FUNCTIONAL NETWORK ARCHITECTURE IN OBESITY: COMPARISON OF TASK-EVOKED AND RESTING STATE CONNECTIVITY

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Functional alterations of the neural networks that support reward valuation and reward-driven decision making may be related to obesity. In support of this hypothesis, obesity is associated with differences in task-evoked and intrinsic functional connectivity. However, few studies have used a hypothesis-driven multimodal approach to compare obesity-related differences in functional network organization evoked by high calorie food cues and in the absence of externally-guided information processing demands. The sample included 122 adults (78% female; age *M* = 44.43, *SD* = 8.67) with body mass index (BMI) in the overweight or obese range (BMI *M* = 31.28, *SD* = 3.92) assessed prior to a behavioral weight loss intervention. Participants completed a functional MRI scan that included a resting period followed by a visual food cue task in which participants viewed alternating blocks of high and low-calorie foods and neutral non-food items. A seed-based approach was used, with seeds being located in regions including the orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC). Whole-brain functional connectivity analyses were conducted to examine seed-to-voxel signal covariation during the presentation of high calorie food and at rest. For all seeds selected for analysis, obesity was associated with *stronger* functional connectivity during the presentation of high calorie food, but *weaker* functional connectivity at rest. While regions located in the default mode network (e.g., mPFC, posterior cingulate cortex) exhibited BMI-dependent modulation of signal coherence in the presence of palatable food cues, regions involved in reward processing (e.g., basal ganglia) exhibited BMI-dependent modulation of signal coherence at rest. These data provide evidence that obesity predicts stronger functional

connectivity between regions involved in reward valuation, self-directed thinking, memory, and emotion processing during the presentation of high calorie food cues, but weaker intrinsic functional connectivity in reward processing regions. These dissociable patterns of functional network organization are suggestive of separate mechanisms potentially contributing to variation in functioning in distinct cognitive, psychological, or behavioral domains. This may have implications for understanding individual differences in obesity.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.0 INTRODUCTION

Obesity is a major public health issue. Within the last several decades, the prevalence of obesity in American adults has risen dramatically, with over one-third meeting clinical criteria for the condition (body mass index (BMI) ≥ 30; Ogden, Carroll, Kit, & Flegal, 2014). Numerous studies have demonstrated an adverse effect of being overweight or obese on health and psychosocial functioning (Cawley & Meyerhoefer, 2012; Finkelstein, Ruhm, & Kosa, 2005; Kopelman, 2000; Wadden, Womble, Stunkard, & Anderson, 2002), making the rise in rates of obesity a significant threat to public health. Obesity is associated with higher mortality, and increased rates of cardiovascular disease, diabetes, hypertension, metabolic syndrome, depression (Stunkard, Faith, & Allison, 2003), anxiety (Gariepy, Nitka, & Schmitz, 2010), as well as neurological illnesses such as Alzheimer's disease (Kivipelto, Ngandu, Fratiglioni, Viitanen, Kåreholt et al., 2005). Further, overweight and obese persons are more likely to experience discrimination in employment, education, and health care settings (Cawley & Meyerhoefer, 2012). Obesity is one of the most costly conditions to treat, with obesity-related illness comprising up to 21% of yearly healthcare expenditures in the United Sates (Cawley & Meyerhoefer, 2012). These findings highlight the fundamental importance of identifying mechanisms underlying obesity to facilitate the development of more effective prevention and treatment interventions. Despite this pressing need, the etiology of obesity remains poorly understood.

Obesity is associated with deficits in executive functioning, suggesting that abnormalities in the brain regions that support it may contribute to the etiology of obesity. Executive function is defined as the ability to select appropriate actions based on ongoing evaluation of environmental demands, current goals, current emotional state, past experiences, and social norms, and encompasses elements of decision making and behavioral self-regulation (e.g., control of reward-driven impulses; Baumeister & Heatherton, 1996; Heatherton & Wagner, 2011). That the construct of executive function is comprised of many different elements, each of which may differ in subtle but important ways, suggests that it is not a unitary construct (e.g., Kramer, Humphrey, Larish, Logan, & Strayer, 1994). Given this issue, it is not well understood how the varied components of executive functioning contribute to obesity. Nevertheless, there is evidence to suggest that components of executive function such as self-regulation, as well as the exertion of control over reward-driven impulses, may be impaired in obesity (Schag, Schönleber, Teufel, Zipfel, & Giel, 2013). For instance, obese individuals exhibit difficulty inhibiting automatic responses on inhibitory control tasks, tending to engage in habitual or overlearned behaviors (Batterink, Yokum, & Stice, 2010; Davis, Patte, Curtis, & Reid, 2010; Gunstad, Paul, Cohen, Tate, Spitznagel et al., 2007). Obese individuals also show a preference for smaller, immediate rewards over larger, delayed rewards relative to normal weight individuals (Weller, Cook, Asvar, & Cox, 2008), a phenomenon referred to as delay discounting. Importantly, steeper discounting of delayed future rewards has been associated with increased purchasing (Nederkoorn, Guerrieri, Havermans, Roefs, & Jansen, 2009) and consumption (Appelhans, Woolf, Pagoto, Schneider, Whited, et al., 2011; Nederkoorn et al., 2009) of highly palatable, calorie dense foods, as well as binge eating disorder (Davis et al., 2010). These findings indicate that deficits in self-regulation and reward processing may predispose some individuals to obesity by influencing decisions regarding diet and exercise.

Poor self-regulation has been shown to predict the probability of treatment failure during a weight loss intervention, with more impulsive individuals losing less weight than those with a greater capacity for self-regulation (Nederkoorn, Jansen, Mulkens, & Jansen, 2007). Indeed, greater capacity for self-regulation has been associated with more frequent consumption of healthy low calorie foods and regular engagement in physical activity, both in healthy weight and obese adults (Crescioni, Ehrlinger, Alquist, Conlon, Baumeister et al., 2011; Gerrits, O'Hara, Piko, Gibbons, de Ridder et al., 2010; Wills, Isasi, Mendoza, & Aineette, 2007). Conversely, impaired self-regulation is associated with consumption of high calorie foods and sedentary lifestyle, even during weight loss attempts (Crescioni et al., 2011). Moreover, one study demonstrated that specifically targeting deficits in self-regulation in a weight loss intervention promoted long term maintenance of weight loss (Wing, Tate, Gorin, Raynor, & Fava, 2006), an outcome that is particularly difficult to achieve using standard weight loss protocols. These data highlight the central role of self-regulation and reward processing in the etiology of obesity. These studies also provide preliminary evidence that deficits in self-regulation and reward processing are modifiable, and that modification of these deficits through treatment improves weight loss and weight maintenance outcomes. Nevertheless, the biological mechanisms underlying deficits in self-regulation and reward processing in obesity remain poorly understood, though a better understanding of these mechanisms is imperative for improving treatment success.

1.1 FRONTOSTRIATAL VARIATION AS A MECHANISM UNDERLYING INDIVIDUAL DIFFERENCES IN OBESITY

Deficits in self-regulation and reward processing in obesity suggest there may be alterations in signaling in the frontostriatal neural circuit (Tomas & Volkow, 2013; Volkow & Bailer, 2015). This circuit links prefrontal cortical (PFC) regions involved in inhibitory control to midbrain regions such as the ventral striatum and nucleus accumbens (NAc) that are involved in reward valuation and behavioral execution. Medial regions of PFC have been implicated in stimulus valuation and emotion generation (Etkin, Egner, & Kalisch, 2011), while lateral regions have been implicated in regulatory processes (Ochsner, Silvers, & Buhle, 2012; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). Together, these regions are thought to contribute to processes requiring the integration of sensory signals, maintenance of attention on goal-relevant stimuli, and retrieval of pertinent memories for the purpose of planning and selecting appropriate, goal-relevant behavioral responses (Kaller, Rahm, Spreer, Weiller, & Unterrainer, 2011; Philiastides, Auksztulewicz, Heekeren, & Blankenburg, 2011), all of which are necessary for successful self-regulation. In support of this, research has shown that individuals who successfully inhibit automatic habitual responses to salient stimuli during an inhibitory control task exhibit significantly more activity in the inferior frontal gyrus (IFG) than individuals who fail to inhibit automatic responses (Casey, Somerville, Gotlib, Ayduk, Franklin et al., 2011). A large meta-analysis of fMRI studies examining the neural basis of executive functioning revealed that inhibitory control is supported by activation in the dorsolateral PFC (dlPFC), and superior and middle frontal gyri (Niendam, Laird, Ray, Dean, Glahn et al., 2012). Indeed, one study demonstrated that activity in the dlPFC and anterior cingulate cortex (ACC) during a monetary decision making task increased as the level of risk involved in each successive decision increased

(Schonberg, Fox, Mumford, Trepel, & Poldrack, 2012), possibly reflecting a shift towards the engagement of inhibitory processes to prevent losses. Overall, these studies provide evidence that inhibitory control and reward valuation are supported by the PFC, and suggest that impaired inhibitory control and reward valuation in obesity may be attributable to altered PFC signaling.

Prefrontal signaling has also been shown to underlie food preferences and the ability to engage in self-control when making dietary decisions. Specifically, ventromedial PFC (vmPFC) activation was associated with food preferences among normal weight individuals on a diet when they were selecting between neutral food items (e.g., granola) and foods of varying taste and nutritional value (Hare, Camerer, & Rangel, 2009). This relationship was modulated by both nutrition content and taste among individuals who exhibited self-control over dietary selections (i.e., chose healthy options even when it was not the preferred food), but modulated only by taste among those who exhibited less self-control. Moreover, successful deployment of self-control was associated with dlPFC activation and concurrent reduction in vmPFC activation (Hare et al., 2009). This pattern of results suggests that the ability to exert self-control when confronted with stimuli that have competing values (e.g., taste vs. health) is mediated by dlPFC-driven modulation of stimulus reward value being encoded by the vmPFC (Hare et al., 2009). Poor dietary behaviors and obesity may therefore arise when there is a **decoupling** between prefrontal regulatory regions and regions involved in reward valuation, leading to a shift in behavior towards the pursuit of short-term goals (e.g., eating appetizing food) rather than long-term goals (e.g., being healthy, losing weight; Volkow & Baler, 2015).

Signaling within the ventral striatum and NAc has been hypothesized to represent the motivational significance of events and the reinforcement of associations between these events and their emotional and behavioral consequences (Cardinal, Parkinson, Hall, & Everitt, 2002; Ochsner

et al., 2012). The ventral striatum and NAc process inputs from other regions signaling the significance of a stimulus or event and utilize this information to initiate contextually suitable behavioral responses (Cardinal et al., 2002; Goldstein, Barnett, Vasquez, Tobia, Kashtelyan et al., 2012), acting as the interface between motor and limbic systems (Mogenson, Jones, & Yim, 1980). Spikes in neuronal activity in the ventral striatum and NAc were found to occur in response to cues signaling the availability of larger relative to smaller rewards (Goldstein et al., 2012; Knutson, Adams, Fong, & Hommer, 2001), indicating that signaling variation in these regions may mediate individual differences in delay discounting specifically, and reward valuation more broadly. Neuronal firing in the NAc has also been shown to elicit abnormal behavioral responses to drug reward, food reward, nociceptive stimuli, and threatening stimuli (Barrot, Olivier, Perrotti, DiLeone, Berton, et al., 2002), demonstrating that altered neural output from the NAc impacts behavioral responses to salient stimuli, including food. Therefore, altered frontostriatal activation may underlie obesity-related variation in reward processing.

Research has demonstrated that failure to recruit prefrontal regions during the presentation of appetitive stimuli may underlie the difficulty in regulating eating behavior, thus increasing susceptibility for weight gain and obesity. Indeed, there is growing evidence that obesity is associated with structural and functional abnormalities in frontostriatal circuitry that may decrease PFC engagement. For instance, obesity is associated with reduced grey matter volume in the medial and inferior frontal gyri, orbitofrontal cortex (OFC), and putamen (Pannacciulli, del Parigi, Chen, Le, Reiman, et al., 2006; Walther, Birdsill, Glisky, & Ryan, 2010). Moreover, reduced grey matter volume predicts deficits in executive functioning, including reduced cognitive flexibility and poor inhibitory control (Walther et al., 2010). Obese individuals exhibit greater activation in frontostriatal regions such as the NAc, striatum, insula, and OFC during reward valuation

compared to normal weight individuals (Opel, Redlich, Grotegerd, Dohm, Haupenthal et al., 2015). During the presentation of palatable food, obese individuals show greater engagement of frontostriatal regions, particularly the ventral striatum, NAc, and other regions of the basal ganglia (Burger & Stice, 2011; Demos, Heatherton, & Kelley, 2012; Dong, Jackson, Wang, & Chen, 2015; Rothemund, Preuschof, Bohner, Bauknecht, Klingebiel et al., 2007; Stice, Yokum, Blum, & Bohon, 2010; Stice, Yokum, Bohon, Smarti, & Smolen, 2010; Stice, Yokum, Burger, Epstein, & Small, 2011; Stoeckel, Weller, Cook, Twieg, Knowlton et al., 2008; Yokum, Ng, & Stice, 2011). Body mass is inversely associated with activation of dlPFC in response to palatable food cues (Kullmann, Pape, Heni, Ketterer, Schick et al., 2012a). Similarly, activation in dlPFC, medial and inferior frontal cortices, and ACC is reduced in obese compared to lean individuals during attempts to regulate craving for unhealthy foods (Giuliani, Mann, Tomiyama, & Berkman, 2014). Similarly, a small meta-analysis of 10 fMRI studies of food cue reactivity in obesity demonstrated that obese individuals exhibited increased activation in regions that support reward valuation (e.g., medial PFC) but reduced activation in regions that support self-regulation (e.g., dlPFC; Brooks, Cedernaes, & Schiöth, 2013). However, this meta-analysis did not observe an effect in the striatum despite strong evidence implicating this region in reward valuation and obesity, a discrepancy that is likely explained by the small number of studies included in the meta-analysis. In general, the findings reported in these studies are largely consistent with the hypothesis that decreased PFC-driven inhibitory control coupled with overvaluation of rewards driven by the striatum influences vulnerability to obesity, though further work is necessary to evaluate whether connections between these regions are altered in obesity in the manner that is suggested by these findings.

Altered signaling in frontostriatal regions has also been shown to be prospectively associated with weight gain and response to weight loss interventions (Demos et al., 2012; Dong

et al., 2015; Stice, Yokum, Bohon et al., 2010; Yokum et al., 2011, 2012). For example, elevated activity in regions such as the lateral PFC, OFC, and insula during a food-specific attention task was associated with attentional biases for appetizing food cues (Yokum et al., 2011). Moreover, activity in these regions predicted weight gain at a one-year follow-up (Yokum et al., 2011), indicating that the relationship between frontostriatal activity and obesity may be partly mediated by attentional processes and may influence food choice and calorie intake. NAc activation in response to food cues, but not to other salient reward cues, predicted increased BMI at a six month follow-up, even among individuals who were not overweight or obese at baseline (Demos et al., 2012). This finding suggests that the relationship between striatal activity and future weight gain is specific to food-related tasks. Higher activation in NAc, ACC, and insula during the presentation of palatable food cues predicts poorer response to a 12-week behavioral weight loss intervention, as well as failure to maintain weight loss over a 9-month follow-up (Murdaugh, Cox, Cook, & Waller, 2012). Conversely, greater baseline PFC activation during the presentation of food cues was associated with greater weight loss during the intervention (Murdaugh et al., 2012). This provides promising evidence that altered frontostriatal responses to food temporally precede weight gain, and may therefore be causally linked to overeating and obesity, a hypothesis that will require further validation in interventions, prospective and high risk obesity samples. Together, these studies implicate frontostriatal signaling as a mechanism underlying food cue reactivity, overeating and caloric intake, and obesity.

1.2 ALTERATION OF NETWORK-LEVEL SIGNALING DYNAMICS IN OBESITY

The majority of fMRI studies of obesity have focused on isolated brain regions, although complex processes like self-regulation and reward valuation are likely to arise from interactions between brain regions rather than from activation of a single brain region. Functional connectivity is one method of capturing dynamic interactions between regions by determining the degree to which signals in different areas are correlated. Functional connectivity analyses provide a metric of how anatomically distinct brain regions are organized into coherent functional networks with specific properties (e.g., highly efficient local connections). This information can then be used to build an understanding of how variation in network organization affects its functional properties and how variation in network functional properties affects the processes supported by the network (Bullmore & Sporns, 2009; van den Heuvel & Pol, 2010). Moreover, characterizing how the functional organization of the brain changes in conditions like obesity may yield new insights about the neural mechanisms underlying these conditions. This may ultimately lead to improvements in treatment and prevention, highlighting the importance of investigating obesity-related differences in functional connectivity.

Currently, 30 studies have investigated functional connectivity within neural networks in obesity. About half of these studies (n = 13) have examined task-evoked changes in functional connectivity during the presentation of appetizing food images and the remainder examined task-independent resting-state connectivity, and the majority (n = 28) of these studies were cross-sectional. The task-evoked studies that have been conducted to date have provided evidence that obesity impacts functional connectivity during the processing of food cues. For example, one study found that obese individuals exhibit greater functional connectivity between amygdala and striatal seed regions and regions involved in executive control and motor planning, including the ACC,

insula, supplementary motor area, and dorsomedial PFC (dmPFC), while passively viewing appetizing foods (Atalayer, Pantazatos, Gibson, McOuatt, Puma et al., 2014). Similarly, obesity has been associated with stronger connectivity between the dorsal striatum, amygdala, and insula (Nummenmaa, Hirvonen, Hannukainen, Immonen et al., 2012), and increased strength in connectivity between the ACC and insula (Kullmann et al., 2012a). Further, striatal connectivity to parahippocampal regions and the cerebellum in response to high calorie foods has been shown to be greater in obese compared to healthy weight individuals (Carnell, Benson, Pantazatos, Hirsch, & Geliebter, 2014), which may reflect planning of behaviors to obtain palatable food in response to relevant environmental cues. Interestingly, one study demonstrated that the pattern of connectivity between regions varied based on whether participants were in a fasted or a satiated state, with fasting being associated with enhanced connectivity between amygdala and ventral striatal seed regions and motor planning regions, particularly among men (Atalayer et al., 2014). This finding may be interpreted as evidence that hunger enhances the reward value of food and promotes communication between emotion and reward processing regions and regions involved in executing movements, possibly to promote food intake. However, because this study did not include a normal weight comparison group, it is unclear if the observed patterns of functional connectivity are specific to obesity. Although this presents an interpretive challenge, these results suggest that hunger influences network-level signaling dynamics, which may underlie hunger-related enhancement of the reward value of food and the shift in motivation towards the immediate goal of alleviating hunger.

In contrast to the studies reporting increased connectivity strength between regions involved in stimulus valuation and motivational processes among obese individuals described above (e.g., Atalayer et al., 2014; Carnell et al., 2014; Kullmann et al., 2012a; Nummenmaa et al.,

2012), there are some studies that have observed obesity-related reductions in connectivity in these regions. For instance, functional coupling of the amygdala with the NAc and OFC was found to be weaker among obese compared to normal weight individuals when viewing high calorie foods after a fasting period (Stoeckel, Kim, Wller, Cox, Cook et al., 2009). Similarly, obesity was shown to predict reduced connectivity between the amygdala and the hippocampus, midbrain, thalamus, and insula during the consumption of a milkshake (Geha, Cecchi, Constable, Abdallah, & Small, 2017). Another study demonstrated that connectivity strength between medial and lateral PFC and regions serving visual and motor functions was reduced in response to both food and monetary reward cues in obese relative to lean individuals (García-García, Jurado, Garolera, Segura, Marqués-Iturria et al., 2013a). This latter finding is consistent with the hypothesis that poor self-regulation and abnormal reward valuation often observed in obesity may be driven by weakened top-down neural communication from prefrontal regulatory regions to regions involved in planning and execution of motivated behaviors. Reductions in connectivity strength between visual and motor regions, including extrastriate cortex, precuneus, and primary motor cortex, and regions involved in inhibitory control like the IFG have also been observed in obese samples (García-García et al., 2013a; Geha et al., 2017; Kullmann et al., 2012a). This may likewise reflect a relative disengagement of PFC-mediated modulation of visuo-spatial attention and motor output, which may promote biased attention to food and execution of behaviors to obtain food regardless of whether these behaviors are consistent with improving long-term health and fitness.

