g., Hollmann et al., 2012). In the Look minus Regulate contrast, we observed activity in the ACC, vmPFC, posterior cingulate cortex, ventral striatum, amygdala, and hippocampus (FDR corrected p=0.05). The PPI analysis revealed functional coupling between the vmPFC (seed) and the left DLPFC and IFG and pre-SMA in the Regulate minus Look contrast (p<0.001, uncorrected) (Figure 4.3B; Table S4.3). The ICA revealed that craving regulation, compared to passive viewing, more strongly activated the salience

($p<0.05$), left fronto-parietal ($p<0.01$) and cognitive control networks ($p<0.01$) (Figure 4.3C). The reverse contrast displayed networks resembling the right fronto-parietal ($p<0.001$), default mode ($p<0.05$) and temporal visual association networks ($p<0.001$).

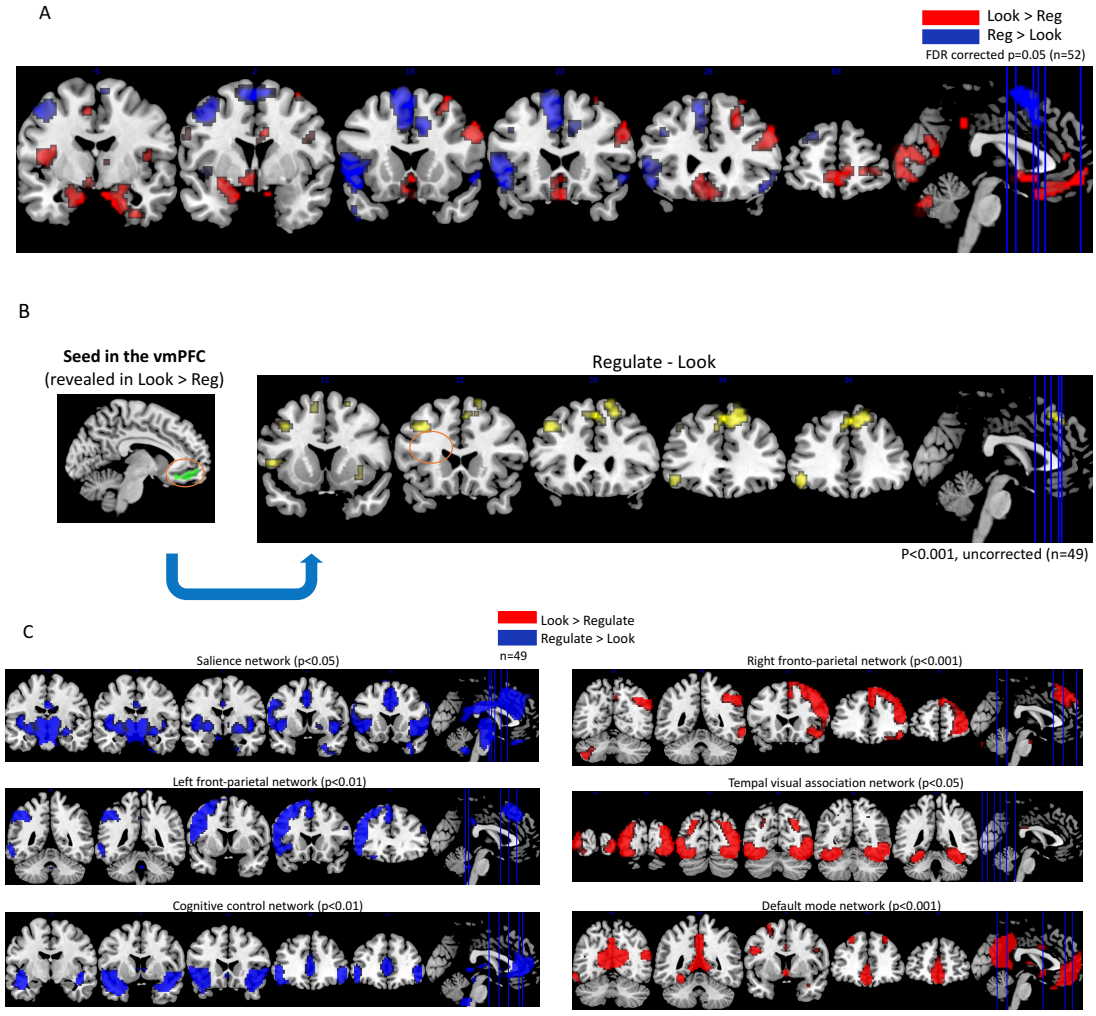

*Figure 4.3. fMRI activity during the food craving regulation task***.** A) The regulation condition compared to the passive viewing condition induced activity in a range of brain regions including the left DLPFC, pre-SMA, and IFG while the reverse contrast revealed activation in the vmPFC, posterior cingulate cortex, and cuneus. B) The gPPI analysis showed that the vmPFC, the seed, was functionally connected to the left DLPFC, pre-SMA and IFG in the regulation versus passive viewing contrast. C) The ICA detected increased activation in the salience, left fronto-parietal and cognitive control networks in the Regulate minus Look contrast, and in the right fronto-parietal, temporal visual association and default mode networks in the reverse contrast.

4.5.4 The two groups differ in regulation-related brain activity and connectivity

The ROI analysis revealed greater Regulate-related activity, in the high UE group compared to the low, in the left DLPFC ($t(47)=2.13$, $p<0.05$) and pre-SMA ($U=182$, $p<0.05$) (Figure 4.4A). In line with this, the DLPFC activity detected in the Regulate minus Look contrast also negatively correlated with participants' scores on the BSCS ($r=-0.32$, $p=0.02$). In the same contrast, we additionally observed diminished vmPFC-DLPFC coupling in the high UE group than the other ($U=196$, $p=0.056$) (Figure 4.4B). Moreover, the connectivity strength was negatively related to the TFEQ hunger ratings ($r=-0.43$, $p=0.002$). Finally, as seen in Figure 4.4C, activation of the salience network in the craving regulation versus passive viewing condition was stronger in individuals with high scores in UE ($t(47)= 2.29$, $p<0.05$) and correlated positively with participants' scores on the TFEQ Cognitive Restraint measure ($r=0.28$, $p=0.04$).

