THE RELATION OF IMPULSIVITY AND OBESITY:

A NEUROIMAGING ANALYSIS

by

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DISSERTATION ABSTRACT

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The current study examined the relation of impulsivity and obesity in three neuroimaging studies using MRI techniques to test the hypothesis that deficits in brain regions responsible for inhibitory control are associated with obesity. The first study used voxel-based morphometry (VBM) to explore volumetric differences in lean, overweight, and obese women (N=83) and found that BMI was negatively correlated with grey matter (GM) in the insula, frontal operculum, and inferior frontal gyrus. BMI was positively correlated with white matter (WM) in the fusiform gyrus, parahippocampal gyrus, Rolandic operculum, and dorsal striatum. Genetic alleles for dopamine expression moderated these relations. Additionally, less GM in the superior frontal gyrus predicted future increases in BMI. The second study used VBM to examine differences between lean adolescents at risk versus not at risk for obesity (N=54). There were no regional GM or WM differences based on risk status. There were also no regional differences that

predicted weight gain over 1-year follow-up. Additionally, genetic alleles for dopamine expression did not moderate any of these regions. These findings suggest that volumetric differences may emerge after excessive weight gain. Finally, the third study used a psychophysiological interaction analysis to test functional connectivity between prefrontal and limbic regions as a function of BMI in lean, overweight, and obese women (N=37) during a go/no-go task. There was no functional connectivity found in seed regions in relation to BMI. Implications for intervention and future research are discussed.

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CHAPTER I

INTRODUCTION

Over 60% of adults in the US are overweight or obese (Hedley et al., 2004). Obesity is associated with increased risk of mortality, atherosclerotic cerebrovascular disease, coronary heart disease, colorectal cancer and death from all causes (Flegal, Graubard, Williamson, & Gail, 2005), is credited with over 111,000 deaths annually in the US alone (Flegal et al., 2005) and shortens the lifespan by 5-10 years (Fontaine et al., 2003). Obesity is clearly a pressing public health problem. Unfortunately, patients in weight loss treatments rarely show maintenance of weight loss (Jeffery et al., 2000) and virtually all obesity prevention programs do not reduce risk for future weight gain (Stice, Shaw, & Marti, 2006). Individual differences in response to food may impact treatment outcome and risk for developing obesity.

The incentive-sensitization model of obesity posits that repeated pairings of reward from food intake and cues that predict impending food intake results in hyper-responsivity of reward circuitry to food cues, which results in elevated craving and overeating that leads to obesity (Berridge, 2009). It has been theorized that impulsive individuals are more sensitive to cues for reward and more vulnerable to the omnipresent temptation of appetizing foods in our environment (Nederkoorn et al., 2006; Pickering et al., 1995), which increases risk for unhealthy weight gain. Trait impulsivity is thought to result in greater sensitivity to reward-predictive cues, which may contribute to compulsive food-seeking behavior (Diergaarde et al., 2009).

Indeed, the inability to delay gratification—one aspect of impulsivity—predicts unhealthy and rapid weight gain in children (Seeyave et al., 2009; Francis & Susman, 2009). Further, self-report and behavioral data suggest that obese versus lean individuals show deficits in several facets of impulsivity (Epstein et al., 2008; Nedekoorn et al., 2006); however, self-report and behavioral measures show only moderate correlations (Parker, Bagby, & Webster, 1993; Parker & Bagby, 1997), raising questions about the validity of these measures. It is possible that self-presentation bias introduces error. In addition, inconsistency among impulsivity measures may be in part due to the multidimensional nature of the construct (Evenden, 1999; Whiteside & Lynam, 2001) and may suggest that current impulsivity measures tap related, yet distinct aspects (Parker & Bagby, 1997).

Facets of Impulsivity

Impulsivity is a broad concept typically defined as the idea of making a hasty or premature decision. Numerous measures exist to assess impulsivity. Personality psychologists and cognitive psychologists have proposed the following components of impulsivity, several of which overlap conceptually: giving in to urges and responding immediately to a stimulus (Buss & Plomin, 1975), behaving without assessing the risk involved (Eysenck et al., 1985), motor impulsiveness, cognitive impulsiveness (problems with attentional control), non-planning impulsiveness (lack of cognitive control; Barratt, 1985; Gerbing et al., 1987), response inhibition deficits (Logan, Schachar, & Tannock, 1997), premature response (Dougherty et al., 1999), immediate reward bias (Dougherty, Mathias, Marsh, & Jagar, 2005), inaccurate time perception (Barratt & Patton, 1983), dysfunctional versus functional impulsivity

(Dickman, 1990), a lack of top-down control (Aron, 2007), and reward sensitivity/inhibition (Gray, 1987; Carver & White, 1994). Although numerous models of impulsivity have been proposed, factor analyses indicate that there may be more overlap than previously suggested. For instance, Parker et al. (1993) found that while impulsivity is a multidimensional construct, several impulsivity measures tap similar constructs (e.g., cautious/spontaneous and methodical/disorganized dimensions) across scales. Likewise, a factor analysis of impulsivity and personality scales also revealed that impulsivity captures three constructs: lack of premeditation/perseverance, sensation seeking, and urgency (Whiteside & Lynam, 2001). Thus, evidence indicates that impulsivity is most likely a multidimensional construct rather than a unidimensional construct.

Although there is general consensus among researchers of the multidimensional nature of impulsivity, there is no one conceptualization that is the most widely accepted model of impulsivity. A significant issue in studying impulsivity is the number of similar concepts represented across impulsivity models bearing different labels. For example, the construct of motor impulsivity is represented in Buss and Plomin's (1975) definition of impulsivity (i.e. responding immediately to a stimulus), Logan et al.'s (1994) deficit in response inhibition, Dougherty et al.'s (2000) premature response, and Barratt's (1985) motor impulsiveness. It will be important for the field to more specifically define these constructs and consolidate the measures used to assess them.

Methods of Assessing Impulsivity and Obesity

Survey Measures

Survey measures that assess impulsivity have been developed primarily by researchers in personality psychology. The most common self-report measures used include the Barratt Impulsivity Scale (Patton et al., 1995), Dickman's (1990) Impulsivity Inventory, Carver and White's (1994) Behavioral Inhibition and Behavioral Activation Scales, the Sensitivity to Punishment and Reward (Caseras et al., 2003; Torrubia et al., 2001), and the Temperament and Character Inventory (Cloninger, 1991; 1993). Self-report measures generally ask the individual to rate how they would respond to a given situation or the extent to which he or she agrees with a statement. Clinical interviews, such as the Structured Clinical Interview of DSM Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 2002), have also been used to assess impulsivity and are also subject to biases. These survey and interview methods are susceptible to demand characteristics and results may not be easily extrapolated to identifying impulsivity as a state or trait characteristic within an individual. Thus, survey measures may not be the most valid method of assessing impulsivity.

Extant evidence supports a link between survey measures of impulsivity and obesity. Obese children show a higher incidence of ADHD compared to the general population (Agranat-Meged et al., 2005) and children with ADHD tend to have higher body mass indexes (BMI; Holtkamp et al., 2004). Self-report measures of general impulsivity correlate positively with objectively measured caloric intake (Guerrieri et al., 2007a; Guerrieri, Nederkoorn, & Jansen, 2007b), activation of

reward circuitry in response to images of food (Beaver et al., 2006), and BMI (Braet, Claus, Verbeken, & Vlierberghe, 2007; Chalmers, Bowyer & Olenick, 1990; Ryden et al., 2003) and negatively with weight loss during obesity treatment (Jonsson, Bjorvell, Levander & Rossner, 1986; Nederkoorn et al., 2007). Binge eating is a disorder characterized by lack of inhibitory control and obese binge eaters self-report more impulsivity than those who are obese without binge eating (De Zwaan et al., 1994; Nasser, Gluck, & Geliebter, 2004). Yet, these studies tell us little about the facets of impulsivity that correlate with obesity.

Behavioral Measures

Behavioral measures are another method of assessing impulsivity. The most common types assess response inhibition/motor impulsiveness, sensitivity to reward, and immediate reward bias/delayed discounting. The Stop Signal (Lappin & Eriksen, 1966) task and its modified versions (i.e., Go/No-Go, and Stop-Change [Band, van der Molen, Overtoom, & Verbaten, 2000]) evaluate deficits in inhibiting a prepotent response. Logan and Cowan (1984) posit that impulsivity is an inability to inhibit a prepotent response due to deficits in executive control. They theorize that there is an executive system that determines whether or not another system carries out a response or behavior. They have also suggested that there are two types of stopping: a fast system that inhibits all responses and a slower system that selectively inhibits responses (Logan, 1994; van Boxtel, van der Molen, Jennings, & Brunia, 2001). Additionally, the execution of a go response is posited to be a race between a go system and a stop system (Logan & Cowan, 1984). When a go stimulus is presented, the go system is activated, likewise for the stop system when a stop stimulus is

presented. The stop system is assumed to suppress the response of the go system if it reaches the go system before the go system reaches threshold to instigate a behavioral response. Thus, response inhibition depends on the relative finishing times of the go and stop systems. Logan and Cowan (1984) posit that the go and stop systems are independent of each other. However, others have posited that these two systems interact because stop durations increase when participants must selectively inhibit their response, indicating feedback between the go and stop system (Boucher, Palmeri, Logan, & Schall, 2007; Szmalec, Demanet, Vandierendonck, & Verbruggen, in press). This delay observed when a selective response is needed is not due to interference or inhibition by a second go system for the alternative response (Verbruggen & Logan, 2009).

Obese versus lean individuals show response inhibition deficits on go/no-go and stop-signal tasks (Bonato & Boland, 1983a; Nederkoorn et al., 2006a; Nederkoorn et al., 2007; Nederkoorn et al., 2006b). Response inhibition deficits on a stop-signal task correlate positively with unobtrusively measured caloric intake among adults (Guerrieri et al., 2007a). Research that has used speeded responses to the Matching Familiar Figure Test has found that obese individuals respond more quickly and make more false-positive response errors (Braet et al., 2007), also suggesting response inhibition deficits. Additionally, rats that show behavioral disinhibition in response to food reward on a serial reaction time task exhibit greater future sucrose seeking behaviors and enhanced sensitivity to sucrose-associated stimuli after extinction, relative to rats that exhibited behavioral inhibition (Diergaarde et al., 2009).

Behavioral measures that assess reward sensitivity include The Door Opening Task (Daugherty & Quay, 1991), Card Arranging Reward Responsivity Objective Test (CARROT; Siegel, 1978), Card Playing Task, Iowa Gambling Task (Bechara, Damasio, Damasio, & Anderson, 1994), and Food Reinforcement Task (Epstein et al., 1991). Researchers have noticed increasing parallels in neurology and behavior between those with drug addictions and those who are prone to overeating, particularly in response to rewarding substances (Davis, Strachan, & Berkson, 2004; Dawe & Loxton, 2004). The incentive-sensitization model posits that people who are more prone to rewards not only will be more sensitive to the reward itself, but will also develop increased sensitivity to cues for that reward (Robinson & Berridge, 2000). These tasks have been used to assess perseveration in pursuit of a reward. Similarly, a joystick task (Solarz, 1960; Duckworth, Bargh, Garcia, & Chaiken, 2002) has been used to assess self-control in approach-avoidance behaviors in response to temptations. Adults who diet are faster at pushing away high-calorie food words versus fitness words whereas non-dieters are faster at pulling high-calorie food words than fitness words, suggesting that those who may be able to focus and maintain weight loss are those who can exert self-control in the face of pleasurable stimuli (Fishbach & Shah, 2006), although others have not found this pattern in response to high-calorie food pictures (Ahern, Field, Yokum, Bohon, & Stice, 2010).

Delayed gratification and delayed discounting (also known as temporal discounting or immediate reward bias) paradigms also assess reward-related impulsivity. Metcalfe and Mischel (1999) propose a “hot” and “cool” system responsible for balancing behavioral responses. The hot system is reflexive, driven by

emotion and stimulus controlled. The cool system is slow, strategic, and cognitive. Delayed gratification tasks assess how long an individual is able to delay receipt of a reward. Delayed/temporal discounting or immediate reward bias tasks measure a similarly related concept. These tasks assess the degree to which individuals are able to choose a larger, delayed reward over a small, yet immediate reward and are derived from behavioral economics literature (Bickel & Johnson, 2003). That is, the subjective value of the reward is a function of the amount of the reward and the duration of delay in receiving it. Individuals who are impulsive tend to discount the delayed reward and overvalue the immediate reward. Based on an individual's responses to task, a temporal discounting functioning can be calculated (Mazur, 1984):

$$V_d = \frac{V_i}{1 + KD}$$

where V_d is the value of the delayed reward, V_i is the value of the reward if it is immediate, D is the delay and K is a scaling constant which is an index of discounting or impulsivity. This formula characterizes the relation between the subjective value of a reward and the time of its delivery as an exponential one. Healthy adult individuals show this exponential function when the reward is real or hypothetical money (Johnson & Bickel, 2002; Madden, Begotka, Raiff, & Kastern, 2003). Further, adults with substance abuse, gambling, or smoking addiction show a hyperbolic function (i.e. a steeper curve) instead of an exponential one, indicating that they value the immediate reward over the delayed one (Kirby, Petry, & Bickel, 1999; Madden,

Petry, Badger, & Bickel, 1997; Petry, 2001; Bickel, Odum, & Madden, 1999). The steeper the curve, the more the individual is choosing the immediate reward over the delayed reward, and the more impulsive the individual.