Frontostriatal and frontoparietal connectivity has also been shown to be reduced in obese compared to normal weight individuals during a decision making task in which participants had to indicate their willingness to pay increasing sums of money for palatable food (Verdejo-Roman, Fornito, Soriano-Mas, Vilar-Lopez, & Verdejo-Garcia, 2017). Importantly, weakened coupling

within these networks predicted greater willingness to pay for palatable food relative to less appealing food of higher nutritional value, providing evidence that such network level impairments may influence real world decisions about which foods one purchases and consumes. Interestingly, successful regulation of craving, as well as successful response inhibition, are associated with the opposite pattern of cortical-subcortical connectivity among obese individuals, with stronger coupling being predictive of more successful attenuation of craving and response inhibition (Dietrich, Hollmann, Mathar, Vrillinger, & Horstmann, 2016; Filbey & Yezhuvath, 2017; Tuulari, Karlsson, Hirvonen, Slaminen, Nuutila et al, 2016). It is important to note that normal weight individuals did not exhibit enhanced connectivity between prefrontal and subcortical regions during successful craving regulation or response inhibition, suggesting that obese individuals exhaust more cognitive resources when regulating craving and behavior. This may explain why some individuals experience frequent dietary self-regulation failures despite having the desire to engage in healthy behaviors. In general, findings from task-evoked connectivity analyses provide evidence that obese individuals exhibit abnormal connectivity patterns in response to high calorie palatable food cues, which may underlie poor dietary self-regulation and weight gain.

Altered functional connectivity in response to palatable food cues may also be related to weight loss. For example, formerly obese individuals examined after recent weight loss were shown to exhibit greater connectivity in the default mode network (DMN) during passive viewing of food images compared to normal weight individuals (Tregellas, Wylie, Rojas, Tanabe, Martin et al., 2011). Given the hypothesized role of the DMN in self-referent thought and internal monitoring, this may reflect a bias of attention to internal states such as hunger and craving (Tregellas et al., 2011). These results suggest that altered DMN connectivity during the processing of food cues persists even after successful weight loss, though it is important to note that responses

to food in the DMN prior to weight loss were not assessed. It is possible that this pattern of connectivity may promote eating in response to food cues and may therefore underlie difficulty with weight maintenance after successful weight loss. Interestingly, there is some experimental evidence that differences in functional connectivity during the processing of food cues that persist following weight loss is modified by leptin, a hormone released by adipose tissue that acts on hypothalamic receptors to signal weight status and regulate appetite (Frederich, Hamann, Anderson, Löllmann, Lowell et al., 1995; Maffei, M., Halaas, Ravussin, Pratley, Lee et al., 1995). Specifically, administration of leptin during dietary weight loss reduced hypothalamic and NAc connectivity to the ACC, OFC, and visual cortex but increased connectivity with the insula during the processing of high calorie foods (Hinkle, Cordell, Leibel, Rosenbaum, & Hirsch, 2013). This may indicate that leptin influences appetite and sensitivity to food cues through downstream effects on connectivity between regions involved in self-regulation, reward valuation, and interoceptive functioning, and could be a useful adjunctive treatment in weight loss interventions if further research documents a relationship between leptin-induced changes in functional connectivity and weight-loss outcomes.

Among obese individuals, greater connectivity between dlPFC and vmPFC at baseline has been associated with the tendency to select the option to consume a larger portion of a preferred meal at a later time rather than a small portion immediately, despite being in a fasted state (Weygandt, Mai, Dommes, Leupelt, Hackmack et al., 2013). This finding suggests that enhanced connectivity between the dlPFC and vmPFC facilitates dietary impulse control, which is consistent with the role that these regions play in self-regulation and in reward and emotion processing respectively. Alternatively, this finding may also be interpreted as evidence that individuals who exhibit enhanced connectivity between the dlPFC and vmPFC simply assign more value to a higher

calorie meal rather than possess more impulse control per se. However, this alternative explanation is weakened by the observation that stronger dlPFC-vmPFC connectivity and selection of larger delayed meals at baseline predicted weight loss following a dietary intervention (Weygandt et al., 2013). Two tentative conclusions can be drawn from these studies. First, the findings reported by Tregellas et al. (2011) and Hinkle et al. (2013) suggest that some obesity-related differences in network-level connectivity may not be attenuated by weight loss. It is possible, therefore, that altered connectivity in obesity may represent a stable marker of the condition that may either increase risk for obesity or facilitate maintenance of unhealthy weight. Alternatively, these differences in functional connectivity may represent state makers of obesity that are not sensitive to modest weight loss, and may potentially increase vulnerability for weight gain after a successful reduction in weight. Second, given that patterns of connectivity associated with enhanced impulse control predict the amount of weight lost following a dietary intervention (Weygandt et al., 2013), it may be argued that network-level connectivity patterns are mechanistically linked to obesity through processes like self-regulation and reward valuation, and may therefore precede the development of obesity. However, it will be necessary to compare connectivity patterns before and after weight loss and stable weight maintenance, as well as to measure connectivity patterns in individuals at high risk for obesity, to evaluate these hypotheses.

Although it is important to understand how differences in the functional organization of the brain during the presentation of food cues may relate to obesity, such studies do not resolve whether such differences are limited to the processing of food cues or whether these areas are related to more domain-general processes (i.e., reward processing). Investigating the functional network connectivity while the brain is not engaged in demanding tasks that require inhibitory control may afford insight into the "intrinsic" functional organization of the brain (Cole, Bassett,

Power, Braver, & Peterson, 2014; Fox & Raichle, 2007). There is evidence to suggest that brain regions which are similarly modulated during the performance of a variety of tasks exhibit a high degree of signal coherence at rest (Cole et al., 2014; Fox & Raichle, 2007). This suggests that regions with overlapping cognitive functions are linked together independently of directed mental activity, perhaps through recurrent alterations in synaptic wiring during the performance of tasks reliant on cognitive functions supported by the connected regions (Cole, Smith, & Beckmann, 2010; Lewis, Baldassarre, Committeri, Romani, & Corbetta, 2009). Examining signal coherence during a state of rest may therefore represent a more efficient method of characterizing functional network architecture, insofar as such an approach may reveal information about inter-regional communication that is not constrained to the performance of a specific task. This information may then be used to draw inferences about the neural mechanisms underlying obesity-related alterations that might be more domain-general or at least involved in several cognitive domains, including executive functioning, attention, self-regulation, and reward processing.

In addition, resting state network characteristics may be heritable (Glahn, Winkler, Kochunov, Almasy, Duggirala et al., 2010; Meyer-Lindenberg, 2009), indicating that genetic factors play a role in shaping the intrinsic architecture of the brain. This observation allows for the possibility that variation in resting state network organization may be an intermediate phenotype linking genetic variation to variation in weight and obesity. Such an observation is critical because it suggests that individual differences in resting state network organization may not be transient or meaningless, but contribute to the etiology of conditions like obesity. Indeed, disruptions in the functional organization of the brain at rest have been described in multiple neurological and psychiatric diseases, including Alzheimer's disease (Wang, Liang, Wang, Tian, Zhang et al., 2007), Attention Deficit Hyperactivity Disorder (Yu-Feng, Yong, Chao-Zhe, Qing-Jui, Man-Qiu

et al., 2007), Major Depression (Greicius, Flores, Menon, Glover, Solvason et al., 2007), and Schizophrenia (Liang, Zhou, Jiang, Liu, Tian et al., 2006). This indicates that altered functional connectivity at rest may be an important marker of disease, and may have diagnostic utility if disease-specific connectivity patterns are identified. Moreover, there is evidence to suggest that changes in resting state functional connectivity predict functional impairment (He, Snyder, Vincent, Epstein, Schulman et al., 2007) as well as disease severity (Greicius et al., 2007), highlighting the potential to use resting state connectivity analyses to reveal prognostic indicators in clinical syndromes like obesity (Fox & Greicius, 2010).

Obesity has been associated with differences in functional connectivity at rest when participants are alert but not engaging in any particular form of mental activity, though there is significant cross-study heterogeneity in the direction of the effect of obesity on resting network architecture. Obese individuals have reduced amygdalar connectivity with the ventromedial PFC (Wijngaarden, Veer, Rombouts, van Buchem, van Dijk et al., 2015) and IFG (Lips, Wijngaarden, vän der Grond, van Buchem, de Groot et al., 2014) accompanied by increased connectivity between the amygdala and insula (Lips et al., 2014), a pattern that was not observed in normal weight individuals. Both the hypothalamus (Lips et al., 2014; Wijngaarden et al., 2015) and the basal ganglia (García-García, Jurado, Garolera, Segura, Sala-Llonch et al., 2013b) have been shown to exhibit increased connectivity with cortical and limbic regions involved in evaluating and assigning valence to incoming information (e.g., ACC, insula, vmPFC) among obese individuals compared to their normal weight counterparts. Moreover, connectivity strength of the basal ganglia was negatively correlated with speed of processing on a cognitive battery completed outside of the scanner, but only among obese individuals (García-García et al., 2013b). This suggests that the predominance of signaling cohesion between brain regions involved in valuation

in obesity may predict worsened performance in cognitive domains relevant to decision making and dietary behavior. Obesity has likewise been associated with stronger NAc connectivity with vmPFC and ACC at rest (Coveleskie, Gupta, Kilpatrick, Mayer, Ashe-McNalley et al., 2015). It is possible that abnormal NAc and basal ganglia connectivity may lead to the overvaluation of food-related information that in turn, leads to engagement in obesogenic behaviors.

Other studies have identified obesity-related alterations in resting state connectivity that diverge from those reported above. A recent study examining how ventral and dorsal striatal networks change in obesity found that the NAc exhibits *weaker* connectivity with the ACC and OFC among obese compared to healthy weight individuals (Contreras-Rodriguez, Martin-Perez, Vilar-lopez, & Verdejo-Garcia, 2015), a finding which contradicts the pattern of NAc connectivity reported by Coveleskie et al. (2015). Further another study did not identify any obesity-related differences in basal ganglia connectivity at the whole-brain level (Kullmann, Heni, Veit, Ketterer, Schick et al., 2012b). Moreover, Kullmann et al. (2012b) found evidence for weaker ACC connectivity with regions of the DMN, including the precuneus and posterior cingulate cortex (PCC), as well as reduced insula connectivity with unspecified temporal lobe structures in obese compared to normal weight individuals. Some studies have documented obesity-related reductions in global connectivity strength, particularly between regions supporting self-regulation in the PFC and regions involved in stimulus valuation. For example, obesity has been associated with reduced centrality of the medial frontal gyrus (MFG; García-García, Jurado, Garolera, Marqués-Iturria, Horstmann et al., 2015), a region that has been implicated in cognitive processes known to be disrupted in obesity, including motor planning, inhibitory control, and conflict monitoring (Rushworth, Walton, Kennerley, & Bannermann, 2004). This indicates that the functional role of

the MFG as a connective hub communicating with many other brain regions is diminished in obesity.

Other studies have also observed obesity-related reductions in task-independent functional connectivity. For instance, functional cohesiveness between nodes of the DMN has been shown to be reduced in obesity, a pattern that was accompanied by increased integration between DMN and other networks more centrally involved in processing externally generated stimuli (e.g., sensorimotor network; Doucet, Rasgon, McEwan, Micali, & Frangou, 2017). Similar patterns have been observed in other studies (Geha et al., 2016; García-García et al., 2013b; Kullman et al., 2012b), including a recent study examining the effect of functional network organization in over 500 individuals (Beyer, Masouleh, Huntenburg, Lampe, Luck et al., 2017). Disruption of the DMN in obesity may reflect a diminished capacity of the DMN to integrate information being generated by externally-driven and internally driven processing. Moreover, functional network disorganization does not appear to be isolated to the DMN. Indeed, obesity has been associated with decreased global and local efficiency, as well as modularity of functional networks throughout the brain (Geha et al., 2016; Baek, Morris, Kundu, & Voon, 2017), suggesting that network architecture in obesity is characterized by reduced efficiency of information transfer both within and between networks. Such global disruptions in functional network organization may underlie many of the widespread cognitive and behavioral abnormalities that have been documented in obesity.

Three recent studies found evidence that diet, exercise, and weight loss surgery modify resting state functional connectivity patterns, suggesting that differences in resting state functional connectivity may be mechanistically linked to obesity. Cross-sectional comparisons between normal weight individuals, obese individuals, and formerly obese individuals who underwent

gastric bypass surgery at least one year prior to enrollment revealed that connectivity between the ACC, OFC, and superior frontal gyrus was stronger among obese individuals compared to normal weight individuals and those who had undergone surgery (Frank, Wilms, Veit, Ernst, Thurnheer et al., 2014). Further, there were no significant differences in connectivity strength between the normal weight and surgery groups (Frank et al., 2014). As such, it is possible that weight loss may induce changes in functional connectivity that promote normalization of reward valuation and enhance self-regulation. However, this interpretation is speculative given that Frank et al. (2014) did not assess baseline resting state connectivity, or examine the relationship between resting state connectivity and cognitive and behavioral risk factors for obesity, including reward processing, impulsivity, or diet. Additional research is necessary to better understand how obesity and weight loss affect resting state connectivity, and whether differences in resting state connectivity are associated with cognitive or behavioral risk factors for obesity.

Data from two intervention studies provide support for the hypothesis that weight loss produces changes in resting state connectivity, particularly in the DMN. Following a 6-month physical activity intervention, participants exhibited reduced connectivity between the precuneus and other regions comprising the DMN relative to baseline (Mcfadden, Cornier, Melanson, Bechtell, & Tregellas, 2013). Similar results were reported by this group using data drawn from the same sample but applying an effective connectivity approach to quantify intervention related changes (Legget, Wylie, Cornier, Melanson, Paschall et al., 2016). Further, greater reduction in DMN connectivity strength over the course of the intervention predicted greater reduction in fat mass and hunger ratings during and after a meal (McFadden et al., 2013), indicating that changes in connectivity may underlie improved behavioral self-regulation in the service of meeting weight loss goals.

Resting state connectivity patterns in the DMN may also vary according to the method of weight loss. Specifically, cross-sectional assessment of individuals who participated in a weight loss intervention demonstrated that those who underwent gastric bypass surgery exhibited increased superior parietal lobe connectivity with the insula, superior temporal lobe, and primary motor cortex during a fasted stated compared to individuals who participated in a dietary restriction program (Lepping, Bruce, Francisco, Yeh, Martin et al., 2015). In addition, connectivity between these regions weakened following the administration of a meal among gastric bypass surgery patients, but not among individuals in the dietary intervention (Lepping et al., 2015). This pattern of results may be interpreted as evidence that behavioral weight loss interventions attenuate biases in attention to signals of hunger and promote awareness of satiety signals, an effect that may be absent in surgical interventions due to their limited focus on changing dietary-related cognitions and behaviors (Lepping et al., 2015). It is possible that differences in DMN connectivity across intervention methods may influence the degree to which each intervention produces changes in dietary behavior and weight. However, this study did not examine whether differences in connectivity either before or after meal administration were associated with degree of weight lost during the intervention, with dietary behaviors outside of the laboratory, or with long term maintenance of lowered weight,. Further, they were unable to examine changes in connectivity from baseline to post-intervention time points, information that could prove useful for understanding mechanisms influencing treatment response. Therefore, it is as of yet unclear whether differences in resting state connectivity between weight loss intervention groups are related to the long-term efficacy of each intervention, an interesting question warranting additional research. These studies provide preliminary evidence that weight loss leads to changes in resting state connectivity that may facilitate or mediate improved control of diet and physical activity.

Moreover, they suggest that altered resting state connectivity patterns may be one mechanism by which obesity develops and/or is maintained.

1.3 GENDER DIFFERENCES IN SELF-REGULATION, REWARD PROCESSING, AND OBESITY

Epidemiological surveys have demonstrated that there are gender disparities in rates of obesity across the globe, with women being more likely than men, on average, to be overweight or obese (Kanter & Caballero, 2012). Such disparities may arise through a variety of mechanisms of social, psychological, and biological origin. One candidate mechanism for which there is growing support is gender-based differences in behavioral and neural responses to rewards like food that may underlie differences in the capacity to exert self-control over eating. Although there is limited evidence of gender differences in impulsivity in healthy-weight individuals (Cross, Copping, & Campbell, 2011), one study reported an association between obesity and impulsivity, but only among women (Horstmann, Busse, Mathar, Müller, Lepsien et al., 2011). Specifically, obese women exhibited steeper discounting of larger future rewards compared to normal-weight women (Horstmann et al., 2011). A number of studies have also documented gender differences in the processing of food cues and hedonic eating. For instance, women were found to experience strong food cravings in the absence of hunger (Rolls, Fedoroff, & Guthrie, 1991), and to consume calorie dense processed foods (Kanter & Caballero, 2012) more often than men. Moreover, frequent food cravings have been associated with greater total daily caloric intake, as well as more frequent consumption of foods high in sugar and fat (Rolls et al., 1991). Women are also more likely than men to engage in disinhibited eating, a pattern of eating that is driven by situational

factors (e.g., low mood, presence of palatable food cues) rather than consideration of long term dietary goals (Leblanc, Bégin, Corneau, Dodin, & Lemieux, 2015). These studies suggest that women may be more sensitive to food-related cues, and have more difficulty regulating dietary impulses when confronted with such cues. Gender differences in food cue reactivity and dietary self-regulation may therefore underlie the observed differences between men and women in rates of obesity.

There is growing body of research demonstrating that the structure and function of brain regions implicated in obesity may also vary by gender. For example, one study documented a strong positive association between dorsal striatal volume and BMI among women but not men (Horstmann et al., 2011). Activity in the superior temporal lobe, ACC, and medial PFC was greater in women compared to men when viewing high calorie compared to low calorie foods, but only when in a fasted state (Frank, Laharnar, Kullmann, Veit, Canova et al., 2010). Responses to food cues did not vary as a function of satiety in men (Frank et al., 2010). Following a fasting period, women also showed elevated striatal responses to palatable food cues relative to men (Geliebter, Pantazatos, McOuatt, Puma, Gibson et al., 2013), suggesting that gender differences in the valuation of food may arise as a consequence of variation in striatal activity, particularly following a fast. Women also exhibit higher glucose metabolism, a proxy marker of neuronal activity, in the amygdala, hippocampus, insula, OFC, and striatum when attempting to inhibit the desire to consume high calorie foods (Wang, Volkow, Telang, Jayne, Ma et al., 2009). This finding suggests that women are less effective at employing cognitive strategies to down-regulate activity in regions involved in emotion and reward processing, which may impair their ability to inhibit a strong desire for food.