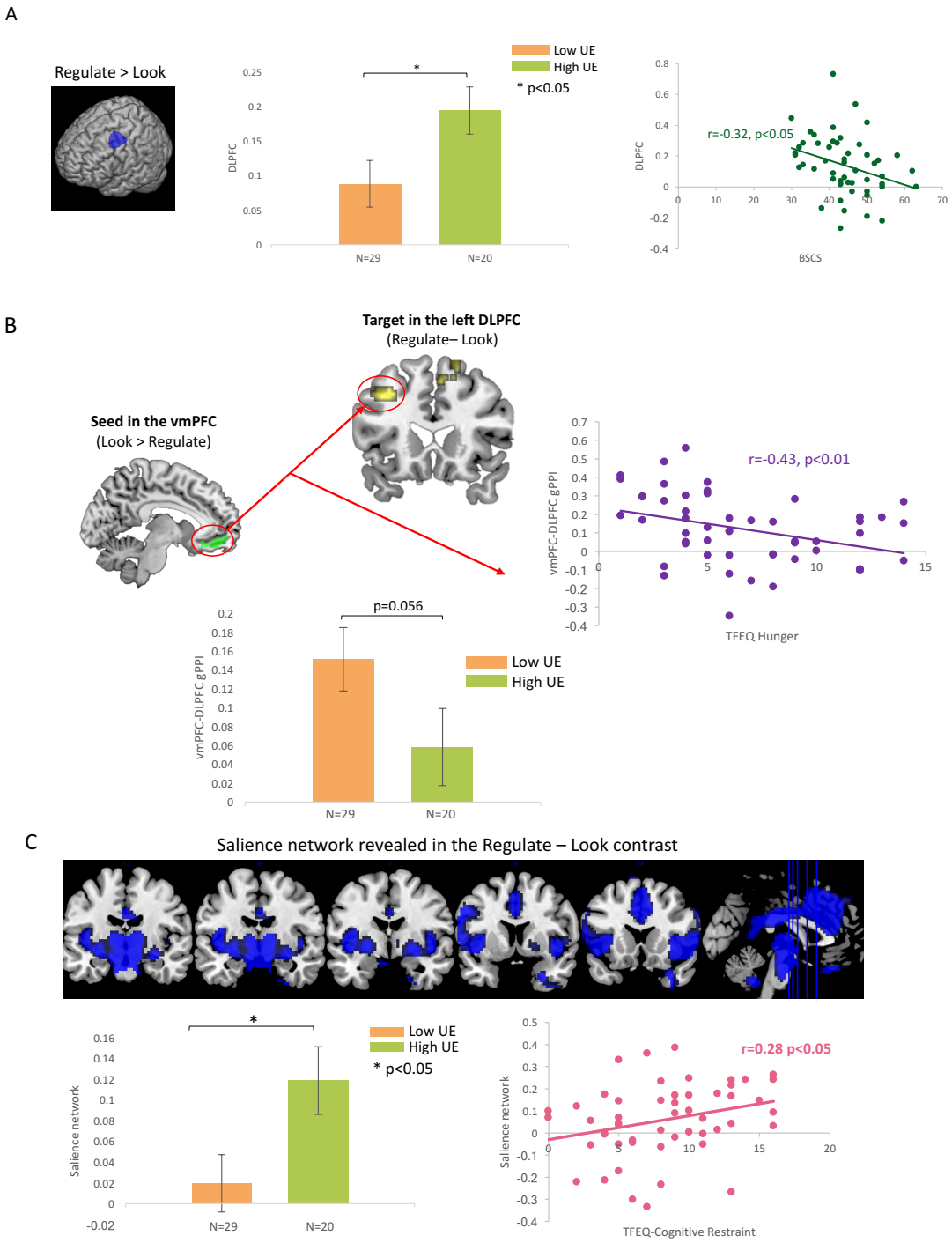

Figure 4.4. Group differences in fMRI activity and connectivity. A) The regulation induced activity in the DLPFC was greater in those with high UE compared to the low UE and was correlated negatively with participants' scores on the Brief Self Control Scale. B) The functional coupling between the vmPFC and DLPFC revealed in the Regulate minus Look contrast was stronger in the low UE group compared to the high UE and correlated inversely with scores on the hunger factor of the Three Factor Eating Questionnaire (TFEQ). C) The regulation-associated activity in the salience network was stronger in those with high UE scores and was related positively with the Cognitive Restraint of the TFEQ.

4.5.5 The two groups differ in the effects of TBS on food decision making

The mixed-design ANOVA revealed no significance in the main effect of stimulation and the interaction between stimulation and group on the total bid amounts. However, we observed that regardless of stimulation condition, the high UE group placed greater overall bids compared to the low UE (p's<0.01; Figure 4.5A). In line with this, our exploratory analyses showed that the degree of fMRI activity in the target DLPFC correlated positively with bid amounts across all conditions (r's>0.30, p's<0.05). However, we observed that individuals who exhibited greater DLPFC activity were more likely to place greater overall bid amounts following iTBS compared to sham (p=0.06, r=0.30; Figure 4.5B). The same ANOVA performed after splitting food images into high- and low-caloric ones, did not yield any significant result. The positive correlation between DLPFC activity and willingness to pay for foods was present for both high and low caloric items, and the greater bid amounts placed by high UE versus low UE individuals did not depend on caloric density of the foods. Finally, our exploratory analysis revealed that the high UE group had greater willingness to pay for low caloric items following inhibition of DLPFC versus sham (t(18)=2.25, p<0.05; Figure 4.5C).

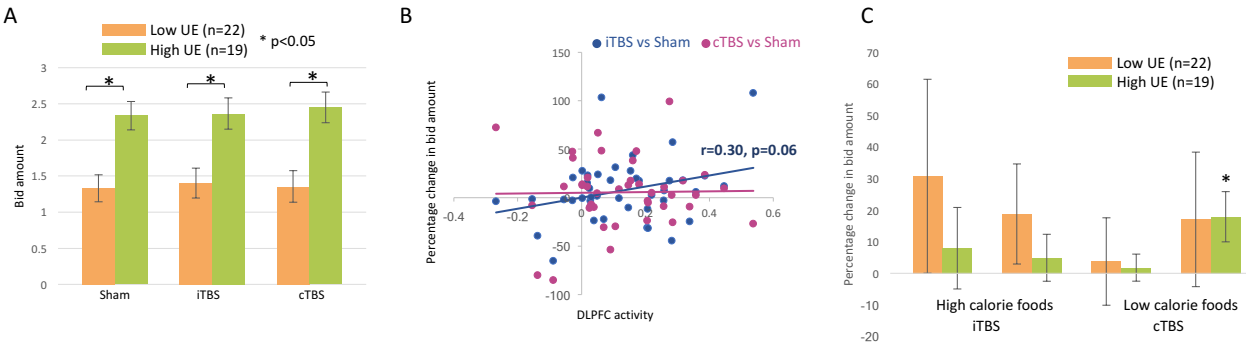

Figure 4.5. Group differences in TBS effects on food decisions. A) Regardless of stimulation condition, individuals with high UE placed greater bid amounts compared to those with low UE. B) The difference in participants' willingness to pay (bid amount) between excitatory and sham stimulations was positively associated with fMRI activity in the TBS target region. C) Only in people with high UE, the bid amount for low calorie foods following inhibitory TBS was significantly greater following sham TBS.

4.6 Discussion

The present study investigated the functional neuroanatomy of dietary self-control. We used fMRI and TMS to compare two groups of individuals who differed on a measure of reward eating drive while they performed a food decision making task. Individuals that scored low in UE compared to those with high UE had lower BMI, consumed less food, and were willing to pay less money for food items. Both groups engaged a range of brain regions during food craving regulation. However, regulation-related brain activity in the DLPFC (TMS target) and pre-SMA was greater in the high UE group compared to the low UE. Moreover, excitatory TMS yielded greater bid amounts in those who showed stronger fMRI activity in the DLPFC. In addition, individuals with high UE scores were willing to pay more for low calorie food items following inhibitory versus sham TMS.

UE is a psychological construct that is commonly assessed by different eating trait questionnaires (to varying degrees), and is associated with obesity (Vainik, García-García, et al., 2018.; Vainik et al., 2015). The RED scale was recently developed to cover a wide range of severity of UE, and taps into lack of control, lack of satiation and preoccupation with food (Epel et al., 2014). Using the RED, we replicated previous findings that people who score high in UE have greater BMI and eat more compared to those with low UE scores. In addition, we were able to expand these findings by further demonstrating that the high UE group, compared to the low UE, was also willing to pay a greater amount of money for food items on the BDM task. Previous studies used similar tasks to show that participants' bid amounts reflected subjective value of food items, and that this appears to be encoded in the vmPFC (Hare et al., 2009; Tang, Fellows, & Dagher, 2014). These studies further revealed that making healthier decisions might be enabled by recruiting the DLPFC to down-regulate the vmPFC value signal (Hare et al., 2009, 2011). The vmPFC-DLPFC coupling was also found to be stronger in individuals demonstrating greater weight loss success and lower behavioural impulsivity (Neseliler et al., 2018). Consistent with these findings, we detected the presence of functional coupling between vmPFC and DLPFC during food craving regulation, and the strength of the connectivity was greater in the low UE group than the high UE. Taken together, we suggest that during dietary decision making, people who are high in UE may be less able to

concurrently engage the DLPFC and vmPFC to reduce reward value of food, which may partly contribute to greater food consumption and weight gain.

