CORTICOSTRIATAL DOPAMINE NETWORKS MEDIATE IMPULSIVITY IN OBESITY AND INSULIN RESISTANCE

By

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DEDICATION

To my family, for their unconditional love and support

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α-MSH	α-melanocyte stimulating hormone
ACC	anterior cingulate cortex
ACT	amphetamine challenge test
AgRP	agouti-related peptide
AMPH	amphetamine
ARC	arcuate nucleus
AUC	area under the curve
BBB	blood brain barrier
BIS	Barratt impulsiveness scale
BLA	basolateral amygdala
BOLD	blood oxygenation level dependent
BMI	body mass index
BPnd	non-displaceable binding potential
CA	caudate
CAH	caudate head
CART	cocaine and amphetamine regulated transcript
CM/Pf	centromedian and parafascicular complex
CRC	clinical research center
CRP	C-reactive protein
cSSD	critical stop signal delay
CNS	central nervous system
D2R	dopamine D2 receptor
DA	dopamine
DAT	dopamine transporter

DI	disposition index
DIO	diet-induced obesity
DLPFC	dorsolateral prefrontal cortex
DLS	dorsolateral striatum
DMN	default mode network
DMS	dorsomedial striatum
FFA	free fatty acid
FFE	fast field echo
fMRI	functional magnetic resonance imaging
FPG	fasting plasma glucose
FPI	fasting plasma insulin
FTO	fat mass and obesity associated
FWHM	full width half maximum
FW-MRI	fat water magnetic resonance imaging
GE	go error
GLM	general linear model
GLP-1	glucagon-like peptide 1
GS	go success
HbA1c	hemoglobin A1c
HFD	high fat diet
HOMA-IR	homeostatic model of assessment for insulin resistance
IFG	inferior frontal gyrus
IMA	inhibitory motor area
IR	insulin receptor
IV	intravenous
LFD	low fat diet

LHA	lateral hypothalamic area
LT	lean tissue
MC4R	melanocortin 4 receptor
MD	mediodorsal nucleus of the thalamus
MeFG	medial frontal gyrus
MFG	middle frontal gyrus
mGRT	median go response time
MGTT	mixed-meal glucose tolerance test
MNI	Montreal neurologic institute
MRI	magnetic resonance imaging
MSN	medium spiny neuron
NAC	nucleus accumbens
NAcs	nucleus accumbens shell
NAcc	nucleus accumbens core
NE	norepinephrine
NET	norepinephrine transporter
NPY	neuropeptide Y
OB	olfactory bulb
OFC	orbitofrontal cortex
PCG	precentral gyrus
PES	post error slowing
PET	positron emission tomography
PFC	prefrontal cortex
POMC	pro-opiomelanocortin
preSMA	pre-supplementary motor area
PU	putamen

PVN	paraventricular nucleus
ROI	region of interest
SAT	subcutaneous adipose tissue
SE	stop error
SFG	superior frontal gyrus
SMA	supplementary motor area
SN	substantia nigra
SPM	statistical parametric mapping
SS	stop success
SSRT	stop signal response time
SST	stop signal task
STN	subthalamic nucleus
T2DM	type 2 diabetes mellitus
TAT	total adipose tissue
TE	echo time
TFE	turbo field echo
TFEQ	three factor eating questionnaire
TI	inversion time
TR	repetition time
VAT	visceral adipose tissue
VTA	ventral tegmental area
VUIIS	Vanderbilt University Institute for Imaging Science
WFS	water-fat shift

CHAPTER I

INTRODUCTION

Understanding the obesity epidemic

Over 1 billion people in the world(Organization 2003), and nearly one-third of children in the United States(Ogden et al. 2012), are currently overweight or obese. The prevalence of obesity has increased dramatically over the past century with a concomitant explosion in obesity-associated disease. Increased obesity is associated with increased risk for a striking number of chronic diseases, including insulin resistance, heart disease, osteoarthritis, and cancer, and obesity alone is the 2nd leading cause of preventable death in the United States(Flegal et al. 2013).

Genetic and endocrine factors alone cannot account for the sudden increase in obesity over the course of a generation(Niswender and Schwartz 2003; Speliotes et al. 2010). The present food environment, including modern food processing, increased food availability, and a sedentary lifestyle, is a more likely contributor to the obesity epidemic(Hill and Peters 1998). But despite increased education about the consequences of food overconsumption and excess weight, the obesity epidemic continues to worsen(Flegal et al. 2010). Subtle dysregulation of internal factors engaged in responding to the external food environment may play a key role in the development and maintenance of obesity.

The brain is critical in regulating feeding behavior and the body's response to food. Recent research in obesity points to the role of the dopamine system, the same brain network disrupted in drug addiction. The brain dopamine system regulates important behaviors, including reward processing, habits, and cognition. Dysfunction in the dopamine system disrupts these behaviors, and may do so in a way that promotes

food overconsumption and weight gain(Adam and Epel 2007; Berridge et al. 2010; Davis, Strachan, and Berkson 2004; Palmiter 2007; Volkow, Wang, and Baler 2011). The mechanisms by which obesity affects brain dopaminergic circuits, and whether these changes are therapeutically reversible, are still unknown. In this introduction, I review the role of the brain in feeding behavior and obesity, focusing on the relationship between dopamine and insulin, and the parallels between addiction and obesity. Based on this information, I then propose a model for dopamine disruption in obesity and discuss the potential for treatment.

Hypothalamic control of energy homeostasis

The hypothalamus regulates food consumption for the purpose of maintaining energy balance around a physiologic set point(Niswender, Baskin, and Schwartz 2004; Schwartz et al. 2000; Morton et al. 2006) by responding to peripheral hormonal signals relaying information about the body's energy state(Moran 2006; Saper, Chou, and Elmquist 2002). Specifically, cells expressing cocaine and amphetamine regulated transcript (CART) and pro-opiomelanocortin (POMC) in the arcuate nucleus (ARC) function to cleave POMC mRNA to α-MSH during post-translational processing. α-MSH then activates melanocortin-4 receptors (MC4R) on second-order neurons in the paraventricular

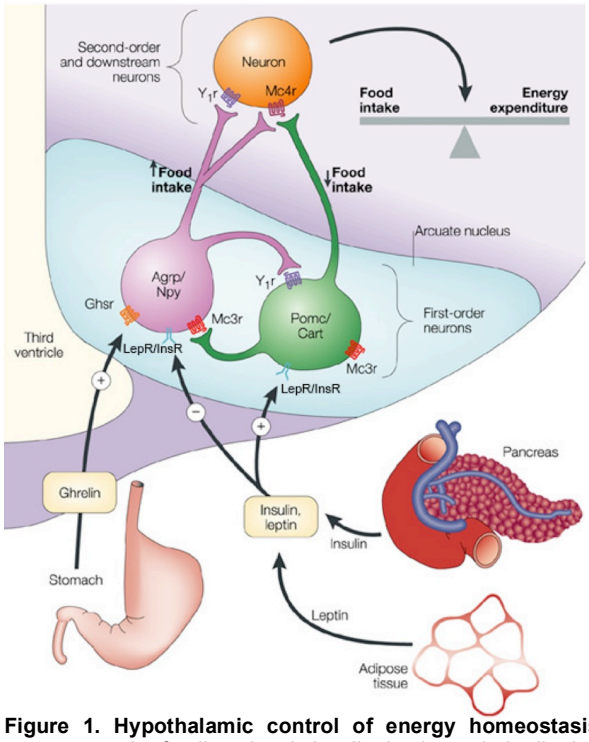

Figure 1. Hypothalamic control of energy homeostasis in response to the feeding signals insulin, leptin, and ghrelin. LepR, leptin receptor; InsR, insulin receptor; Ghsr, growth hormone secretagogue receptor; Mc3/4r, melanocortin 3/4 receptor; Y_1R, neuropeptide Y receptor. Adapted with permission from Barsh & Schwartz (2002)

nucleus (PVN) and lateral hypothalamic area (LHA) to suppress appetite and decrease food intake. ARC neurons expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP) counterbalance the POMC/CART system to increase appetite and food intake by inhibiting POMC neurons and MC4R activation(Cone 2006; Ellacott and Cone 2006) (see Figure 1).

These hypothalamic neurons are targets of peripheral feeding signals including leptin, insulin, and ghrelin(Schwartz et al. 2000). The anorexigenic peptides leptin and insulin are negative feedback satiety signals respectively circulating in proportion to body fat mass and plasma glucose levels. In the hypothalamus, these peptides activate POMC/CART neurons while inhibiting NPY/AGRP neurons, indicating that the body is in a positive energy balance and suppressing feeding to bring the body back into energy equilibrium. In contrast, the orexigenic gut peptide ghrelin, whose levels inversely correlate with adiposity, signal a negative energy balance by promoting NPY/AgRP neuron activity to stimulate feeding directly(Nakazato et al. 2001; Garin et al. 2013). This system thus tightly regulates energy intake and energy expenditure through active processes that control body weight and composition.

Dopamine and insulin resistance in obesity

In addition to their action in the hypothalamus, peripheral hormonal signals also interact with multiple neurotransmitters outside the hypothalamus to affect feeding behavior. The brain dopamine system modulates reward, habits, and cognition through an extensive network of neurons projecting from the midbrain ventral tegmental area (VTA) and substantia nigra (SN) diffusely to corticostriatal regions. Current evidence suggests that peripheral hormonal signals influence feeding behavior by modulating central dopamine signaling. Gut peptides signaling a positive energy balance negatively modulate midbrain dopamine (DA) neurotransmission and food reward while those

signaling a negative energy balance are positive DA modulators. For example, leptin acts directly on the DA neurons of the ventral tegmental area (VTA) to inhibit action potential firing(Hommel et al. 2006; Fulton et al. 2006) and reduce food intake(Hommel et al. 2006). In contrast, ghrelin activates VTA DA neurons, triggering feeding(Abizaid et al. 2006).

Insulin and dopamine systems converge in the central nervous system; insulin receptors (IRs) colocalize with DA neurons, and insulin binding to IRs modulates dopamine neurotransmission(Figlewicz 2003). Insulin/IR binding promotes the intracellular trafficking and surface expression of the dopamine transporter (DAT), increasing dopamine clearance in subcortical dopaminergic brain areas(Carvelli et al. 2002; Daws et al. 2011; Figlewicz et al. 2003; Garcia et al. 2005; Williams et al. 2007). Peripheral insulin depletion in rodents leads to internalization of DAT, blunting dopamine clearance, while insulin restores DAT surface expression(Williams et al. 2007).

Central insulin resistance induced by a high-fat diet can further impair DAT surface expression and dopamine homeostasis(Speed et al. 2011). Lower DAT availability in the striatum is observed in high body mass index (BMI) humans(Chen et al. 2008), in whom it is likely that tissue insulin signaling is blunted(Kahn et al. 2001). Unlike the subcortical targets of dopamine innervation, extracellular dopamine in cortical regions is cleared to a significant degree by the norepinephrine transporter (NET)(Wayment, Schenk, and Sorg 2001; Moron et al. 2002). In contrast to DAT, NET trafficking and surface expression is inhibited by insulin(Robertson et al. 2010), suggesting that impaired insulin signaling might increase dopamine clearance in cortex. Dopamine functions on an inverted-U shaped curve in both subcortical and cortical dopaminergic brain areas, where either too much or too little dopamine impairs brain function(Gjedde et al. 2010; Cools and D'Esposito 2011; Goldman-Rakic 1998; Takahashi 2013; Dent and Neill 2012). Thus, insulin's opposing effect on surface

expression of DAT and NET suggests a convergent mechanism by which impaired insulin signaling may uncouple the subcortical and cortical (corticostriatal) dopamine circuits regulating feeding behavior (see Figure 2).

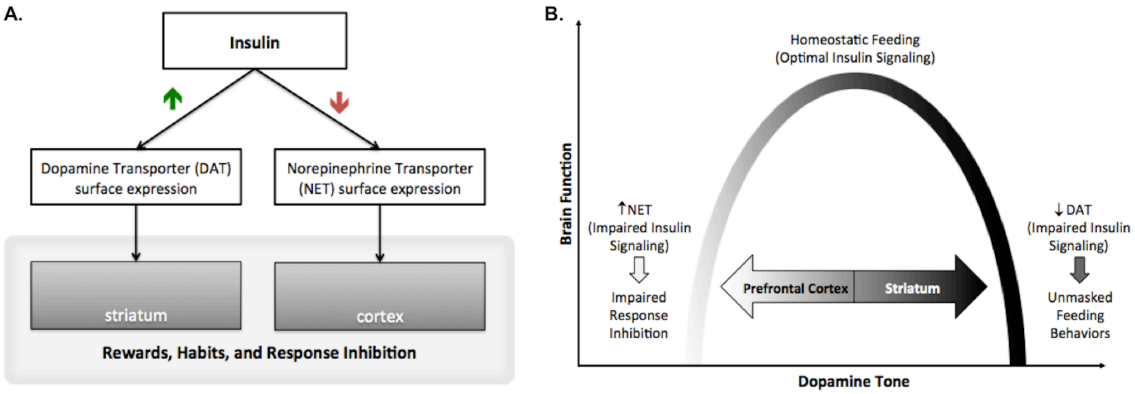

Figure 2. Insulin modulation of reward, habitual motor, and inhibitory neural circuits. A) Insulin action at brain insulin receptors promotes the intracelleular trafficking and surface expression of the dopamine transporter (DAT) while inhibiting that of the norepinephrine transporter (NET). The DAT and NET are largely responsible for dopamine reuptake in the striatum and cortex respectively, regions involved in reward, habits, and response inhibition. B) Impaired insulin signaling decreases expression of the DAT and increases expression of NET. The opposing action of insulin on these transporters may uncouple corticostriatal circuits involved in the regulation of feeding behavior.

Disrupted striatal dopamine neurotransmission in obesity and addiction

In the central nervous system, dopamine functions as a modulatory neurotransmitter in circuits crucial for regulating reward, habits, and cognitive control. In the mesolimbic pathway, connecting the midbrain ventral tegmental area (VTA) to limbic regions including the ventral striatum (nucleus accumbens), dopamine encodes the expectation of, motivation for, and approach behaviors seeking reward(Berridge and Robinson 1998; Schultz 2007; Schultz, Dayan, and Montague 1997). Consistent with dopamine's role in reward, dopamine levels are elevated during food seeking(Hernandez and Hoebel 1988; Salamone et al. 1991), exposure to and consumption of novel food stimuli(Bassareo and Di Chiara 1997, 1999), and daily intermittent consumption of both sugar(Avena, Rada, and Hoebel 2008; Avena et al. 2006; Rada, Avena, and Hoebel

2005) and fat(Rada et al. 2010; Liang, Hajnal, and Norgren 2006). The phasic firing of these dopamine neurons encodes food reward(Roitman et al. 2004; Roitman, Wheeler, and Carelli 2005; Roitman et al. 2008; Schultz, Dayan, and Montague 1997).

The nigrostriatal dopamine pathway plays a similar role for feeding, connecting the substantia nigra to the dorsal striatum. Studies in dopamine deficient mice, a severely hypoactive phenotype which will die of starvation without supplemented dopamine, show that restoration of dopamine to the nucleus accumbens does not restore feeding behavior(Heusner et al. 2003; Palmiter 2007). However, restoration of dopamine to the dorsal striatum rescues the dopamine-deficient phenotype and induces feeding(Darvas and Palmiter 2010; Hnasko et al. 2006; Szczypka et al. 2001), suggesting a role for dopamine outside the mesolimbic reward system in supporting feeding behavior. In fact, it is the dorsal striatum that appears to mediate habit formation, such as the repeated seeking of reward-conditioned, highly salient, food stimuli(Faure et al. 2005; Graybiel 2008; Yin, Knowlton, and Balleine 2004).

Habits are “sequential, repetitive, motor, or cognitive behaviors elicited by external or internal triggers that, once released, can go to completion without conscious oversight”(Graybiel 2008). They begin as goal-directed behaviors in response to rewarding stimuli(Berridge, Robinson, and Aldridge 2009) that evolve with repeated reward training to cue-mediated behaviors that persist even with reward devaluation(Balleine and Dickinson 1998; Dickinson, Nicholas, and Adams 1983). This progression involves an underlying ventral-to-dorsal striatal shift(Graybiel 2008; Koob and Volkow 2010; Hyman, Malenka, and Nestler 2006) as dopamine-directed reward behaviors of the ventral striatum are replaced by dorsal striatal cue-initiated action sequences(Yin 2010; Yin, Knowlton, and Balleine 2005; Graybiel 2008; Ikeda et al. 2013). Indeed, this shift is well defined with food reward, indicating that foods and food cues are sufficient to initiate reward-seeking and the subsequent habitual behaviors

characteristic of drug, and possibly food, addiction(Koob and Volkow 2010; Kalivas 2009).

The observed disruptions in dopamine neurotransmission in obesity are strikingly similar to the known dysregulation of dopamine pathways that contribute to the compulsive drug seeking and use that characterize drug addiction. Dopaminergic drugs that impair the activity of DAT increase synaptic dopamine levels, and with prolonged use, it is hypothesized that these drugs produce an allostatic downregulation of the dopamine receptor (D2R) in the striatum(Wee et al. 2007; Nader et al. 2006; Koob and Le Moal 2001; Koob and Volkow 2010), effectively blunting dopamine neurotransmission. Indeed, recent human positron emission tomography (PET) studies demonstrate BMI-associated reductions in striatal D2R availability that are similar to those observed in substance use disorders(Wang et al. 2001; Volkow, Wang, Fowler, et al. 2008). Like the plasticity in dopamine circuits seen in chronic drug addiction(Beveridge et al. 2009; Barak et al. 2011), studies show that rats given extended access to an obesogenic cafeteria diet gain weight and have reduced striatal D2R availability compared with pair chow-fed animals(Bello, Lucas, and Hajnal 2002; Fetissov et al. 2002; Hamdi, Porter, and Prasad 1992; Johnson and Kenny 2010). Studies in humans are fewer, and less consistent. Both increases(Steele et al. 2010a) and decreases(Dunn et al. 2010) in striatal D2R availability have been reported in obese patients within weeks following bariatric surgery. These results should be interpreted with caution as such surgeries alter multiple endocrine/incretin signals known to or suspected of influencing central dopamine systems. Nonetheless, these findings combined with the BMI-dependent decrease in DAT availability in humans(Chen et al. 2008), suggest the possibility of allostatic striatal D2R responses resulting from impaired dopamine clearance by DAT, itself a consequence of obesity-associated impaired insulin signaling.

Disrupted brain networks in obesity and addiction

In conjunction with the similarities in striatal dopamine dysregulation, functional magnetic resonance imaging (fMRI) studies reveal homology in patterns of altered brain activation between obesity and drug addiction suggesting that changes in the neural circuitry underlying obesity and drug addiction may be mediated by similar mechanisms(Volkow, Wang, and Baler 2011; Volkow and Wise 2005). Brain activation patterns in response to reward-cues for obesity (food) and addiction (drug) reveal overlapping regions of activation in the amygdala, anterior and middle insula, orbitofrontal cortex, and striatum(Tang et al. 2012), highlighting the role of reward processing and salience attribution. Overweight and obese individuals further demonstrate BMI-dependent increases in activation in circuits related to drug and food reward in response to the visual presentation of food cues including the striatum(Fletcher et al. 2010; Rothemund et al. 2007; Stoeckel et al. 2008). Activation in these regions is significantly potentiated by hunger in obese compared to healthy weight individuals(Small et al. 2001; Uher et al. 2006; Cornier et al. 2009; Del Parigi et al. 2002; LaBar et al. 2001; Pelchat et al. 2004), supporting dysfunctional reward responsiveness in obesity. The BMI-dependent potentiation of activity in the striatum suggests a model for molecular disruptions in striatal dopamine neurotransmission associated with insulin resistance, as dopamine levels in the striatum correlate with fMRI activity(Knutson and Gibbs 2007).

Imaging studies of obese individuals also reveal disruptions in frontal areas(Stoeckel et al. 2008; Simmons, Martin, and Barsalou 2005; Rothemund et al. 2007; Stice et al. 2009), including prefrontal cortex, that receive dopaminergic projections from the midbrain. One fMRI study specifically demonstrated a BMI-dependent decrease in activation in the prefrontal areas related to inhibitory control during response inhibition(Batterink, Yokum, and Stice 2010). The PFC plays a role in

'top-down' regulation of subcortical function to promote situation and task-relevant behaviors(Li, Huang, et al. 2006; Arnsten 2009; Miller and Cohen 2001; Robbins and Arnsten 2009), including the inhibition of dorsal striatal cue-initiated action sequences when they are inappropriate. There is strong evidence for the specific role of dopamine in regulating such PFC activity(Goldman-Rakic 1998; Seamans and Yang 2004) through volume transmission maintaining extrasynaptic dopamine tone(Seamans and Yang 2004). Dopamine appears to improve prefrontal cortical function(Phillips, Ahn, and Floresco 2004; Mehta and Riedel 2006; Chudasama and Robbins 2004) by enhancing glutamatergic signaling through DA receptor binding(Kruse et al. 2009; Sarantis, Matsokis, and Angelatou 2009); however, this effect is non-linear, where either too much(Zahrt et al. 1997) or too little(Crofts et al. 2001; Robbins and Roberts 2007) dopamine actually impairs proper PFC function.

The inverted-U model for dopamine modulation of prefrontal cortical function is readily seen in measures of response inhibition, where both deficits(Langley et al. 2004; Eagle et al. 2007; Bari et al. 2011; Congdon, Lesch, and Canli 2008) and excesses(Colzato et al. 2009) in central dopamine degrade PFC performance, including a decreased ability to rapidly inhibit unwanted responses. Impaired response inhibition is a hallmark of addiction(Li, Milivojevic, et al. 2006; Li, Morgan, et al. 2010; Li, Luo, et al. 2010; Li, Huang, Yan, Bhagwagar, et al. 2008; Fillmore and Rush 2002; Lawrence et al. 2009; Monterosso et al. 2005; Tolliver et al. 2012) and impulse control disorders(Solanto et al. 2001; Lijffijt et al. 2005; Schachar et al. 2000). As dopamine tone in the prefrontal cortex may be under the regulatory influence of insulin through its action on NET, even minor deviations from optimal tone, such as what might occur with central insulin resistance, could alter PFC function(Seamans and Yang 2004). Indeed, a small preliminary fMRI study demonstrated BMI-dependent impairments in the prefrontal circuits mediating response inhibition in obesity(Hendrick et al. 2011). Given that ready

availability and promotion of highly palatable food in the modern environment requires the continuous inhibition of cue-mediated feeding behaviors, it is easy to see how impairments in prefrontal response inhibition could unmask the established, and possibly enhanced, subcortical salience attributions and response patterns leading to excess feeding and consequent obesity(George and Koob 2010) (see Figure 2B).

Bridging molecules and brain systems to inform obesity treatment: a hypothesis

The similarities of the molecular and neural correlates of obesity to those of classical addiction, and the potential impact of obesity-associated impairments in central insulin signaling on dopaminergic function, suggest a model by which the modern obesogenic diet might disrupt brain dopaminergic circuits: insulin plays an important role in the appropriate coding of food reward, and cognitive control of feeding by maintaining dopamine homeostasis. Mild insulin resistance resulting from repeated consumption of highly palatable food may drive an increase in striatal synaptic dopamine resulting from decreased insulin-mediated dopamine clearance. This would lead to an allostatic downregulation of dopamine receptor availability, effectively blunting the impact of phasic dopamine reward signaling and facilitating the emergence of cue-driven food seeking behavior. Further, concomitant cortical neuroadaptations in DA signaling driven by insulin resistance could then unmask response patterns of cue-directed non-homeostatic food acquisition and consumption (see Figure 3).

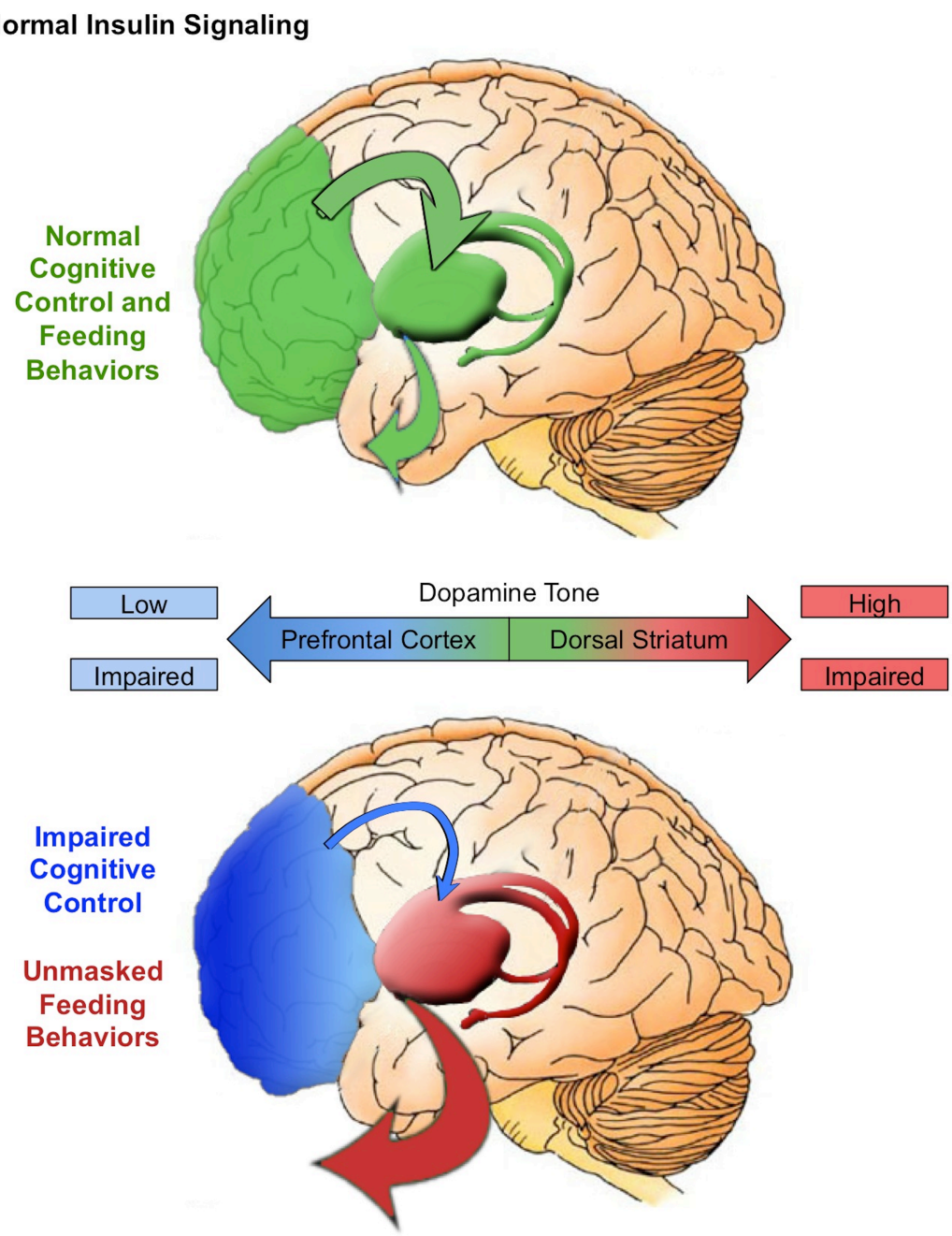

Figure 3. Proposed model for dopamine neurotransmission in the context of A) normal insulin signaling and B) impaired insulin signaling

Although the precise etiology of dopamine dysregulation in obesity remains unclear, imaging studies support the idea that plasticity in brain DA circuits contribute to the development of obesity. Restoration of normal DA signaling might offer an effective strategy for promoting and, more importantly, maintaining weight loss. Promising observations come from preclinical and clinical studies demonstrating that bariatric surgery(Steele et al. 2010a) and weight loss(Thanos et al. 2008) increase D2 receptor levels and decrease functional activity in dopamine reward circuitry(Ochner et al. 2011) while increasing activity in the prefrontal cortex(McCaffery et al. 2009). One explanation for these effects on dopamine circuits is the drastic changes in insulin sensitivity following bariatric surgery; however, there have been no longitudinal controlled human-subjects trials to examine the direct effect of insulin on normalizing dopamine neurotransmission in obesity. Such research will be critical in understanding the pathogenesis of obesity, potential therapeutic targets in insulin signaling pathways, and future opportunities for treatment.