Generally, studies assessing this aspect of impulsivity find that weight is positively correlated with delayed discounting. In healthy controls, percent body fat correlates with discounting food, but not monetary reward (Rasmussen, Lawyer, & Reilly, 2010). Obese versus lean individuals show a preference for immediate monetary reward versus a larger delayed monetary reward (Epstein, Dearing, Temple & Cavanaugh, 2008; Weller, Cook, Avsar & Cox, 2008), though findings have not always replicated (Bonato & Boland, 1983; Nederkoorn et al., 2006a). Obese versus lean individuals also show a preference for immediate food reward versus a larger delayed food reward (Bonato & Boland, 1983; Epstein et al., 2008; Sobhany & Rogers, 1985), though not in all studies (Bourget & White, 1984).

Studies assessing reward sensitivity via the Food Reinforcement Task (Epstein et al., 1991) have found that those who rate snack foods as more hedonically pleasurable work harder for the snack foods (Goldfield & Legg, 2006) and obese participants also work for more food compared to lean participants (Saelens & Epstein, 1996). One other study has not found this difference in high restrainers, who have a significantly higher BMI than low restrainers (Ahern, Field, Yokum, Bohon, & Stice, 2010)

In sum, the mixed findings across studies examining the relation of impulsivity to obesity may be due to the use of self-report and behavioral measures, which are vulnerable to self-presentation bias. Additionally, self-report and behavioral measures

of impulsivity show only moderate correlations (Parker & Bagby, 1997; Parker, Bagby, & Webster, 1993), suggesting that the two types of measures might be tapping different domains. Overall, there tends to be high correlation within self-report measures and their corresponding subscales, and within behavioral measures of impulsivity, but low to none between the two methodologies (Lane et al., 2003; Reynolds, Ortengren, Richards, & de Wit, 2006; Reynolds, Penfold, & Petak, 2008; Loxton & Dawe, 2007). Further, Lane et al. (2003) found that behavioral measures tend to assess response inhibition and delayed discounting while self-report measures assess one factor. Although a two-factor model for behavioral measures has been replicated (Reynolds et al., 2005), factor analyses of self-report measures tend to find multiple constructs (e.g. Gerbing et al., 1987; Miller, Joseph, & Tudway, 2004). Low correlations between self-report and behavioral measures may also be due to the multidimensional nature of the impulsivity construct. Thus, appropriately operationalizing impulsivity is important to understanding the nature of impulsivity as it relates to a particular clinical disorder. Additionally, using objective techniques to assess impulsivity may be a more precise method of measuring this construct. Few studies have used neuroimaging techniques, which may provide a more objective measure of impulsivity.

Neuroimaging Methods

Response Inhibition

The frontal region of the brain is considered to be the locus of inhibitory control. Self-report impulsivity has been found to negatively correlate with activation in the prefrontal cortex during failed no-go trials (PFC; Asahi et al., 2004; Brown,

Manuck, Flory, & Hariri, 2006) and positively correlate with activation during successful no-go trials (Horn, Dolan, Elliott, Deakin, & Woodruff, 2003). Animal studies demonstrate that the PFC, particularly the dorsolateral frontal cortex is involved in response inhibition (Pribram, Mishkin, Rosvold, & Kaplan, 1952). A lesion study in humans has also demonstrated that lesions in the frontal cortex negatively affect ability to inhibit responses (Drewe, 1975).

Studies using event-related potentials (ERP) in humans also provides evidence of prefrontal involvement in response inhibition. The N200, a negative wave that is maximally active over the frontal cortex after a no-go stimulus, is believed to reflect a central inhibitory control center (Band & Boxtel, 1999). The N200 is larger in amplitude when more motor preparation is needed to inhibit a response in humans (Jodo & Kayama, 1992; Eimer, 1993) and stimulation of the frontal cortex region in which the N200 occurs results in an inhibition of a motor response in monkeys (Sasaki, Gemba, & Tsujimoto, 1989). Further, magnetoencephalography (MEG) studies in humans show that activity in the dorsolateral PFC positively correlates with correct response inhibition (Sasaki, Gemba, Nambu, & Matsuzaki, 1993). Collectively, these results suggest that prefrontal regions are responsible for inhibitory control.

Data from fMRI studies with humans have identified specific PFC regions that are most likely to be involved in an inhibitory control system. Studies report that the dorsalateral PFC, ventrolateral PFC, inferior frontal gyrus (IFG), superior frontal gyrus (SFG), parietal cortex, medial frontal cortex, fusiform gyrus, and lateral frontal cortex show increased activation during response inhibition (Casey, Trainor, Orendi,

Schubert et al., 1997; Rubia, Russel, & Taylor, 1998; Smith, Kiehl, Mendrek, Forster, Hare, & Liddle, 1998; Liddle, Kiehl, & Smith, 2001). Additionally, activation in the IFG is negatively correlated with reaction time in go/no-go tasks (Aron, Behrens, Smith, Frank & Poldrack, 2007).

A meta-analysis of go/no-go paradigms, working memory, and fMRI reveal that the IFG and middle frontal gyrus (MFG) are also significantly activated during inhibition of a response (Buchsbaum, Greer, Chang, & Berman, 2005). Additionally, another meta-analysis comparing the complexity of go/no-go paradigms and fMRI demonstrates that the pre-supplementary motor area, fusiform gyrus, MFG and IFG, inferior parietal regions, putamen and left premotor cortex were activated across all types of go/no-go tasks (Simmonds, Pekar, & Mostofsky, 2008), suggesting that these regions are globally responsible for inhibitory control. They also found that the MFG, IFG, and dorsolateral PFC were consistently activated in complex go/no-go tasks that required increased attention and working memory. It could be that these regions are responsible for a top-down control of other regions in correctly suppressing a response. Indeed, Hare, Camerer, and Rangel (2009) that healthy controls that exercised self-control in the face of appetizing yet unhealthy foods show increased activation in the dorsolateral PFC.

Furthermore, Hare et al. (2009) found that activation in the ventromedial PFC occurred regardless of whether subjects were able to choose the healthy option in the face of a pleasing yet unhealthy option. Connectivity analyses showed that the dorsolateral PFC results in inhibitory control by modulating activation of the ventromedial PFC, which encodes the value of the stimulus. This is the first study to

demonstrate that the dorsolateral PFC exerts this modulation on the ventromedial PFC via the IFG. In sum, a number of studies have shown that prefrontal regions, particularly the dorsolateral PFC and the IFG, are necessary in successful inhibition of a behavioral response.

Delayed or Temporal Discounting and Immediate Reward Bias

In studies with healthy humans, activation in the ventral striatum, medial PFC and posterior cingulate cortex increases as the amount of monetary reward increases, and decreases as delay of that reward increases (Kable & Glimcher, 2007). It has been proposed that two systems are involved in evaluating immediate and delayed rewards. McClure et al. (2004) posit that two systems compete to produce immediate reward bias. One system favors immediate rewards, which is due to activation of the ventral striatum, medial OFC, and medial PFC. The other system favors delayed rewards and show preferential activation of the lateral PFC. In response to the primary reward, juice, McClure et al. (2007) found that regions of reward sensitivity (nucleus accumbens, medial OFC, and the posterior cingluate cortex) are differentially activated for choosing immediate versus delayed rewards while the anterior insula and dorsolateral PFC are engaged in choosing delayed rewards over immediate rewards. To date, only one fMRI study has examined substance abusers (i.e. methamphetamine) versus healthy controls using a delayed discounting task and did not find evidence of differential activation between the two groups (Monterosso, Ainslie, Xu, Cordova, Domier, & London, 2007). However, one study of sober alcoholics versus healthy controls did find that waiting for the delayed reward is correlated with activation in the lateral OFC (Boettiger, Mitchell, Tavares, Robertson,

Joslyn, D'Esposito, & Fields, 2007). Others have suggested that one system modulates the activity in the other, which produces response inhibition (Hare et al., 2009). These results suggest that these regions are involved in valuing a reward not only by measuring the subjective value of the reward, but also accounting for the delay in receiving that reward.

Although data from fMRI studies using delayed discounting tasks suggest that the ventromedial PFC is responsible for encoding reward value, data from neuroimaging studies in social psychology suggest that the ventromedial PFC may also involved in envisioning a "future self" (Mitchell, 2009). It has been posited that failure to envision this future self enjoying an activity, also called affective forecasting, leads to an immediate reward bias. One neuroimaging study using affective forecasting and delayed discounting tasks has found that activation in the ventromedial PFC decreased for all participants when they imagined a future self versus a present self enjoying activities (Mitchell, Schirmer, Ames, & Gilbert, 2010). Further, those who are biased towards immediate rewards versus those who are not show greater activation in the ventromedial PFC when predicting their enjoyment about activities in the present versus in the future. It may be that individuals who are more prone to choosing immediate rewards over delayed rewards are less able to project an idea of himself/herself in the future. This is important to note in studying obesity because it may be that individuals who are obese have even greater difficulty envisioning a future self who makes healthy choices or lives a healthy lifestyle compared to lean individuals. To date, no neuroimaging study has examined these effects in obese and lean adults, which could provide a measure of how regions

involved in immediate reward bias interact with processing of a primary reward, and whether this is a risk factor for the development of obesity.

Reward Sensitivity

Neuroimaging studies examining reward regions of the brain have identified the medial PFC, ventromedial PFC, orbitofrontal cortex (OFC), amygdala, and striatum as regions responsible for encoding the value of reward (Hare et al., 2009; Gottfried, O'Doherty, & Dolan, 2003; Hommer et al., 2003; Wunderlich, Rangel, O'Doherty, 2009). PET studies also demonstrate that dopamine release in the dorsal striatum and caudate correlate with the pleasantness of food in healthy humans (Small, Jones-Gotman, & Dagher, 2003), indicating that these regions also encode reward value. The OFC especially has been found to encode the value of rewards, including monetary and primary rewards such as food (Plassmann ,O'Doherty, & Rangel, 2007; Hare, O'Doherty, Camerer, Schultz, & Rangel, 2008). Specifically, Hare et al. (2008) found that the medial OFC correlates with values placed on the reward (i.e. willingness to pay for food) and the central OFC correlates with the value of receiving the reward.

The OFC has been particularly implicated in food reward. The OFC receives inputs from primary sensory regions of the brain, including those for taste, smell, touch and sight (Zald & Kim, 1996). The OFC in monkeys also responds specifically to properties of food such as texture and food smells (Rolls & Baylis, 1994; Rolls, Verhagen, & Kadohisa, 2003). In humans, activation of the OFC scales with the difficulty of making a choice between high-valued food items (Arana, Parkinson, Hinton et al., 2003) and decreases with increasing satiety (Small, Zatorre, Dagher, et

al., 2001). These findings suggest that the OFC is particularly sensitive to food reward, although the OFC is also implicated in decision-making. It may be that the OFC is involved in top-down processes of decision-making for rewarding stimuli. Moreover, it has been proposed that a circuit of the OFC, amgydala and nucleus accumbens/ventral striatum is involved in reward processing (McClure, York, & Montague, 2004). This circuit is activated across various types of rewarding stimuli including primary rewards such as food, appetizing smells, and sex, and conditioned stimuli such as money and abstract cues. Although there is not consistent evidence for the specific roles of particular regions within the OFC, amygdala and ventral striatum, there is general support for the involvement of the OFC in reward valuation during decision-making, the amygdala in encoding the salience of stimuli (whether aversive or rewarding), and the ventral striatum/nucleus accumbens in evaluating errors in reward predictions (e.g. learning what types of behaviors lead to rewards during reinforcement; McClure et al., 2004).

Neuroimaging studies of individuals with versus without addictive or impulse control disorders such as gambling. substance abuse, and aggression also show increased activations in reward processing regions, indicating that abnormalities in these regions play a role in either placing such individuals at risk for the disorder or that such abnormalities are a result of long-term addictive behavior. It has been posited that deficits in the mesolimbic dopamine reward system are involved in addictive behavior (Blum, Braverman, Holder, et al., 2000). Neuroimaging studies show that pathological gamblers show decreased activity in the ventral striatum when winning money (Reute, Raedler, Rose, Hand, Glascher, & Buchel, 2005) and that

cocaine abusers show decreased dopamine receptor availability in the striatum and increased metabolism in the OFC (Wang et al., 1997). Long-term cannabis users versus healthy controls show hypoactivation in the nucleus accumbens, caudate nucleus, putamen, and thalamus in response to anticipating receipt of monetary reward (van Hell, Vink, Ossewaarde, Jager, Kahn, & Ramsey, 2010). Abstinent alcoholic individuals versus healthy controls also show decreased activation in the ventral striatum in response to anticipated monetary reward, but increased activation in the ventral striatum to alcohol cues, which correlate with craving (Wrase et al., 2007). Further, alcohol dependent individuals compared to healthy controls show decreased volume of the hippocampus and ventral striatum, and smaller grey matter volume of the amgydala correlates with craving (Wrase et al., 2008). Collectively, these results indicate that those with addictive disorders show deficits in regions responsible for encoding reward value, which may contribute to difficulty in controlling impulsive acts towards rewards, even when faced with detrimental consequences.