While the results of vmPFC-DLPFC coupling were expected, it was somewhat surprising to observe greater activity in the DLPFC and the salience network during craving regulation in the high UE compared to the low UE group. The salience network is implicated in attention allocation toward salient and relevant stimuli and top-down appraisal, and its functioning appears to depend on BMI and individuals' self-control ability (García-García et al., 2013; Han, Boachie, Garcia-Garcia, Michaud, & Dagher, 2018; Kullmann et al., 2013; Steimke et al., 2017; Uddin, 2015). The DLPFC is well-documented to be recruited during emotion regulation and cognitive control in multiple domains including eating. In addition, previous studies reported that DLPFC activity in response to food images was positively associated with selection of healthier foods, weight loss success, and self-reported diet importance (Hare et al., 2009, 2011; Jensen & Kirwan, 2015; Smeets, Kroese, Evers, & de Ridder, 2013; Weygandt et al., 2013). Moreover, inhibiting DLPFC activity using TMS led to greater food craving while upregulation of its activity decreased craving (Hall et al., 2017; Lowe et al., 2017). These studies appear to suggest positive association between the degrees of self-control implementation and engagement of the DLPFC. However, it is important to note that the above-mentioned fMRI studies explored DLPFC activity that was associated with food cue valuation or reactivity, but not modulation of cue response. Therefore, their findings can be interpreted as showing that individuals with greater willingness and ability to practice healthy eating (i.e., successful self-controllers) are likely to spontaneously engage the self-control circuit during mere perception of food cues. This possibility is important to consider when interpreting our results. In the current study, regulation-related fMRI response was derived from contrasting the craving regulation condition against the passive viewing condition. Therefore, the smaller difference detected between the two conditions in people who had low UE scores compared to those with high UE might be attributable to the involvement of the DLPFC even during the passive viewing condition in the low UE group.

Conversely, our fMRI findings are also consistent with the presence of greater reward drive in high UE individuals, demanding greater cognitive resources (and greater DLPFC activation)

during voluntary self-control. In line with this, we also observed that the high UE group, with higher BMI, consumed more snacks and placed greater value on foods in the dietary decision making task. Individuals with higher BMI and at genetic risk for weight gain tend to show greater reward sensitivity to foods in brain imaging studies (Stice & Yokum, 2016). Overweight and obese adults have also been characterized by impaired performance on food and nonfood tasks tapping into executive functions such as inhibition (Dassen, Houben, Allom, & Jansen, 2018; Yang, Shields, Guo, & Liu, 2018). Due to greater salience of food and potentially inefficient executive functioning, it seems plausible that individuals with higher UE and higher BMI need to exert more effort when trying to reduce food craving. Indeed, Scharmuller and colleagues showed that obese individuals compared to the lean showed greater DLPFC activity during intentional attenuation of food craving (Scharmüller, Übel, Ebner, & Schienle, 2012). In another study, participants' scores on the TFEQ sub-scale measuring Cognitive Restraint were observed to correlate positively with DLPFC activity induced by volitional food craving regulation. High Cognitive Restraint was considered by Hollmann's group to indicate successful self-control, subserved via the DLPFC. However, there is accumulating evidence that Cognitive Restraint is positively related to UE and BMI (Banna, Panizza, Boushey, Delp, & Lim, 2018; Karunathilaka, Hewage, Wimalasekera, & Amarasekara, 2018; Kullmann et al., 2013; Megalakaki, Mouveaux, Hubin-Gayte, & Wypych, 2013). We observed that individuals who scored high on Cognitive Restraint belonged to the high UE group with greater BMI and food intake. In addition, Cognitive Restraint scores correlated positively with regulation-induced activity in the salience network. Taken together, another plausible explanation of stronger DLPFC activity in the high UE group might be the greater effort demanded by the food craving regulation task in these individuals who perceive palatable foods as more salient. Moreover, considering the weaker vmPFC-DLPFC coupling in the high UE group, we suggest that the DLPFC in these individuals may be less efficient in modulating food value despite greater efforts made to exert dietary self-control, leading to their heightened motivation to pay for food and greater food intake.

Given that most analysis conducted in our TBS data were exploratory and the significant results had weak effects, these findings need to be interpreted with caution. Previous studies have

shown that stimulating the DLPFC appears to modulate food craving in a similar direction in individuals with normal and high BMI (Lee, Elias, & Lozano, 2018; Lowe et al., 2017). However, the ability of DLPFC-TMS to affect food intake remains inconsistent in the literature (Lowe et al., 2017). In line with the TMS studies with null findings on food consumption, we observed that bid amounts did not differ across the stimulation conditions. Moreover, regardless of stimulation, participants' bid amounts correlated positively with the amount of fMRI activity in the TBS target, which is in line with greater willingness to pay documented in the high UE compared to the low UE group. However, we observed that bid amounts placed in the iTBS compared to the sham condition were higher in individuals with greater DLPFC activity. These individuals were more likely to belong to the high UE group who exhibited stronger activity in the DLPFC and salience network. The possibility that interindividual differences in responsiveness to TMS may be partly attributed to activation state in the TMS target and its related networks is further supported by our inhibitory TBS results. We observed that, only in individuals with high UE scores, the changes in bid amounts for low-caloric foods were significant between the inhibitory and sham conditions. Taken collectively, it appears that the high UE group, characterized by higher BMI and greater regulation-induced activity in the DLPFC and the salience network, may be more susceptible to brain stimulation. This supports the interpretation of higher DLPFC activity in the Regulate > Look contrast as reflecting greater food reward drive requiring more effortful self-regulation. It also suggests that previous inconsistencies in brain stimulation studies targeting the DLPFC and food intake may be partly due to their failure to consider trait self-control and other relevant personality variables.

The direction of TBS effects we observed is more difficult to reconcile with previous findings. In contrast to pre-existing evidence for the effects of TBS on food craving, we observed no TBS-related changes in dietary decisions in the low UE group. It is possible that this group of individuals with potentially more effective and robust DLPFC functioning (as discussed above) may be less susceptible to TBS in the current paradigm. The absence of expected decrease in bid amounts following excitation of DLPFC can also be attributed to a floor effect in which the willingness to pay for foods in those with low UE scores cannot be reduced. This speculation gains support from

previous DLPFC-TMS studies investigating self control-related processes. For instance, a meta-analysis discovered that the ability of DLPFC stimulation to improve performance on a working memory task was at least moderately significant in clinical samples but only borderline to small in healthy volunteers (Brunoni & Vanderhasselt, 2014). Moreover, a recent review focusing on the excitatory TBS protocol showed that its effects on more complex tasks of executive functioning were highly significant in older adults, but null in most studies of young, healthy individuals (Lowe, Manocchio, Safati, & Hall, 2018).