Summary

Recent scientific evidence demonstrating that central nervous system dopamine is regulated by insulin suggests a plausible mechanism for understanding obesity as a dysregulation of dopaminergic circuits controlling reward, habits, and cognitive control. The molecular processes underlying insulin's effect on dopamine circuitry and feeding behavior suggest a mechanistic model whereby the progressive uncoupling of prefrontal cortical and subcortical striatal dopamine circuits, driven by progressive central insulin resistance, might lead to obesity in the modern food environment. The hypothesis of insulin's ability to reset central dopamine tone and subsequently reshape feeding behavior offers exciting new opportunities for the clinical management of obesity.

To address this hypothesis, we use a longitudinal human-subjects research design where participants with mild-to-moderate obesity and insulin resistance either receive insulin or remain insulin-naïve over the course of four weeks. Functional magnetic resonance imaging (fMRI) and dopamine D2 receptor positron emission tomography (PET) were collected before and after insulin treatment. Using this design to examine insulin's ability to reset central dopamine tone and dopamine-associated corticostriatal circuits, we examine:

- behavioral and neural dysregulation in individuals prior to insulin therapy (Chapter 2)
- relationship of striatal dopamine to behavioral and neural dysregulation prior to insulin therapy (Chapter 3)
- insulin's ability to normalize basal striatal dopamine neurotransmission and prefrontal cortical brain activity (Chapter 4)

CHAPTER II

BRAIN MOTOR AND ATTENTION NETWORKS MEDIATE IMPULSIVITY IN INSULIN RESISTANCE

Introduction

A growing body of behavioral and psychometric findings supports an association between obesity and deficits in behavioral self-regulation(Nederkoorn et al. 2010; Hendrick et al. 2011; Yokum, Ng, and Stice 2011; Batterink, Yokum, and Stice 2010; Nederkoorn et al. 2006). Recent neuroimaging studies support these findings and have identified specific structural, functional and molecular differences between healthy-weight and obese individuals in brain areas implicated in impulsive responding and impaired inhibitory control(Hendrick et al. 2011; Volkow, Wang, Telang, et al. 2008; Yokum, Ng, and Stice 2011).

The degree to which obesity-associated deficits in the regulation of feeding are a consequence of impaired inhibitory control and/or heightened drive or wanting remains unclear. Impaired inhibitory control is a hallmark of substance use disorders, and is reflected in the brain as depressed basal frontal activity and blunted activation of fronto-striatal inhibitory circuits(Bari and Robbins 2013; Elton et al. 2012; Fillmore and Rush 2002; Li, Huang, Yan, Bhagwagar, et al. 2008; Li et al. 2009; Monterosso et al. 2005; Volkow et al. 2004). Increased activation of attention and dorsal striatal motor systems in response to salient cues is also a defining feature of the addicted brain(Everitt and Robbins 2005; Hyman, Malenka, and Nestler 2006; Koob and Volkow 2010). Similar patterns of cue reactivity and depressed frontal activity have been observed in obesity(Stoeckel et al. 2008; Volkow, Wang, and Baler 2011; Volkow, Wang, Fowler, et

al. 2008; Wang et al. 2004), suggesting that drug- and obesogenic food-seeking behaviors may share overlapping neural and molecular substrates.

Potential mechanisms linking these changes to harmful changes in feeding behavior are beginning to emerge from pre-clinical studies in animals. The importance of endocrine and incretin reporters of energy balance in regulating brain areas/networks beyond those traditionally associated with energy homeostasis - particularly those subserving reward, habits, and cognitive control - suggest that obesity-associated blunting of the sensitivity of these networks to peripheral satiety signals may contribute to impaired regulation of non-homeostatic feeding(Baicy et al. 2007; Jastreboff et al. 2013; Malik et al. 2008). For example, it is now clear that impairments in central insulin signaling can disrupt synaptic and extracellular dopamine dynamics(Garcia et al. 2005; Robertson et al. 2010; Speed et al. 2011; Williams et al. 2007), suggesting a mechanism by which obesity and insulin resistance might degrade inhibitory and/or heighten impulsivity and food-cue reactivity.

The stop signal task (SST)(Logan and Cowan 1984) is a frequently-used and well-validated paradigm for assessing inhibitory control(Logan 1994) and impulsivity(Winstanley, Eagle, and Robbins 2006). One preliminary neuroimaging study of obesity using the stop signal task found no BMI-dependent effect on the behavioral aspects of inhibitory control but did observe a BMI-dependent decrease in activity in brain areas subserving inhibitory control(Hendrick et al. 2011). The degree to which BMI impacts impulsivity remains unclear, as does the impact of insulin resistance on inhibitory and impulsivity brain circuits.

We therefore examined the association of behavioral, psychometric and neural measures of inhibitory/self regulatory capacity with obesity and insulin resistance in our sample, prior to insulin treatment. We hypothesized that poorer inhibitory control would be associated with increased BMI and/or insulin resistance, and that this association

would be mediated by decreased neural activity in brain areas implicated in inhibitory control, and/or increased activity in those identified as substrates of salience attribution and cue reactivity.

Methods

Research Participants

The Vanderbilt University Institutional Review Board approved all research procedures. Men and women between the ages of 31 and 60 years, with a BMI range between 30 and 50 kg/m^2, were recruited through print, radio, and internet advertisements. To be eligible for the study, all participants were required to be mildly diabetic (hemoglobin A1c [HbA1c] levels between 6 and 8%) but otherwise healthy, have maintained a stable body weight during the previous three months, and have never received insulin treatment for type 2 diabetes. Participants were excluded for: significant physical medical conditions (neurologic disease, cardiovascular disease, atherosclerotic disease, pulmonary disease, metabolic disease, liver or renal insufficiency, uncontrolled hypertension, anemia, endocrinologic disorders); substance abuse or dependence; tobacco use in the past 3 months; current Axis I psychiatric disorders as determined by the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)*(First et al. 2002); use of centrally acting medications such as stimulants, anti-depressants excluding SSRIs, mood stabilizers, anti-psychotics in the last 12 months; polycystic ovarian disease; weight loss surgery; dietary or weight loss supplements; any MRI incompatibility due to metal implants, claustrophobia or pregnancy.

General Study Protocol

Visit Schedule. The study lasted 6 weeks from the initial consent visit (week 0). The initial consent visit included informed consent, treatment arm randomization, and screening to determine if participants met the aforementioned inclusion/exclusion criteria. All participants completed a mock scan with the stop signal task (described below) to acclimate them to the scanner environment, confirm their understanding of the stop signal task, and achieve stable behavioral data prior to one fMRI study. All participants successfully completing the mock task provided signed informed consent prior to participation.

At each visit (weeks 2 and 6), participants arrived for imaging in the afternoon at 1:30pm with instructions to have eaten breakfast and a light lunch before 11:00am and then after water only. All subjects abstained from alcohol, caffeine, and physical exercise for 48 hours prior to the imaging study. Participants were admitted to the Vanderbilt Clinical Research Center where recent dietary intake was evaluated and they completed the Barratt Impulsiveness Scale (BIS-11)(Patton, Stanford, and Barratt 1995) and the Three Factor Eating Questionnaire (TFEQ)(Stunkard and Messick 1985) to assess trait impulsiveness and disordered eating. Following initial evaluation, participants were escorted by wheelchair to the Vanderbilt University Institute for Imaging Science (VUIIS) where magnetic resonance imaging (MRI) and positron emission tomography (PET) began at approximately 4:00pm. Study visits were four weeks apart (see Figure 4).

Insulin Treatment. Participants randomized to receive insulin began treatment following the initial imaging visit (Week 2). Insulin detemir, a long-acting insulin analog, was administered subcutaneously in the thigh or abdomen using a 3 ml FlexPen. Subjects maintained the same injection area throughout the trial. Insulin was given daily with the evening meal or at bedtime as add-on to additional oral antihyperglycemia

medication. Insulin dosing began at 0.1-0.2 U/kg and, under the supervision of trained study personnel, was titrated up by 3 units until participants' morning fasting glucose levels were normoglycemic (90-110 mg/dl). Participants were instructed to monitor fasting glucose levels daily and if morning hypoglycemia (blood sugars less than 70 mg/dl) occurs, daily insulin dose was reduced.

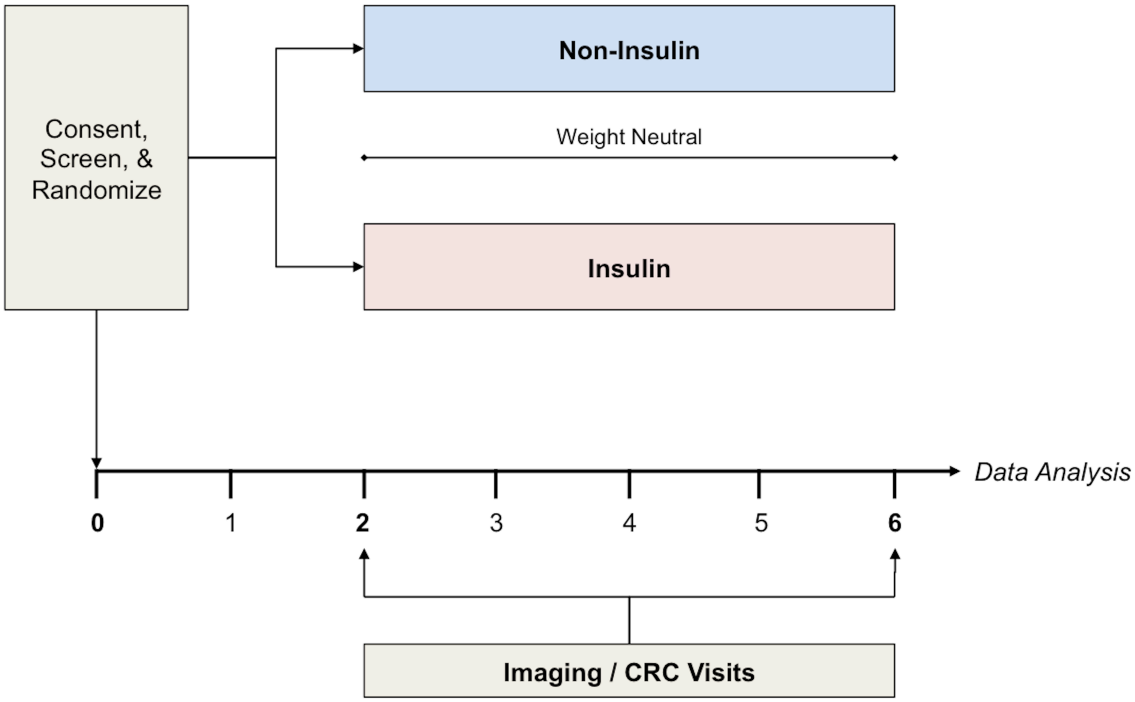

Figure 4. Study design and timeline. Participants were consented, screened for inclusion and exclusion criteria, and enrolled at Week 0. Upon enrolment, participants were randomized to a treatment arm to receive or not receive insulin detemir. Collection of imaging and physiologic / metabolic data were performed at baseline (Week 2) and four weeks later (Week 6). All participants maintained a weight neutral state during the study in order to assess the effect of insulin treatment. CRC, clinical research center.

Biochemical Evaluation. All participants completing the study stayed overnight at the Vanderbilt Clinical Research Center (CRC) during each visit. At each visit, participants were in a food-intake controlled state and fasted until the following morning (approximately 10:00am) when the mixed-meal glucose tolerance test (MGTT) was performed. An intravenous (IV) catheter was placed into a superficial vein of the hand or forearm and IV function was verified prior to the onset of the MGTT. Beginning at time

point 0, participants ingested a 75gram glucose load via a mixed meal. Sampling times for plasma glucose, insulin and C-peptide concentrations include two baseline samples at -5 and 0 minutes and at 10, 20, 30, 60, 90, 120, 150, 180, and 240 minutes post glucose load. The 11-sample protocol for minimal model index of insulin sensitivity(Caumo, Bergman, and Cobelli 2000), which highly correlates with the frequently sampled (22 samples) oral glucose tolerance test(Breda et al. 2001), was used. The approximate total blood volume collected during MGTT was 80-110ml.

Samples were stored at -20 to -70°C. Plasma glucose concentrations were determined using the glucose oxidase method with an Analox GM10 glucose analyzer (Analox Instruments). Plasma insulin, leptin, ghrelin, and C-Peptide were measured using a double-antibody radioimmunoassay as previously described(Thorell and Lanner 1973; Morgan and Lazarow 1963; Ma et al. 1996). Free fatty acids (FFAs) were quantified using a coupled enzyme assay. Insulin resistance was calculated using both the homeostatic model of insulin resistance(Matthews et al. 1985) (HOMA-IR) and disposition index(Utzschneider et al. 2009) (DI). HOMA-IR was calculated as HOMA-IR = (fasting plasma glucose [FPG] * fasting plasma insulin [FPI])/405. The disposition index (DI) was calculated as DI = $(\Delta I_{0-30}/\Delta G_{0-30})$ x (1/fasting insulin) where $\Delta_{0\text{-}30}$ represents the baseline and 30-minute values for plasma insulin (I) and plasma glucose (G) derived from the MGTT. Area under the curve (AUC) measurements for C-Peptide, insulin, and glucose during the MGTT were calculated using a spline rule consisting of a trapezoidal function and cubic spline function(Ivaz and Taghvafard 2006).

Amphetamine Challenge. Structural and functional brain MRI were performed on Day 1 at baseline without amphetamine (Brain Pre-AMPH) and following oral administration of amphetamine on Day 2 (Brain Post-AMPH). Structural and functional MRI was performed using the same protocol as performed on Day 1 with the addition of oral Dextro-amphetamine administration. D-amphetamine was provided to each

participant 45 minutes prior to brain imaging at a dosage of 0.43 mg/kg orally as 5mg tablets rounded upwards to the nearest whole tablet based on weight. AMPH dosage was prepared by the Vanderbilt Investigational Drug Service. Maximum allowable dosage was 45mg.

All participants were screened for contraindications prior to receiving amphetamine. Inclusion criteria for AMPH were a resting blood pressure less than 140/90 mmHg. Following drug administration, heart rate and blood pressure was measured every 15 minutes prior to entering the scanner, and every 20 minutes throughout the scan. Participants were observed for a minimum of 4 hours after AMPH dosing and two normal blood pressures separated by 20 minutes were required prior to discharge. Participants receiving amphetamine were instructed to contact the study physician with any concerning symptoms after discharge.

Imaging Protocol

Magnetic resonance imaging (MRI) and positron emission tomography (PET) were performed at Week 2 and repeated at Week 6 (see Figure 5).

Dopamine D2 Receptor Positron Emission Tomography (D2R-PET). Participants received the dopamine D2 receptor ligand 18F-Fallypride. Prior to each PET study an IV line was placed and a brief neurological examination by the study physician was performed. Each subject was asked to lie supine on the PET scanner with his/her head positioned in the scanner, and 5 mCi of 18F-Fallypride (specific activity greater than 2,000 Ci/mmol, mass of less than 2.5 nanomoles) was injected over a 15 second period. Trained staff in the Vanderbilt Radiology Department of the Vanderbilt University Medical Center administered the radioligand.

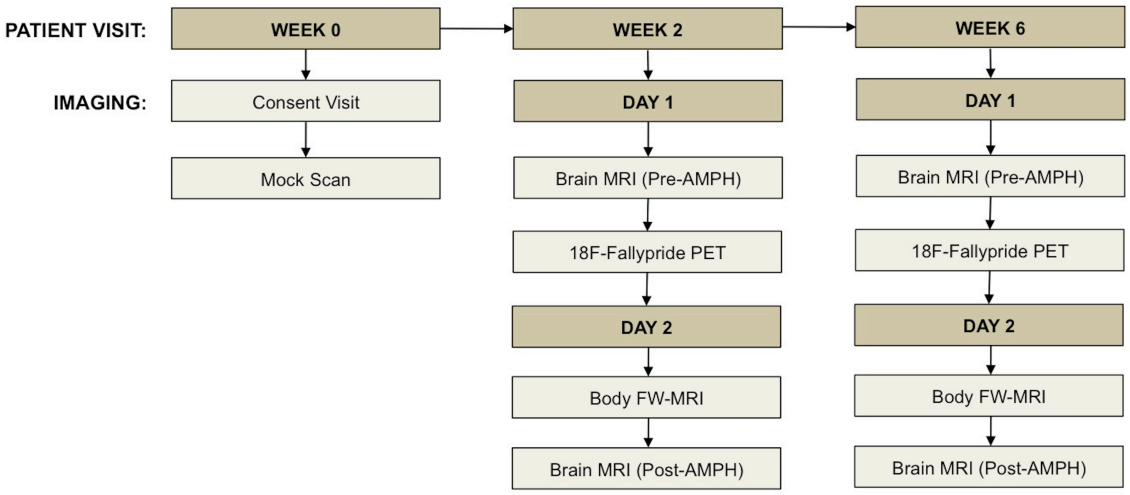

Figure 5. Imaging timeline. Imaging data was collected at baseline (Week 2) and 4 weeks later (Week 6). Each imaging visit lasted two days. Pre-amphetamine functional and structural brain magnetic resonance imaging (MRI) and 18F-Fallypride positron emission tomography (PET) occurring on day 1 and fat water imaging (FW-MRI) and post-amphetamine MRI occurring on day two. The same imaging parameters were used at each visit.

All PET studies were performed using a GE Discovery DSTE PET/CT scanner. Images were collected with a reconstructed resolution of 5 mm in plane, 3.2 mm axially, and 47 planes over a 15 cm axial field of view. The mass dose of 18F-Fallypride given occupied no more than 5% of D2R in all brain regions ensuring that mass dose does not affect regional estimates of BP_{ND}. Twenty-seven serial scans of increasing duration (4x15s, 9x20s, 5x60s, 4x150s, 2x5min, and 4x10min) were performed over the 70 minutes following injection. After the initial scans, subjects received a 15-minute break followed by a second set of scans (4x15min) collected over a 60-minute period. A second break of 20-25 minutes was followed by a third set of scans lasting 60 minutes. This total sequence lasted approximately 3.5 hours. At the conclusion of the PET study, a brief neurological motor examination, withdrawal of 12 ml of blood for CBC, differential and comprehensive metabolic panel, and vital signs were repeated.

MRI. Imaging was performed using a 3T Phillips Achieva MRI Scanner using an 8-channel head coil. High-resolution anatomical images were collected using a 3D T1-weighted TFE gradient echo with an isotropic resolution of $1mm^3$, 5° flip angle, TI/TR/TE

=959.74/8.3/3.9 ms, in 170 volumes. T2*-Weighted Gradient FFE Echoplanar BOLD (EPI-BOLD) were acquired using TR/TE = 2000/35 ms, 79° flip angle, SENSE factor = 1.8, 3x3x4.5mm^3 voxel size interpolated to 1.8x1.8x4.95mm, and acquired parallel to the AC-PC line based on the 3D structural image. Fat-water MRI (FW-MRI) consisted of a multi-slice, multi-echo gradient echo (fast field echo, FFE) acquisition across 12 slices, slice thickness 8mm, zero slice gap. Acquisition details include: TR/TE1/TE2/TE3 [ms] = 75/1.34/2.87/4.40; FA=20°; water-fat shift (WFS) = 0.325 pixels (BW=1335.5 Hz/pixel); field of view (FOV) = 500 mm × 390 mm, acquired matrix size = 252 × 195; acquired voxel size = 2 mm × 2 mm × 8 mm. Total scan time lasted approximately 90 minutes.

Stop Signal Task. All participants completed stop signal task(Logan and Cowan 1984), which requires participants to execute a motor response to a visual "go" cue (Go Trials) on a majority of trials and inhibit this motor response on less frequent "stop" cues (Stop Trials). Trials were presented in a pseudo-randomized order. Each trial was preceded by a yellow dot centered on the viewing screen to promote attention and eye fixation (fore-period; lasting from 1 and 5 seconds). Go trials were presented in a 3:1 ratio with stop trials in order to entrain a prepotent motor response. Go trials began with the appearance of the yellow fixation cue which turned into a green circle after the pseudorandomized fore-period. This circle served as the motor prompt for the participant to press the response button with his/her right index finger. The green circle disappeared following a button press or after 1s had passed, whichever came first. A go trial where the button was pressed prematurely, pressed after 1s, or was never pressed, was considered incorrect. Stop trials were the same as go trials except that a red X, serving as the stop cue, appeared after a variable stop signal delay (SSD). Upon the appearance of the red X, participants must withhold their response. Each trial was separated by a fixed 2s interval (see Figure 6A).

The SSD began at 200 msec and progressed across stop trials according to a staircase design: if the participant successfully inhibited his/her response, the SSD increased by 64ms, whereas if the response was unsuccessfully inhibited, the SSD decreased by 64ms. By using this staircase design, variations in participant responding can be controlled by maintaining an individual success rate at approximately 50% and the critical stop signal delay (cSSD) can be calculated(Levitt 1970). Specifically, individual trials were grouped into runs, where each run was defined as a monotonically increasing or decreasing series, and the mid-run estimate of every other run was averaged to derive the cSSD(Li, Yan, et al. 2008; Wetherill, Chen, and Vasudeva 1966). The stop signal reaction time (SSRT), the time required to inhibit a prepotent motor response after seeing the stop signal, was then calculated by subtracting the cSSD from the median go response time (mGRT, see Figure 6B). Post-error slowing (PES), the phenomenon by which individuals slow down following an error(Rabbitt 1966), was calculated as the difference in go response time before and after an error on a stop trials(Dutilh et al. 2012).

The mGRT and SSRT are dissociable components of the stop signal task reflecting the respective speeds of “going” and “stopping”, while the cSSD represents overall SST performance as the difference in speeds between the go and stop horses(Logan 1994) (see Figure 6B). A shorter mGRT indicates impulsivity while a longer SSRT indicates poor response inhibition(Bari et al. 2011; Li, Huang, et al. 2006; Eagle et al. 2011). Post-error slowing (PES), the phenomenon by which individuals slow down following an error, indicates the speed of error monitoring and cognitive control processes(Botvinick et al. 2001; Rabbitt 1966).

On the day of scanning, participants completed five minutes of the stop signal task prior to entering the fMRI scanner. Participants were reminded of the stop signal task instructions. Specifically, participants were informed that they would see three

types of cues in the scanner: a yellow “get ready” cue, a green circle (“GO”), and a green circle followed by a red X (STOP). Participants were instructed to, as soon as the “go” stimulus appeared, press the response button as quickly as possible. Conversely, participants are instructed to abstain from pressing the button during the “stop” trial.

In the scanner, participants completed three runs of the stop signal task, with each run consisting of 100 trials (75 go trials, 25 stop trials) and lasting approximately 10 minutes. All participants used their right hands to respond to the visual cues using an MRI-compatible response box. The presentation of stimuli and collection of response data were completed using E-Prime Software v2.0 (Psychology Software Tools).

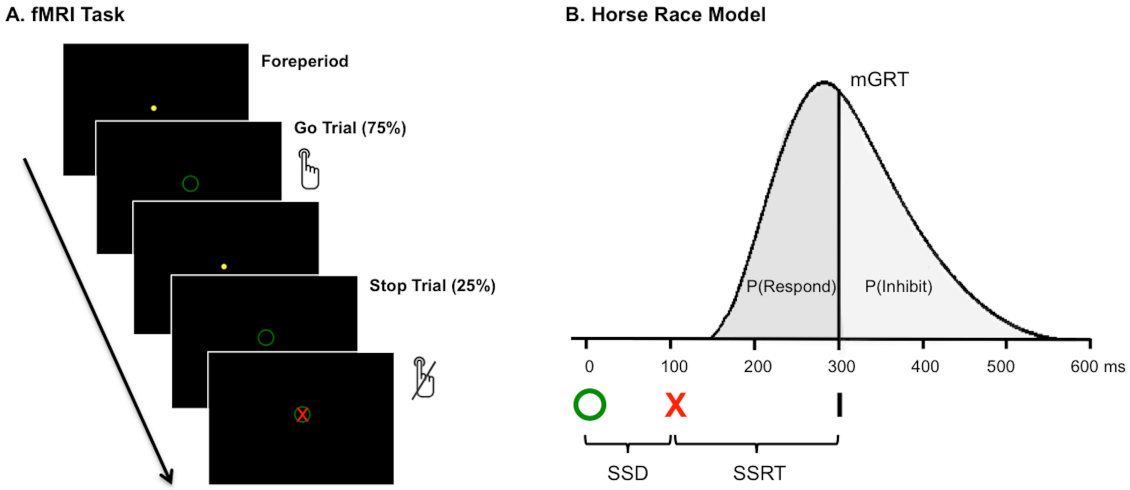

Figure 6. Stop signal task. A) The stop signal task in an fMRI design where the green circle begins each trial and is preceded by a variable-length foreperiod. In stop trials, the red X is presented following a variable stop signal delay (SSD). A button press on a go trial is a go success (GS) while failing to press the button on a go trial is a go error (GE). Inhibiting the button press on the stop trial is a successful stop (SS) while pressing the button on a stop trial is a stop error (SE). B) The horse race model assumes that the go and stop processes are independent where the inhibitory response (stop signal response time) is calculated by subtracting the critical stop signal delay (the time between the “go” signal [green circle] and “stop” signal [red X]) from the median go response time). SSRT, stop signal response time; SSD, stop signal delay; mGRT, median go response time.