Neuroimaging and Obesity

Few neuroimaging studies have used behavioral impulsivity tasks to test impulsivity in obesity. However, neuroimaging tasks assessing reward sensitivity find that obese individuals experience a hyperactivation in gustatory and reward valuation regions in response to food cues and food receipt (Stice, Spoor, Bohon, Veldhuizen, & Small, 2008b; Ng, Stice, Yokum, & Bohon, 2011). Few brain-imaging studies have compared activation in response to food receipt in lean versus obese individuals. Yang and Meguid (1995) found that obese versus lean rats show more phasic release

of dopamine during feeding. Del Parigi et al. (2004; 2005) found that the dorsal insula, midbrain, and posterior hippocampus remain abnormally responsive to consumption of food in previously obese compared to lean individuals using PET. fMRI studies with adolescents have found that obese versus lean adolescents show greater activation in the gustatory cortex (frontal operculum and anterior insula) and somatosensory cortex (Rolandic operculum, parietal operculum, posterior insula) in response to receipt of chocolate milkshake (versus a tasteless solution) and that increased activation in the insula/frontoparietal operculum to milkshake receipt correlated positively with current BMI (Stice, Spoor, Bohon, Veldhuizen & Small, 2008a; Stice et al., 2008b). Another fMRI study found that blunted dorsal striatum response to milkshake receipt correlated negatively with current BMI and with future weight gain over a 1-year follow-up among participants with an A1 allele of the Taq1A DRD2 gene (Stice et al., 2008a), which was also found in another study (Stice et al., 2008b). Individuals with this polymorphism have been found to have 30 to 40% fewer number of D2 receptors in the striatum than those without (Pohjalainen et al., 1998; Jonsson et al., 1999; Ritchie & Nobel, 2003).

Likewise, only a few studies have compared brain activation in response to presentation of food cues among obese versus lean individuals. Karhunen et al. (1997) found increased activation in the right parietal and temporal cortices after exposure to pictured food in obese but not lean women. Rothemund et al. (2007) found greater dorsal striatum response to pictures of high-calorie foods in obese verse lean adults and that BMI correlated positively with response in insula, claustrum, cingulate, postcentral gyrus (somatosensory cortex) and lateral OFC. Additionally,

one study using pictures of appetizing and unappetizing food found greater activation in the lateral OFC, putamen, superior frontal gyrus, frontal, parietal and Rolandic opercula and ventrolateral PFC in obese versus lean women (Stice, Yokum, Bohon, Marti, & Smolen, 2010). Moreover, the Taq1A1 allele and DRD4-7R allele (responsible for dopamine receptor expression) moderated activation in these regions such that those with these alleles and blunted activation in the putamen, frontal operculum, and OFC showed increased risk for weight gain, but those without the allele and heightened activation in the frontal operculum and OFC showed increased risk for future weight gain (Stice et al., 2010). Stoeckel et al. (2008) also found greater activation in the medial and lateral OFC, amygdala, ventral striatum, medial prefrontal cortex, insula, anterior cingulate cortex, ventral pallidum, caudate, and hippocampus in response to pictures of high-calorie versus low-calorie foods for obese relative to lean individuals. Interestingly, activation of the dlPFC has been negatively correlated with ad libitum food intake (Cornier, Salzberg, Endly, Bessesen, & Tregellas, 2010).

Further, Wang and colleagues (2002) found that obese relative to lean individuals showed greater resting metabolic activity in the oral somatosensory cortex, a region associated with sensation in the mouth, lips, and tongue. Stice et al. (2008a) also found that obese versus lean adolescents showed greater activation of Rolandic, temporal, frontal, and parietal opercular regions in response to anticipated receipt of chocolate milkshake versus tasteless solution. The only study to date that has tested reward abnormalities in adolescents at-risk for obesity found increased activation in the caudate, insula, OFC, and parietal and frontal opercula in those at-

risk versus those not at-risk (Stice, Yokum, Burger, Epstein, & Small, 2011). Collectively, these data suggest that heightened responsivity of neural circuitry to food images and cues increases risk for overeating and consequent weight gain.

Other findings are consistent with the thesis that obese individuals show a hypo-responsive reward system. Obese relative to lean individuals have reduced dopamine receptor binding potential in the striatum (Volkow et al., 2008; Wang et al., 2001), implying that they show reduced D2 receptor density in reward circuitry. In addition, Stice et al. (2008a; 2008b) found that obese versus lean adolescents show less activation in the dorsal striatum in response to consumption of chocolate milkshake (versus tasteless solution). These results echo evidence that substance abuse is associated with low D2 receptor density and blunted sensitivity of reward circuitry (Goldstein et al., 2007). Wang et al (2002) posit that deficits in D2 receptors may predispose individuals to use psychoactive drugs or overeat to boost a sluggish dopamine reward system. Further, D2 receptor density in the striatum is positively correlated with resting metabolism in the prefrontal cortex, which may increase risk for overeating because this latter region is involved in inhibitory control (Volkow et al., 2008). Yet, it is possible that consumption of a high-fat, high-sugar diet leads to down-regulation of D2 receptors (Davis et al., 2004), paralleling neural response to chronic use of psychoactive drugs (Volkow, Fowler, & Wang, 2002). Indeed, obese versus lean rats show downregulated D2 receptors in the striatum and downregulated D1 and D2 receptors in the nucleus accumbens when exposed to a high-calorie diet (Johnson & Kenny, 2010; Alsio et al., 2010). However, fMRI studies have shown that individuals who show weaker activation of the dorsal striatum to food receipt are at

increased risk for future weight gain if they have an A1 allele of the Taq1A DRD2 gene (Stice et al., 2008b; Stice et al., 2010). Collectively, these data imply that obese individuals may show a hypo-responsivity of the striatum to food receipt, which might be due in part to a history of overeating or eating a diet of high-fat and high-sugar foods, even if it does not result in weight gain (Alsio et al., 2010). As well, these data hint at a possible interaction between responsivity of reward regions to food and regions involved in inhibitory control.

Although there is increasing fMRI evidence of reward sensitivity abnormalities associated with obesity, a key gap in the literature is that few studies have used objective brain imaging paradigms to test whether response inhibition deficits correlate with BMI and no studies have tested whether immediate reward bias correlates with BMI. Although a number of studies demonstrate that obese relative to lean individuals report and exhibit more impulsive traits, only one study has found that self-reported impulsivity positively correlates with activation in reward circuitry in response to images of palatable foods in healthy women (Beaver, Lawrence, van Ditzhuijzen, Woods & Calder, 2006). That is, women who reported greater impulsivity showed greater activation of reward circuitry to food cues, which may reflect anticipatory food reward. Further, only one fMRI study has addressed response inhibition related to BMI (Batterink, Spoor, & Stice, 2010) and found that obese versus lean individuals showed more rapid responding and less behavioral response inhibition to pictures of appetizing foods in a go/no-go task, weaker activation of frontal inhibitory regions (middle/inferior frontal gyrus medial

prefrontal cortex, ventrolateral prefrontal cortex, and OFC), and greater activation of regions implicated in food reward (temporal operculum, insula).

Functional Connectivity, Impulsivity, and Obesity

Extant fMRI studies suggest that abnormalities in reward encoding, valuation, and inhibitory control regions contribute to obesity (e.g., Stice et al., 2008b, Batterink et al., 2010), but no neuroimaging study has yet examined how these brain regions network with each other in relation to obesity. Neuroimaging studies suggest that a prefrontal-cingulate network is responsible for impulse control. An ERP study found that PFC activation preceded ACC activation during a standard Stroop task (Markela-Lerenc, 2003) and an fMRI study showed that activation of the ACC correlates with activation in other regions related to reward processing and behavior control, including the striatum, amygdala, cingulate gyrus, and medial and later PFC (Cohen & Ranganath, 2005). Further, a study using DTI found abnormalities in the connectivity of white matter tracts of adults with ADHD (Konrad et al., 2010). An fMRI study showed resting connectivity among the dorsal ACC, thalamus, insula and brainstem in those with ADHD versus without (Tian et al., 2006).

The only study that has investigated connectivity between inhibitory control and reward processing regions found that the relation between activation in the dlPFC and successful inhibitory control is mediated by activation of the ventral striatum (Kober et al., 2010). However, this has not been explicitly tested in relation to BMI. Collectively, these studies suggest that impairment in a network involving prefrontal and limbic regions may contribute to impulse control disorders. Although not examining connectivity, one study using a go/no-go task found that men with higher

self-reported impulsivity showed greater activation the posterior cingulate and insula during inhibition, while less self-reported impulsive men showed greater activation in the medial SFG (Horn et al., 2003). No study has yet examined connectivity of regions implicated in reward processing and inhibitory control in obesity.

Morphology Associated with Obesity

Evidence from the few fMRI studies discussed above converge with findings that structural differences may underlie functional abnormalities observed in obesity. Woodward et al. (2009) has shown that D2 receptor binding is positively correlated with grey matter (GM) volume in the midbrain, ACC, medial PFC, parahippocampal gyrus, IFG, caudate, thalamus, and amygdala in healthy adults. The caudate, putamen, thalamus, and amgydala are regions that receive the majority of DA projections from the midbrain (Riccardi, et al., 2006). Additionally, several studies have found a relation between regional brain volume differences and neural responsivity (Cook et al., 2002; Steffener, Brickman, Rakitin, Gazes, & Stern, 2008). EEG-measured connectivity mediates the relation between white matter volume and cognitive performance in older adults (Cook et al., 2002). Additionally, regardless of age, lower regional grey matter volume was associated with greater use of one of two networks involved in working memory (Steffener et al., 2008). Thus, because genetic variations of DA receptor expression genes (i.e., TaqIA A1 and DRD4 alleles) are implicated in functional abnormalities observed in relation to BMI, these findings suggest that regions involved in reward and behavioral inhibition and may also be associated with BMI at a structural level.

No study has explicitly tested structural abnormalities associated with impulsivity in obesity. However, several morphology studies have found an inverse relation between BMI and global brain volume (Ward, Carlsson, Trivedi, Sager, & Johnson, 2005; Gustafson, Lissner, Bengtsson, Björkelund, & Skoog, 2004), although one has not (Haltia et al., 2007). In particular, reduced volume has been found in regions implicated in taste processing and reward valuation. Obese versus lean adults show less GM density in the cerebellum, frontal operculum, postcentral gyrus, putamen, and PFC/middle frontal gyrus (Pannacciulli et al., 2006). Additionally, they show greater GM density in the calcarine cortex, middle occipital gyrus, inferior frontal gyrus and cuneus.

In healthy individuals, BMI has been negatively correlated with global GM volume (Taki, Kinomura, Sato et al., 2008). In patients with fronto-temporal lobar degeneration, a disorder characterized by atrophy in the frontal lobes, overeating and a preference for sweet foods was associated with less grey matter density in the OFC, inferior frontal gyrus, caudate nucleus and dorsolateral PFC regions, which have also been implicated in food reward and impulsivity (Whitwell, Sampson, Loy, Warren et al., 2007). These data suggest that deficits in prefrontal regions (areas associated with response inhibition) may interact with food reward circuitry to contribute to weight gain.

White matter (WM) consists of myelinated axon tracts that connect various GM regions and differences in WM have also been associated with BMI. Obese mice appear to have lower amount of myelin compared to normal mice (Sena, Sarlieve, & Rebel, 1985). Pannacciulli et al. (2006) has found no WM density differences except

in the putamen in obese versus lean adults. In the elderly, BMI is negatively correlated with GM and WM volume in the OFC, ACC, medial temporal lobe, hippocampus, basal ganglia, putamen, globus pallidus, and thalamus (Raji et al., 2009). Interestingly, one study has found that low-calorie dieting for six weeks reverses WM volume differences in obese adults and reduces global white matter (Haltia et al., 2007). Prior to dieting, obese versus lean adults showed greater WM volume in the superior, middle, and inferior temporal gyri, fusiform gyrus, parahippocampal gyrus, brain stem and cerebellum. Because serum free fatty acids were positively correlated with white matter density, Haltia et al. (2007) suggest that WM may reflect an accumulation of lipids in the brain.

It may be that morphological changes observed in obesity are due to inflammatory markers. Inflammatory cytokines/adiopokines such as fibrinogen, IL-1β, IL-6, and C-reactive protein are associated with excess adipose tissue (Duncan et al., 2000; Festa et al., 2001; Hirosumi et al., 2002; Doupis et al. 2011) and elevated levels of such inflammatory markers are positively correlated with insulin resistance, metabolic syndrome, and type 2 diabetes (Spranger et al., 2003; Hu, Meigs, Li, Rifai, & Manson, 2004; Guerre-Millo, 2002). In fact, elevated fibrinogen predicts weight gain in adults (Duncan et al., 2000), suggesting that such inflammatory markers may play a role the onset and maintenance of obesity.

One study of adults with versus without metabolic syndrome using DTI has found deterioration in the anterior corpus callosum, a structure in the frontal lobe (Seguar et al., 2009). Additionally, VBM studies show that those with elevated blood sugar levels (as measured by HbA1c levels) have less GM density in the posterior,

temporal and cerebellar regions (Musen et al., 2006). Further, those with versus without type 2 diabetes also have less global GM and less regional GM in the anterior cingulate, OFC, and parieto-occipital region (Kumar et al., 2008; Last et al., 2007). Findings regarding WM volume are mixed; one has found less global WM and less WM in frontal regions in those with diabetes (Last et al., 2007), but one has not (Kumar et al., 2008).

Collectively, these studies of metabolic disorders suggest that inflammatory markers may play a role in altering cerebral volume. Indeed, in overweight and obese individuals, fibrinogen level is negatively correlated with GM in the OFC and positively with the amgydala and parietal regions (Cazettes, Cohen, Yau, Talbot, & Convit, 2010). Additionally, the inflammatory marker IL-6 in the hippocampus interferes with neurogenesis (Monje, Toda, & Palmer, 2003) and neural plasticity (Heyser, Masliah, Samimi, Campbell, & Gold, 1997). IL-6 levels are negatively correlated with global brain volume and regional GM volume in the hippocampus and medial PFC (Jefferson et al. 2007). In fact, IL-6 levels mediate the association between body fat and hippocampal grey matter volume (Marsland, Gianaros, Abramowitch, Manuck, & Hariri, 2008). Further, monkeys on a long-term, calorie-restricted diet show reduced levels of IL-6 and decreased IL-6-related global GM and WM atrophy, as well as GM atrophy in parietal and temporal regions (Willette et al., 2010). Both rat and human studies have shown that a low-calorie diet restricts protein expression of IL-6 (e.g., Arvidsson et al., 2004; You, Sonntag, Leng, & Carter, 2007). In sum, inflammatory markers, particularly IL-6 and fibrinogen, may be the mechanisms by which obesity is related to morphological alterations in the brain.