On the other hand, in the high UE group, exhibiting greater fMRI response in the DLPFC, we observed TBS-induced changes in bid amounts. However, in contrast to the pre-existing evidence for the opposite modulatory effects of iTBS and cTBS, the directions of TBS-induced changes were similar for the two real stimulation conditions. It needs to be kept in mind, however, that the majority of previous studies utilized stimulation methods other than TBS and more frequently investigated effects of inhibitory stimulation only, making it challenging to directly compare the outcomes of inhibitory and excitatory stimulations, whose findings remain inconsistent. Furthermore, there is some evidence that the two types of TBS protocols may indeed yield similar neuronal effects. For instance, Ulrich's group recently administered TBS to the part of the ventrolateral prefrontal cortex (VLPFC) functionally connected to the portion of the ventral tegmental area (VTA) more sensitive to high calorie food images, and subsequently measured fMRI activity during a food/non-food discrimination task (Ulrich et al., 2018). They observed that following both cTBS and iTBS compared to baseline, activity in the VLPFC (stimulation target) increased in response to low calorie images while activity in the VTA decreased for high calorie images. Moreover, in another study exploring after-effects of DLPFC-TBS using EEG, both iTBS and cTBS resulted in very similar changes, including decreased delta and theta power in the left DLPFC and no effects in the alpha band (Woźniak-Kwaśniewska, Szekely, Aussedat, Bougerol, & David, 2014). These findings suggest that, in some situations, iTBS and cTBS may modulate brain activity or behaviour in the same direction.

4.6.1 Limitations

Several limitations of the present study are notable. The food craving regulation task that was

administered during fMRI is relatively simple and has been shown to reliably and robustly induce activity in cognitive control-related brain regions. However, in such a task, it is challenging to estimate the degree to which participants actually deploy self-control, since there is no real food choice. This aspect is particularly important in the current study considering that our participants were classified based on their ability to regulate eating. It is possible that the two UE groups differed qualitatively and quantitatively in following the instruction to reduce food craving. In addition, efforts were made in this study to reduce the well-known interindividual variability in responsiveness to TMS, by targeting person-specific and task-relevant coordinates and matching participants for age and biological sex. However, we could not control some other relevant factors such as genetic polymorphisms, cortical excitability, and functional connectivity, which may differ between our two groups. For example, interindividual variability in responsiveness to brain stimulation appears to depend on genetics and responsivity of the intercortical network (Suppa et al., 2016). We cannot rule out the possibility that reactivity by DLPFC-TMS may differ in people with different degrees of risk for weight gain. These possibilities need to be more systematically addressed in future studies with a greater number of participants.

4.6.2 Conclusion

To summarize, the present work characterizes the potential neural underpinning of a trait, UE, that predicts BMI and food intake. We observed that individuals with high UE, compared to those with low UE, engaged neural circuits subserving self-control during food craving regulation to a greater extent. Furthermore, stimulation of the DLPFC modified food decisions only in people with high UE. Taken together, the findings appear to suggest that responsivity of the DLPFC to stimulation and during food value modulation may differ between individuals with high and low UE scores. We suggest that greater DLPFC activation in people with high UE reflects greater food reward drive and greater demands on self-control circuitry. As it provides potential neural underpinning of the link between UE and eating- and weight-related outcomes, the current work signifies the importance of considering this trait in exploration of brain response to foods, and ultimately in designing brain-stimulation-based treatments for obesity.

4.7 Supplementary materials

Table S4.1. *Items in the RED scale*

Item
1. I feel out of control in the presence of delicious food
2. When I start eating, I just can't seem to stop
3. It is difficult for me to leave food on my plate
4. When it comes to foods I love, I have no willpower
5. I get so hungry that my stomach often seems like a bottomless pit
6. I don't get full easily
7. It seems like most of my waking hours are preoccupied by thoughts about eating or not eating
8. I have days when I can't seem to think about anything else but food
9. Food is always on my mind
10. If food tastes good to me, I eat more than usual
11. If I see or smell a food I like, I get a powerful urge to have some
12. When I know a delicious food is available, I can't help myself from thinking about having some
13. I find that when I start eating certain foods, I end up eating much more than planned
14. Sometimes things just taste so good that I keep on eating even when I am no longer hungry
15. I tend to eat too much of my favourite food
16. I find myself continuing to consume certain foods even though I am no longer hungry
17. I feel hungry all the time
18. I can't stop thinking about eating no matter how hard I try

Table S4.2. *FMRI responses to food craving regulation*

	Region	*L/R*	*t stat*	*x*	*y*	*z*
Regulate > Look	Pre-supplementary motor area	L	6.06	-9	11	61
	Anterior mid cingulate cortex	L	5.1	-6	20	40
	Superior frontal gyrus	L	4.56	-6	14	70
	Middle temporal Gyrus	R	5.31	48	-34	-2
	Supermarginal gyrus	L	5.23	-51	-49	31
	Frontal operculum	L	5.22	-51	11	-2
	Inferior frontal gyrus	L	4.91	-48	23	7
	Insula	L	4.61	-42	8	1
	Middle frontal gyrus /precentral gyrus	L	5.17	-45	8	46
			4.61	-39	2	58
	Postcentral gyrus	L	3.99	-48	-7	52
	Middle temporal gyrus	L	4.47	-63	-40	1
	Anterior mid-cingulate cortex	R	4.4	15	14	40
	Middle frontal gyrus	L	4.33	-27	50	25
	Supermarginal gyrus	R	4.11	66	-40	28
	Temporal pole	R	4.03	57	14	-5
	Insula	R	3.78	48	11	-8
	Inferior frontal Gyrus	R	3.57	54	26	-8
	Cerebellum	R	3.71	30	-85	-38
	Temporal pole	L	3.69	-51	11	-29
	Temporal pole	R	3.55	51	14	-23
Look > Regulate	Cerebellum	L	5.82	-6	-73	-29
			3.59	-15	-73	-50
			3.02	-18	-67	-41
	Cerebellum	R	5.63	27	-49	-26
	Amygdala	R	4.4	21	-7	-26
	Hippocampus	R	3.66	30	-16	-23
	Fusiform gyrus	R	5.2	39	-40	-23

Angular gyrus	R	5.13	36	-64	37
Rolandic operculum/Insula	L	4.56	-45	-7	13
Ventromedial prefrontal cortex	L	4.54	-9	50	-11
Ventromedial prefrontal cortex	R	4.31	3	35	-17
Ventromedial prefrontal cortex	L	4.09	-12	32	-14
Inferior frontal gyrus	R	4.52	51	38	16
		3.98	45	11	28
Middle frontal gyrus	R	3.98	48	32	22
Superior frontal gyrus	R	4.48	27	41	49
Superior/Middle frontal gyrus	R	3.76	24	29	40
Superior frontal gyrus	R	2.89	30	26	58
Amygdala	L	4.33	-15	-4	-23
Putamen	L	4	-27	5	-14
Caudate	L	3.46	-6	5	-5
Cerebellum	L	4.32	-36	-70	-50
		3.96	-42	-73	-35
Inferior parietal lobule	L	4.26	-54	-22	37
Postcentral gyrus	L	4.16	-48	-28	55
Superior temporal gyrus	L	3.62	-60	-19	7
Pons	R	4.07	6	-34	-41
Fusiform gyrus	L	4.03	-36	-37	-23
		3.91	-36	-49	-17
Lingual gyrus	L	3.77	-30	-88	-14
Precuneus	R	3.97	3	-43	40
Posterior cingulate gyrus	L	3.76	-9	-37	37
Hippocampus	L	3.7	-21	-34	-5
Parahippocampus	L	3.38	-21	-31	-17
Thalamus	L	3.34	-12	-31	1
Mid-occipital gyrus	L	3.69	-33	-79	28
		3.4	-33	-88	28
Occipital/Lingual gyrus	L	3.57	-15	-52	1
Lingual gyrus	L	3.31	-12	-46	-5

