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SAN DIEGO STATE UNIVERSITY

Neural correlates of taste and pleasantness evaluation in metabolic syndrome: An fMRI study

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

in

Clinical Psychology

by

Erin Green

Committee in Charge:

University of California, San Diego State University

Professor Mark Bondi
Professor Terry Jernigan

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Professor Claire Murphy, Chair
Professor Paul Gilbert
Professor Sarah Mattson

2014

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Chair

University of California, San Diego

San Diego State University

2014

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Chapters 1-4, in part are currently being prepared for submission for publication of the material. Green, E; Jacobson, A; Haase, L; & Murphy, C. The dissertation author was the primary investigator and author of this material.

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Zamora, R., Bartholow, J., **Green, E.,** Morgan, C., & Murphy, C. (2012). Adiposity measures predict olfactory processing speed in older adult carriers of the apolipoprotein E ε4 allele. Clinical Neurophysiology, 123, 918-924.

Haase, L., Wang, M., **Green, E.,** & Murphy, C. (2011). Functional connectivity during an olfactory memory paradigm in individuals genetically at risk for the development of Alzheimer's disease. Human Brain Mapping, 34(3), 530-542.

Haase, L., **Green, E.,** & Murphy, C. (2011). Males and females show differential brain activation to taste when hungry and sated in gustatory and reward areas. Appetite, 57, 421-434.

Green, E., Jacobson, A., Haase, L., & Murphy, C. (2011). Reduced nucleus accumbens and caudate nucleus activation to a pleasant taste is associated with obesity in older adults. Brain Research, 1386, 109-117.

Jacobson, A., **Green, E.,** & Murphy, C. (2010). Age-related functional changes in gustatory and reward processing regions: An fMRI study. Neuroimage, 53, 602-610.

ABSTRACT OF THE DISSERTATION

Neural correlates of taste and pleasantness evaluation in metabolic syndrome: An fMRI study

by

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Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2014

San Diego State University, 2014

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The metabolic syndrome (MetS) is a constellation of vascular and metabolic abnormalities that commonly occur together and increase risk for cardiovascular disease (CVD) and type II diabetes (T2DM). Having MetS, especially during middle-age, increases the risk for dementia in later life. Because of these issues, prevention of MetS has become an important public health initiative. Abdominal obesity is causally linked to MetS; therefore, increased efforts to prevent obesity and to better understand what predicts weight gain is of extreme importance. Related research suggests that

altered processing of food reward in the brain of obese persons is a possible mechanism related to overeating. Therefore, the study aimed to investigate potential differences in brain response according to metabolic status during pleasantness evaluation of sweet and bitter tastes when hungry and sated.

Fifteen healthy middle-aged (44-54 years old) adults and sixteen middle-aged adults with MetS were recruited from the San Diego community. The subjects participated in two functional magnetic resonance imaging (fMRI) scans: (1) after a 12-hour fast; and (2) after a nutritional preload. While in the scanner, participants rated the pleasantness of caffeine (bitter) and sucrose (sweet) solutions. Data were analyzed using voxelwise linear mixed-effects modeling and region of interest (ROI) analyses. Exploratory analyses were also conducted to examine associations between ROI activation and adiposity, and differential brain responses in participants diagnosed with T2DM.

The results suggest that middle-aged individuals with MetS have decreased brain responses during pleasantness evaluation of sweet and bitter tastes in regions involved in sensory and higher-level taste processing. Additionally, hypothalamic activation was positively associated with adiposity when hungry, and negatively associated with adiposity when sated. This suggests the presence of altered hypothalamic functioning in obese middle-aged adults. It is speculated that this is due to altered hormonal nutrient signaling and/or chronic overeating. Finally, the results suggest that insulin resistance plays a large role in central taste processing during pleasantness evaluation. It is hypothesized that altered fMRI responses in participants

with T2DM may be related to greater disinhibition in combination with increased necessity for dietary monitoring and carbohydrate restrictions in these individuals.

I. INTRODUCTION

Cardiovascular disease (CVD) is the single leading cause of death in the United States (Murphy, Xu, & Kochanek, 2012), and 2200 Americans die of CVD each day, many of whom (just under 20%) have not yet reached 65 years of age (Xu, Kochanek, & Tejada-Vera, 2009). In 2008 alone, the total direct and indirect cost of CVD, stroke, and other related conditions was estimated to be almost $300 billion, which is more than any other diagnostic group (Roger et al., 2012).

Metabolic Syndrome

There are several pathophysiological abnormalities that occur together more often than would be expected by chance. The clustering of these abnormalities has been termed the metabolic syndrome (MetS) and the presence of MetS is associated with increased risk for cardiovascular disease (CVD; Lakka et al., 2002) and type 2 diabetes mellitus (T2DM; Reaven, 1988). The health problems/risk factors most commonly linked to metabolic syndrome include insulin resistance, dyslipidemia (elevated triglyceride and low high-density lipoprotein [HDL] cholesterol levels), central obesity, elevated blood pressure, impaired glucose tolerance or diabetes mellitus, and high rates of atherosclerotic disease. Markers of inflammation and accelerated hemostasis/impaired fibrinolysis have also been suggested as risk factors in metabolic disease (Leroith, 2012). Each of the risk factors in MetS exert independent effects on the cardiovascular system, which can result in cardiovascular system disorders such as myocardial infarction and stroke (Ford, 2005b). Patients with MetS are at twice the risk of developing CVD over the next 5 to 10 years, and are

5 times more likely to develop T2DM compared to individuals without the syndrome (Alberti et al., 2009).

Metabolic Syndrome Definitions, Prevalence Rates, and Burden to Society

There has been some debate as to how to define MetS, and several diagnostic criteria have been proposed by the World Health Organization (WHO; Alberti & Zimmet, 1998), the National Cholesterol Education Program Adult Treatment Panel III (ATP, 2002), the International Diabetes Federation (IDF; Alberti, Zimmet, & Shaw, 2005), and the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI; Grundy et al., 2005). The different guidelines generally stipulate exceeding a threshold of 3 risk factors out of the following in order to meet criteria: insulin resistance, abdominal obesity, elevated blood pressure, high triglyceride levels, and low HDL levels. However, differences have arisen in terms of whether or not one criterion should be emphasized and consequently, required as 1 of the 3 risk factors. For example, the first proposed classification system by the WHO suggested that insulin resistance was the underlying mechanism and required evidence of this for a patient to be diagnosed with MetS (Alberti & Zimmet, 1998). In 2005, the IDF suggested that abdominal obesity (using waist circumference cutoffs) must be required as 1 of the 3 risk factors for diagnosis (Grundy et al., 2005). In 2009, the IDF and AHA/NHLBI held discussions to resolve the discrepancy between the diagnostic criteria, and concluded that no one factor should be required for the diagnosis of MetS (Alberti et al., 2009). Having at least 3 of the 5 risk factors outlined in Table 1 represents the most recent criteria for establishing a clinical diagnosis of metabolic syndrome.

Table 1: Criteria for clinical diagnosis of the metabolic syndrome (Alberti et al., 2009). Abbreviations: HDL-C = high-density lipoprotein cholesterol.
✪ The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose ω-3 fatty acids presumes high triglycerides.
✣ Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria

Measure	**Categorical Cut Points**
Elevated waist circumference	Population and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator) ✪	≥ 150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator) ✪	<40 mg/dL (1.0 mmol/L) in males <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or Diastolic ≥85
Elevated fasting glucose ✣ (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL

The metabolic syndrome is highly prevalent among U.S. adults, with recent estimates from the National Health and Nutrition Examination Survey (NHANES) ranging between 34% and 39% of adults over the age of 20 (Ervin, 2009; Ford, Li, & Zhao, 2010). This suggests that the actual number of adults in the U.S. meeting criteria for metabolic syndrome is between 77 and 86 million. Data from the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD) national survey (Bays et al., 2007; Clark, Fox, & Grandy, 2007) suggest, however, that far fewer individuals may be aware of having MetS, with only 0.6% of over 200,000 adults reporting that they have the syndrome (Lewis, Rodbard, Fox, & Grandy, 2008).

Prevalence rates of MetS are rising, and have increased in recent years from previous estimates of 21%-33% in the San Antonio Heart Study (Meigs et al., 2003), 23% in NHANES III, and 26.7% in NHANES 1999-2000 (Ford, 2005a). Specific prevalence rates increase with age, with middle-aged adults (ages 40-59) and older adults (ages 60+) approximately three and more than four times more likely than young adults, respectively, to meet criteria (Ervin, 2009). Prevalence rates may also vary by race/ethnicity, but this differs for males and females (Ervin, 2009). Specifically, African American males are less likely than non-Hispanic white males to have MetS, but African American and Hispanic females are more likely than non-Hispanic white females to meet criteria for MetS.

Central obesity and insulin resistance as linking risk factors

The underlying pathophysiological processes leading to development of MetS are still relatively unknown, despite a large body of literature on the topic. In the aforementioned debate over how to diagnostically classify the syndrome, both abdominal obesity and insulin resistance have been proposed as the primary mechanisms of MetS (Abbasi, Brown, Lamendola, McLaughlin, & Reaven, 2002; Alberti et al., 2009; Despres, 2006).

Obesity, defined as a body mass index (BMI) greater than or equal to 30, has become a global health epidemic. The World Health Organization estimates that in 2005, approximately 400 million adults were obese and this number is projected to increase to more than 700 million by 2015 (WHO, 2012). Obesity is characterized by the accumulation of excess adipose tissue and suggests that an individual is at increased risk of developing various comorbid health conditions. Interestingly, the

association between obesity (using the BMI cutoff criteria) and the presence of cardiometabolic abnormalities is not clear cut. For example, many obese patients can have a relatively normal metabolic risk factor profile, while some individuals who may not be as significantly overweight can meet criteria for a variety of metabolic and vascular abnormalities (Despres, 2006). In fact, it is actually the amount of visceral adipose tissue, which tends to accumulate in the abdominal region, that correlates with increased markers of inflammation and vascular and metabolic abnormalities (Bacha, Saad, Gungor, Janosky, & Arslanian, 2003; Despres, 2006; Despres, Moorjani, Ferland, et al., 1989; Despres, Moorjani, Tremblay, et al., 1989; Ross, Freeman, Hudson, & Janssen, 2002). This suggests that viscerally obese (or abdominally obese) individuals represent a subgroup of obese patients at higher risk for MetS, CVD, and T2DM.

Importantly, viscerally obese individuals are the most severely insulin resistant (Bacha et al., 2003; Despres, 2006; Despres, Moorjani, Ferland, et al., 1989; Despres, Nadeau, et al., 1989; Ross et al., 2002). Insulin is a hormone that is produced and secreted from beta cells in the pancreas. It is important, both for peripheral nervous system functions in the skeletal muscle, fat and liver (e.g., glucose uptake, suppression of hepatic glucose production), and energy homeostasis and other functions moderated by the central nervous system that will be discussed below (CNS; Plum, Schubert, & Bruning, 2005). Insulin resistance is the inability of insulin to suppress hepatic glucose output and to stimulate glucose uptake adequately in muscles and adipocytes. When insulin resistance occurs, the pancreas compensates by increasing insulin secretion, resulting in potentially toxic levels of insulin (hyperinsulinemia) and glucose

(hyperglycemia) circulating in the blood. This can eventually culminate in the development of T2DM (Leroith, 2012).

The relationship between increased visceral adipose tissue and the development of insulin resistance is complex and still under investigation. Multiple products are released from adipocytes, and in the presence of excess abdominal fat, they are released in abnormal amounts (Grundy, 2004). The products that have been most implicated in the development of MetS are nonesterified fatty acids, inflammatory cytokines, PAI-1, adiponectin, leptin, and resistin. In addition, increased visceral adipose tissue is related to impaired free fatty acid (FFA) metabolism (Marette et al., 1997; Zierath et al., 1998), and it has been suggested that increased flux of FFAs toward the liver leads to hypertriglyceridemia, reduced hepatic degradation of apolipoprotein B and insulin, and eventually hyperinsulinemia and increased hepatic glucose production. This combination of hyperinsulinemia and increased hepatic glucose production can contribute to glucose intolerance (Adeli, Taghibiglou, Van Iderstine, & Lewis, 2001; Arner, 2001). Additionally, viscerally obese patients have impaired triglyceride clearance, suggesting that increased visceral adiposity may contribute to fasting hypertriglyceridemia by altering FFA metabolism in the postprandial state (Couillard et al., 1998).

Metabolic Syndrome and the Brain

Metabolic syndrome is composed of several cerebrovascular risk factors, the effects of which are described below. Having MetS increases the risk for ischemic stroke, periventricular hyperintensities, and subcortical white matter lesions (WMLs; Bokura, Yamaguchi, Iijima, Nagai, & Oguro, 2008; Kwon et al., 2006; Kwon et al.,

2009; Park et al., 2008). Notably, having a larger number of risk factors is related to an increased number of silent brain infarctions (Kwon et al., 2009).

Abdominal obesity is considered to be an important linking factor in developing the syndrome and epidemiological evidence suggests that obesity during mid-life increases the risk for Alzheimer's disease and vascular dementia (Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005). There is also some evidence that MetS is associated with cognitive impairment (including Alzheimer's disease), although most studies are cross sectional and examined samples of older adults (Dik et al., 2007; Razay, Vreugdenhil, & Wilcock, 2007; Vanhanen et al., 2006). Notably, one prospective study suggests that MetS during middle age is associated with increased risk for cognitive impairment and dementia in late life (Kalmijn et al., 2000). Additionally, higher BMI is associated with reduced brain volumes in frontal, temporal, parietal, and occipital lobe regions in patients with mild cognitive impairment or AD. In the AD group, obesity was also linked to ventricular expansion (Ho et al., 2010).

Hypertension

Although the definition of hypertension varies, it is generally defined as sustained systolic blood pressure greater than 140mm of mercury (Hg; Chobanian et al., 2003) or 160 mm Hg (Beevers, Lip, & O'Brien, 2001), and a diastolic blood pressure greater than 90 mm Hg (Raz, Rodrigue, & Acker, 2003). Hypertension affects approximately 65 million individuals in the United States (Egan, Zhao, & Axon, 2010). Generally, aging is associated with increases in blood pressure until approximately age 75-80, at which time blood pressure tends to decrease (Landahl,

Bengtsson, Sigurdsson, Svanborg, & Svardsudd, 1986). In older adults, chronic hypertension is a major risk factor for stroke, and is also associated with cognitive declines (Hannesdottir et al., 2009; Israeli-Korn et al., 2010; Kilander, Nyman, Boberg, Hansson, & Lithell, 1998; Reitz, Tang, Manly, Mayeux, & Luchsinger, 2007; Sierra & Coca, 2006; Triantafyllidi et al., 2009) that are suspected to be partially mediated by alterations in brain structure such as elevated white matter lesion (WML) burden (Carmelli et al., 1999; de Groot et al., 2000, 2002; Raz, 2000). Individuals with uncontrolled chronic hypertension are therefore at increased risk for development of mild cognitive impairment (Israeli-Korn et al., 2010; Reitz et al., 2007), and vascular dementia or Alzheimer's disease (Kivipelto, Laakso, Tuomilehto, Nissinen, & Soininen, 2002; Launer et al., 2000; Petrovitch et al., 2000; Posner et al., 2002).

Importantly, recent evidence suggests that when in the lifespan an individual has hypertension is especially important for predicting future cognitive decline. Specifically, hypertension during middle age is a risk factor for late-life dementia, including the Alzheimer's subtype (Kivipelto, Helkala, et al., 2002; Kivipelto et al., 2001; Launer, Masaki, Petrovitch, Foley, & Havlik, 1995; Shah et al., 2012; Yamada et al., 2003). In contrast, blood pressure is lower in individuals with dementia (Guo, Viitanen, Fratiglioni, & Winblad, 1996; Hogan, Ebly, & Rockwood, 1997; Molander, Gustafson, & Lovheim, 2010b; Skoog, Andreasson, Landahl, & Lernfelt, 1998) and tends to decrease during the years prior to the diagnosis (Molander, Gustafson, & Lovheim, 2010a; Qiu, von Strauss, Winblad, & Fratiglioni, 2004; Ruitenberg et al., 2001; Skoog et al., 1996).

In addition to being a risk factor for stroke and subsequently, vascular dementia, hypertension is also related to microvascular pathologic changes. WML severity is positively associated with systolic and diastolic blood pressure levels (Breteler et al., 1994; de Leeuw et al., 2002; Fujishima, Ibayashi, Fujii, & Mori, 1995; Longstreth et al., 1996; van Swieten et al., 1991). Although the mechanisms underlying WMLs are unclear, it has been suggested that they may arise from factors related to hypoperfusion, and breakdown of the blood-brain barrier (Kitagawa, 2010; Roman, Erkinjuntti, Wallin, Pantoni, & Chui, 2002). Elevated blood pressure during middle and late life is related to increased global brain atrophy in later life (DeCarli et al., 1999; Manolio et al., 1994). However, low blood pressure or declines in blood pressure over time in older adults is also associated with significant atrophy (Heijer et al., 2003; Skoog et al., 1998; Swan et al., 2000).

Not all regions of the brain appear to be equally affected by elevated blood pressure. High midlife blood pressure is associated with hippocampal atrophy (Korf, White, Scheltens, & Launer, 2004) and the characteristic pathological abnormalities (neurofibrillary tangles and neurtic plaques) of Alzheimer's disease in the hippocampus (Petrovitch et al., 2000). Additionally, in hypertensive relative to normotensive individuals, regional cerebral blood flow is lower in the hippocampus, basal ganglia structures (i.e., striatum, globus pallidus), thalamus, prefrontal and orbitofrontal cortices, and anterior cingulate gyrus (Beason-Held, Moghekar, Zonderman, Kraut, & Resnick, 2007; Dai et al., 2008; Fujishima et al., 1995).

Hyperlipidemia

Hyperlipidemia is an elevation of lipid or lipoprotein levels in the blood. Two of the most clinically important plasma lipids are cholesterol and triglyceride (Brown & Goldstein, 1986). Cholesterol's functional role in the body is as a component of cell membranes, the precursor for steroid hormones, vitamin D, oxysterols, and bile acids, and it is required for activation of neuronal signaling molecules (Brown & Goldstein, 1986). Triglyceride is made up of FFAs and is an important energy source (Hegele, 2009). Due to insolubility, lipids are transported through the circulation in complexes with proteins called lipoproteins (Lusis & Pajukanta, 2008). The main lipoproteins that transport cholesterol are LDL and HDL (Hegele, 2009). Chronic excess plasma LDL levels can lead to atherogenic plaques, and LDL cholesterol that has been exposed to free radicals causing it to become oxidized within the endothelium can also trigger an inflammatory process that accelerates vascular disease (Lusis, 2000). In contrast, HDL is considered protective against vascular disease due to its role in the transport of cholesterol from the blood vessel wall back to the liver. If HDL levels are low, this process becomes inefficient, and cholesterol can build up in the vessel wall (Toth, 2003).

According to the NCEP ATP III, an optimal lipid profile with the lowest risk for CVD is as follows: (1) total cholesterol < 200; (2) LDL cholesterol <100; (3) HDL cholesterol ≥ 60 (ATP, 2002). In terms of prevalence, it is estimated that approximately 45% of the population has total cholesterol levels exceeding 200 mg/dL. Similarly, one third of the population is estimated of having LDL levels exceeding 130 mg/dL (Lloyd-Jones et al., 2009).

Hyperlipidemia has been linked to ischemic stroke risk (Iso, Jacobs, Wentworth, Neaton, & Cohen, 1989; Kurth et al., 2007; Zhang et al., 2012), compromised regional white matter integrity (Williams et al., 2012), and vascular dementia (Moroney et al., 1999; Solomon, Kivipelto, Wolozin, Zhou, & Whitmer, 2009). The association between cholesterol levels and stroke is most likely mediated by the development of generalized atherosclerosis in the cerebrovasculature (Ansell, 2000). Additionally, the use of a class of cholesterol lowering drugs, statins, has been associated with reduced ischemic stroke risk (McKinney & Kostis, 2012; O'Regan, Wu, Arora, Perri, & Mills, 2008).

Cholesterol metabolism in the brain, and increased cholesterol release through synaptic degeneration has been implicated in the development of Alzheimer's disease (Bogdanovic et al., 2001; Heverin et al., 2004; Morris et al., 2003; Notkola et al., 1998; Papassotiropoulos et al., 2002; Refolo et al., 2001; Shobab, Hsiung, & Feldman, 2005; Wollmer et al., 2003). Apolipoproteins are involved in the control of lipoprotein metabolism and lipid transport and Apolipoprotein E (APOE) is the most prevalent lipoprotein in the central nervous system (Elshourbagy, Liao, Mahley, & Taylor, 1985). APOE has three common isoforms: ε2, ε3, and ε4. The ε4 allele in particular is related to higher plasma LDL cholesterol levels and has also been established as an important risk factor for AD (Corder et al., 1993; Hsiung, Sadovnick, & Feldman, 2004; Jarvik et al., 1995; Rubinsztein & Easton, 1999). Several epidemiological studies have reported that statins are linked to lower risk of AD (Jick, Zornberg, Jick, Seshadri, & Drachman, 2000; Li et al., 2004; Rea et al., 2005; Rockwood et al., 2002;

Wolozin, Kellman, Ruosseau, Celesia, & Siegel, 2000; Yaffe, Barrett-Connor, Lin, & Grady, 2002; Zandi et al., 2005).

Recent evidence suggests that similar to other vascular risk factors, the time of life during which hyperlipidemia develops is important. Hyperlipidemia during middle-age correlates with greater risk for cognitive impairment than development of hyperlipidemia in late life (Reynolds, Gatz, Prince, Berg, & Pedersen, 2010; Solomon et al., 2009) and serum concentrations of cholesterol in during midlife may also be most important in determining the risk of AD (Shobab et al., 2005).

Insulin Resistance and Diabetes

Insulin is a hormone produced by the pancreas. Insulin is not only important for peripheral nervous system function, but also plays an important role in maintaining energy balance through its action on the central nervous system (Figlewicz, 2003b; Porte, Baskin, & Schwartz, 2005). Insulin crosses the blood-brain barrier to act on the CNS (Baskin, Figlewicz, Woods, Porte, & Dorsa, 1987; Baura et al., 1993) and obesity has been linked to a deficiency in CNS insulin (Kern et al., 2006). Low levels of insulin in the CNS are associated with increased drive for energy intake and alternatively, high levels are linked to reduced motivation for food intake (Air, Benoit, Blake Smith, Clegg, & Woods, 2002; Brief & Davis, 1984; Carvalheira et al., 2003; McGowan, Andrews, Fenner, & Grossman, 1993; Obici, Feng, Karkanias, Baskin, & Rossetti, 2002; Plum et al., 2005). Orally ingested glucose raises plasma insulin levels, and the response to a glucose load is related to the level of insulin sensitivity (Matsuda & DeFronzo, 1999). In addition, the level of insulin sensitivity is predictive of weight gain in individuals without diabetes; a lesser response to glucose is

predictive of more weight gain at follow up (Pannacciulli et al., 2007). Therefore, excess adiposity (i.e., obesity) may represent a pathophysiological state in which either: (1) adipose signals (insulin levels, which should be increased with excess adiposity) are actually decreased in the CNS, or (2) there is CNS resistance to the actions of these signals (Figlewicz, 2003b).