Data Analysis

Behavioral Analyses. The percentage of successful go and stop trials were calculated for each participant, as well as the median of the go response time (mGRT).

Custom Matlab (Mathworks) code was used to calculate the cSSD, SSRT, and PES as previously described. These measures were calculated for each of the three runs separately and for the entire imaging session. Performance criteria for inclusion in behavioral analyses were successful inhibition on 25-75% of Stop trials and >60% response rate on Go trials(Congdon et al. 2012; Ghahremani et al. 2012).

PET Analyses. An in-house algorithm(Dunn et al. 2010) was used for kinetic modeling of raw images to produce voxel-wise maps of non-displaceable binding potentials (BP_{ND}) using the cerebellum as a reference region(Byas-Smith et al. 2004). BP_{ND}'s were coregistered and normalized to MNI space, and smoothed with a 6mm Gaussian kernel in SPM8.

fMRI Analyses. All data were analyzed using Statistical Parametric Mapping (SPM8, Welcome Department of Imaging Neuroscience, University College London, UK). Data were motion corrected to the central slice using a 6-parameter spatial transformation and realigned to the mean image of all the runs from each subject, slice-time corrected, and high-pass temporally filtered with a cutoff of 128 sec. The mean functional image from the slice time correction was then coregistered with the high-resolution 3D anatomic image using an affine transformation, spatially normalized to MNI space using a 12-parameter nonlinear transformation, then spatially smoothed using a Gaussian kernel of 6.0 mm FWHM(Ashburner and Friston 1999). Subjects exceeding motion parameters (3° rotation, 3mm translation) were excluded from future analysis.

Four types of trial outcomes were identified: go success (GS; successful go trials), go error (GE; unsuccessful go trials), stop success trials (SS), and stop error trial (SE; unsuccessful stop trials). The onset and reaction times for each trial were identified and entered into a statistical design matrix for each participant using a general linear model (GLM). Realignment parameters (rotation and translation) were also entered into the

model. During the first level analysis, the onsets associated with each trial type were convolved with a canonical hemodynamic response function(Friston et al. 1995), and constructed into first-level contrasts: GS vs SS to identify the neural correlates of "stopping" and "going", and SS vs SE to determine the neural correlates of successful and failed stops. The individual participant contrasts maps were then entered into a second-level group analysis for the same contrasts.

Statistical Analyses. Stop signal performance measurements, including the SSRT, cSSD, mGRT, and PES, are linked to the adequate functioning of brain dopamine systems. Based on the hypothesis that obesity and insulin-resistance produce dopaminergic disruption, we determined the degree to which stop signal performance was influenced by markers of obesity (BMI) and insulin resistance (HOMA-IR). Stop signal performance markers were entered into a multiple linear regression as dependent variables (those being affected by BMI and/or HOMA-IR associated dopaminergic disruptions) and BMI and HOMA-IR as independent variables, while controlling for nuisance variables that may impact performance including age(Cohen et al. 2010) and insulin-sensitizing medications (data not shown). Results were considered statistically significant at $p \leq 0.05$ and marginally significant at $p \leq 0.08$.

Voxelwise and volume-of-interest (VOI) analyses were implemented to examine the relationship between brain activation, BMI, and HOMA-IR. After examining the group-level GS vs. SS and SS vs. SE contrasts ($p_{unc}<0.001$, $k_E = 10$ voxels), we performed wholebrain voxelwise regressions within these contrasts against stop signal performance to identify the neural correlates of impulsivity, inhibition, and error monitoring. These maps were generated at an uncorrected threshold of $p=0.005$ with a cluster extent threshold of 10 voxels. Significant clusters from these voxelwise regressions were considered VOIs within which to examine the effects of HOMA-IR and

BMI on brain activation. Marsbar was used to calculate the individual participant weighted parameter estimates of the activity within the VOIs(Brett et al. 2002). These measures of activation were then used in statistical comparisons with stop signal behavior and biochemical composition. Regression analyses were corrected for multiple comparisons using an FDR threshold of $p<0.05$. Regression analyses are presented without correction for multiple comparisons, however regions meeting significance with FDR correction are mentioned as such in the text.

Finally, we performed a mediation model to determine whether brain activation mediated the effects of BMI or HOMA-IR on stop signal performance. Within this model we examined both the direct mediation effects and indirect mediation effects. The indirect mediation effects were calculated using the Goodman test(Goodman 1960). All statistical analyses were performed in SPSS v20 (SPSS Statistics). For

Results

Participant demographics and clinical information

Table 1 summarizes the demographic and clinical characteristics of the study cohort. Fifty-eight subjects were enrolled in the study (age: 47.55 ± 0.89 yrs [mean ± SE]; BMI: 36.95 ± 0.60 kg/m^2; 36 female, 22 male). Of the enrolled 58 subjects, thirty-two received PET imaging (age: 46.44 ± 1.29 yrs, BMI: 37.86 ± 0.63 kg/m^2, 22 female, 10 male), and fifty received stop signal fMRI imaging. Three participants were excluded from the behavioral analysis because they did not meet the behavioral performance thresholds previously described(Congdon et al. 2012; Ghahremani et al. 2012). Performance criteria for inclusion were: successful inhibition on 25-75% of stop trials and >60% response rate on Go trials. Seventeen participants did not meet the strict motion

parameters (3° rotation, 3mm translation) for fMRI analysis and were further excluded from the imaging analysis only. In total, data from forty-seven participants (age, 47.1 ± 1.0 yrs (mean ± SE); BMI, 37.1 ± 0.7 kg/m^2; HOMA-IR, 7.8 ± 0.8; 18 male, 29 female) were included in the behavioral analysis and a representative subset of thirty participants (age, 48.1 ± 1.25 yrs (mean ± SE); BMI, 36.5 ± 0.74 kg/m^2; HOMA-IR, 6.29 ± 0.63; 12 male, 18 female) was included in the fMRI analysis.

Table 1. No difference in demographics and clinical information between analysis subgroups (mean ± SE)**.** Analysis subgroups include the total sample (n=53), the 18F-Fallypride PET subset (n=32), the stop signal task behavior subset (n=47), and the stop signal task imaging subset (n=30).

	Total Sample	PET	Stop Signal Task: Behavior	Stop Signal Task: fMRI	p-value
N	58	32	47	30	-
Sex	36F, 22M	22F, 10M	29F, 18M	18F, 12M	-
Race	25B, 3H, 30W	15B, 2H, 15W	20B, 2H, 25W	11B, 1H, 18W	-
Age (yrs)	47.55 ± 0.89	46.44 ± 1.29	47.12 ± 1.03	48.10 ± 1.25	0.797
Education (yrs)	14.81 ± 0.22	14.87 ± 0.31	14.81 ± 0.29	15.07 ± 0.37	0.926
BMI (kg/m2)	36.95 ± 0.60	37.86 ± 0.63	37.14 ± 0.70	36.45 ± 0.74	0.607
HOMA-IR	7.66 ± 0.70	7.90 ± 0.90	7.83 ± 0.80	6.29 ± 0.63	0.510
Disposition Index	1.37 ± 0.41	1.50 ± 0.55	0.96 ± 0.12	1.03 ± 0.16	0.689
C-Peptide AUC (ng/ml)	1058.8 ± 86.9	1105.0 ± 93.6	1006.1 ± 78.52	1037.7 ± 101.2	0.889
Glucose AUC (mg/dl)	10375.1 ± 675.8	9807.9 ± 744.6	10329.5 ± 719.2	10295.9 ± 827.7	0.947
Insulin AUC (uu/ml)	15332.8 ± 2176.6	16497.9 ± 2991.9	14833.86 ± 2321.9	12738.9 ± 1556.7	0.789
Fasting AcylGhrelin (pg/ml)	23.7 ± 2.10	25.7 ± 2.32	24.65 ± 2.44	24.20 ± 2.68	0.931
Fasting C-Peptide (ng/ml)	4.12 ± 0.27	4.35 ± 0.31	4.12 ± 0.29	3.71 ± 0.26	0.572
Fasting Glucose (mg/dl)	130.2 ± 6.08	122.9 ± 5.05	126.68 ± 6.09	125.54 ± 7.74	0.864
Fasting Insulin (uu/ml)	24.8 ± 1.80	25.3 ± 2.43	25.17 ± 1.98	21.16 ± 1.79	0.498
Fasting Leptin (ng/ml)	27.6 ± 1.89	27.8 ± 2.07	27.25 ± 2.18	27.43 ± 2.37	0.998

Note: Values in the same row with a subscript are significantly different at p< .05 in the two-sided test of equality for column means.

Across subjects, body mass index averaged 36.95 ± 0.60 kg/m^2 (mean±SE; normal weight ≤ 25 kg/m^2), indicating that the sample is comprised of Class I and Class II mildly obese individuals. Markers of insulin resistance and glucose disposal demonstrate the anticipated mild impairments in insulin sensitivity: HOMA-IR values averaged 7.66 ± 0.70 (normal range < 2), fasting plasma glucose averaged 130.2 ± 6.08

mg/dl (normal range 70 mg/dl to 99 mg/dl), FPI averaged 24.8 ± 1.80 μU/ml (normal range 5-15 μU /ml) and C-peptide averaged 4.12 ± 0.27 ng/ml (normal range 0.51 to 2.72 ng/ml)(Mager et al. 2010).

Demographic and clinical information was similar across the behavioral and imaging subsets. No differences were observed in participant age or education, BMI, HOMA-IR, and measurements of insulin, glucose, c-peptide, leptin, or acylghrelin. All behavioral and imaging subsets had a small female bias, with approximately 60-70% of each subset being female. Further, there was no difference between the behavioral and fMRI imaging subsets with respect to stop signal behavior (see Table 2). The homology between analysis subgroups indicates that the results within each subgroup are generalizable to the sample as a whole. Notably, there was no correlation between individual volunteers' BMI and HOMA-IR (R^2 = 0.006, p = 0.627, behavioral; R^2 = 0.030, p = 0.399, fMRI), allowing for the relationship of behavioral and neural responses to obesity and insulin sensitivity to be examined independently.

Table 2. No difference in stop signal task performance between behavioral and imaging subgroups (mean ± SE).

	Behavioral Analysis	Imaging Analysis	p-value
cSSD (ms)	309.6 ± 17.4	319.1 ± 23.1	0.742
SSRT (ms)	295.1 ± 4.7	300.6 ± 5.5	0.456
mGRT (ms)	604.7 ± 15.6	619.7 ± 21.0	0.562
PES (ms)	52.8 ± 7.5	35.7 ± 7.9	0.132

Stop signal task performance in insulin resistance and obesity

SST performance was similar to that previously observed in comparable healthy control subjects(Hendrick et al. 2011; Zandbelt et al. 2013; Li, Huang, Yan, Paliwal, et al. 2008): cSSD (310 ± 17 ms; mean ± SE), mGRT (605 ± 16 ms), SSRT (295 ± 5 ms).

There was a significant slowing of Go responses following stop error (PES; 53 ± 7 ms), but not stop success trials.

Within the behavioral sub-group, there was a significant reduction of cSSD with increasing HOMA-IR (R^2 = 0.140, p = 0.046), but no relationship between cSSD and BMI. Insulin resistance was also a predictor of mGRT where faster "Go" responding is associated with increasing HOMA-IR (R^2 = 0.124, p = 0.061). No relationship was observed between HOMA-IR and SSRT; however, SSRT showed a weak positive association with BMI (R^2 = 0.096, p = 0.101). Interestingly, PES increased with HOMA-IR (R^2 = 0.261, p = 0.005), but showed no dependence on BMI (Table 3, Figure 7). The association of increasing PES with HOMA-IR was not explained by the impact of HOMA-IR on mGRT. We additionally tested for a BMI x HOMA interaction, finding no significant interaction effect on stop signal performance (data not shown). This suggests that impaired insulin signaling promotes a faster 'go' response when 'braking' circuits are engaged to prospectively show impulsive responding.

Table 3. Impulsiveness and error monitoring in a stop-signal task are predicted by insulin resistance (HOMA-IR), but not BMI. The critical stop signal delay (cSSD), a measure of the difference between the stop signal response time (SSRT) and median go response time (mGRT), is predicted by HOMA-IR. The median go response time (mGRT), the representative components of impulsivity, and post-error slowing (PES). a measure of error monitoring and attention, are further by predicted HOMA (n=47). BMI does not predict any aspect of stop signal behavior.

	Model		**BMI**		**HOMA-IR**	
	F	**p**	**R**	**p**	**R**	**p**
cSSD	3.352	0.011	0.038	0.845	**-0.374**	**0.046**
SSRT	1.118	0.381	0.311	0.101	0.126	0.513
mGRT	3.138	0.015	0.144	0.457	**-0.352**	**0.061**
PES	2.095	0.079	0.260	0.173	**0.511**	**0.005**

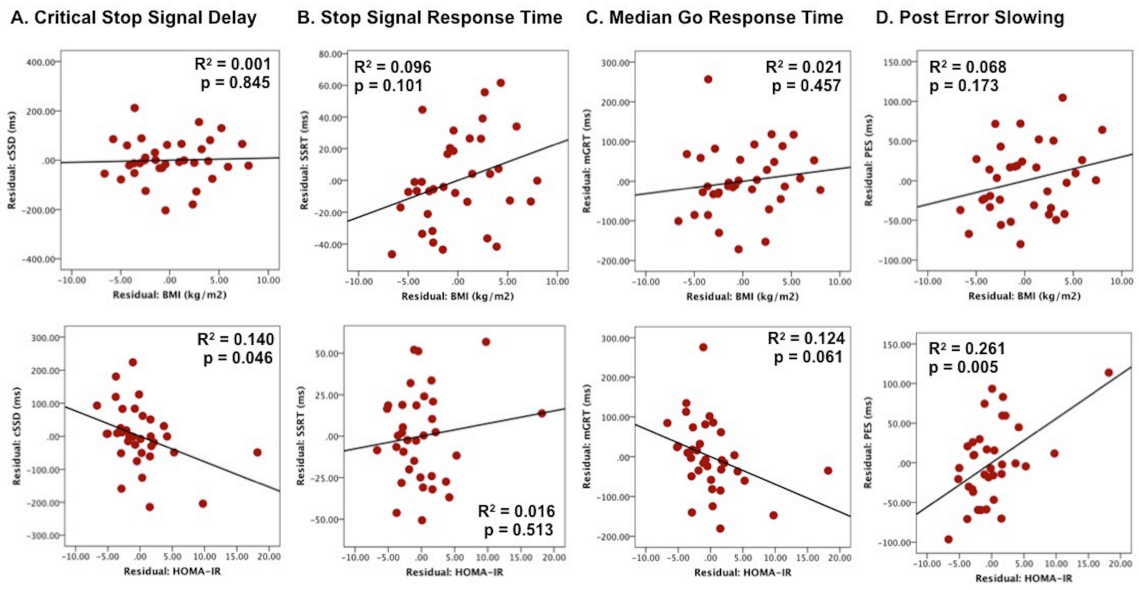

Figure 7. Insulin resistance (HOMA-IR) and body mass index (BMI) respectively predict dissociable impulsive, inhibitory, and error monitoring components of the stop signal task. A) Increasing HOMA-IR predicts impaired stop signal task performance delineated by the critical stop signal delay (cSSD). This effect can separated into behaviors underlying the respective go and stop processes. Specifically, B) increasing BMI impairs response inhibition (SSRT) at trend levels, while HOMA-IR significantly predicts C) impulsive responding (mGRT), and D) error monitoring / attention (PES).

Insulin resistance and BMI predicts neuropsychological measures of impulsivity and disordered eating

The Barratt Impulsiveness Scale (BIS-11)(Patton, Stanford, and Barratt 1995) and the Three Factor Eating Questionnaire (TFEQ)(Stunkard and Messick 1985) self-report tests respectively measure impulsive personality traits and disordered food intake and feeding behavior. In conjunction with the relationship between HOMA-IR and impulsivity in the stop signal task, the attentional component of the Barratt Impulsiveness Scale (BIS-11) was positively correlated with HOMA-IR (R^2 = 0.099, p = 0.043), but not BMI (see Table 4). Supporting the trend-level finding of impaired SSRT with obesity, increasing BMI was a positive predictor of the total Three Factor Eating Questionnaire (TFEQ-51) score (R^2 = 0.070, p = 0.071) and the cognitive restraint subscale (R^2 = 0.096, p = 0.032).

Table 4. HOMA-IR and BMI respectively predict impulsiveness and disordered eating in the BIS-11 and TFEQ-51 self report measures.

	BMI		**HOMA-IR**	
	R	p	R	p
Barratt Impulsiveness Scale (BIS-11)				
Attention	-0.190	0.186	**0.314**	**0.043**
Motor	-0.151	0.295	0.101	0.524
Non-Planning	-0.195	0.174	0.139	0.379
TOTAL	-0.224	0.118	0.205	0.192
Three Factor Eating Questionnaire (TFEQ-51)				
Cognitive Restraint	**0.263**	**0.071**	-0.050	0.755
Disinhibition	0.235	0.108	0.050	0.755
Hunger	0.126	0.393	0.265	0.095
TOTAL	**0.310**	**0.032**	0.073	0.652

Brain networks of response inhibition in obesity and insulin resistance

The neural substrates of "going" and "stopping" are revealed in the stop signal task by comparing stop success (SS) and go success (GS) trials. Brain regions active in these contrasts are consistent with previous studies of response inhibition, impulsivity, and performance/error monitoring(Ghahremani et al. 2012; Li, Huang, et al. 2006; Li, Huang, Yan, Paliwal, et al. 2008; Zandbelt et al. 2013; Cohen et al. 2010). Whole-brain analyses of stop success and go success trials revealed greater activation in SS compared to GS trials bilaterally in cortico-striatal-thalamo-cortical regions subserving cognitive and motor control including inferior, middle, medial, and superior frontal gyri, supplementary and pre-supplementary motor areas, precentral gyrus, insula, cingulate gyrus, thalamus, and the dorsal striatum. Bilateral activation was also observed in parietal attention and visual areas (see Table 5, Figure 8A).

In contrast, GS trials showed greater activation than SS trials bilaterally in the precuneus (see Figure 8B). Limited research is available examining the go component

of the stop signal task, as the SST is specifically designed to assess response inhibition. Studies reporting activation compared GS trails to a baseline null condition, finding contralateral activation of motor cortex and bilateral visual cortex (Congdon et al. 2010; Cohen et al. 2010). Faster response times are linked with activation of motor cortex while slower go response times have been associated with greater antecedent activity of the default mode network (DMN) including the precuneus (Hinds et al. 2013). This suggests that the present contrast may not have the temporal resolution to resolve faster response times in order to observe motor activation. However, the precuneus has been linked with visuospatial processing and shifting attention during the planning and execution of motor performance(Cavanna and Trimble 2006), and has numerous connections to frontal- and oculo-motor regions that are implicated in the visual guidance of hand motion(Goldman-Rakic 1988; Ferraina et al. 1997). The observed activation may thus be due to the role of the precuneus in the attention shift between the visual go cue and the motor button press.

Table 5. Brain activation in the stop signal task comparing stop success (SS) and go success (GS) trials. All maps were generated at an uncorrected threshold of p<0.001 and a cluster size of greater than 10 voxels

Brain Region	Hemi	Voxels	Max. T-statistic	x	y	z
Stop Success greater than Go Success (SS>GS)						
Anterior Cingulate Gyrus	R	10	4.6325	12	35	13
Caudate	L	41	5.1681	-9	11	4
Cerebellum	L/R	331	7.823	-18	-67	-35
Cingulate Gyrus	L/R	13	3.8179	6	-22	34
Frontal Lobe / Striatum	L	680	6.8426	-45	26	31
	R	1820	6.9749	42	26	34
- Inferior Frontal Gyrus						
- Middle Frontal Gyrus						
- Medial Frontal Gyrus						
- Superior Frontal Gyrus						
- Supplementary Motor Area						
- Pre-Supplementary Motor Area						
- Precentral Gyrus						
- Insula						
- Caudate						
- Putamen						
Hippocampus	L	35	4.5435	-27	8	-14
	R	22	4.6423	33	-13	-8
Occipital / Parietal Lobes	L/R	2058	8.4912	57	-46	-8
	L	736	8.4461	-33	-46	37
- Cuneus						
- Precueus						
- Lingual Gyrus						
- Inferior Occipital Gyrus						
- Fusiform Gyrus						
- Middle Temporal Gyrus						
- Superior Temporal Gyrus						
- Inferior Temporal Gyrus						
- Supramarginal Gyrus						
- Angular Gyrus						
- Inferior Parietal Lobule						
Paracentral Lobule	L	27	5.0715	-12	-37	64
	R	12	4.0237	6	-25	70
Precuneus	R	82	4.3958	9	-70	58
Superior Temporal Gyrus	L	16	5.4897	33	5	-11
Thalamus	L	24	4.5245	-24	-28	-2
	R	19	4.8633	18	-28	1
Go Success greater than Stop Success (GS>SS)						
Precuneus	L/R	112	5.3432	27	-46	22
	R	17	4.7917	6	-58	22

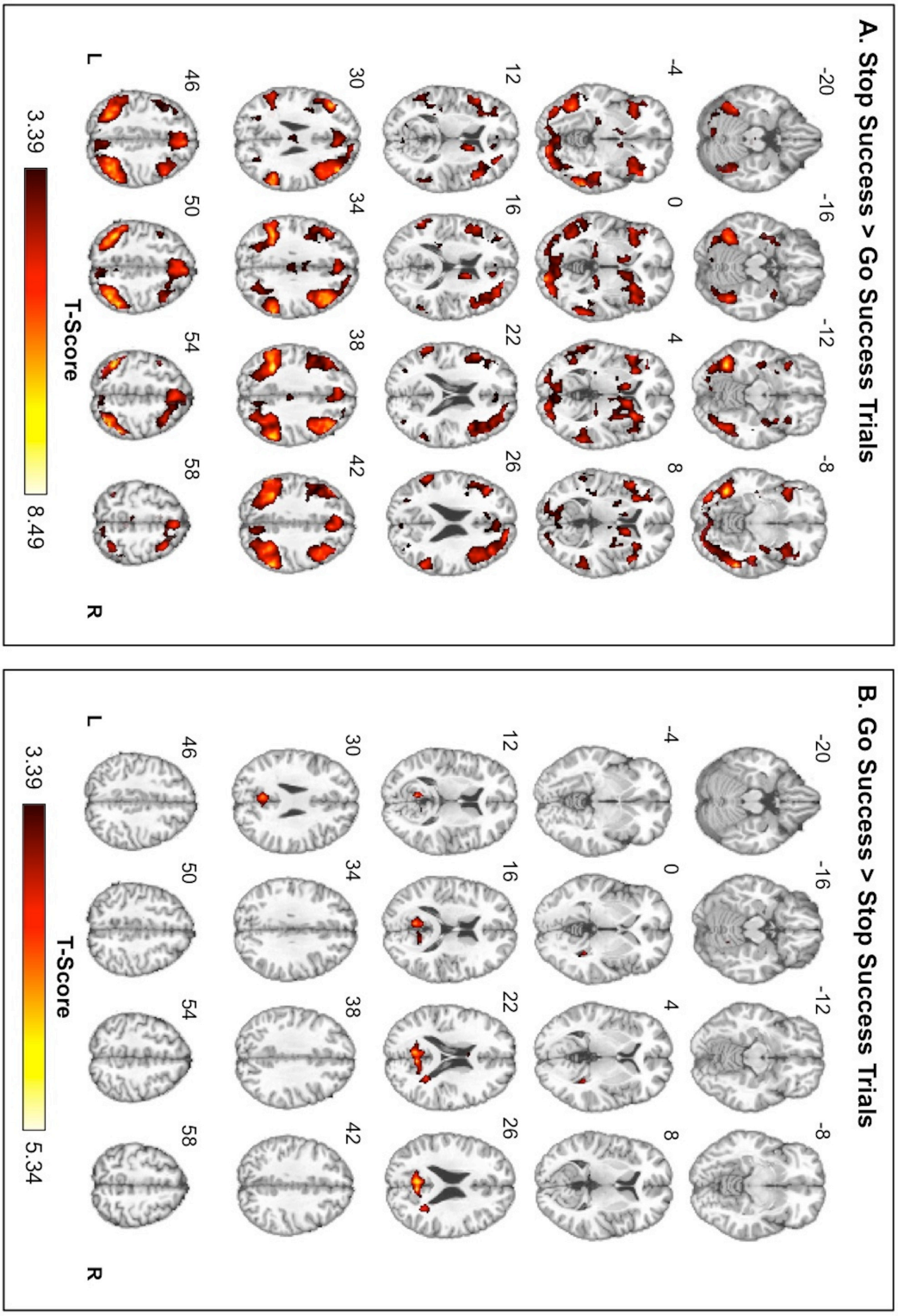

Figure 8A-B. Regional brain activation T-maps in the stop signal task. In comparing stop success (SS) and go success (GS) trials, there is A) greater activation in SS trials bilaterally in the frontal regions (IFG/MFG/SFG/MeFG/SMA), dorsal striatum, cingulate gyrus, insula, thalamus, temporal gyri, inferior parietal cortex, angular gyrus, fusiform gyrus, supramarginal gyrus, and occipital gyrus, and B) greater activation in GS trials in the precuneus bilaterally.