Although women exhibit greater food cue reactivity than men in brain regions that encode reward value when hungry, there is evidence to suggest that activity in cognitive control regions (e.g., dlPFC) is greater in women than men in a satiated state. Indeed, men have been shown to exhibit higher ventral striatal but lower medial PFC activity relative to women when tasting chocolate after having consumed enough chocolate to become satiated (Smeets, de Graaf, Stafleu, van Osch, Nievelstein et al., 2006). This may be interpreted as evidence that men are more responsive to palatable food than women, even after the induction of sensory-specific satiety. However, there were no gender differences in subjective desire to eat or palatability of chocolate in either the fasted or fed states (Smeets et al., 2006), calling into question whether the observed sex differences in neural activity are associated with meaningful behavioral or psychological consequences relevant to obesity. Further, a larger study reported that blood flow to the vmPFC was greater in men compared to women following a meal (del Parigi, Chen, Gautier, Salbe, Pratley et al., 2002), contradicting the findings described by Smeets et al. (2006). Women, on the other hand, exhibited greater blood flow to the dlPFC, precuneus, and other regions of the DMN when satiated than did men (del Parigi et al., 2002), and greater dlPFC activation in response to high calorie foods (Cornier, Salzberg, Endly, Bessesen, & Tregellas, 2010; Geliebter et al., 2013) when satiated than did men. These patterns of neuronal activity may be indicative of more thorough processing of satiety signals and the exertion of inhibitory control following a meal among women compared to men. Moreover, dlPFC activation evoked by palatable food cues predicted subsequent food intake, with higher dlPFC activation being associated with lower intake (Cornier et al., 2010). Together, these studies indicate that hunger induces a shift among women in the processing of food cues from regions that support inhibitory control to regions that encode reward and affective value. Such a shift in regional processing of food cues may reflect heightened salience of food

cues during a state of hunger among women, which may promote impulsive dietary decisions. More generally, it is clear that gender is an important moderator of dietary self-regulation as well as valuation of and response to food cues at both a neural and behavioral level. Gender differences in these processes may be indicative of gender-specific mechanisms underlying obesity, highlighting the need to consider gender when investigating etiological factors influencing risk for obesity.

1.4 GAPS IN THE EXISTING LITERATURE

There is strong evidence to suggest that obesity is associated with altered frontostriatal signaling, and that these signaling alterations may promote obesity through their effects on self-regulation and reward processing. However, much of the available research has focused on the contribution of isolated brain regions to the pathophysiology of obesity. While these studies provided the necessary foundation about the role of the frontostriatal network in obesity, it is increasingly clear that the processes supported by this network emerge as a result of dynamic communication between multiple regions rather than from the activity of any single region. Due to recent advances in functional neuroimaging and statistical methodologies, it is now possible to characterize functional network organization. These methods can be used to quantify the degree to which spatially distributed regions exhibit coherence in either evoked or spontaneous activity. As described above, researchers have used these techniques to reveal abnormal connectivity patterns in multiple neural networks among obese individuals. The majority of these studies have documented abnormal connectivity patterns across the brain, specifically during the processing of

palatable food cues. These findings provide a more complex understanding of the neural mechanisms underlying impaired dietary self-regulation in obesity. However, only 14 studies have explored how obesity modulates regional connectivity during the processing of food cues, and these studies are limited by small sample sizes (mean total *N* =35; mean total obese *n* = 22). Further, none of these studies have examined task-evoked and task-independent intrinsic functional connectivity in the same sample. This approach, which has been adopted in the present project, would provide some indication as to whether obesity-related abnormalities in functional connectivity are constrained to the evaluation of food or represent more fundamental, context-independent alterations in the functional organization of the brain.

There remain several outstanding questions about whether obesity is associated with changes in the intrinsic functional architecture of the brain independent of a specific task, and if so, what the exact nature of these changes are. Only 17 fMRI studies of obesity have examined task-independent variation in resting state functional connectivity. Moreover, many of the studies published to date are limited by the use of small samples (mean total *N* = 104; mean total obese *n* = 40) and heterogeneity in statistical approaches used to quantify connectivity strength, emphasizing the need for additional research in this area. There are multiple approaches used to quantify resting state connectivity, all of which address different questions about how the brain is functionally organized and vary in the degree to which they test *a priori* hypotheses about network signaling dynamics. A predominant method that has been used to examine resting state connectivity in many populations is seed-based connectivity analysis. A seed based approach has significant advantages, but has only been applied in four studies examining resting state connectivity in obesity. In this approach, a defined region of interest is selected for analysis based on previous research, from which the signal time series (i.e., BOLD signal fluctuations over the

period of the resting state scan) is extracted and correlated with the signal time series of each voxel in the brain. This generates a connectivity map for each individual participant reflecting the correlations between the BOLD signal in the seed region and BOLD signal in all other voxels in the brain. Seed-based connectivity approaches have several advantages over other approaches. First, because it is hypothesis driven, the results derived from seed-based analyses are reasonably straightforward to interpret in the context of previously published observations about the function of the seed region. Further, the connectivity maps generated using seed-based approaches have been found to be fairly reliable despite there being many potential sources of noise (e.g., variation in alertness across participants, variation in image preprocessing methods) that could produce significant heterogeneity across scanning periods and across samples (Shehzad, Kelly, Reiss, Gee, Gotimer et al., 2009). Finally, it is possible to observe differences in the functional organization of multiple networks across the brain using a seed-based method, which may uncover additional inter-regional associations that were not previously specified. Therefore, although the seed-based approach is necessarily limited in what it reveals by the selection of a specific region of interest, this approach is fairly robust and can be used to test mechanistic hypotheses. Despite these advantages, few studies examining obesity-related differences in resting state network organization have used seed-based methods, with the remainder applying more data-driven exploratory methods (e.g., independent components analysis) to characterize differences in functional connectivity. Further, because resting techniques have only recently been developed, the majority of studies that have applied these techniques to the study of obesity have focused first on establishing whether there are any obesity-related differences in connectivity at rest rather than testing mechanistic hypotheses about the involvement of a particular network. Indeed, only one study specifically selected a frontostriatal region of interest from which to derive connectivity

maps (NAc; Coveleskie et al., 2015). This study, while featuring many strengths, was conducted in a much smaller sample (N = 50) than being proposed here (N = 125), and only included women.

In summary, there are several gaps in the existing obesity neuroimaging literature. First, compared to the number of studies examining regional differences in food-cue reactivity, relatively few studies have explored obesity-related differences in functional connectivity, particularly in the absence of specific task-related cognitive processing. Second, there is limited overlap in the methods used to quantify connectivity across these studies. Because each method addresses different questions about the organization of the brain, and because of the lack of consensus regarding which method is the most valid or informative, it is important that additional multi-modal functional connectivity studies are conducted in obesity. Third, the few studies of obesity that have examined functional connectivity during rest periods have applied a limited number of techniques to characterize resting state network organization. Fourth, no studies have simultaneously analyzed task-evoked and resting state connectivity in obesity, or sought to examine whether observed differences in regional functional connectivity at rest correspond to variation in connectivity during the processing of food cues. Finally, only one study has examined the moderating effect of gender on functional connectivity in obesity (Atalayer et al., 2014), and this study focused only on task-evoked differences in connectivity. Therefore, it remains to be determined if gender moderates resting state connectivity in obesity. To address these gaps in the literature, the proposed study has the following aims:

> **Aim 1:** Determine whether BMI modulates task-evoked connectivity between a subcortical seed region selected based on changes in activation evoked by high calorie food, and other regions of the brain during the processing of high and low calorie food images.
>
> **Hypothesis 1:** Higher BMI will associated with reduced connectivity between selected subcortical seed regions and lateral regions of PFC, but with increased connectivity between regions involved in motor planning and execution (e.g., premotor cortex, inferior

parietal cortex, cerebellum) and those involved in reward valuation (e.g., amygdala, vmPFC, OFC).

Aim 2: Determine whether BMI modulates resting state connectivity between a subcortical seed region selected based on changes in activation evoked by high calorie food, and other regions of the brain at rest when participants are not engaged in any particular form of mental activity.

Hypothesis 2: Higher BMI will be associated with reduced connectivity between selected subcortical seed regions and lateral regions of PFC, but with increased connectivity between regions involved in motor planning and execution (e.g., premotor cortex, inferior parietal cortex, cerebellum) and those involved in reward valuation (e.g., amygdala, vmPFC, OFC). BMI will also be associated with decreased connectivity between the seed region and regions of DMN (e.g., PCC).

Aim 3: Examine the moderating effect of gender on task-related activation/connectivity and resting state functional connectivity.

Hypothesis 3a: Women will exhibit greater responses to high calorie food compared to men, particularly in regions involved in reward valuation (e.g., NAc, amygdala, vmPFC, OFC).

Hypothesis 3b: The association between obesity and functional connectivity (task-evoked and resting) will be stronger in women compared to men.

By using a multi-method approach to characterize how obesity affects the functional organization of the brain, the current study has the potential to further elucidate neural mechanisms underlying obesity. Specifically, by comparing functional network organization during the processing of food to task-independent functional network organization, it will be possible to determine whether the effects of obesity on patterns of neural communication are task specific (i.e., food cue reactivity) or whether obesity perturbs neural communication even in a state of rest outside the presence of food stimulation. These findings could provide some indication of the degree to which disruptions in food cue processing are central to the pathophysiology of obesity, and thus whether treatment of obesity should include a component that targets how individuals respond to food cues in their environment. Further, discrepancies in the patterns of connectivity observed during the processing of food cues compared to patterns

observed at rest may suggest separate mechanisms, which may help to generate new hypotheses or refine existing hypotheses about the etiology of obesity. Additionally, identifying obesity-related differences in functional network organization may reveal novel or previously unsubstantiated biomarkers of obesity. This information could be used in prospective research to identify individuals at risk for weight gain, or in treatment research to identify individuals for which types of obesity treatments may be more or less effective. Finally, examining the influence of sociodemographic variables such as gender on obesity-related variation in functional network organization may provide valuable insight regarding individual differences that could be relevant for tailoring of treatment and prevention efforts. Therefore, the present study represents an important step towards fully characterizing the relationship between functional network organization and obesity to improve health outcomes.

2.0 METHODS

2.1 PARTICIPANTS

Participants were drawn from the neuroimaging arm of a behavioral weight loss intervention study, which is currently ongoing. There were 125 overweight or obese adults aged 18-55 years that completed the baseline assessments. Participants were recruited through newspaper and radio advertisements, and direct mailings. Both the intervention and neuroimaging arms of the study were approved by the University of Pittsburgh Institutional Review Board.

2.2 PROCEDURES

Prior to the start of the study, participants provided informed consent and underwent an MRI safety assessment. This safety assessment consisted of an interview evaluating factors that may contraindicate participation in the MRI scanning portion of the study, including having metallic implants or claustrophobia. Exclusion criteria are as follows: women who are currently pregnant, breastfeeding, or report planning a pregnancy in the next 12 months, history of bariatric surgery, report of current medical condition or treatment for a medical condition that could affect body weight (e.g., diabetes mellitus, hyper- or hypothyroidism, etc.), report of a current cardiovascular condition (e.g., congestive heart failure), myocardial infarction in the previous 12 months, cardiac surgery within the previous 12 months, resting systolic blood pressure $\geq$160mmHg or resting diastolic blood pressure $\geq$90mmHg, eating disorders, alcohol or substance abuse, current

psychological treatment, taking psychotropic medication in the previous 12 months, hospitalization for depression within the previous five years, having metallic implants, report of claustrophobia, or any form of traumatic brain injury or neurological illness. Left-handed individuals or individuals with any form of traumatic brain injury or neurological illness are specifically excluded from the MRI portion of the study. Given these exclusion criteria, it is expected that the sample will be in generally good health apart from being overweight or obese. The baseline and post-intervention assessments are identical, and are separated by a 1-year interval during which the intervention takes place. To date, 125 participants have completed the baseline and post-intervention assessments. However, the intervention assessments have only recently been completed, and researchers are still blinded to which intervention group each participants belongs to.

2.2.1 Intervention

Due to the fact that the intervention has only recently been completed, no intervention-specific analyses were planned for the current project. However, a brief description of the intervention is provided for informational purposes. The intervention was a standard 12-month behavioral weight-control program delivered in a group format. Specifically, groups of 15-20 participants met weekly for one hour for the first 6 months of the intervention, and meet bi-monthly for the remainder of the intervention. Participants were contacted individually by phone for brief check-ins twice per month. The intervention also includer intermittently scheduled behavioral sessions, in which groups of participants were educated on a specific behavioral topic related to weight loss, diet, or exercise. Participants were randomized to one of three intervention groups. The first group was a **diet-only** group; these participants were prescribed a restricted diet that

involves reducing daily calorie intake to 1200-1800 kilocalories (kcal) depending on initial body weight. These individuals were also provided with meal plans and a calorie counter book to facilitate adherence to the diet. The second intervention group was a **moderate exercise** group; these participants received the dietary intervention described above. In addition, they were prescribed a physical activity regimen progressing to 30 minutes 5 days per week. The third intervention group was a **high exercise** group; the prescription for this group was identical to the moderate exercise group with the exception that participants in this group progressed to 50 minutes per day of physical activity.

2.2.2 Assessments

Baseline data analyzed in this project include BMI and fMRI data collected during a resting period and during a visual food cue task. MRI was performed using a Verio 3 Tesla MRI scanner (Siemens, Inc.) at the Scientific Brain Imaging Research Center on the Carnegie Mellon University campus. Resting state scans were obtained prior to the administration of any tasks. For the resting state scan, participants were instructed to lie quietly while viewing a fixation point for five minutes and 28 seconds. Following the completion of the resting state segment of the scan, participants completed a visual food cue stimulation paradigm that has been shown to elicit robust activity in frontostriatal regions across a variety of populations, including obese adults (Beaver, Lawrence. van Ditzhuijzen, Davis, Woods et al., 2006; Stice et al., 2009). Briefly, participants passively viewed alternating 24 second blocks of high calorie food images (e.g., pizza, cake), low calorie food images (e.g., carrots, lettuce), and images of neutral non-food items (e.g., houses, cars), with two second rest periods occurring between each block. Periodically, participants were asked to rate their level of hunger on a Likert scale ranging from 0 (not at all hungry) to 10 (very hungry)

using a finger pad. This was done to ensure that participants were awake and attending to the task. Cardiac and respiratory signals were measured throughout the duration of the scan.

2.2.3 MRI parameters and preprocessing

For the visual food cue task, 204 functional *T*2*-weighted volumes were obtained for each participant using a fast echo-planar imaging (EPI) pulse sequence with BOLD contrasts (time repetition = 2000ms, echo time = 28ms, flip angle = 90°). Thirty-four slices were imaged at 3.2mm thickness in the posterior to anterior direction. For the resting state scan, 210 functional *T*2*-weighted volumes were obtained for each participant using an EPI pulse sequence with BOLD contrasts (time repetition = 1540ms, echo time = 25ms, flip angle = 90°). Thirty slices were imaged at 3.5mm thickness in the posterior to anterior direction. High resolution *T*1-weighted anatomical volumes were also collected in the sagittal plane using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence for each participant (256 slices, voxel dimensions 1x0.976562x0.976562mm).

After reconstruction, task-related and resting state functional data for every participant was preprocessed using FEAT version 5.98, part of FSL (FMRIB's Software Library; http://www.fmrib.ox.ac.uk/fsl/). Images were slice-time corrected to account for variation in the timing of slice acquisition. Motion correction was conducted using MCFLIRT (Jenkinson. Bannister, Brady, & Smith, 2002), with the middle image in the scanning sequence designated as the reference. A threshold of 1.7mm (half the size of a single voxel) displacement in any direction was used to identify spikes or excessive movement. Functional volumes from the visual food cue task were temporally filtered with a Gaussian high-pass cutoff of 100 seconds to reduce low frequency noise due to scanner drift (i.e., drift in the strength of the magnetic field). Conversely, a

bandpass temporal filter between 0.001 and 0.01 Hz was applied to resting state volumes to remove high frequency noise attributable to physiological processes (e.g., respiration) and low frequency noise due to scanner drift. Images from both functional scans were spatially smoothed with a 5-mm full-width half-maximum 3-dimensional Gaussian kernel. Non-brain matter (i.e., skull) was removed using the robust brain extraction technique (BET; Smith, 2002). An EPI image representing mean BOLD signal across the time series was constructed for each participant. These mean functional images were then registered to the corresponding *T*1-weighted images using a 7-parameter affine function, after which *T*1-weighted images were registered to standard MNI space (Montreal Neurological Institute – International Consortium for Brain Mapping) using a 12-parameter transformation. Registration to high resolution structural and standard space images was carried out using FMRIB's linear image registration tool (FLIRT; Jenkinson & Smith, 2001; Jenkinson et al., 2002). Registration quality was assessed visually, and no errors were observed.

2.3 ANALYTIC APPROACH

2.3.1 Analysis of task-related regional activation and functional connectivity

Subject and group level analyses of neuroimaging data were conducted using general linear models in FSL (FMRIB, Oxford, UK). Time series data from the visual food cue task were convolved using a gamma function to model the shape and latency of the hemodynamic response. A GLM using multiple regression was created to examine signal change during each block (i.e., neutral non-food images, high calorie food images, and low calorie food images). Contrast parameters were created to compare BOLD signals during high and low calorie conditions relative

to neutral conditions and relative to one another. Parameters were entered into an ANOVA model for each participant using FSL FEAT. To further minimize the influence of excess motion, individuals who exhibited motion displacement exceeding 1mm in any direction were identified, and the motion parameters for the directions of excess motion were included as nuisance covariates of no interest in those individual models. A total of 32 participants exhibited motion exceeding the defined threshold in at least 1 direction, thus requiring additional motion correction for all first-level analyses of visual food cue data.

Results from these individual-level comparisons were then forwarded to higher-level mixed-effects group analyses using FSL FEAT to identify regions where BOLD signal significantly changed during each of the conditions and for each contrast modeled at the first-level. To assess the effect of BMI, age, and gender on BOLD signal variation during the task, group-level models included contrasts for these variables, with the BMI contrast being of primary interest. Frame-to-frame head motion during the task was estimated by calculating mean frame-wise displacement (FD) across volumes for each individual, and these values were also included as a covariate of no-interest to further correct for excess head motion. The statistical parametric maps generated for each contrast were thresholded using a voxelwise threshold of $p < 0.01$ and a cluster extent threshold of 25 contiguous voxels. Although this threshold is less stringent than would typically be applied for such an analysis, this relaxed threshold was adopted because regional activation patterns were not the primary focus of the study and were used only to identify seeds for the primary connectivity analyses, as well as to ensure adequate power to identify potential seeds. Regions meeting this threshold that have also previously been linked to processes known to be disrupted in obesity were selected for further analysis.

Functional connectivity during the visual food cue task was assessed using a psychophysiological interaction (PPI) approach. A PPI analysis quantifies BOLD signal covariation between a seed region and all voxels across the brain, and determines the degree to which seed-to-voxel covariation is modulated by contextual factors like task condition (Friston, Buechel, Fink, Morris, Rolls, et al., 1997). The PPI approach to quantifying task-related functional connectivity has been shown to yield connectivity patterns that are consistent across studies employing similar task, and patterns that are specific to a given seed (Smith, Gseir, Speer, & Delgado, 2016; Smith & Delgado, 2016). Further, although the PPI method cannot be used to make directional claims regarding which region generated the correlated signal in a pair of regions, results obtained from PPI have been shown to overlap with causal modeling techniques that do assess effective (directional) connectivity (Passamonti, Rowe, Ewbank, Hampshire, Keane et al., 2008). Therefore, notwithstanding statistical and interpretive issues inherent to all functional connectivity analytic techniques, PPI is an easily implemented and fairly reliable approach.