In sum, cross-sectional studies of BMI suggest that there is a relation between BMI and reduced GM volume and to a limited extent with increased WM volume. It could be hypothesized that reduced GM and/or increased WM volume contributes to future weight gain. An alternative hypothesis is that BMI increases cause these structural changes. Only one longitudinal study thus far has tested structural changes over time related to BMI (Haltia et al., 2007). These findings suggest that WM changes may be secondary to weight changes; however, no study has yet tested whether individual differences in regional brain volume predict future increases in BMI.

Genes Associated with Impulsivity and Obesity

It is important to take genetic variation into consideration as it may contribute to differences in global and regional brain volume in obesity, as well as functional differences. Feeding is associated with dopamine release in the dorsal striatum, and the degree of pleasure from eating correlates with amount of dopamine release (Smalll, Jones-Gotman, Dagher, 2003). As discussed earlier, variations in dopaminergic candidate genes such as the A1 allele of the TaqIA DRD2 gene and DRD4-7R or long allele have been associated with abnormalities related to BMI. For instance, individuals with the A1 allele show fewer of D2 receptors in the striatum (Volkow et al, 2008; Wang et al., 2001) and those with the TaqIA and the DRD4-7R show decreased activation in the striatum, which increases risk for future weight gain (Stice et al., 2008b).

To our knowledge, studies have not examined how genotypes interact with BMI in relation to brain matter volume. However, anatomical studies in rodents,

nonhuman primates, and humans have established that genes are major determinants of overall brain size (Cheverud et al., 1990; Leamy, 1985; Finlay & Darlington, 1995). Moreover, in addition to impacting activation in reward sensitivity to food and risk for weight gain, variations in dopaminergic candidate genes (TaqIA A1 and DRD4) are also related to regional GM volume. For example, the TaqIA A1 allele is related to smaller areas of the midbrain (Cesara et al., 2009), while the DRD4-long allele is related to smaller fronto-striatal GM volumes (Durston et al., 2005). In addition, humans with versus without one or more DRD4 long (7R-10R) alleles have higher maximum lifetime body mass in samples at risk for obesity (e.g., Guo, North, Gordon-Larsen, & Bulik, 2007; Kaplan et al., 2008; Levitan et al., 2004). Thus, it is important to account for genetic influences on brain morphology and function.

Aims of the Present Study

The overarching goal of this dissertation is to address a gap in the neuroimaging literature related to obesity. Although extant neuroimaging studies indicate abnormal responses in brain regions implicated in reward encoding and evaluation, to date few studies have examined morphological abnormalities that may underlie functional differences. Additionally, no study has yet examined structural differences that include a consideration of genetic risk factors for obesity. Further, few studies have prospectively tested structural differences in a sample at risk of developing obesity. Adolescent children of obese versus normal-weight parents show a fourfold increase in risk for obesity onset (Whitaker et al., 1997; Magarey et al., 2003). Specifically, the following three studies aim to: 1) replicate and extend previous findings of GM and WM differences in regions associated reward

processing and inhibitory control in lean, overweight, and obese young women, 2) test for GM and WM differences in lean adolescents at high versus low risk for obesity, and 3) examine functional connectivity between reward and inhibitory control regions and its relation to BMI. It was also hypothesized that differences in GM/WM volume and functional connectivity would predict BMI increases. Finally, it was hypothesized that the TaqIA A1 and DRD4 alleles would moderate volumetric and functional connectivity differences.

CHAPTER II

STUDIES

Study I: Morphology in Lean, Overweight and Obese Women

This study tested the relation between GM/WM volume and BMI and whether any abnormalities predicted weight gain over 1-year follow-up using voxel-based morphometry (VBM). Based on previous cross-sectional data, it was hypothesized that BMI would be correlated with reduced overall GM volume and with reduced GM volume in regions involved in taste (anterior insula/frontal operculum, Rolandic operculum), reward (orbitofrontal cortex, dorsal striatum), and behavior control (inferior-, middle-, and superior frontal gyri). It was also hypothesized that BMI would be positively correlated with WM volume in the dorsal striatum, inferior-, middle- and superior temporal gyrus, the fusiform gyrus, and parahippocampal gyrus. Further, it was hypothesized that the negative relations between GM and BMI and the positive relations between WM volume and BMI would be most significant for individuals carrying the TaqIA A1 allele or the DRD4 long allele in regions where dopamine receptors are preferentially expressed, namely the dorsal striatum and prefrontal regions.

This study also sought to test whether structural differences are related to weight gain. If changes in brain volume are secondary to weight gain, then there should be no significant relations of regional GM and WM volume to BM increases over 1-year follow-up. However, if such differences do predict weight gain, the findings will support the theory that volumetric differences confer risk for subsequent weight gain.

Methods

Participants

Participants were 83 young women (M age = 18.4; SD = 2.8), 6.0% African Americans, 78.3% European Americans, 4.8% Native Americans, 1.2% Native Hawaiian or other Pacific Islander, and 9.6% mixed racial heritage. Thirty-eight subjects (*M* age = 15.7, *SD* = .94; *M* BMI =24.3; *SD* = 4.98; BMI range = 17.3-38.9) were recruited from a larger prevention trial of female high school students with body image concerns. Individuals in this larger study who gave consent to be contacted about other studies were asked to participate in a study on the neural response to presentation of food. Another forty-five subjects (*M* age = 20.7, *SD* = 1.5; *M* BMI =27.9; *SD* = 2.6; BMI range = 24.4-33.2) participated in a study evaluating the efficacy of a behavioral weight loss treatment using fMRI. Participants in both samples were scanned at baseline prior to the trials. Exclusion criteria were diagnosis of an eating disorder (e.g., bulimia nervosa), any use of psychoactive drugs, current Axis I psychiatric disorder, and standard fMRI contraindications (e.g., head injury with a loss of consciousness and pregnancy).

Measures

Body mass. Body mass index (BMI = kg/m^2) was used to reflect adiposity (Dietz & Robinson, 1998). After removal of shoes and coats, height was measured to the nearest millimeter using a stadiometer and weight was assessed to the nearest 0.1 kg using a digital scale. Two measures of each were obtained and averaged. BMI correlates with direct measures of total body fat such as dual energy x-ray absorptiometry (*r* = .80 to .90) and with health measures such as blood pressure,

adverse lipoprotein profiles, atherosclerotic lesions, serum insulin levels, and diabetes mellitus (Dietz & Robinson, 1998). Participants provided BMI data at baseline, 6-month, and 12-month follow-up. Participants were categorized as lean, overweight, and obese based on their BMI to test global brain volume differences among the three groups. Participants aged 20 years or younger were categorized as lean, overweight, or obese based on the Centers for Disease Control BMI-for-age growth chart for girls (Kuczmarski et al., 2000). For those aged 21 years and older (N=29), participants were categorized based on adult cut-offs (lean = 20<BMI<25, overweight = 25<BMI<30, obese = BMI>30).

Genotyping. Participants were asked to provide saliva, from which epithelial cells were collected, using a commercial product, Oragene® (DNA-genotek, Ottawa, ON, Canada). DNA was extracted from the samples using standard salting-out and solvent precipitation methods, yielding an average of 45 μg of DNA (TaqMan®, ABI, Foster City, CA) method (Haberstick & Smolen, 2004) on an ABI Prism® 7000 Sequence Detection System using the allelic discrimination mode (Livak, 1999). Reactions containing 20 ng of DNA were performed in 10 μl reactions with TaqMan® Universal PCR Master Mix using the standard cycling conditions. Sequences of the primers and probes are: Forward Primer: 5' – GTGCAGCTCACTCCATCCT-3'; Reverse Primer: 5' – GCAACACAGCCATCCTCAAAG-3'; A1 Probe: 5'- VIC-CCTGCCT**T**GAC-CAGC-NFQMGB-3'; A2 Probe: 5'- FAM-CTGCCT**C**GACCAGC-NFQMGB-3'. Each 96 cell plate included non-template and DNA standards of known genotype. Two investigators independently scored each genotype.

Because genotype data collection was initiated after the start of the larger prevention study, genotype data was successfully completed for N = 77. TaqIA was coded A1/A1 or A1/A2 versus A2/A2; 26 participants had at least one A1 allele of the TaqIA gene and 51 did not. The assay for the 48-base pair (bp) exon 3 VNTR polymorphism in the DRD4 gene was a modification (Anchordoquy, McGeary, Krauter, & Smolen, 2003) of the method of Lerman and colleagues (1998). The primer sequences were forward: 5'-VIC- GCT CAT GCT GCT GCT CTA CTG GGC -3'; and reverse: 5'- CTG CGG GTC TGC GGT GGA GTC TGG -3', which yield PCR products from 279 (2R) to 519 (7R) bp. Following PCR, the amplicons were analyzed on an ABI PRISM® 3130xl Genetiz Analyzer (Foster City, CA). Based on studies suggesting that the 7 repeat or longer allele confers a functional difference in D4 receptors (Asghari et al., 1995), participants were classified as having at least one 7R variant or none; 30 participants had the 7R variant of the DRD4 gene and 47 did not. None of the subjects had DRD4 alleles longer than 7R.

MRI acquisition

Scanning was performed in a Siemens Allegra 3-Tesla, head-only MRI scanner. A standard birdcage coil was used to acquire data from the entire brain. A thermo foam vacuum pillow and additional padding was used to restrict head motion. High-resolution structural MRI scans (160 sagittal slices, 1x1x1 mm, FOV: 256x256 mm^2, TR = 2000 ms, TE = 30 ms, flip angle = 80°) were acquired using inversion recovery T1-weighted sequence (MP-RAGE) along the AC-PC transverse, oblique plane as determined by the midsagittal section.

Non-brain tissue was removed using the Brain Extraction Tool (BET; Smith, 2002) in FSL (Analysis Group, FMRIB, Oxford, UK). Data were manually realigned to the AC-PC and analyzed using SPM8 software (Wellcome Department of Imaging Neurosicence, London, UK) in MATLAB (Mathworks, Inc., Sherborn, MA; 37). T1 images were preprocessed using the VBM8 Toolbox developed by Christian Gaser (University of Jena, Psychiatry Department) in SPM8. Images were normalized to the MNI space using high-dimensional Dartel normalization segmented into GM, WM, and cerebrospinal fluid (CSF). To preserve the total amount of grey matter in the original images, normalized images were scaled by the amount of contraction used in normalization to produce modulated images (Ashburner & Friston, 2000). These modulated images were used in analyses to examine volumetric differences. Images were then smoothed to an 8 mm full-width at half maximum (FWHM) Gaussian kernel. Sample homogeneity was checked to identify images of poor quality.

Statistical analysis

Total GM volume was statistically corrected in all GM analyses and total WM volume was statistically corrected in all WM analyses to account for differences in individual cranial size. Correlations of GM and WM volumes with BMI (N = 83) were computed using multiple regressions. Participants were also categorized as lean (n=31), overweight (n=36), and obese (n=17) based on their BMI and a full-factorial ANOVA model was used to test group differences in global GM and WM volumes.

To test whether the genotypes moderated the relations, genotyping data (N=77) was entered as a covariate in a full-factorial interaction in all models of

analyses. Factors of interest were BMI, genotype (Taq1A, DRD4), and the interaction between genotype and BMI.

To test whether differences in GM and WM volumes predicted weight change over 1-year follow-up, BMI slopes (N = 81) were entered into a multiple regression model, controlling for initial BMI. BMI measurements taken at baseline, 6-month, and 12-month follow-up were used to calculate BMI slope coefficients.

Region of interest (ROI) masks were created using the WFUPickatlas (Maldijian, Laurienti, Kraft, & Burdette, 2003) to test specific GM and WM hypotheses. Based on prior functional and VBM studies, ROIs for GM included the insula, Rolandic operculum, OFC, dorsal striatum, and inferior-, middle-, and superior frontal gyri. ROIs for WM included the dorsal striatum, inferior-, middle-, superior temporal gyrus, fusiform gyrus and parahippocampal gyrus. T-maps were thresholded at $p<0.001$ uncorrected with a cluster extent of 93 for GM and 79 for WM. Cluster extents were determined by the cluster size expected for a $p<.001$ uncorrected threshold. Predicted activations were considered to be significant at $p<0.05$ after correcting for multiple comparisons (pFDR) across the voxels within the *a priori* defined regions of interest. Peaks outside the hypothesized regions were considered to be significant at $p<0.05$ FDR corrected across the whole brain.

Results

Group differences in global GM and WM volume

There was a significant difference in global GM volume among the three groups, $F(2)=5.5$, $p=.006$. Post hoc tests showed that lean participants ($M=542.78$, $SD=60.30$) had greater overall GM volume compared to obese ($M=499.54$,

SD=49.68; p=.011). Overweight (*M*=542.90, *SD*=40.52) also had greater GM volume compared to obese (*p* =.010). There was no difference between lean and overweight in global GM volume.

There was a significant difference in overall WM volume among the three groups, *F*(2)=3.80, *p*=.027. Overweight participants (*M*=486.34, *SD*=43.84) had more overall WM volume compared to obese (*M*=452.27, *SD*=45.06; *p*=.025). There was no difference in WM volume between lean (*M*=465.81, *SD*=46.04) and obese or lean and overweight.