Contrasting “stop success” with “stop error” trials (i.e. SS>SE) to isolate those areas specifically associated with successful motor inhibition revealed increased activity in precentral gyrus/supplementary motor areas (SMA) and the dorsal striatum. This pattern of activation is consistent with numerous studies implicating these areas in controlling successful stopping (Li, Huang, et al. 2006; Duann et al. 2009; Ide and Li 2011; Rubia et al. 2001; Swick, Ashley, and Turken 2011). SE trials showed greater activation than SS trials in salience attribution, error monitoring, and motor control areas including the bilateral cerebellum, cingulate gyrus, insula, and pre-SMA / medial frontal gyrus (see Table 6, Figure 8C-D). No areas of prefrontal activation were observed in this contrast, suggesting that that the cognitive control component response inhibition is best visualized in the SS>GS contrast; however, other cognitive processes such as attention or saliency can confound the interpretation of the SS>GS contrast.

Table 6. Brain activation in the stop signal task comparing stop success (SS) and stop error (SE) trials. All maps were generated at an uncorrected threshold of p<0.001 and a cluster size of greater than 10 voxels

Brain Region	Hemi	Voxels	Max. T-stat.	x	y	z
Stop Success greater than Stop Error (SS>SE)						
Anterior Cingulate Gyrus	R	13	5.5957	6	32	-2
Caudate/Putamen	L	147	6.4413	-18	11	-5
	R	196	6.8297	18	14	-2
Hippocampus	L	13	4.6395	-33	-43	1
Middle Occipital Gyrus	L	57	5.6398	-42	-70	7
	R	44	5.614	21	-85	7
Middle Temporal Gyrus	R	37	5.3596	45	-67	4
Parahippocampal Gyrus	L	10	4.103	-24	-19	-17
Postcentral Gyrus	R	11	4.5868	54	-16	49
Precentral Gyrus	L	54	5.9114	-33	-19	49
	R	85	4.9799	33	-28	49
Precuneus	L	54	4.9169	-30	-73	34
	R	17	5.4281	27	-76	34
SMA	L/R	264	5.8732	-3	-25	58
Superior Parietal Lobule	R	16	5.3096	24	-55	55
Stop Error greater than Stop Success (SE>SS)						
Cerebellum	L	14	3.7239	-36	-58	-26
	R	75	5.1984	21	-58	-20
Cingulate Gyrus	L/R	17	4.5074	0	23	34
Insula	L	37	4.5641	-45	5	-5
	R	18	4.94	42	8	-5
preSMA / Medial Frontal Gyrus	R	37	4.8283	12	20	61
	L	11	4.3431	-9	26	58

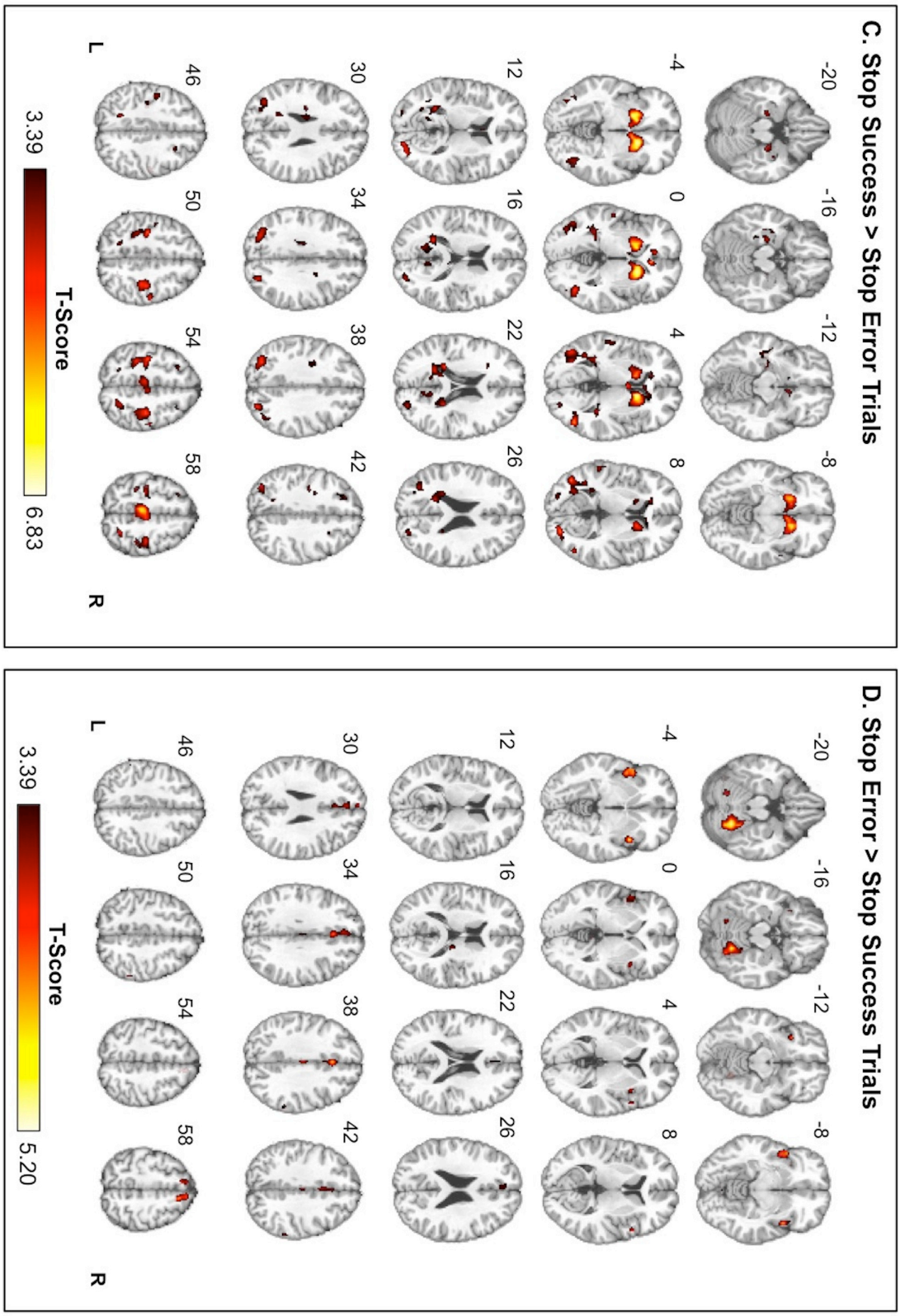

Figure 8C-D. Regional brain activation T-maps in the stop signal task. In comparing stop success and stop error (SE) trials, there is C) greater activation in SS trials in in the bilateral dorsal striatum, precentral gyrus, supplementary motor and visual areas, as well as the right cingulate gyrus, temporal gyri, and right superior parietal lobule and D) greater activation in SE trials in the bilateral cingulate gyrus, medial frontal gyrus/preSMA, insula, and cerebellum in stop error trials. All charts were generated at $p_{uncorrected}<0.001$, $k_E>10$ voxels.

Brain activation predicts stop signal task performance

The neural substrates of "going" and "stopping", revealed widespread activation in the expected motor, cognitive, salience, and attention networks. Given the specific relationship of obesity and insulin resistance to stop signal behavior, we performed whole-brain regressions of brain activation against these behaviors. Because the horse race model (Logan, Cowan, and Davis 1984) parameterizes SST performance as the difference in speeds between the "go" and "stop" processes, we regressed performance against the contrasts where the go and stop processes compete: stop success greater than go success (SS>GS; "stop" wins) and stop error greater than stop success (SE>SS; "go" wins). In the former contrast the "stop" horse wins to successfully inhibit a motor response, suggesting regions with greater activation will be associated with successful inhibitory SST performance (long cSSD, long mGRT, short SSRT). In the latter contrast the "go" horse wins in the stop trials to generate an error, indicating that regions with greater activation promote failed inhibition (short cSSD, short mGRT, long SSRT) (see Table 7).

Table 7. Interpretation of Stop Signal Task Regressions

	SS>GS	**SE>SS**
Interpretation of ↑ Brain Activity	Successful inhibition due to appropriate cognitive and motor mechanisms	Failed inhibition; may be due to impulsivity or impaired cognitive control
Associated SST Behavior (direction of correlation [r])	long cSSD (+r) long mGRT (+r) short SSRT (-r)	short cSSD (+r) short mGRT (+r) long SSRT (-r)

As the critical stop signal delay (cSSD) represents overall SST performance as the difference in speed between the "go" and "stop" processes, we first regressed cSSD against brain activation. Several brain regions appeared to modulate overall SST performance (see Table 8, Figure 9A). In SS>GS trials, increasing cSSD was associated with both areas of increased and decreased regional brain activation.

Positive correlations between cSSD and brain activity were observed in a predominantly left-sided network including the left insula, middle and superior temporal gyri, putamen, and the right amygdala. The involvement of limbic and emotional processing regions (Cauda et al. 2011; Olson, Plotzker, and Ezzyat 2007; Ostrowsky et al. 2002) with successful stopping suggests that the perceived salience of the "stop" acts to facilitate response inhibition.

In contrast, negative correlations between cSSD and brain activity were observed in a predominantly right-sided inhibitory motor and attention network including the angular gyrus, middle and inferior frontal gyrus, precentral gyrus, pre-supplementary motor area, thalamus, and the left supplementary motor area. The association of poorer overall performance (shorter cSSD due to faster "go" horse) with greater activation in motor control regions suggests that heightened inhibitory network activity is required to maintain performance. When examining activation during stop error trials, we found that poorer performance was associated primarily with greater activation of dorsal striatal inhibitory motor regions, potentially due to the activation of striatal movement pathways (Aron and Poldrack 2006) (see Figure 9B).

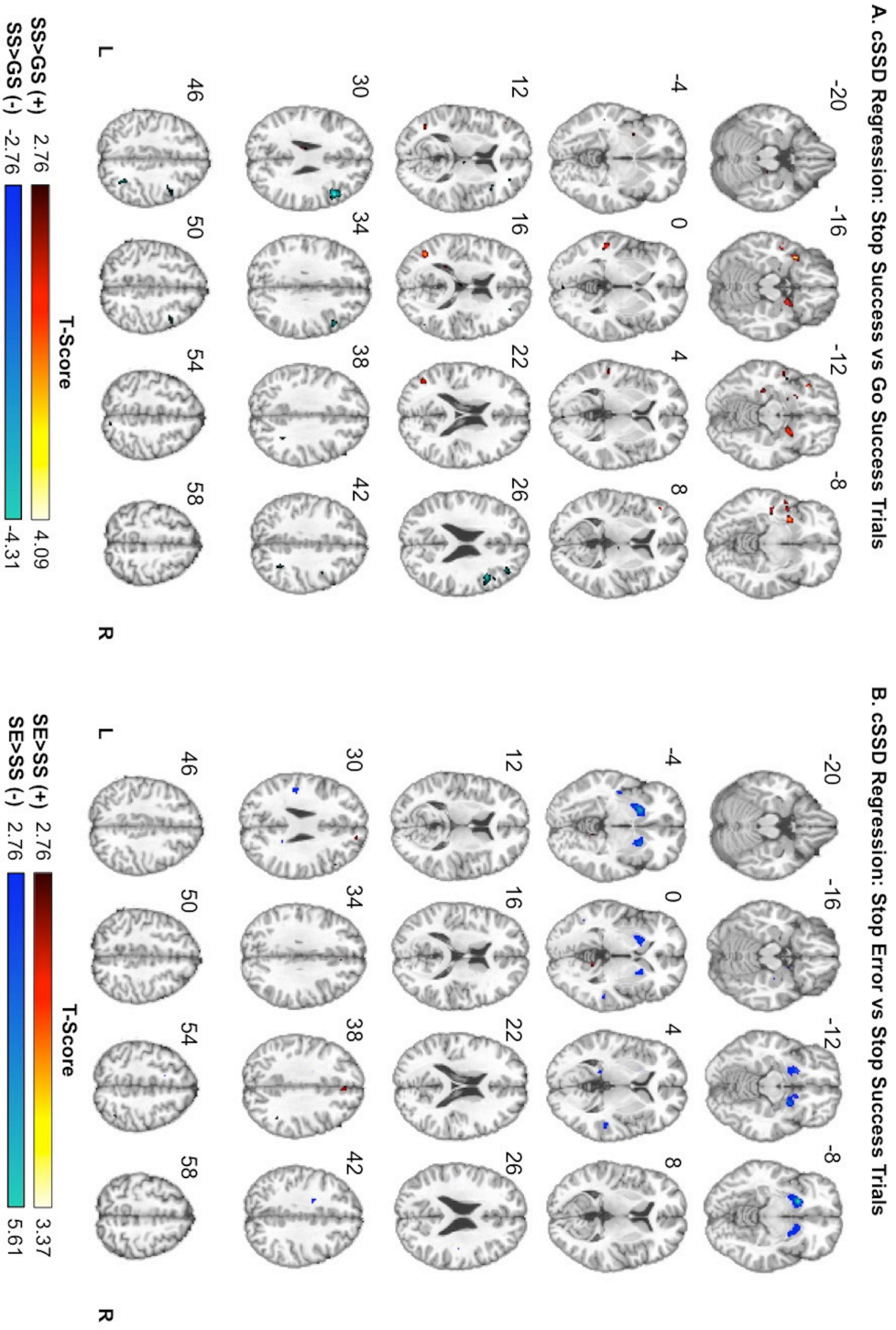

Figure 9. Stop signal delay duration modulates brain activity in inhibitory motor, attention, and salience circuits where impaired (shorter) cSSD produces A) greater activity in inhibitory motor and attention regions including the precentral gyrus, supplementary motor area, middle and inferior frontal gyrus, thalamus, and angular gyrus in stop success compared with go success trials but less activity in dorsal striatum and emotional / salience processing regions including the ventral insula, temporal gyri, and amygdala; B) greater activity in inhibitory motor regions including the bilateral putamen during stop error trials. (+) indicates a positive relationship between cSSD and brain activity, (-) indicates a negative relationship between cSSD and brain activity. All charts were generated at $p_{uncorrected}<0.001$, $k_E>10$ voxels.

Table 8. Brain regions sensitive to the stop signal delay predicted through the wholebrain regression of cSSD against brain activation

Brain Region	Hemi.	Voxels	Max. T-Statistic	x	y	z	R	p
Correlation with SS > GS Activation								
Angular Gyrus	R	28	3.5825	30	-52	43	-0.592	0.001
Inferior Frontal Gyrus	R	10	3.4569	39	20	13	-0.592	0.001
Middle Frontal Gyrus*	R	21	4.0997	36	38	25	-0.630	<0.001
	R	64	4.6625	48	17	28	-0.642	<0.001
Precentral Gyrus†	R	28	3.4062	42	5	49	-0.567	0.001
preSMA	R	15	3.3207	12	14	61	-0.598	<0.001
Supplementary Motor Area	L	27	3.7179	-6	-10	67	-0.562	0.001
Thalamus†	R	14	3.0165	9	-16	10	-0.518	0.003
Amygdala*	R	30	4.8119	21	2	-14	0.549	<0.001
Insula	L	19	5.3167	-36	11	-17	0.675	<0.001
	L	11	3.74	-42	-19	-8	0.590	0.001
Middle Temporal Gyrus	L	36	4.1704	-39	-64	16	0.615	<0.001
	L	24	4.3562	-51	-31	1	0.610	<0.001
Putamen	L	20	4.3891	-30	5	-8	0.677	<0.001
Superior Temporal Gyrus	L	28	4.0017	-54	-1	-8	0.643	<0.001
Correlation with SE > SS Activation								
Inferior Parietal Lobule	L	15	3.5565	-32	-25	28	-0.654	<0.001
Putamen	L	110	5.6124	-18	14	-8	-0.544	0.002
	R	76	4.34	24	14	-2	-0.571	0.001
Superior Temporal Gyrus	R	10	4.1208	51	-31	4	-0.675	<0.001
Medial Frontal Gyrus	R	11	3.3752	6	35	34	0.599	<0.001

Brain regions and the associated t-statistic, cluster sizes, and MNI coordinates are from the location of peak voxel at each local cluster maxima. Maps were thresholded at an uncorrected p<0.005.

† HOMA-IR predicts brain activity in these regions

* BMI predicts brain activity in these regions

Since “go” and “stop” speeds interact to determine overall SST performance, we next performed whole brain regressions against mGRT and SSRT to dissociate the neural correlates of “going” and “stopping”. Regression of SS>GS against mGRT revealed regions similar to the cSSD regression. Faster mGRT was associated with greater activation in inhibitory motor and attention regions including the precentral gyrus, supplementary motor area, thalamus, middle frontal gyrus, precuneus, cuneus and angular gyrus during SS trials, but decreased activation of emotional and salience processing regions including the amygdala, insula, middle temporal gyrus, and inferior

frontal gyrus. Faster mGRTs were also associated with increased activation in the putamen during stop error trials, suggesting heightened engagement of subcortical motor circuits facilitate impulsive responding to "drive" an error in a stop trial (see Table 9, Figure 10A-B). Regression of SS>SE against SSRT did not yield any areas that might be potential predictors of successful stopping; however, regression of SS>GS against SSRT, a less stringent screen for neural correlates of stopping performance, revealed negative correlations with SSRT (i.e. greater activation contrast with faster "stopping") in the left superior, middle, and inferior frontal gyri (Table 9, Figure 10C).

Table 9. Neural correlates of "going" and "stopping" in the stop signal task

Contrast	Brain Region	Hemi.	Voxels	T-Statistic	x	y	z	R	p
Median Go Response Time									
SS>GS	Angular Gyrus	R	16	3.3998	33	-58	43	-0.548	0.002
	Cuneus	L/R	13	3.6767	3	-88	1	-0.530	0.003
	Middle Frontal Gyrus*	R	21	3.7815	36	38	25	-0.608	<0.001
		R	57	4.216	48	17	28	-0.620	<0.001
	Precentral Gyrus†	R	21	3.5566	42	5	49	-0.552	0.002
	Precuneus†	R	11	3.362	15	-73	52	-0.513	0.003
	Supplementary Motor Area†	L	25	3.6703	-6	-10	67	-0.560	0.001
	Thalamus†	L/R	20	3.1663	9	-16	10	-0.528	0.001
	Amygdala	R	28	4.9367	21	2	-14	0.652	<0.001
	Inferior Frontal Gyrus	L	12	4.4576	-36	11	-17	0.624	<0.001
		L	11	3.984	-45	38	10	0.482	0.007
	Insula	L	10	3.7112	-45	-16	-8	0.576	0.001
	Middle Temporal Gyrus	L	30	3.8062	-39	-64	16	0.582	0.001
		L	25	4.109	-51	-31	1	0.611	<0.001
		L	16	3.8012	-54	-1	-8	0.580	0.001
	Putamen	L	11	3.8772	-30	5	-8	0.578	0.001
SE>SS	Putamen†	L	104	5.5469	-18	14	-8	-0.645	<0.001
		R	88	4.6923	24	5	-11	-0.677	<0.001
	Insula	R	12	3.2916	45	-4	13	-0.569	0.001
Stop Signal Response Time									
SS>GS	Supramarginal Gyrus	R	24	3.5862	33	-49	31	0.592	0.001
	Insula	R	12	3.4889	39	17	7	0.703	<0.001
	Superior Frontal Gyrus	L	11	4.0994	-18	-1	55	-0.711	<0.001
	Middle Frontal Gyrus	L	13	3.5829	-21	8	46	-0.684	<0.001
	Inferior Frontal Gyrus	L	46	4.5674	-30	17	-14	-0.551	0.002
		L	17	4.9397	-39	29	-14	-0.611	<0.001

Brain regions and the associated t-statistic, cluster sizes, and MNI coordinates are from the location of peak voxel at each local cluster maxima. Maps were thresholded at an uncorrected p<0.005.

† HOMA-IR predicts brain activity in these regions

* BMI predicts brain activity in these regions

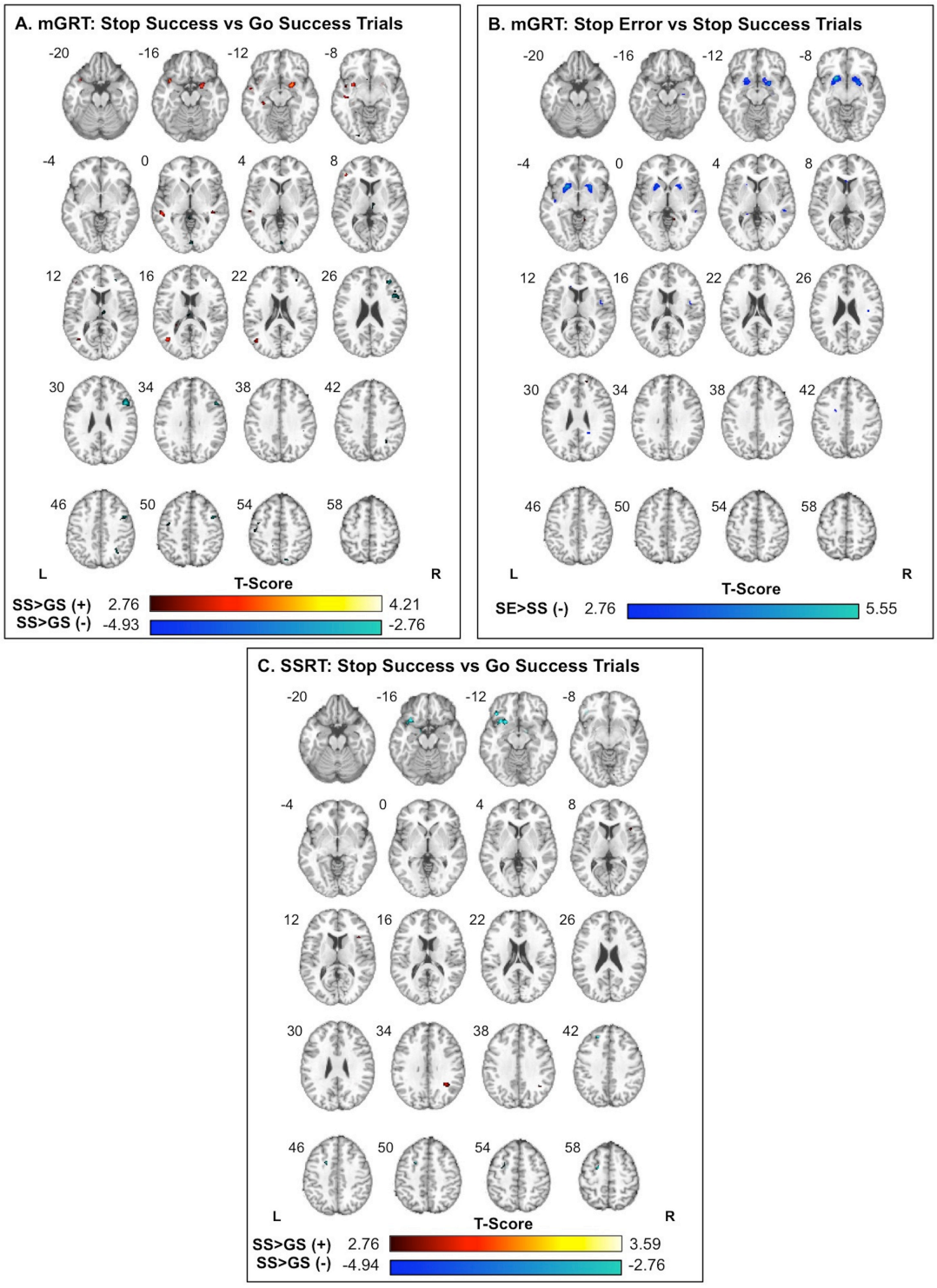

Figure 10. Neural correlates of "going" and "stopping" in the stop signal task A) faster responding is associated with greater activity in motor control and attention regions including the precentral gyrus, supplementary motor area, middle frontal gyrus, precuneus, thalamus, and angular gurus in stop success compared with go success trials but less activity in the ventral insula, middle temporal gyrus, and amygdala; B) faster responding is also associated with greater activity in the bilateral putamen during stop error trials; C) improved stopping performance is associated with increased activation in the inferior, middle, and superior frontal gyri and less activation in the supramarginal gyrus and the insula. All charts were generated at $p_{uncorrected}<0.001$, $k_E>10$ voxels.

Impact of insulin resistance on obesity on SST-associated brain activation

To address the hypothesis that obesity and/or impairments in central insulin signaling may influence SST performance, we next determined whether BMI and/or HOMA-IR explained inter-individual variations in the strength of activation in any brain areas previously identified as neural predictors of cSSD, mGRT, and/or SSRT (see Table 10). Of those areas identified in the SS>GS contrast as neural predictors of cSSD, we found a significant negative correlation of activation with HOMA-IR in right precentral gyrus (R^2 = 0.305, p = 0.014) and marginally in the right thalamus (R^2 = 0.182, p = 0.068). We also found a negative correlation between activation in the right middle frontal gyrus and BMI (R^2 = 0.421, p = 0.003), and a positive correlation with amygdala activation and BMI (R^2 = 0.203, p = 0.053), in SS>GS trials (see Table 10, Figure 11). None of these relationships remains significant after correcting for multiple comparisons at p_{FDR}<0.05. No correlation between activation in SE>SS and HOMA and/or BMI was observed.

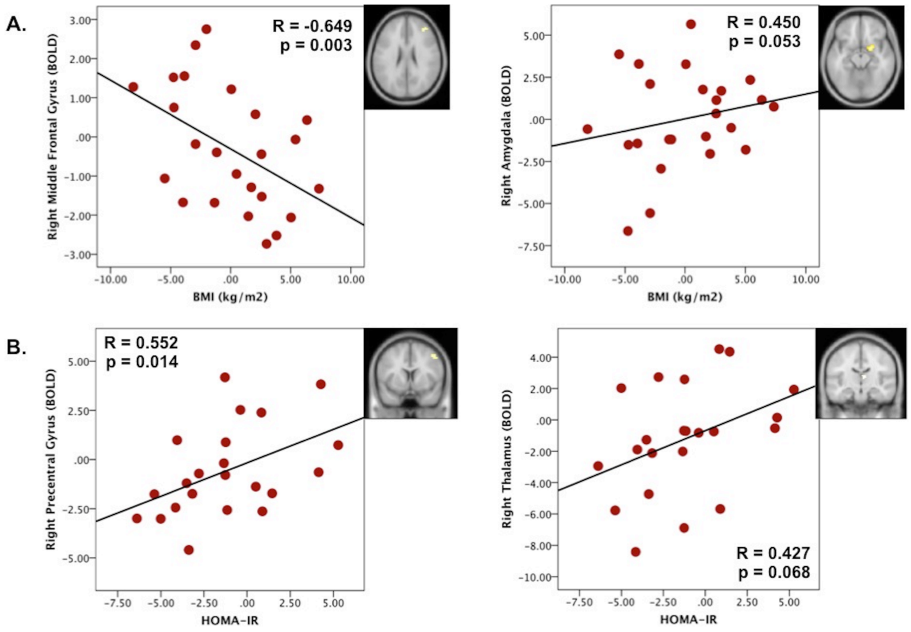

Figure 11. BMI and HOMA predict cSSD-related regional brain activity involved in emotional, inhibitory motor, and cognitive control A) brain activity in the right middle frontal gyrus negatively correlates with both cSSD and BMI while right amygdala brain activity correlates positively at trend-levels with both cSSD and BMI in SS>GS trials B) brain regions whose activity negatively correlates with cSSD but positively correlates with HOMA in SS>GS trials, including the right thalamus and right precentral gyrus .