PPI seed regions were chosen based on regional activation patterns observed during the task according to the following criteria: 1) a given region exhibited differential activation in response to food images (high or low calorie) relative to neutral, non-food images, 2) regional change in activation in response to food images significantly correlated with BMI, 3) the change in activation met the statistical threshold described above, and 4) a given region had been previously linked with obesity or to processes known to be disrupted in obesity. Preference was given to prefrontal and subcortical regions involved in self-regulation and/or valuation. Seed masks were created for regions meeting these criteria by placing a 10mm sphere around detected maxima coordinates. An inverse transformation then placed these seed masks into native space for each individual, after which the BOLD signal time series from each seed mask was extracted for

each individual. The seed region time series was then entered into a general linear model along with a psychological variable representing the task contrast of interest and a psychophysiological interaction term representing the interaction between the seed region time series and the task contrast. In this case, the contrast of interest was BOLD responses to high calorie food images vs. BOLD responses during the baseline fixation, as this contrast was likely to yield the greatest differences in connectivity. The general linear model including these three terms was then fitted to voxels in a whole-brain analysis, generating correlation maps for each individual participant. The beta values for the psychophysiological interaction term represented the degree to which task-evoked variation in the BOLD signal within a given voxel corresponds to task-evoked variation in the seed region, providing an indication of whether activity in a given voxel and activity in the seed region are similarly modulated during the processing of food cues.

The beta values derived from these individual-level analyses were then forwarded to higher level general linear models to examine whether BMI was associated with variation in seed-to-voxel correlations during the presentation of high calorie food images relative to baseline fixation. To assess the effect of BMI, age, and gender on BOLD signal variation during the task, group-level models included contrasts for these variables, with the BMI contrast being of primary interest. FD values were also included as a covariate of no interest. The statistical parametric maps generated for each contrast were thresholded using the default cluster threshold in FSL. This is a cluster-based thresholding tool that relies Gaussian Random Field Theory to set a cluster extent threshold. The default thresholding carried out by FSL sets a voxelwise threshold of $p < 0.01$, and cluster-defining FWE threshold of $p < 0.05$ (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012).

2.3.2 Resting state analyses

A seed-based approach was used to assess resting state functional connectivity, with the same seeds used in the task-evoked connectivity analysis being designated as the seeds for the resting state analysis. This permitted comparison of seed-to-voxel connectivity during the presentation of food cues with task-independent seed-to-voxel connectivity to determine if there is any evidence of overlap in functional network organization across these two conditions. Results derived from resting state connectivity analyses are highly susceptible to the influence of non-neural sources of BOLD signal variation, including head motion and motion induced by cardiac and respiratory cycles (Murphy, Birn, & Bandettini, 2013), necessitating more careful pre-processing of resting state data. If not properly accounted for in resting state analyses, these sources of noise can be misinterpreted as neural effects on BOLD signal and may therefore yield spurious correlations that would not otherwise be evident. Indeed, head motion has been shown to systematically alter functional connectivity between regions in well-established resting state networks (Van Dijk, Sabuncu, & Buckner, 2012). Cardiac and respiratory variation have also been shown to correlate with BOLD signal variation, presumably due to the effects of these physiological processes on cerebral blood pressure, flow, and volume (Murphy et al., 2013). It is particularly important to consider the effect of these processes when studying conditions like obesity, given that obesity is known to induce vascular changes (e.g., Wildman, Mackey, Bostom, Thompson, & Sutton-Tyrrell, 2003) that may impact the BOLD signal independently of neuronal changes.

To reduce the influence of physiological confounds on estimates of connectivity, functional volumes were segmented in grey matter, white matter, and cerebrospinal fluid (CSF). Using the 9-parameter de-noising model described by Ciric, Wolf, Power, Roalf, Baum et al., (2017),

physiological noise as represented by the first two principal components of estimate noise from white matter and CSF voxels were then regressed out of the total whole-brain time series. The global signal and estimates of motion displacement (in mm) for 6 directions of motion (x, y, z, pitch, roll, yaw) were also regressed out of the whole-brain time series. Seed masks were then converted to native space for each individual, after which the BOLD signal time series for the selected seed region was extracted from each individual's preprocessed data. The mean time course was entered into a GLM using multiple regression to model BOLD signal covariation between the seed region and all voxels across the brain. A contrast parameter was created to examine which voxels positively and negatively covaried with the seed region time series. To further minimize the influence of excess motion, the motion displacement variables for 6 directions of motion were also included as covariates in all first-level general linear models. The beta values derived from these individual-level analyses were then forwarded to higher level general linear models to examine whether BMI was associated with variation in seed-to-voxel correlations at rest. Group-level models included contrasts for BMI, age, and gender, with the BMI contrast being of primary interest. FD values were also included as a covariate of no interest. The statistical parametric maps generated for each contrast were thresholded using a voxelwise threshold of $p < 0.01$, and cluster-defining FWE threshold of $p < 0.05$.

2.3.3 Exploratory analyses

To aid in the interpretation of any observed correlations between BMI and metrics of functional connectivity, additional analyses were conducted to examine whether seed-to-ROI connectivity was associated with variation in reward related decision making as indexed using the Iowa Gambling Task (IGT). The IGT is a widely used measure of monetary decision making in

conditions of reward, punishment, and uncertainty that quantifies the degree to which individuals are able to learn which decision making strategy will lead to the highest earnings, as well as the extent to which an individual will make disadvantageous selections when presented with a probabilistically unlikely opportunity to win a large sum of money (Bechara, Damasio, Tranel, & Damasio, 2005). Impaired performance on the IGT has been associated with a number of conditions characterized by cognitive and behavioral dysfunction, including obesity (Brogan, Hevey, & Pignatti, 2010), as well as functional differences in regions of the brain involved in decision making and inhibitory control (e.g., dlPFC), as well as reward valuation (vmPFC; Li, Lu, D'Argembeau, Ng, & Bechara, 2010). Briefly, participants were presented with four decks of 40 cards each labeled A, B, C, and D. Each card within the decks is associated with either a win or a loss of a specified monetary value. Decks A and B are considered disadvantageous because they yield high gains but also yield high losses, as well as a net negative score. Conversely, decks C and D are considered advantageous because they yield smaller gains but relatively small losses, as well as a net positive score.

Participants were instructed to select 100 cards one at a time from whichever decks they wished, with the goal of maximizing the amount of money won at the end of the task. Card selections were divided into five blocks to permit evaluation of decision making trajectories over the course of the task. Several metrics were derived based on participants' selections. First, a net payoff score was calculated by subtracting the total number of cards selected from the disadvantageous decks from the total number of cards selected from the advantageous decks ((C + D) – (A + B)). Higher payoff scores are indicative of a greater proportion of selections being made from advantageous decks. Net payoff scores were also calculated for each of the five blocks. Second, a difference score was calculated by subtracting the net payoff score in block one from

the net payoff score in block five to quantify change in decision making over the task. Higher difference scores are suggestive of a positive learning curve, such that an individual used performance feedback on early trials to inform the adoption of a more successful decision making strategy in later trials. Third, a bias for infrequent losses score was calculated by subtracting the total number of cards selected from decks characterized by frequent but small losses from the total number of cards selected from decks characterized by infrequent but large losses ((A + C) – (B + D)). This value serves as an index of punishment avoidance despite negative consequences, with higher scores being indicative of a bias for infrequent losses.

To assess the relationship between IGT performance and estimates of functional connectivity, ROIs were first identified based on which clusters exhibited significant BMI-dependent signal covariation with the seed region during the task and at rest, and selected for further analysis. For each participant, covariation between the time series of each identified ROI and the time series of the seed region were estimated using pairwise correlation coefficients, which were then normalized using a Fisher *r*-to-*z* transformation. The FSL featquery function was used to extract the mean parameter estimates for the identified ROIs. For each ROI demonstrating significant variation in task-evoked or resting connectivity with a given seed as a function of BMI, six independent multiple linear regression analyses were conducted using model 4 of the PROCESS macro (Hayes, 2012) for SPSS version 24.0 (IBM Corp., Armonk, NY) to examine whether the relationship between BMI and performance on the IGT was mediated by task-evoked or resting state functional connectivity. Mean correlation coefficient was entered as the mediating variable in three of these analyses, while mean change in z-transformed correlation values was entered as the mediating variable in the remaining analyses. Connectivity values were inspected for outliers, and all extreme values were removed prior to conducting analyses.

2.3.4 Socio-demographic covariates

To specifically assess the effect of gender on task-related connectivity and resting state connectivity, gender was included as a main effect in multiple linear regression models in SPSS for each ROI identified as described above. A gender x BMI interaction term was also included in these models to determine if gender moderates the relationship between BMI and task-evoked or resting state functional connectivity. In addition to gender, there is also evidence that age is associated with impairments in self-regulation (Steinberg, Albert, Cauffman, Banich, Graham et al., 2008), reward valuation and decision making (Eppinger, Hämmerer, & Li, 2011; Marschner, Mell, Wartenburger, Villringer, Reischies et al., 2005), obesity (Ogden et al., 2014), and frontostriatal function (Dreher, Meyer-Lindenberg, Kohn, & Berman, 2008; Jacobson, Green, & Murphy, 2010). Therefore, age was included as a covariate in all models. Connectivity values were inspected for outliers, and all extreme values were removed prior to conducting analyses.

3.0 RESULTS

3.1 PARTICIPANT CHARACTERISTICS

Of the 125 individuals who completed baseline assessments, 3 did not complete the visual food cue task. Therefore, the final sample included 122 middle-aged individuals (M_{age} = 44.43, *SD* = 8.67; 78.7% female) with BMI in the overweight or obese range (M_{BMI} = 32.41, *SD* = 3.95, range = 25.10 – 40.29). The sample was predominantly Caucasian (74.6%) and non-Hispanic (97.5%). BMI was not significantly associated with race (β = -0.03, p = 0.73), ethnicity (β = -0.02, p = 0.87), gender (β = 0.03, p = 0.76), age (β = -0.119, p = 0.73), hunger during the task (β = -0.359, p = 0.09), likelihood of having fMRI data corrected for excess motion (*OR* = 0.334, p = 0.52), IGT net payoff score (β = -0.028, p = 0.76), or bias for infrequent losses (β = 0.062, p = 0.50). BMI was marginally associated with change in net payoff score from block one to block five (β = -0.159, p = 0.08), with lower BMI predicting greater improvements in decision making over the course of the task. Table 1 includes additional demographic and IGT performance information.

Table 1. Demographic characteristics of sample

	Mean *(SD)*
Age	44.43 (8.67)
BMI	32.42 (3.95)
Hunger	3.54 (0.66)
IGT net payoff score	49.97 (9.52)
IGT difference score	4.42 (19.55)
IGT infrequent loss bias score	-31.16 (29.67)
	n (%)
Gender (female)	96 (78.7)
Race	
Caucasian	91 (74.5)
African American	26 (21.3)
Asian	5 (4.1)
Native American	1 (0.8)
Other	1 (0.8)
Ethnicity (Hispanic)	3 (2.5)

3.2 SEED SELECTION: REGIONAL ACTIVATION DURING THE VISUAL FOOD CUE TASK

Several brain regions met cluster thresholding ($z > 2.3$, $p < 0.05$) in the group level analysis of regional activation during the visual food cue task. Further, there were a few regions that exhibited differences in activity that were correlated with BMI using the thresholding criteria described above. Specifically, BMI was inversely associated with activation in regions located in the left OFC, right OFC, left dmPFC, right vmPFC, and left vlPFC during the presentation of food compared to neutral images (Table 2).

Table 2. MNI coordinates of local maxima in regions associated with BMI in the food > neutral contrast

	Maximum Z-score	X	y	z
Left orbitofrontal cortex	3.6	-36	24	-14
Right orbitofrontal cortex	3.5	18	20	-18
Left dorsomedial prefrontal cortex	3.47	-16	58	22
Right ventromedial prefrontal cortex	2.52	10	58	-16
Left ventrolateral prefrontal cortex	3.37	-44	44	-12

Note. Regions met a voxel-wise threshold of $z > 2.3$ and cluster extent threshold of 25 contiguous voxels.

There were no regions positively associated with BMI located within the circuitry of interest for this contrast, except for a region in left occipital cortex. For the high calorie food > low calorie food contrast, BMI was positively associated with activation in regions located in the left OFC, right OFC, and right pallidum (Table 3). The OFC regions for this contrast were not located in the same area of OFC as those regions that were identified in the food > neutral contrast. The left OFC region in high calorie food > low calorie food contrast was more medial than the region identified in the food > neutral contrast, whereas the right OFC seed for the high calorie food > low calorie food contrast was more lateral than the region identified in the food > neutral contrast. BMI was negatively associated with activation in a region of the left hippocampus during the presentation of high calorie compared to low calorie food (Table 3). A significant association between BMI and activation during this contrast was also observed near the right MFG, but the area of activation largely overlapped with white matter voxels and was therefore not included as a seed region for connectivity analyses.

Table 3. MNI coordinates of local maxima in regions associated with BMI in the high calorie food > low calorie food contrast

	Maximum Z-score	x	y	z
Left orbitofrontal cortex	3.35	-30	20	-16
Right orbitofrontal cortex	2.64	24	26	-12
Right pallidum	3.28	12	0	-6
Left hippocampus	2.99	-32	-14	-20

Note. Regions met a voxel-wise threshold of $z > 2.3$ and cluster extent threshold of 25 contiguous voxels.

3.3 AIM 1: BMI-RELATED VARIATION IN FUNCTIONAL CONNECTIVITY EVOKED BY HIGH CALORIE FOOD

It was hypothesized that, during the presentation of high calorie food cues, higher BMI would be associated with reduced connectivity between selected subcortical seed regions and lateral regions of PFC, but with increased connectivity between regions involved in motor planning and execution (e.g., premotor cortex, inferior parietal cortex, cerebellum) and those involved in reward valuation (e.g., amygdala, vmPFC, OFC). Overall, these hypotheses were supported. Specifically, BMI was associated with stronger task-evoked functional connectivity between regions involved in reward valuation. However, only one region exhibited BMI-related variation in functional connectivity with lateral PFC during the task, and the association was in the opposite direction of what had been hypothesized.

3.3.1 Left lateral OFC (MNI coordinates -36, 24, -14)

Several regions exhibited significant BMI-dependent differences in functional connectivity with the left OFC seed during the processing of high calorie food (Figure 1). Consistent with the

hypothesized functional relationship between regions such as the OFC known to be involved in reward valuation, BMI was associated with stronger left lateral OFC functional connectivity with other regions involved in sensory processing, memory formation and recall, reward valuation, and self-directed thinking during the presentation of high calorie food cues compared to baseline fixation. Specifically, BMI was positively correlated with functional connectivity between the left lateral OFC seed, and regions involved in located in the left MFG, right hippocampus, right thalamus, medial PCC, and medial precuneus (Figure 1, Table 4).

Table 4. MNI coordinates (in mm) of local maxima in regions showing BMI-related increases in functional connectivity with the left lateral OFC seed

	Maximum Z-score	x	y	z
Left middle frontal gyrus	3.15	-40	12	28
Right hippocampus	3.32	24	-18	-22
Right thalamus	3.66	18	-26	4
Posterior cingulate cortex	3.26	-4	-36	32
Precuneus	3.49	0	-54	12
Right medial temporal gyrus	2.79	60	-20	-10

To determine whether the patterns of BMI-dependent differences in left lateral OFC functional connectivity were specific to processing of high calorie food or representative of BMI related variation in object processing more generally, these results were compared to patterns of connectivity during the presentation of neutral non-food objects. The relationship between BMI and connectivity with the left lateral OFC was significantly stronger in the presence of food cues for the right hippocampus (F (2, 120) = 5.349, p = 0.02), medial PCC (F (2, 120) = 9.375, p = < 0.01), and right thalamus (F (2, 120) = 11.449, p = < 0.01), but only marginally so for the medial precuneus (F (2, 120) = 2.961, p = 0.09) and left MFG (F (2, 120) = 1.952, p = 0.16). BMI-related increases in left lateral OFC functional connectivity were lateralized to the right hemisphere for

the hippocampus (F (2, 120) = 4.587, p = 0.03) and thalamus (F (2, 120) = 3.919, p = 0.05). No other regions exhibited significant hemispheric differences in the strength of the relationship between BMI and left lateral OFC connectivity. Finally, when examining BOLD signal covariation with the left lateral OFC seed during the presentation of neutral non-food objects compared to baseline fixation, no regions met cluster thresholding, suggesting that the effect of BMI on left OFC functional connectivity during the task was specific to the presentation of high calorie food.

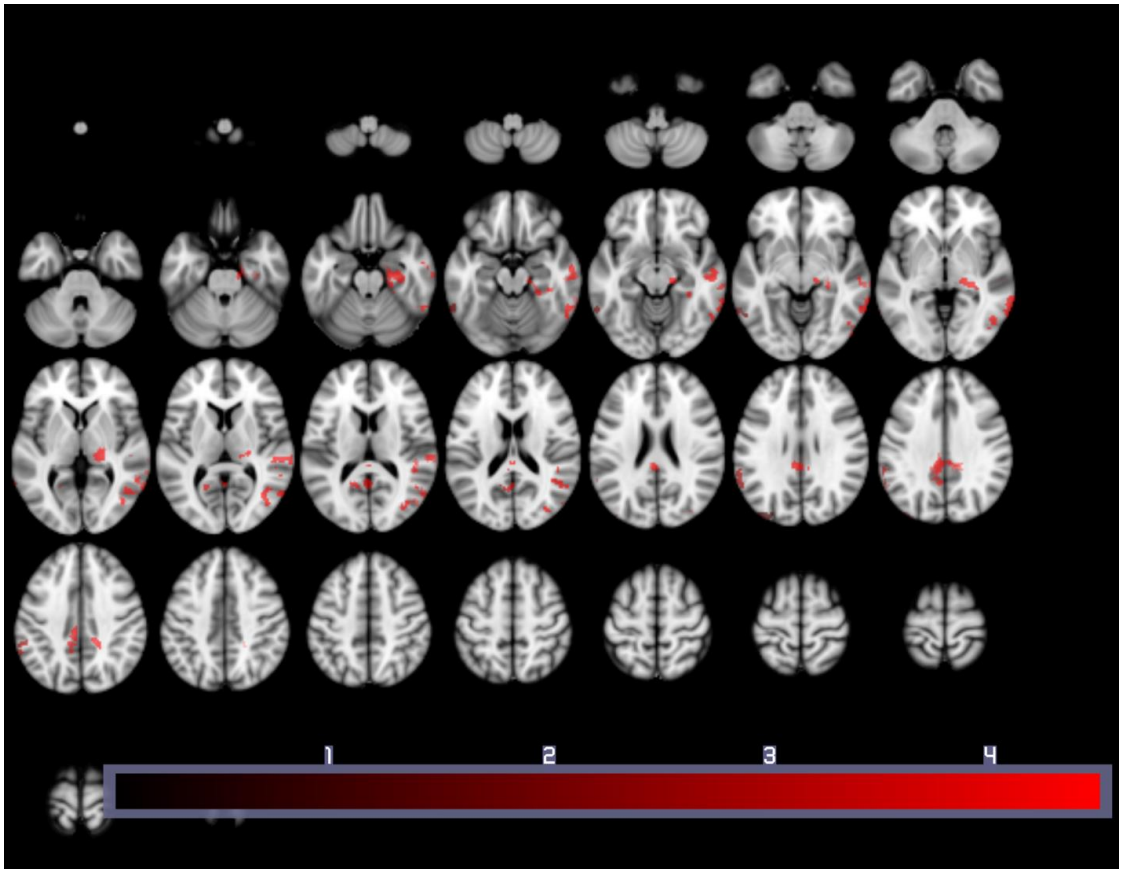

Figure 1. Regions in which BOLD signal covariation with the left lateral OFC seed (MNI coordinates -36, 24, -14) during the presentation of high calorie food was positively associated with BMI.