Relations between GM volume and BMI

There were no significant correlations between BMI and GM volume in the *a priori* ROIs, although there were trend-level negative correlations between BMI and GM volumes found in the right mid insula and right frontal operculum (pFDR's = 0.08). There was a positive correlation between BMI and GM volume outside the hypothesized regions, namely in the right middle occipital gyrus (Table 1).

Relations between WM volume and BMI

BMI was positively correlated with WM volume in the right ventrolateral prefrontal cortex, bilateral middle temporal gyrus, left fusiform gyrus, bilateral parahippocampal gyrus, and left Rolandic operculum (Table 1). A positive correlation between BMI and WM volume was also found in the middle occipital gyrus.

TaqIA and DRD4 long interactions

To test if TaqIA A1 and DRD4 alleles interacted with BMI (N = 77) to predict GM and WM volume, separate full-factorial interaction models were used. For those with the TaqIA A1 allele, BMI was negatively correlated with GM volume in the

bilateral inferior frontal gyrus and bilateral frontal operculum (Table 1; Figure 1). There were no interactive effects for DRD4 and no main effects of TaqIA or DRD4.

Relation between GM and WM volume and BMI over 1-year follow-up

The average change in BMI over the 1-year follow-up period was .04 (SD =.95, range = -2.62 – 2.27). Less GM volume in the bilateral superior frontal gyrus predicted future increases in BMI over 1-year follow-up (Figure 2). WM volume did not significantly predict change in future BMI.

Post-hoc Analyses: Age Effects

Because the sample was drawn from two larger samples that differed in age, GM and WM differences were tested within the younger group (M age = 15.7 years, SD=.94) and the older group (M age = 20.7 years, SD = 1.5). In the younger group, there was no negative correlation between BMI and GM volume. However, there was a trend for a positive correlation between BMI and GM volume in the left lingual gyrus (-2, -75, 0, z = 4.20, pFDR=.07). In the older group, there were no significant relations between BMI and GM volume.

In terms of WM differences, in the younger group there were trends of positive correlations between BMI and WM in the right dlPFC (30, 44, 9, z=4.47, pFDR=.08), right fusiform gyrus (-27, -64, -9, z=4.24, pFDR=.08), and right middle frontal gyrus (38, 5, 52, z=4.00, pFDR=.08). In the older group, there were also trends of positive correlations between BMI and WM in the anterior cingulate (15, 30, 33, z=3.53, pFDR=.07), vmPFC (15, 48, -3, z=3.84, PFDR=.07), left parahippocampal gyrus (-12, -31, -8, z=3.98, pFDR=.07), middle temporal gyrus (54, -27, -12, z=3.72, pFDR=.07), left thalamus (-4, -12, 15, z=3.54, pFDR=.07), and

bilateral OFC (-12, 38, -23, z=3.51, pFDR=.07; 9, 42, -24, z=3.11, pFDR=.07). In both the younger and older groups, there were no negative correlations between BMI and WM.

Discussion

Across BMI groups, obese individuals had significantly reduced overall GM volume compared to lean and overweight participants. This result is comparable to findings of a previous study in middle-aged adults (Ward et al., 2005). Interestingly, overweight individuals showed greater overall WM volume compared to obese. There were no significant differences in global WM volume between obese and lean individuals or between overweight and lean individuals. A possible explanation for the null findings in global WM volume differences between obese versus lean individuals is the relatively small sample size. Only 17 participants in the sample of the present study were obese, which potentially limited the statistical power to detect small effects. However, there were regional WM differences between obese and lean individuals, suggesting that there was adequate sensitivity to detect regional differences.

In contrast to the findings of Pannacciulli et al. (2006), BMI was not correlated with reduced GM volume in the insula, although individuals with higher BMIs showed trend-level negative correlations with GM volumes in the insula and frontal operculum compared to normal weight individuals. Because the female participants in the present study were overall younger and less obese compared with those in the earlier studies, it is possible that only more severe and chronic obesity negatively influences GM volume. Further, Taki et al. (2007) found a significant

correlation between BMI and reduced GM in men, but not women, suggesting possible sex differences in the relation between BMI and regional GM volume. They also suggested that the null findings in women may be due to gender differences in fat distribution because visceral fat predominates in men and subcutaneous fat predominates in women (Kotani et al., 1994). Visceral fat is likely indicative of metabolic syndrome (Masuzaki et al., 2001; Bergman et al., 2006), which is associated with elevated serum levels of inflammatory markers. As discussed earlier, inflammatory markers have been associated with changes in GM and WM volume (e.g., Jefferson et al., 2007; Marsland et al., 2008). Additional studies are needed to ascertain whether types of fat distribution affect regional GM volumes differently and whether sex interacts with body fat patterning in altering GM/WM structure.

Interestingly, there was a positive correlation between BMI and regional GM volume in the middle occipital gyrus. This result was not an *a priori* defined region of interest, but does dovetail with the finding of a previous study (Pannacciulli et al., 2006), in which GM density in the middle occipital lobe was greater in obese compared to lean individuals. Occipital regions are typically involved in visual processing such as object recognition, color perception, and selective attention (Wandell, 1999; Kanwisher & Wojciulik, 2000). Using a food-based visual attention task, one neuroimaging study has found that BMI positively correlates with selective attention to appetizing food and greater activation in reward processing regions including the anterior insula, ventrolateral PFC and lateral OFC (Yokum, Ng, & Stice, 2011). Further, a meta-analysis of visual processing of food and non-food cues found that activation in the lateral occipital complex (a region extending from the

posterior fusiform gyrus to the inferior occipital gyrus) is positively correlated with food cues (van der Laan, de Ridder, Viergever, & Smeets, 2011). Given that individuals with a higher BMI show increased selective attention toward appetitive stimuli, it is possible that greater GM in the visual cortex (e.g., occipital region) reflects this difference in neural activity.

As hypothesized, BMI correlated positively with WM volume in the vlPFC, middle temporal gyrus, fusiform gyrus, parahippocampal gyrus, postcentral gyrus, and dorsal striatum. These results converge with previous findings (Pannacciulli et al., 2006; Haltia et al., 2007). The vlPFC and the postcentral gyrus have been found to be activated by taste of palatable food (Del Parigi et al., 2001) and obese versus lean individuals show greater activation in these regions in response to palatable food (Stice et al., 2008a). The vlPFC is also involved in the maintenance of information in working memory and low-level control (Robinson & Berridge, 2001). This area is an important part of the circuitry in which associations between visual cues and the actions or choices they specify are formed and is thought to play a role in selecting the correct course of action from multiple behavioral choices (Fillmore & Rush, 2001).

Inferior temporal areas, including the fusiform gyrus are associated with top-down modulation of the processing of food signals via gustatory imagery, retrieval of gustatory memories and modification of behavioral strategies (Hinton et al., 2004; Kobayashi et al., 2004; Kringelbach & Rolls, 2004). It is possible that an increase in WM volume may negatively impact the neural functioning of the abovementioned regions, resulting in an increased risk for overeating and future weight gain. Future

prospective studies with larger samples should investigate the interaction between individual differences in brain volume and BMI on neural activity in regions related to feeding behavior, reward, and behavior control.

The TaqIA A1 allele significantly moderated the relations between BMI and regional GM volumes. These interactive effects suggest that obese individuals show reduced GM volume in the inferior frontal gyrus and frontal operculum if they possess the TaqI A1 allele, indicating that BMI in combination with genotypes associated with compromised dopamine functioning negatively influence regional brain structure. There were no effects for the DRD4 allele, which is contrary to expectations. It is possible that the DRD4 allele does not impact GM/WM volume as much as the TaqIA allele. The DRD4 allele has been associated with a more novelty-seeking, impulsive personality (Ebstein et al., 1996; Benjamin et al., 2004), but one study has found the opposite relation (Malhorta et al., 1996). However, it has been consistently demonstrated that those with the TaqIA allele are at increased risk for disorders associated with reward sensitivity such as alcohol and substance abuse (Noble, 2000). It may be that the TaqIA allele is more directly related to dysfunction in regions involved in reward processing than the DRD4 allel. Overall, these results suggest that the TaqIA show the strongest effect on regional GM volume in obese individuals. To date, this is the first study to examine the interactive effects of BMI and genes on brain volume. It will be important for future studies with larger samples to attempt to replicate these findings.

Reduced GM volume in the superior frontal gyrus was associated with weight gain over 1-year follow-up, while controlling for initial BMI. This converges with

previous findings that activation in the SFG is positively correlated with successful inhibition (Casey et al., 1997) and negatively correlated with a self-report measure of trait impulsivity in those with borderline personality disorder, a clinical disorder characterized by impulsive behaviors (Mortensen, Rasmussen, & Haberg, 2010). Additionally, individuals with a higher BMI show less behavioral inhibitory control and less activation in the SFG in a go/no-go task (Batterink, Yokum, & Stice, 2010). To date, this is the first study reporting the relations between brain volume and change in future BMI. Therefore, it is possible that reduced GM volume in regions involved in inhibitory control contributes to overeating, resulting in future increase in BMI. Future prospective repeated-measure studies with larger sample sizes should be carried out to examine these relations more closely.

Due to the difference in age between the two samples that were used for the present study, volumetric differences were examined in each cohort. In the younger sample, there was a trend of a positive correlation between BMI and GM in the lingual gyrus, a region of the occipital lobe that is responsible for visual attention processing (Macaluso, Frith, & Driver, 1994), which is in line with the finding from the full sample of greater GM volume in the middle occipital gyrus, a region also involved in processing visual cues. There were also a trend of positive correlations between BMI and WM in both the younger and older groups, but the older group showed positive correlations with more regions, including the anterior cingulate, parahippocampal gyrus, and OFC, regions previously implicated in reward processing in functional neuroimaging studies of BMI (e.g., Stoeckel et al., 2008; Rothemund et al., 2007; O'Doherty et al., 2002). Interestingly, the younger group showed greater

WM in relation to BMI in regions involved in inhibitory control, namely the dlPFC and middle frontal gyrus. These findings could suggest that WM in inhibitory control regions may be affected initially in relation to overeating, but that over time, reward regions are differentially affected. However, it should be noted that the younger sample varied in BMI from lean to obese, but the older sample were only of those who were overweight or obese. Thus, the lack of volumetric differences in the older group may be because those individuals had already gained excessive weight.

Limitations

First, due to possible registration errors and smoothing, it cannot be excluded that some GM volume is included in the total WM volume and vice versa. Second, the current study was conducted solely with young females, thus results should be generalized with caution to males and to adults. Third, while BMI was used as an indicator of obesity other measurements of adiposity, such as body fat percentage or waist-to-hip circumference ratio (WHR), were not used. WHR is an indicator of metabolic syndrome and is positively correlated with elevated levels of inflammatory cytokines IL-1β and IL-6 (Spranger et al., 2003), which increase risk for insulin resistance and type 2 diabetes (Hu, Meigs, Li, Rifai, & Manson, 2004). WHR is also an indicator of increased risk for obesity and its associated medical sequelae including hypertension, cardiovascular disease, stroke, and cancer (Kissbah & Krakower, 1994; Gillum, 1999; Gower, Nagy, & Goran, 1999; Borugian et al., 2003). Because GM/WM volumetric differences may be due to the influence of inflammatory markers (e.g., Marsland et al., 2008; Cazettes et al., 2010; Willette et al., 2010), WHR or waist circumference may be more sensitive than BMI in detecting

brain volume alterations as a result of excess adipose tissue, particularly in the abdominal region, which is reflective of visceral versus subcutaneous fat in adolescents (Taylor, Jones, Williams, & Goulding, 2000). Although BMI measurements are widely used, BMI does not account for body fat patterning. Future studies would benefit from collecting other measurements of adiposity to examine its relation to regional and global brain volume.

Despite the aforementioned limitations, the current findings suggest that elevated weight is associated with reduced global GM and increased GM in the middle occipital region. Additionally, we found that elevated weight is associated with increased WM in food-related and reward processing regions (e.g., middle temporal gyrus, vlPFC, dorsal striatum). Results also indicate that genes related to compromised dopamine functioning moderate the relations between BMI and GM volume. Finally, reduced GM volume in the superior frontal gyrus was associated with increases in BMI, suggesting that structural abnormalities in regions of inhibitory control may be a risk factor for weight gain. These findings suggest that regional and global brain volume abnormalities are related to BMI and more importantly, to increases in BMI at a relatively young age, potentially resulting in greater risk for future declines in cognition or other brain functions.

Study II: Morphology in At-Risk Adolescents

Study 2 aimed to extend findings from Study 1 to a sample of male and female adolescents at-risk of obesity by virtue of parental obesity. It was hypothesized that adolescents at-risk for obesity versus those not at-risk would show greater GM and WM volume in somatosensory, gustatory, and reward regions (e.g.,

insula, frontal operculum, vmPFC, mOFC, striatum, and posterior cingulate cortex) and less GM and WM volume in prefrontal regions (e.g., dlPFC, middle PFC, vlPFC and superior frontal gyrus). Further, due to TaqIA A1 interactions with BMI, it was hypothesized that variants in dopamine gene expression would also moderate relations with BMI percentile change over 1-year follow-up.

Methods

Participants

Participants were 27 male and 27 female adolescents (M age = 15.1, SD=1.07). Of the sample, 84% identified as White/Caucasian, 6% Hispanic, 3% Black/African-American, 2% Asian American, 5% American Indian/Native Hawaiian. Thirty-one were high-risk adolescents of two obese or overweight parents (BMI $\geq$ 27) and twenty-three were low-risk adolescents of two lean parents (BMI $\leq$ 25). Participants in the high-risk group had a mean initial BMI = 20.4 (SD=1.70). Participants in the low-risk group had a mean initial BMI = 20.6 (SD = 1.98). The same exclusion criteria from Study 1 were used in Study 2. There were no differences between high- and low-risk groups on age, sex distribution, or BMI.