To distinguish the impact of obesity and insulin resistance on speed of going and stopping, we also tested areas identified as neural correlates of mGRT and SSRT, for any association of contrast strength with HOMA-IR and/or BMI. Consistent with our findings that insulin sensitivity had no significant impact on SSRT, none of the areas identified as neural predictors of SSRT in the SS>GS contrast showed any significant association of activation strength with HOMA-IR or BMI. However, there was a significant positive association of activation strength with HOMA-IR for several areas identified as neural correlates of mGRT in the SS>GS and SE>SS contrasts. In the SS>GS contrast, the right precentral gyrus (R^2 = 0.278, p = 0.020), right precuneus (R^2 = 0.558, p < 0.001), left SMA at trend-levels (R^2 = 0.178, p = 0.072), and right thalamus (R^2 = 0.215, p = 0.046) were all positively correlated with HOMA-IR. In the SE>SS contrast, activation in the right putamen also positively correlated with HOMA-IR (R^2 = 0.192, p = 0.053) (see Table 10, Figure 12). After correcting for multiple comparisons at p_{FDR}<0.05, only the relationship between HOMA-IR and the right precuneus remains significant.

Table 10. BMI and HOMA-IR predict SST-related regional brain activity in attention, motor, and cognitive control circuits. *regression analyses meets FDR correction of p<0.05.

Critical Stop Signal Delay (cSSD)		*R*	*p*
BMI	Right Middle Frontal Gyrus	-0.649	0.003
	Right Amygdala	0.450	0.053
HOMA-IR	Right Precentral Gyrus	0.552	0.014
	Right Thalamus	0.427	0.068
Median Go Response Time (mGRT)		*R*	*p*
HOMA-IR	Right Precentral Gyrus	0.527	0.020
	Right Precuneus	0.747	<0.001*
	Left Supplementary Motor Area	0.422	0.072
	Right Thalamus	0.464	0.046
	Right Putamen	0.438	0.053

Brain activation mediates the effects of insulin resistance

Given that insulin resistance is associated the median go response time and the neural circuits subserving the mGRT, we performed a mediation analysis to examine whether these neural circuits mediated HOMA-IR's effect on stop signal performance (see Table 11, Figure 13). Here we have shown the effects of HOMA-IR on brain activation (a path) and stop signal performance (c path), and the effect of brain activation on stop signal performance (b path). When controlling for regional brain activation, HOMA-IR does not predict stop signal performance implying that brain activation mediates HOMA-IR's effect on the mGRT (c' path, direct analysis). Testing the degree to which brain activation mediates HOMA-IR's effect on stop signal performance (a x b path), we performed an indirect mediation analysis showing that the brain regions correlating with both stop signal performance and insulin resistance mediated HOMA-IR's effect on behavior. These results indicate that it is through these brain networks that insulin resistance produces the impulsivity observed in obesity.

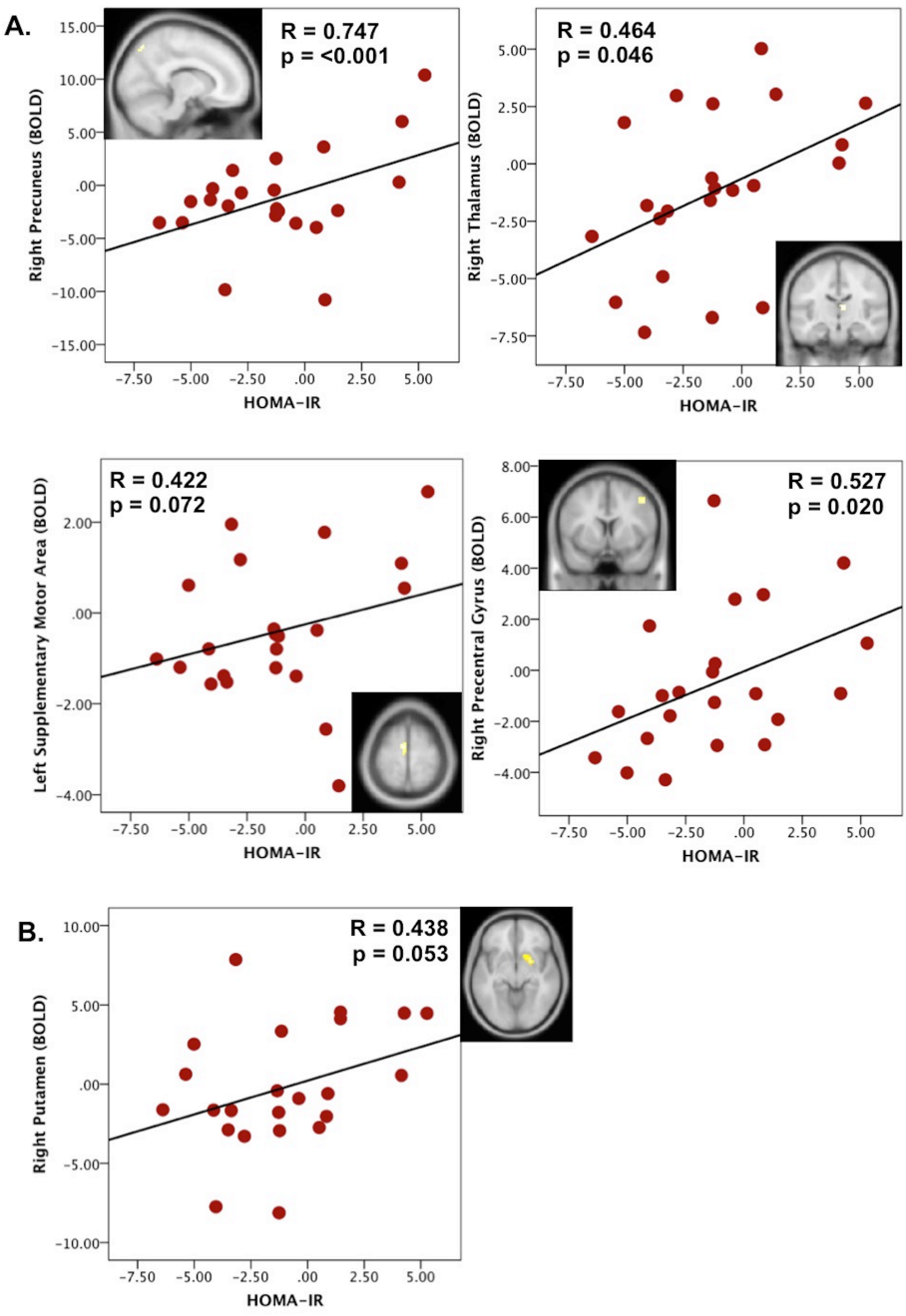

Figure 12. Insulin resistance predicts brain activation in regions whose activity correlates with mGRT in the stop signal task. A) Brain regions whose activity negatively correlates with mGRT but positively correlates with HOMA in SS>GS trials, including the right precuneus, right thalamus, left supplementary motor area, and right precentral gyrus. B) Brain activity in the right putamen negatively correlates with mGRT but positively correlates with HOMA in SE>SS trials.

Table 11. Regional brain activation mediates the relationship between HOMA-IR and the median go response time. Mediation is shown by the loss of significance of HOMA-IR on stop signal performance when brain activation is included as a mediating variable in the analysis directly (c' path) and indirectly (ab path).

Brain Region	Effect of HOMA-IR on brain activation	Effect of brain activation on mGRT	Effect of HOMA-IR on mGRT	Effect of HOMA-IR on mGRT controlling for regional brain activation	Effect of HOMA-IR on mGRT mediated by regional brain activation
	a path	*b path*	*c path*	*c' path (Direct)*	*a x b path (Indirect)*
			Effect (p-value)		
R Precentral Gyrus	0.34 (0.02)	-13.71 (0.002)	-6.93 (0.06)	-3.50 (0.44)	-2.13 (0.03)
R Precuneus	0.79 (<0.001)	-6.86 (0.004)	-6.93 (0.06)	-3.82 (0.42)	-2.66 (0.01)
L Supplementary Motor Area	0.17 (0.07)	-19.51 (0.001)	-6.93 (0.06)	-4.20 (0.31)	-1.72 (0.08)
R Thalamus	0.42 (0.04)	-8.88 (0.003)	-6.93 (0.06)	-3.91 (0.36)	-1.87 (0.06)
R Putamen	-0.36 (0.05)	19.51 (<0.001)	-6.93 (0.06)	-2.46 (0.53)	-1.93 (0.05)

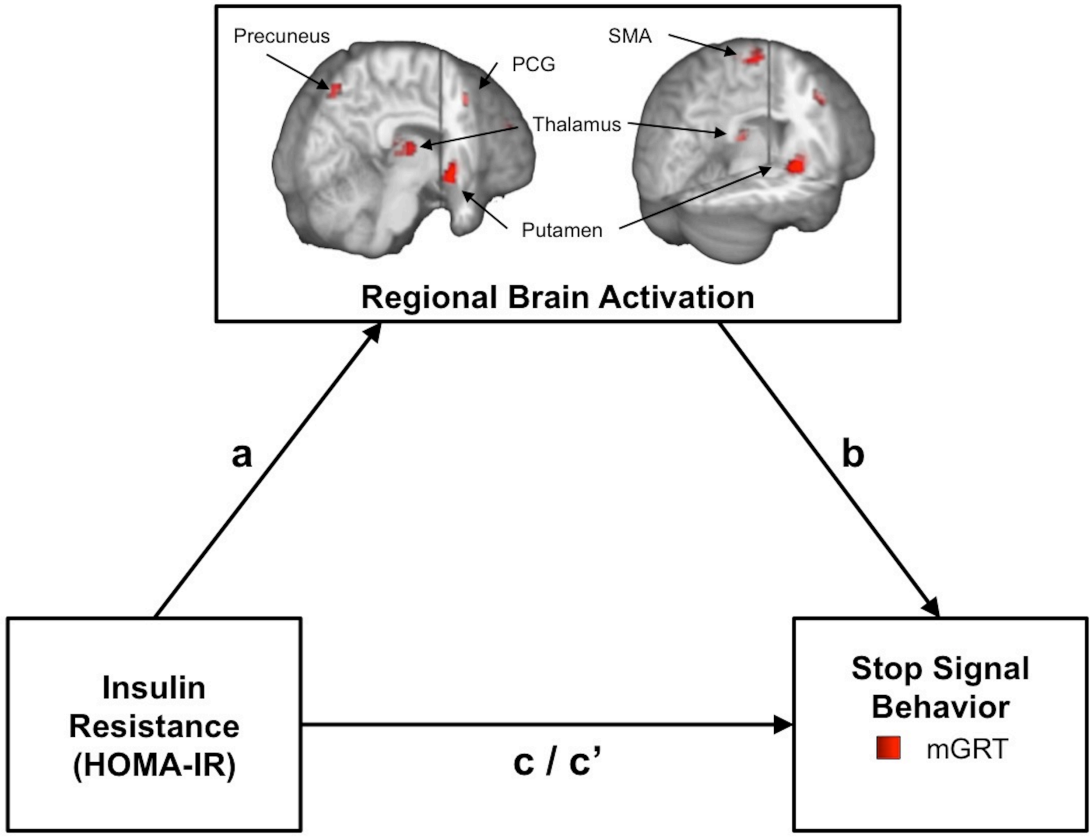

Figure 13. Regional brain activation mediates the effect of insulin resistance on the median go response time. Corticostriatal circuits subserving impulsivity [red, mGRT] mediate HOMA's effect on the median go response time in the stop signal task. All fronto-cortical and striatal brain regions where the HOMA predicted brain activation in the stop signal task (a), as determined by the wholebrain regressions with mGRT (b), significantly mediated HOMA's effect on stop signal behavior (c) using both a direct (c') and indirect (ab) mediation model.

Discussion

Here we demonstrate that obesity and insulin resistance have dissociable effects on stop signal performance. Insulin resistance enhanced impulsivity and performance monitoring. Although the trend-levels were not significant, obesity may have impaired response inhibition and cognitive restraint. Activation in attention and dorsal striatal motor neural networks significantly mediated the relationship between insulin resistance and impulsivity, suggesting that insulin resistance differentially impacts brain systems promoting the responsiveness to and acquisition of salient (e.g. food) stimuli.

Action Control in Obesity and Insulin Resistance

Action control is the cognitive and behavioral processes underlying the execution or inhibition of a response. The independent processes of going and stopping act in concert with attention and cognitive flexibility to monitor and adjust performance(Boucher et al. 2007; Bari and Robbins 2013; Logan and Cowan 1984). Operational definitions of inhibition and impulsivity are challenging. Response inhibition refers to “inhibition of impulses to act” and encompasses both the cognitive and motor action of inhibition. Impulsivity is the inability to inhibit a response or thought, which may be due to the failed inhibition of motor responses and/or the enhanced motivation/wanting for salient stimuli (Logan, Schachar, and Tannock 1997; Skaggs 1929; Nigg 2000; Winstanley, Eagle, and Robbins 2006).

Several studies have examined response inhibition in obesity (Nederkoorn et al. 2010; Hendrick et al. 2011); however, this is the first study that finds even trend-level impaired response inhibition with increased BMI. Other studies using a stop signal or go/no-go task link obesity to impulsivity(Yokum, Ng, and Stice 2011; Batterink, Yokum, and Stice 2010; Nederkoorn et al. 2006), which coincides with our novel finding of an

accelerated mGRT in insulin resistance. In a cohort for which obesity and insulin resistance are unrelated, we found a dissociation between obesity and insulin resistance in measures of action control. This suggests that the underlying mechanisms behind the BMI-dependent deficits in response inhibition and HOMA-IR-dependent enhancements of impulsivity may be separable.

The molecular underpinnings of inhibition and impulsivity are becoming clearer and may inform our present results. The go process is heavily dependent on dopamine(Robbins and Arnsten 2009; Dalley, Everitt, and Robbins 2011; Dalley et al. 2007) and the speed of the go response is a measure of impulsivity(Muggleton et al. 2010). Elevated synaptic DA decreases go response time(Eagle et al. 2007) and antagonizing dorsal striatal D2R increases mGRT(Eagle et al. 2011). In humans, an increase in striatal DA due to amphetamine-evoked DA efflux from DAT is linked with heightened impulsivity(Buckholtz et al. 2010). These effects may be due to increased activation of the direct pathway of movement(Aron and Poldrack 2006), although recent data support that the direct and indirect pathways of movement cooperatively act to initiate motor responding to reward(Isomura et al. 2013; Cui et al. 2013). Increased impulsiveness in obesity may be due to insulin-mediated elevations in DA due to impaired DAT expression at the level of the dorsal striatum, which promotes enhanced responsiveness to salient stimuli. However, our analyses are at this point associational and it may be that impulsivity is an endophenotype that drives the brain-associated changes leading to obesity.

Inhibition of an already initiated response, such as in the stop signal task, is under the influence of prefrontal noradrenergic and, to a lesser degree, dopamine neurotransmission(Bari et al. 2011; Eagle, Bari, and Robbins 2008). How this works is unclear, as is the mechanism behind why obesity but not insulin resistance, would selectively impair stopping. Increasing BMI is associated with elevated leptin,

triglycerides, and free fatty acids, each of which been linked with cognitive deficits(Tschritter et al. 2009; Farr et al. 2008; Morrison 2009). These factors may underlie BMI's effect on inhibition in the absence of an effect of HOMA-IR. In addition to metabolic factors, elevated BMI has also been associated with hormonal elevations due to chronic stress(Dallman et al. 2003), and preliminary studies show that chronic stress impairs prefrontal executive function(Mika et al. 2012) and response inhibition(Zack et al. 2011).

We further find insulin resistance is associated with increased post-error slowing (PES). Dopamine contributes to modulation of post-error slowing, where both methylphenidate(Moeller et al. 2012) and amphetamine(Wardle, Yang, and de Wit 2012) increase PES. This is consistent with our model of elevated DA due to insulin-mediated impairments of DAT expression. However, the positive relationship between HOMA-IR and PES contrast with the addiction literature where current(Lawrence et al. 2009) and abstinent(Li, Milivojevic, et al. 2006) substance abusers fail to slow down after an error. Many theories of PES posit that the increase in reaction time following an error is an adaptive mechanism to reduce future errors and that the deficient cognitive control in addiction impairs such slowing (Botvinick et al. 2001). However, others propose PES is an orienting response that occurs following an unexpected and salient event(Notebaert et al. 2009) and that PES represents a failure to disengage from the error(Compton et al. 2011). In the context of insulin resistance, this failure of attention reorientation may be driving the delayed response time on the subsequent trial and is consistent with the correlation of insulin resistance with attentional impulsivity on the Barrett Impulsiveness Scale. Insulin resistance may therefore modulate dopamine neurotransmission in a way that biases towards impulsivity and error-related braking and is reminiscent of binge eating and crash dieting.

Motor and Attention Networks Mediate Effects of Insulin Resistance on Impulsivity

Using the stop signal task, we replicated the cortical and subcortical brain regions involved in successful stopping in an obese, mildly insulin resistant cohort. Activation of inhibitory motor areas (IMAs; including pre-supplementary motor area [preSMA], supplementary motor area [SMA] and precentral gyrus [PCG]), the subthalamic nucleus (STN), and the dorsal striatum are consistently implicated in the motor component of response inhibition(Aron, Behrens, et al. 2007; Aron, Durston, et al. 2007; Boehler et al. 2010; Ghahremani et al. 2012; Li, Huang, et al. 2006; Mostofsky et al. 2003; Rubia et al. 2001; Rubia et al. 2003; Swick, Ashley, and Turken 2008; Swick, Ashley, and Turken 2011; Zandbelt et al. 2013); however, SMA and PCG are also engaged in motor execution(Rowe, Hughes, and Nimmo-Smith 2010). Regions such as the dorsolateral prefrontal cortex (DLPFC) and insula contribute to inhibitory processes by processing motivational and emotional components of inhibition(Dosenbach et al. 2008). Parietal regions and precuneus are engaged due to the attentional component of the task(Rubia et al. 2001).

To elicit the circuits engaged in going and stopping, we studied the regression of participants' stop signal behavioral performance against brain activation. We found performance-specific activation of the expected motor, saliency, and attention networks. Consistent with the behavioral and psychometric data, the effect of insulin resistance on impulsive responding was mediated through a cortico-striatal-thalamo-cortical network including the putamen, PCG, SMA, thalamus, and precuneus.

Cortico-striatal-thalamo-cortical circuits are heavily implicated in emotional, motor, and cognitive processing(Haber 2003). The mediodorsal nucleus (MD) and the centromedian/parafasicular (CM/Pf) subregions of the thalamus were engaged during impulsive responding. These nuclei are important relay nuclei linking the basal ganglia

and cortex(Haber and Calzavara 2009). Both nuclei project to the dorsal and ventral striatum(Cheatwood, Reep, and Corwin 2003; Eckert et al. 2012) but differ in their cortical projections, with MD projecting to regions such as SMA/PCG(Jakab, Blanc, and Berenyi 2012; Rouiller et al. 1999) and CM/Pf projecting to more ventral regions including the anterior insula(Eckert et al. 2012; Jasmin et al. 2004). Consistent with their projections, MD is involved in the acquisition of goal-directed behavior(Corbit, Muir, and Balleine 2003; Mitchell, Browning, and Baxter 2007), action selection(Ostlund and Balleine 2008) and behavioral flexibility(Block et al. 2007; Pickens 2008) while CM/Pf is involved in motor preparation, attention, and saliency processing(Metzger et al. 2010; Nelson et al. 2010; Smith et al. 2009). These regions reflect those in our identified HOMA-dependent network, with the putamen, SMA, and PCG likely participating in the motor component of the response(Zandbelt et al. 2013) and the precuneus engaging as part of the frontoparietal attention network(Petersen and Posner 2012). Activation in saliency processing regions, including the hippocampus and insula, also correlated with impulsive responding but only correlated at trend-levels ($p = 0.08$-0.10) when regressed against HOMA-IR. This may reflect the ability of the stop-signal task to detect areas involved in saliency processing rather than an inability of insulin resistance to modulate those regions, as the insular response to salient food cues has been previously identified as being dependent on insulin resistance(Jastreboff et al. 2013). The heightened activation of these regions with both insulin resistance and impulsive responding suggests that the brain's response to insulin resistance promotes goal-directed impulsive responding through attention and motor cortico-striatal-thalamo-cortical networks, however additional studies are necessary to determine the functional coupling of these circuits in insulin resistance.

This insulin-dependent impulsivity network that includes key cortico-striatal-thalamo-cortical regions coincides with the role of dopamine in impulsive responding.

Corticostriatal and thalamostriatal glutamatergic projections converge alongside dopaminergic terminals on medium spiny neurons (MSNs) in the dorsal striatum(Moss and Bolam 2008; Huerta-Ocampo, Mena-Segovia, and Bolam 2013). Together, these glutamatergic and dopaminergic projections interact to guide attention, action selection, and motor function through reciprocal engagement of these loops (Kimura et al. 2004; Thorn and Graybiel 2010; Doig, Moss, and Bolam 2010; Alexander, DeLong, and Strick 1986). Increases in dopaminergic activation of striatal movement pathways induced by impaired DAT expression in insulin resistance could facilitate the observed heightened engagement of these attention and motor networks and, in turn, impulsivity.

Mild Obesity and Insulin Resistance as an Early Process in Addiction

The hypothesized overlap between obesity and substance use disorders is heavily discussed in research and the popular press, with much of the literature highlighting the involvement of the dopamine system(Pelchat 2009; Taylor, Curtis, and Davis 2010; Avena 2011; Kenny 2011; Volkow et al. 2013). Although there may be similarities in reward, salience, motivation, and cognitive control, there are important differences between obesity and addiction including the clinical definition of tolerance and withdrawal to food(Salamone and Correa 2012; Ziauddeen, Farooqi, and Fletcher 2012) and the unclear role of dopamine in the development of obesity(Dunn et al. 2010; Wang et al. 2001; Steele et al. 2010b). Prior studies have shown that both methamphetamine(Monterosso et al. 2005; Tolliver et al. 2012) and cocaine(Li, Milivojevic, et al. 2006; Fillmore and Rush 2002) dependent subjects exhibit blunted inhibitory processing through a slowing of the stop signal response time and the go response time. Behavioral impairments are associated a hypoactivation of inhibitory circuits(Li, Milivojevic, et al. 2006; Elton et al. 2012). These deficits in inhibitory control are considered to be a core component of substance use disorders(Koob and Volkow

2010; Volkow, Wang, Fowler, et al. 2008); however, we fail to find similar parallels in inhibitory networks in obesity and insulin resistance.

Heightened impulsivity, however, is a central process early in the addiction cycle(Koob and Volkow 2010). We demonstrate striking associations between insulin resistance and cortico-striatal-thalamo-cortical impulsivity networks suggesting that mild obesity and insulin resistance may parallel the early stages of addiction. Longitudinal research across a wider range of insulin resistance and obesity will be useful in determining whether similarity exists between the neurobiological substrates in the transition to addiction or obesity.

Conclusion

In summary, we have identified a specific cortico-striatal-thalamo-cortical network whose activity mediates the link between insulin resistance and impulsivity. These findings indicate that insulin resistance may have specific action in the central nervous system to promote the responsiveness to, and acquisition of, salient stimuli. Similar dysregulation occurs during early stages of addiction, suggesting the developmental trajectory of obesity and insulin resistance may parallel the transition from substance use to abuse.

CHAPTER III

THE IMPACT OF VISCERAL ADIPOSE AND INSULIN RESISTANCE ON STRIATAL DOPAMINE AND IMPULSIVITY

Introduction

Parallels between obesity and substance use disorders highlight the role of the dopaminergic striatum due to its role in reward, habits, and cognitive control(Berridge and Robinson 1998; Schultz 2007; Schultz, Dayan, and Montague 1997; Faure et al. 2005; Graybiel 2008; Yin, Knowlton, and Balleine 2004). Our prior work identified a cortico-thalamo-striatal-cortical network mediating the effects of insulin resistance on impulsivity. Impaired striatal dopamine signaling promotes impulsivity(Eagle et al. 2007; Eagle et al. 2011; Buckholtz et al. 2010), suggesting that insulin's effect on the impulsivity may be due to its action on dopamine neurotransmission in the striatum.

The striatum is divided into its ventral and dorsal components: the ventral striatum (nucleus accumbens [NAc]) receives its dopaminergic projections from the ventral tegmental area (VTA) via the mesolimbic pathway while the dorsal striatum (caudate [Ca], putamen [Pu]) is the recipient of dopamine neurons from the substantia nigra (SN) via the nitrostriatal pathway. While striatal subregions receive different projections, they are engaged sequentially during addictive processes as dopamine signals encode behaviors progressing from reward-driven actions to cue-mediated habits(Graybiel 2008; Koob and Volkow 2010; Hyman, Malenka, and Nestler 2006; Yin 2010; Yin, Knowlton, and Balleine 2005). Heightened dopamine signaling in combination with dopamine excess driven by drugs of abuse is believed produce an allostatic downregulation of the dopamine receptor (D2R) in the striatum(Koob and Le

Moal 2001; Koob and Volkow 2010). Similar to addiction, reductions in striatal D2R are observed with an obesogenic diet(Bello, Lucas, and Hajnal 2002; Fetissov et al. 2002; Hamdi, Porter, and Prasad 1992; Johnson and Kenny 2010) and increasing BMI(Wang et al. 2001; Volkow, Wang, Fowler, et al. 2008).