Insulin is also hypothesized to play a role in reward processing in the brain. Specifically, insulin can interact with midbrain dopamine (DA) and opioid pathways that are integral to the subjective experience of reward and can actually decrease food reward or act as a satiety signal after a meal (Figlewicz & Sipols, 2010; Hallschmid, Higgs, Thienel, Ott, & Lehnert, 2012). In addition, the highest concentration of insulin receptors in the brain are found in regions related to olfaction (olfactory bulb), the limbic system (hippocampus, amygdala), regulation of energy homeostasis (hypothalamus), and reward processing (Corp et al., 1986; Plum et al., 2005; Schulingkamp, Pagano, Hung, & Raffa, 2000; Unger, Livingston, & Moss, 1991; Werther et al., 1987; Zahniser, Goens, Hanaway, & Vinych, 1984). Exogenous insulin infusion is associated with increased metabolism in the ventral striatum and prefrontal cortex in insulin sensitive adults, but is significantly reduced in insulin resistant adults (Anthony et al., 2006), suggesting that central insulin resistance occurs concurrently with peripheral insulin resistance. This also suggests that there are alterations in the functions of brain regions related to reward in individuals with insulin resistance.

Another important role of insulin in the CNS is its effect on cognitive function, including memory. Cognitive declines related to insulin resistance can be detected as early as middle-age (Young, Mainous, & Carnemolla, 2006) and hyperinsulemia or

T2DM has been linked to Alzheimer's disease (Kalmijn, Feskens, Launer, Stijnen, & Kromhout, 1995; Kuusisto et al., 1997; Okereke, Hankinson, Hu, & Grodstein, 2005; Ott et al., 1996; Peila, Rodriguez, White, & Launer, 2004; Vanhanen et al., 1998). Inflammation due to oxidative stress may be a mechanism linking insulin resistance to the development of AD (Young et al., 2006), and elevated insulin levels in the CNS may increase amyloid β levels (Brownlee, 1995; Kuusisto et al., 1997).

Diabetes refers to a group of chronic metabolic conditions characterized by hyperglycemia from impaired insulin secretion and/or action. Type I Diabetes is caused by an absolute deficiency in insulin secretion. The more prevalent form, Type II Diabetes, refers to a combination of severe insulin resistance and an impaired insulin secretory response ("Diagnosis and classification of diabetes mellitus," 2012). In Type II Diabetes, hyperglycemia and a degree of insulin resistance may be present for a long period of time prior clinical symptoms and diagnosis. The hyperglycemia caused by T2DM can sometimes be treated and controlled with weight reduction, diet, exercise, and specific pharmacologic interventions (i.e., oral glucose lowering agents), but more severe cases may require exogenous insulin treatment. According to the American Diabetes Association, criteria for the diagnosis of diabetes mellitus include: (1) symptoms of diabetes plus plasma glucose concentration ≥ 200mg/dl any time of day, regardless of time since last meal, or (2) fasting (no caloric intake for at least 8 hours) plasma glucose ≥ 126 mg/dl, or (3) glucose ≥ 200 mg/dl 2-hours post glucose load ("Diagnosis and classification of diabetes mellitus," 2012).

Taste and Flavor

Eating causes simultaneous stimulation of gustatory, olfactory, and somatosensory systems from input to the oral and nasal cavities. Therefore, "flavor" refers to the integration of the abovementioned sensory systems into a single percept (Murphy & Cain, 1980; Murphy, Cain, & Bartoshuk, 1977; Small & Prescott, 2005). Retronasal olfaction is defined as odors reaching receptors on the olfactory epithelium via the mouth; this is in contrast to orthonasal olfaction, which refers to odors reaching the olfactory epithelium via the nostrils (Rozin, 1982). Somatosensory information (e.g., temperature, touch, and irritation) is also relayed to the central nervous system via the trigeminal nerve. Interestingly, although the perception of flavor develops from central integration of these three sensory systems, it is often misattributed to taste alone (Murphy & Cain, 1980).

Taste refers to the stimulation of taste cells in the oral cavity, which produces the sensations of sweet, sour, salty, bitter, or umami. Taste buds, the peripheral sensory organs of the gustatory system are located on the tongue, soft palate, pharynx, larynx, epiglottis, uvula, upper third of the esophagus and lips and cheeks. Taste information is relayed to the central nervous system via the chorda tympani branch of the facial nerve (VII), the glossopharyngeal nerve (IX), and the vagus nerve (X), which terminate in the rostral region of the nucleus of the solitary tract (NST) of the medulla (Norgren, 1990). In this region of the brainstem, there is evidence of some overlap and integration of taste and somatosensory information arising from the spinal trigeminal nucleus (Scott, Yaxley, Sienkiewicz, & Rolls, 1986; Travers, 1988). Subsequently, taste information is projected ipsilaterally to mediodorsal and

ventroposteromedial (VPM) thalamic nuclei (Beckstead, Morse, & Norgren, 1980; Pritchard, Hamilton, Morse, & Norgren, 1986). From the VPM thalamic nuclei, taste information is projected to an anterior region of the insular cortex and adjoining frontal opercular cortex. Research involving non-human primates (Patton & Ruch, 1946; Pritchard et al., 1986; Yaxley, Rolls, & Sienkiewicz, 1990) and humans (Faurion et al., 1999; Mathy, Dupuis, Pigeolet, & Jacquerye, 2003) provide evidence that this region is the human primary gustatory cortex (PGC).

The caudolateral orbitofrontal cortex (OFC) extends only several millimeters anterior to the primary taste cortex and has been deemed the secondary cortical taste area where taste afferents converge with projections from the primary olfactory cortex (Rolls, Yaxley, & Sienkiewicz, 1990). This region is reciprocally connected with the anterior cingulate and medial prefrontal cortex (Carmichael & Price, 1996), and also has bidirectional connections with the lateral hypothalamus, which allows modulation by physiological state (Rolls, Murzi, Yaxley, Thorpe, & Simpson, 1986). Projections from the PGC also innervate the central nucleus of the amygdala, and from there, the lateral hypothalamus and midbrain dopaminergic regions (Simon, de Araujo, Gutierrez, & Nicolelis, 2006). The PGC and OFC also project to the dorsal and ventral striatum (Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000; Chikama, McFarland, Amaral, & Haber, 1997; Fudge, Breitbart, Danish, & Pannoni, 2005). The cerebellum is also potentially involved in CNS processing of taste and flavor. It is hypothesized that this region is involved in the modulation of food intake via its bidirectional connections with hypothalamic nuclei (Cavdar, San, Aker, Sehirli,

& Onat, 2001; Dietrichs, 1984; Wen, Zhu, Zhang, & Wang, 2004; Zhu & Wang, 2008; Zhu, Zhang, Song, & Wang, 2004).

Nutrient Sensing in the Gut

Meal consumption results in satiation via gastric distention, motility, and emptying, and the release of peptides involved in the modulation of hunger and satiety from enteroendocrine cells. The gastrointestinal tract releases over 20 different peptide hormones in response to distension of the stomach, digestion of food, and neuronal signals (Adrian et al., 1985; Murphy & Bloom, 2006). Pancreatic and gut hormones including insulin, glucagon-like peptide-1 (GLP-1), peptide-YY (PYY), and ghrelin respond to nutrients in the gut and play a large role in mediating appetite and regulating food intake (Cummings & Overduin, 2007; Strader & Woods, 2005).

In addition to residing in taste buds in the oral cavity, taste receptors are also located in the nasal epithelium, the trachea, and throughout the stomach, intestine, and pancreas (Finger et al., 2003; Finger & Kinnamon, 2011; Hofer, Puschel, & Drenckhahn, 1996; Sbarbati et al., 2004; Tizzano et al., 2010; Wu et al., 2002). In particular, bitter, sweet, and umami taste receptors in the gut, and the function of these cells in digestion and the regulation of food intake, has been extensively studied in recent years. Stimulation of taste cells in the gut is one mechanism through which gut hormones are released.

Stimulation of bitter taste receptors in the gut results in the release of the peptide hormone CCK, which reduces gut motility and, hypothetically, inhibits further ingestion of a potentially harmful substance (Glendinning, Yiin, Ackroff, & Sclafani, 2008). In contrast, sweet taste and umami receptors in the gut signal the ingestion of

carbohydrate and amino acid (protein) macronutrient sources, respectively. At the beginning of the meal, stimulation of these receptors initiates the release of ghrelin, an orexigenic peptide, resulting in further energy consumption (Hass, Schwarzenbacher, & Breer, 2007, 2010). Enteroendocrine cells farther down the gastrointestingal tract secrete GLP-1 when sweet substances are detected. GLP-1 stimulates the release of insulin from the pancreas resulting in enhanced glucose uptake from the bloodstream (Finger & Kinnamon, 2011). PYY, another important satiation-inducing hormone, is also secreted postprandially, and in proportion to calories consumed. Similar to GLP-1, PYY exerts an anorexic effect, thus aiding the satiation process (Degen et al., 2005).

Neural signals of short-term nutrient availability converge in the NST of the brainstem via gastrointestinal vagal afferents, which are then projected to the hypothalamus (Bewick, 2012). Gut hormones also alter activity of gut-brain vagal pathways, act directly on the NST, and directly relay information regarding short-term nutrient availability to the arcuate nucleus of the hypothalamus in the CNS. The arcuate nucleus also receives inputs from insulin and leptin signaling long-term energy stores (Jobst, Enriori, & Cowley, 2004; Porte, Baskin, & Schwartz, 2002). These neurons project to other hypothalamic nuclei and brain regions involved in feeding and reward modulation.

Aging is linked to reductions in appetite, which is potentially mediated by alterations in both short-term (CCK, PYY, ghrelin), and long-term (insulin, leptin) hunger and satiety signals. Aging is associated with increased plasma concentrations of both CCK and PYY (Di Francesco et al., 2005; MacIntosh et al., 1999) and CCK infusion results in a greater satiation effect in older compared to young adults (Tai,

Feinle-Bisset, Horowitz, Wishart, & Chapman, 2010). Similarly, older adults have elevated fasting (Di Francesco et al., 2006; Gomez et al., 2003; Ruhl & Everhart, 2001; Zamboni et al., 2004) and postprandial (Di Francesco et al., 2006) plasma leptin and insulin (Di Francesco et al., 2006). There are mixed findings as to whether or not fasting ghrelin, an appetite-enhancing hormone, is lower in older adults. Lower fasting ghrelin levels have been reported in older relative to young adults (Rigamonti et al., 2002; Schneider et al., 2008; Serra-Prat et al., 2007), but others have not supported these finding (Di Francesco et al., 2006).

Reward Value

Reward is an operational construct related to the positive experience and reinforcement derived from a stimulus or behavior. The neural processes that underlie disordered eating and obesity have become a significant focus of research, and one of the dominant hypotheses relates to altered neural processing of food reward as a mechanism of weight gain and obesity (Green, Jacobson, Haase, & Murphy, 2011; Stice, Spoor, Bohon, & Small, 2008; Wang et al., 2001; Wang, Volkow, Thanos, & Fowler, 2009). Food reward is a critical factor driving dietary selection and energy consumption (Saper, Chou, & Elmquist, 2002; Wang et al., 2001), and caloric intake can play a significant role in weight gain (Sherwood, Jeffery, French, Hannan, & Murray, 2000). Foods that are energy dense (i.e., contain a large amount of energy [e.g., kilocalories] per unit weight [e.g., gram] of food) are highly palatable and are often eaten to excess (Drewnowski, 1998). Therefore, greater understanding of the impact of alterations in reward processing on eating behavior may have the potential

for significant contributions in the development of interventions for pathological eating.

Food reward is an integrative process that reflects a combination of flavor, learned associations (e.g., avoiding foods that have caused food poisoning and ingesting foods associated with positive sensory, perceptual, and cephalic phase responses), and physiological state (Berridge, 1996). The hedonic tone of a stimulus is modulated by internal signals; pleasure is not solely a reflection of the sensory properties of a stimulus itself, but of the internal state of the individual (Cabanac, 1971). Normally, food is the most pleasant to consume when an individual is hungry and there is a physiological need for energy balance; similarly, the pleasantness of food decreases as an individual eats to satiety.

Sensory specific satiety is a similar phenomenon that is driven by internal cues and encourages a varied diet. It refers to the decrease in the hedonic tone of all of the sensory properties of a specific food (e.g., texture, taste, smell) after it has been consumed (Rolls, Rolls, Rowe, & Sweeney, 1981). For example, the pleasantness of the taste, smell, texture, and sight of steak will decrease after its consumption, but the taste, scent, texture, or sight of a different food (e.g., chocolate) may still be appealing and stimulate physiological reward signals.

These phenomena have been demonstrated using taste stimulation and cell recordings in nonhuman primates. Although cells in the PGC respond to taste stimuli independently of hunger (Rolls, Scott, Sienkiewicz, & Yaxley, 1988; Yaxley, Rolls, & Sienkiewicz, 1988), higher-level regions involved in taste hedonics and reward, including the orbitofrontal cortex (Critchley & Rolls, 1996; Rolls, Sienkiewicz, &

Yaxley, 1989), and hypothalamus (Rolls et al., 1986), are modulated by physiological state. Human neuroimaging studies have also illustrated differential cortical activation according to motivational state in the orbitofrontal cortex, amygdala, striatum, insula, and hypothalamus (Frank et al., 2012; Haase, Cerf-Ducastel, Buracas, & Murphy, 2007; Haase, Cerf-Ducastel, & Murphy, 2009; Haase, Green, & Murphy, 2011; Jacobson, Green, & Murphy, 2010; O'Doherty et al., 2000; Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001). The shift in activation of brain regions involved in food reward during satiation is likely a physiological signal for meal termination. However, with the rising availability of energy-dense foods, these physiological signals may no longer be sufficient to induce meal termination, resulting in consumption beyond satiety (Rolls, 2007; Volkow, Wang, & Baler, 2011).

Food reward consists of incentive salience, hedonic impact, and learned associations. Incentive salience refers to "wanting" or the desire/motivation to obtain food, while hedonic impact refers to "liking" or the pleasure derived from consumption of that food (Berridge, 1996, 2009; Berridge & Robinson, 1998). Wanting and liking are linked through learning. For example, remembering that consuming chocolate cake was a pleasant experience may result in increased wanting of that food the next time it is encountered. In contrast, learning is important for avoidance of certain foods that cause adverse reactions (allergies, food poisoining, etc.). Notably, some preferences are innate, and taste can be informative about a food's nutritive value (Scott & Verhagen, 2000). Sweet taste generally suggests that a food is energy dense, while bitter taste can warn against poisonous food, or food that has gone bad and shouldn't be eaten.

Reward Processing in Obesity

The mesolimbic DA system modulates the experience of food reward and thus, plays an important role in energy intake (Martel & Fantino, 1996). DA release in the dorsal striatum facilitates feeding (Szczypka et al., 2001) and correlates with pleasantness ratings (Small, Jones-Gotman, & Dagher, 2003). DA receptor agonists suppress appetite and lead to weight loss (Leddy et al., 2004; Towell, Muscat, & Willner, 1988), while DA antagonists tend to increase appetite and lead to weight gain (Baptista, 1999).

There is evidence to suggest that abnormal functioning of the DA system may underlie disordered eating in obesity. In 1990, Kenneth Blum's research group published a study linking increased incidence of the presence of the A1 allele of the TaqIA restriction fragment length polymorphism to alcoholism (Blum et al., 1990). The A1 allele of the TaqIA polymorphism is associated with the dopamine D2 receptor (DRD2) gene, and individuals with at least one A1 allele have 30-40% fewer D2 dopamine receptors than those with A2/A2 (Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991; Thompson et al., 1997). It has since been suggested that individuals with this genetic predisposition for lower D2 receptor expression may be at risk for substance use disorders and obesity. Specifically, Blum and colleagues introduced the concept of "reward deficiency syndrome", which refers to a condition in which a reduced DA reward response leads to increased behaviors related to seeking out quickly rewarding stimuli. The theory suggests that individuals compensate for a sluggish reward response by overindulgence (Blum et al., 1990).

There is research specifically linking the A1 allele to obesity (Noble et al., 1994; Spitz et al., 2000). In addition, D2/D3 agonist administration greatly reduces rats' preference for chocolate (Cooper & Al-Naser, 2006) and D2 receptor levels are decreased in the striatum of pathologically obese persons (Wang et al., 2001). A study in 2008 demonstrated that a blunted striatal response to a chocolate milkshake was associated with BMI (greater adiposity was related to reduced striatal activation) and this relationship was strongest in individuals with the A1 allele (Stice, Spoor, Bohon, & Small, 2008).

Aging is associated with declines in the DA system (Kaasinen et al., 2000; Volkow et al., 1998; Volkow et al., 2000) including significant losses in D2 receptor levels (Joseph, Roth, & Strong, 1990) which likely have implications for the link between aging and reward processing (Dreher, Meyer-Lindenberg, Kohn, & Berman, 2008). Interestingly, reduced activation in the nucleus accumbens, caudate nucleus, and amygdala is strongly related to both BMI and increased waist circumference in older adults (Green et al., 2011).

Pathological eating may also be related to exaggerated responsivity to cues associated with food. Greater reward sensitivity (assessed using surveys) has been linked to higher BMIs (Davis, Strachan, & Berkson, 2004; Franken & Muris, 2005) and greater activation to food images in a fronto-striatal-amygdala-midbrain network (Beaver et al., 2006). Similarly, obese individuals have demonstrated greater activation in response to food pictures relative to leaner individuals (Karhunen, Lappalainen, Vanninen, Kuikka, & Uusitupa, 1997; Rothemund et al., 2007; Stoeckel et al., 2008). Finally, obese adolescents have higher taste sensitivity to sucrose and

salt than nonobese adolescents (Pasquet, Frelut, Simmen, Hladik, & Monneuse, 2007). Taken together, the research on food reward and obesity suggests the possibility that overeating may be a result of overactivation of the reward system to food cues (e.g., pictures of food) and a blunted reward response during actual food consumption.

Significance and Purpose of the Proposed Study

Having metabolic syndrome and its individual risk factors during middle age substantially increases the risk for future cognitive impairment and dementia. It has been suggested that abdominal obesity is causally linked to MetS, and lifestyle factors (e.g., overconsumption of palatable food) play a significant role in the development of obesity. Thus, increased efforts to prevent obesity and to better understand why some individuals gain weight are of extreme importance. To date, there are no studies examining fMRI of food reward in middle age, or the potential for altered response to food reward in the brain of individuals with metabolic syndrome.

The purpose of the study was to examine the potential for altered responses in gustatory and reward-related areas of the brain of middle-aged adults with MetS. The experiment used taste stimulation, paired with a pleasantness-rating task during the physiological states of hunger and satiety. Participants evaluated the pleasantness of two gustatory stimuli at different ends of the hedonic spectrum (sweet and bitter) during functional magnetic resonance imaging. This paradigm has previously been demonstrated to elicit activation of prototypical taste areas (thalamus, anterior insula, somatosensory areas) and higher-order regions involved in hunger modulation (OFC, hypothalamus), and reward valuation (striatum, amygdala, dopaminergic midbrain) in young (Cerf-Ducastel, Haase, & Murphy, 2012; Green & Murphy, 2012; Haase et al.,

2007; Haase et al., 2009; Haase et al., 2011), middle-aged (Green, Jacobson, Haase, & Murphy, 2012), and older adults (Green et al., 2011; Jacobson et al., 2010).

Specific Aims

Aim #1: To directly compare fMRI activation of healthy middle-aged adults and middle-aged adults with metabolic syndrome during pleasantness evaluation of a sweet and a bitter taste during a motivated physiological state.

Hypotheses: It was hypothesized that, due to the ecological importance of bitter taste in signaling rotten or poisonous food, there would be no difference in fMRI activation during hedonic evaluation of caffeine (the bitter taste). However, it was hypothesized that, consistent with the literature, adults with MetS would have a reduced fMRI response relative to the healthy group in brain regions involved in reward processing (caudate, nucleus accumbens, amygdala) during hedonic evaluation of sucrose (the sweet nutritive taste).

Aim #2: To explore the effect of satiety on activation of reward and hunger-modulated brain regions in middle-aged adults with and without metabolic syndrome.

Hypotheses: As previously described, activation of pleasure and reward regions (amygdala, caudate nucleus, inferior insula, orbitofrontal cortex) decreases from hunger to satiety in response to pleasant food-related stimuli (Critchley & Rolls, 1996; Frank et al., 2012; Haase et al., 2009; O'Doherty et al., 2000; Small et al., 2001). In the satiety condition, it was hypothesized that there would be no group differences in brain activation during pleasantness evaluation of the bitter taste. However, during pleasantness evaluation of the sweet taste, it was hypothesized that the middle-aged adults with metabolic syndrome would not demonstrate the same decreased response

in activation of brain regions that modulate taste hedonics (OFC, amygdala), and reward regions (striatum) as the healthy middle-aged adults during the physiological state of satiety. In other words, the MetS group would have greater activation than healthy middle-aged adults in brain regions that are generally modulated by physiological state.

Chapter 1, in part, is currently being prepared for submission for publication of the material. Green, E; Jacobson, A; Haase, L; & Murphy, C. The dissertation author was the primary investigator and author of this material.

II. Methods

Participants

Thirty-one middle-aged adults (aged 44-54 years old) were recruited from the San Diego community, Kaiser Permanente, and the UCSD Bariatric and Metabolic Institute. Fifteen of the middle-aged adults that participated in the study had less than 3 of the 5 risk factors for MetS and served as a comparison group. The metabolic syndrome group consisted of 16 middle-aged adults who met the criteria outlined in Table 1 for MetS. For one of the participants with MetS, data were only available for psychophysical testing and fMRI data analyses during the satiety session (see description of sessions below). Participants gave informed consent and received monetary compensation for their participation.

Procedure

Participants completed three separate sessions. The first session served as an initial screening in order to: (1) determine metabolic status, and (2) screen for exclusionary criteria. During the second and third sessions, the neuroimaging (described below) took place.

Screening Session

During the first session, participants were screened for exclusionary criteria including ageusia, anosmia, upper respiratory infection or allergies within the prior two weeks, left-handedness, positive history for head injury with a loss of consciousness exceeding five minutes, and any contraindications for fMRI (e.g., metal in the body). To screen for ageuesa, taste thresholds for all participants were assessed

using a forced choice procedure with a series of varying concentrations (.0032M to .36M) of sucrose solutions (Murphy, Gilmore, Seery, Salmon, & Lasker, 1990). Odor thresholds for each nostril were assessed using a forced-choice, procedure with varying concentrations of n-butyl alcohol presented monorhinically (Murphy et al., 1990).

Participants were also screened for MetS criteria using the most recent IDF guidelines for clinical diagnosis of MetS (Alberti et al., 2009). Specifically, participants in the "metabolic syndrome group" had 3 of 5 of the following risk factors: elevated waist circumference (≥ to 94 cm for males and 80 cm for females) or BMI (≥ 30kg/m^2), elevated triglycerides (≥150 mg/dL or receiving pharmacologic treatment for raised triglycerides), reduced HDL cholesterol levels (<50 mg/dL for women and <40 mg/dL for men, or receiving drug treatment for reduced HDL cholesterol), elevated blood pressure (systolic ≥ 130 and/or diastolic ≥85, or drug treatment for hypertension), or elevated fasting glucose (a diagnosis of T2DM also satisfied this criteria). To assess for obesity, waist circumference, weight, and height were measured during the screening session. To measure waist circumference, each participant's waist was measured at the midpoint between the highest point of the iliac crest and the lowest point of the rib cage. Height and weight were also measured during the screening session using a stadiometer and digital scale, respectively. Height and weight measurements were used in order to calculate BMI (weight in kilograms divided by height in meters squared). Blood pressure was recorded as the average of 3 consecutive measurements using a blood pressure monitor. If a participant recruited from Kaiser Permanente or the UCSD Bariatric and Metabolic

Institute did not have a diagnosis of hyperlipidemia, his or her HDL cholesterol levels and triglycerides were assessed using CardioChek Triglyceride and HDL Cholesterol Strips after a 12 hour fast. Finally, a self-report questionnaire was used to determine if participants were currently being treated for hypertension, dyslipidemia, or T2DM.