Measures

Genotyping and BMI data were collected and assessed in the same manner as in Study 1. However, BMI for this sample was collected at two time points (baseline and 1-year after baseline). Because this current sample consisted of adolescents, percent change in BMI percentile from baseline to year 2 was used as a measure of weight gain. BMI percentiles adjusted for age were calculated using an online

calculator developed by Roman Shypailo (Baylor College of Medicine, Children's Nutrition Research Center).

MRI acquisition

Scanning, image acquisition parameters and preprocessing were identical to those in Study I. Because this sample consisted of adolescents, T1 images were segmented into GM, WM, and CSF based on age-specific tissue probability maps customized for the present sample using data from a National Institutes of Health study of 404 children (Template-O-Matic Toolbox; Wilke, Holland, Altaye, & Gaser, 2008).

Statistical analysis

All analyses controlled for sex, global GM and global WM volume in respective GM and WM analyses. All models tested for differences in regional GM and WM. ANOVA models were used to compare high- versus low-risk groups and differences within males and within females. Regression models were used to test regional differences related to percent change in BMI percentile in high- versus low-risk groups. Full factorial interaction ANOVA models were used to test whether each of the genetic alleles for dopamine gene expression (TaqIA A1 and DRD4 alleles) moderated percent change in BMI percentile.

Region of interest (ROI) masks were created using the WFUPickatlas to test specific GM hypotheses. ROIs for inhibitory control included the IFG, middle frontal gyrus/PFC, dlPFC, posterior cingulate, medial frontal gyrus, and SFG. ROIs for reward processing included the insula, thalamus, Rolandic operculum, orbitofrontal cortex, dorsal striatum, and inferior-, middle-, frontal and parahippocampal gyri. T-

maps were thresholded at $p<0.001$ uncorrected with a cluster extent of 90 for GM 69 for WM. Cluster extent thresholds were empirically determined based on the expected number of voxels per cluster for a $p<0.001$ uncorrected threshold. Predicted activations were considered to be significant at $p<0.05$ after correcting for multiple comparisons (pFDR) across the voxels within the *a priori* defined regions of interest. Peaks outside the hypothesized regions were considered to be significant at $p<0.05$ FDR corrected across the whole brain.

Results

There were no differences found across any contrasts at a threshold of pFDR<.05 within either *a priori* regions or across the whole brain (GM effect size r range = .42 - .56; WM effect size r range = .43 - .58). There were also no differences in global GM or WM between high- and low-risk groups, $t_{GM}(52)=.07$, p=.95 and $t_{WM}(52)=.34$, p=.73. Additionally, there were no main effects of regional differences in GM or WM for the TaqIA A1 and DRD4 alleles.

Discussion

In conjunction with the results of Study 1, these findings suggest that volumetric differences in GM and WM are not due to risk status and may emerge as a consequence of excessive weight gain. A possibility of null effects is that in the present study, all participants consisted of lean, relatively healthy adolescents and prior studies have only tested for volumetric differences related to BMI. Normal GM and WM development in adolescents show dramatic increases prior to puberty followed by decreases post-puberty (Giedd et al., 1999; Sowell, Thompson, Tessner, & Toga, 2001). Additionally, longitudinal studies demonstrate that volumetric

atrophy naturally occurs over the lifespan (Sowell et al., 2003). Thus, because this study utilized a young, lean sample, it is possible that no significant atrophy has yet occurred. Further, the adolescents in this sample reported no current or known prior history of an Axis I disorder or substance abuse. Major depression, bipolar depression, schizophrenia, anorexia nervosa, and substance use have been associated with morphological deficits in children and adolescents (e.g., Thompson et al., 2001; Chang et al., 2005; Lopez-Larson et al., 2011; Steingard et al., 2002; Gaudio et al., 2011). Collectively, these data suggest that null effects may have been due to the age and relative health of the participants in both groups. It is highly likely that there was no atrophy significant enough in GM or WM for group comparisons in a sample of young, healthy adolescents. Thus, risk status for obesity may not influence GM and WM at this stage.

As in Study 1, due to possible registration errors and smoothing, it cannot be excluded that some GM volume is included in the total WM volume and vice versa. Additionally, there was no difference in BMI or percent change in BMI percentile between the high- and low-risk groups over 1-year follow-up, further limiting the likelihood of detecting morphological changes related to weight. Follow-up over a longer period of time would be a better test of risk for future weight gain, as weight is typically gained over several years. Indeed, the prevalence of obesity doubles from childhood to adulthood (Kimm et al., 2002). However, it could also be that adolescents in the high risk group are more resilient to obesity because they have stayed lean throughout early adolescence, despite having two obese or overweight parents. In the larger sample from which the current participants were drawn, there

was a trend for the low risk group to gain more body fat than the high risk group. It is likely then, that the high risk group actually represents a group more resilient to obesity than the typical adolescent. As discussed in Study 1, changes in body fat percentage and WHR may be a more accurate measure of adiposity-related differences in GM/WM volume. Future studies should test whether body fat/WHR change is more directly related to GM/WM volume as it may be a more sensitive test of differences in this population.

Additionally, risk status may not contribute to alterations in brain volume as much as excessive weight gain, which could suggest that lifestyle is a more potent risk factor for predicting neurological changes. It is not yet clear how genetic and lifestyle factors interact in predicting obesity (Parsons, Power, Logan, & Summerbell, 1999). It may be that genes (e.g., parental obesity) confers more risk for obesity an early age while lifestyle factors are more predictive of obesity during adolescence as children become more independent in their choice of diet and activity. In a study of early childhood risk factors for obesity at age 7 years, parental obesity predicted childhood obesity more than a sedentary lifestyle (i.e., more than 8 hours of television viewing), although both were the top eight risk factors for obesity (Reilly et al., 2005).

Further, other factors such as socioeconomic status can also influence risk for obesity. Future neuroimaging studies should examine the relative contributions of genes versus lifestyle (e.g., diet and exercise) on GM/WM volume in adolescents and adults, which may aid in clarifying how other environmental factors (e.g., SES) contribute to the development of obesity. In a laboratory study, increasing the price of

unhealthy or healthy foods leads to decreased purchase of those foods in adolescents (Epstein et al., 2006). Additionally, low SES individuals are more likely to purchase convenient, high-calorie, low-nutrient foods and have less exposure to environments in which to exercise and purchase healthier foods (Yeh et al., 2008; Smoyer-Tomic et al., 2008). If diet rather than genes is more directly related to cerebral changes, then prevention programs should aim to reduce environmental risks for obesity. On the other hand, if genes confer more risk, then knowledge of these genetic factors could aid in identifying individuals more in need of interventions to prevent excessive weight gain. Finally, because inflammatory markers are associated with GM and WM differences, future studies should also assess measures of inflammatory cytokines such as IL-6 or fibrinogen in relation to volumetric changes in the brain. Indeed, elevated levels of fibrinogen in lean individuals are negatively correlated with GM volume in the PFC and parietal and occipital regions (Cazettes et al., 2010), which could contribute to risk for future weight gain. A prospective study evaluating inflammatory markers and genetic risk in lean and overweight/obese individuals would be better able to examine how these risk factors may or may not differ in influencing weight gain.

Study III: Functional Connectivity of Impulsivity and Reward

Neuroimaging studies suggest that a prefrontal-cingulate network is responsible for impulse control, but no study has yet examined connectivity of regions implicated in reward processing and inhibitory control in obesity. Accordingly, Study 3 examined whether abnormalities in connections between the PFC and amygdala and striatum relate to BMI in a go/no-go task. Because prior

neuroimaging studies have found functional abnormalities in inhibition (Batterink et al., 2010) and reward sensitivity (Stice et al., 2008a; 2008b), it was hypothesized that obese versus lean participants would have reduced connectivity between prefrontal and reward processing regions during inhibition (no-go) as compared to no inhibition (rest).

Method

Participants

Participants were 38 women (M age = 15.7, SD = 0.93; M BMI = 24.5, range = 17.3-38.9); 2% Asian/Pacific Islanders, 2% African Americans, 86% European Americans, 5% Native Americans, and 5% who reported mixed racial heritage. Participants were recruited from a larger prevention trial of female high school students with body image concerns. Individuals in this larger study who gave consent to be contacted about other studies were asked to participate in a study of the neural response to presentation of food. Exclusion criteria were the same as in Study 1 and 2.

BMI and genotyping were collected and assessed using the same methods as in Study 2. For this study, BMI was assessed at baseline, 6-month, and 1-year follow-up. One participant dropped out of the study during the follow-up period and was not included in any analyses using BMI change, although her data was included for all other analyses.

fMRI paradigm

Participants were asked to consume their regular meals, but to refrain from eating/drinking for 4-6 h immediately preceding their imaging session for

standardization purposes. The go/no-go paradigm was designed to examine inhibition of prepotent responses to appetizing food items. Two functional runs were carried out and each run consisted of 48 trials. For each trial, a picture of a vegetable (go trial, 75% occurrence) or a picture of a dessert (no-go trial, 25% occurrence) was presented for 500 ms. Participants were instructed to respond with a button press to all vegetables (go trials), but to withhold their responses to desserts (no-go trials), and to respond as quickly and accurately as possible. The percentage of go and no-go trials was intended to test inhibition of a prepotent response towards desserts. Examples of go trials included pictures of broccoli, carrots, cabbage, and eggplants. Examples of no-go trials included pictures of chocolate cake, pie, ice cream, and cookies. Trials were separated by a fixation cross.

Reaction times were measured from the beginning of trial onset and collected with a fiber-optic response box system. Trials were presented in pseudo-randomized order, designed so that desserts appeared with equal frequency after 1, 2, and 3 vegetable presentations. Stimuli were presented visually using the Presentation software package (Version 9, Neurobehavioral Systems, Davis, CA) and were displayed using a video projector that illuminated a rear projection screen located at the end of the magnet. Participants viewed stimuli through an adjustable mirror attached to the head coil. MRI acquisition was synchronized with the paradigm.

Behavioral analyses

For each participant, median reaction times for incorrect go and incorrect no-go trials were calculated. The mean rate of commission errors was calculated as the total number of failures of inhibition divided by the total number of no-go trials. The

mean rate of omission errors was calculated as the total number of failures of response divided by the total number of go trials. Spearman's rho was used to calculate the correlation between reaction time, rate of commission errors, and BMI.

Image acquisition and preprocessing

Scanning was performed in the same scanner as in Studies 1 and 2, as were the parameters for collection of anatomical images. Functional scans used a T2*-weighted gradient single-shot echo planar imaging sequence (TE=30ms, TR=2000 ms, flip angle=80°) with an in plane resolution of 3.0x3.0 mm^2 (64x64 matrix; 192x192 mm^2 field of view). To cover the whole brain, 32 4 mm slices (interleaved acquisition, no skip) were acquired along the AC-PC transverse, oblique plane as determined by the midsagittal section.

Data were preprocessed and analyzed using SPM8 software in MATLAB. Non-brain tissue from all functional and structural images was removed using BET in FSL. Volumes were manually realigned to the AC-PC. Each functional image was spatially realigned to the mean of all functional images for that participant, minimizing the effects of head movement. Functional and anatomical images were coregistered and all images were normalized to the standard MNI template in FSL (MNI152). Functional images were smoothed with a 6 mm FWHM isotropic Gaussian kernel.

Statistical Analysis

Condition-specific effects at each voxel were estimated using general linear models for each participant. Vectors of the onsets for each event of interest were compiled for correct responses to go trials, correct responses to no-go trials, and

incorrect responses to both go and no-go trials. For participants with no incorrect responses, an onset from the end of the trial was inserted as a placeholder for the vector of incorrect responses so that analyses could be performed. A 128 sec high-pass filter was used to remove low-frequency noise and slow drifts in the signal. Linear contrasts were computed for correct go>rest (i.e. baseline) and correct no-go>rest. A psycho-physiological (PPI) analysis was used to test the hypothesis of a negative correlation between BMI and reduced connectivity between prefrontal and reward regions. PPI examines whether the activity in one region (i.e., a "seed" region) differs according to the task and then tests the connectivity in activity between the seed region and other regions (Friston, Buechel, Fink, Morris, Rolls, & Dolan, 1997).

Normality assumptions were not violated. To identify seed regions for the PPI analysis, a robust regression was performed on contrasts from the individual fixed effects models with BMI as a covariate using the robust regression toolbox developed by Tor Wager in MATLAB (Wager, Keller, Lacey, & Jonides, 2005). The robust regression technique has been shown to decrease rates of false positive effects due to outliers, thereby increasing statistical power (Wager et al., 2005).

A psychophysiological interaction between the seed regions and contrast condition (i.e., no-go>rest) was created for each participant and then used to construct a new fixed effects model. A robust regression was then performed at the random effects level for group analysis. BMI scores were entered into this second-level model as a covariate to assess BMI-related differences in patterns of connectivity. To correct for multiple comparisons, 3DClustSim (an updated version of AlphaSim) was used,

which is a Monte Carlo simulation program. 3DClustSim accounts for voxel-wise and cluster-volume thresholds to establish a false discovery rate of 5%.

Results

Behavioral data

As previously reported in Batterink et al. (2010), median reaction time for go trials was 651 ms (SD=140 ms). Median reaction time for no-go trials that were incorrectly responded to was 588 ms (SD=261 ms). The mean rate of commission errors was 11.3% (SD=13.5) and the mean rate of omission errors was 2.5% (SD=4.5). Median reaction time to go trials was negatively correlated with baseline BMI (N=35, r=-0.54, p=0.0001), such that participants with higher BMI scores showed significantly faster reaction times.