Having uncovered the impact of insulin resistance on striatal activation and impulsivity, we sought to determine the molecular underpinnings behind this dysregulation. We hypothesized that obesity and insulin resistance would be associated with reductions in striatal D2R that in turn would facilitate impulsive responding.

Methods

General Study Protocol

Research participants, visit schedule, biochemical evaluation, PET / fMRI imaging parameters, and the stop signal task behavioral and imaging analysis were implemented as discussed in Chapter 2.

Fat Water Imaging (FW-MRI)

Lean and adipose tissue volumes were measured using fat water imaging on the second visit day at approximately 8:00am. A multi-station protocol with multiple table positions was used to acquire whole-body data. Each stack consisted of a multi-slice, multi-echo gradient echo (fast field echo, FFE) acquisition with 12 slices, slice thickness 8mm, zero slice gap. Other acquisition details include: TR/TE1/TE2/TE3 [ms] = 75/1.34/2.87/4.40; FA=20°; water-fat shift (WFS) = 0.325 pixels (BW=1335.5 Hz/pixel); field of view (FOV) = 500 mm × 390 mm, acquired matrix size = 252 × 195; acquired voxel size = 2 mm × 2 mm × 8 mm. First order shimming was performed for each slice stack and flyback gradients were employed between echoes so that the chemical shift

direction for all echo readouts was the same. Acquired and deidentified FWI data were analyzed by collaborators at the University of Uppsala. FW-MRI data were reconstructed, segmented, and quantified into lean tissue (LT), total adipose tissue (TAT), subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) compartments using previously described methods(Kullberg et al. 2009). Adipose tissue volumes were normalized to participant lean tissue volume to examine the specific effects of adipose tissue depots.

Statistical Analyses

Adipose tissue depot volumes, biochemical markers, stop signal associated activation and behavioral performance, and D2R non-displaceable binding potentials were examined for relationships between obesity, insulin resistance, and brain structure and function. Adipose tissue depots were comprised of SAT (normalized to LT) and VAT (normalized to LT). Stop signal performance measurements included the SSRT, cSSD, mGRT, and PES. SST-associated brain activation included the parameter estimates from stop success greater than go success (SS>GS), stop error greater than stop success (SE>SS), and the regression of brain activity in these contrasts against behavior discussed in Chapter 2.

To determine the degree to which D2R PET, stop signal activation, and SST behaviors were influenced by markers of obesity (BMI, VAT%LT, SAT%LT) and insulin resistance (HOMA-IR), these measurements were entered into a multiple linear regression as dependent variables with obesity and insulin resistance markers as independent variables, while controlling for nuisance variables that may impact performance including age(Cohen et al. 2010) and insulin-sensitizing medications. Results were considered statistically significant at $p \leq 0.05$ and marginally significant at $p \leq 0.08$.

For all potential direct and indirect relationships between the aforementioned variables, mediation analyses were performed to determine whether brain structure and function mediated the effects of obesity and insulin resistance on stop signal performance. The indirect mediation effects were calculated using the Goodman test(Goodman 1960). All statistical analyses were performed in SPSS v20 (SPSS Statistics).

Results

Demographics and clinical information

The demographic and clinical characteristics of the study cohort are summarized in Table 1. At baseline, fifty-eight subjects were enrolled in the study. Of the enrolled 58 subjects, thirty-two received PET imaging (age: 46.44 ± 1.29 yrs, BMI: 37.86 ± 0.63 kg/m^2, 22 female, 10 male), forty-seven completed the behavioral component of the stop signal task (age: 47.12 ± 1.03 yrs; BMI: 37.14 ± 0.70 kg/m^2; 29 female, 18 male) and thirty successfully completed the fMRI component of the stop signal task (age: 48.10 ± 1.25 yrs; BMI: 36.45 ± 0.74 kg/m^2; 18 female, 12 male). There were no differences in the clinical profiles between these sub-groups, allowing for the data collected across these groups to be compared in a single model.

Visceral adipose tissue predicts striatal dopamine D2 receptors and brain activation

Having established that striatal brain activation mediates the relationship between insulin resistance and impulsivity (see Figure 13), we sought to examine the relationship of obesity and insulin resistance to striatal D2 receptors prior to short-term insulin treatment. While we were unable to link striatal D2R to BMI as previously

reported(Wang et al. 2001) in the literature, or to insulin resistance, we found a strong relationship between visceral adipose tissue (VAT) and striatal D2R (see Figure 14A). Increasing VAT was negatively associated with striatal D2R in the caudate (R^2 = 0.498, p = 0.001), caudate head at trend-levels (R^2 = 0.203, p = 0.058), nucleus accumbens (R^2 = 0.293, p = 0.021), and putamen (R^2 = 0.356, p = 0.009).

Interestingly, increasing VAT was also marginally associated with increased brain activation in the functionally-defined dorsal striatum during stop error greater than stop success trials (R^2 = 0.195, p = 0.067; see Figure 14B), the same pattern observed between insulin resistance and activation in the putamen in SE>SS trials (see Figure 12B). Although the ventral striatum was not significantly activated in the SE>SS contrast, brain activity extracted from the atlas-defined nucleus accumbens also increased at non-significant trend-levels during SE>SS trials with greater VAT (R^2 = 0.204, p = 0.060).

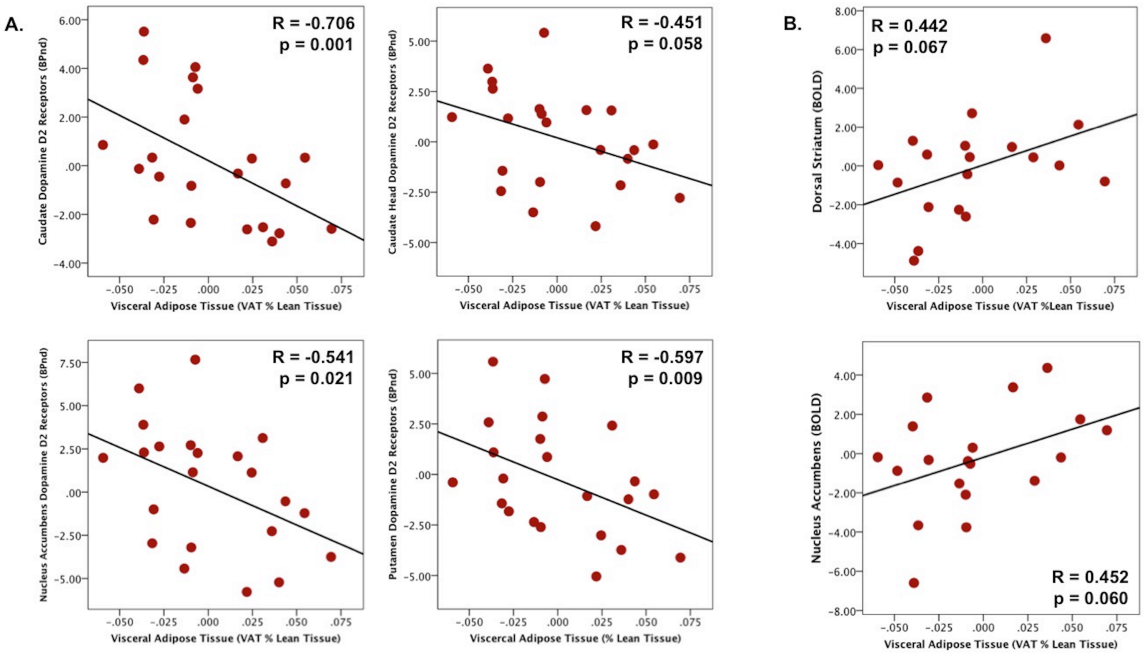

Figure 14. Visceral adipose tissue predicts striatal dopamine D2 receptors and activation at baseline A) increasing VAT is associated with decreased striatal D2R across striatal sub-regions including the caudate, caudate head, nucleus accumbens, and putamen B) increasing VAT is associated with increased dorsal and ventral striatal brain activation during stop error trials compared with stop success trials (SE>SS)

Striatal activation and dopamine D2 receptors predicts impulsive behavior

We next examined the link between striatal D2R and stop signal performance. Although we found no relationship between stop signal response time (SSRT) and striatal D2R, we found strong association between striatal D2R and the median go response time (mGRT). Both ventral striatal (R^2 = 0.184, p = 0.036) and dorsal striatal D2R (R^2 = 0.187, p = 0.035) were positively associated with the mGRT, linking lower D2R with impulsive responding (see Figure 15).

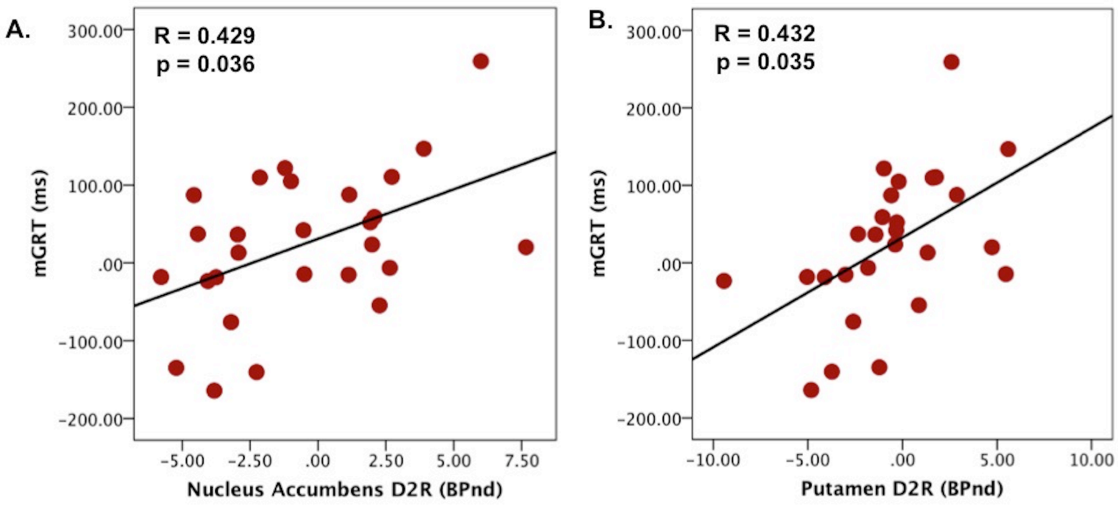

Figure 15. Decreased striatal D2R predict impulsive behavior in the stop signal task in the A) ventral striatum and B) dorsal striatum

Striatal dopamine circuits mediate the effect of visceral adipose and insulin resistance on impulsive behavior

Although lower ventral and dorsal striatal D2R are associated with increased VAT and increased impulsivity, we found only a trend-level negative relationship between VAT and mGRT (R^2 = 0.110, p = 0.104). However, because of the link

between HOMA and impulsivity, and the relationship of VAT to both ventral and dorsal striatal D2R and activity, we performed multiple mediation analyses to examine the degree to which both increasing insulin resistance and increasing VAT promote impulsivity through striatal circuits (see Figure 16).

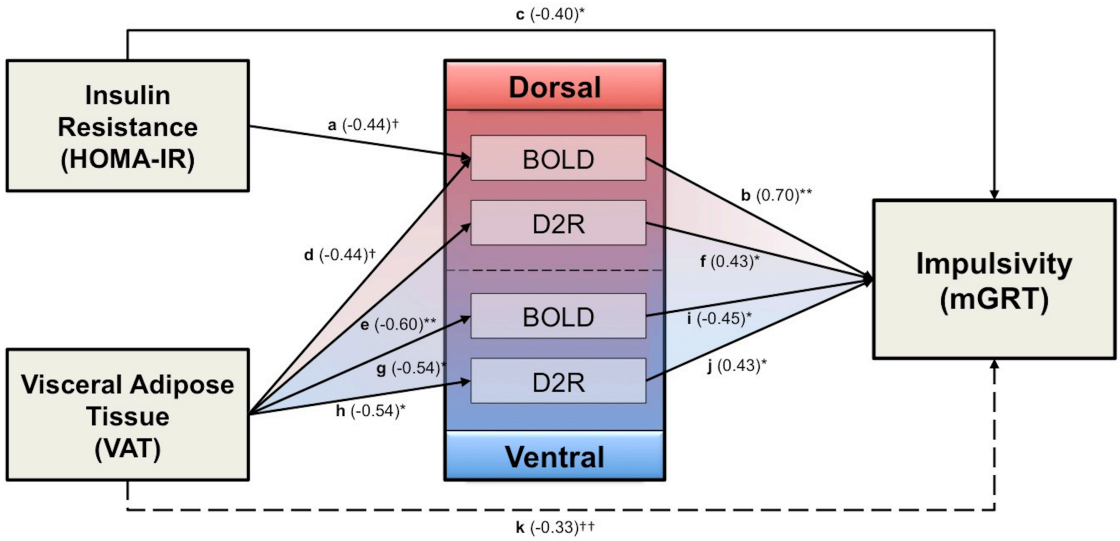

Figure 16. Multiple mediation model for the influence of insulin resistance and visceral adipose tissue on impulsivity via dorsal and ventral striatal circuits. Each path is represented by a letter with the associated R-value ††p=0.10, †p<0.10, *p<0.05, **p<0.01.

The impact of HOMA-IR on impulsivity was mediated at non-significant trend levels through dorsal striatal brain activity (ab-path, p = 0.058) as reported in Chapter 2. Using the Goodman indirect mediation analysis(Goodman 1960), we next tested the degree to which VAT impacted impulsivity through striatal circuits. Dorsal striatal brain activity (db-path, p = 0.068) and, to a lesser degree, ventral striatal brain activity (gi-path, p = 0.089) during SE>SS trials marginally mediated VAT's effect on increased impulsivity. Similarly, dorsal striatal D2R (ef-path, p = 0.062) and less significantly, ventral striatal D2R (hj-path, p = 0.078) marginally mediated VAT's effect on increased impulsivity (see Table 12 for individual path strengths and mediation effects).

Together, these results indicate that the dorsal and ventral striatum may serve as an important focal point through which insulin resistance and visceral adipose tissue produce dysregulation of neural networks promoting impulsivity.

Table 12. Mediation model for the influence of insulin resistance (HOMA-IR) and visceral adipose tissue (VAT) on impulsivity (mGRT) via dorsal and ventral striatal brain activation (BOLD) and dopamine D2 receptors (D2R). Effect size and p-value from the Goodman test are reported.

Path Strength	Effect Size	p-value
a: impact of HOMA-IR on dorsal striatal BOLD	-0.359	0.053
b: impact of dorsal striatal BOLD on impulsivity	17.501	0.001
c: impact of HOMA-IR on impulsivity	-8.068	0.022
d: impact of VAT on dorsal striatal BOLD	32.933	0.067
e: impact of VAT on dorsal striatal D2R	-57.239	0.009
f: impact of dorsal striatal D2R on impulsivity	11.619	0.035
g: impact of VAT on ventral striatal BOLD	32.514	0.060
h: impact of VAT on ventral striatal D2R	-54.027	0.021
i: impact of ventral striatal BOLD on impulsivity	-19.028	0.011
j: impact of ventral striatal D2R on impulsivity	11.072	0.036
k: impact of VAT on impulsivity	-853.913	0.104
Indirect Path Strength	**T-statistic**	**p-value**
ab: impact of HOMA on impulsivity via dorsal striatal BOLD	-1.891	0.058
db: impact of VAT on impulsivity via dorsal striatal BOLD	1.822	0.068
ef: impact of VAT on impulsivity via dorsal striatal D2R	-1.862	0.062
gi: impact of VAT on impulsivity via ventral striatal BOLD	-1.697	0.089
hj: impact of VAT on impulsivity via ventral striatal D2R	-1.762	0.078

Discussion

In this study, we examined predictors of striatal neurotransmission to better understand dopamine dysregulation in obesity. Visceral adipose tissue (VAT) burden was associated with lower D2 receptors and heightened activation during stop error trials

in the striatum. Blunted D2R and heightened activation further predicted impulsiveness in the stop signal task. While VAT burden increased impulsivity at only trend-levels, these effects were significantly mediated by striatal D2R and activation. Notably, both dorsal and ventral striatal neurotransmission marginally mediated the effect of VAT on impulsivity. This extends our prior finding that the dorsal striatum facilitates the effect of insulin resistance on impulsivity, and points to an additional role for ventral striatal dysregulation in obesity and insulin resistance.

The Dopaminergic Striatum and Impulsivity in the Shift from Reward-Seeking to Habits

Interpreting the impact of obesity and insulin resistance on striatal neurotransmission requires an understanding of how the ventral and dorsal striatum and their associated behaviors are temporally engaged in the transition from substance use to dependence. A spiraling striato-nigro-striatal dopaminergic circuit including the nucleus accumbens shell (NAcs), nucleus accumbens core (NAcc), dorsomedial striatum (DMS), and dorsolateral striatum (DLS) is engaged in series as behavior shifts from voluntary, goal-directed actions to habitual, stimulus-response patterns(Belin et al. 2013; Everitt and Robbins 2013; Ikeda et al. 2013; Haber 2003; Yin, Knowlton, and Balleine 2004).

Unexpected rewards or exteroceptive simuli predicting reward produce phasic dopamine release in the NAc and act as positive reinforcement for the goal-directed behavior(Schultz 2002). The nucleus accumbens receives its dopaminergic innervation from the VTA, but additionally integrates cognitive/behavioral input from the prefrontal cortex (PFC) and limbic input from the basolateral amygdala (BLA)(Goto and Grace 2008b, 2008a). Phasic dopamine release promotes limbic inputs via activation of postsynaptic D1Rs while presynaptic D2Rs in the NAc facilitate the inhibitory effects of the PFC. This balance coordinates goal-directed motor output(Haber et al. 1985). Over

time, these goal-directed behaviors progress to stimulus-response habits where a specific response pattern can be elicited without reinforcement by contextual cues previously associated with a reward. The transition to habitual behavior is reflected by a ventral-to-dorsal shift whereby the dorsolateral striatum and its inputs from the substantia nigra are progressively recruited for behavioral control(Faure et al. 2005; Zapata, Minney, and Shippenberg 2010). This ventral-to-dorsal shift is believed to underlie impaired habit learning in drug addiction(Everitt and Robbins 2005).

Impulsiveness is highly related to striatal function across this transition. The impulsive phenotype promotes goal-directed reward seeking and predicts risk for addiction, increasing drug use, and relapse(Dalley et al. 2007; Perry et al. 2005; Piazza et al. 1989; Diergaarde et al. 2008; Radwanska and Kaczmarek 2012; Oberlin and Grahame 2009; Broos et al. 2012). Impulsivity further predicts the transition from goal-directed behavior to habitual response patterns in the development of addiction(Belin et al. 2008). While several neurotransmitter systems are implicated, there is a clear role for impaired dopamine neurotransmission with impulsivity that may underscore the relationship between impulsivity and substance use. Impulsivity is associated with lower dopamine D2Rs and D2R mRNA in ventral striatum prior to drug exposure(Dalley et al. 2007; Besson et al. 2013; Caprioli et al. 2013), but with increased D1-receptor-mediated neurotransmission(Pezze, Dalley, and Robbins 2007). Further, impulsiveness increases with D2R blockade in the NAc(Besson et al. 2010) but decreases D1R(Pattij et al. 2007). Following chronic drug exposure, lower D2R are observed in the dorsolateral, but not ventral, striatum(Besson et al. 2013; Volkow et al. 2004; Lee et al. 2009). This suggests that impulsivity blunts NAc-mediated dopamine neurotransmission at the postsynaptic D2Rs on prefrontal glutamatergic projections to facilitate limbic drive of NAc goal-directed behavior.

Parallels in this ventral-to-dorsal shift are demonstrated in obesity. As with drug addition, there is a heightened ventral striatal response to high calorie foods(Goldstone et al. 2009; Stoeckel et al. 2008; Fletcher et al. 2010) that correlates with reward(Prechtl de Hernandez et al. 2009), predicts subsequent weight gain(Lawrence et al. 2012; Demos, Heatherton, and Kelley 2012), and predicts poorer response to weight loss treatment(Murdaugh et al. 2012). In healthy weight individuals, BMI positivity correlates with D2R sensitivity when imaging with a D2R agonist(Caravaggio et al. 2013), similar to drug early addiction(Seeman, McCormick, and Kapur 2007). In obese individuals, there is a BMI-dependent decrease in dorsal striatal D2R(Wang et al. 2001), reduced reward sensitivity with increased compulsivity(Johnson and Kenny 2010), and greater activity in the dorsal striatum to high-calorie food cues(Rothemund et al. 2007) predicts treatment failure(Murdaugh et al. 2012). Obesity and insulin resistance are linked to heightened impulsivity(Yokum, Ng, and Stice 2011; Batterink, Yokum, and Stice 2010; Nederkoorn et al. 2006) (see Chapter 2), however whether impulsivity is an endophenotype that predicts obesity and insulin resistance remains to be seen.

In the present study of developing obesity and insulin resistance, we demonstrate that obesity (VAT) was associated with lower D2 receptors and heightened activation in the dorsal and ventral striatum. Insulin resistance additionally predicted dorsal striatal brain activation. In turn, impaired striatal neurotransmission predicted impulsiveness. The finding that both ventral and dorsal striatal dysfunction mediated the effects of VAT and insulin resistance on impulsive responding suggests our cohort may represent a population transitioning from reward-seeking to habitual responding, and these early effects may be due to the combined role of visceral adiposity and insulin resistance. The ventral-to-dorsal shift occurs more rapidly with drugs compared with food rewards(Dickinson, Wood, and Smith 2002), which may be reflected in the observed dysregulation in both the dorsal and ventral striatum. This pattern may

alternatively be distinct from drug addiction as food is necessary for survival and readily accessible in the modern environment. Future work should focus on the relationship between striatal neurotransmission and changes in weight, adiposity, and insulin resistance to determine placement on the ventral-to-dorsal striatal shift and response to treatment.

Impact of Visceral Adiposity on the Brain

Contrary to our hypothesis that insulin resistance would primarily drive changes in striatal dopamine neurotransmission, we found that visceral adipose tissue burden instead predicted striatal D2R and activation. While the mechanism behind the association between VAT and the brain is unclear, prior research has demonstrated its impact on brain structure. As measured by whole-body CT or MRI, increasing visceral adipose tissue is associated with decreasing total brain and hippocampal volume(Anan et al. 2010; Debette et al. 2010; Isaac et al. 2011), decreasing gray matter density in sensorimotor regions of the cerebellum(Raschpichler et al. 2013), and increasing white matter lesions(Anan et al. 2009). These deficits were associated with increasing VAT independent of individual BMI and insulin resistance. Our study is the first to link VAT burden with molecular and functional changes in the brain, demonstrating that increasing VAT is associated with decreasing striatal D2Rs and hyperactivation during response errors. The specific negative relationship between VAT and striatal D2Rs independent of BMI suggests that prior observations of decreasing striatal D2R with increasing body mass(Wang et al. 2001) may be specifically due to the deleterious effects of VAT.

Visceral (intra-abdominal) adipose is a physically and metabolically unique tissue conferring specific risk for insulin resistance, cardiovascular disease, and certain cancers(Kuk et al. 2006; Kang et al. 2010; Despres 1993). By virtue of its increased rate of lipolysis(Reynisdottir et al. 1997), VAT is associated with elevated

triglygerides(Veilleux et al. 2011) and “bad” cholesterol(Hoffstedt et al. 2010) (LDL, VLDL). VAT additionally produces inflammatory cytokines including tumor necrosis factor-α(Cartier et al. 2010) and interleukin-6(Fried, Bunkin, and Greenberg 1998). Intra-abdominal adipose, unlike subcutaneous or epicardial fat deposits, is uniquely drained by the portal vein. This directly exposes the liver to free fatty acids (FFAs) and inflammatory cytokines released from visceral fat and results in an increase in the liver-produced inflammatory factor C-reactive protein (CRP)(Bjorntorp 1990; Yudkin et al. 1999; Lemieux et al. 2001). Both inflammatory factors and FFAs have been associated with alterations in brain function(Tschritter et al. 2009; Felger and Miller 2012; Debette et al. 2010). While CRP and FFAs did not explain the effect of VAT in our cohort (data not shown), we cannot exclude the possibility that other inflammatory cytokines may play a role.

Visceral adiposity has also recently been associated with elevated endocannabinoids(Cote et al. 2007; Bartelt et al. 2011; Frost et al. 2010). Endocannabinoids cross the blood brain barrier and bind to endocannabinoid receptors(Willoughby et al. 1997). The endocannabinoid receptor (CB1R) is expressed presynaptically on ventral striatal neurons and is functionally opposed to D2Rs(Pickel et al. 2006) to modulate prefrontal cortical input to the striatum(Fitzgerald, Shobin, and Pickel 2012; Mathur and Lovinger 2012). CB1R activation enhances VTA burst firing(Cheer et al. 2004) and facilitates cue-mediated behavior(Oleson et al. 2012), while blocking CB1R activation reduces food and drug consumption(Horder et al. 2010; Navarro et al. 2001; De Vries et al. 2001; Cohen et al. 2002; Colombo et al. 1998). It has recently been shown that CB1R antagonist increases striatal dopamine D2 receptor availability(Crunelle et al. 2013) indicating that VAT-associated elevations in endocannabinoid signaling may contribute to the observed decrease in striatal D2R with greater VAT burden. Notably, endocannabinoids have recently been shown to inhibit

DAT and DA reuptake(Oz et al. 2010; Pandolfo et al. 2011), similar to that observed in diet-induced obesity and insulin resistance. No studies have examined the direct effect of VAT-associated endocannabinoid signaling on brain dopamine systems, however this may offer a non-insulin mediated mechanism functioning as a "second-hit" for dopamine dysfunction in obesity and insulin resistance.

Implications for Treatment

Despite substantial questions regarding mechanism, this research offers exciting opportunities for treatment strategies. Alongside diet and/or exercise for management of obesity and insulin resistance(Vissers et al. 2013; Goss et al. 2013), these results suggest that targeting a reduction in VAT and impulsivity may improve dopamine neurotransmission and promote healthy weight and improved insulin sensitivity. For example, treatment with bupropion/naltrexone, currently in phase III clinical trials(Apovian et al. 2013), reduces VAT(Smith et al. 2013) and alters brain activation in obese subjects(Wang et al. 2013) although it's effect on impulsivity is unknown. This effect may partially be due to bupropion's effect as a dopamine reuptake inhibitor and improved dopamine signaling(Arias, Santamaria, and Ali 2009). Alternatively, the success of combined bupropion/naltrexone instead may be due to its modulation of multiple neurotransmitters involved in addiction other than dopamine, including opioids and norepinephrine. Future work examining the combined interactions of VAT and insulin signaling on multiple neurotransmitter systems involved in impulsivity and addiction will be necessary to determine effective pharmaceutical treatment approaches for weight loss and insulin resistance.