3.3.2 Right medial OFC (MNI coordinates 18, 20, -18)

Several regions exhibited significant BMI-dependent variation in functional connectivity with the right medial OFC seed during the processing of high calorie food cues. Similar to the patterns of connectivity observed in the left lateral OFC and consistent with study hypotheses, regional connectivity with the right medial OFC was positively correlated with BMI during the presentation of high calorie food relative to baseline fixation (Figure 2, Table 5). For instance, BMI was associated with stronger connectivity between the right medial OFC and right hippocampus and right MTG, two regions known to be involved in object processing, self-referential processing, and memory processes. As was the case with the left lateral OFC seed, BMI was positively correlated with connectivity of the right medial OFC.

Table 5. MNI coordinates of local maxima in regions showing BMI-related increases in functional connectivity with the right medial OFC seed

	Maximum Z-score	x	y	z
Right medial temporal gyrus	4.45	62	-16	-16
Right hippocampus	3.15	28	-22	-14

When comparing the strength of right medial OFC connectivity during the presentation of high calorie food to connectivity during the presentation of neutral non-food objects, the relationship between BMI and connectivity with the right medial OFC was significantly stronger in the presence of food cues for the right hippocampus (F (2, 120) = 6.706, p = 0.02) and right MTG (F (2, 120) = 7.886, p = < 0.01). BMI-related increases in right OFC functional connectivity were lateralized to the right hemisphere for both the hippocampus (F (2, 120) = 9.103, p = < 0.01) and MTG (F (2, 120) = 7.838, p = < 0.01). Finally, when examining BOLD signal covariation with

the right OFC seed during the presentation of neutral non-food objects compared to baseline fixation, BMI was found to be positively correlated with connectivity to a cluster located in the cerebellum. Nevertheless, the effect of BMI on right OFC functional connectivity to the hippocampus and MTG during the task was specific to the presentation of high calorie food.

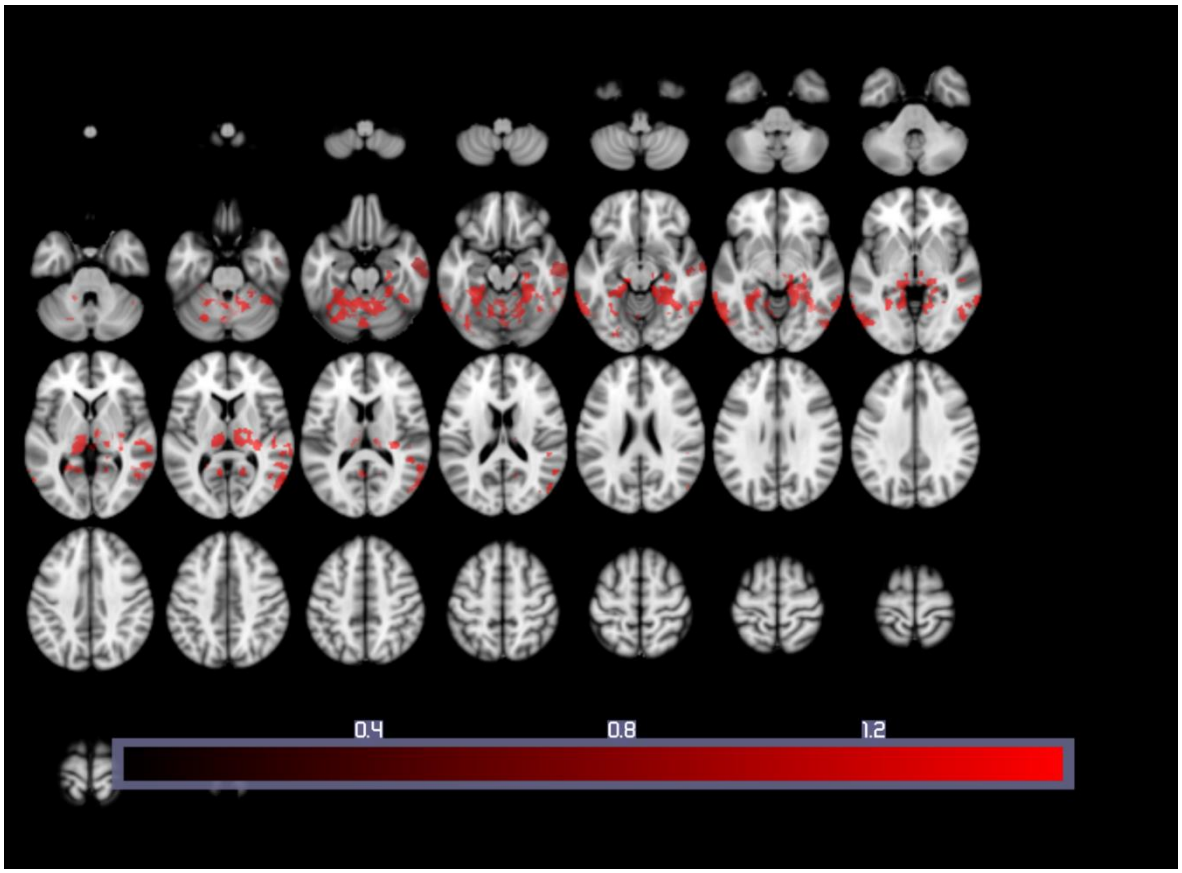

Figure 2. Regions in which BOLD signal covariation with the right medial OFC seed (MNI coordinates 18, 20, -18) during the presentation of high calorie food was positively associated with BMI.

3.3.3 Left dorsomedial PFC (MNI coordinates -16, 58, 22)

Several regions exhibited significant BMI-dependent variation in functional connectivity with the left dmPFC seed. As was the case with both OFC seeds, regional connectivity with the

left dmPFC was positively correlated with BMI during the presentation of high calorie food relative to fixation baseline (Figure 3, Table 6). The regions exhibiting stronger functional coupling with the left dmPFC seed were largely located within the basal ganglia, a collection of midbrain regions involved in the organization of behavior to support reward and goal attainment. Specifically, BMI was associated with stronger connectivity between the left dmPFC and left caudate, bilateral putamen, and right pallidum. BMI was also associated with stronger left dmPFC connectivity to the medial subcallosal cortex (Figure 3, Table 6).

Table 6. MNI coordinates of local maxima in regions showing BMI-related increases in functional connectivity with the left dorsomedial PFC seed

	Maximum Z-score	x	y	Z
Left caudate	3.30	-12	-2	18
Left hippocampus	3.36	-30	-12	20
Left putamen	3.15	-28	0	0
Right putamen	3.31	18	10	-2
Right pallidum	4.22	-18	2	0
Medial subcallosal cortex	3.44	-2	12	-10

When comparing the strength of left dmPFC connectivity during the presentation of high calorie food to connectivity during the presentation of neutral non-food objects, the relationship between BMI and connectivity with the left dmPFC was significantly stronger in the presence of food cues for the right putamen (F (2, 120) = 8.385, p = < 0.01) and medial subcallosal cortex (F (2, 120) = 6.955, p = < 0.01), but only marginally so for the left caudate (F (2, 120) = 2.846, p = 0.10), left putamen (F (2, 120) = 2.3381, p = 0.13), and right pallidum (F (2, 120) = 3.477, p = 0.07). BMI-related increases in left dmPFC functional connectivity were lateralized to the right hemisphere for the pallidum (F (2, 120) = 5.452, p = 0.02). No others regions exhibited significant hemispheric differences in the strength of the relationship between BMI and left dmPFC

connectivity. These results suggest that the effect of BMI on left dmPFC functional connectivity to regions involved in reward valuation and emotion processing during the task was specific to the presentation of high calorie food.

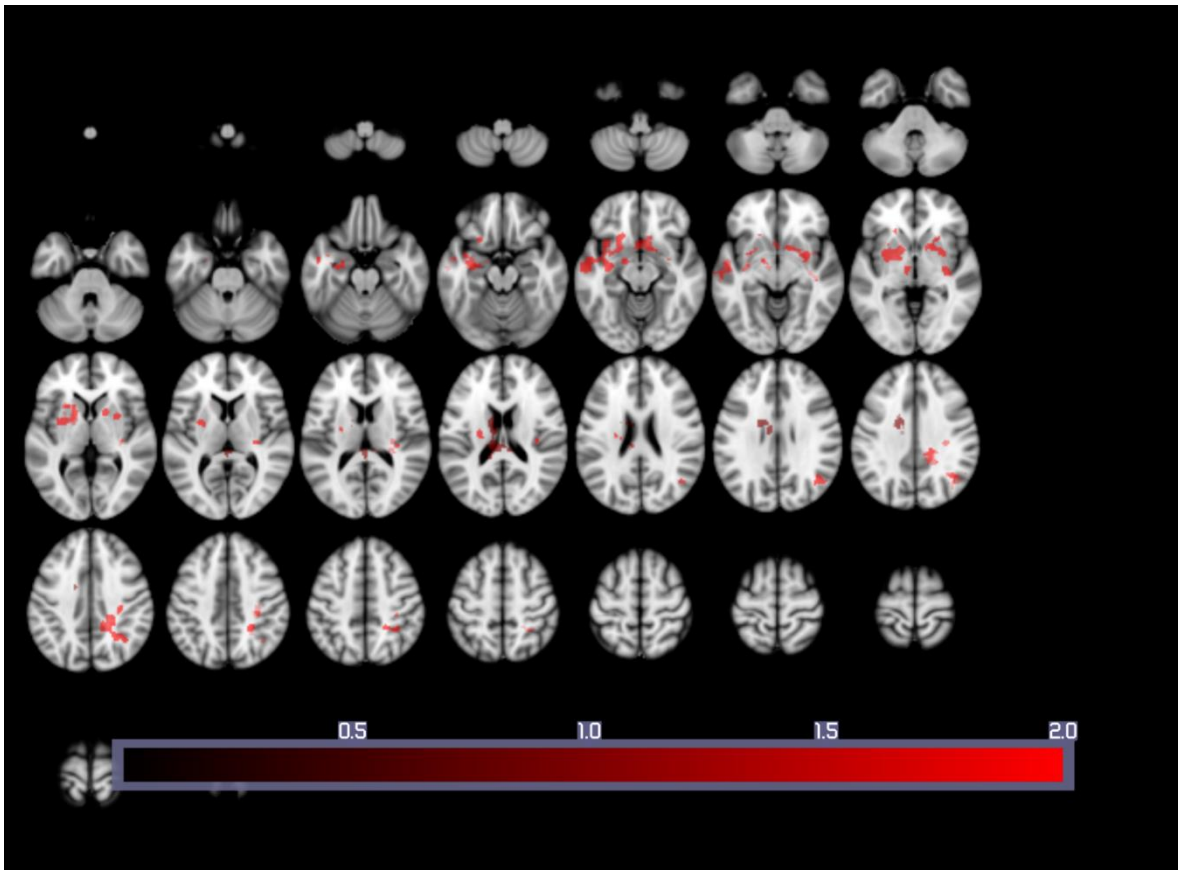

Figure 3. Regions in which BOLD signal covariation with the left dorsomedial PFC seed (MNI coordinates -16, 58, 22) during the presentation of high calorie food was positively associated with BMI.

3.3.4 Right ventromedial PFC (MNI coordinates 10, 58, -16)

Two clusters exhibited significant BMI-dependent differences in functional connectivity with the right vmPFC seed during the presentation of high calorie food. Consistent with the expected effect of BMI on regional signal covariation with vmPFC, functional connectivity with

right vmPFC was positively correlated with BMI during the presentation of high calorie food relative to baseline fixation. Specifically, BMI was associated with stronger connectivity between the right vmPFC and right superior temporal gyrus and left vmPFC. Contrary to study hypotheses, seed-to-ROI connectivity strength between did not differ significantly during the presentation of high calorie food cues compared to neutral non-food objects. Indeed, the correlations between BMI and right vmPFC connectivity during the processing of neutral non-food objects was negative for both the left vmPFC seed (%signal change: r = -0.185, p = 0.04; z-score: r = -0.091, p = 0.32), and right superior temporal gyrus (%signal change: r = -0.105, p = 0.25; z-score: r = -0.149, p = 0.10). Moreover, BMI was associated with decreased connectivity between the right vmPFC and several clusters across the brain during the presentation of neutral non-food objects compared to baseline fixation. These regions included the PCC, superior temporal gyrus, MTG, insula, and MFG. Based on these observations, it is likely that that the effect of BMI on right vmPFC connectivity is related to object processing more generally rather than being specific to disease relevant stimuli.

3.3.5 Left ventrolateral PFC (MNI coordinates -44, 44, -12)

It was predicted that regions of lateral PFC would show *weaker* connectivity with areas of the brain involved in reward valuation and reward guided behavioral planning and execution, a pattern which was not observed in the present study. In contrast to the predicted relationship between BMI and lateral PFC connectivity during the presentation of high calorie food, BMI was positively correlated with functional connectivity between the left vlPFC and a cluster of voxels in the right MTG. Moreover, the effect of BMI left vlPFC connectivity to the right MTG was significantly stronger during the presentation of high calorie food compared to the presentation of neutral non-food objects (F (2, 119) = 14.448, p = < 0.01). This was partially driven by a small-

to-moderate negative correlation between BMI and connectivity values during the presentation of neutral non-food objects (%signal change: r = -0.178, p = 0.05; z-score: r = -258, p = <0.01) coupled with a positive correlation during the presentation of high calorie food. The relationship between BMI and left vlPFC – right MTG connectivity did not differ significantly by hemisphere (F (2, 119) = 2.595, p = 0.11).

3.3.6 Left medial OFC (MNI coordinates -30, 10, -16)

Several regions exhibited significant BMI-dependent differences in functional connectivity with the left medial OFC seed (Table 7). Consistent with the hypothesized relationship between BMI and left medial OFC connectivity during the task, functional connectivity of this seed was shown to be stronger with increasing BMI during the presentation of high calorie food cues. Specifically, BMI was positively correlated with functional connectivity between the left medial OFC seed and a region located in the right postcentral gyrus, right medial temporal gyrus, and left supramarginal gyrus. The relationship between BMI and left medial OFC – right postcentral gyrus connectivity was significantly stronger during the presentation of high calorie food than it was during the presentation of neutral non-food objects (F (3, 119) = 8.353, p = < 0.01), and was lateralized to the right hemisphere (F (3, 119) = 7.211, p = < 0.01).

Table 7. MNI coordinates of local maxima in regions showing BMI-related increases in functional connectivity with the left medial OFC seed

	Maximum Z-score	x	y	z
Right medial temporal gyrus	2.34	60	-20	-10
Right postcentral gyrus	3.20	60	-14	34
Left supramarginal gyrus	3.51	-62	-38	34

3.3.7 Left hippocampus (MNI coordinates -32, -14, -20)

Several regions exhibited significant BMI-dependent differences in functional connectivity with the left hippocampus seed. Similar to the patterns of connectivity observed in other seeds, regional connectivity with the left hippocampus was positively correlated with BMI during the presentation of high calorie food relative to baseline fixation (Figure 4, Table 8).

Table 8. MNI coordinates of local maxima in regions showing BMI-related increases in functional connectivity with the left hippocampus seed

	Maximum Z-score	x	y	z
Left dorsomedial prefrontal cortex	4.19	-4	66	16
Right inferior temporal gyrus	3.74	62	-42	-16
Left dorsolateral prefrontal cortex	3.30	-38	50	12

Specifically, BMI was associated with stronger connectivity between the left hippocampus and left dmPFC, right inferior temporal gyrus, and left dlPFC. When comparing the strength of left hippocampus connectivity during the presentation of high calorie food to connectivity during the presentation of neutral non-food objects, the relationship between BMI and connectivity with the left hippocampus was significantly stronger in the presence of food cues for the left dmPFC (F (2, 120) = 4.314, p = 0.04) and right inferior temporal gyrus (F (2, 120) = 21.263, p = < 0.01). However, this was not the case for the effect of BMI on left hippocampal connectivity to the left dlPFC (F (2, 120) = 1.897, p = 0.17), suggesting that this effect was not specific to processing of food cues. BMI-dependent differences in connectivity between the left hippocampus and right inferior temporal gyrus was significantly lateralized to the right hemisphere (F (2, 120) = 7.434, p = < 0.01). There was no evidence of hemispheric laterality in the relationship between BMI and functional connectivity with the other seeds.

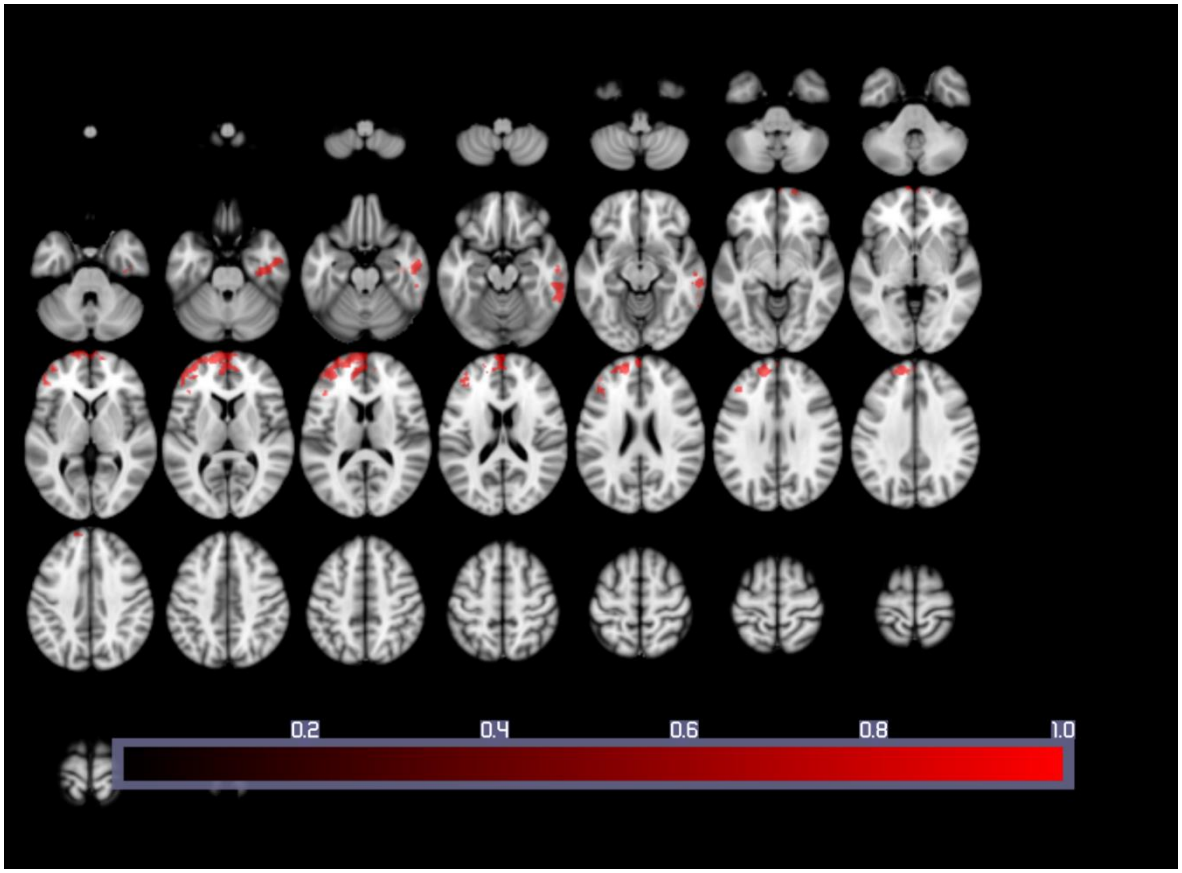

Figure 4. Regions in which BOLD signal covariation with the left hippocampus seed (MNI coordinates -32, -14, -20) during the presentation of high calorie food was positively associated with BMI

3.3.8 Right lateral OFC (MNI coordinates 26, 26, -18)

Although activation in the right lateral OFC seed during the processing of food cues was associated with BMI, no regions exhibited BMI-dependent differences in task-evoked functional connectivity with the right lateral OFC at the cluster threshold of $z > 2.3$ and $p < 0.05$. Therefore, no further analyses were performed using this seed.