Superior frontal gyrus	R	3.56	30	62	1
Cerebellum	L	3.45	-24	-37	-47
		2.76	-15	-43	-50
Precuneus	L	3.24	-9	-64	22
Postcentral gyrus	R	3.23	63	-16	40
Superior/Middle frontal gyrus	R	3.23	30	17	61
		2.93	27	14	52
Ventromedial prefrontal cortex	R	3.22	3	47	13
		2.78	12	47	16
Cerebellum	R	3.17	9	-76	-41
Precentral gyrus	L	3.15	-57	8	31
Heschl's gyrus	R	3.11	57	-10	7
Supramarginal gyrus	R	3.11	54	-31	46
Supplementary motor area	L	3.05	-6	-7	52
Insula	R	3	42	-1	13
Thalamus	R	2.97	9	-13	7
Cerebellum	L	2.92	-12	-79	10
Middle frontal gyrus	R	2.9	39	8	61

Table S4.3. *Results of the gPPI analysis with the vmPFC seed*

	Region	*L/R*	*t stat*	*x*	*y*	*z*
Regulate > Look	Pre- supplementary motor area	R	5.2	9	35	46
	Superior frontal gyrus	R	4.27	18	32	52
			3.82	15	29	61
	Middle frontal gyrus	L	5.11	-36	17	40
			4.81	-39	26	40
	Orbitofrontal cortex	L	4.91	-45	38	-11
	Angular gyrus	R	4.12	42	-52	37
	Planum temporale	L	4.09	-48	-4	-8
	Frontal operculum	L	4.07	-48	14	4
			3.95	-54	8	7
	Putamen	R	3.88	33	8	-2
	Superior frontal gyrus	L	3.84	-12	11	58
			3.5	-12	5	67
	Heschl's gyrus	L	3.81	-51	-22	1
	Middle frontopolar gyrus	R	3.8	24	56	4
	Superior frontal gyrus	R	3.66	18	5	61
	Precentral gyrus	L	3.6	-48	-13	28
	Precentral gyrus	R	3.58	45	-13	46
			3.52	60	-1	16
	Striate area	L	3.51	-18	-79	1
	Middle frontal gyrus	R	3.49	48	32	40
	Temporal pole	L	3.46	-30	17	-29
	Middle temporal gyrus	L	3.44	-60	-37	-2
	Mid-cingulate gyrus	R	3.32	12	20	34
	Inferior frontal gyrus	L	3.3	-51	29	22
	Subgenual anterior cingulate cortex	R	3.28	6	29	-14
	Insula	R	3.27	36	20	4
	Frontal operculum	L	3.27	-36	29	-2

Look > Regulate	Cerebellum	L	3.96	-15	-31	-17
	Cerebellum	R	3.81	21	-31	-23
	Inferior temporal gyrus	R	3.31	45	-37	-17

Chapter 5 - General Discussion

Obesity is a multifaceted, neurobehavioural disease, which is currently a leading risk factor for mortality worldwide. Considering that overconsumption of food is a major contributor to weight gain, elucidating the complexities of eating is of importance. Appetitive behaviours are thought to be driven not only by energy deficits, governed by the homeostatic system, but also reward response to food and food-related cues that involve the appetitive system, which can be regulated to meet one's health-related goals and other factors through the self-control system (Neseliler, Han, & Dagher, 2017). In humans, the interactions amongst the homeostatic, appetitive and self-control systems, and their alterations in individuals with or at risk for obesity, have been most commonly studied using correlational methods. For instance, functional coupling between regions subserving self-control (e.g., DLPFC) and those involved in food cue valuation (e.g. vmPFC) tends to be related to food decisions and weight loss success (Hare, Camerer, & Rangel, 2009; Hare, Malmaud, & Rangel, 2011; Neseliler et al., 2018; Weygandt et al., 2013). There is a great need for human modulatory studies that can verify and further elucidate correlational findings. In addition to neural measures, other factors such as personality traits have been investigated to explain individual differences in weight gain. UE appears to stand out, as it correlates strongly with BMI and food intake (Vainik, García-García, & Dagher, 2018; Vainik, Neseliler, Konstabel, Fellows, & Dagher, 2015). The trait taps into sensitivity to food reward and dietary self-control ability, and their related neural circuits have been observed to be altered in obesity (Michaud, Vainik, Garcia-Garcia, & Dagher, 2017; Vainik et al., 2018). The central aim of the thesis was to develop and apply modulation approaches to investigate how the homeostatic and self-control systems affect the appetitive system and behaviour. We additionally examined the influence of UE on responsivity of the dietary self-control system and its interaction with the appetitive system.

5.1 Interaction between the homeostatic and appetitive systems

In order to test if modulating the homeostatic system affects the appetitive system (Figure 5.1), a pharmacological dose of an orexigenic homeostatic hormone, ghrelin, was administered to healthy volunteers. To test ghrelin's effects on the appetitive system in behaviour and the brain, participants underwent fMRI during which they performed a conditioning task where they learned to associate abstract images with food and non-food odours.

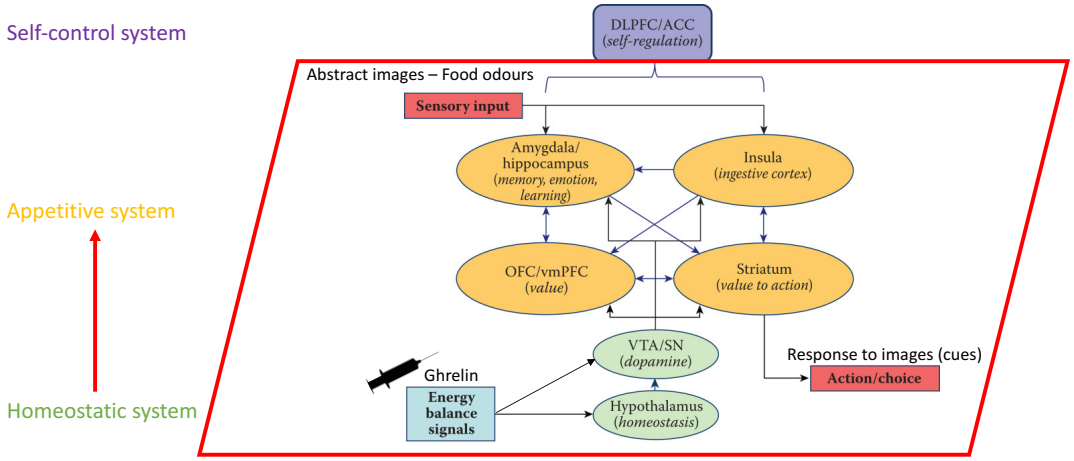

Figure 5.1. Modulation of the homeostatic system to influence the appetitive system. Study I modulated a homeostatic signal, ghrelin, to show its effects on food odour conditioning in behaviour and fMRI response