Conclusions

Here we demonstrate that visceral adipose tissue and insulin resistance alter striatal dopamine neurotransmission and activity in a way that may bias towards impulsive behaviors. The function of both the dorsal and ventral striatum was impaired by VAT suggesting a ventral-to-dorsal striatal disruption, similar to addictive processes that could underlie a transition from reward-driven food consumption to compulsive eating. Given the impact of both visceral adiposity and insulin resistance, it is likely that several mechanisms are involved in this shift, offering novel treatment approaches for improving weight and insulin resistance.

CHAPTER IV

SHORT-TERM INSULIN TREATMENT HAS NO EFFECT ON BASAL CORTICOSTRIATAL DOPAMINE CIRCUITS

Introduction

In the previous chapters, we identified specific neural and behavioral impairments in insulin resistance. Given these deficits, we next sought to examine whether improving insulin sensitivity could restore the behavioral impairments and their underlying neural circuits. The mainstay of initial treatment for obesity and type 2 diabetes mellitus (T2DM) is dietary modification, weight loss, and exercise to achieve healthy blood glucose levels(Henry, Scheaffer, and Olefsky 1985; Wing et al. 1994; Schneider et al. 1992). Insulin therapy is commonly used for glycemic control as endogenous insulin secretion decreases and insulin resistance increases. However, weight gain causes and is a consequence of insulin therapy (UK Prospective Diabetes Study [UKPDS] 1998; Diabetes Control and Complications Trial [DCCT] 2001) and weight gain as a result of treatment may further promote insulin resistance(Russell-Jones and Khan 2007). Treatment-induced weight gain thus represents a substantial challenge in the management of T2DM. One form of insulin, the basal insulin analogue detemir, has recently been shown to have beneficial weight-sparing effects(Hermansen et al. 2006; Hermansen and Davies 2007; Meneghini et al. 2013; Rojas, Printz, and Niswender 2011) that may be due to detemir's ability to regulate insulin signaling not only peripherally, but also centrally in the brain(Hennige et al. 2006; Hallschmid et al. 2010; Tschritter et al. 2007).

Insulin acts at the level of the hypothalamus as an adiposity negative feedback signal to limit food intake and weight gain(Bruning et al. 2000; Woods et al. 1998; Niswender et al. 2003). While the weight-sparing effects of detemir may be due to its anorexigenic action in the hypothalamus, insulin therapy has been shown to impact more diffuse brain circuits (Guthoff et al. 2011; Guthoff et al. 2010). Within these circuits, dopamine acts as a key modulator of numerous behaviors that may facilitate addictive processes, including the pleasure derived from and motivation to seek reward, habitual motor patterns, and the cognitive control of behavior(Palmiter 2007).

Despite the previously-discussed impairments in dopamine neurotransmission in obesity and insulin resistance, there appears to be plasticity in these striatal dopamine circuits. Animal studies demonstrate that rats given extended access to an obesogenic cafeteria diet gain weight and have reduced striatal D2R compared with pair chow-fed animals(Bello, Lucas, and Hajnal 2002; Fetissov et al. 2002; Hamdi, Porter, and Prasad 1992; Johnson and Kenny 2010), but that insulin therapy can restore dopamine release, transporter function, and dopamine-mediated behavior(Schoffelmeer et al. 2011; Sevak et al. 2007). Clinical studies further show alterations in striatal D2R availability in obese human subjects following bariatric surgery(Steele et al. 2010a; Dunn et al. 2010). Given its action in the central nervous system, we hypothesize that treatment with insulin detemir modulates corticostriatal dopamine circuits in a way that is beneficial for weight loss and behavior modification. Specifically, we hypothesize that short-term insulin detemir treatment will improve impaired striatal D2R, prefrontal cortical activation in a task of cognitive control, and dopamine-associated cognitive performance.

Methods

General Study Protocol

Research participants, visit schedule, insulin treatment, biochemical evaluation, PET / fMRI imaging parameters, and the stop signal task behavioral and imaging analysis were implemented as discussed in previous chapters.

Statistical Analysis

Atlas-defined regions of interest including the dorsal striatum (caudate, head of caudate, putamen), ventral striatum (nucleus accumbens), and prefrontal cortex (PFC) were defined using WFU Pickatlas(Maldjian et al. 2003). ROIs for the ventral tegmental area (VTA), substantia nigra (SN) and olfactory bulb (OB) were defined on participants' individual T1W structural images using MIPAV(Bazin et al. 2007).

For 18F-Fallypride PET imaging, D2R non-displaceable binding potentials (BP_{ND}) were extracted from the defined striatal ROIs while activation (BOLD) during the stop signal task was extracted from the prefrontal cortex using Marsbar(Brett et al. 2002). D2R BP_{ND}'s were extracted from manually-defined ROIs using MIPAV. Independent sample t-tests were performed at baseline to assess differences in SST behavior, SST-related brain activation, and striatal D2R binding between treatment arms. To test whether insulin treatment altered striatal dopamine levels, we performed a repeated measures 2x2 ANOVA (treatment arm x visit week) while controlling for age(Cohen et al. 2010). All statistical analyses were performed in SPSS v20 (IBM SPSS Statistics). Results were considered statistically significant at $p \leq 0.05$ and marginally significant at $p \leq 0.08$.

Results

No difference in baseline characteristics between treatment arms

Participants' clinical and demographic information has been described in previous chapters. The ability to assess changes in corticostriatal dopamine circuits and associated behaviors following insulin therapy depends on the correspondence between treatment arms at baseline. Prior to receiving insulin treatment, there were no differences in body mass index ($p = 0.854$), HOMA-IR ($p = 0.147$), disposition index ($p = 0.562$), plasma glucose AUC ($p = 0.608$), plasma insulin AUC ($p = 0.540$), plasma C-peptide AUC ($p = 0.737$), fasting plasma leptin ($p = 0.951$), and fasting plasma acylghrelin ($p = 0.871$) between treatment arms (see Figure 17).

Sixteen of the thirty-two subjects with successful 18F-Fallypride PET imaging received insulin treatment. There was no baseline difference in dopamine D2 receptor non-displaceable binding potential (BPnd) in the caudate ($p = 0.182$), caudate head ($p = 0.480$), putamen ($p = 0.271$), and nucleus accumbens ($p = 0.589$) (see Table 13, Figure 18). Across all subjects, baseline D2R BPnd in the caudate (21.8 ± 0.60, mean ± SE), caudate head (15.7 ± 0.44), putamen (24.5 ± 0.63), and nucleus accumbens (17.0 ± 0.63) are consistent with those observed in the literature for healthy controls(Rominger et al. 2012; Kegeles et al. 2010).

Table 13. No difference in baseline striatal dopamine D2 receptor non-displaceable binding potentials (BPnd; mean ± SE) between the no insulin (n=16) and insulin (n=16) treatment arms in the caudate, caudate head, nucleus accumbens, and putamen.

Striatal Subregion	Arm	D2R BPnd	p-value
Caudate	*Total*	*21.8 ± 0.60*	0.182
	No Insulin	22.7 ± 0.76	
	Insulin	21.0 ± 0.91	
Caudate Head	*Total*	*15.7 ± 0.44*	0.480
	No Insulin	15.4 ± 0.71	
	Insulin	16.0 ± 0.53	
Nucleus Accumbens	*Total*	*17.0 ± 0.63*	0.271
	No Insulin	16.3 ± 0.99	
	Insulin	17.7 ± 0.78	
Putamen	*Total*	*24.5 ± 0.63*	0.589
	No Insulin	24.1 ± 1.03	
	Insulin	24.8 ± 0.77	

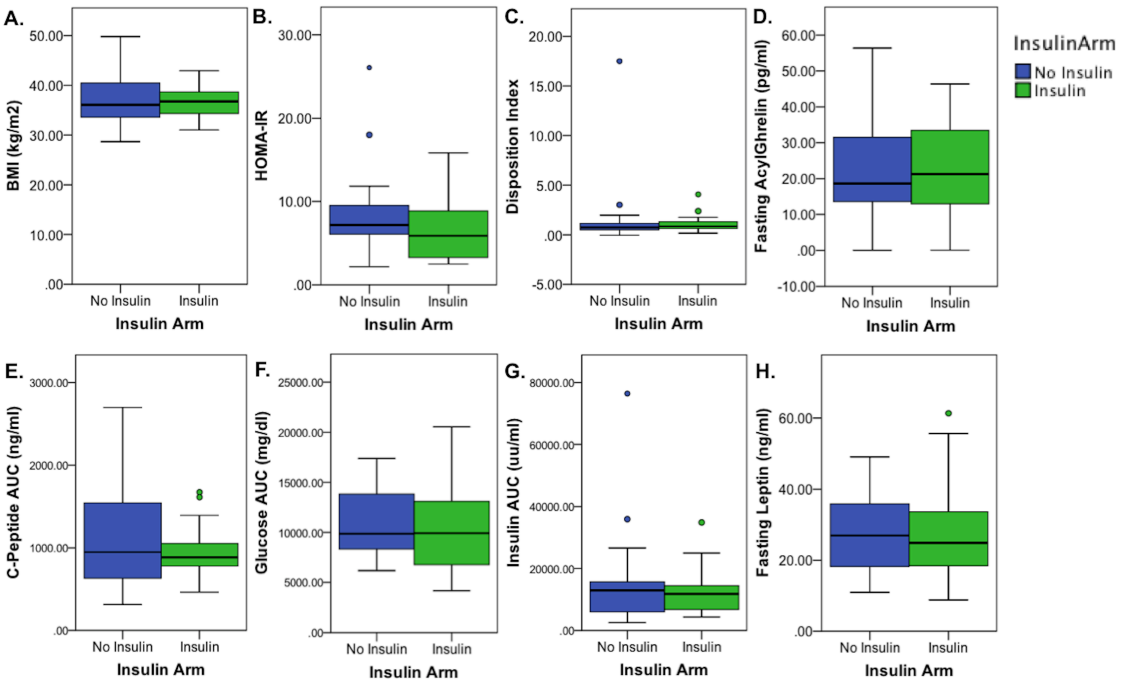

Figure 17. Obesity, insulin resistance, and metabolic markers do not differ between treatment arms at baseline. Box plots of non-displaceable binding potentials (BPnd) for D2R shown for striatal sub-regions. The dark horizontal lines represent the median, with the box representing the 25th and 75th percentiles, the whiskers represent 1.5*interquartile range, and outliers are represented by the dots. A) body mass index (BMI; p = 0.854) B) HOMA-IR (p = 0.147) C) disposition index (DI; p = 0.562), D) fasting acylghrelin (p = 0.871) E) c-peptide AUC (0.737) F) glucose AUC (p = 0.608) G) insulin AUC (p = 0.540) H) fasting leptin (p = 0.951)

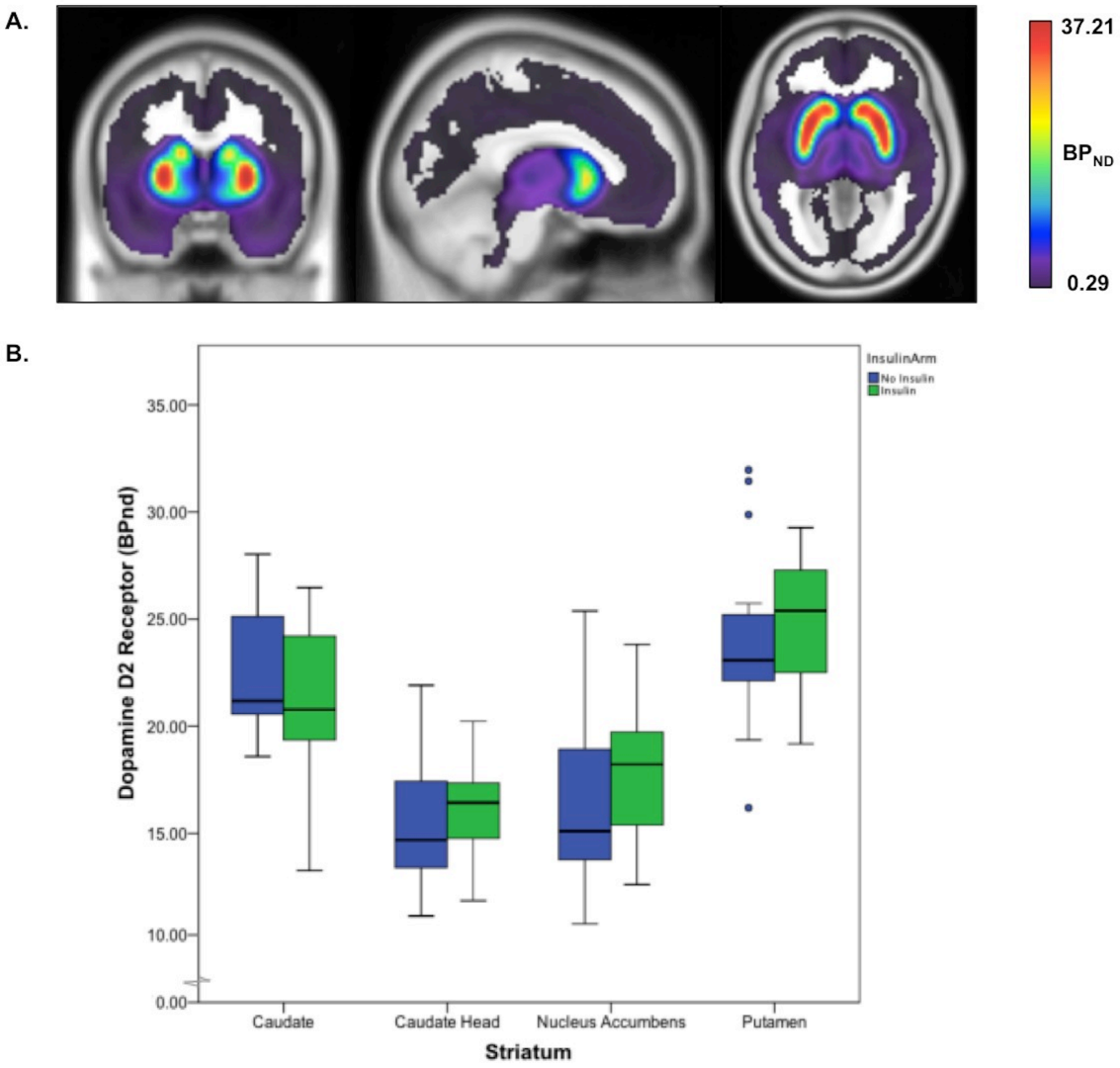

Figure 18. Striatal dopamine D2R non-displaceable binding potentials do not differ between treatment arms at baseline. A) Wholebrain binding potential map demonstrating high [18F]-Fallypride binding in the dorsal and ventral striatum, and extrastriatal binding frontocortical regions [n=32] B) Box plots of striatal D2R BPnd shown for striatal sub-regions comparing the insulin (n=16) and no insulin (n=16) arms. The dark horizontal lines represent the median, with the box representing the 25th and 75th percentiles, the whiskers represent 1.5*interquartile range, and outliers are represented by the dots. For all regions, $p > 0.05$.

Finally, there were no differences between treatment arms in stop signal task performance including the critical stop signal delay (cSSD, $p = 0.831$), stop signal response time (SSRT, $p = 0.791$), median go response time (mGRT, $p = 0.751$), and post-error slowing (PES, $p = 0.084$; see Table 14, Figure 21A). Together, these data

show no baseline differences between treatment arms, allowing for the evaluation of short-term insulin therapy on corticostriatal dopamine circuits and associated behaviors.

Table 14. No difference in baseline stop signal task performance (mean [ms] ± SE) between the no insulin (n=26) and insulin (n=21) treatment arms for the critical stop signal delay (cSSD), stop signal response time (SSRT), median go response time (mGRT), and post-error slowing (PES).

SST Performance	Arm	D2R BPnd	p-value
cSSD	*Total*	*309.6 ± 17.4*	0.831
	No Insulin	306.2 ± 24.1	
	Insulin	313.8 ± 25.6	
SSRT	*Total*	*296.1 ± 4.74*	0.791
	No Insulin	294.0 ± 6.51	
	Insulin	296.5 ± 7.05	
mGRT	*Total*	*604.7 ± 15.6*	0.751
	No Insulin	600.1 ± 20.4	
	Insulin	610.3 ± 24.6	
PES	*Total*	*52.8 ± 7.45*	0.084
	No Insulin	64.3 ± 9.75	
	Insulin	38.4 ± 11.0	

Insulin treatment has no effect on striatal or extrastriatal D2R

Twenty-five (n=11, non-insulin; n=14, insulin) of the original thirty-two subjects successfully completed 18F-Fallypride imaging 4 weeks after the initial imaging visit. Dopamine D2 receptor non-displaceable binding potentials in the dorsal and ventral striatal sub-regions were not significantly altered by short-term insulin treatment (see Table 15, Figure 19); no differences were observed in the caudate ($p = 0.768$), caudate head ($p = 0.979$), nucleus accumbens ($p = 0.964$), or putamen (0.963). Present results are corrected for participant age to control for the age-related decrease in dopamine D2R(Kaasinen et al. 2000; Backman et al. 2000). Subsequent analyses controlling for baseline levels of obesity and insulin resistance similarly did not reach significance (data not shown). Extrastriatal D2R-rich regions were also unaffected by short-term insulin

treatment. No alterations in D2R BPnd were observed in the olfactory bulb (p = 0.556), ventral tegmental area (p = 0.823), and substantia nigra (p = 0.541).

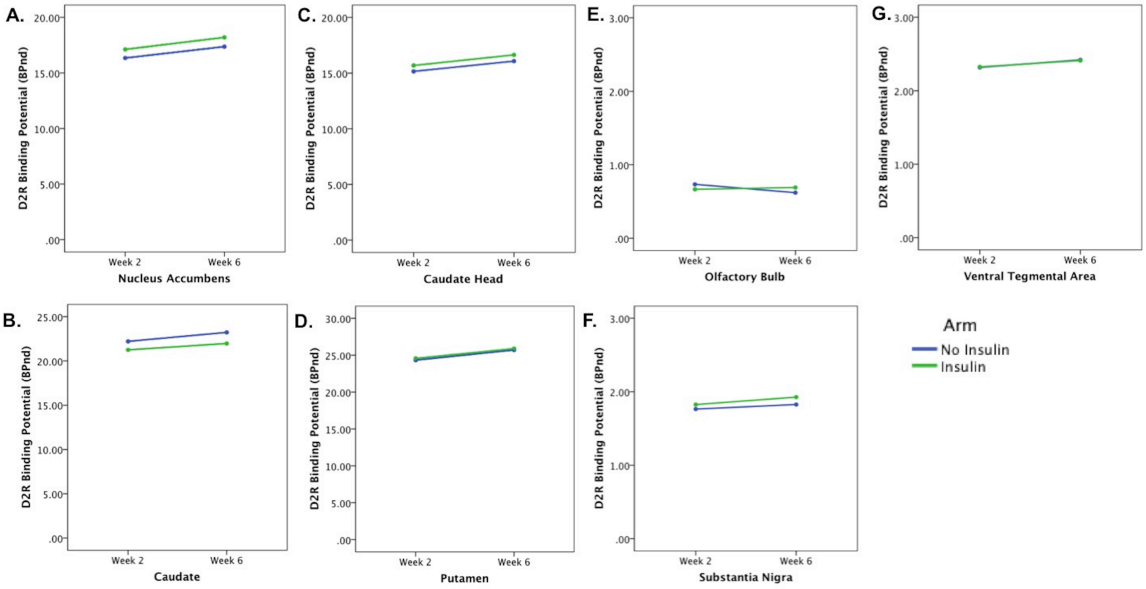

Figure 19. Short-term insulin treatment has no effect on dopamine D2 receptors in the striatum or extrastriatal D2R-rich brain regions A) nucleus accumbens, p = 0.964 B) caudate, p = 0.768 C) caudate head p = 0.979 D) putamen p = 0.963 E) olfactory bulb, p = 0.556 F) substantia nigra, p = 0.541G) ventral tegmental area, p = 0.823 (n=25)

Given the hypothesis that insulin modulates the corticostriatal circuits underlying response inhibition, we lastly defined the dorsal striatum functionally using the SS>SE contrast that identifies brain regions active during motor component of successful inhibition. Consistent with the results from atlas-derived dorsal striatal ROIs, short-term insulin treatment had no impact on D2Rs in the functionally-defined dorsal striatum (p = 0.468, see Table 15, Figure 20).

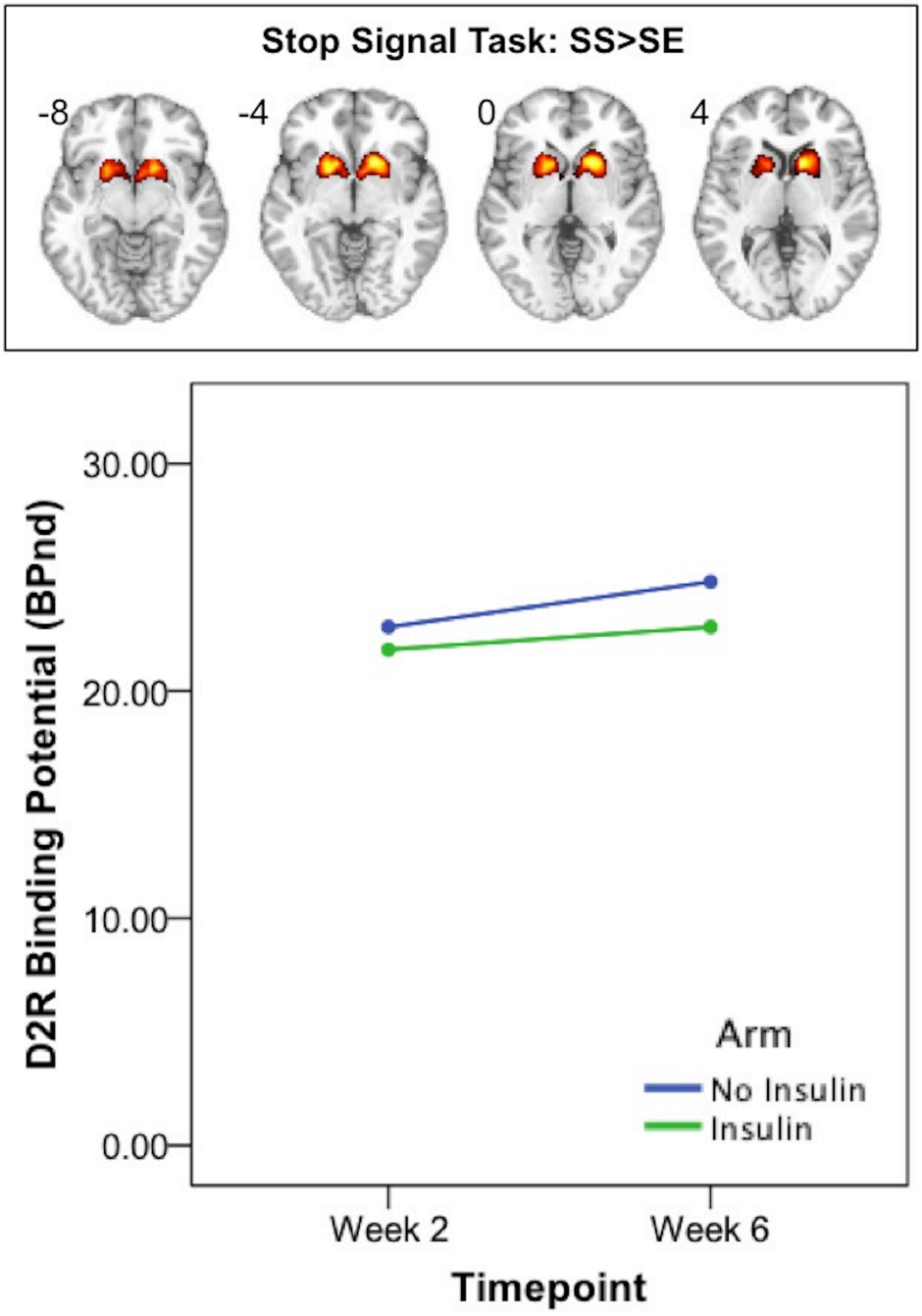

Figure 20. Short-term insulin treatment does not effect functionally-defined striatal dopamine D2 receptor non-displaceable binding potential (BPnd) from the dorsal striatal region during successful inhibition during the stop signal task. The dorsal striatum was defined based on activation during stop success compared with stop error trials (SS>SE; n=25; p = 0.468).

Table 15. Insulin therapy does not alter dopamine D2 receptors, stop signal task performance, or brain activation. A 2x2 repeated measures ANOVA comparing treatment arm by time-point for dopamine D2 receptors and stop signal task associated performance and brain activation.