3.3.9 Right pallidum (MNI coordinates 12, 0, -6)

Contrary to the hypothesized effect of BMI on functional connectivity in the basal ganglia, no regions exhibited BMI-dependent differences in task-evoked connectivity with the right pallidum at the cluster threshold of $z > 2.3$ and $p < 0.05$. Therefore, no further analyses were performed using this seed.

3.4 AIM 2: BMI-DEPENDENT VARIATION IN RESTING STATE FUNCTIONAL CONNECTIVITY

Similar to the hypotheses regarding the relationship between BMI and task-evoked connectivity, it was hypothesized that higher BMI would be associated with reduced resting state connectivity between selected subcortical seed regions and lateral regions of PFC, but with increased connectivity between regions involved in motor planning and execution, and those involved in reward valuation. Additionally, it was predicted that BMI would be associated with decreased resting connectivity between the seed region and regions of DMN (e.g., PCC). While the former hypothesis was not supported, the latter hypothesis was. Across each seed selected for analysis, BMI was associated with weaker seed-to-ROI connectivity.

3.4.1 Left lateral OFC (MNI coordinates -36, -24, -14)

To further examine whether BMI-related variation in functional connectivity in the left lateral OFC was context specific (i.e., only evident in the presence of high calorie food cues), or represented a more fundamental change in functional network architecture (i.e., also observable at rest), the relationship between BMI and connectivity of the left lateral OFC seed at rest was also examined. It was hypothesized that the relationship between BMI and resting state functional connectivity would be similar to patterns observed during the presentation of food cues. However, in contrast to the patterns of connectivity observed during the task, BMI was associated with *weaker* connectivity between the left lateral OFC and regions involved in sensory processing, reward valuation, and conflict monitoring, including the left thalamus, right vmPFC, right NAc, and the medial ACC (Figure 5, Table 9). BMI-related decreases in left OFC functional connectivity were lateralized to the right hemisphere for the NAc (F (2, 120) = 4.186, p = 0.04) and left hemisphere for the thalamus (F (2, 120) = 6.418, p = 0.01). There was no evidence of hemispheric laterality for the ROI located in the vmPFC (F (2, 120) = 0.006, p = 0.94).

Table 9. MNI coordinates of local maxima in regions showing BMI-related decreases in resting functional connectivity with the left lateral OFC seed

	Maximum Z-score	x	y	z
Left thalamus	3.64	-10	-10	14
Right ventromedial prefrontal cortex	3.91	32	56	4
Right nucleus accumbens	3.21	14	18	-8
Medial anterior cingulate cortex	3.16	0	34	22

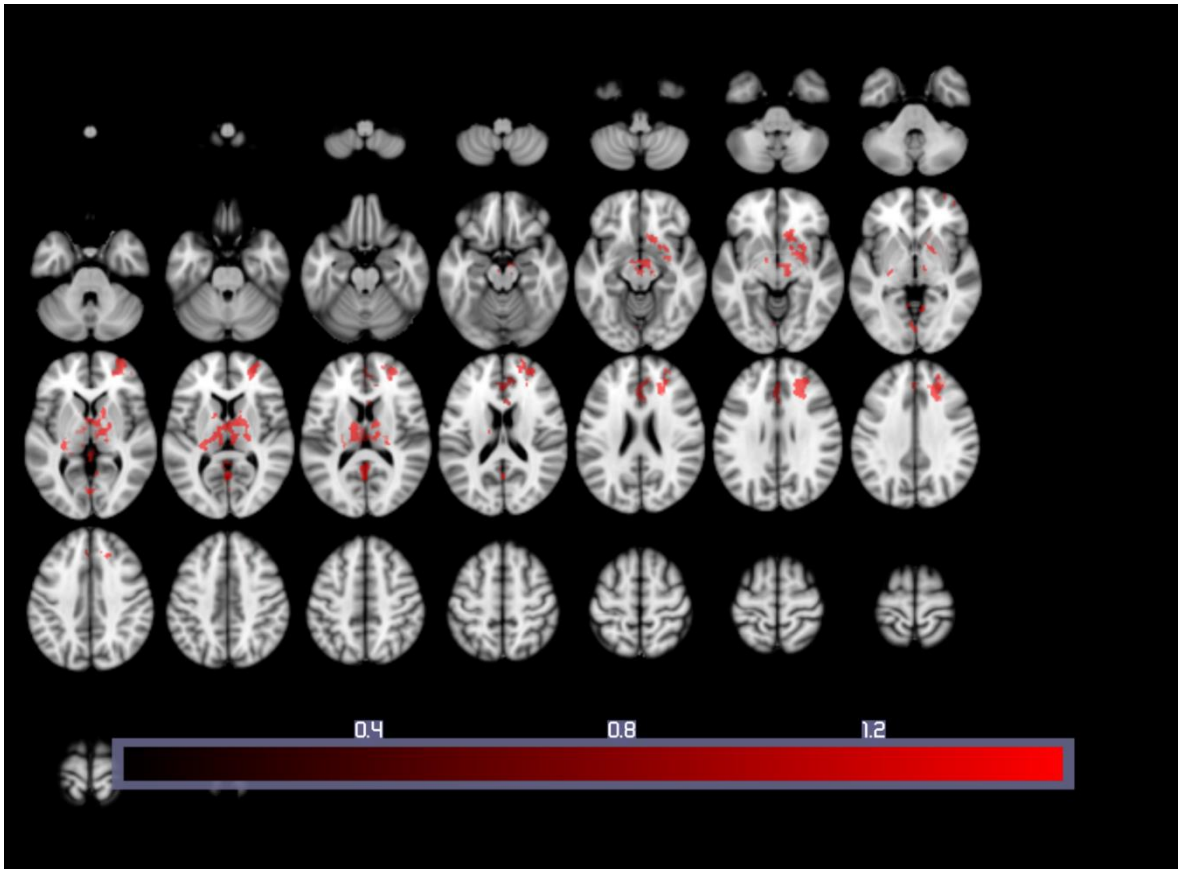

Figure 5. Regions in which BOLD signal covariation with the left lateral OFC seed (MNI coordinates -36, 24, -14) at rest was negatively associated with BMI

3.4.2 Right medial OFC (MNI coordinates 18, 20, -18)

At rest, patterns of right medial OFC connectivity were similar to those observed in the left lateral OFC, albeit with different regions meeting cluster thresholding. This was in contrast to the predicted effect of BMI on connectivity of seeds located in regions involved in reward valuation. Specifically, BMI was associated with weaker connectivity between the right medial OFC and regions involved in reward valuation, self-directed information processing, habit formation, and emotion processing, including the left amygdala, left paracingulate gyrus, left vmPFC, medial PCC, medial precuneus, right ACC, right caudate, and right NAc (Figure 6, Table 10). BMI-related

decreases in right medial OFC functional connectivity was lateralized to the right hemisphere for the caudate (F (2, 120) = 7.279, p = < 0.01). There was no evidence of hemispheric laterality in right medial OFC connectivity with any other ROI.

Table 10. MNI coordinates of local maxima in regions showing BMI-related decreases in functional connectivity with the right medial OFC seed

	Maximum Z-score	x	y	z
Left amygdala	3.86	-28	-6	-16
Left paracingulate gyrus	3.91	-4	50	0
Left ventromedial prefrontal cortex	3.56	-10	50	-6
Medial posterior cingulate cortex	3.24	-4	-36	38
Medial precuneus	3.05	-4	-58	18
Right ACC	3.63	4	40	8
Right caudate	4.11	16	18	12
Right nucleus accumbens	3.41	14	18	-8

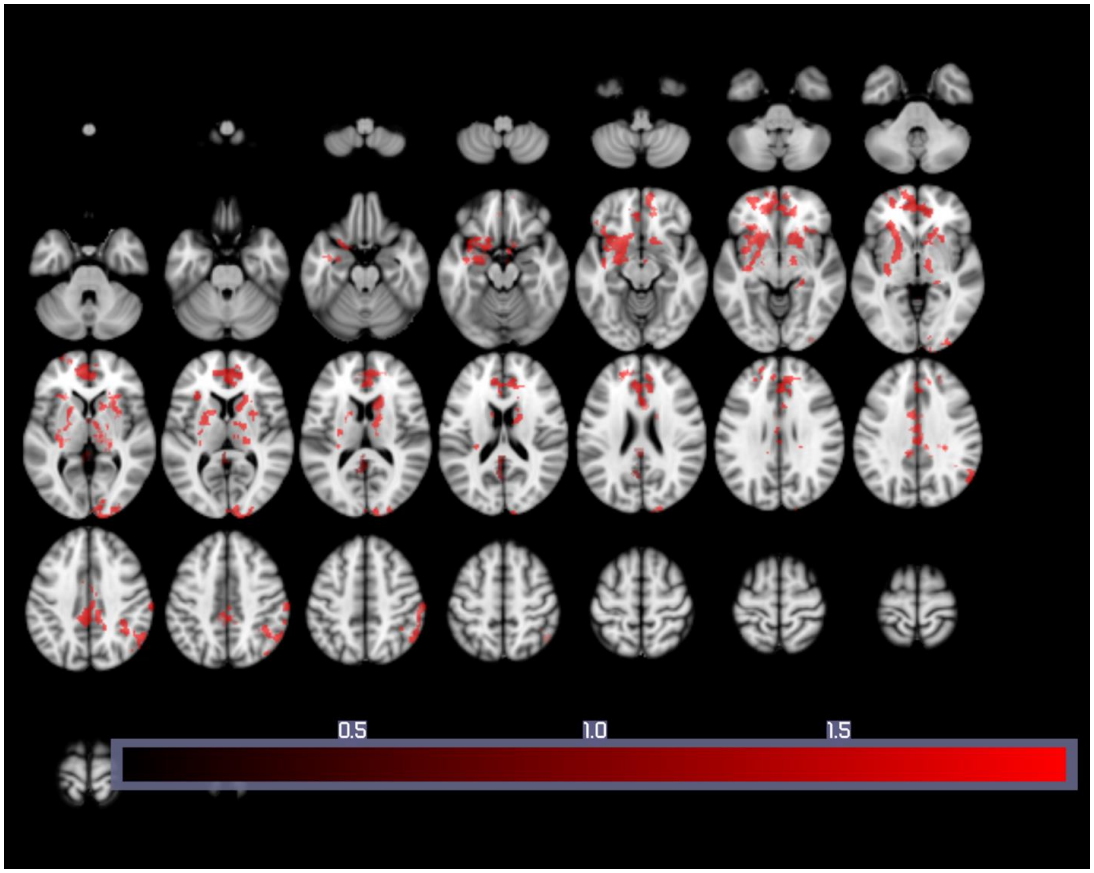

Figure 6. Regions in which BOLD signal covariation with the right medial OFC seed (MNI coordinates 18, 20, -18) at rest was negatively associated with BMI

3.4.3 Left dorsomedial PFC (MNI coordinates -16, 58, 22)

The same pattern of weaker resting state connectivity as BMI increases observed for the left and right OFC seeds was also evident for the left dmPFC seed. Given the role of the dmPFC in goal-directed motor planning and execution, it was expected that a seed located in this region would exhibit stronger rather than weaker connectivity between regions involved in reward valuation, self-directed thinking, and reward-based action selection. Contrary to this hypothesis, BMI was associated with reduced connectivity between the left dmPFC and regions located in the medial PCC, left dmPFC, right dmPFC, right insula, right putamen, and right pallidum (Figure 7,

Table 11). BMI-related decreases in left dmPFC functional connectivity was lateralized to the right hemisphere for the putamen (F (2, 120) = 4.086, p = 0.045) and to the left hemisphere for the ROI located in the mPFC (F (2, 120) = 4.599, p = 0.03). There was no evidence of hemispheric laterality in left dmPFC connectivity with any other ROI.

Table 11. MNI coordinates of local maxima in regions showing BMI-related decreases in functional connectivity with the left dorsomedial PFC seed

	Maximum Z-score	x	y	z
Medial posterior cingulate/precuneus	3.10	0	-42	26
Left dorsomedial prefrontal cortex	3.43	-10	66	14
Right dorsomedial prefrontal cortex	3.20	22	44	34
Right insula	3.14	40	-6	8
Right putamen	3.44	30	6	-2
Right pallidum	2.96	16	6	0

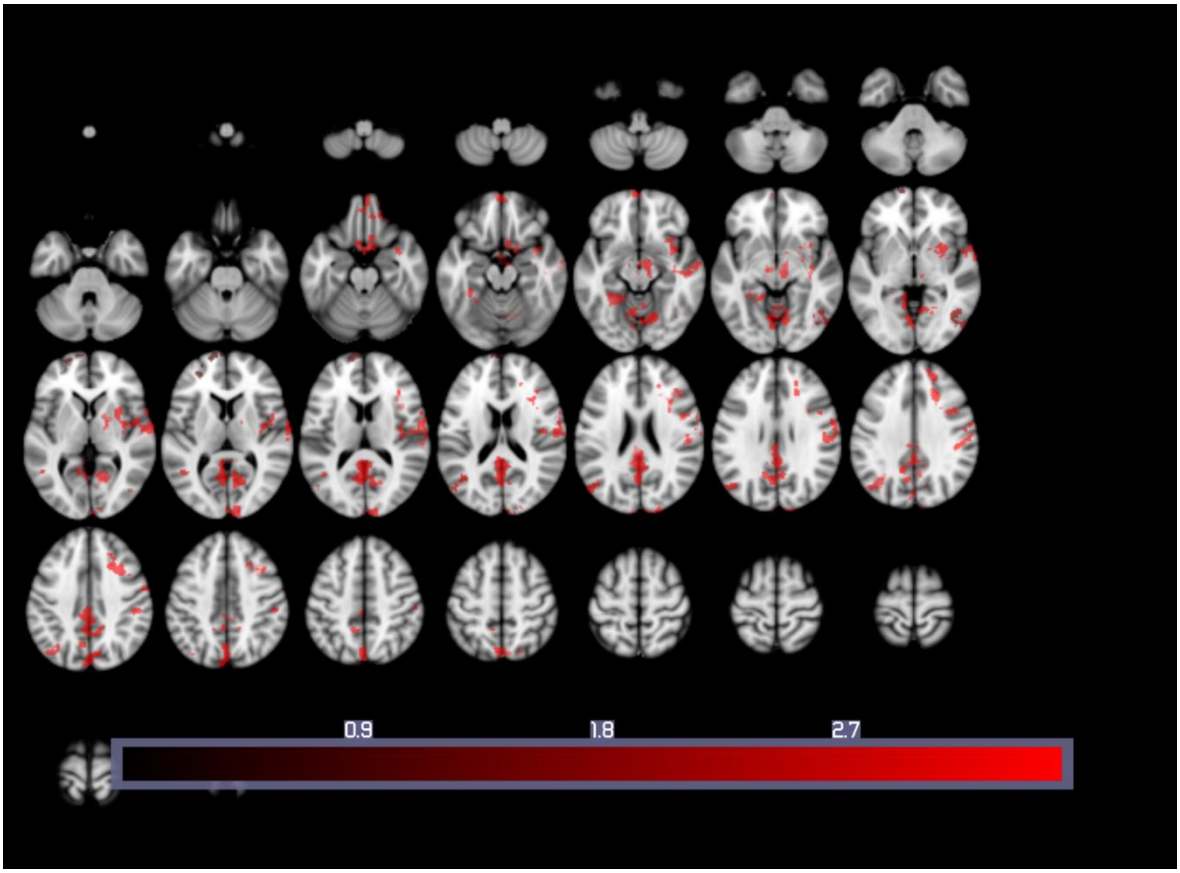

Figure 7. Regions in which BOLD signal covariation with the left dorsomedial PFC seed (MNI coordinates -16, 58, 22) at rest was negatively associated with BMI

3.4.4 Right ventromedial PFC (MNI coordinates 10, 58, -16)

Contrary to study hypotheses, there were no regions exhibiting BMI-dependent differences in resting state functional connectivity with the right vmPFC at the cluster threshold of $z > 2.3$ and $p < 0.05$. Therefore, no further analyses were performed using this seed.

3.4.5 Left ventrolateral PFC (MNI coordinates -44, 44, -12)

Contrary to study hypotheses, there were no regions exhibiting BMI-dependent differences in functional connectivity with the left vlPFC at the cluster threshold of $z > 2.3$ and $p < 0.05$. Therefore, no further analyses were performed using this seed.

3.4.6 Left medial OFC (MNI coordinates -30, 20, -16)

The same pattern of weaker resting state connectivity with increasing BMI observed previously was also evident for the left medial OFC seed. In contrast to the predicted relationship between BMI and OFC connectivity at rest, BMI was associated with reduced connectivity between the left medial OFC and regions involved in working memory, conflict monitoring, and reward learning. These regions specifically included the right ACC, right superior frontal gyrus, right putamen, and right NAc (Figure 8, Table 12). There was no evidence of hemispheric laterality in BMI-related differences in connectivity.

Table 12. MNI coordinates of local maxima in regions showing BMI-related decreases in functional connectivity with the left medial OFC seed

	Maximum Z-score	x	y	z
Right anterior cingulate cortex	3.04	10	42	18
Right putamen	2.77	22	8	-10
Right superior frontal gyrus	3.03	24	40	32
Right nucleus accumbens	3.07	12	20	-6

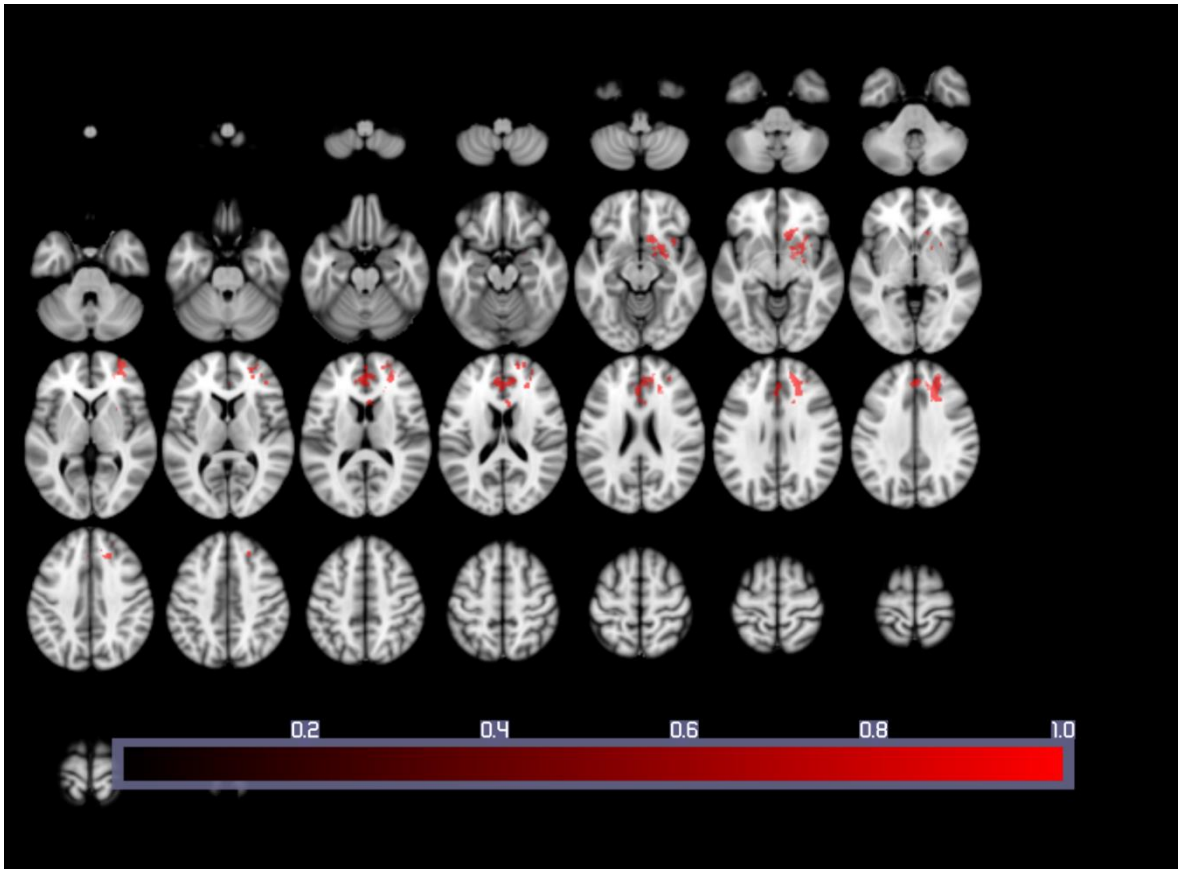

Figure 8. Regions in which BOLD signal covariation with the left medial OFC seed (MNI coordinates -30, 20, -16) at rest was negatively associated with BMI

3.4.7 Left hippocampus (MNI coordinates -32, -14, -20)

Consistent with the patterns of resting state functional connectivity observed in other seeds, BMI was associated with reduced connectivity between the left hippocampus and regions located in the medial ACC, medial paracingulate gyrus, and vmPFC (Figure 9, Table 13). There was no evidence of hemispheric laterality in hippocampal connectivity.