Neuroimaging Sessions

The neuroimaging sessions were conducted at the University of California, San Diego Center for Functional Magnetic Resonance Imaging (fMRI). Participants were scanned on two separate occasions; one session was designated as the "hunger" scan, and participants were scanned after fasting overnight for a minimum of 12 hours. The other session was designated as the "satiety" scan, and participants were scanned after consuming a 700 kilocalorie (kcal) nutritional preload. The order of the hunger and satiety sessions were counterbalanced. Seven participants in each group fasted for their first scanning session and consumed a preload on the second, final scanning day. Eight participants in each group consumed a preload on the first day of scanning and fasted for 12 hours for the second, final scanning day.

Prior to and post-fMRI scans, participants were asked to report psychophysical ratings of pleasantness and intensity of the two taste stimuli (specified below), and hunger using modified versions of the General Labeled Magnitude Scale (gLMS; Figure 1; Bartoshuk et al., 2004; Green et al., 1996; Green, Shaffer, & Gilmore, 1993). In the satiety condition, participants were asked to report the same psychophysical ratings after the preload and prior to entering the scanner.

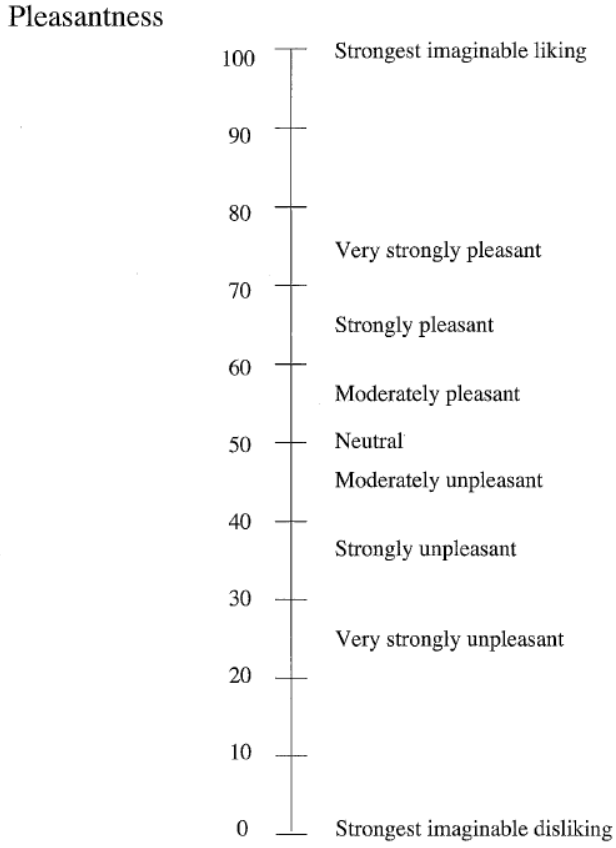


Figure 1: Modified general labeled magnitude scale for pleasantness

Stimulus delivery. A detailed description of the protocol and the system for delivering taste stimuli in the fMRI environment used in the proposed study are outlined in the Journal of Neuroscience Methods (Haase et al., 2007). The critical elements are briefly described below.

The current study was designed to investigate fMRI activation during pleasantness evaluation of taste stimuli that fall at the two ends of the hedonic spectrum: pleasant and aversive. Therefore, the study examined brain activation in response to pleasantness evaluation of sucrose (0.64M; sweet) and caffeine (0.02M; bitter) presented as aqueous solutions. Participants lay supine in the scanner and were

fitted with a bite bar (see Figure 2). The purpose of the bite bar was to minimize head movement, including that associated with swallowing, and to allow the tubing for taste delivery to rest comfortably between the lips. The stimuli were individually filled in syringes and delivered to the tongue of the participant through 25-foot long tubing connected to programmable pumps located in the operator room. The syringe pumps were triggered at the beginning of each scan. The pumps were computer-programmed to push the syringes so that 0.3 ml of solution was presented in 1 sec from each syringe at the appropriate time.

Two functional scans were performed on each day of scanning. Each stimulus was delivered 8 separate times per functional run, presented pseudo-randomly with a 10s inter-stimulus interval (ISI). Distilled water was presented twice after each stimulus; the first time as a rinse, and the second to be used as a baseline for data analysis. A minimum of 30-seconds elapsed before the same stimulus was presented again (except for water delivery, no stimulus was presented twice in a row). This procedure was designed to minimize habituation and adaptation of the gustatory system.

During the functional scans, taste stimulation was paired with a pleasantness evaluation task. The 10-second ISI allowed 1 second for taste delivery, 2 seconds for swallowing (with a cue "please swallow" presented on a screen), and 7 seconds for providing a magnitude estimate of the pleasantness of the taste. A joystick was employed by participants in order to place a crosshair on a number corresponding to a modified general labeled magnitude scale (gLMS) for pleasantness. This whole process was completed with the use of an interactive computer interface displayed on

a screen, visible to the participants via a mirror (see Figure 2 and Haase et al. 2007 for more detail).

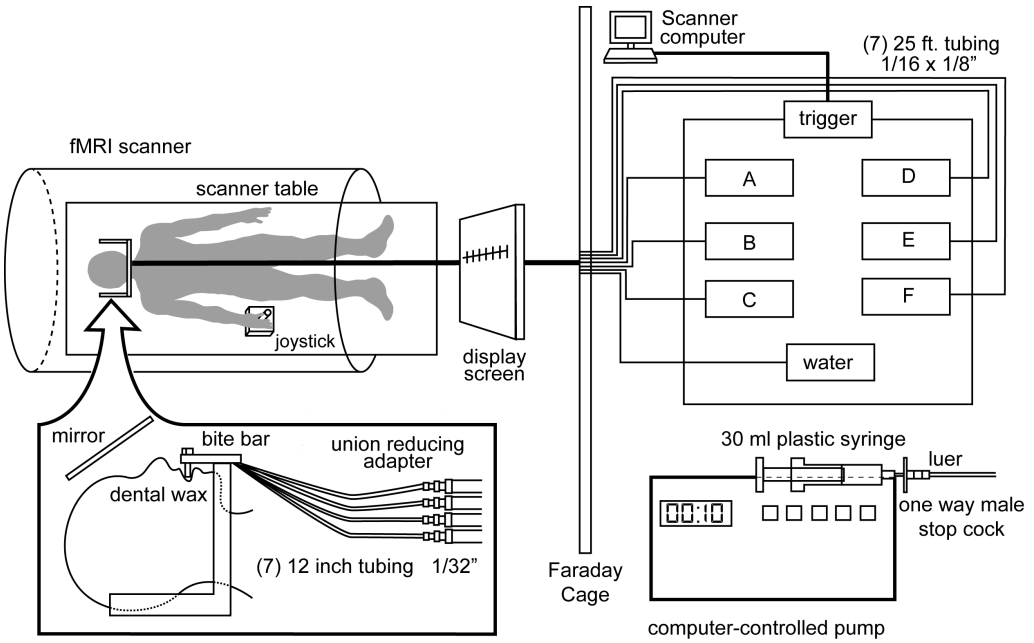


Figure 2: Taste delivery in the scanning environment. Figure reproduced from Haase, Cerf-Ducastel, Buracas, and Murphy, 2007, with permission.

Image acquisition. The neuroimaging data were collected on two 3 Tesla scanners (pre- and post-upgrade) at the UCSD Center for fMRI. Therefore, 19 participants (12 controls and 7 individuals with metabolic syndrome) were scanned using a 3T General Electric (GE) Signa EXCITE research scanner and the remaining 12 participants (3 controls and 9 individuals with metabolic syndrome) were scanned on a 3T GE Discovery MR750 scanner. All voxelwise statistical analyses corrected for any potential effect of scanner by including it as a variable of no interest in the model (see below).

Structural images for anatomical localization of functional images were collected prior to the functional scans using a high-resolution T1-weighted whole-

brain FSPGR sequence (Field of view (FOV) = 25.6cm, slice thickness = 1.2mm, resolution 1x1x1 mm^3, echo time (TE) = 30ms, Locs per slab = 190, flip angle = 15°). The structural images for the last 8 participants (3 controls and 5 individuals with MetS) were collected using a T1-weighted IRSPGR sequence (Field of view (FOV) = 24cm, slice thickness = 1.2mm, resolution 0.9375x0.9375x1.2 mm^3, echo time (TE) = 3ms, Locs per slab = 170, flip angle = 8°) with a real-time, image-based prospective motion correction technique (PROMO) (Brown et al., 2010; White et al., 2010). For functional data, a whole brain gradient echo planer pulse sequence was used to acquire T2*-weighted functional images (32 axial slices, FOV = 19.2cm, matrix size = 64X64, spatial resolution = 3X3X3 mm^3, flip angle = 90°, echo time (TE) = 30ms, repetition time (TR) = 2000ms).

Image analysis. Functional data were processed using Analysis of Functional NeuroImage (AFNI) software (Cox 1996) and FMRIB Software Library (Smith et al., 2004). The data were preprocessed using motion correction and alignment of the anatomical image and functional runs. An automated in vivo shimming method using 3-dimensional field maps was employed to correct for heterogeneity of the magnetic field and to reduce signal dropout around the sinuses using FSL. Images were spatially smoothed to 4 full width at half maximum (FWHM), automasked to clip voxels outside of the brain, and normalized to Talaraich space to control for individual structural differences using AFNI. The two functional runs in each condition (hunger or satiety) were individually rescaled to a baseline of 100 and concatenated for each participant.

A deconvolution was run on each individual's concatenated runs using 3dDeconvolve in AFNI (Cox, 1996). A deconvolution uses Ordinary Least Squares regression to estimate the hemodynamic response at each voxel in a participant's run given the experimental paradigm (i.e., stimulus onset timing). In other words, the onset of each taste stimulus (i.e., sucrose, caffeine) and the water baseline were specified and used in the creation of contrasts (i.e., sucrose minus water; caffeine minus water). The output from running 3dDeconvolve contains fit coefficients (i.e., beta weights) for each voxel, indicating the amplitude of the signal model for each contrast, and corresponding t-statistics. The purpose of creating contrasts (as opposed to investigating the response to sucrose or caffeine alone) was to control for individual differences in the blood oxygen level dependent (BOLD) response.

A region of interest (ROI) analysis was also run on fMRI data for each participant and each condition using 3dROIstats in AFNI (Cox, 1996). The definition of Brodmann Area 11 and 47 (OFC), the nucleus accumbens, amygdala, hypothalamus, caudate head, body, and tail, and insula were anatomically defined by using the Talairach Daemon database. The datasets containing the delineated ROIs were resampled to match the functional dataset grid to produce masks. The masks were applied to the output datasets from the deconvolution for each participant in order to extract mean beta values corresponding to each region and condition.

Statistical Methods

Demographics and Psychophysical Data

One-Way Analyses of Variance (ANOVAs) were run on height, weight, BMI, waist circumference, odor threshold, and taste threshold in order to examine potential

demographic, psychophysical, or body measurement differences between groups. Psychophysical ratings of hunger, intensity and pleasantness were analyzed using mixed-model ANOVAs to explore changes in hunger, intensity and pleasantness of each taste (sucrose or caffeine) over time (pre- and post-scan; pre-and post-preload), and to determine if any potential changes differed according to metabolic status.

Neuroimaging Data

Several thresholding steps were taken in an attempt to control for Type I error in all group analyses. Individual voxels were thresholded at $p \leq 0.015$. To protect a whole-brain probability of false positives at an overall alpha of 0.05, group statistical maps were corrected for multiple comparisons at the cluster level using the AFNI program AlphaSim (Cox, 1996). AlphaSim uses Monte Carlo simulations to compute the probability of generating a random "significant" cluster of noise (i.e., a false positive) given the individual voxel threshold, the voxel connection radius, the amount of blurring, and the search volume (i.e., overall dataset size). A table is produced illustrating the cluster size necessary to control for false positives at a specific alpha level. For an overall alpha level of 0.05 and the current study's parameters, a cluster threshold of 21 contiguous voxels was applied.

At the group level, one-sample t-tests were run on the fit coefficient at each voxel separately for the two groups (the healthy middle-aged adults and the middle-aged adults with MetS) in each condition: (1) caffeine minus water after a fast; (2) sucrose minus water after a fast; (3) caffeine minus water after a preload; and (4) sucrose minus water after a preload. Next, linear mixed-effects (LME) analyses were conducted with the 3dLME program in AFNI (Chen, Saad, Britton, Pine, & Cox,

2013) to examine between-group differences in response to pleasantness evaluation of caffeine and sucrose. The LME model included scanner (pre- or post-upgrade) as an additive, explanatory factor of no interest, metabolic status as a between-subject factor, and taste as a within-subject factor. To address the two Aims of the dissertation, fMRI responses during pleasantness evaluation of sucrose and caffeine were directly compared: (1) after a 12-hour fast (the hunger condition) and (2) after a nutritional preload (the satiety condition).

Prior to running analyses on ROIs, preliminary statistical analyses were run to determine if scanner was significantly related to fit coefficients averaged over ROIs and if scanner should be included as an explanatory factor of no interest in further ROI analyses. Therefore, 2 (scanner: pre- or post-upgrade) x 2 (metabolic status) ANOVAs were run on brain activation averaged over anatomically-defined regions of interest (regions: amygdala, OFC, insula, hypothalamus, and caudate). Metabolic status was included in these analyses in order to remove any actual effects of interest from the relationship between scanner and ROI fit coefficients. The results of this analysis suggested no significant effect of scanner on brain activation when averaged over ROI (see Table 2) so further ROI analyses were conducted without using scanner as a covariate.

A mixed-model ANOVA was run in SPSS on mean activation (the fit coefficients) with region (i.e., orbitofrontal cortex/BA 11 and 47, amygdala, caudate nucleus, hypothalamus, and insula), taste (sucrose or caffeine), and physiological state (hunger or satiety) as within-group variables; and MetS as the between-group variable.

Newman Keuls post-hoc tests were run to follow-up significant interactions and determine individual mean differences.

Table 2: Effect of scanner on ROI activation.
Abbreviations: OFC BA 11 = Orbitofrontal Cortex/Brodmann Area 11, OFC BA 47 = Orbitofrontal Cortex/Brodmann Area 47, AMYG = Amygdala, HYPOTH = Hypothalamus

		F (1, 26)	Significance	Partial Eta Squared
OFC BA 11	Caffeine	0.06	$p = 0.80$	$\eta^2 = 0.003$
	Sucrose	2.81	$p = 0.11$	$\eta^2 = 0.11$
OFC BA 47	Caffeine	0.85	$p = 0.36$	$\eta^2 = 0.03$
	Sucrose	0.13	$p = 0.73$	$\eta^2 = 0.005$
INSULA	Caffeine	0.85	$p = 0.37$	$\eta^2 = 0.03$
	Sucrose	2.36	$p = 0.14$	$\eta^2 = 0.08$
HYPOTH	Caffeine	0.04	$p = 0.84$	$\eta^2 = 0.002$
	Sucrose	0.16	$p = 0.69$	$\eta^2 = 0.006$
CAUDATE	Caffeine	1.80	$p = 0.19$	$\eta^2 = 0.07$
	Sucrose	.600	$p = 0.45$	$\eta^2 = 0.02$
AMYG	Caffeine	0.38	$p = 0.54$	$\eta^2 = 0.014$
	Sucrose	0.002	$p = 0.96$	$\eta^2 = 0.007$

Exploratory Analyses

Exploratory analyses were run to investigate: (1) associations between ROI activation and adiposity in middle-aged adults, and (2) differences between participants with MetS and T2DM and participants with MetS without T2DM

BMI Correlations

Previous research using a similar paradigm in young and older adults revealed strong negative correlations between BMI and brain activation during pleasantness evaluation of sucrose (Green et al., 2011). To investigate this relationship in middle-aged adults, correlations were run between BMI and brain activation in areas involved in hunger modulation, pleasantness evaluation, and reward: (Brodmann Areas 11 and

47 of the OFC, hypothalamus, caudate head, body, and tail, nucleus accumbens, amygdala, and insula) during pleasantness evaluation of sucrose in the hunger and satiety conditions.

MetS with and without T2DM

This neuroimaging study is part of a larger study investigating MetS throughout the lifespan, and data using the same paradigm have also been collected on older adults (aged 60+). In order to investigate the effect of T2DM on brain response to taste during pleasantness evaluation, data from the current study were combined with data from the older adult sample. The three groups were matched on gender and age group. Eighteen participants were middle-aged adults (6 healthy controls, 6 with MetS and no T2DM, and 6 with MetS plus T2DM). Twelve participants in the analysis were from the older adult group (4 healthy controls, 4 with MetS and no T2DM, and 4 with MetS plus T2DM) resulting in 10 participants in each group (30 total in the analysis). Older adults were screened for all exclusionary criteria described above. Additionally, the Dementia Rating Scale (Mattis, 1976) and the Mini-Mental Status Examination (Folstein, Robins, & Helzer, 1983) were also included as brief measures of general cognition in order to screen for dementia.

First, one-sample t-tests were run on the fit coefficient at each voxel separately for each group (healthy controls, MetS with no T2DM, and MetS with an active diagnosis of T2DM) in each condition: (1) caffeine minus water after a fast; (2) sucrose minus water after a fast; (3) caffeine minus water after a preload; and (4) sucrose minus water after a preload. Next, two mixed-model ANOVAs were run

using 3dLME with scanner as a factor of no interest, taste (caffeine or sucrose) and group as explanatory variables in both the hunger and satiety conditions.

The taste by group interaction effects for the hunger and satiety conditions were explored further by extracting mean activation (beta coefficients) from clusters of activation reaching significance. It has been suggested that using region of interest (ROI) analyses as follow-up tests to ANOVA in fMRI are non-independent analyses and can result in inflation of beta values (Vul, Harris, Winkielman, & Pashler, 2009). Therefore, functional ROI data from taste by group interactions in the hunger and satiety conditions were plotted in order to visually examine effects. No further statistical analyses were run on the functional ROIs due to the potential inflation of beta values.

An ROI analysis was also conducted using anatomically-defined ROIs. Specifically, a mixed-model ANOVA was run in SPSS on mean activation (the fit coefficients) with region (i.e., orbitofrontal cortex/BA 11 and 47, amygdala, caudate nucleus, hypothalamus, and insula), taste (sucrose or caffeine), and physiological state (hunger or satiety) as within-group variables; and group (control, MetS, or T2DM) as the between-group variable. Newman Keuls post-hoc tests were run to follow-up significant interactions and determine individual mean differences.

Chapter 2, in part, is currently being prepared for submission for publication of the material. Green, E; Jacobson, A; Haase, L; & Murphy, C. The dissertation author was the primary investigator and author of this material.

III. RESULTS

Demographics, Preliminary Psychophysics, and MetS Criteria

A total of 31 middle-aged adults from the San Diego community participated in the study comparing participants with MetS and without MetS. One participant in the MetS group did not participate in the third session (satiety). One-way ANOVAs revealed no differences between the two groups on age, left and right nostril odor thresholds, taste threshold, or height (*p*s > 0.05; see Table 3). However, as expected, the groups significantly differed on weight (lbs), body mass index (BMI; kg/m^2), waist circumference (cm), and mean systolic and diastolic blood pressure measurements (mmHg; see Table 3). Table 4 outlines the frequency of meeting cutoffs for obesity, elevated blood pressure, dyslipidemia, and Type II Diabetes in the group with MetS.

Table 3: Participant demographics, psychophysics, and body measurements

	Mean (SE)				
	Healthy (N=15)	MetS (N=16)	F	Significance	Partial Eta Squared
Age	48.7 (0.8)	50.6 (0.8)	2.84	$p = 0.10$	$\eta^2 = 0.089$
Odor Threshold L	7.2 (0.5)	7.0 (0.3)	0.12	$p = 0.73$	$\eta^2 = 0.004$
Odor Threshold R	6.4 (0.4)	6.8 (0.4)	0.59	$p = 0.48$	$\eta^2 = 0.020$
Taste Threshold	0.0033 (0.001)	0.0060 (0.002)	0.87	$p = 0.36$	$\eta^2 = 0.029$
Height (cm)	170.53 (2.05)	170.34 (2.45)	0.004	$p = 0.95$	$\eta^2 < 0.001$
Weight (lbs)	162.6 (5.92)	250.8 (7.33)	86.27	$p < 0.001$	$\eta^2 = 0.748$
BMI (kg/m2)	25.25 (3.3)	39.26 (2.2)	85.06	$p < 0.001$	$\eta^2 = 0.746$
Waist Circumference (cm)	91.34 (3.30)	121.33 (2.25)	57.65	$p < 0.001$	$\eta^2 = 0.665$
Systolic Blood Pressure (mmHg)	122.9 (4.70)	141.2 (2.57)	12.10	$p = 0.002$	$\eta^2 = 0.294$
Diastolic Blood Pressure (mmHg)	76.1 (2.84)	83.7 (1.89)	5.16	$p = 0.03$	$\eta^2 = 0.151$

Table 4: Metabolic syndrome criteria

	MetS (n=16)
Elevated Waist Circumference or BMI >30	100% (16)
Elevated blood pressure or antihypertensive drug treatment	100% (16)
Elevated triglycerides, reduced HDL-C or pharmacologic treatment for dyslipidemia	87.5% (14)
Type II Diabetes	37.5% (6)

Hunger and Taste Psychophysics

Psychophysical ratings of hunger, and the intensity and pleasantness of caffeine and sucrose were recorded at several times during the scanning sessions. On the hunger (i.e., no preload) day, psychophysical ratings were recorded prior to the participant entering the scanner (after a 12-hour fast) and after the scan. On the satiety (i.e., preload) day, psychophysical ratings were recorded three times: (1) at the beginning of the session, after the 12-hour fast and prior to consuming the preload; (2) after consuming the preload, prior to the scan; and (3) post-scan. Mean psychophysical ratings of hunger, intensity, and pleasantness are displayed separately for each group in Tables 5 and 6.

Hunger Ratings

Hunger ratings were examined in both the hunger and satiety conditions using a mixed-model design with MetS and time (hunger session: pre- or post-scan; satiety session: prior to consuming the preload, post-preload consumption, and post-scan) as explanatory variables. During the hunger condition, there was no effect of time, $F(1, 28) = 0.89$, $p = 0.35$, partial $\eta^2 = .03$, metabolic syndrome, $F(1, 28) = 0.20$, $p = 0.66$, partial $\eta^2 = .01$, or metabolic syndrome by time interaction, $F(1, 28) = 2.911$, $p = 0.10$, partial $\eta^2 = .09$, on hunger ratings.

A separate analysis was run on hunger ratings during the satiety condition. Mauchly's test indicated that the assumption of sphericity had been violated for the effect of time, ($\chi^2(2) = 46.07$, $p < 0.001$). Therefore, degrees of freedom for this effect were corrected using the Greenhouse-Geisser estimate of sphericity ($\varepsilon = 0.55$). The analysis revealed no significant main effect of MetS, $F(1, 28) = 0.27$, $p = 0.61$, partial

$\eta^2 = 0.01$, or MetS by time interaction, $F(2, 28) = 2.911$, $p = 0.10$, partial $\eta^2 = .09$. There was, however, a significant main effect of time/preload on hunger ratings in this condition, $F(2, 28) = 57.63$, $p < 0.001$, partial $\eta^2 = .67$. Newman-Keuls Multiple Range Tests revealed that participants were significantly less hungry post preload (M = 3.63, SE = 5.06) and post-scan (M = 4.03, SE = 1.81) when compared to the first hunger rating after the 12-hour fast/prior to consuming the preload (M = 41.05, SE = 5.06). The hunger ratings collected after participants consumed the preload did not differ across groups.