Ghrelin's effects on the appetitive system were evident in behaviours. More specifically, following ghrelin, but not saline, injection, participants' response time to food-related cues was faster compared to cues paired with non-food odours, and they rated food odour-paired cues as more pleasant in the ghrelin condition following a 24-hour delay. These behavioural findings support a role for ghrelin in enhancing food-cue conditioning. This finding is in agreement with the animal study that showed that acquisition of food-place association required functional ghrelin receptors (Perello et al., 2010). In another study investigating ghrelin's effects on appetitive behaviours, animals' willingness to work for food was increased following ghrelin injection while blockade of the GHSR reduced ghrelin-induced food motivation (Skibicka, Hansson, Alvarez-Crespo, Friberg, & Dickson, 2011). Prior to the study described in this thesis, there existed only one human study that modulated the levels of ghrelin to test its effects on response to food cues (Malik, McGlone, Bedrossian, & Dagher, 2008). In line with their finding that ghrelin did not heighten pleasantness of

the food images, we did not observe differences between the ghrelin and saline conditions in pleasantness ratings of the images paired with odours, provided during fMRI (however, note that on the delayed pleasantness rating task, the images associated with food odours following ghrelin injection were indeed perceived to be more pleasant). Ghrelin's role in rewarding properties of food is suggested to be subserved via the hormone's ability to stimulate DA (Perello & Dickson, 2015). The results that in-scanner pleasantness ratings were not affected by ghrelin appear to be consistent with the role of DA as a signal of "wanting" but not "liking" (Berridge & Robinson, 2016). In addition to being a motivation signal, DA is thought to play a key role in reward-cue learning (Schultz, 2016). By directly testing and confirming ghrelin's promoting influence on food-specific learning, assessed using reaction time to food cues, we were able to extend Malik et al's findings that ghrelin enhanced memory of food images (Malik et al., 2008).

Unlike animal studies that focused on the ghrelin injection site and changes in behaviours, human fMRI investigations allow observations of ghrelin-related changes in activity throughout the whole brain. Malik et al. showed that ghrelin increased activation in the appetitive network including the amygdala, insula, OFC and striatum in response to food images (Malik et al., 2008). We analyzed neuroimaging data using a learning model (Rescorla, & Wagner, 1972), which estimated not only RPE that drives learning, but also incentive value of food cues, allowing us to replicate Malik's results. In other words, we were able to explore neural correlates of both food motivation and learning that involve DA neuronal activity, which is directly increased by ghrelin. In line with animal studies, we observed during food-related learning that ghrelin enhanced RPE-related activity in the striatum and hippocampus, and value-related activity in the vmPFC. Furthermore, ghrelin enhanced functional coupling between the hippocampus and striatum on food trials. Our results are consistent with animal studies reporting that GHSR is expressed on the DA neurons of the VTA as well as in the striatum and hippocampus (Perello & Dickson, 2015), through which ghrelin can influence DA-responsive brain regions and their associated functions. In investigating ghrelin's effects on learning-related brain activity, we focused only on the regions that have been identified by meta-analyses to subserve RPE (Chase, Kumar, Eickhoff, & Dombrovski, 2015) and incentive value (Bartra, McGuire, & Kable, 2013), which did not include the insula, hypothalamus and VTA, that are also part of the appetitive network (Figure 5.1). In addition, owing

to their location and size, the hypothalamus and VTA are hard to capture with fMRI. Taken together, although the use of fMRI, the selected task, and our analysis methods limited the scope of the appetitive system that was investigated, Study I clearly demonstrated, at both the behavioural and neural levels, that a homeostatic signal, ghrelin, can modulate food-specific appetitive learning.

5.2 Interaction between self-control and appetitive systems

In addition to modulating the homeostatic system, currently available tools such as TMS permit non-invasive manipulation of the self-control system. To examine interaction between the self-control and appetitive systems (Figure 5.2), Study III used TBS, a form of rTMS, to up- and down-regulate activity in the DLPFC in healthy, non-obese volunteers. The effects of TBS on the appetitive system were captured using the BDM task where participants were asked to place bid amounts for high and low calorie food items. The BDM provides a measure of "wanting" or current value of an item. In addition to being the first TBS study to examine food valuation, our investigation was unique in the selection of the stimulation target. Unlike previous studies on eating-related responses that chose their target coordinates for the DLPFC based on the past literature or the standard EEG coordinate system, we targeted person-specific sites derived from fMRI data collected while participants performed a food craving regulation task. This approach was considered particularly important given the interindividual differences in neuroanatomy and in responsiveness to TMS (Hinder, Reissig, & Fujiyama, 2014; López-Alonso, Cheeran, Río-Rodríguez, & Fernández-del-Olmo, 2014; Suppa et al., 2016).

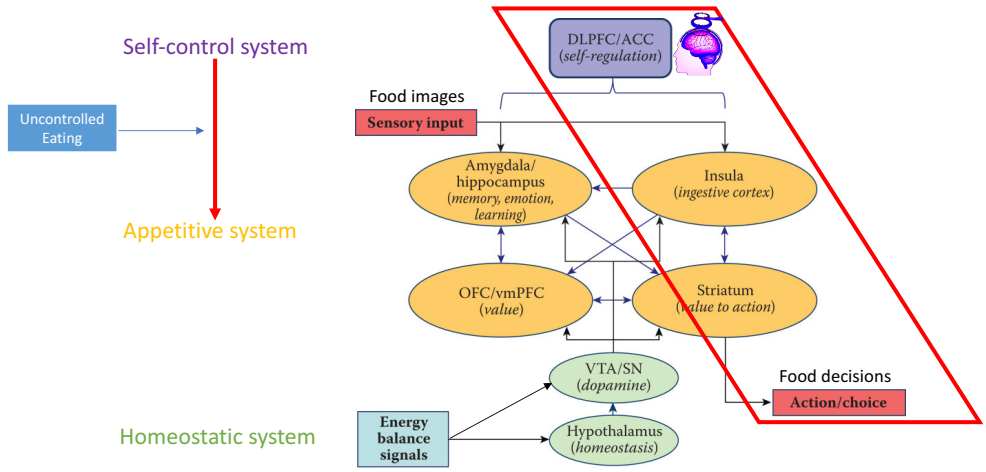

Figure 5.2. Modulation of the self-control system to affect appetitive behaviour. Study III manipulated activity in the DLPFC using TBS to observe its effects in food decisions. In the whole group, TBS had no effect on dietary decisions, however UE modulated the TBS effects.

Our study revealed that neither inhibitory nor excitatory TBS influenced dietary decisions overall. Even in the subsequent analysis that considered the caloric density of the food items, the findings remained null. These results are not fully consistent with pre-existing evidence. Using the food BDM task, several neuroimaging studies using fMRI or EEG yielded findings that imply that the DLPFC may modulate food value computed in the vmPFC such that decisions are congruent with an individual's eating-related goals (Hare et al., 2009, 2011; Harris, Hare, & Rangel, 2013). Moreover the DLPFC-vmPFC coupling during food decision making is observed to be greater in successful dieters (Neseliler et al., 2018; Weygandt et al., 2013). Applying TMS to the DLPFC was shown to modulate DA release in the appetitive network including the OFC and striatum (Cho & Strafella, 2009; Ko et al., 2008; Strafella, Paus, Barrett, & Dagher, 2001) as well as food craving (Hall, Lowe, & Vincent, 2017; Lowe, Vincent, & Hall, 2017). Our null results were unexpected given the converging evidence for the role of the effects of DLPFC-TMS on food motivation.

On the other hand, there is some evidence that may support the results of Study III. A meta-analysis revealed that while DLPFC stimulation reliably affected food desire in healthy individuals, its influence on food consumption may be inconsistent (Hall et al., 2017; Lowe et al., 2017). This

discrepancy may be related to findings of studies that examined functions of DA that is, at least partly, targeted by DLPFC-TMS (Cho & Strafella, 2009; Ko et al., 2008; Strafella et al., 2001). More specifically, both animal and human studies that manipulated DA availability or observed activity in dopaminergic brain regions demonstrated evidence for DA's role in food motivation (Berridge & Robinson, 2016). However, in a pharmacological study in healthy humans, neither a DA agonist nor an antagonist modified participants' bid amounts on the food BDM task, although the drugs were able to change value-related brain activity (Medic et al., 2014). Decisions to eat are driven not only by the extent to which food is craved, but also by other factors such as habits, the desire to practice healthy eating, and the ability to exert self-control. It is plausible that while DLPFC stimulation can modulate food desire, it may not (reliably) affect other factors that are simultaneously considered during dietary decision making. It is also possible that the contribution of the DLPFC in food decision-making varies among individuals, according to certain personality traits. A good candidate seems to be an obesity-related personality trait, UE, which indeed influenced our TBS findings as discussed below.