Table 13. MNI coordinates of local maxima in regions showing BMI-related decreases in functional connectivity with the left hippocampus seed

	Maximum Z-score	x	y	z
Medial anterior cingulate cortex	3.64	-4	32	22
Medial paracingulate gyrus	3.17	10	46	12
Ventromedial prefrontal cortex	3.14	-4	48	-10

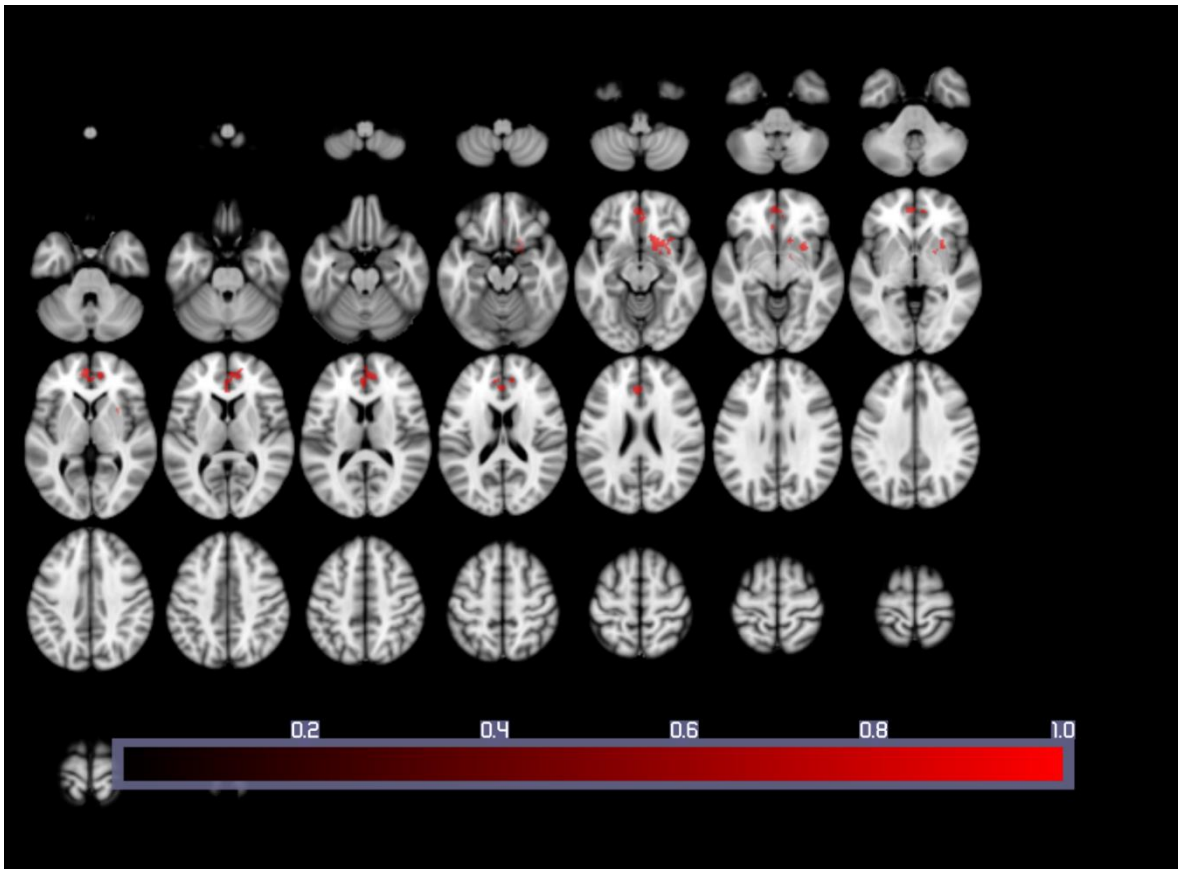

Figure 9. Regions in which BOLD signal covariation with the left hippocampus seed (MNI coordinates -32, -14, -20) at rest was negatively associated with BMI

3.5 AIM 3: EFFECT OF GENDER ON THE RELATIONSHIP BETWEEN BMI AND FUNCTIONAL NETWORK ORGANIZATION

The hypothesized effect of gender on BMI-related changes in functional connectivity was not supported in the present study. Specifically, gender did not moderate the relationship between BMI and whole-brain functional connectivity of any seed, either during the processing of high calorie food or at rest. This is in contrast to a limited number of previous studies suggesting that women may exhibit greater reactivity to food cues compared to men. However, the sample size of the present study was far larger than prior investigations of the effect of gender on the processing of food cues, so it is possible that these investigations were underpowered to test moderation.

3.6 EXPLORATORY AIM: RELATIONSHIP BETWEEN FUNCTIONAL NETWORK ORGANIZATION AND REWARD-BASED DECISION MAKING

In an effort to contextualize the observed effects of BMI on functional network organization by relating them to an obesity-relevant behavior, additional analyses were conducted to determine whether BMI-dependent variation in task evoked or resting state functional connectivity was associated with reward-related decision making as assessed by the IGT. Unexpectedly, functional connectivity during the processing of high calorie food was not associated with IGT performance. In contrast, intrinsic functional connectivity with several OFC seeds was associated with IGT performance, with stronger connectivity consistently being associated with more advantageous decision making. For instance, left lateral OFC connectivity with medial ACC at rest was positively associated with improved decision making over the course

of the IGT (z score: $t(119) = 2.313$, $p = 0.02$). The same pattern was observed for left lateral OFC – right NAc connectivity (%signal change: $t(119) = 2.315$, $p = 0.02$; z score: $t(119) = 2.139$, $p = 0.03$), and left lateral OFC – right vmPFC connectivity (%signal change: $t(119) = 2.197$, $p = 0.03$; z score: $t(119) = 2.465$, $p = 0.02$). Moreover, right vmPFC connectivity significantly mediated the relationship between BMI and improvements in decision making (%signal change: $\beta = -0.379$, $p = 0.06$; z-score: $\beta = -0.441$, $p = 0.03$), such that higher BMI was associated with inflexible decision making through weakened connectivity between the left OFC and right vmPFC at rest.

Similarly, left medial OFC connectivity with the right NAc at rest was positively associated with change in net payoff score from block one of the task to block 5 (%signal change: $t(119) = 2.008$, $p = 0.047$; z-score: $t(119) = 2.622$, $p = < 0.01$), indicating that stronger functional connectivity between the left OFC and right NAc was associated with the adoption of more advantageous monetary decision making in response to performance feedback. Left OFC – right NAc connectivity also significantly mediated the relationship between BMI and change in IGT performance (%signal change: $\beta = -0.279$, $p = 0.09$; z-score: $\beta = -0.407$, $p = < 0.01$), such that higher BMI was associated with inflexible decision making through weakened connectivity between the left OFC and right NAc at rest.

Finally, right medial OFC connectivity with the right NAc at rest was positively associated with net payoff IGT score (z score: $t(119) = 2.525$, $p = 0.01$), indicating that stronger functional coupling between the right medial OFC and right NAc was associated with more advantageous monetary decision making overall. Moreover, right NAc connectivity significantly mediated the relationship between BMI and payoff scores (z-score: $\beta = -0.232$, $p = 0.03$), such that higher BMI was associated with impaired decision making through weakened connectivity between the right medial OFC and right NAc at rest. Overall, these results suggest that task-independent disruptions

in OFC connectivity with regions involved in reward valuation (e.g., NAc) are associated with deficits in reward-based decision making in obesity.

4.0 DISCUSSION

The present study examined the association between obesity and functional network organization during the processing of high calorie food cues, as well as at rest, to determine whether the association between obesity and patterns of neural communication is only apparent in specific contexts (i.e., in the presence of high calorie food cues) or is evident even in the absence of external demands on cognition. Consistent with the hypothesized effect of obesity on functional connectivity during a visual food cue task, individuals with excess weight exhibited stronger functional connectivity between regions involved in reward valuation, motor planning, memory formation and recall, and self-referent thought during the presentation of high calorie food cues. In contrast, obesity was associated with weaker connectivity with these same regions at rest. This pattern of increased connectivity evoked by high calorie food images accompanied by decreased connectivity at rest was observed across all seeds selected for analysis, though the regions showing BMI-dependent changes in connectivity with each seed during the task largely differed from those exhibiting BMI-dependent changes in connectivity at rest. These results suggest that obesity is associated with changes in both context-dependent and intrinsic functional connectivity of regions known to be involved in reward valuation, emotion processing, and decision making (i.e., OFC, mPFC).

4.1 RELATIONSHIP BETWEEN OBESITY AND REGIONAL ACTIVATION IN RESPONSE TO FOOD CUES

Though the primary focus of the present study was to examine the effect of obesity on functional network organization as opposed to regional activation, regional activation patterns during the visual food cue task were used as the basis for the selection of regions to be used as seeds in functional connectivity analyses. Further, the effect of obesity on OFC reactivity to food cues was unexpected, and warrants a brief discussion. Overall, obesity was shown to modulate regional activation in response to the presentation of food cues, a finding which replicates those reported in a number of studies (Burger & Stice, 2011; Demos, Heatherton, & Kelley, 2012; Dong et al., 2015; Rothemund et al., 2007; Stice et al., 2010a; Stice et al., 2010b; Stice et al., 2011; Stoeckel et al., 2008; Yokum et al., 2011). With regard to the OFC, higher BMI was associated with increased activation of the OFC bilaterally in response to high calorie compared to low calorie food. The inverse association between BMI and OFC activation was observed when collapsing across food types, such that higher BMI was associated with reduced OFC activation in response to food compared to neutral non-food objects. The nutritional content of food has previously been identified as an important moderator of neural responses to food, particularly among obese individuals (e.g., Frank et al., 2010; van der Laan, de Ridder, Viergever, & Smeets, 2011; Siep, Roefs, Roebroeck, Havermans, Bonte et al., 2009). However, few studies have compared responses to food cues of any nutritional value to responses observed only in the presence of palatable high calorie foods, with only one documenting a negative association between obesity and OFC activation in response to low calorie food (Killgore & Yurgelun-Todd, 2005). The OFC is involved in assignment of incentive value, representation of reward expectancy-outcome discrepancies, and reward-related decision making (Kringelbach, 2005; Riceberg & Shapiro, 2017;

Wilson, Takahashi, Schoenbaum, & Niv, 2014), and has been shown to exhibit structural and functional abnormalities in obesity (Thompson, Drysdale, Baimel, Kaur, MacGowan et al., 2017; Yokum et al., 2011). It is possible that elevated activity in the OFC in response to high calorie food among obese individual may reflect overvaluation of such cues, with high calorie food failing to become devalued due to excess consumption as it does in healthy weight individuals (Castellanos, Charboneau, Dietrich, Park, Bradley et al., 2009; Horstmann, Dietrich, Mathar, Possel, Vrillinger et al., 2015). The fact that OFC activation was negatively associated with BMI once low calorie food cues were included in the comparison suggests that obese individuals assign less value to low calorie food than do healthy weight individuals. This divergent pattern of OFC responsivity to food cues may promote overconsumption of palatable, calorie dense food even in the absence of hunger, and may therefore be involved in the pathogenesis of obesity.

4.2 RELATIONSHIP BETWEEN OBESITY AND FUNCTIONAL NETWORK ORGANIZATION

Examination of the effect of obesity on functional connectivity evoked by the presentation of high calorie food to intrinsic, task–independent functional connectivity within the same set of seed regions revealed interesting though somewhat unexpected patterns of network signaling dynamics. For each seed, obesity was associated with stronger regional connectivity in the presence of palatable food, but weakened connectivity at rest. This suggests that regions which participate in reward valuation, learning, and memory are organized into dissociable functional networks in obesity, and that this organization is dependent on the cognitive processes being engaged. Further, these networks may mediate distinct cognitive, affective, and behavioral

processes known to be disrupted in obesity. In support of this hypothesis, weakened resting state functional connectivity between subdivisions of the mPFC and regions involved in reward valuation (NAc, vmPFC) and cognitive control (ACC) was associated with impaired monetary decision making, while there was no relationship between functional connectivity during the presentation of high calorie food and monetary decision making. It is commonly assumed that all appetitive stimuli are processed in a similar manner by similar networks. However, there is evidence that obese individuals engage discrete functional networks when evaluating food cues as compared to monetary rewards (Verdejo-Roman et al., 2017), a finding which is consistent with the patterns of functional connectivity observed in the present study.

4.2.1 Involvement of the default mode network in processing of food cues

Many of the regions that exhibited BMI-dependent increases in connectivity in the presence of high calorie food cues are located within the DMN, including the precuneus, PCC, medial temporal gyrus, and hippocampus. This was particularly the case when examining regional connectivity with the OFC, which is also a major hub of the DMN. The DMN is a robust functional network that supports internally-guided and self-referential cognitive processes (Greicius, Krasnow, Reiss, & Menon, 2003; Fransson & Marrelec, 2008), and has been previously shown to be disrupted in obesity in response to high calorie food (Garcia-Garcia et al., 2013; Tregelles et al., 2011), the administration of insulin (Kullmann, Neni, Veit, Scheffler, Machann et al., 2017), and at rest in the absence of external input (Beyer et al., 2017; Doucet et al., 2017; Kullmann et al., 2012b). The DMN is characterized by extensive within- and between-network connectivity, a feature which is thought to support integration of externally and internally generated signals arising from disparate parts of the brain (Gu, Satterthwaite, Medaglia, Yang, Gur et al., 2015; Vatansever,

Menon, Manktelow, Sahakian, & Stamatakis, 2015). Obesity-related increases in task-induced connectivity to regions of the DMN may reflect more thorough engagement with and enhanced processing of high calorie food cues that extends beyond responding to the reward value inherent to these cues. It is possible that exposure to palatable food not only provokes the experience of reward or pleasure in obese individuals, but may also elicit recall of personal memories about food (e.g., sharing meals with friends) and the affective states associated with these memories. Interestingly, elevated DMN activation during moderately demanding cognitive tasks has been associated with poor task performance and attentional difficulties (Fassbender, Zhang, Buzy, Cortes, Mizuiri et al., 2009), particularly if motivation to perform well is low (Liddle, Hollis, Batty, Groom, Totman et al., 2010). It is possible that increased engagement of the DMN in the presence of food cues in obesity may come at the expense of optimal performance in other cognitive domains. Additional research will be necessary to characterize the cognitive and behavioral correlates of altered functional connectivity evoked by high calorie food in obesity, including whether these patterns of functional network organization predict problematic eating behavior.

4.2.2 Involvement of the hippocampus in processing of food cues

In addition to increased coupling of the hippocampus with the OFC described above, unique functional pathways linking the hippocampus to other regions of the brain during the processing of food cues were revealed when using this region as a seed. Obesity was associated with stronger hippocampal connectivity to the dmPFC, IFG, and dlPFC in the presence of high calorie food, an association that has not been previously reported. A recent study found evidence that obesity is associated with lower regional activation in the hippocampus and dlPFC during the recall of successfully encoded episodic memories, with reductions in activity being associated with

impaired recall (Cheke, Bonnici, Clayton, & Simmons, 2017). The dlPFC is involved in processing and manipulation of information drawn from memory (Barbey, Koenigs, & Grafman, 2013), and stimulation of the dlPFC neurons improves working memory performance (Brunoni & Vanderhasselt, 2014). In the context of exposure to high calorie food, it is possible that increased signal coherence between the hippocampus and dlPFC may suggest that obese individuals are not only recalling food-related memories with strong affective content (as indicated by increased OFC-hippocampal connectivity), but are also more thoroughly processing the details of these memories (e.g., what, where, when, and how). Hippocampal connectivity with the IFG and dmPFC, two regions that have also been shown to support aspects of working memory (Horst & Laubach, 2009; Liakakis, Nickel, & Seitz, 2011), may similarly reflect enhanced processing of memories involving palatable food in obesity. In addition to the role of the dmPFC in working memory function, the dmPFC participates in the orchestration of behavior to promote goal attainment (Narayanan & Laubach, 2006), a process which is dependent on recall of action-outcome contingencies relevant to currently active goals. It may be that stronger functional connectivity of the dmPFC with the hippocampus in obesity is also indicative of increased engagement in motor planning informed by past interactions with food stimuli. While it remains unclear the exact mechanism by which functional connectivity of the hippocampus evoked by high calorie food cues may contribute to obesity, these results suggest that alterations in hippocampal communication with regions involved in learning, memory, valuation, and motor control are an important feature of obesity.

4.2.3 Functional network organization at rest

Higher body mass was associated with weaker intrinsic functional connectivity, regardless of which region was used as a seed. Many of the regions exhibiting BMI-dependent reductions in

signal coherence have been previously linked to reward valuation, reward-guided action selection, and cognitive control, including the NAc, vmPFC, caudate, pallidum, putamen, amygdala, ACC, and paracingulate gyrus. Weakened functional integration of regions involved in reward processing and reward related decision making in the absence of externally directed cognitive processing has been observed in substance abuse and dependence (Gu, Salmeron, Ross, Geng, Zhan et al., 2010; Motzkin, Baskin-Sommers, Newman, Kiehl, & Koenigs, 2014; Sutherland, Carroll, Salmeron, Ross, & Stein, 2013; Wilcox, Pommy, & Adinoff, 2016), as well as behavioral addictions (Yuan, Yu, Cai, Feng, Li et al., 2015; although see Ma, Liu, Li, Wang, Zhang et al., 2010), and has been linked to increased drug craving (Sutherland et al., 2013) and poor emotional and behavioral regulation (Wilcox et al., 2016). This pattern of reduced coherence between nodes in reward and cognitive control networks is thought to reflect the transition from drug taking behavior that is guided by the rewarding properties of intoxication to habitual consumption despite devaluation of the drug taking experience as pharmacological dependency develops (Gu et al., 2010; Sutherland, McHugh, Pariyadath, & Stein, 2012). To the extent that network-level disruption characteristic of substance dependence is shared with obesity, it is possible that reduced intrinsic functional connectivity between regions that support reward valuation and cognitive control may be indicative of impaired reward processing and contingency learning in obesity. Further, given that weaker resting connectivity between several of these regions was associated with impaired monetary decision making, and that these patterns were not observed in the presence of high calorie food, it is possible that the observed disruptions in functional network organization reflect a generalized reward processing deficit in obesity. Additional research will be necessary to further explore the mechanisms through which weakened functional connectivity between reward processing regions affects cognitive and behavioral processes known to be altered in obesity.