Intensity Ratings

Intensity of the sucrose and caffeine were also examined separately for each session using mixed model ANOVAs with metabolic status, taste (sucrose or caffeine), and time (pre- or post-scan for the hunger condition, and prior to consuming the preload, post-preload consumption, and post-scan for the satiety condition) as explanatory variables. In the hunger condition, there was no main effect of time, $F(1, 28) = 0.82$, $p = 0.37$, partial $\eta^2 = .03$, taste, $F(1, 28) = 0.01$, $p = 0.91$, partial $\eta^2 < .001$, or MetS, $F(1, 28) = 0.75$, $p = 0.39$, partial $\eta^2 = .026$. In addition, there were no significant time by MetS, $F(1, 28) = 0.14$, $p = 0.71$, partial $\eta^2 = .005$, taste by MetS $F(1, 28) = 0.33$, $p = 0.57$, partial $\eta^2 = .01$, or time by taste by MetS, $F(1, 28) = 0.07$, $p = 0.80$, partial $\eta^2 = .002$, interactions.

During the satiety session, there was no main effect of taste, $F(1, 29) = 0.51$, $p = 0.48$, partial $\eta^2 = 0.02$, or MetS, $F(1, 29) = 0.66$, $p = 0.42$, partial $\eta^2 = 0.02$. There were also no significant time by MetS, $F(2, 29) = 0.44$, $p = 0.64$, partial $\eta^2 = 0.016$,

taste by MetS, $F(1, 29) = 0.14$, $p = 0.72$, partial $\eta^2 = 0.005$, or time by taste by MetS, $F(2, 29) = 0.66$, $p = 0.52$, partial $\eta^2 = 0.02$, interactions on intensity ratings. However, there was a significant main effect of time, $F(2, 29) = 3.85$, $p = 0.028$, partial $\eta^2 = 0.13$, and significant time by taste interaction, $F(2, 29) = 4.21$, $p = 0.02$, partial $\eta^2 = 0.14$. Newman-Keuls Multiple Range Tests revealed that intensity ratings of sucrose, but not caffeine, increased significantly between the 2nd time point (post-preload consumption; M = 33.57, SE = 3.85) and 3rd time point (post-scan; M = 44.16, SE = 4.09).

Pleasantness Ratings

Pleasantness ratings of the taste stimuli were also examined separately for the hunger and satiety conditions using mixed-model ANOVAs. In the hunger condition, there were no main effects of time, $F(1, 28) = 2.28$, $p = 0.142$, partial $\eta^2 = 0.08$, or MetS, $F(1, 28) = 0.57$, $p = 0.46$, partial $\eta^2 = 0.02$. There were also no significant interactions between time and MetS, $F(1, 28) = 0.34$, $p = 0.57$, partial $\eta^2 = 0.01$, taste and MetS, $F(1, 28) = 0.22$, $p = 0.65$, partial $\eta^2 = 0.01$, or time, taste, and MetS, $F(1, 28) = 0.23$, $p = 0.64$, partial $\eta^2 = 0.01$. There was a significant effect of taste on pleasantness ratings, $F(1, 28) = 62.45$, $p < 0.001$, partial $\eta^2 = 0.69$. Specifically, sucrose was rated as more pleasant (M = 59.29, SE = 2.17) than caffeine (M = 35.87, SE = 1.76) controlling for time and MetS.

In the satiety condition, Mauchly's test indicated that the assumption of sphericity had been violated for the interaction between time and taste ($\chi^2(2) = 26.07$, $p < 0.001$). Therefore, degrees of freedom for the time by MetS interaction was

corrected using the Greenhouse-Geisser estimate of sphericity ($\varepsilon = 0.65$). During the satiety session, there were no main effects of time, $F(2, 28) = 1.45$, $p = 0.24$, partial $\eta^2 = 0.05$, or MetS, $F(1, 28) = .004$, $p = 0.95$, partial $\eta^2 < 0.001$. There were also no significant time by MetS, $F(2, 28) = 1.29$, $p = 0.28$, partial $\eta^2 = 0.05$, taste by MetS, $F(1, 28) = 2.17$, $p < 0.15$, partial $\eta^2 = 0.07$, or time by taste by MetS $F(2, 28) = 0.03$, $p < 0.90$, partial $\eta^2 = 0.001$, interactions. Again, there was a significant effect of taste on pleasantness ratings, $F(1, 28) = 61.17$, $p < 0.001$, partial $\eta^2 = 0.69$. Specifically, sucrose was rated as more pleasant (M = 58.72, SE = 1.80) than caffeine (M = 35.59, SE = 2.10) controlling for time and MetS.

Table 5: Psychophysical ratings of hunger and taste (hunger condition)

		Mean (SE)	
		Controls (n=15)	MetS (n=15)
Hunger Pre-Scan		29.73 (6.21)	40.2 (6.44)
Hunger Post-Scan		32.67 (7.12)	30.0 (7.42)
Intensity	Caffeine Pre-Scan	42.47 (7.84)	32.27 (5.52)
	Caffeine Post-Scan	45.47 (8.00)	39.13 (6.68)
	Sucrose Pre-Scan	40.46 (6.49)	37.00 (4.57)
	Sucrose Post-Scan	41.07 (5.31)	38.67 (5.89)
Pleasantness	Caffeine Pre-Scan	38.13 (3.80)	38.40 (2.90)
	Caffeine Post-Scan	33.00 (4.36)	33.93 (3.33)
	Sucrose Pre-Scan	59.23 (3.95)	60.60 (3.17)
	Sucrose Post-Scan	56.00 (2.64)	61.33 (2.21)

Table 6: Psychophysical ratings of hunger and taste (satiety condition)

		Mean (SE)	
		Controls (n=15)	MetS (n=16)
Hunger Pre-Preload		38.93 (7.06)	42.03 (6.86)
Hunger Post-Preload		3.27 (1.50)	3.87 (8.53)
Hunger Post-Scan		3.07 (5.39)	4.03 (2.13)
Intensity	Caffeine Pre-Preload	43.73 (7.48)	30.50 (3.15)
	Caffeine Post-Preload	47.92 (8.08)	40.31 (6.60)
	Caffeine Post-Scan	47.13 (8.22)	41.25 (6.18)
	Sucrose Pre-Preload	37.07 (5.16)	35.00 (5.81)
	Sucrose Post-Preload	37.28 (5.79)	29.75 (5.11)
	Sucrose Post-Scan	42.67 (6.15)	42.94 (4.90)
Pleasantness	Caffeine Pre-Preload	37.87 (4.08)	39.31 (2.37)
	Caffeine Post-Preload	34.31 (4.06)	36.94 (3.98)
	Caffeine Post-Scan	27.07 (4.61)	37.31 (3.92)
	Sucrose Pre-Preload	61.53 (1.94)	57.69 (2.73)
	Sucrose Post-Preload	60.53 (2.44)	53.75 (3.47)
	Sucrose Post-Scan	59.47 (4.10)	58.44 (3.47)

Neuroimaging Results

One sample t-tests were run separately for the two groups for the caffeine minus water and sucrose minus water conditions. Figures 3 and 4 illustrate significant areas of activation during hunger and satiety conditions in response to pleasantness evaluation of caffeine and sucrose, respectively. See Tables 7-10 for a complete list of regions and Talaraich atlas coordinates for both groups in these conditions.

Table 7: Activation during pleasantness evaluation of caffeine (hunger condition). Abbreviations: Hem = Hemisphere; Tlrc Coor = Talairach Coordinates; Max. Int. = Maximum intensity.

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Caffeine During Hunger						
Control						
Culmen	R	17	-49	-19	7175	7.91
Postcentral Gyrus	L	-38	-33	53		
Inferior Parietal Lobule	R	35	-38	53		
Superior Parietal Lobule	R	22	-60	53		
Precuneus	R	12	-60	53		
Superior Parietal Lobule	L	-14	-63	53		
Precuneus	L	-17	-55	53		
Postcentral Gyrus	R	52	-11	46		
Inferior Parietal Lobule	L	-38	-31	42		
Middle Frontal Gyrus	L	-30	35	42		
Precentral Gyrus	L	-53	-6	42		
Precentral Gyrus	R	49	-7	42		
Supramarginal Gyrus	L	-31	-50	37		
Supramarginal Gyrus	R	42	-44	37		
Inferior Frontal Gyrus	R	47	6	32		
Inferior Frontal Gyrus	L	-47	8	32		
Middle Frontal Gyrus	R	36	13	27		
Caudate	R	20	-6	22		
Caudate	L	-17	0	22		
Insula	L	-24	-16	22		
Posterior Cingulate	L	-2	-36	22		
Middle Occipital Gyrus	L	-27	-76	18		
Middle Occipital Gyrus	R	28	-78	18		
Lentiform Nucleus	R	22	11	18		
Thalamus	R	17	-20	15		
Thalamus	L	-11	-16	15		
Lentiform Nucleus	L	-22	4	15		
Claustrum	R	31	-8	10		
Cuneus	L	-7	-65	6		
Cuneus	R	6	-62	6		
Claustrum	L	-35	-3	-1		
Inferior Temporal Gyrus	R	42	-72	-1		
Inferior Temporal Gyrus	L	-44	-72	-1		
Fusiform Gyrus	R	44	-52	-7		
Fusiform Gyrus	L	-39	-55	-7		
Culmen	L	-2	-55	-7		
Cingulate Gyrus	L	-4	-19	35	452	5.87
Cingulate Gyrus	R	8	7	35		
Medial Frontal Gyrus	L	-6	11	43		
Paracentral Lobule	L	-4	-19	46		
Medial Frontal Gyrus	R	6	9	46		
Paracentral Lobule	R	3	-19	46		
Posterior Cingulate	L	-5	-34	23		
Brodmann Area 24	L	-3	6	36		
Brodmann Area 31	L	-3	-26	38		
Brodmann Area 32	L	-2	15	36		
Brodmann Area 32	R	5	15	36		
Brodmann Area 24	R	8	5	33		
Brodmann Area 23	L	-4	-37	24		
Brodmann Area 31	R	6	-36	29		
Brodmann Area 23	R	6	-34	27		
Middle Frontal Gyrus	R	35	53	11	102	5.09
Inferior Frontal Gyrus	R	43	18	2		
Superior Frontal Gyrus	R	32	44	27		
Brodmann Area 10	R	37	49	12		
Brodmann Area 9	R	35	40	36		
Brodmann Area 46	R	45	40	16		
Right Brodmann Area 8	R	28	31	44		
Brodmann Area 45	R	49	25	10		
Anterior Cingulate	R	11	38	5	26	-4.12
Brodmann Area 24	R	8	5	33		

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Caffeine During Hunger						
MetS						
Precentral Gyrus	L	-40	8	8	577	5.5
Precuneus	L	-10	-59	53		
Inferior Parietal Lobule	L	-35	-45	53		
Superior Parietal Lobule	L	-30	-54	50		
Postcentral Gyrus	L	-45	-28	50		
Supramarginal Gyrus	L	-36	-47	37		
Cuneus	L	-27	-73	32		
Inferior Frontal Gyrus	L	-49	4	32		
Insula	L	-29	12	21		
Middle Occipital Gyrus	L	-33	-82	15		
Lentiform Nucleus	L	-25	5	11		
Claustrum	L	-31	6	6		
Brodmann Area 47	L	-38	22	1		
Inferior Parietal Lobule	R	33	-40	35	245	4.28
Superior Parietal Lobule	R	10	-63	54		
Precuneus	R	20	-58	54		
Supramarginal Gyrus	R	38	-43	37		
Insula	R	35	14	17	129	5.29
Middle Frontal Gyrus	R	36	16	21		
Claustrum	R	28	14	18		
Inferior Frontal Gyrus	R	57	8	14		
Brodmann Area 47	R	34	19	1		
Cingulate Gyrus	R	11	26	32	110	6.73
Cingulate Gyrus	L	-2	14	36		
Medial Frontal Gyrus	R	7	33	32		
Fusiform Gyrus	L	-40	-49	-13	86	4.3
Lingual Gyrus	L	-30	-71	-8		
Declive	L	-27	-64	-11		
Culmen	L	-26	-50	-20		
Middle Frontal Gyrus	R	32	38	29	79	4.18
Superior Frontal Gyrus	R	28	39	29		
Brodmann Area 10	R	34	41	22		
Inferior Frontal Gyrus	R	43	32	13		
Fusiform Gyrus	R	29	-55	-10	74	4.05
Declive	R	33	-60	-14		
Culmen	R	12	-49	-14		
Thalamus	R	11	-13	14	51	4.74
Thalamus	L	-13	-22	-1	32	4.89
Lentiform Nucleus	R	17	2	14	27	4.2
Caudate Body	R	10	5	13		
Putamen	R	21	-1	13		
Caudate	L	-4	23	5	21	-5.27
Anterior Cingulate	L	-16	30	6		

Table 8: Activation during pleasantness evaluation of caffeine (satiety condition) Abbreviations: Hem = Hemisphere; Tlrc Coor = Talairach Coordinates; Max. Int. = Maximum intensity.

Caffeine During Satiety						
Control						
Culmen	R	26	-40	-16	1514	6.63
Precuneus	R	21	-59	50		
Precentral Gyrus	R	43	-3	42		
Postcentral Gyrus	R	47	-27	42		
Inferior Parietal Lobule	R	35	-48	42		
Middle Frontal Gyrus	R	49	7	38		
Superior Occipital Gyrus	R	30	-72	27		
Middle Temporal Gyrus	R	31	-66	23		
Middle Occipital Gyrus	R	28	-78	18		
Middle Occipital Gyrus	L	-43	-69	-8		
Lingual Gyrus	L	-16	-80	-8		
Declive	L	-23	-64	-15		
Declive	R	9	-61	-15		
Precuneus	L	-22	-55	38	1250	7.22
Precentral Gyrus	L	-35	-22	54		
Medial Frontal Gyrus	L	-6	-19	54		
Superior Parietal Lobule	L	-17	-64	54		
Inferior Parietal Lobule	L	-33	-51	54		
Medial Frontal Gyrus	R	10	-5	49		
Paracentral Lobule	L	-9	-21	45		
Cingulate Gyrus	L	-9	-21	41		
Cingulate Gyrus	R	7	12	41		
Middle Frontal Gyrus	L	-41	5	38		
Superior Frontal Gyrus	L	-35	42	33		
Supramarginal Gyrus	L	-44	-38	33		
Thalamus	L	-4	-15	19		
Parahippocampal Gyrus	R	26	-4	-10	847	7.23
Amygdala	R	26	-4	-10		
Caudate Body	R	13	10	19		
Thalamus	R	12	-16	15		
Lentiform Nucleus	R	25	1	15		
Insula	R	35	-2	15		
Inferior Frontal Gyrus	R	48	19	11		
Putamen	R	23	-6	11		
Thalamus	L	-8	-15	11		
Lentiform Nucleus	L	-21	2	11		
Caudate Body	L	-10	10	11		
Precentral Gyrus	L	46	18	7		
Claustrum	R	27	16	3		
Brodmann Area 47	L	37	20	-1		
Culmen	R	5	-27	-16		
Culmen	L	-6	-26	-16		
Insula	L	-43	14	5	152	4.96
Precentral Gyrus	L	-48	10	7		
Inferior Frontal Gyrus	L	-37	24	7		
Brodmann Area 47	L	-39	24	3		
Precentral Gyrus	R	32	-7	50	115	5.87
Middle Frontal Gyrus	R	27	-4	49		
Middle Frontal Gyrus	L	-31	41	35	50	4.36
Superior Frontal Gyrus	L	-36	38	30		
Middle Frontal Gyrus	R	32	47	23	49	4.34
Superior Frontal Gyrus	R	27	48	19		
Superior Temporal Gyrus	R	35	8	-19	30	4.79
Uncus	R	31	0	-19		
Cingulate Gyrus	R	8	-13	32	26	4.49
Inferior Parietal Lobule	R	44	-43	53	24	4.37
Postcentral Gyrus	R	36	-35	49		
Lentiform Nucleus	R	14	-10	-7	22	4.85
Parahippocampal Gyrus	R	12	-12	-10		

Caffeine During Satiety						
MetS						
Precuneus	L	-28	-46	50	153	4.84
Postcentral Gyrus	L	-54	-25	52		
Precentral Gyrus	L	-38	-19	49		
Supramarginal Gyrus	L	-29	-49	37		
Postcentral Gyrus	R	50	-19	26	136	4.57
Precentral Gyrus	R	49	-1	39		
Middle Frontal Gyrus	R	48	2	39		
Inferior Frontal Gyrus	R	40	5	33		
Inferior Parietal Lobule	R	46	-19	27		
Inferior Frontal Gyrus	R	41	20	8	83	4.18
Insula	R	40	15	15		
Brodmann Area 13	R	31	22	12		
Claustrum	R	28	22	9		
Precentral Gyrus	R	46	19	9		
Brodmann Area 47	R	40	24	3		
Precentral Gyrus	L	-55	5	35	76	4.46
Brodmann Area 6	L	-55	5	35		
Middle Frontal Gyrus	L	-56	2	42		
Inferior Frontal Gyrus	L	-56	8	33		
Precuneus	R	20	-70	44	71	4.75
Middle Temporal Gyrus	R	31	-65	30		
Cuneus	R	28	-69	30		
Superior Occipital Gyrus	R	28	-76	27		
Declive	R	29	-55	-13	68	6.49
Lingual Gyrus	R	28	-59	-6		
Fusiform Gyrus	R	28	-59	-9		
Culmen	R	19	-62	-9		
Dentate	R	17	-50	-18		
Claustrum	L	-34	-4	5	64	5.41
Lentiform Nucleus	L	-22	11	15		
Caudate	L	-19	14	12		
Putamen	L	-22	9	12		
Caudate Body	L	-13	8	12		
Insula	L	-31	5	12		
Brodmann Area13	L	-36	2	12		
Thalamus	L	-13	-22	8	52	3.79
Thalamus	R	15	-10	12		
Middle Frontal Gyrus	R	38	29	26	28	3.9
Brodmann Area 9	R	37	40	36		
Superior Frontal Gyrus	R	37	42	33		
Brodmann Area 10	R	37	45	24		
Cingulate Gyrus	R	11	-25	26	22	4.29
Cingulate Gyrus	L	-4	-25	30		

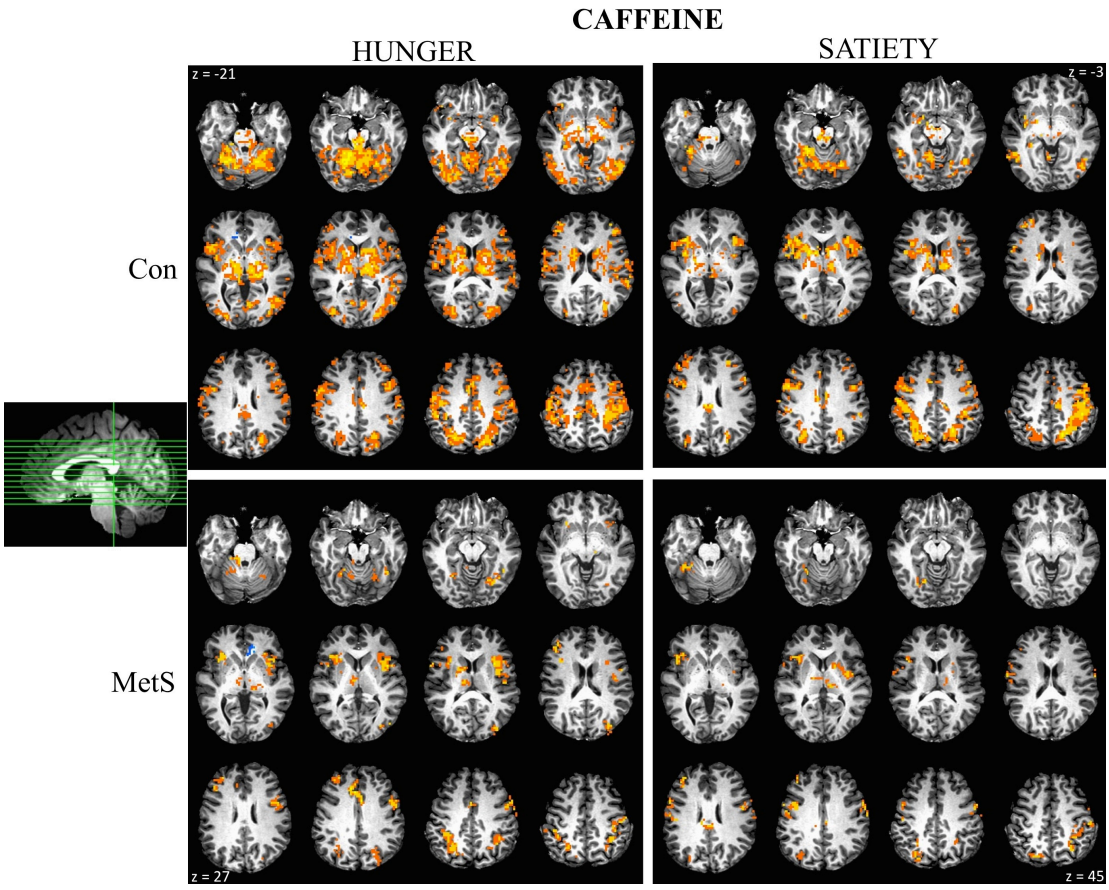


Figure 3: Activation during pleasantness evaluation of caffeine.
Abbreviations: Con = Control, MetS = Metabolic Syndrome.

Table 9: Activation during pleasantness evaluation of sucrose (hunger condition). Abbreviations: Hem = Hemisphere; Tlrc Coor = Talairach Coordinates; Max. Int. = Maximum intensity.