Rate of commission errors was also positively correlated with baseline BMI (N=35, r=0.50, p=0.0002), such that participants with higher BMI scores showed significantly more false positive responses. Change in BMI over 1-year was not significantly correlated with any behavioral measures of response inhibition deficits (N=35, range r=0.382 to -0.322, n.s).

Identification of seed regions: Correlates of successful inhibition (no-go>rest)

Robust regression analyses at the fixed effects level identified five regions that showed increased activation during successful inhibition controlling for BMI: vmPFC (-6, 50, 25), anterior insula (-33, 20, -11; 36, 17, -8), medial PFC (0, 38, 43), and dlPFC (45, 20, 13). These regions were entered as seed regions into a PPI analysis for each participant.

Functional connectivity during successful inhibition

Two robust regressions were performed at the group level. The first regression was run to determine connectivity with the seed regions independent of BMI (main effects) and the second was run to determine connectivity in relation to BMI. Results of the first regression showed that activity in the anterior insula correlated negatively with activity in the SFG (-30, 60, 16, z=4.04, k=17, p<.001). Activity in the vmPFC correlated positively with the thalamus (-6, -28, -5, =4.77, k=12, p<.001), inferior temporal gyrus (-45, -61, -5, z=4.71, k=79, p<.001), postcentral gyrus (-30, -43, 55, z=4.25, k=35, p<.001), middle frontal gyrus (-30, -7, 58, z=4.60, k=12, p<.001). A second robust regression testing the relation of activity in seed regions to BMI did not find any significant correlations.

Discussion

Expected regions were found in response to successful inhibition including the dlPFC and IFG, which were entered as seed regions into connectivity analyses. Main effects of the connectivity analyses showed a negative correlation between activity in the anterior insula and the SFG, a region involved in inhibitory control. This finding suggests that during successful inhibition the SFG may dampen activity in a reward-associated region or that successful inhibition requires less activation of reward circuitry relative to increased activation of regions involved in inhibitory control. Results also showed that activity in the vmPFC was positively correlated with activity in the thalamus, postcentral gyrus, and inferior temporal gyrus. As discussed earlier, the vmPFC is implicated in encoding the value of a potential reward. Activation of the thalamus during successful no-go trials has been found in previous studies

(Duann, Ide, Luo, & Li, 2009; Rubia, Smith, Talor, & Brammer, 2007) and is hypothesized to function in an indirect inhibitory pathway (Alexander, Crutcher, & DeLong, 1999). The postcentral gyrus is a somatosensory region (Corkin, Milner, Rasmussen, 1970) and in particular, increased blood flow occurs in this region in response to pictures of palatable food (Wang et al., 2004). The inferior temporal gyrus is involved in processing color and shape in visual cues (Newcombe, Ratcliff, & Damasio, 1987; Haxby et al., 1988). Thus, it appears that a network involving reward valuation, inhibitory control, and somatosensory and visual processing regions are also activated during successful inhibition. It may be that even in the face of greater value and primary sensory processing of an object, the indirect inhibitory pathway that functions partly through the thalamus is able to successfully override the "go" response towards an appetitive stimulus.

Contrary to hypotheses there was no significant functional connectivity between regions involved in inhibitory control and reward processing in relation to BMI. Null effects for the connectivity analyses related to BMI could be due to the low base rate of incorrect no-go responses. A contrast of correct versus incorrect no-go responses may be more revealing about the relation between activity in inhibitory control and reward regions because incorrect no-go trials reflect failure of the inhibitory control system. In the present study, only successful inhibition responses could be analyzed. However, these findings do suggest that these regions may not interact during tasks requiring inhibitory control in relation to BMI. Theorists have suggested that a successful, behavioral inhibitory response can be the product of two networks: an indirect pathway that consists of connections from the caudate, globus

pallidus, and sub-thalamic nuclei to the thalamus (i.e., cortico-striatal-thalamic pathway; Alexander et al., 1990) or a direct cortico-subthalamic pathway (Nambu, Tokuno, & Takada, 2002). In fact, one experimental study has suggested that there may be three networks (indirect, fronto-parietal, and parietal-premotor pathways) involved in successful inhibitory control, but that the indirect network exerts more control over the others in healthy adolescents and adults (Stevens, Kiehl, Pearlson, & Calhoun, 2007). Additionally, several studies have found that the IFG is more positively correlated with activation in the presupplementary motor region (a region responsible for motor response), caudate, thalamus and cerebellum in correct no-go versus incorrect no-go trials (Duann et al., 2009; Rubia et al., 2007). It may be that several pathways differ in their relative strength as BMI increases, which the current study was not designed to test. Further, activation of these pathways may differ due to response speed. Greater activity in the IFG and subthalamic nucleus (direct pathway) has been found in faster versus slower successful no-go responders as defined by subtracting the average time elapsed on no-go trials from correct go trials (i.e., race model; Aron & Poldrack, 2006). It may be that BMI interacts with response speed in the activation of particular inhibitory control networks.

If it is the case that there are two or more pathways to successful inhibition, the findings of the current study highlight the importance of examining incorrect no-go responses in order to test the contribution of varying inhibitory control networks. Inclusion of an adequate number of incorrect no-go trials could elucidate which network is responsible for failed inhibitory control or how these networks interact in relation to weight. In addition, tests of these specific inhibitory control networks in

response to food stimuli have not been examined. It has been suggested that the relative activation of such networks may vary in response to the inhibitory task (Stevens et al., 2007). This would have implications for a better understanding of the factors involved in the onset or maintenance of overweight, as different inhibitory control pathways may vary in their relative importance as BMI increases.

It is also possible that null effects were due to the age and BMI of the sample. Participants were young high school students (M age = 15 years) and the majority of them were in the lean range. Because young adulthood is one of the high risk periods for obesity, many of the girls at the time of data collection who were categorized as lean would have gained excessive weight by adulthood. Thus, functional connectivity between prefrontal and reward regions as a function of BMI may have not emerged due to the fact that many in the sample would become overweight. It is also possible that covariates such as SES obscured differences in connectivity. Individuals from a low versus high SES tend to experience more stress, maladaptive coping styles, and poorer diet (Hulshof et al., 1991; Kristenson, Eriksen, Slulter, Starke ,& Ursin, 2003). Those from low SES backgrounds perform more poorly on tests of cognitive functioning, showing significant deficits in memory, working memory, and cognitive control (Farah et al., 2006). Further, chronic stressors increase activity in the amgydala and anterior cingulate gyrus (Gianaros et al. 2008) and decrease GM volume in the caudate and hippocampus (Gianaros et al., 2007; Cohen et al., 2006). It may also be possible that connectivity differences emerge slowly over time. For instance, Stanek et al. (2011) found that the extent of WM tracts in obese adults was less than that in lean adults, and that this effect was more pronounced in older adults.

Because WM is involved in networking various cortical regions, it could be that connectivity abnormalities emerge over a longer period of time. Evidence also suggests that SES influences obesity prevalence

It may also be the case that connectivity between prefrontal and reward regions do not differ as a function of BMI. The results of the present study suggest that there is no connectivity between prefrontal and reward processing regions related to BMI, which is the first study to examine functional connectivity in inhibitory control using a food-related task. Although prior research suggests that inhibitory control may be a result of a network of regions both in the prefrontal cortices and those in limbic/reward processing regions (e.g., Markela-Lerenc, 2003) it may be that differences in inhibitory control as it relates to BMI may be more of a dysfunction within one network rather than an abnormality in the connection between networks. Indeed, Stoeckel et al. (2009) have found that obese versus lean women show stronger connectivity from the OFC to nucleus accumbens, but reduced connectivity between the amygdala and OFC, and amygdala and nucleus accumbens, indicating that dysfunction within a reward network is related to BMI. A similar dysfunction in an inhibitory control network has not yet been tested in obesity. Thus, it is possible that abnormalities within a reward or inhibitory control network could be related to BMI rather than abnormalities between these networks. A more nuanced understanding of the neural pathways involved not only in inhibitory control, but specifically, in inhibitory control related to excess weight is needed.

CHAPTER III

DISCUSSION

General Discussion

The general goal of these studies was to contribute to neuroimaging research on impulsivity factors related to obesity. It was hypothesized that those with a higher BMI or at-risk for obesity versus at a lower BMI or not at-risk would show structural differences in regions related to reward processing and inhibitory control. In Study 1, these differences were supported in that less global GM and WM volume was found as BMI increased in young women ranging in BMI from lean to obese. Although BMI was not associated with regional GM differences, BMI was positively correlated with WM volume in the vlPFC, middle temporal gyrus, parahippocampal gyrus, the Rolandic operculum and negatively correlated in the mOFC. These results suggest that a higher BMI is associated with greater WM in regions involved in taste processing and behavioral control. Further, less GM volume in the SFG, a region associated with inhibitory control, predicted future increases in BMI over 1-year follow-up.

Additionally in Study 1, the TaqIA A1 allele moderated differences in GM and WM. Those with an A1 allele and a higher BMI had less GM volume in the IFG, a region involved in inhibitory control, and the frontal operculum, a somatosensory region. This allele has been shown to decrease glucose metabolism in inhibitory control and reward regions including the IFG, caudate, putamen, medial PFC and middle frontal gyrus (Noble, Gottschalk, Fallon, Ritchie, & Wu, 1997). These findings suggest that BMI, in combination with genotypes associated with

compromised dopamine functioning, negatively influences regional brain structure. To date, this is one of the first studies examining the interaction of genotyping and BMI on structural abnormalities. Further, it is the first study to prospectively test relations between BMI and future weight gain. These findings suggest that a structural deficit in a region involved in inhibitory control predicts future weight gain.

Study 2 tested for structural differences in male and female adolescents between those at high and low risk for obesity by virtue of parental obesity. There were no global or regional differences in GM/WM between high- and low-risk adolescents and no differences moderated by genetic alleles for dopamine expression. It may be that there are no differences in brain volume in lean and relatively healthy adolescents. The findings from Study 1 and Study 2 collectively suggest that structural changes in GM and WM may not occur until excessive weight has already been gained. If so, it appears that after weight gain, structural changes may occur in regions implicated in reward processing and successful behavioral inhibition. Larger prospective studies are needed to replicate these findings. If it is the case that morphological changes in the brain do not occur until after excessive weight gain, a larger study following those who do and do not show excessive weight would be better able to test whether GM and WM volumetric differences emerge as a consequence of weight gain. Although Study 1 found that less GM volume in the SFG predicted weight gain over 1-year follow-up, excessive weight may occur over the course of several years. If these findings are replicated in prospective trials, it would indicate that differences in GM and WM volume are not risk factors for

obesity, but may be a consequence of weight gain, perpetuating the maintenance of unhealthy weight.

Further, the genetic results from Study 1 and 2 suggest that the Taq1A and DRD4 long alleles may not be risk factors for GM/WM volumetric changes, but instead may moderate GM/WM volume after excessive weight has been gained. The Taq1A allele has been found to alter learning such that adults with this allele show more difficulty in maintaining a new and rewarded behavior compared to those without the allele, which is also reflected as decreased engagement of the ventral striatum and the OFC in those with versus without the allele (Jocham et al., 2009). It could be that part of the reason why it is difficult to lose weight is that those who are obese must engage in a new yet potentially rewarding behavior such as exercise or healthier eating (which has long-term rewards such as prevention of illness and improvement in quality of life). The Taq1A allele may contribute to the maintenance of obesity not only in altering brain structures but also by altering the functionality of these regions. If that is the case, prospective studies should also consider genetic influence on volumetric changes. Findings from Study 2 of high and low risk youth by virtue of parental obesity also suggest that genes may not be as potent risk factors as lifestyle habits in the development of obesity. Future studies should test whether environmental influences such as type of diet or activity level impact GM and WM volume.

Additionally, because GM/WM changes may be linked with inflammatory markers (e.g., Jefferson et al., 2007; Marsland et al., 2008; Cazettes et al., 2010), measures of adiposity more sensitive to these markers such as body fat percentage

may be better able to indicate morphological changes in brain tissue. Because the waist-to-hip ratio (WHR) is indicative of metabolic syndrome, which leads to an increased level of inflammatory cytokines (Zhu, Wang, Shen, Heymsfield, & Heshka, 2003), WHR may also be a more sensitive than BMI in detecting morphological changes in the brain. Inflammatory cytokines/adiopokines such as fibrinogen, IL-1β, IL-6, and C-reactive protein are associated with excess adipose tissue (Duncan et al., 2000; Festa et al., 2001; Hirosumi et al., 2002; Doupis et al. 2011). Elevated levels of such inflammatory markers are positively correlated with insulin resistance, metabolic syndrome, type 2 diabetes (Spranger et al., 2003; Hu, Meigs, Li, Rifai, & Manson, 2004; Guerre-Millo, 2002) and predict weight gain in adults (Duncan et al., 2000).

WHR and body fat percentage are indicators of metabolic syndrome (Zhu et al., 2003) and are positively correlated with elevated levels of inflammatory cytokines IL-1β and IL-6 (Spranger et al., 2003; Wisse, 2004), which also increase risk for insulin resistance and type 2 diabetes (Hu, Meigs, Li, Rifai, & Manson, 2004). WHR and body fat percentage are also an indicator of increased risk for obesity and its associated medical sequelae including hypertension, cardiovascular disease, stroke, and cancer (Kissbah & Krakower, 1994; Gillum, 1999; Gower, Nagy, & Goran, 1999; Borugian et al., 2003). Thus, measures such as WHR and body fat may be more sensitive than BMI to structural alterations in the brain, since increased WHR and body fat correlate with elevated levels of inflammatory cytokines.