Signal coherence between regions of the DMN at rest was also found to be inversely associated with body mass, replicating findings reported by several previous studies (Beyer et al., 2017; Doucet et al., 2017; Kullmann et al., 2012b). Reduced functional cohesion of the DMN may lead to less effective integration of signals from spatially distributed regions, and subsequent dysregulation of processes dependent on such integration (Doucet et al., 2017; Gu et al., 2015; Vatansever et al., 2015). For instance, the ability to regulate behavior in such a way that is context-appropriate and in the service of attaining desired goals requires the processing and integration of information from a variety of sources, both external and internal (Kaller et al., 2011; Philiastides et al., 2011). The DMN is also thought to be engaged during self-directed information processing, which may support important functions such as memory consolidation, recall, and elaboration (Philippi, Tranel, Duff, & Rudrauf, 2015; Spreng, Mar, & Kim, 2009), future planning (Spreng et al., 2009), and social processes such as moral judgement, empathy, and comprehension of others' motives (Chiong, Wilson, D'Esposito, Kayser, Grossman et al., 2013; Schilbach, Eickhoff, Rotarska-Jagiela, Fink, & Vogeley, 2008). Disrupted functional cohesion of the DMN may contribute to impaired cognitive function in obesity, and may be one mechanism through which midlife obesity leads to cognitive decline and dementia in later life. Given the role of the DMN in self-referential memory recall and future planning, it is also possible that reduced functional connectivity in this network leads to a diminished capacity to effectively plan and execute new behaviors that would promote weight loss, and a consequent reliance on habitual yet unhealthy behaviors.

The pattern of resting state functional connectivity observed in the present study is compatible with findings reported by some studies that have examined resting state functional connectivity in obesity (Beyer et al., 2017; Contreras-Rodriguez et al., 2015; Doucet et al., 2017;

García-García et al., 2015; Geha et al., 2016; Kullmann et al., 2012b), but conflicts with findings reported by others (Coveleskie et al., 2015; García-García et al., 2013b; Lips et al., 2014 Wijngaarden et al., 2015). There are several methodological characteristics of the present study that may explain apparent discrepancies with other studies. First, in contrast to the majority of studies examining the effect of obesity on functional connectivity, the present study did not include healthy weight individuals. Rather, all participants were either overweight or obese, and BMI was used as a continuous predictor of brain function. This approach revealed that functional network organization varies even among overweight and obese individuals, a finding which would not have emerged using the more common approach of comparing overweight and obese individuals to healthy weight individuals. An important implication of this finding is that alterations in functional network properties are magnified with increasing weight. Further, this suggests that obesity may be a heterogeneous clinical phenomenon, with differing functional trajectories depending on the amount of excess weight an individual carries. Additional research will be necessary to better characterize the heterogeneity of obesity, and to identify subgroups within this overarching clinical category. Doing so may reveal differential mechanisms underlying obesity, as well as foster the development of individualized treatments designed to specifically target the causal mechanism. Second, many investigations have used a hypothesis-free, data driven approach to characterize the effect of obesity on resting state functional connectivity. Although this approach is valuable, it would not have been appropriate for addressing the specific questions about how obesity effects signaling between regions involved in valuation and decision making that were the focus of the current study. Third, with the exception of a few more recent studies (e.g., Beyer et al., 2017; Doucet et al., 2017), many studies were conducted using small samples. This may partially explain inconsistencies in the patterns of connectivity that have been reported. In light of these

methodological differences, it may not be the case that the effect of obesity on resting state functional connectivity observed in the present study is truly inconsistent with findings reported in previous studies, but rather represents an extension of what is known about how intrinsic functional network organization differs in overweight and obese individuals compared to their normal weight counterparts.

4.2.4 Intrinsic and evoked modulation of basal ganglia connectivity

Obesity was associated with differences in connectivity between the dmPFC and several regions of the basal ganglia, including the dorsal caudate nucleus, putamen, and pallidum, both at rest and during the presentation of high calorie food cues. Specifically, BMI was positively correlated with connectivity between the dmPFC and basal ganglia during the presentation of high calorie food cues, while this association was negative at rest. The observed effect of BMI on patterns of connectivity evoked by high calorie food are consistent with a meta-analysis of fMRI investigations examining the effect of obesity on responsivity to food cues, demonstrating that higher weight individuals exhibit increased dmPFC activation in response to high calorie food (Brooks, Cederneas, & Schioth, 2013). The dmPFC is thought to be involved in planning and selecting context-appropriate behavioral responses that maximize the probability of goal attainment, including the receipt of a valued reward such as food (Fuchs, Evans, Ledford, Parker, Case et al., 2005; Jaffard, Longcamp, Velay, Anton, Roth et al., 2008; Narayanan & Laubach, 2006). The orchestration of motor behavior carried out by the dmPFC is mediated by functional interactions with regions of the basal ganglia such as the putamen (Jaffard et al., 2008). Subpopulations of dmPFC neurons have been shown to predict premature responding in a task requiring motor inhibition over a delay period in order to obtain a food reward (Narayanan &

Laubach, 2006). Further, inhibition of dmPFC neurons prevented the reinstatement of cocaine seeking behavior when rats were placed in the environment they had previously self-administered cocaine (Fuchs et al., 2005), suggesting that dmPFC signaling is necessary for the initiation of approach behavior in response to reward cues. As such, it is possible that increased signal coherence between the dmPFC and regions of the basal ganglia during the processing of high calorie food cues among obese individuals may be indicative of a stronger tendency to imagine physically interacting with the food as it is presented. This may be one mechanism through which food cues in the environment influence eating behavior, and may contribute to biasing of attention toward food cues in obesity (Castellanos et al., 2009; Werthmann, Roefs, Nederkoorn, Mogg, Bradley et al., 2011).

In contrast to the functional relationship between the dmPFC and basal ganglia in the presence of high calorie food, BMI was associated with weaker connectivity between these regions at rest. Previous research has suggested that functional interactions between the dmPFC and basal ganglia support performance monitoring and flexible adjustment of behavior to prevent future errors (Ullsperger, Fischer, Nigbur, & Endrass, 2014), and is also thought to promote the acquisition of action-outcome contingencies (Kim & Hikosaka, 2015) necessary for the execution of behaviors that lead to optimal outcomes. Further, decreased functional connectivity between the dmPFC and basal ganglia has been associated with experiencing more apathy (Fazio, Logroscino, Taurisano, Amico, Quarto et al., 2016), indicating that disruptions in this circuit may lead to affective disengagement and reduced motivation to engage in goal-directed behavior. In the context of obesity, weaker signal coherence between the dmPFC and basal ganglia at rest may contribute to difficulty adopting healthy lifestyle behaviors and the failure to devalue high calorie food despite the negative medical and social consequences associated with overconsumption of

such foods. It will be important to examine whether dmPFC – basal ganglia connectivity predicts weight loss, as well as adherence to physical activity and dietary prescriptions.

4.2.5 Impact of gender on functional network organization

Contrary to study hypotheses, gender did not moderate any association between BMI and functional connectivity, either during the processing of food cues or in the absence of externally directed cognitive processing. This is contrary to several previous studies, which have generally found that women exhibit increased regional activation in response to palatable food cues compared to men (Cornier et al., 2010; Frank et al., 2010; Geliebter et al., 2013; Horstmann et al., 2011; del Parigi et al., 2002; Smeets et al., 2006; Wang et al., 2009). One possible explanation for the discrepancy between the current study and previous research may be that many of the studies reporting gender differences in regional activation were limited by small sample sizes (mean total $N = 42$), and may have been underpowered to examine moderation. However, it is important to note that women represented nearly 80% of the current sample, so it may be the case that having relatively few men impeded the ability to detect a moderating effect of gender. Nevertheless, prior studies were also limited by a focus on activation patterns of independent regions rather than network-level variation in responsivity to food cues. It is possible that gender may be associated with the way in which individual regions respond to food, but not to the patterns of communication between regions. Alternatively, factors such as menstrual phase and menopausal status known to influence neural processing of rewards (Dreher, Schmidt, Kohn, Furman, Rubinow et al., 2007; Thomas, Météreau, Déchaud, Pugeat, & Dreher, 2014) were not assessed or controlled for in the present study, leaving open the possibility that variation in these factors among women may have

limited the ability to detect a moderating effect of gender. Future studies should consider carefully evaluating the effect of these hormonal factors on processing of food cues in obesity.

4.3 STRENGTHS OF THE PRESENT STUDY

There are several strengths of the present study. First, analyses were conducted using a comparatively large sample of overweight and obese individuals, lending some confidence in the reliability of the observed relationships between obesity and functional network organization. Second, the current study is one of the few to use a multimodal approach to examine the effect of obesity on functional network organization, which made it possible to determine that the effects of obesity on patterns of neural communication were both domain specific (i.e., food cue reactivity) but also independent of context or cognitive domain. Further, given that discrepancies in the patterns of connectivity were observed during the processing of food cues compared to patterns observed at rest suggests separate mechanisms, a finding which may have important etiologic and treatment implications. Third, data was carefully preprocessed according to the most up to date methods deemed adequate for removing signal artifacts and confounds. Although perspectives on the best approaches for addressing these issues are continually shifting, care was taken to apply what is currently considered the best approach. Fourth, efforts were made to be thorough in the analytic approach. For example, in order to determine with greater certainty that the effect of obesity on functional connectivity evoked by high calorie food was context-dependent, all PPI analyses were repeated using the neutral non-food object contrast. Further, all connectivity analyses were conducted in a right OFC control region that did not exhibit BMI-dependent modulation in activity during the visual food cue task as a means of statistically testing

for laterality effects, which confirmed that there were no significant differences between hemispheres in task evoked or resting connectivity. Similarly, in order to determine whether patterns of functional network organization observed in the present study were specific to the 10mm seeds selected for analysis, all analyses were repeated using an OFC seed associated with food processing in an automated meta-analysis of relevant studies using Neurosynth.org (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). The effect of BMI on functional connectivity evoked by high calorie food cues was similar in this seed, suggesting that results were not idiosyncratic to the seeds selected for examination.

4.4 LIMITATIONS AND FUTURE DIRECTIONS

Although there are notable strengths of the present study, results should be interpreted in the context of several important limitations. The chief limitation is the use of a cross-sectional design, which precludes the ability to draw any inferences about causality. It is unclear whether the patterns of functional network organization that were observed in the present study were present before the development of obesity, and thus predispose individuals for cognitive and behavioral disruptions known to promote weight gain. There is some evidence that normal weight adolescents who are at greater risk for obesity due to positive family history exhibit enhanced responsivity to food cues in striatal and somatosensory regions relative to adolescents with no family history of obesity (Stice et al., 2011). This suggests that abnormal neural responses to high calorie food cues precedes the onset of obesity, and may represent a mechanism of risk for weight gain. Alternatively, because obesity exerts dramatic negative effects on a number of systems whose integrity are important for brain health, including the cardiovascular (Ciccone, Miniello,

Marchioli, Scicchitano, Cortese et al., 2011; Must, Spadano, Coakley, Filed, Colditz et al., 1999) and immune systems (de Heredia, Gómez-Martínez, & Marcos, 2012), it is possible that the observed disruptions in neural communication arose as a consequence of obesity-related differences in physiology. In support of this hypothesis, a recent study of siblings discordant for obesity found that altered functional network architecture was evident in obese individuals but not in their healthy weight siblings (Doucet et al., 2017).

In order to determine the temporal relationship between obesity and the patterns of functional network organization observed in the present study, it will be necessary to use longitudinal approaches in future research. One such approach that will be possible to adopt in the current sample is to examine how or whether network-level signaling dynamics change following successful weight loss, as several studies have demonstrated (Hinkle et al., 2013; Lepping et al., 2015; Tregellas et al., 2011; Weygandt et al., 2013). While this design will not resolve whether the observed relationship between obesity and functional network architecture was caused by or the consequence of having excess weight, it will provide some indication as to whether abnormal functional network architecture is a modifiable state marker of obesity, or whether it represents a stable characteristic of individuals who are prone to obesity. Importantly, each of these possible outcomes has different mechanistic implications, and may yield alternative approaches to treatment and prevention. Further, in order to more directly assess mechanistic pathways linking functional network disruption to obesity, it will be important to develop interventions that directly target the cognitive processes supported by these networks and assess whether modifying the targeted processes produces weight loss, and whether weight loss is accompanied by differences in network integrity or organization. Doing so will provide more direct evidence for the involvement of the implicated networks in the pathophysiology of obesity. Finally, it will also be

imperative to conduct prospective longitudinal research in populations at high genetic or environmental risk for obesity. This will allow characterization of how task-dependent and intrinsic functional networks change over time, and how trajectories of change differ in individuals who go on to become obese as compared to those who do not despite being at high risk.

The present study was also limited by relatively sparse phenotyping. There were few assessments of the cognitive, affective, or behavioral processes that are known to be disrupted in obesity and putatively linked to the neural networks that were the focus of study. Without the ability to demonstrate an effect of altered functional network organization on these processes (e.g., emotion regulation, reversal learning, inhibitory control, memory, diet), it is difficult to interpret the functional importance of the observed relationship between obesity and measures of functional connectivity. Future studies should consider including an extensive cognitive, psychological, and behavioral assessment battery to help contextualize neuroimaging results in disease relevant processes. Likewise, more thorough characterization of research samples has the potential to facilitate the identification of subgroups within the clinical construct of obesity based on phenotypic differences in one or more domains, an important advancement that would not only generate new hypotheses about the etiology/etiologies of obesity, but also help to refine and personalize treatments according to individual functional profiles. Related to this, the present study only examined functional network organization evoked during the processing of food cues and at rest. It would be interesting to compare and contrast regional signal covariation across a variety of tasks tapping into separate cognitive processes. Although it may be cost and time prohibitive to include more than a few relevant tasks, such an approach has the potential to reveal dissociable mechanisms underlying distinct aspects of functioning in obesity, and ultimately may yield distinct targets for treatment.

The current study was also limited by the fact that biological factors that may have mediated or moderated the effect of obesity on brain function were not included in the study or used as covariates. For instance, obesity is known to cluster with other metabolic risk factors for cardiovascular disease and type II diabetes, including insulin resistance and impaired glucose control (Després & Lemiuex, 2006). There is evidence that these metabolic risk factors exert independent effects on neuronal health (e.g., Launer, Miller, Williamson, Lazar, Gerstein et al., 2011; Raz, Rodrigue, & Acker, 2003), effects which may be compounded in individuals carrying multiple risk factors (Hoth, Gonzales, Tarumi, Miles, Tanaka et al., 2011; Jennings, Heim, Kuan, Gianaros, Muldoon, et al., 2013; Onyewuenyi, Muldoon, Christie, Erickson, & Gianaros, 2014). It is conceivable that functional network disruption may have been magnified in individuals with excess body weight who also exhibited elevated values on one or more of these additional cardiovascular risk factors. It is important to note, however, that individuals in the current sample were selected on the basis of being in good cardiovascular health in an effort to limit the potential for adverse cardiac events during the physical activity intervention. Therefore, although variation within the limits of what is considered normal for glucose tolerance, insulin sensitivity, and blood pressure may have moderated the observed effect of obesity on functional network organization, the effects would likely be small. Nevertheless, the selection of individuals in relatively good health is an additional limitation of the present study, as these results may not generalize to individuals with multiple cardiovascular risk factors who are more representative of the typical patient with obesity. Because obesity is so often comorbid with other risk factors for a range of diseases, it will be important to determine how the accumulation of risk factors relates to the integrity of functional networks, as well as whether functional network organization varies as a function of which specific factors an individual carries.

The present study is further limited by the use of BMI as a measure of obesity. BMI is an indirect measure of adiposity, which introduces significant error in the identification of individuals with excess body fat (Rothman, 2008). When compared to objective measures of adiposity like densitometry or DEXA, BMI was found to have less specificity (i.e., greater likelihood of classifying an individual as obese when they would not otherwise be based on direct measures of body fat), as well as weaker sensitivity (i.e., failing to classify an individual as obese when they would qualify for that classification based on direct measures of body fat; Deurenberg, Andreoli, Borg, & Kukkonen-Harjula, 2001). Moreover, body fat percentage has been shown to be more closely related to cardiometabolic risk and disease than BMI (De Lorenzo, Bianchi, Maroni, Iannarelli, Di Daniele et al., 2013), with there being evidence that assessment of body fat can identify individuals with prediabetes or type II diabetes with greater sensitivity than BMI (Gómez-Ambrosi, Silva, Galofré, Escalada, Santos et al., 2011). Therefore, although there have been no studies to date directly comparing the effect of BMI and objectively measured body fat on indices of brain function, it is likely that there would be discrepancies in the relationships observed. Reliance on BMI to assess obesity may have obscured adiposity- related functional impairments that may be central to understanding the neural mechanisms underlying obesity, a hypothesis that will require empirical testing. As such, it will be essential to include objective measures of body mass in future research investigating the effect of obesity on brain function.

Another important limitation of the current study is that, by design, analyses were constrained to those networks exhibiting significant signal covariation with a relatively small number of seed regions, with the selection of seeds further being constrained by regional activation during a single task, albeit a highly disease relevant one. This approach was adopted in order to test specific mechanistic hypotheses regarding the pathways underlying weight gain and weight

maintenance. However, it is likely that obesity exerted an effect on functional architecture in other networks that were not assessed in the present study, and examination of these effects may have revealed patterns that are suggestive of alternative mechanisms not captured by or assessed in this study. Given evidence that obesity alters communication between networks in a manner that may disrupt information processing necessary for adaptive, flexible behavior (e.g., Doucet et al., 2017), future studies may consider using a combination of analytic approaches to simultaneously assess multiple facets of network architecture. Finally, an inherent limitation of fMRI research is that the BOLD signal is an indirect measure of neuronal activity. As such, it is difficult to make inferences about what the observed effects of obesity on functional network organization as operationalized by regional BOLD signal covariation actually reflects at a molecular and anatomical level. Although there is evidence that intrinsic and task-evoked functional network connectivity reflects underlying structural connectivity (Greicius, Supekar, Menon, & Dougherty, 2009; Hermundstad, Bassett, Brown, Aminoff, Clewitt et al., 2013; Van Den Heuvel, Mandl, Kahn, Pol, & Hilleke, 2009), results from any fMRI investigation should be interpreted with this important caveat in mind.

4.5 SUMMARY

Results from the present study provide evidence that obesity is associated with altered functional connectivity of seed regions located in the OFC and mPFC, with there being dissociable patterns of functional network organization that are dependent on information processing demands. During the presentation of high calorie food cues, obesity was associated with *stronger* functional connectivity between OFC and mPFC seeds and regions involved in reward valuation,

emotion processing, contingency learning, memory formation and recall, and self-referential cognitive processes. In contrast, obesity was associated with *weaker* connectivity of the same OFC and mPFC seeds with regions that support reward valuation, reward-guided action selection, and cognitive control. This suggests that there are dissociable neural mechanisms that may underlie obesity-related disruption in separate domains of information processing, namely valuation of high calorie food and internally-directed cognitive processes. These dissociable patterns of evoked and intrinsic functional network organization associated with obesity may be contributing to individual differences in distinct functional domains previously shown to be disrupted in obesity. To further understand the mechanisms linking perturbed functional network organization to obesity, additional research evaluating the cognitive (e.g., inhibitory control, attention, reward valuation), psychological (emotion reactivity and regulation), and behavioral (diet, physical activity) correlates of disruption in the identified functional networks is warranted. In the future, these findings may be leveraged to develop treatments that directly target the processes supported by these networks, a strategy that will ideally maximize treatment efficacy by modifying the underlying neurobiological systems.

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