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Sucrose During Hunger						
Control						
Culmen	R	20	-55	-19	4579	8.19
Precentral Gyrus	R	36	-7	51		
Postcentral Gyrus	L	-42	-23	51		
Inferior Parietal Lobule	L	-39	-45	51		
Superior Parietal Lobule	L	-30	-58	51		
Precuneus	L	-21	-63	51		
Precuneus	R	14	-64	51		
Superior Parietal Lobule	R	33	-46	51		
Middle Frontal Gyrus	R	39	-3	46		
Inferior Frontal Gyrus	L	-43	7	33		
Inferior Frontal Gyrus	R	45	7	33		
Middle Frontal Gyrus	L	-45	28	29		
Caudate Body	R	14	4	21		
Insula	R	40	-9	21		
Middle Temporal Gyrus	R	34	-74	21		
Thalamus	R	13	-19	14		
Middle Occipital Gyrus	R	28	-79	14		
Lentiform Nucleus	R	21	4	9		
Putamen	R	21	4	9		
Superior Temporal Gyrus	R	52	-13	9		
Middle Occipital Gyrus	L	-32	-81	5		
Middle Temporal Gyrus	L	-45	-62	1		
Inferior Temporal Gyrus	R	51	-68	1		
Lingual Gyrus	R	17	-90	-2		
Inferior Occipital Gyrus	R	36	-82	-2		
Inferior Occipital Gyrus	L	-36	-81	-2		
Inferior Temporal Gyrus	L	-50	-62	-2		
Lingual Gyrus	L	-27	-61	-6		
Fusiform Gyrus	R	42	-60	-12		
Fusiform Gyrus	L	-37	-58	-12		
Declive	R	7	-59	-12		
Declive	L	-6	-55	-12		
Culmen	L	-13	-56	-17		
Thalamus	L	-16	-19	8	379	6.23
Caudate Body	L	-9	5	20		
Insula	L	-35	-1	15		
Lentiform Nucleus	L	-23	7	15		
Precentral Gyrus	L	-52	9	9		
Putamen	L	-20	2	9		
Cingulate Gyrus	R	2	-31	29	104	5.72
Cingulate Gyrus	L	-12	-41	29		
Posterior Cingulate	L	-11	-42	23		
Posterior Cingulate	R	10	-38	23		
Cingulate Gyrus	R	11	23	38	40	4.99
Medial Frontal Gyrus	R	5	6	45		
Cingulate Gyrus	L	-6	20	38		
Paracentral Lobule	L	-10	-25	44	36	4.24
Cingulate Gyrus	L	-12	-26	41		
Cingulate Gyrus	R	8	-4	32	25	4.61
Superior Temporal Gyrus	R	-49	-37	11	24	4.94

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Sucrose During Hunger						
MetS						
Precentral Gyrus	L	-55	-10	38	1409	7.63
Precuneus	L	-12	-56	54		
Postcentral Gyrus	L	-49	-13	51		
Middle Frontal Gyrus	L	-49	1	39		
Inferior Frontal Gyrus	L	-48	3	33		
Anterior Cingulate	L	-7	8	21		
Caudate Body	L	-15	8	21		
Lentiform Nucleus	L	-20	1	21		
Insula	L	-36	-3	21		
Superior Frontal Gyrus	L	-18	52	15		
Thalamus	L	-12	-18	15		
Medial Frontal Gyrus	L	-14	50	9		
Putamen	L	-23	-10	6		
Caudate Head	L	-13	12	3		
Brodmann Area 47	L	-34	19	0		
Thalamus	R	14	-16	14	1067	6.06
Postcentral Gyrus	R	56	-23	47		
Cingulate Gyrus	R	8	3	44		
Precentral Gyrus	R	40	-4	41		
Cingulate Gyrus	L	-7	5	37		
Inferior Frontal Gyrus	R	42	4	33		
Superior Frontal Gyrus	R	39	36	33		
Anterior Cingulate	R	9	13	24		
Insula	R	34	14	18		
Thalamus	R	11	-16	15		
Caudate Body	R	8	6	15		
Lentiform Nucleus	R	20	8	15		
Claustrum	R	32	-3	12		
Putamen	R	19	8	6		
Caudate Head	R	14	14	3		
Brodmann Area 47	R	40	20	0		
Middle Occipital Gyrus	L	-25	-85	2	499	5.76
Superior Occipital Gyrus	L	-31	-76	28		
Cuneus	L	-25	-70	28		
Precuneus	L	-26	-74	26		
Lingual Gyrus	L	-19	-81	-1		
Fusiform Gyrus	L	-41	-55	-8		
Declive	L	-32	-56	-12		
Culmen	L	-18	-58	-20		
Pyramis	L	-17	-59	-26		
Lingual Gyrus	R	23	-79	-4	269	5.51
Middle Temporal Gyrus	R	30	-57	27		
Declive	R	20	-71	-11		
Culmen	R	26	-48	-14		
Precuneus	R	14	-67	41	103	4.75
Cingulate Gyrus	L	-7	-25	29	60	5.18
Cingulate Gyrus	R	2	-20	32		
Posterior Cingulate	R	5	-43	16		
Cingulate Gyrus	L	-7	-13	41	37	4.19

Table 10: Activation during pleasantness evaluation of sucrose (satiety condition). Abbreviations: Hem = Hemisphere; Tlrc Coor = Talairach Coordinates; Max. Int. = Maximum intensity

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Sucrose During Satiety						
Control						
Supramarginal Gyrus	L	-31	-49	38	660	6.55
Precuneus	L	-17	-65	41		
Cingulate Gyrus	L	-25	-36	41		
Middle Frontal Gyrus	L	-46	6	41		
Precentral Gyrus	L	-57	-5	41		
Postcentral Gyrus	L	-47	-23	32		
Cuneus	L	-24	-70	32		
Fusiform Gyrus	L	-42	-59	-8		
Thalamus	R	14	-19	-1	322	8.22
Caudate Body	L	-13	-3	19		
Thalamus	L	-10	-16	14		
Lentiform Nucleus	R	22	-17	0		
Lentiform Nucleus	L	-11	-4	-4		
Culmen	R	17	-52	-13	295	6.28
Lingual Gyrus	L	-3	-73	-3		
Culmen	L	-4	-63	-8		
Declive	L	-27	-59	-15		
Declive	R	16	-60	-15		
Inferior Frontal Gyrus	R	35	29	-1	168	6.23
Brodmann Area 47	R	36	29	-2		
Insula	R	41	14	8		
Lentiform Nucleus	R	24	7	8		
Putamen	R	27	6	8		
Precentral Gyrus	R	42	8	8		
Precentral Gyrus	L	-31	-19	47	145	5.04
Middle Frontal Gyrus	L	-34	-3	50		
Postcentral Gyrus	L	-51	-15	50		
Precuneus	L	-18	-62	50		
Precentral Gyrus	R	53	-10	35	132	4.65
Middle Frontal Gyrus	R	49	2	42		
Inferior Frontal Gyrus	R	40	8	30		
Middle Occipital Gyrus	R	29	-79	20	98	5.44
Cuneus	R	29	-74	27		
Precuneus	R	28	-75	27		
Posterior Cingulate	R	29	-71	12		
Lingual Gyrus	R	33	-71	0		
Superior Parietal Lobule	R	29	-52	41	95	5.68
Inferior Parietal Lobule	R	34	-44	42		
Precuneus	R	28	-47	42		
Superior Parietal Lobule	R	23	-67	47	92	5.22
Precuneus	R	21	-54	57		
Insula	L	-40	11	2	88	6.42
Brodmann Area 13	L	-34	-11	18		
Inferior Frontal Gyrus	L	-41	18	12		
Precentral Gyrus	L	-41	17	9		
Superior Temporal Gyrus	L	-51	12	3		
Lentiform Nucleus	L	-32	-1	3		
Cingulate Gyrus	L	-1	-22	29	76	6.53
Cingulate Gyrus	R	1	-25	30		
Precuneus	L	-25	-58	50	56	4.37
Inferior Parietal Lobule	L	-36	-47	57		
Superior Parietal Lobule	L	-32	-52	57		
Midbrain	R/L	5	-19	-13	42	4.46
Culmen	L	-2	-32	-9		
Middle Frontal Gyrus	R	35	-7	47	38	3.97
Medial Frontal Gyrus	R	22	-1	51		
Precentral Gyrus	R	45	-1	48		
Superior Temporal Gyrus	R	56	-49	20	33	-5.48
Supramarginal Gyrus	R	53	-50	30		
Middle Frontal Gyrus	L	-25	47	11	24	4.05
Superior Frontal Gyrus	L	-26	46	18		
Medial Frontal Gyrus	L	-25	40	12		
Inferior Frontal Gyrus	L	-30	37	6		
Medial Frontal Gyrus	L	-4	11	47	23	4.47
Superior Frontal Gyrus	R	5	11	51		
Superior Frontal Gyrus	L	0	11	48		

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Sucrose During Satiety						
MetS						
Fusiform Gyrus	R	38	-13	-13	290	5.29
Cuneus	R	19	-93	0		
Lingual Gyrus	R	24	-90	-3		
Inferior Occipital Gyrus	R	31	-86	-6		
Brodmann Area 18	R	31	-86	-6		
Middle Occipital Gyrus	R	39	-72	-9		
Culmen	R	10	-54	-12		
Declive	R	31	-62	-12		
Dentate	R	16	-51	-18		
Fastigum	R	8	-53	-21		
Nodule	R	3	-62	-24		
Uvula	L	-6	-68	-27		
Uvula	R	6	-65	-27		
Pyramis	R	16	-65	-27		
Tuber	R	40	-59	-27		
Cerebellar Tonsil	R	21	-56	-30		
Postcentral Gyrus	L	-37	-28	50	67	5.22
Inferior Parietal Lobule	L	-50	-31	54		
Culmen	L	-31	-49	-28	65	4.27
Fusiform Gyrus	L	-42	-47	-18		
Tuber	L	-35	-60	-24		
Uvula	L	-31	-65	-24		
Cerebellar Tonsil	L	-28	-50	-30		
Declive	L	-19	-79	-16	54	3.94
Lingual Gyrus	L	-13	-83	-6		
Fusiform Gyrus	L	-38	-56	-9		
Inferior Temporal Gyrus	L	-53	-53	-12		
Precuneus	L	-22	-61	50	33	3.87
Superior Parietal Lobule	L	-25	-53	57		

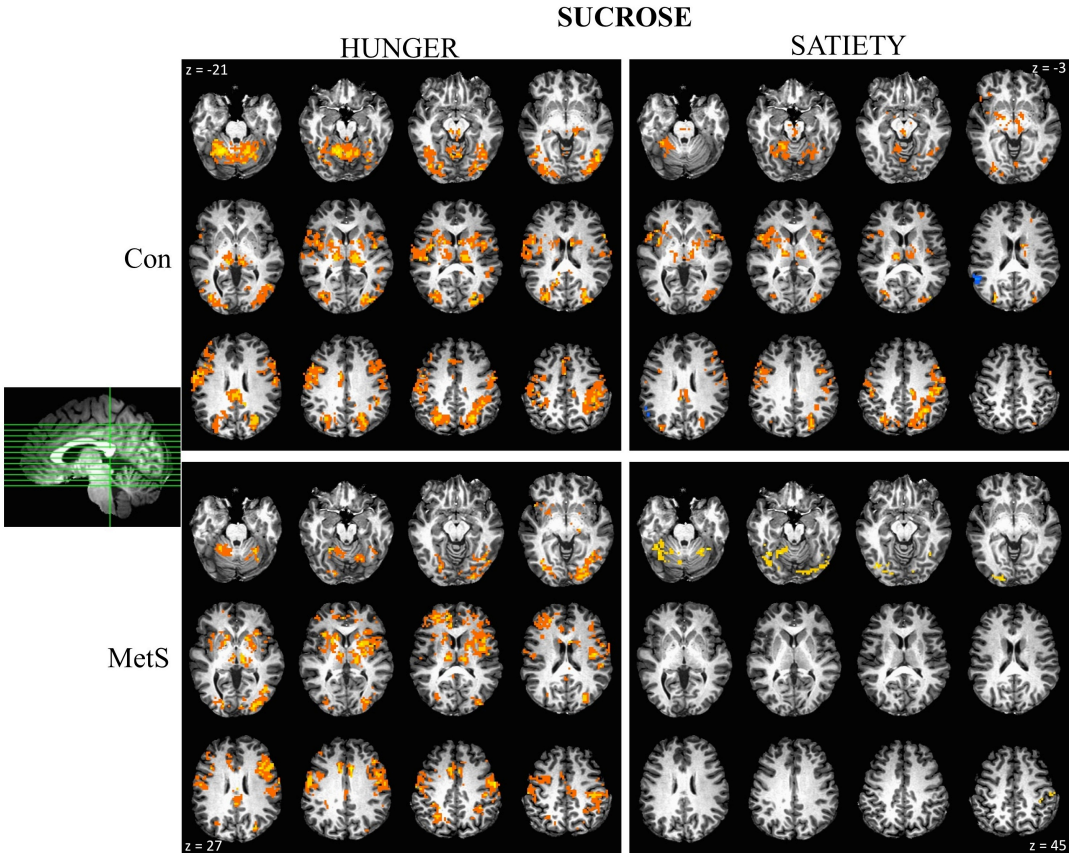


Figure 4: Activation during pleasantness evaluation of sucrose.
Abbreviations: Con = Control, MetS = Metabolic Syndrome.

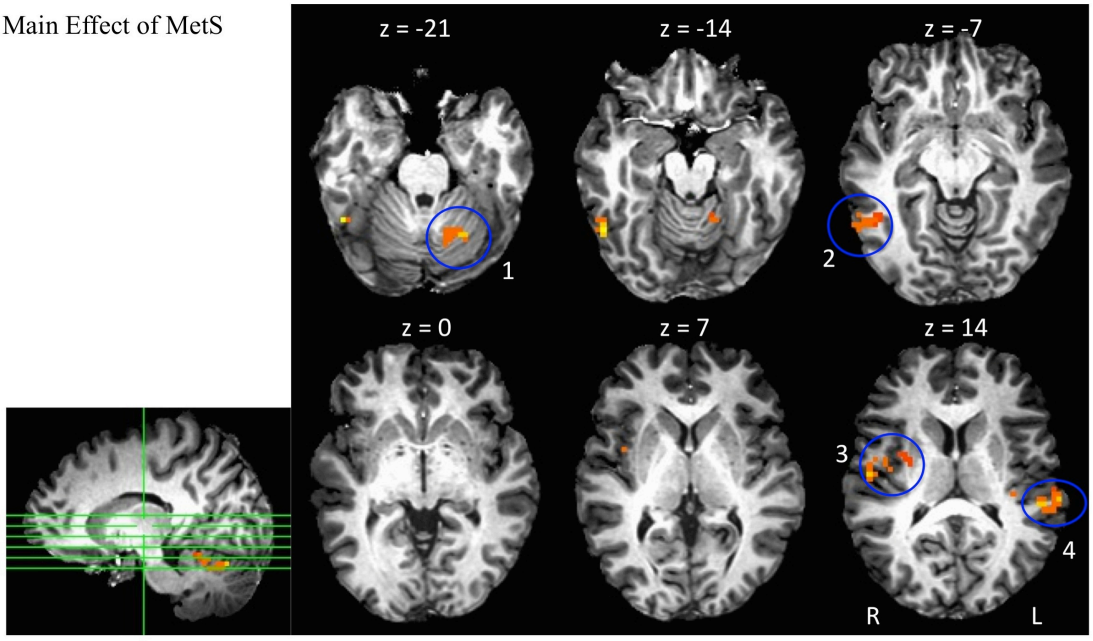
Aim #1: Comparison of fMRI activation of healthy middle-aged adults and middle-aged adults with MetS during pleasantness evaluation of a sweet and bitter taste in hunger condition.

The results of the linear mixed-effects modeling analysis for the hunger condition, including the main effect of MetS, the main effect of taste, and the taste by MetS interaction, are listed in Table 11. Statistical maps of clusters reaching significance are illustrated in Figure 5.

Table 11: Main and interaction effects during hunger. Abbreviations: L = left; R = right, Hem = hemisphere, BA = Brodmann Area.

Direction of Response	Brain Region Activated	Hem	TLRC Coordinates			# Voxels	F statistics for maximum intensity voxel
			x	y	z		
Main Effect of MetS							
Control >MetS							
	Lentiform Nucleus/Putamen	R	29	-7	14	31	15.16
	Insula	R	42	-8	10		
	Precentral Gyrus	R	51	-14	13		
	Postcentral Gyrus	R	52	-9	15		
	Inferior Temporal Gyrus/BA 20	R	53	-52	-13	29	21.08
	Fusiform Gyrus	R	52	-50	-15		
	Cerebellem (Culmen)	L	-16	-55	-22	29	15.91
	Cerebellem (Declive)	L	-14	-60	-22		
	Superior Temporal Gyrus/BA 42	L	-61	-28	14	24	14.02
	Insula	L	-36	-22	17		
Main Effect of Taste							
Sucrose > Caffeine							
	Anterior Cingulate	R	14	35	5	65	19.17
	Medial Frontal Gyrus/BA 10	R	6	48	-4		
	Anterior Cingulate	L	-4	29	5	24	16.01
Caffeine > Sucrose							
	Paracentral Lobule	R	5	-16	44	29	18.58
	Cingulate Gyrus	L	-3	-9	41		
	Lingual Gyrus	L	-7	-64	2	24	11.93
MetS x Taste Interaction							
No interaction							

a. Main Effect of MetS



b. Main Effect of Taste

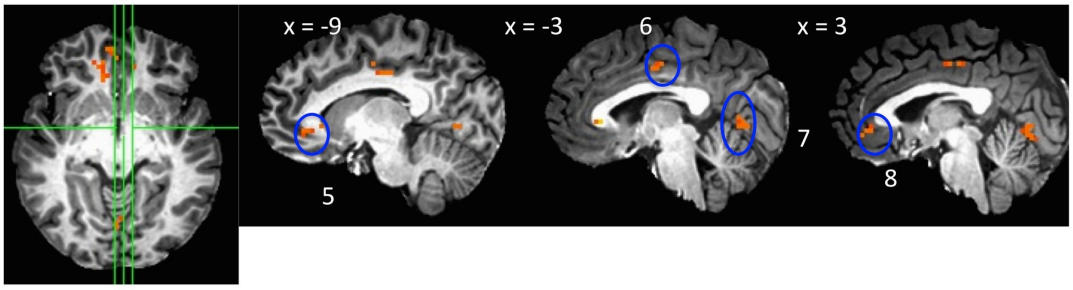


Figure 5: Main effects of metabolic syndrome and taste during hunger. (a) Statistical map of the main effect (F values) of metabolic syndrome (controls > MetS) in left cerebellum(1), right inferior temporal gyrus/BA 20, fusiform gyrus(2), right lentiform nucleus, insula, putamen(3), and left superior temporal gyrus/BA 42, insula(4). (b) Statistical map of the main effect (F values) of taste in the left anterior cingulate (sucrose > caffeine)(5), right paracentral lobule and left cingulate gyrus (caffeine > sucrose)(6), left lingual gyrus (caffeine > sucrose)(7), and right anterior cingulate and Brodmann Area 10 (sucrose > caffeine)(8)

Aim #2: Comparison of fMRI activation of healthy middle-aged adults and middle-aged adults with MetS during pleasantness evaluation of a sweet and bitter taste in satiety condition.

The results of the linear mixed-effects modeling analysis for the satiety condition, including the main effect of MetS, the main effect of taste, and the taste by MetS interaction, are listed in Table 12. Statistical maps of clusters reaching significance are illustrated in Figure 6.

Table 12: Main and interaction effects during satiety. Abbreviations: L = left; R = right, Hem = hemisphere, BA = Brodmann Area.

Direction of Response	Brain Region Activated	Hem	TLRC Coordinates x	y	z	# Voxels	F statistics for maximum intensity voxel
Main Effect of MetS							
Control >MetS							
	Cerebellum (Declive)	L	-4	-67	-13	83	12.29
	Declive	R	7	-66	-14		
	Culmen	L	-11	-54	-16		
	Culmen	R	29	-57	-21		
	Superior Temporal Gyrus/BA 10	R	14	65	14	21	14.53
Main Effect of Taste							
No main effect of taste							
MetS x Taste Interaction							
No interaction							

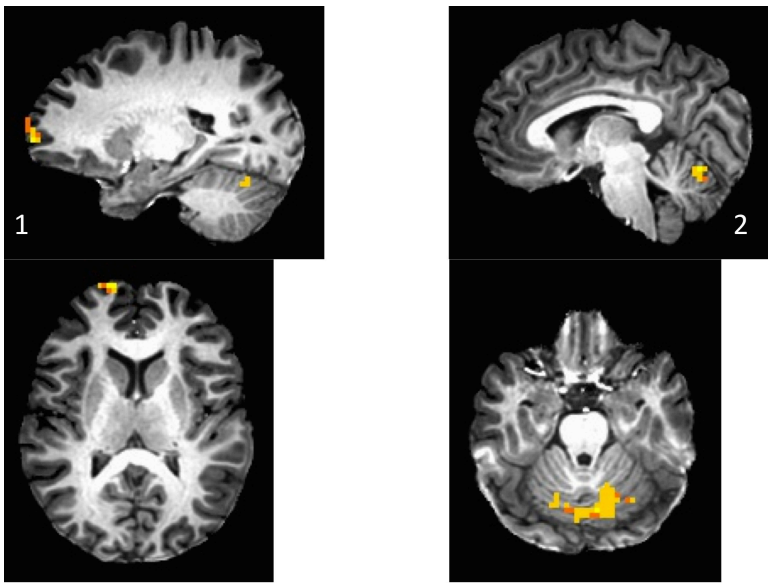


Figure 6: Main effect of metabolic syndrome during satiety. Healthy controls demonstrated greater activation than the group with MetS in the right prefrontal cortex/Brodmann Area 10(1) and Cerebellum(2).

A mixed-model ANOVA was run on mean ROI activation (the fit coefficients) in SPSS with three within-group factors: region (i.e., amygdala, orbitofrontal cortex/BA 11, orbitofrontal cortex/BA 47, insula, and caudate head), taste (caffeine and sucrose), and hunger condition (hunger or satiety); and MetS as the between-group variable. Results of this analysis are displayed in Figure 7. Mauchly's test indicated that the assumption of sphericity had been violated for the Region, ($\chi^2(14) = 58.28$, $p < 0.001$), Taste by Region ($\chi^2(14) = 110.65$, $p < 0.001$), Hunger by Region ($\chi^2(14) = 88.34$, $p < 0.001$), and Taste by Hunger by Region, within-subject effects, ($\chi^2(14) = 113.10$, $p < 0.001$). Therefore, degrees of freedom were corrected using Greenhouse–Geisser estimates of sphericity (εs = 0.41, 0.28, 0.35, and 0.29, respectively). The analysis revealed a significant Hunger by Region interaction, $F(5,110) = 3.45$, $p = 0.047$, partial $\eta^2 = .14$, with no effect of taste stimulus, $F(1,22) = 2.33$, $p = 0.14$, partial $\eta^2 = 0.10$, or MetS, $F(1,22) = 1.57$, $p = 0.22$, partial $\eta^2 = 0.07$.

Newman Keuls post-hoc tests revealed that activation of the medial OFC (see Fig. 8) during the hunger condition (M = 0.44; SE = 0.14) was significantly greater than activation in this region after a nutritional preload (M = − 0.041, SE = 0.14).

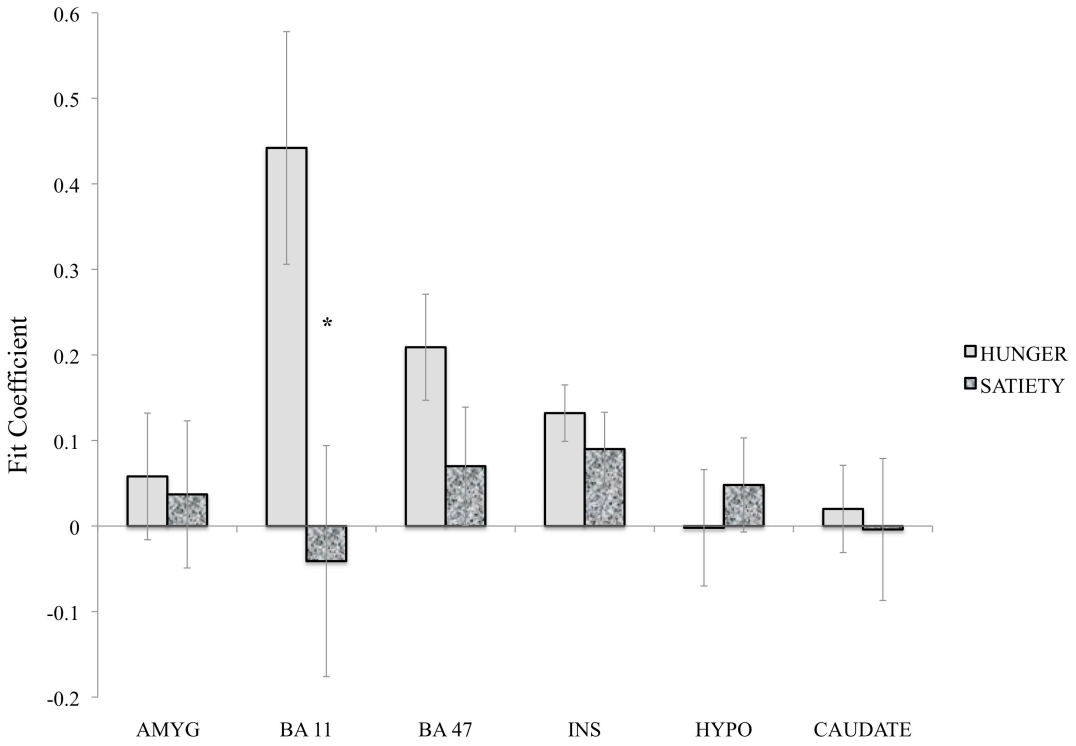


Figure 7: Direct comparison of ROI activation in hunger and satiety conditions. Abbreviations: AMYG = Amygdala, BA 11 = Orbitofrontal Cortex/Brodmann Area 11, BA 47 = Orbitofrontal Cortex/Brodmann Area 47, INS = Insula, HYPO = Hypothalamus. *Activation of the medial OFC, BA11, was significantly greater in the hunger relative to the satiety condition.