Nevertheless, other explanations for our unexpected null results need to be considered. Our stimulation target was selected based on fMRI data collected prior to TBS. We chose the part of/close to the DLPFC that was responsive to food craving regulation, a slightly different task than the food BDM task administered following TBS. It could be that different parts of PFC are involved in inhibitory control and value modulation. Importantly, in Study II, which was a meta-analysis of fMRI studies on dietary self-control, we observed that distinctive parts of the left DLPFC tended to be engaged by the food craving regulation tasks versus food decision-making tasks. Indeed, during the fMRI task administered in Study III, the location of the cluster of regulation-related activation, chosen as the TBS target site, differed from that of the part shown to be functionally coupled with the vmPFC. If the latter had been chosen as the TBS target, given that the BDM task is known to engage the interaction of the DLPFC and vmPFC, the results could have been different. It is also possible that, similar to what Medic et al. (2014) observed, TBS might have induced neural changes, without (sufficiently) affecting behaviours that were tested. Finally, Study III selected only those who scored either high or low in UE (using the 0.5 SD criterion). Although our participants were young, healthy and non-obese individuals, the two groups differed in terms of BMI, in-laboratory food

intake and the amount of fMRI activity in the TBS target. Previous DLPFC-TMS studies (with positive effects), on the other hand, did not consider personality traits during subject recruitment. Therefore, our null findings may be attributable to our participant selection.

The primary aim of the work presented in this thesis was to take modulatory approaches to more precisely explore the interaction amongst the homeostatic, appetitive and self-controls systems that influence eating. This objective was fulfilled by Studies I and III. The first study clearly showed the ability of a homeostatic signal to modulate the appetitive system at both the behavioural and neural levels, while Study III mapped the influence of prefrontal self-control systems on appetitive behaviour. Overall, TBS of the DLPFC region activated by conscious food self-regulation did not affect food choice. However, this does not necessarily indicate that food choice is more strongly affected by homeostatic signals than by the self-control system. First, Studies I and III employed different methods to manipulate the systems. With the first study, a pharmacological dose of ghrelin was infused, and its effects on the brain were confirmed by the hormone's ability to raise the levels of growth hormone. On the other hand, the underlying mechanisms of TBS used in Study III remain unclear. Moreover, despite the well-documented presence of individual variability in responsiveness to TMS, we did not verify stimulation effects and their strength on the brain (e.g. with fMRI). Second, with much animal research on the role of ghrelin and its actions on DA, we were able to make informed decisions about the task and analysis methods to optimally test ghrelin's effects. However, in addition to the lack of knowledge of mechanisms underlying TMS, only a handful of stimulation studies targeting eating-related responses are available, with inconsistent results. Therefore, the hypotheses of Study III were more exploratory, and the results were challenging to interpret. Finally, Studies I and III differed in participant selection. Participants in the third study differed in the degree to which they exhibited an obesity-related personality trait, assumed to affect the systems of appetite control. Indeed, there were effects of TBS on food choice in individuals with high UE, although these effects were subtle. On the other hand, the group recruited in Study I was more homogeneous. If we recruited individuals who differed in factors known to influence ghrelin functioning such as BMI (Makris et al., 2017), they would likely have exhibited varying responses following ghrelin injection. Although the participant selection method employed in Study III did

not permit direct comparison to other stimulation studies with more homogenous groups of participants, it allowed us to examine the role of the trait, UE, in responsivity of the self-control system.

5.3 Neural- and personality- characterization of vulnerability to obesity

Obese individuals tend to show neural activity patterns reflecting heightened reward response and diminished self-control in response to food cues. These processes are captured in a personality trait referred to generally as impulsivity, or, in a way that is more specific for feeding behaviour, UE. UE, as measured by the RED Scale, among others, predicts BMI and food consumption (Michaud et al., 2017; Vainik et al., 2018). Study II and III attempted to better characterize neural and personality correlates of vulnerability to obesity.

This trait has also been investigated with functional neuroimaging. Previous studies have shown that food cue-induced activity in brain regions subserving self-control is associated with various eating-related measures such as food desire and intake, value placed on dieting, healthy eating, BMI, and weight loss success (Frankort et al., 2015; Hare et al., 2009, 2011; Lopez, Hofmann, Wagner, Kelley, & Heatherton, 2014; Murdaugh, Cox, Cook, & Weller, 2012; Smeets, Kroese, Evers, & de Ridder, 2013). Moreover, despite some evidence that eating-specific rather than general self-control may be a stronger predictor of eating-related behaviours and outcomes (Vainik et al., 2015), no previous meta-analyses had mapped neural correlates of eating-specific self-control. To fill this gap in the literature, our second study collected fMRI studies using tasks that captured deployment of dietary self-control, with which we performed a meta-analysis to identify brain regions that are consistently engaged during eating-specific self-control. Furthermore, to test the relevance of neural circuits involved in dietary self-control to obesity, Study II conducted another meta-analysis on a subset of dietary self-control fMRI studies that also explored the influence of BMI. It was revealed that eating-specific self-control recruited a range of brain regions including the IFG, DLPFC, and temporal-parietal junction, that are thought to be involved in emotion regulation and cognitive control (Ardila, Bernal, & Rosselli, 2017; Giuliani & Berkman, 2015; Morawetz, Bode, Derntl, & Heekeren, 2017). Given that the regions subserving dietary self-control overlap with those engaged in other domains, exploring the influence of BMI was crucial to identify eating-

specific parts of the self-control circuits. We observed association between greater activity in the vmPFC, IFG and DLPFC during dietary self-control and lower BMI. These results are consistent with TMS studies reporting increased food craving following inhibition of DLPFC activity and decreased craving following up-regulation of the region (Hall et al., 2017; Lowe et al., 2017).

To further investigate individual differences in the self-control circuit related to vulnerability to overeating and obesity, Study III selected individuals who are more or less vulnerable to obesity, determined based on the personality trait, UE. We then tested how UE may influence responsivity of the dietary self-control system, by measuring fMRI activity during a food craving regulation task and recording food decisions following inhibition and excitation of DLPFC activity with TMS (as described above). First, we verified that high UE individuals had greater BMI and ate more snacks provided during the experiment, compared to the low UE group. This is consistent with previous personality, behavioural and neuroimaging studies associating higher BMI with greater reward sensitivity and blunted self-control (Sutin, Ferrucci, Zonderman, & Terracciano, 2011; Vainik, Dagher, Dubé, & Fellows, 2013; Vainik et al., 2015). Study III further revealed that both fMRI activity and responsiveness to TBS were modulated by UE. More specifically, the high UE group compared to the low UE exhibited greater fMRI activity in the DLPFC (TBS target) and the salience network, but reduced vmPFC-DLPFC coupling during food craving regulation. As discussed above, DLPFC-TBS did not affect dietary decisions in the analyses conducted in all participants. However, we observed that only in individuals with high UE, inhibitory stimulation of DLPFC activity yielded greater willingness to pay for low caloric foods compared to the sham condition. Our TBS results find some support from the literature. A recent study demonstrated that TBS-induced changes in performance on the Stroop task (a measure self control-related processes) correlated with TBS-related changes in food consumption, but not food craving (Lowe, Staines, Manocchio, & Hall, 2018). Furthermore, a simultaneous TMS-fMRI study detected greater DLPFC-TMS effects in the brain in those with stronger connectivity between the stimulation target site and the salience network (Hawco et al., 2018). Together with these findings, Study III seems to indicate that responsiveness to DLPFC-TBS may depend on individual differences in self-control, which is partly assessed by the UE measure.