Measurement	Arm	Week 2 (mean ± SE)	Week 6 (mean ± SE)	p-value
Dopamine D2 Receptors (BPnd)				
Caudate	No Insulin	22.7 ± 0.8	24.0 ± 0.9	0.768
	Insulin	21.0 ± 0.9	21.2 ± 1.0	
Caudate Head	No Insulin	15.4 ± 0.7	16.5 ± 1.0	0.979
	Insulin	16.0 ± 0.5	15.5 ± 0.9	
Nucleus Accumbens	No Insulin	16.3 ± 1.0	17.8 ± 1.4	0.964
	Insulin	17.7 ± 0.8	16.7 ± 1.1	
Putamen	No Insulin	24.1 ± 1.0	26.1 ± 1.1	0.963
	Insulin	24.8 ± 0.8	24.5 ± 0.9	
Olfactory Bulb	No Insulin	0.7 ± 0.2	0.6 ± 0.1	0.556
	Insulin	0.6 ± 0.1	0.7 ± 0.1	
Substantia Nigra	No Insulin	1.7 ± 0.1	1.9 ± 0.1	0.541
	Insulin	1.8 ± 0.1	1.8 ± 0.1	
Ventral Tegmental Area	No Insulin	2.4 ± 0.1	2.5 ± 0.1	0.823
	Insulin	2.3 ± 0.1	2.3 ± 0.1	
Stop Signal Performance (ms)				
cSSD	No Insulin	306.2 ± 24.1	334.5 ± 27.5	0.862
	Insulin	313.8 ± 25.6	351.0 ± 36.0	
SSRT	No Insulin	293.9 ± 6.5	276.0 ± 10.9	0.356
	Insulin	296.5 ± 7.1	279.5 ± 6.7	
mGRT	No Insulin	600.2 ± 20.5	610.5 ± 24.1	0.712
	Insulin	610.3 ± 24.6	630.5 ± 33.2	
PES	No Insulin	64.3 ± 9.8	34.7 ± 11.7	0.531
	Insulin	38.4 ± 11.0	10.4 ± 16.1	
Functionally-Defined Striatal and Prefrontal Regions				
Dorsal Striatum (D2R BPnd)	No Insulin	23.6 ± 0.9	26.7 ± 1.8	0.468
	Insulin	22.2 ± 0.9	23.0 ± 0.1	
Prefrontal Cortex (BOLD)	No Insulin	1.5 ± 0.6	1.6 ± 0.8	0.911
	Insulin	2.2 ± 0.4	1.4 ± 0.4	

Insulin treatment has no effect on prefrontal networks subserving response inhibition

To evaluate impact of short-term insulin treatment on prefrontal executive control networks, we first examined insulin's effect on stop signal performance data. The critical stop signal delay (cSSD) represents the difference in speed between "go" and "stop" processes and is therefore influenced by the measure of response inhibition, the stop signal response time (SSRT)(Logan and Cowan 1984). Stop processes engage inhibitory motor areas (IMAs), including regions of the prefrontal cortex(Li, Huang, et al.

2006; Aron, Durston, et al. 2007). Similarly, prefrontal brain networks have been shown to be active during the "go" and error monitoring processes(Sakai et al. 2013; Li, Huang, Yan, Paliwal, et al. 2008). Thirty-nine (n=21, non-insulin; n=18, insulin) of the forty-seven subjects completed Week 6 of the stop signal task. In concordance with the lack of effect of insulin on striatal circuits, there was no impact of insulin on stop signal behavior (see Table 15, Figure 21B-E); cSSD (p = 0.862), SSRT (0.356), median go response time (mGRT, p = 0.712), post-error slowing (PES, p = 0.531).

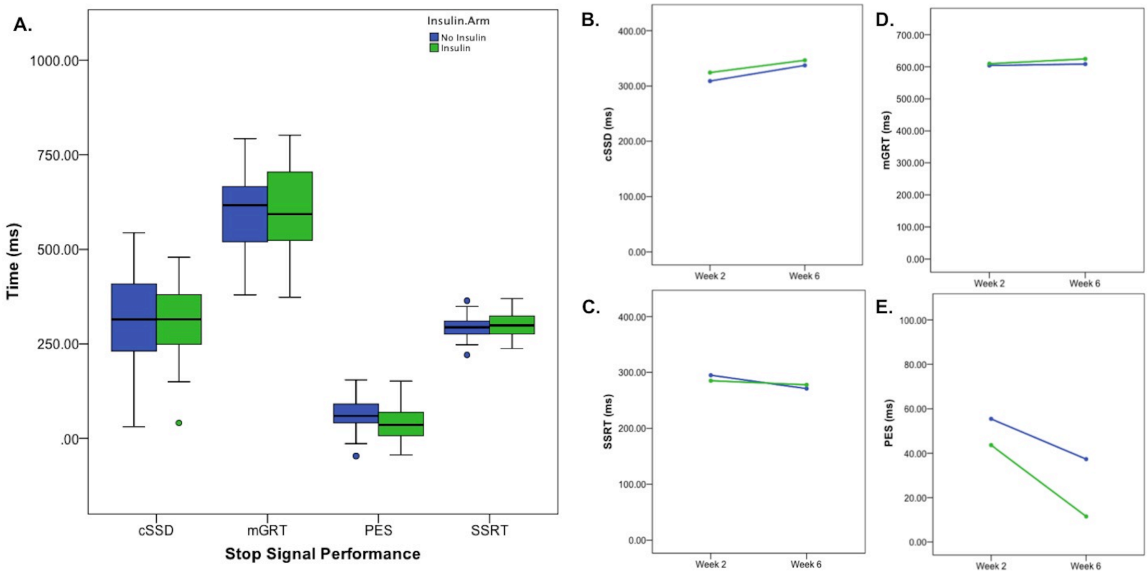

Figure 21. Short-term insulin treatment has no effect on stop signal behavior A) Box plots showing no difference in SST performance between arms. The dark horizontal lines represent the median, with the box representing the 25th and 75th percentiles, the whiskers represent 1.5*interquartile range, and outliers are represented by the dots. Stop signal performance in unaffected by insulin treatment, B) critical stop signal delay [cSSD, p=0.862], C) stop signal response time [SSRT, p=0.356], D) median go response time [mGRT, p=0.712], E) post error slowing [PES, p=0.531] (n=39)

As previously discussed, prefrontal cognitive control networks are more active when comparing successful stop greater than successful go trials. Twenty-three (n=13, no insulin; n=10, insulin) of the baseline thirty subjects had successful Week 6 stop signal task imaging. Prefrontal cortical networks active during the SS>GS contrast were

unresponsive to insulin treatment (p = 0.911; see Table 15, Figure 22). Combined with the results from the longitudinal 18F-Fallypride and stop signal behavior, the lack of prefrontal modulation with insulin treatment suggests that short-term insulin treatment has no effect on corticostriatal inhibitory circuits and the underlying striatal dopamine D2 receptors.

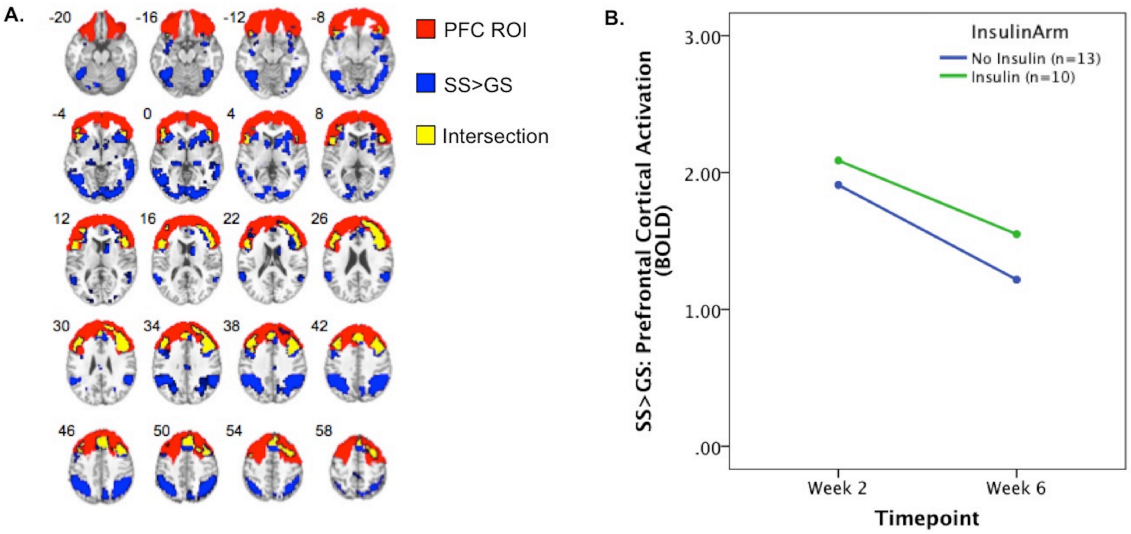

Figure 22. Short-term insulin treatment does not affect prefrontal cortical brain activity during successful stopping in the stop signal task. A) Prefrontal cortical circuits were engaged during stop success compared with go success trials (SS>GS). The conjunction [yellow] between the prefrontal cortex [red] and successful inhibition [blue] defines the region of interest B) inhibition-related prefrontal brain activity was unaffected by short-term insulin treatment (p=0.911, n=23)

Discussion

In this study, we demonstrate that four weeks of insulin detemir treatment does not significantly change striatal dopamine D2 receptors, prefrontal cortical activation during successful inhibition in the stop signal task, or SST behavioral performance. This contrasts with our original hypotheses.

Blocking insulin receptors(Doolen and Zahniser 2001) and their downstream signaling components(Carvelli et al. 2002; Garcia et al. 2005) reduces DAT expression.

In animal models of diabetes and diet-induced obesity (DIO)(Speed et al. 2011), insulin can restore reduced striatal DAT expression. Four weeks of treatment with detemir in DIO animals decreased food intake and body weight(Rojas, Printz, and Niswender 2011), and feeding behaviors have been strongly linked to dopamine(Johnson and Kenny 2010; Palmiter 2007). BMI-dependent decreases in striatal DAT expression have also been observed in humans(Chen et al. 2008). The hypothesis that detemir acts by restoring impaired DAT in obesity is thus plausible, and several factors may explain our divergent findings.

Insulin, Insulin Resistance, and the Brain

Determir's ability to act on the brain depends on its ability to enter the central nervous system (CNS). The majority of endogenous insulin acting in the brain is produced in peripheral tissues and transported into the CNS across the blood brain barrier (BBB) through a unidirectional and saturatable transport system(Schwartz et al. 1991; Baura et al. 1993; Pardridge et al. 1995; Banks et al. 1997). Insulin transporters are not uniformly distributed throughout the BBB, so the passage of insulin into the brain varies by location(Banks and Kastin 1998; Banks, Kastin, and Pan 1999). Most exogenous insulin does not cross the BBB, but detemir's ability to do so is unclear. Acute peripheral administration of detemir promotes brain insulin receptor action, alters brain function, and reduces food intake(Hallschmid et al. 2010; Hennige et al. 2006). Other studies report that detemir is not directly transported into the CNS(Banks et al. 2010). Although detemir may affect brains of healthy adults, this may not be true in all cases. Inflammatory cytokines, triglycerides, and blood glucose levels regulate insulin transport across the blood brain barrier(Banks, Jaspan, and Kastin 1997; Banks et al. 2008; Kaiyala et al. 2000). Because these factors are disrupted in obesity and insulin resistance, detemir may not enter the CNS and act directly on the brain.

Another possibility for the lack of detemir effect is the ability of neurons to respond to insulin. T2DM is characterized by both a lack of insulin production and the development of tissue insulin resistance. Exogenous insulin administration is critical in addressing the insulin lack; however, alternative treatments are necessary to improve tissue insulin sensitivity. Neurons can become insulin resistance, and neuronal insulin resistance differs from peripheral insulin resistance(Bhumsoo et al. 2011; Pratchayasakul et al. 2011; Gupta and Dey 2012). Although peripheral detemir administration can be helpful in achieving glycemic control, it may have limited or no action centrally if neurons are unable to respond to insulin itself.

Table 16. Sample size to detect a difference after insulin treatment with 95% power

Measurement	**Sample Size**
Striatal D2 Receptors	*n*
Nucleus Accumbens	128
Caudate	171
Caudate Head	162
Putamen	64
Stop Signal Task Behavior	*n*
cSSD	97
mGRT	229
SSRT	51
PES	136
Stop Signal Task fMRI	*n*
Prefrontal Cortex	41

The small sample size and lack of a lean control arm are major limitations to the present study, and may explain the lack of an observed effect. A post-hoc power analysis for the variables of interest demonstrated that a much larger sample size is necessary to detect differences between treatment arms (see Table 16). The power analysis supports the conclusion that short-term insulin treatment has no effect on striatal D2R and components of stop signal behavior. Increasing the sample size to 50 individuals may provide sufficient power to detect an effect of detemir treatment on prefrontal cortical activation and its behavioral component, the stop signal response time.

Using Baseline Dopamine Tone to Inform Insulin Treatment

The inverted U model for dopamine tone and corticostriatal function is conceptually appealing because it implies that normalizing dopamine tone will resolve the underlying neural deficits perpetuating a disorder. This is clinically challenging because dopamine-modifying pharmaceutical treatments either attenuate or enhance dopamine function, and the same drug can have opposing effects depending on which arm of the inverted U an individual is assigned to. Baseline dopamine tone on the inverted U is determined in part by genetic factors in addition to the diet- and insulin resistant-induced impairments in DAT. For example, the enzyme catechol-O-methyltransferase (COMT) metabolizes dopamine in the prefrontal cortex. A common variant of the COMT gene translates valine (Val) to methionine (Met) and decreases DA metabolism. Val/Mat heterozygotes and Met/Met homozygotes have lower COMT activity and higher baseline dopamine tone(Chen et al. 2004; Meyer-Lindenberg et al. 2005; Bilder et al. 2004). In ADHD, this single polymorphism dictates the response to treatment with the DAT/NET reuptake inhibitory methylphenidate. Individuals with the Val/Val genotype (lower baseline dopamine tone) respond significantly better to dopamine enhancement with methylphenidate compared to their Met/Met counterparts (higher baseline dopamine tone)(Cheon, Jun, and Cho 2008) indicating that pharmacologic treatment of dopamine-mediated disorders requires a personalized approach depending on baseline dopaminergic function(Farrell et al. 2012; Levy 2013).

Similar disruptions in dopamine-regulating genes have been observed in obesity. The TaqA1 1A allele, MC4R mutation, and FTO variants are each associated with increased obesity(Balthasar et al. 2005; Frayling et al. 2007; Spitz et al. 2000), decreased dopamine neurotransmission(Cui et al. 2012; Hess et al. 2013; Neville, Johnstone, and Walton 2004), and impaired brain dopamine function(Cui and Lutter 2013; Hess et al. 2013; Stice et al. 2008). Without knowing participants' genotype, a

pharmaceutical amphetamine challenge test (ACT) can be used as a probe for dopamine neurotransmission. AMPH binds to the dopamine transporter and induces dopamine efflux in proportion to the amount of DAT expressed in the plasma membrane(Silberman et al. 1981; Kavoussi and Coccaro 1993; Kravitz et al. 1990; Schulz et al. 1988). Based on the inverted U model, participants with lower baseline dopamine tone would demonstrate improvements following amphetamine (AMPH) while participants with higher dopamine tone would improve to a lesser degree or worsen. The inverted U model for treatment has been utilized in the stop signal task, where baseline response inhibition determines response to treatment. Specifically, those with poorer response inhibition (longer SSRT) improved with methylphenidate and amphetamine treatment, whereas those with short SSRTs got worse (Eagle and Robbins 2003; Eagle et al. 2007; Feola, de Wit, and Richards 2000; Hamidovic et al. 2010a, 2010b; Hamidovic et al. 2009; Dlugos et al. 2009). This raised the question of whether, in the current cohort, the response to amphetamine could unmask the baseline dopaminergic tone to inform treatment with insulin detemir.

Preliminary analysis of stop signal task performance data during an ACT at baseline reveals a differential response to amphetamine based on pre-amphetamine behavior that is consistent with these prior studies and support an inverted U model. Specifically, participants with longer pre-amphetamine SSRT (slower inhibition) demonstrated the greatest improvement (negative ΔSSRT) while participants with faster pre-AMPH SSRT worsened (see Figure 23A). As the stop signal response time is related to dopamine tone(Eagle et al. 2011), the opposing response to AMPH indicates our sample is comprised of individuals on both sides of the inverted U (see Figure 23B; U is not inverted because longer SSRT indicates impairment).

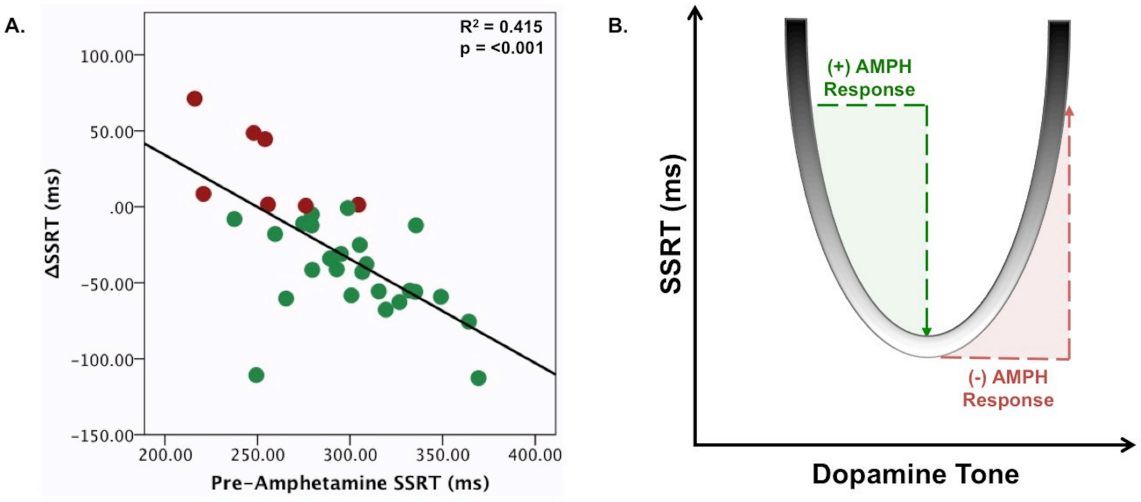

Figure 23. Effects of AMPH-induced changes in stop signal response time (SSRT) depend on baseline performance. A) Poorer pre-amphetamine SSRT is associated with greater improvements following amphetamine administration. Green circles represent participants whose SSRT improved with AMPH. Red circles represent subjects whose performance got worse with AMPH B) Model for how amphetamine-induced alterations depend on underlying dopamine tone [U is not inverted because longer SSRT indicates impairment]

Insulin treatment has been shown to restore impairments in amphetamine-induced dopamine efflux (Williams et al. 2007). Using the behavioral response to amphetamine as a probe of dopaminergic status, our preliminary analysis suggests that insulin detemir improves amphetamine-induced response inhibition (Huda et al. 2013) (see Figure 24). While significant future research is required to interpret the observed insulin effect, these data suggest that insulin detemir does have central brain action that may be beneficial for modulating behaviors facilitating weight maintenance or loss.

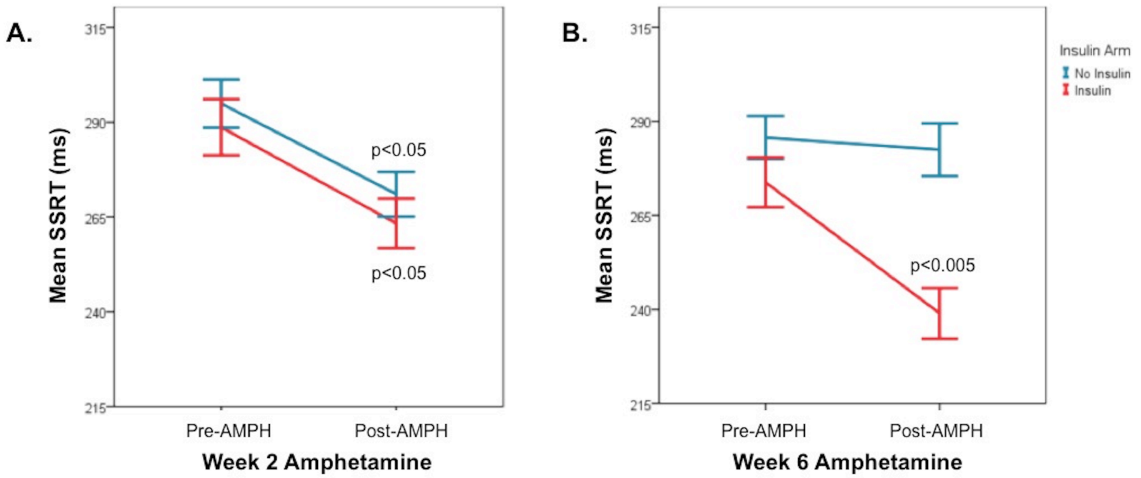

Figure 24. Insulin detemir treatment improves amphetamine-induced response inhibition A) amphetamine administration improves the stop signal response time (SSRT) at baseline (mean ± SE) B) insulin detemir treatment significantly improves amphetamine-induced SSRT performance (data courtesy of Imran Huda).

Study Limitations

The lack of a healthy-weight control arm is a significant limitation to the present study. Although the decreases in DAT expression in healthy-weight individuals(Chen et al. 2008) and the decreases in D2R availability in morbidly obese individuals(Wang et al. 2001) are BMI-dependent, no studies have been performed in the mild-to-moderate obese population. Our study assumes that deficits in dopamine neurotransmission are present in mild-to-moderate obesity based on the literature citing a BMI-dependence; however, the hypothesis that we can normalize dopamine neurotransmission to levels occurring in the healthy-weight population is not testable without this reference arm.

Because the injectable administration insulin and the risk of hypoglycemia challenge the feasibility and ethics of blinding to treatment, participants in this study were not blinded to their treatment arm. This poses problems as research suggests that patients on insulin therapy increase their carbohydrate intake to avoid hypoglycemia(Russell-Jones and Khan 2007; Gordon et al. 1992). Although participants in the present study were motivated to improve their health, patients on insulin therapy may perceive the insulin treatment as the means to this end, and patients not receiving

insulin may rely more heavily on lifestyle modification, such as improving their diets. Despite participants' maintaining their weight during the 4-week treatment period, a change in diet in the absence of weight gain is sufficient to blunt DAT and dopamine reuptake(Cone et al. 2013), and may contribute to the lack of an observed insulin effect.

PET imaging with 18F-Fallypride measures striatal and extrastriatal D2R(Riccardi et al. 2008; Slifstein et al. 2010), but is not a direct measure of extracellular dopamine or dopamine transporter expression. Techniques used to measure extracellular dopamine in animals are invasive and not readily accessible in humans(Robinson et al. 2003; Phillips et al. 2003; Clapp-Lilly et al. 1999). PET techniques to measure extracellular dopamine in humans increase radiation exposure and potential harm when performing longitudinal measurements. Our selection of 18F-Fallypride as a PET radioligand allowed for the measurement of molecular aspects of dopamine neurotransmission and provided minimal risk to participants, but was still an indirect measure of synaptic dopamine and reuptake. Future PET studies quantifying DAT expression(Zoghbi et al. 2006; Goodman et al. 2000) will be valuable for determining the central effects of insulin on the dopamine system.

Conclusions

Preliminary research using amphetamine-induced dopamine efflux shows promising results for an effect of detemir on the brain, short-term insulin treatment with insulin detemir had no observable effect on basal dopamine neurotransmission. Several biologic and experimental factors may account for this null finding including neural insulin resistance, genetic elements altering dopamine neurotransmission, and study design.

CHAPTER V

SYNOPSIS AND CONCLUSIONS

Addressing the rapid increase in the prevalence of obesity and insulin resistance in the United States and globally is a vital clinical and research priority. Research linking obesity and insulin resistance to the brain dopamine system, the same network impaired by drug addiction, suggests treatments targeting brain dopamine disruptions may be beneficial in controlling and/or reducing obesity. In this dissertation, I proposed the following model for impaired dopamine neurotransmission in obesity: impaired insulin signaling uncouples corticostriatal dopamine circuits involved in regulating feeding behavior, and this uncoupling impairs executive function and promotes excessive food intake. Further, I hypothesized that treatment with a formulation of insulin known to have central nervous system action would restore impaired striatal dopamine signaling and dopamine-associated behaviors disrupted in obesity and insulin resistance.

In this 6-week human subjects trial using multimodal imaging techniques, I demonstrate that the effects of obesity and insulin resistance on cognitive performance can be dissociated (Chapter 2). Insulin resistance was associated with significantly heightened impulsivity, while obesity was associated with impaired cognitive restraint to a lesser degree. Heightened impulsivity in insulin resistance was dependent on brain activity in a cortico-thalamo-striatal-cortical motor and attention network. This suggests that mild insulin resistance biases brain systems to respond to and acquire salient stimuli.

I next linked the impulsivity to striatal dopamine neurotransmission, showing that heightened impulsivity was associated with lower striatal D2R and increased striatal brain activity in both the dorsal and ventral striatum (Chapter 3). Although striatal D2R

were unrelated to insulin resistance in this cohort, visceral adipose tissue (VAT) was associated with decreased striatal D2R and increased striatal activation. Striatal D2R and neural activity independently mediated the effects of insulin resistance and VAT on impulsivity, suggesting that there are multiple mechanisms underlying striatal dopamine dysregulation in the development and pathogenesis of obesity.

Short-term insulin treatment did not restore basal corticostriatal dopamine neurotransmission (Chapter 4); however, there were some significant limitations in the present study. Evaluating dopamine D2 receptors as the sole measure of dopamine neurotransmission and not accounting for baseline dopamine tone to assess the therapeutic potential of insulin detemir could have affected the results. Prior research strongly suggests that insulin detemir has central action that supports weight loss, thus the inability to detect an effect in this study is likely due to the specific outcome measurements used in this study rather than insulin's lack of action on the brain. Preliminary work in the same cohort using amphetamine-induced dopamine efflux as a measure of insulin signaling suggests that insulin detemir does have central brain action that may underlie detemir's beneficial effects.

To date, no other studies have specifically examined a population of mildly obese and insulin resistant individuals to characterize the relative contributions of obesity and impaired insulin signaling on the brain. The results presented in this dissertation suggest that obesity, visceral adiposity, and insulin resistance exert widespread detrimental effects on brain activity and function in a manner that diverges from chronic substance use. Instead of the expected behavioral impairments in response inhibition, insulin resistance and adiposity specifically enhanced impulsivity. The impulsiveness resulted from blunted striatal dopamine and heightened neural attention and motor network activity. This pattern mimics the heightened cue-reactivity and ventral striatal dysfunction observed early during hedonic food or drug seeking. Consistent with my

proposed model, mild obesity and insulin resistance represent a phenotype in transition from ventral striatal reward-seeking to dorsal striatal habitual responding, although brain dysregulation has not reached a stage of “chronic” impairment similar to that of drug addiction.

The idea that the neural circuitry of mild obesity and insulin resistance is an intermediate state rather than an endpoint offers exciting opportunities for treatment. In this study, visceral adiposity and insulin resistance impaired brain dopamine function and thus represent therapeutic targets. Preliminary research combined with the present results suggests that reducing visceral adiposity and improving insulin sensitivity to healthy levels normalizes the behavioral and neural impairments observed in obesity and insulin resistance. In conclusion, this research demonstrates that mild obesity, insulin resistance, and visceral adiposity are associated with impairments in behavioral control, widespread neural dysregulation, and blunted striatal dopamine neurotransmission.

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