Exploratory Analyses

Correlations Between Brain Activation and BMI

Significant correlations between BMI and brain activation in ROIs during pleasantness evaluation of sucrose are listed in Table 13. Positive correlations indicate that increased levels of adiposity are related to increased activation, while negative correlations suggest that increased adiposity is associated with decreased activation.

Table 13: Correlations between body mass index (BMI) and activation in ROIs during pleasantness evaluation of sucrose. Abbreviations: L = left; R = right, BA = Brodmann Area, Hypoth = Hypothalamus.
* Correlation is significant when participants with T2DM are removed from analysis.

		No-Preload	Preload
L	**BA 11**		
R			***r* = -0.41, *p* =.04**
L	**BA 47**		
R			
L	**CAUDATE HEAD**	***r* = 0.39, *p* = .034**	
R		***r* = 0.40, *p* = .028**	
L	**HYPOTH**		***r* = 0.49, *p* = .015**
R		***r* = -0.40, *p* = .033**	

MetS with and without T2DM

A total of 30 participants were included in the first exploratory analysis. One-way ANOVAs revealed no differences between the three groups on age, left and right nostril odor thresholds, taste threshold, height, or mean systolic and diastolic blood pressure measurements (*p*s > 0.05; see Table 14). However, as expected, the groups significantly differed on weight (lbs), body mass index (BMI; kg/m^2), and waist

circumference (cm). Post-hoc analysis using pair-wise comparisons and Bonferroni corrections to control for Type I error revealed that the control group weighed less ($p < 0.001$), had a lower BMI ($p < 0.001$), and smaller waist circumference ($p < 0.001$) than both the MetS and T2DM groups. The MetS and T2DM groups did not differ significantly on any of these measures.

Table 14: Exploratory analysis: Participant demographics, psychophysics, and body measurements

	Mean (SE)					
	Healthy (N=10)	MetS (N=10)	T2DM (N=30)	F	Significance	Partial Eta Squared
Age	57.5 (3.15)	58.7 (2.72)	54.8 (1.93)	0.57	$p = 0.57$	$\eta^2 = 0.040$
Odor Threshold L	6.7 (0.56)	6.8 (0.32)	6.6 (0.34)	0.04	$p = 0.96$	$\eta^2 = 0.003$
Odor Threshold R	5.9 (0.53)	6.7 (0.44)	6.4 (0.63)	0.50	$p = 0.61$	$\eta^2 = 0.037$
Taste Threshold	0.003 (0.001)	0.011 (0.005)	0.004 (0.002)	2.32	$p = 0.12$	$\eta^2 = 0.146$
Height (cm)	169.52 (3.59)	172.6 (3.11)	169.5 (2.94)	0.35	$p = 0.70$	$\eta^2 = 0.026$
Weight (lbs)	160.7 (9.60)	233.2 (12.33)	244.3 (7.58)	20.48	$p < 0.001$	$\eta^2 = 0.603$
BMI (kg/m2)	25.11 (0.82)	35.6 (1.54)	39.2 (1.91)	24.03	$p < 0.001$	$\eta^2 = 0.640$
Waist Circumference (cm)	90.7 (5.06)	116.7 (4.03)	121.2 (2.22)	17.43	$p < 0.001$	$\eta^2 = 0.564$
Systolic Blood Pressure (mmHg)	133.4 (7.44)	141.8 (4.61)	141.2 (6.27)	0.58	$p = 0.58$	$\eta^2 = 0.041$
Diastolic Blood Pressure (mmHg)	72.8 (3.22)	82.2 (4.06)	78.6 (2.18)	2.12	$p = 0.14$	$\eta^2 = 0.136$

In the T2DM group, 4 participants were not taking any medications for diabetes (i.e., controlling with only diet/exercise), 3 participants were taking Metformin alone for diabetes, 2 participants were taking Metformin plus at least one other non-insulin prescription medication for diabetes, and 1 participant was taking Metformin plus insulin. Of the 4 participants who were not taking diabetes

medication at the time of the study, 2 had previously taken Metformin and discontinued the medication at least one year prior to study participation.

Prior to examining brain activation in T2DM, psychophysical ratings of hunger and the intensity and pleasantness of the tastes were also analyzed in order to determine if there were any group differences in psychophysical responses. Mean psychophysical ratings of hunger, intensity, and pleasantness are displayed separately for each group in Tables 15 and 16.

Hunger Ratings

Hunger ratings were examined in both the hunger and satiety conditions using a mixed-model design with group (control, MetS, or T2DM) and time (hunger session: pre- or post-scan; satiety session: prior to consuming the preload, post-preload consumption, and post-scan) as explanatory variables. During the hunger condition, there was no effect of time, $F(1, 26) = 0.39$, $p = 0.54$, partial $\eta^2 = .02$, group, $F(2, 26) = 0.94$, $p = 0.40$, partial $\eta^2 = .07$, or group by time interaction, $F(2, 26) = 0.90$, $p = 0.42$, partial $\eta^2 = .07$, on hunger ratings.

In the satiety condition, Mauchly's test indicated that the assumption of sphericity had been violated for the effect of time, ($\chi^2(2) = 11.12$, $p = 0.004$). Therefore, degrees of freedom for this effect were corrected using the Greenhouse-Geisser estimate of sphericity ($\varepsilon = 0.73$). The analysis revealed no significant main effect of group, $F(2, 25) = 2.31$, $p = 0.12$, partial $\eta^2 = 0.16$, or group by time interaction, $F(2, 25) = 1.59$, $p = 0.22$, partial $\eta^2 = .11$. There was, however, a significant main effect of time/preload on hunger ratings in this condition, $F(2, 25) = 55.92$, $p < 0.001$, partial $\eta^2 = .69$. Newman-Keuls Multiple Range Tests revealed that

participants were significantly less hungry post-preload (M = 3.39, SE = 1.35) and post-scan (M = 8.39, SE = 2.85) when compared to the first hunger rating after the 12-hour fast/prior to consuming the preload (M = 40.29, SE = 4.83). The hunger ratings collected after participants consumed the preload did not differ from each other.

Intensity Ratings

Mean psychophysical ratings of intensity in both sessions over time are displayed in Tables 15 and 16 for caffeine and sucrose. In the hunger condition, there was no main effect of time, $F(1, 27) = 0.25$, $p = 0.62$, partial $\eta^2 = .009$, taste, $F(1, 27) = 1.24$, $p = 0.28$, partial $\eta^2 = .04$. In addition, there were no significant Time by Group, $F(2, 27) = 0.87$, $p = 0.43$, partial $\eta^2 = .06$, Taste by Group $F(1, 28) = 0.33$, $p = 0.57$, partial $\eta^2 = .01$, or Time by Taste by Group, $F(2, 27) = 1.05$, $p = 0.36$, partial $\eta^2 = .07$, interactions. There was a significant effect of Group, $F(1, 27) = 9.59$, $p = 0.001$, partial $\eta^2 = .42$. Specifically, Newman Keuls posthoc tests revealed that the control group (M = 48.58, SE = 4.47) and the T2DM group (M = 45.20, SE = 4.47) rated the tastes as more intense than the MetS group (M = 23.10, SE = 4.47).

During the satiety session, there was no main effect of taste, $F(1, 25) = 0.02$, $p = 0.90$, partial $\eta^2 = 0.001$, or time, $F(2, 25) = 0.86$, $p = 0.43$, partial $\eta^2 = 0.03$. There were also no significant time by group, $F(4, 25) = 0.26$, $p = 0.90$, partial $\eta^2 = 0.02$, taste by group, $F(2, 25) = 0.78$, $p = 0.47$, partial $\eta^2 = 0.06$, time by taste, $(2, 25) = 2.84$, $p = 0.07$, partial $\eta^2 = 0.10$, or time by taste by group, $F(4, 25) = 0.66$, $p = 0.54$, partial $\eta^2 = 0.04$, interactions on intensity ratings. However, there was a significant main effect of group, $F(2, 25) = 4.50$, $p = 0.021$, partial $\eta^2 = 0.27$. Newman Keuls posthoc tests revealed that again, the control group (M = 43.65, SE = 5.20) and the T2DM

group (M = 43.28, SE = 4.65) rated the tastes as more intense than the MetS group (M = 26.07, SE = 4.65).

Pleasantness Ratings

Mean psychophysical ratings of pleasantness in both sessions over time are displayed in Tables 15 and 16 for caffeine and sucrose. In the hunger condition, there were no main effects of time, $F(1, 27) = 1.26$, $p = 0.27$, partial $\eta^2 = 0.05$, or group, $F(2, 27) = 1.12$, $p = 0.34$, partial $\eta^2 = 0.08$. There were also no significant interactions between time and group, $F(2, 27) = 0.47$, $p = 0.63$, partial $\eta^2 = 0.03$, taste and group, $F(2, 27) = 0.62$, $p = 0.55$, partial $\eta^2 = 0.04$, or time by taste by and group, $F(2, 27) = 1.26$, $p = 0.30$, partial $\eta^2 = 0.09$. There was a significant effect of taste on pleasantness ratings, $F(1, 27) = 58.72$, $p < 0.001$, partial $\eta^2 = 0.69$. Specifically, sucrose was rated as more pleasant (M = 58.92, SE = 1.87) than caffeine (M = 37.73, SE = 1.56) controlling for time and group**.**

In the satiety condition, Mauchly's test indicated that the assumption of sphericity had been violated for the interaction between time and taste ($\chi^2(2) = 9.24$, $p = 0.01$) on pleasantness ratings. Therefore, degrees of freedom for the time by group interaction were corrected using the Greenhouse-Geisser estimate of sphericity ($\varepsilon = 0.76$). During the satiety session, there were no main effects of time, $F(2, 25) = 0.53$, $p = 0.56$, partial $\eta^2 = 0.02$, or group, $F(2, 25) = 0.49$, $p = 0.62$, partial $\eta^2 < 0.038$. There were also no significant time by group, $F(4, 25) = 0.63$, $p = 0.62$, partial $\eta^2 = 0.05$, taste by group, $F(2, 25) = 2.42$, $p = 0.11$, partial $\eta^2 = 0.16$, or time by taste by group $F(4, 25) = 1.57$, $p = 0.21$, partial $\eta^2 = 0.11$, interactions. Again, there was a significant effect of taste on pleasantness ratings, $F(1, 25) = 68.78$, $p < 0.001$, partial

$\eta^2 = 0.73$. Specifically, sucrose was rated as more pleasant (M = 57.43, SE = 2.29) than caffeine (M = 34.06, SE = 1.60) controlling for time and group.

Dietary Restraint and Disinhibition

Finally, the Three Factor Eating Questionnaire was given to all participants to determine if there were any group differences on the first (dietary cognitive restraint) or second (disinhibition) factors (Stunkard & Messick, 1985). The result of one-way ANOVAs suggested a significance effect of group on disinhibition, $F(2, 29) = 6.61$, $p < 0.005$, partial $\eta^2 = 0.33$, but not cognitive restraint, $F(2,29) = 1.31$, $p = 0.29$, partial $\eta^2 = 0.85$. Post hoc tests, corrected using a Bonferroni adjustment, revealed that the control group reported significantly lower (M = 4.4, SE = 0.78) disinhibited eating than both the group with MetS (M = 9.40, SE = 1.45) and the group with T2DM (M = 8.90, SE = 0.85; *p*s = 0.006 and 0.003).

Table 15: Exploratory analysis: Psychophysical ratings of hunger and taste (hunger condition).

		Mean (SE)		
		Controls (n=10)	MetS (n=10)	T2DM (n=10)
Hunger Pre-Scan		31.40 (6.99)	29.10 (7.89)	41.30 (7.56)
Hunger Post-Scan		34.89 (7.95)	21.30 (8.54)	35.50 (7.58)
Intensity	Caf Pre-Scan	44.50 (9.23)	20.90 (6.49)	36.60 (6.99)
	Caf Post-Scan	52.00 (7.53)	22.40 (4.38)	43.70 (8.21)
	Suc Pre-Scan	53.40 (5.57)	27.30 (5.96)	46.20 (6.48)
	Suc Post-Scan	44.40 (6.19)	21.80 (3.09)	54.30 (7.92)
Pleasantness	Caf Pre-Scan	40.10 (3.67)	44.30 (1.86)	32.20 (5.26)
	Caf Post-Scan	34.70 (4.54)	38.80 (2.70)	36.30 (3.06)
	Suc Pre-Scan	59.10 (5.67)	61.80 (2.40)	61.00 (4.07)
	Suc Post-Scan	56.70 (3.45)	56.90 (1.81)	58.00 (5.43)

Table 16: Exploratory analysis: Psychophysical ratings of hunger and taste (satiety condition)

		Mean (SE)		
		Controls (n=10)	MetS (n=10)	T2DM (n=10)
Hunger Pre-Preload		43.10 (8.38)	27.90 (7.82)	53.10 (7.88)
Hunger Post-Preload		2.20 (1.99)	0.40 (0.27)	7.50 (3.18)
Hunger Post-Scan		3.22 (2.32)	8.44 (5.93)	13.50 (5.53)
Intensity	Caf Pre-Preload	48.00 (7.62)	23.40 (4.89)	36.00 (8.36)
	Caf Post-Preload	50.50 (8.64)	31.80 (9.95)	47.00 (7.90)
	Caf Post-Scan	48.20 (7.11)	24.00 (4.54)	39.70 (9.52)
	Suc Pre-Preload	38.20 (4.65)	21.80 (3.35)	48.50 (9.42)
	Suc Post-Preload	42.63 (5.71)	22.30 (5.07)	38.50 (6.90)
	Suc Post-Scan	39.10 (3.79)	33.10 (5.46)	50.00 (8.40)
Pleasantness	Caf Pre-Preload	36.30 (4.22)	38.90 (3.07)	29.50 (4.25)
	Caf Post-Preload	32.38 (3.48)	37.20 (3.65)	35.30 (4.09)
	Caf Post-Scan	22.60 (4.06)	41.60 (3.96)	33.00 (4.08)
	Suc Pre-Preload	61.00 (3.53)	53.50 (4.48)	60.50 (5.35)
	Suc Post-Preload	63.50 (2.82)	56.30 (0.68)	54.50 (4.97)
	Suc Post-Scan	59.30 (4.88)	55.60 (3.64)	51.30 (8.19)

Neuroimaging Results

One sample t-tests were run separately for the 3 groups for the caffeine minus water and sucrose minus water conditions. Figures 8 and 9 illustrate significant areas of activation during hunger and satiety conditions in response to pleasantness evaluation of caffeine and sucrose, respectively. See Tables 17-20 for a complete list of regions and Talaraich atlas coordinates for all 3 groups in these conditions.

Table 17: Exploratory analysis: Activation during pleasantness evaluation of caffeine (hunger condition). Abbreviations: Hem = Hemisphere; Tlrc Coord = Talaraich coordinates; Max Int = Maximum intensity; G = Gyrus

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Caffeine During Hunger						
Control						
Cingulate G	R	8	8	35	7993	12.94
Postcentral G	L	-38	-21	51		
Precentral G	L	-37	-10	51		
Medial Frontal G	L	3	-22	51		
Medial Frontal G	L	-4	-6	51		
Precentral G	R	27	-9	51		
Middle Frontal G	L	-31	-4	48		
Paracentral Lobule	L	-11	-24	48		
Postcentral G	R	43	-24	48		
Inferior Parietal Lobule	R	54	-35	48		
Inferior Parietal Lobule	L	-33	-40	45		
Precuneus	R	10	-32	45		
Cingulate G	L	-15	-32	45		
Precuneus	L	-23	-67	42		
Middle Frontal G	R	45	2	39		
Supramarginal G	R	58	-37	33		
Supramarginal G	L	-58	-41	33		
Inferior Frontal G	L	-41	7	30		
Inferior Frontal G	R	45	4	30		
Cuneus	R	31	-73	30		
Cuneus	L	-28	-72	30		
Insula	L	-25	-12	27		
Caudate	R	15	-9	24		
Caudate	L	-18	-17	24		
Lentiform Nucleus	L	-22	3	21		
Caudate Body	L	-14	4	18		
Caudate Body	R	12	3	18		
Thalamus	R	20	-14	18		
Thalamus	L	-12	-18	18		
Insula	R	43	-4	18		
Posterior Cingulate	L	-5	-34	18		
Posterior Cingulate	R	11	-41	18		
Middle Occipital G	R	28	-80	18		
Middle Occipital G	L	-24	-83	18		
Lentiform Nucleus	R	22	-9	15		
Superior Temporal G	L	-49	-50	15		
Pulvinar	R	10	-23	6		
Pulvinar	L	-16	-24	6		
Claustrum	L	-27	11	6		
Middle Temporal G	L	-51	-56	30		
Lingual G	L	-5	-70	3		
Lingual G	L	9	-64	3		
Middle Temporal G	R	42	-60	3		
Insula	L	-40	12	0		
Parahippocampal G	L	-22	-32	-7		
Parahippocampal G	R	31	-30	-7		
Fusiform G	R	40	-59	-7		
Fusiform G	R	-23	-57	-7		
Culmen	R	3	-49	-10		
Culmen	L	-4	-49	-10		
Declive	L	-6	-59	-15		
Declive	R	4	-59	-15		
Precuneus	L	-19	-64	47	203	5.52
Superior Parietal Lobule	L	-15	-64	53		
Superior Parietal Lobule	R	15	-64	53		
Precuneus	R	17	-69	46		
Superior Frontal G	L	-28	50	29	54	5.51

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Caffeine During Hunger						
MetS						
Insula	R	32	20	8	133	5.48
Precentral G	R	37	8	36		
Inferior Frontal G	R	52	4	33		
Claustrum	R	27	11	10		
Brodmann area 47	R	33	17	-6		
Inferior Parietal Lobule	R	31	-34	32	116	4.94
Precuneus	R	11	-58	55		
Angular G	R	30	-53	37		
Postcentral G	R	40	-28	37		
Fusiform G	L	-40	-49	-7	99	4.65
Parahippocampal G	L	-28	-58	-3		
Inferior Temporal G	L	-44	-45	-6		
Middle Occipital G	L	-43	-55	-6		
Lingual G	L	-29	-59	-6		
Declive	L	-27	-51	-14		
Culmen	L	-35	-51	-18		
Lentiform Nucleus	L	-22	-1	14	63	4.79
Claustrum	L	-27	-3	14		
Putamen	L	-27	-3	14		
Insula	L	-43	14	5		
Brodmann area 47	L	-32	17	1		
Inferior Frontal G	L	-30	22	-2		
Lentiform Nucleus	R	25	-6	14	50	5.01
Caudate Body	R	12	6	14		
Putamen	R	23	-6	14		
Fusiform G	R	32	-55	10	48	6.24
Lingual G	R	26	-60	-6		
Culmen	R	19	-48	-12		
Declive	R	16	-62	-12		
Cingulate G	R	5	-16	29	36	4.78
Posterior Cingulate	R	5	-31	24		
Middle Frontal G	L	-40	14	32	31	4.05
Inferior Frontal G	L	-45	5	33		
Middle Temporal G	R	50	-31	2	23	4.67
Superior Temporal G	R	47	-29	3		
Anterior Cingulate	L	-1	29	8	23	-6.06
Anterior Cingulate	R	2	30	12		
Posterior Cingulate	R	11	-52	11	23	5.2

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Caffeine During Hunger						
T2DM						
No Significant Clusters						

Table 18: Exploratory analysis: Activation during pleasantness evaluation of caffeine (satiety condition). Abbreviations: Hem = Hemisphere; Tlrc Coord = Talaraich coordinates; Max Int = Maximum intensity; G = Gyrus

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Caffeine During Satiety						
Control						
Precentral Gyrus	R	29	-9	50		
Precentral G	R	29	-9	50		
Precuneus	R	21	-66	50		
Paracentral Lobule	L	-5	-19	45		
Paracentral Lobule	R	6	-19	45		
Postcentral G	R	53	-18	45		
Supramarginal G	R	31	-47	38		
Middle Frontal G	R	49	10	38		
Cingulate G	R	12	-30	35		
Cingulate G	L	-9	-27	35		
Inferior Frontal G	R	43	4	32		
Precuneus	L	-27	-66	32		
Superior Occipital G	R	32	-76	27		
Caudate Body	R	16	-9	24		
Caudate Body	L	-16	-6	24		
Posterior Cingulate	R	2	-46	24		
Posterior Cingulate	L	-1	-48	24		
Brodmann area 10	R	32	47	24		
Thalamus	L	-14	-17	18		
Thalamus	R	11	-15	18		
Claustrum	R	28	0	18		
Lentiform Nucleus	L	-22	2	18		
Lentiform Nucleus	R	24	0	18		
Putamen	R	24	0	18		
Insula	R	35	-7	18		
Cuneus	R	23	-81	18		
Cuneus	L	-23	-83	18		
Middle Occipital G	R	29	-77	15		
Middle Occipital G	L	-26	-78	15		
Caudate Head	L	-8	4	5		
Middle Temporal G	L	45	-55	1		
Parahippocampal G	R	32	-44	-7		
Fusiform G	L	-34	-59	-7		
Fusiform G	R	37	-59	-7		
Lingual G	R	14	-84	-7		
Lingual G	L	-16	-78	-7		
Declive	R	2	-67	-12		
Declive	L	-8	-66	-12		
Inferior Frontal G	L	-40	8	32	476	7.31
Postcentral G	L	-40	-19	48		
Inferior Parietal Lobule	L	-43	-36	48		
Precentral G	L	-32	-22	48		
Middle Frontal G	L	-40	5	42		
Inferior Frontal G	L	-53	9	24		
Middle Frontal G	L	-43	41	17	226	7.69
Brodmann area 10	L	-38	39	14		
Insula	L	-34	17	14		
Brodmann area 47	L	-39	22	1		
Middle Frontal G	L	-34	29	44	33	4.62
Superior Frontal G	L	-35	40	33		
Parahippocampal G	R	26	-4	-10	29	5.35
Amygdala	R	26	-4	-10		
Insula	R	39	-10	-4		
Lentiform Nucleus	R	22	-4	-4		
Cerebellar Tonsil	R	8	-52	-31	28	4.12
Cerebellar Tonsil	L	-3	-57	-31		
Inferior Parietal Lobule	R	47	-39	53	28	3.61
Superior Temporal G	L	-58	-25	5	24	5.44
Middle Temporal G	L	-63	-38	4		