On the other hand, the fMRI results of Study III seemed contradictory to our hypotheses

based on previous studies that related greater dietary success to stronger DLPFC response (Hare et al., 2011; Murdaugh et al., 2012), which was further confirmed by Study II findings. We expected greater fMRI DLPFC activation during self-regulation in participants with low UE, but found the opposite. In reconciling the results of Studies II and III, we can consider the types of dietary self-control tasks utilized and processes that are being captured in the RED scale we selected to measure UE. In our second study, investigation of the brain-BMI relationship predominantly included fMRI studies that used decision making tasks. These studies typically focused on task trials where participants made healthier choices to examine neural correlates of dietary self-control. Therefore, the DLPFC activity that inversely correlated with BMI in Study II may reflect successful implementation of self-control in response to food cues. On the other hand, the fMRI portion of Study III used another dietary self-control task where participants were merely instructed to reduce food craving, and success of their self-control attempts was not verified. Therefore, while stronger DLPFC response in high UE individuals may indicate greater recruitment of executive resources, it may not indicate that self-control was successfully implemented. This theory is indeed supported by reduced coupling between the DLPFC and vmPFC seen in individuals with high UE, as the strength of the vmPFC-DLPFC interaction is thought to reflect the ability of self-control regions to modulate food value to produce food decisions consistent with health goals (Hare et al., 2009, 2011; Neseliler et al., 2018; Weygandt et al., 2013). Moreover, the RED scale we used to measure UE taps into reward sensitivity and self-control (Epel et al., 2014; Vainik et al., 2018). Based on the activity patterns of the DLPFC and the salience network, high UE, at least in our study, may predominantly reflect enhanced food reward. If the RED scale instead mostly captured reduced self-control, we might have expected to observe diminished DLPFC activation in people with high scores on the scale. Therefore, individuals with high UE, due to their heightened reward sensitivity, may more strongly (but less successfully) recruit inhibitory resources, reflected in greater DLPFC activity. This hypothesis is further supported by the TBS finding that individuals with high UE or stronger DLPFC response were more susceptible to the effects of stimulation on food decision making.

Although the speculations made above need to be clarified in future studies, Studies II and III collectively suggest that neural circuits involved in implementation of dietary self-control are relevant for obesity, and that individual differences in responsivity of these circuits may be reflected

in an eating-specific personality trait, UE.

5.4 Future directions

Given the animal research findings that show ghrelin's ability to stimulate DA signalling and DA's role in associative learning, our interpretation of Study I was largely based on ghrelin's interaction with DA. Such hypothesis needs to be properly tested in humans. This could perhaps be done by administering a DA antagonist or by reducing DA levels using tyrosine depletion (Carbonell et al., 2014), or recruiting participants with different alleles that affect DA functioning, although the latter can be confounded by obesity which also shows differences in ghrelin and DA signaling. We argued that ghrelin's actions are food-specific given the previous findings that ghrelin causes hunger rather than a non-specific increase in motivation, and our study method that compared behavioural and neural responses between stimuli associated with food and non-food odours that were similar in pleasantness, intensity and familiarity. Our interpretation regarding ghrelin's food specificity finds further support from a recent study that utilized optogenetics to identify neurons in the OFC that responded selectively to food stimuli (Jennings et al., 2019). Nevertheless, there is some evidence that ghrelin may influence processing of alcohol and recreational drugs, subserved by DA (Zallar, Farokhnia, Tunstall, Vendruscolo, & Leggio, 2017). Therefore, future studies need to directly compare food-related stimuli to other reinforcers with motivational salience such as alcohol, drugs and money to further specify ghrelin's effects on the appetitive system. To date, there is only one other study that examined ghrelin's effects on food cue responses in the brain after manipulating the levels of the peptide in humans (Malik et al., 2008). Therefore, there are many other eating-related processes that need to be examined in relation to homeostatic signals. One good candidate task is the food decision making task, which can help capture the potential influence of homeostatic signals on the interaction between the appetitive and the self-control networks. Finally, there is also a need to examine ghrelin's effects in the brain of individuals with abnormal weight status. In addition to neuroimaging findings of heightened food cue reactivity and diminished self-control, obesity is characterized by altered ghrelin signaling. More specifically, obese individuals show lower ghrelin levels at baseline, blunted postprandial suppression, and greater receptor sensitivity to ghrelin, some of which are affected by weight loss (Makris et al., 2017). Therefore, how the obese brain responds

to ghrelin needs to be explored. Findings of the proposed studies are believed to address some of the unresolved challenges posed in attempts to design pharmacological treatments targeting ghrelin signaling for obesity (Howick, Griffin, Cryan, & Schellekens, 2017).

The meta-analysis conducted in this thesis was the first to focus only on eating-specific self-control tasks. However, the observed regions greatly overlap with those that are recruited during implementation of regulation in other cognitive and emotional domains. In order to locate the parts of the core brain regions of self-control that are specific to eating, a future study should perform a meta-analysis to directly compare the neural correlates of self-control in different domains. This is particularly important given some evidence from behavioural and personality research that dietary self-control measures more strongly predict eating and weight status, compared to those that assess general self-control (Vainik et al., 2015). Study II additionally compared the two commonly used tasks of dietary self-control to investigate how BMI influenced brain activity associated with dietary self-control. The results are however preliminary given the small number of studies currently available. Future meta-analyses need to validate our findings using a larger number of studies and investigate the influence of other related factors such as food intake, personality traits and hunger levels.

Some findings seen in Study III were in contrast to pre-existing evidence and difficult to interpret. As stronger DLPFC activity has been thought to indicate greater success in self-control implementation, it was unexpected to observe higher DLPFC activation during craving regulation in low self-controllers. As discussed above, this may have to do with processes that are involved in different types of dietary self-control tasks and elements of UE being targeted. This speculation needs to be tested, for example, by comparing high and low UE individuals in their brain response to different dietary self-control and food cue reactivity tasks while paying attention to task contrasts and participants' performance. The TBS results were challenging to interpret given the relative lack of pre-existing stimulation studies on appetitive behaviours and insufficiency in available knowledge of mechanisms underlying brain stimulation. In order to help clarify our behavioural findings, we will perform analysis of EEG data that were collected during TBS task performance, in the hope that its results will help detect more precise TBS effects. Furthermore, as suggested above, one's ability to exert self-control may determine if decisions to eat, but not food craving, would be modulated by

TMS. This hypothesis needs to be tested by recruiting participants who score high, low or average in UE, and administering food craving, decision making and consumption tasks as well as a measure of generic self-control (e.g., the Stroop task) following inhibitory and excitatory stimulations. Such investigation will help identify factors influencing responsivity to brain stimulation tools, a crucial knowledge to be utilized in designing brain-stimulation-based treatments for obesity.

To conclude, the work presented in this thesis furthers our understanding of the interactions among the homeostatic, appetitive and self-control systems that influence eating. In addition, our findings highlight the importance of considering obesity-related measures such as BMI and relevant personality traits in interpreting neuroimaging studies as well as in designing brain-stimulation-based treatments for obesity.

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