Nevertheless, findings from Studies 1 and 2 indicate that morphological changes do occur in GM and WM in regions responsible for inhibitory control.

Morphological changes also correlated with weight status, suggesting that such changes may underlie functional abnormalities observed between obese and lean individuals in impulsivity. However, the signficance of volumetric differences, particularly those of WM, is unclear. Although several studies have found decreased regional WM in obese versus lean (Pannacciulli et al., 2006; Raji et al., 2009), one other study has found increased global WM in obese individuals (Haltia et al., 2007). It could be that abnormalities in the integrity of WM more directly underlie cognitive functioning that WM volume. One spectroscopic study has found that BMI is negatively correlated with a marker of neuronal viability in WM in frontal and parietal regions and membrane metabolism in frontal regions (Gazdzinski, Kornak, Weiner, & Meyerhoof, 2008). To better evaluate the role of WM in cognitive functioning in obesity, future studies should examine factors that affect WM integrity such as microscopic lesions, membrane metabolites, and myelination. Further, it may be possible to reverse structural changes as Haltia et al. (2007) found with a low-calorie diet. However, regional changes in GM and WM as a function of long-term weight loss have not yet been tested. Based on the findings from Studies 1 and 2, prospective studies are needed to determine whether excessive weight gain causes volumetric changes, how these changes interact with genetic factors, and to examine if environmental influences are predictive of volumetric changes.

Finally, Study 3 examined whether reward and inhibitory control regions were functionally related in young women during a go/no-go task in relation to BMI. Although increased activation of the dlPFC and IFG was found in response to successful no-go responses, no connectivity with other regions correlated with BMI

were found. Future studies with an improved design of the go/no-go task are needed to address this question. Due to the low base rate of incorrect no-go responses, it may be necessary to modify the go/no-go paradigm to become increasingly more difficult (e.g., decreasing stimuli presentation intervals, increasing number of go stimuli prior to presentation of a no-go stimulus with an adaptive design) depending on prior performance so that an adequate number of errors will occur. It would also be beneficial for future studies to include go trials to desserts and no-go trials to vegetables so that instruction type and stimulus type are not confounded. A more balanced design may also increase ability to detect connectivity effects as one study has found that during behavioral inhibition in response to negatively-valenced stimuli, activity in the inferior frontal cortex is negatively correlated with amygdala and insula activation, which is not present during go trials toward the same stimuli (Berkman, Burklund, & Lieberman, 2010). It could be that desserts are associated with positive emotions and vegetables with negative ones, particularly for those who overconsume unhealthy foods. If so, connectivity differences between inhibitory and reward processing regions as a function of BMI may emerge with a more balanced design.

It is also possible that no connectivity exists between prefrontal and reward processing regions as a function of BMI. Future studies should test whether connectivity within an inhibitory control network such as the IFG-basal ganglia network suggested by Aron et al. (2007) differs in relation to BMI. Still, findings from the first two studies, in conjunction with other prospective risk factor studies (Seeyave et al., 2009; Francis & Susman, 2009) suggest that impulsivity may play a

role in weight gain in that structural deficits in inhibitory regions may contribute to the maintenance of obesity. Additional studies should test whether volumetric differences observed after weight gain can be reversed with long-term maintenance of weight loss. Collectively, these findings indicate a need for interventions to improve deficits in impulsivity, as it may prevent the onset of and maintenance of obesity. Neuroimaging methods may aid in elucidating active components of obesity interventions most beneficial for particular individuals.

Implications and Conclusion

Findings from the present series of studies suggest that neurological changes related to impulsivity occur after unhealthy weight gain, although less GM in inhibitory control regions may predict weight gain in adults. Interventions to increase inhibitory control may be most effective for children and adolescents, as this is a critical period for the development of executive control (Chambers, Taylor, Potenza, 2003). Indeed, grey matter development in the frontal lobe peaks at around 12 years of age (Giedd et al., 1999) and the prefrontal cortex is one of the last regions to mature at around late adolescence (Gogtay et al., 2004). Development of WM does not reach maturity until the late 20's (Paus, 2001). Further, activation of inhibitory control networks differs in adolescents compared to adults; adolescents show less engagement of the fronto-striatal-thalamic network (indirect pathway) and no evidence of a relation between the indirect pathway and a fronto-parietal pathway compared to adults during successful inhibitory control (Stevens et al., 2007). Thus, the most effective efforts in preventing obesity onset may be those that target this population. One neuroimaging study with overweight children has found that aerobic

exercise versus non-exercise improves activation in the PFC and decreases activation in the posterior parietal cortex from pre- to post-intervention (Davis et al., 2011). In that study, scores on a clinician-administered assessment of executive function also increased proportionally to the amount of aerobic exercise performed, suggesting that aerobic exercise could be an effective intervention in increasing impulse control in children. A meta-analysis of aerobic fitness has found that regular exercise impacts executive control the most compared to other cognitive functions (Colcombe & Kramer, 2003) and of note, older adults who engaged in regular, high-aerobic activity versus low-activity adults show increased activity in regions of the PFC (e.g., middle- and superior- frontal gyrus) and less activity in the ACC (Colcombe, 2004). Further, after 6 months of an aerobic exercise intervention, older adults showed functional changes in the same regions as well as better performance on behavioral tasks.

It could be that aerobic/cardiovascular exercise increases neural functioning via increasing blood flow and nerve growth proteins (e.g., brain-derived neurotrophic factor) as demonstrated in animal studies (Cotman & Berchtold, 2002) or that exercise is one method of practicing engagement in long-term, goal-directed behavior (Tomporowski et al., 2008), which theoretically should improve performance on tasks requiring executive control. In addition, there may be differential impact of type of aerobic activity (e.g., group versus individual) on executive control. Perhaps learning to function in a team-oriented, aerobic activity (e.g, soccer, basketball) impacts cognitive abilities differently from individual aerobic activities (e.g., track, swimming). In rats, play fighting with others increases growth in the OFC, a region that has also been implicated in decision-making and planning behavior (Pellis &

Pellis, 2007). Regions implicated in executive control, such as the PFC, do not operate in isolation from other regions (Krawczyk, 2002) and it may be that the context of physical activity impacts other regions of brain function that also influence activity in executive control regions.

In addition to exercise interventions, neurocognitive training (i.e., tasks that directly improve cognitive function) may promote behavioral inhibition. For instance, improving working memory using tasks to increase digit span and word memory has been found to improve delay discounting in adults in treatment for stimulant abuse (Bickel, Yi, Landes, Hill, & Baxter, 2011), but did not improve response inhibition. It has been suggested in drug addiction that neural changes occur in response to intake of a rewarding substance, reflecting the conditioning process (Everitt & Robbins, 2005). Tasks that involve inhibiting a response toward food stimuli such as exposure and response prevention or habitual practice in reallocating attention toward non-food specific stimuli may improve behavioral inhibition by decoupling the conditioned association of a habitual response with reward. Additionally, reinforcing goals when performing a currently non-rewarding task (e.g., exercise, restricting consumption of high-calorie foods) may over time, condition individuals to pair that activity with a positive thought that in and of itself can be rewarding (goals), thereby reducing the conditioned response to impulsively act toward food stimuli or away from physical activity.

The continuing rise in rates of obesity and its associated medical sequelae including diabetes, cardiovascular disease, and cancer, indicate that current prevention and treatment efforts are inadequate in effectively addressing long-term

maintenance of a healthy weight. Neuroimaging methods can provide an objective method of elucidating etiologic and risk factors involved in unhealthy weight gain. Data from the present series of studies suggest that structural abnormalities related to regions involved in inhibitory control may not be a risk factor for obesity, but may emerge as an outcome of overeating. Consequently, neuronal changes as a result of chronic overeating may contribute to the maintenance of such behavior, creating a vicious cycle. Morphological abnormalities emerging after weight gain in regions involved in inhibitory control may be a factor in explaining why weight loss is difficult to achieve and maintain for so many individuals. Future research examining how specific aspects of impulsivity impact brain functioning in relation to obesity can better inform prevention and treatment efforts addressing this epidemic.

APPENDIX

TABLES AND FIGURES

Table 1. Locations of significant regional differences in grey and white matter volume

Region and regression condition	L/R	*x*[a]	*y*	*z*	*V*[b]	Z value	*p*FDR corrected	Effect size (r)
Grey matter								
Positive correlation with BMI								
Middle occipital gyrus	R	44	-90	1	833	5.40	0.004[c]	.59
Negative correlation with increase in BMI								
Superior frontal gyrus	R	8	-4	72	545	3.99	0.02	.44
	R	24	-6	72	95	3.57	0.02	.39
Negative correlation with BMI and TaqIA A1 allele								
Inferior frontal gyrus	L	-45	14	13	251	4.08	0.04	.45
	R	53	17	18	115	3.76	0.04	.41
Frontal operculum	L	-48	18	6	251	3.65	0.04	.40
	R	44	18	3	103	3.67	0.04	.40
White matter								
Positive correlation with BMI								
Middle occipital gyrus	R	29	-84	9	1868	4.87	0.03[c]	.53
Ventrolateral prefrontal cortex	R	30	41	10	461	4.35	0.03	.48
Middle temporal gyrus	R	41	-63	6	141	4.11	0.04	.45
Fusiform gyrus	L	-30	-73	-18	251	4.37	0.01	.48
Parahippocampal gyrus	R	14	-45	3	257	3.91	0.02	.43
Rolandic operculum	L	-53	-4	10	193	3.76	0.02	.41

[a] Stereotactic coordinates in MNI space. Coordinates of the voxel of greatest activation within the MNI coordinate system are listed.
[b] Spatial extent (in contiguous voxels)
[c] FDR corrected <0.05 across the whole brain

Figure 1. Obese individuals who carried the TaqIA A1 allele showed reduced GM volume in the bilateral operculum (MNI: -48, 18, 6, voxels = 251, z = 3.65, pFDR = 0.04; 44, 18, 3, z = 3.67, voxels = 103, pFDR = 0.04).

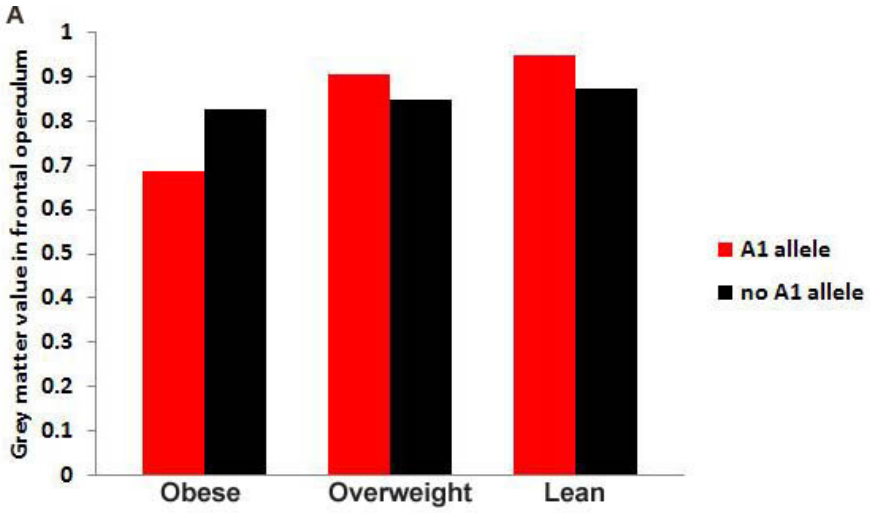
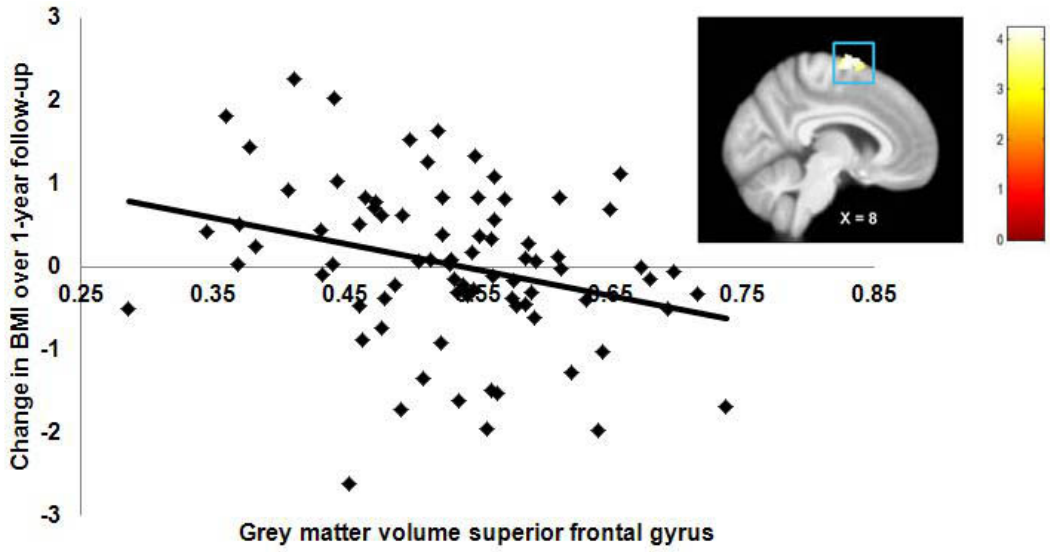


Figure 2. Reduced GM in the superior frontal gyrus (MNI: 8, -4, 72, z = 3.99, voxels = 545, pFDR = 0.02) predicted increase in BMI over 1-year follow-up.



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