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Caffeine During Satiety						
MetS						
Middle Frontal Gyrus	L	-46	0	41		
Middle Frontal G	L	-46	0	41		
Precentral G	L	-48	-2	38		
Inferior Frontal G	L	-56	10	28		
Insula	L	-39	16	11		
Caudate	L	-19	12	11		
Lentiform Nucleus	L	-17	8	6		
Putamen	L	-23	13	6		
Inferior Frontal G	R	44	17	11	214	6.49
Middle Frontal G	R	52	15	36		
Superior Frontal G	R	29	42	32		
Insula	R	34	23	17		
Brodmann area 10	R	43	40	12		
Brodmann area 47	R	44	17	2		
Postcentral G	R	41	-22	41	169	5.23
Inferior Parietal Lobule	R	45	-36	45		
Precentral G	R	53	-5	40		
Cuneus	R	28	-72	29	142	4.13
Inferior Parietal Lobule	R	36	-48	45		
Precuneus	R	32	-66	38		
Angular G	R	36	-67	32		
Superior Occipital G	R	31	-75	30		
Middle Occipital G	R	31	-72	10		
Inferior Parietal Lobule	L	-37	-37	44	77	4.6
Postcentral G	L	-49	-23	46		
Medial Frontal G	L	-4	26	38	64	5.13
Medial Frontal G	R	6	28	38		
Cingulate G	R	12	15	38		
Cingulate G	L	-3	22	35		
Anterior Cingulate	R	14	28	25		
Anterior Cingulate	L	-4	25	25		
Middle Frontal G	L	-34	38	23	63	4.61
Superior Frontal G	L	-29	40	31		
Brodmann area 10	L	-33	42	23		

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Caffeine During Satiety						
T2DM						
Thalamus	L	-21	-18	20		
Thalamus	L	-21	-18	20		
Claustrum	L	-26	-13	17		
Lentiform Nucleus	L	-23	-5	14		
Putamen	L	-23	-6	11		
Precentral G	L	-49	2	26	32	4.31
Inferior Frontal G	L	-50	3	25		
Insula	L	-44	-7	14		
Thalamus	R	14	-7	14	27	5.83
Caudate Body	R	19	-4	19		
Lentiform Nucleus	R	19	-3	16		

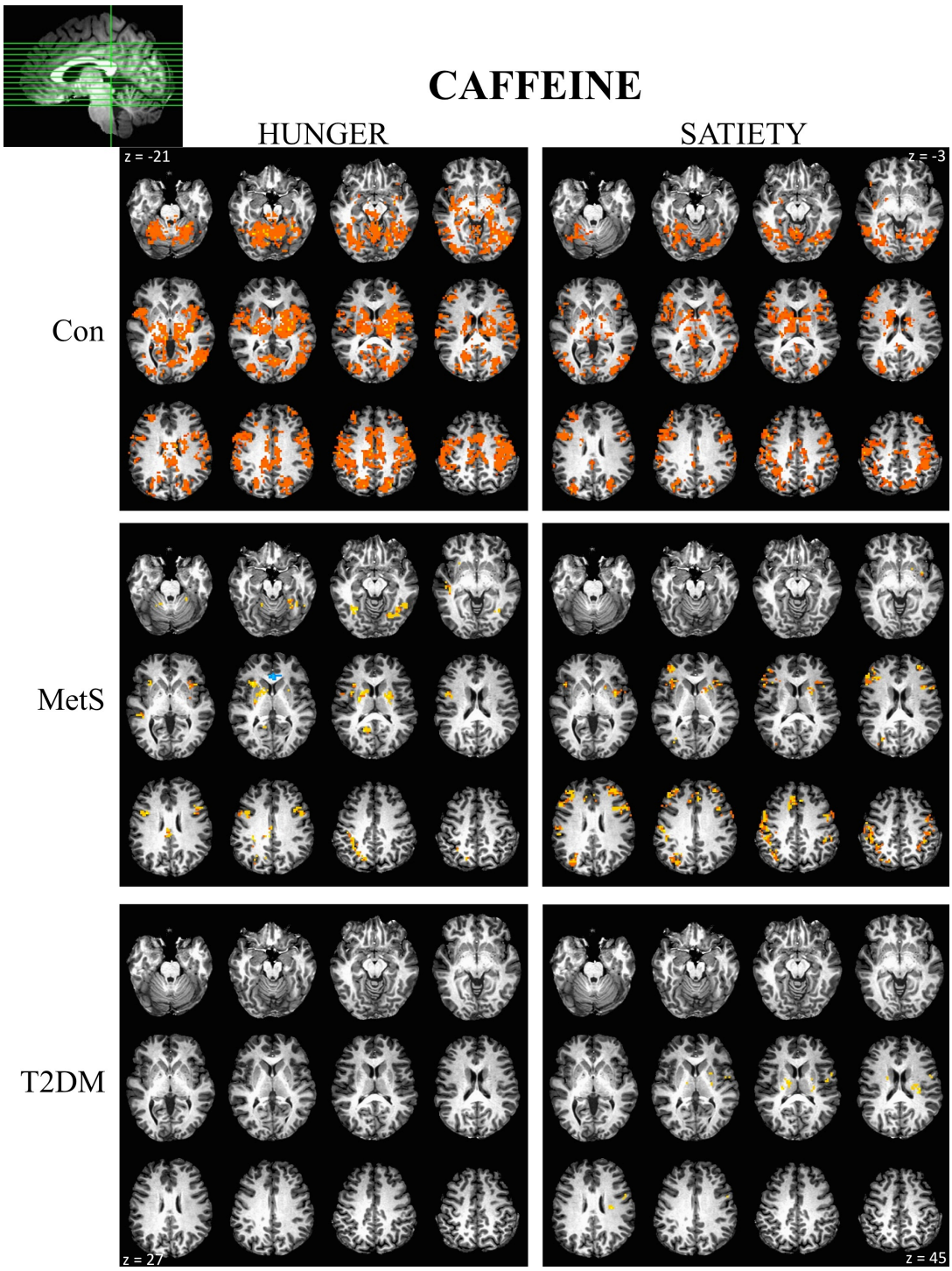


Figure 8: Exploratory Analysis: Activation During Pleasantness Evaluation of Caffeine. Abbreviations: Con = healthy control group; MetS = group with metabolic syndrome but no diabetes; T2DM = type II diabetes mellitus.

Table 19: Exploratory analysis: Activation during pleasantness evaluation of sucrose (hunger condition)

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Sucrose During Hunger						
Control						
Declive	R	35	-58	-22	1653	8.41
Middle Frontal G	R	26	-7	49		
Postcentral G	R	54	-23	45		
Inferior Parietal Lobule	R	33	-47	41		
Precuneus	R	25	-65	41		
Supramarginal G	R	31	-49	37		
Precentral G	R	57	-4	32		
Superior Occipital G	R	32	-75	28		
Inferior Frontal G	R	54	4	21		
Middle Temporal G	R	31	-71	21		
Insula	R	46	-20	15		
Middle Occipital G	R	35	-79	7		
Lingual G	R	17	-90	-3		
Inferior Occipital G	R	31	-85	-3		
Fusiform G	R	37	-56	-9		
Culmen	R	3	-60	-9		
Culmen	L	-3	-59	-9		
Nodule	R	8	-61	-24		
Middle Occipital G	L	-28	-85	14	1184	9.09
Postcentral G	L	-42	-21	51		
Inferior Parietal Lobule	L	-37	-47	51		
Precuneus	L	-19	-64	51		
Superior Parietal Lobule	L	-24	-64	46		
Cingulate G	L	-13	-29	42		
Cuneus	L	-26	-70	29		
Inferior Frontal G	L	-54	5	20		
Middle Temporal G	L	-48	-65	4		
Inferior Temporal G	L	-45	-68	0		
Inferior Occipital G	L	-40	-77	-5		
Fusiform G	L	-37	-59	-10		
Lingual G	L	-24	-79	-10		
Declive	L	-36	-59	-16		
Thalamus	L	-16	-22	8	78	7.15
Superior Parietal Lobule	L	26	-61	47	66	6.97
Precuneus	L	10	-55	51		
Cingulate G	R	2	-31	26	50	6.04
Cingulate G	L	-5	-36	31		
Posterior Cingulate	R	10	-41	19		
Paracentral Lobule	L	-10	-25	44	43	4.98
Medial Frontal G	L	-1	-16	53		
Precuneus	R	17	-55	23	40	6.25
Posterior Cingulate	R	11	-57	19		
Thalamus	R	8	-13	5	32	4.6
Caudate Body	R	11	5	14	24	4.69
Cingulate G	L	-4	-7	29	22	4.65
Medial Frontal G	R	2	5	47	22	4.28
Medial Frontal G	L	-1	10	47		

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Sucrose During Hunger						
MetS						
Caudate Body	L	-13	8	11	903	22.18
Middle Frontal G	L	-45	5	39		
Precentral G	L	-32	7	36		
Inferior Frontal G	L	-42	7	32		
Postcentral G	L	-43	-10	23		
Insula	L	-41	-12	20		
Lentiform Nucleus	L	-19	4	14		
Putamen	L	-19	4	14		
Claustrum	L	-25	21	11		
Thalamus	L	-10	-16	5		
Caudate Head	L	-16	19	5		
Culmen	R	26	-49	-13	232	5.9
Middle Temporal G	L	-48	-53	-4		
Lingual G	L	-30	-60	-4		
Fusiform G	L	-23	-60	-7		
Declive	L	-20	-59	-13		
Culmen	L	-28	-48	-13		
Fusiform G	R	32	-47	-13		
Culmen	R	12	-50	-16		
Supramarginal G	R	30	-51	35	110	3.11
Precuneus	R	17	-65	43		
Inferior Parietal Lobule	R	36	-38	38		
Middle Temporal G	R	31	-59	31		
Cuneus	R	28	-71	31		
Inferior Frontal G	R	56	5	29	52	4.57
Precentral G	R	52	-4	40		
Postcentral G	R	57	-15	29		
Lingual G	R	17	-73	-7	45	4.57
Middle Occipital G	R	31	-72	11		
Anterior Cingulate	R	17	35	20	39	3.94
Middle Frontal G	R	34	48	20		
Medial Frontal G	R	19	43	17		
Superior Frontal G	R	34	49	17		
Medial Frontal G	L	-1	47	20	36	5.16
Superior Frontal G	L	-10	51	26		
Medial Frontal G	R	1	49	23		
Brodmann area 10	R	9	49	10		
Anterior Cingulate	R	20	29	26	34	5.46
Cingulate G	R	11	31	29		
Middle Frontal G	R	27	34	26		
Precuneus	L	-13	-73	38	28	4.03
Cingulate G	R	11	11	35	24	5.94

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Sucrose During Hunger						
T2DM						
Cingulate G	R	8	8	38	39	4.56
Cingulate G	L	-7	14	35	39	5.01
Medial Frontal G	R	2	27	36		

Table 20: Exploratory analysis: Activation during pleasantness evaluation of sucrose (satiety condition). Abbreviations: Hem = Hemisphere; Tlrc Coord = Talaraich coordinates; Max Int = Maximum intensity; G = Gyrus.

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Sucrose During Satiety						
Control						
Postcentral G	L	-46	-22	44	103	9.39
Inferior Parietal Lobule	L	-41	-33	45		
Superior Occipital G	R	35	-76	26	74	5.26
Cuneus	R	27	-76	26		
Middle Temporal G	R	32	-72	23		
Middle Occipital G	R	30	-83	19		
Culmen	R	17	-55	-16	65	4.88
Declive	R	25	-64	-14		
Middle Occipital G	L	-31	-76	14	54	6.05
Precentral G	L	-58	5	29	51	6.18
Middle Frontal G	L	-49	5	39		
Inferior Frontal G	L	-51	9	31		
Middle Occipital G	L	-49	-64	-4	28	4.57
Inferior Temporal G	L	-46	-66	-2		
Superior Frontal G	L	-1	11	50	21	5.64
Superior Frontal G	R	3	11	50		
Medial Frontal G	R	6	17	46		
Medial Frontal G	L	-4	17	46		

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Sucrose During Satiety						
MetS						
Postcentral G	L	-49	-19	20	463	7.11
Middle Frontal G	L	-47	2	42		
Precentral G	L	-47	-1	39		
Brodmann area 9	L	-47	8	36		
Inferior Frontal G	L	-40	8	33		
Superior Frontal G	L	-25	33	30		
Inferior Parietal Lobule	L	-39	-39	24		
Caudate	L	-19	-7	24		
Insula	L	-32	11	21		
Lentiform Nucleus	L	-22	5	21		
Brodmann area 13	L	-35	-10	21		
Superior Temporal G	L	-60	-44	21		
Caudate Body	L	-11	7	18		
Thalamus	L	-16	-10	18		
Putamen	L	-24	1	18		
Claustrum	L	-25	8	18		
Lateral Globus Pallidus	L	-16	0	9		
Ventral Lateral Nucleus	L	-16	-10	9		
Ventral Posterior Latera	L	-16	-17	6		
Medial Dorsal Nucleus	L	-10	-20	6		
Pulvinar	L	-10	-22	6		
Mammillary Body	L	-10	-17	0		
Culmen	R	29	-46	-25	238	6.24
Thalamus	R	8	-25	-6		
Substanntia Nigra	R	11	-22	-9		
Culmen	L	-7	-29	-18		
Dentate	R	14	-47	-18		
Declive	R	14	-57	-18		
Dentate	L	-12	-53	-18		
Declive	L	-17	-57	-18		
Fastigium	R	5	-51	-24		
Nodule	R	7	-54	-24		
Pyramis	R	7	-65	-24		
Nodule	L	-4	-56	-24		
Fastigium	L	-8	-56	-24		
Cerebellar Tonsil	R	22	-41	-27		
Postcentral G	R	44	-28	35	124	6.41
Precentral G	R	46	-4	48		
Inferior Parietal Lobule	R	43	-28	42		
Brodmann area 40	R	43	-28	42		
Middle Frontal G	R	31	-16	39		
Middle Occipital G	R	41	-61	-7	79	4.56
Middle Temporal G	R	53	-62	3		
Lingual G	R	24	-80	3		
Inferior Temporal G	R	40	-65	0		
Fusiform G	R	39	-59	-3		
Inferior Occipital G	R	40	-67	-3		
Middle Occipital G	L	-40	-61	-7	51	6.15
Middle Temporal G	L	-53	-65	6		
Inferior Temporal G	L	-53	-68	0		
Parahippocampal G	L	-38	-51	-3		
Fusiform G	L	-38	-52	-3		

Region	Hem.	Tlrc Coord			# Voxels	Max. Int.
		x	y	z		
Sucrose During Satiety						
T2DM						
No clusters found						

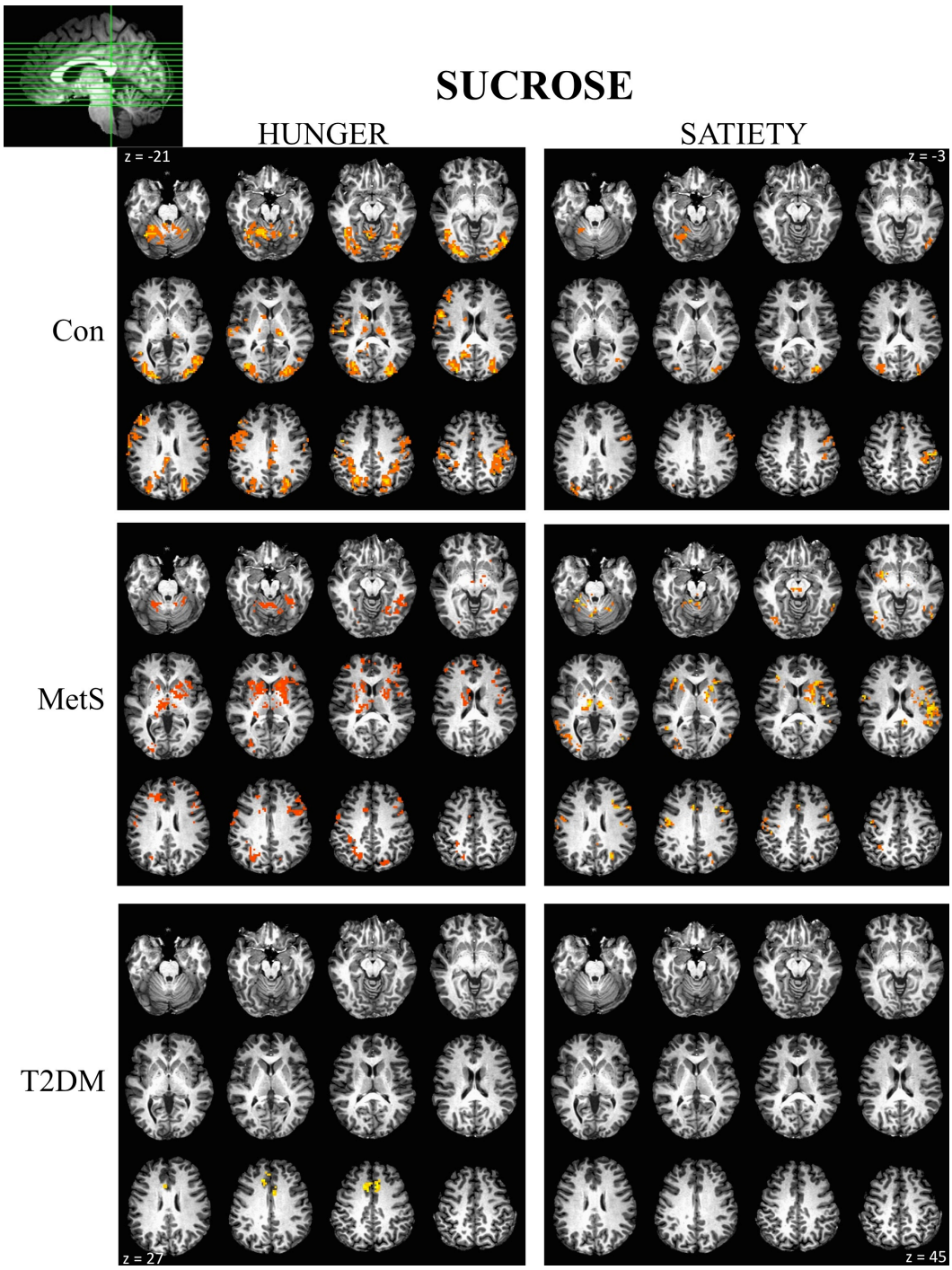


Figure 9: Exploratory analysis: Activation during pleasantness evaluation of sucrose. Abbreviations: Con = healthy control group; MetS = group with metabolic syndrome but no diabetes; T2DM = type II diabetes mellitus.

Two mixed-model ANOVAs were run on brain activation in the hunger and satiety conditions, respectively in order to investigate the effect of T2DM on brain activation in middle-aged adults and older adults without MetS, with MetS but no T2DM, and with MetS and a diagnosis of T2DM. Clusters of activation reaching significance for main effect of group, taste, and the group by taste interactions are listed in Table 21 for the hunger and Table 22 for the satiety conditions. Data from clusters reaching significance for the group by taste interaction were extracted and plotted in Figures 10 and 11.

Table 21: Exploratory analysis: Main and interaction effects during hunger. Abbreviations: L = left; R = right, Hem = hemisphere, BA = Brodmann Area.

Direction of Response	Brain Region Activated	Hem	TLRC Coordinates			# Voxels	F statistics for maximum intensity voxel
			x	y	z		
Main Effect of Group							
	Insula	L	-32	-22	11	99	11.25
	Superior Temporal Gyrus	L	-49	-27	7		
	Insula	R	44	-7	-1	84	
	Precentral Gyrus	R	48	-5	8		
	Superior Temporal Gyrus	R	47	-28	2	63	11.63
	Declive	L	-19	-58	-10	53	
	Culmen	L	-13	-61	-10		
	Fusiform Gyrus	R	41	-55	-7	44	10.01
	Parahippocampal Gyrus	R	26	-37	-1	33	9.22
	Cingulate Gyrus	L	-1	-25	41	28	9.07
	Cingulate Gyrus	R	6	-19	41		
	Parahippocampal Gyrus	R	11	-31	-1	25	11.69
Main Effect of Taste							
Caffeine > Sucrose							
	Lingual Gyrus	L	-19	-61	-7	466	36.1
	Lingual Gyrus	R	12	-54	-1		
	Parahippocampal Gyrus	R	28	-41	-4		
	Culmen	L	-8	-46	2		
	Culmen	R	18	-60	-7		
	Inferior Parietal Lobule	R	53	-28	26	181	34.51
	Postcentral Gyrus	R	60	-26	20		
	Caudate	R	23	-19	23	57	20.9
	Lentiform Nucleus/Putamen	R	23	-4	11		
	Cingulate Gyrus	L	-13	-22	38	54	16.42
	Cingulate Gyrus	R	7	-22	38		
	Inferior Temporal Gyrus	L	-46	-7	-19	50	20.62
	Insula	R	41	11	14	42	13.59
	Precentral Gyrus	R	50	5	8		
	Cingulate Gyrus	L	-1	11	35	41	20.82
	Parahippocampal Gyrus	R	29	-7	-25	27	23.97
	Middle Temporal Gyrus	R	59	-55	-2	26	16.35
	Parahippocampal Gyrus	R	29	-7	-25	25	24.41
	Inferior Frontal Gyrus	L	-55	20	5	23	17.91
	Thalamus	R	11	-16	8	21	25.28
Sucrose > Caffeine							
	Precentral Gyrus	L	-31	-25	50	25	16.09
	Postcentral Gyrus	L	-48	-27	50		
Group x Taste Interaction							
	Cingulate Gyrus	R	14	14	35	151	19.61
	Cingulate Gyrus	L	-7	13	37		
	Anterior Cingulate	R	8	33	22		
	Lentiform Nucleus/Putamen	R	29	-7	14	122	11.95
	Insula	R	38	-1	8		
	Caudate	R	35	-31	-4	83	13.79
	Parahippocampal Gyrus/Hippocampus	R	31	-30	-5		
	Lingual Gyrus	L	-19	-61	-7	67	14.91
	Fusiform Gyrus	L	-23	-56	-7		
	Culmen	L	-12	-61	-7		
	Thalamus	R	11	-16	8	37	16.48
	Insula	L	-28	-25	14	28	11.28
	Posterior Cingulate	R	8	-67	11	25	9.61
	Posterior Cingulate	L	-14	-62	11		

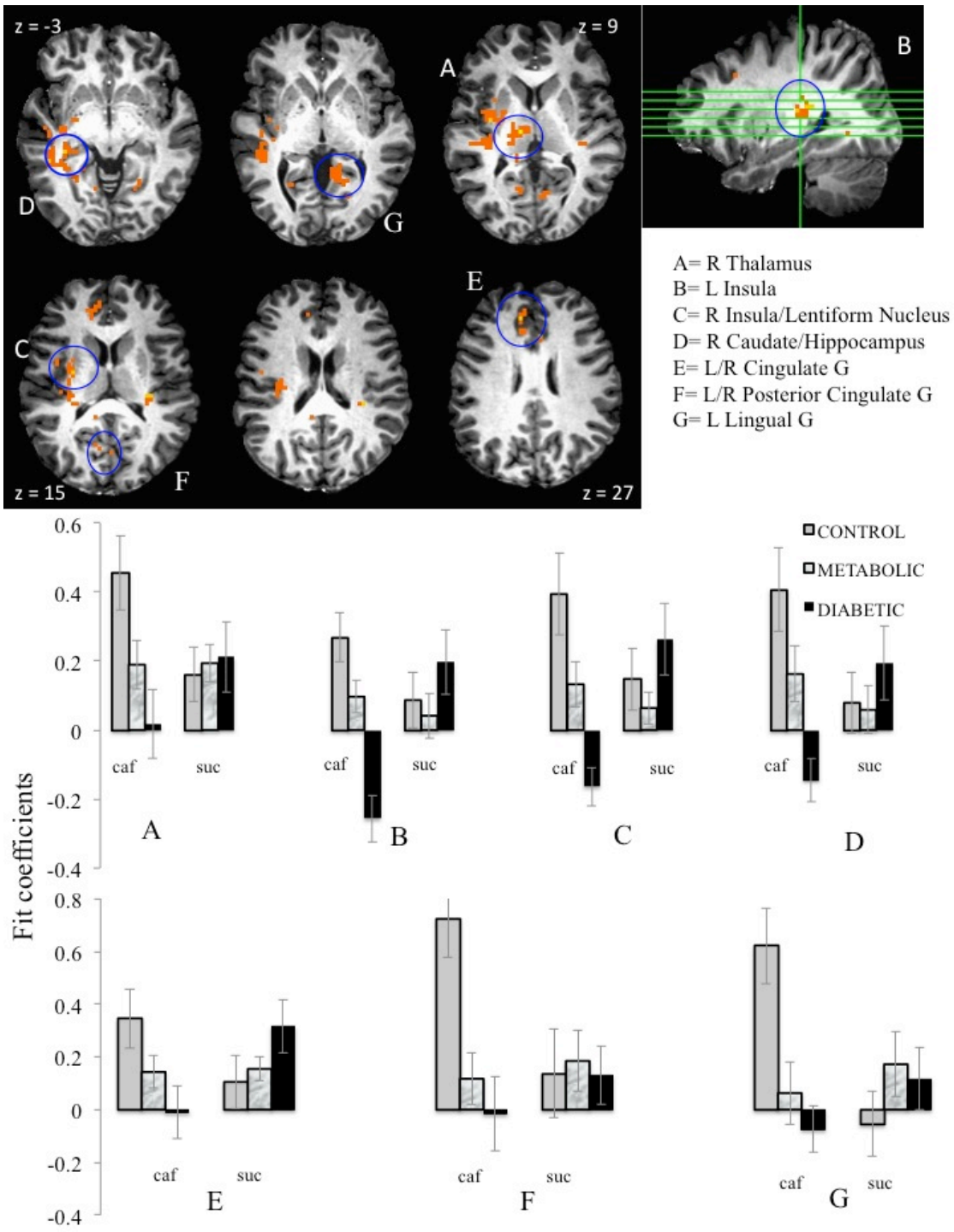


Figure 10: Exploratory analysis: Group by taste interaction effects during hunger. Abbreviations: caf = caffeine; suc = sucrose; L = left; R = right; G = gyrus

Table 22: Exploratory analysis: Main and interaction effects during satiety. Abbreviations: L = left; R = right, Hem = hemisphere, BA = Brodmann Area.

Direction of Response	Brain Region Activated	Hem	TLRC Coordinates			# Voxels	F statistics for maximum intensity voxel
			x	y	z		
Main Effect of Group							
	Medial Frontal Gyrus/BA 8	R	8	35	38	96	8.4
Main Effect of Taste							
Caffeine > Sucrose							
	Inferior Parietal Lobule	R	65	-37	35	169	25.88
	Inferior Parietal Lobule	L	-58	-43	41	107	24.75
	Middle Temporal Gyrus	R	56	-46	-4	59	19.04
	Cerebellum	R	2	-64	-34	49	20.35
	Precuneus	L	-4	-73	44	49	20.55
	Middle Frontal Gyrus/BA 6	R	44	2	41	35	18.27
	Cerebellar Tonsil	L	-16	-52	-43	32	9.3
	Superior Parietal Lobule	L	-25	-64	62	30	15.16
	Middle Temporal Gyrus	L	-46	-52	8	23	15.6
Sucrose > Caffeine							
	Cerebellar Tonsil	L	-13	-43	-34	23	15.08
Group x Taste Interaction							
	Postcentral Gyrus	L	-43	-16	29	114	10.6
	Insula	L	-31	-16	17		

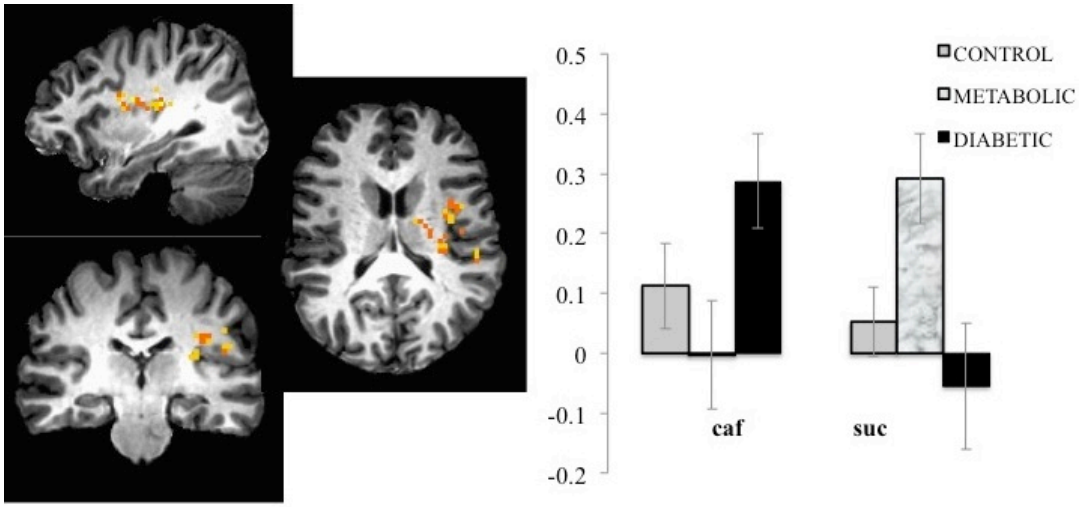


Figure 11: Exploratory analysis: Group by taste interaction effect in the left postcentral gyrus/insula during satiety.

ROI Analysis

A mixed-model ANOVA was run on mean ROI activation (the fit coefficients) in SPSS with three within-group factors: region (i.e., amygdala, orbitofrontal cortex/BA 11, orbitofrontal cortex/BA 47, insula, and caudate head), taste (caffeine and sucrose), and hunger condition (hunger or satiety); and Group (control, MetS, and T2DM) as the between-group variable. Mauchly's test indicated that the assumption of sphericity had been violated for the Region, ($\chi^2(14) = 38.91$, $p < 0.001$), Taste by Region ($\chi^2(14) = 87.98$, $p < 0.001$), Hunger by Region ($\chi^2(14) = 74.52$, $p < 0.001$), and Taste by Hunger by Region, within-subject effects, ($\chi^2(14) = 98.61$, $p < 0.001$). Therefore, degrees of freedom were corrected using Greenhouse–Geisser estimates of sphericity (εs = 0.48, 0.28, 0.36, and 0.28, respectively). The analysis revealed a significant main effect of taste, $F(1,19) = 4.39$, $p = .05$, partial $\eta^2 = .19$, and a significant Hunger by Region interaction, $F(5, 95) = 3.26$, $p = .032$, partial $\eta^2 = .17$, with no effect of Group, Hunger, or Region (ps > 0.05). Across all regions, the caffeine stimulus elicited greater activation (M = 0.178, SE = .05) than the sucrose stimulus (M = 0.058, SE = .07). There were also no significant Region by Group, Taste by Group, Hunger by Group, Region by Taste, Region by Taste by Group, Region by Hunger by Group, Taste by Hunger by Group, Region by Taste by Hunger, or Region by Taste by Hunger by Group interactions (ps > 0.05). Newman Keuls post-hoc tests revealed that activation of the medial OFC (see Fig. 12) during the hunger condition (M = 0.46; SE = 0.18) was significantly greater than activation in this region after a nutritional preload (M = − 0.16, SE = 0.15).

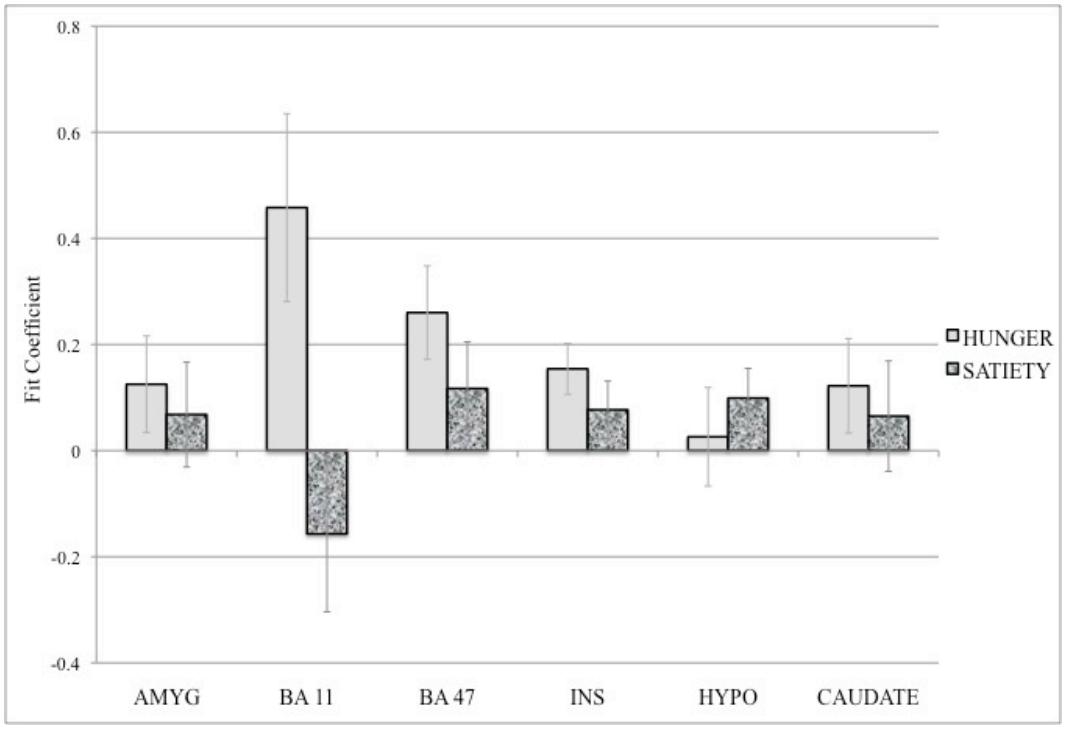


Figure 12: Exploratory analysis: Direct comparison of ROI activation in hunger and satiety conditions. Abbreviations: AMYG = Amygdala, BA 11 = Brodmann Area 11, BA 47 = Orbitofrontal Cortex/Brodmann Area 47, INS = Insula, HYPO = Hypothalamus. *Activation of the medial OFC, BA11, was significantly greater in the hunger relative to the satiety condition.

Chapter 3, in part, is currently being prepared for submission for publication of the material. Green, E; Jacobson, A; Haase, L; Murphy, C. The dissertation author was the primary investigator and author of this material.

IV. DISCUSSION

The overall objective of the study was to investigate potential differences in brain response according to metabolic status during pleasantness evaluation of sweet and bitter tastes during the physiological states of hunger and satiety. Previous studies suggest that an altered response in reward-related brain regions may underlie disordered eating and obesity (Green et al., 2011; Stice, Spoor, Bohon, & Small, 2008). However, this phenomenon has not yet been explored in the subset of obese individuals with multiple vascular and metabolic risk factors. This has also not been investigated in individuals between young and older adulthood, a time of life when obesity and other vascular risk factors may play a crucial role in late life health outcomes.

Initial statistical analyses were run on psychophysical responses of participants during the scanning sessions, to determine if there were any group differences in subjective ratings of hunger, or taste intensity/pleasantness that might affect interpretation of imaging data. There were no effects of MetS on psychophysical ratings of hunger, intensity, and pleasantness. The 700 kcal nutritional preload decreased participants' hunger ratings to nearly zero, indicating that the meal was effective at inducing satiety. As expected, all participants rated the sweet sucrose stimulus as pleasant and all participants rated the bitter caffeine stimulus as unpleasant on the gLMS.

Effect of MetS on Brain Activation During Hunger and Satiety

Brain activation during pleasantness evaluation of taste in the hunger condition was greater in the middle-aged control group relative to the group with MetS in brain

regions involved with sensory processing of taste information (pre- and postcentral gyri, insula), and reward value (lentiform nucleus, putamen). The latter regions are part of the basal ganglia complex that receive dopaminergic projections from midbrain nuclei and are involved in higher-level processing of gustatory information. Dopamine modulates the experience of reward, and decreased dopamine efficiency has been implicated in overeating (Wang et al., 2009). The current results might suggest decreased reward processing in the group with MetS during the physiological state of hunger. However, the effect is significant when averaged over the pleasant and unpleasant tastes, rendering interpretation in the context of reward processing complicated.

A main effect of MetS was also demonstrated in the fusiform gyrus. The fusiform gyrus is consistently activated using the present study's paradigm (Haase et al., 2009; Haase et al., 2011; Jacobson et al., 2010), in response to visual food cues (Frank et al., 2010; Heni et al., 2013; Killgore & Yurgelun-Todd, 2007; Siep et al., 2009; van der Laan, de Ridder, Viergever, & Smeets, 2011), and is often discussed as aiding the visual system in discrimination of high from low calorie foods. Additionally, activation of this region is amplified after intranasal insulin administration (Guthoff et al., 2010), and reduced in obese individuals (Frank et al., 2013), and structural differences according to BMI have also been reported (Yokum, Ng, & Stice, 2012), suggesting altered processing of food stimuli in this region in obese and insulin-resistant individuals.

An anterior, lower portion of Brodmann Area 10, part of the frontopolar prefrontal cortex was activated to a greater degree in the control group relative to the

MetS group after a preload. Abnormalities in prefrontal gray matter volumes in obese individuals have been reported, but results are difficult to interpret; both positive (Taki et al., 2008), and negative associations (Pannacciulli et al., 2006) have been documented. Baseline metabolic activity in BA 10 is reduced in obese individuals (Volkow et al., 2009), and it has been posited that this might reflect reduced dopamine activity.

Brodmann Area 10 comprises the most anterior portion of the frontal lobe, and its functions are poorly understood, although it is considered to represent the highest level of abstract cognition in the human brain (Ramnani & Owen, 2004). One theory of BA 10 function implicates the region in the selection and maintenance of abstract internal goals while other goals are being performed (Badre & D'Esposito, 2007; Burgess, Dumontheil, & Gilbert, 2007; Gilbert, Frith, & Burgess, 2005; Koechlin & Summerfield, 2007) and in monitoring of internal states and stimuli (Christoff & Gabrieli, 2000). The task of rating the pleasantness of the stimuli in the current study requires a participant to sense the taste and note any characteristics relevant to determining its pleasantness (quality, intensity, learned associations, etc.) prior to the motor task of using a joystick to record their pleasantness judgment. During the satiety condition, participants may take into consideration his or her current physiological state (i.e., not intrinsically motivated to consume energy) when judging the pleasantness of the tastes. Greater activation of BA 10 in the control group may suggest that this population utilizes more cognitive resources involved in integrating internal information (including his or her current state of energy balance) in making hedonic judgments. A group more attune to this information might be more successful

in refraining from emotional eating in the absence of physiological hunger, which would have implications for the success of weight management.

During both physiological conditions, there was less activation of the cerebellum in the group with MetS compared to the healthy control group. Although considered to be mainly involved in motor function, there is also a body of research implicating the cerebellum as playing a key role in autonomic function, including food intake and energy homeostasis (Cavdar et al., 2001; Dietrichs, 1984; Wen et al., 2004; Zhu & Wang, 2008; Zhu et al., 2004). Anatomically, there are direct bidirectional connections between the cerebellum and the hypothalamus (Cavdar et al., 2001; Dietrichs, 1984; Dietrichs & Haines, 1984; Dietrichs, Wiklund, & Haines, 1992); cerebellohypothalamic projections arise from all cerebellar nuclei and terminate in hypothalamic nuclei well known for modulating feeding behavior (i.e,. lateral hypothalamic nuclei, dorsal medial nucleus, ventromedial nucleus, and periventricular nuclei). Additionally, there are indirect cerebellar-hypothalamic connections via taste/feeding and higher-order emotion/limbic regions (e.g., nucleus of the solitary tract, amygdala, neocortex). It is hypothesized that the cerebellar nuclei may influence caloric intake via connections with the hypothalamic nuclei mentioned above (Zhu & Wang, 2008; Zhu et al., 2004).

The cerebellum is consistently activated in response to taste and olfactory stimuli (Cerf-Ducastel et al., 2012; Cerf-Ducastel & Murphy, 2001; Haase et al., 2009; Jacobson et al., 2010; Sobel et al., 1998) and activation to food-related stimuli is modulated by hunger (Gautier et al., 2001; Haase et al., 2009; Haase et al., 2011; Liu, Gao, Liu, & Fox, 2000; Tataranni et al., 1999). Leptin receptors are densely expressed

in the cerebellum (Burguera et al., 2000) and leptin replacement therapy alters the BOLD response within the posterior cerebellum, further implicating this region in the regulation of food intake. Interestingly, the decrease in regional cerebral blood flow from hunger to satiety in the cerebellum is greater in obese relative to lean men (Gautier et al., 2000). The current study adds to a growing body of literature suggesting altered activity of the cerebellum during hunger and satiety in individuals with differing levels of adiposity.

Exploratory analyses were run in an effort to account for any within-group variance that might have affected the power to detect group differences in an ANOVA design. First, associations between adiposity and brain response during pleasantness evaluation of the sweet tastes were explored. In another exploratory analysis, the participants with T2DM were compared with both a healthy control group and a group with MetS, but no diabetes.

Exploratory Analyses: Relationships between BMI and Activation of ROIs

A previous study using fMRI during pleasantness evaluation of sweet taste documented very strong, negative correlations between adiposity and brain activation of the caudate, nucleus accumbens, and amygdala in older adults (Green et al., 2011). In the aforementioned study, young adults also demonstrated strong associations between increased BMI and decreased activation of the caudate. Negative associations between adiposity and activation of reward regions to flavor have also been reported in young adults and adolescents (Stice, Spoor, Bohon, & Small, 2008; Stice, Spoor, Bohon, Veldhuizen, & Small, 2008). Notably, containing the A1 allele of the TaqIA polymorphism is associated with a stronger link between striatal

activation to a milkshake and BMI. The A1 allele has been linked to alcoholism, obesity, reduced D2 receptors, and is associated with compromised striatal dopamine signaling, suggesting that inefficient dopamine function in the striatum may be related to obesity and alcohol abuse (Blum et al., 1990; Noble et al., 1991; Noble et al., 1994).

The link between brain activation in response to a food-related stimulus and adiposity has not yet been examined in middle-aged adults. Activation of the hypothalamus was negatively correlated with BMI when participants were fasted, and positively associated with BMI when sated. The hypothalamus plays a crucial role in the maintenance of energy homeostasis through modulation of eating behavior, neuroendocrine function, and reward (Berthoud & Morrison, 2008). Hypothalamic nuclei integrate hormone and nutrient signals regarding an individual's current state of energy balance. The arcuate nucleus of the hypothalamus is sensitive to the body's state of energy balance (Berthoud & Morrison, 2008). The lateral hypothalamus receives inputs from the arcuate nucleus in addition to other regions involved in sensory processing, reward value, and learning and memory (OFC, nucleus accumbens, amygdala, ventral tegmental area, insula) and has widespread projections to the cortex (Berthoud, 2002). Activation of the lateral hypothalamus is strongly related to feeding behavior, and projects widely throughout the brain. Electrical stimulation of this area in sated rats leads to feeding, which terminates once the stimulation is no longer present (Hettes et al., 2010; Stanley, Ha, Spears, & Dee, 1993; Stanley, Willett, Donias, Dee, & Duva, 1996). The periventrical nucleus of the hypothalamus also receives input from the arcuate nucleus, has widespread projections

in the cortex, and is associated with neuroendocrine function and the hypothalamic-pituitary axis.

Activation of the hypothalamus is decreased immediately following a preload (Haase et al., 2009; Liu et al., 2000; Smeets, de Graaf, Stafleu, van Osch, & van der Grond, 2005; Smeets et al., 2007), but this effect is reduced in obese individuals (Matsuda et al., 1999). The reduced BOLD response in the hypothalamus after energy consumption is likely related to its role in modulating the satiation process, and this may be disrupted in obese individuals. The results of the present study converge with this hypothesis; activation of the hypothalamus was reduced in obese participants when hungry. In addition, the expected decrease in hypothalamic response after a preload was attenuated in the participants with the highest levels of body fat.

Alterations in hypothalamic response to a sweet taste in participants with greater levels of adiposity may be an indication of deficiencies in signaling long-term energy stores (i.e., leptin and/or insulin resistance) or short-term energy needs. High circulating leptin and insulin after a meal and in individuals with higher levels of body fat should serve to reduce the reward response. Deficiencies in nutrient signaling might lead to a disconnection between gastrointestinal signals of energy availability and CNS regulation of hunger. In addition, obese individuals may not be cognizant of or reactive to satiety signals, which may result in eating beyond satiety. An altered hypothalamic response after consuming a meal in these individuals may be a result of chronic overeating.

Exploratory Analyses: Type II Diabetes

Although the MetS classification was developed in order to better identify individuals at increased risk for CVD and T2DM, this categorization still encompasses a population with metabolic abnormalities that exist on a continuum. For example, individuals with MetS often (but not always) have insulin resistance, which is considered to be one of the hallmark pathophysiological abnormalities of the syndrome. At the extreme end of the spectrum, insulin resistance can reach the threshold of T2DM and even result in decreased number of insulin-secreting beta cells, indicating the necessity of insulin injections. On the other end of the continuum, an individual may meet criteria for MetS and still have relatively normal insulin function. Given that insulin functions in the CNS to regulate food intake, individuals with MetS at these two ends of the resistance spectrum would likely respond differentially to food-related stimuli after a fast, and especially after a 700 kcal preload. Therefore, categorizing them as belonging to the same "diagnostic group" for statistical analyses would lead to a high degree of within-group variability and likely reduced the statistical power.

Six middle-aged individuals in the MetS group had an active diagnosis of T2DM. In an exploratory analysis, the individuals with a diagnosis of T2DM were separated from the MetS group to investigate possible differences in brain response during pleasantness evaluation of sweet and bitter taste stimuli during hunger and satiety. In order to increase statistical power, 12 older adult participants (aged 60+) were also included in the analysis (i.e., 4 older adult participants in each diagnostic group). Therefore, 10 participants without MetS (normal controls), 10 participants

with MetS but no T2DM diagnosis, and 10 participants with MetS and a diagnosis of T2DM were compared. Participants were matched on gender and age group.

In the hunger condition, there was a taste (bitter vs. sweet) by group (control vs. MetS vs. T2DM) interaction in brain regions involved in early sensory processing of taste (thalamus, superior insula), reward (lentiform nucleus, caudate tail), the limbic system (hippocampus, cingulate gyrus, posterior cingulate), and occipital and cerebellar regions often activated in taste and eating-related studies (Gautier et al., 1999; Geliebter et al., 2006; Green & Murphy, 2012; Haase et al., 2011; Jacobson et al., 2010; Malik, McGlone, Bedrossian, & Dagher, 2008; Rosenbaum, Sy, Pavlovich, Leibel, & Hirsch, 2008) but rarely discussed (lingual gyrus, fusiform gyrus, culmen).

The largest effect of group appeared to be in response to the bitter taste. Plots of mean activation suggested greatest activation in the normal control group, with less activation in the MetS group, and least activation in the T2DM group. This effect was consistent across brain regions ranging from primarily sensory (thalamus) to more reward and pleasantness-related limbic and dopaminergic regions (lentiform nucleus, caudate, hippocampus, cingulate). Interestingly, the T2DM and MetS without T2DM groups did not rate the caffeine as less pleasant or more intense than the control group.

Notably, the pattern of responses from the unpleasant (bitter taste) condition to the pleasant (sweet taste) condition differed for each group. The control group had the greatest response to bitter relative to sweet in most significant regions. The MetS group demonstrated roughly equivalent brain responses across taste conditions and the group with T2DM appeared to have the greatest brain response to the sweet taste relative to the bitter taste. Although there are currently no studies using neuroimaging

to investigate differences in CNS taste processing in MetS or T2DM, one recent fMRI study found increased activation to food pictures relative to nonfood pictures, and activation was strongest in diabetics relative to controls in regions involved in taste (insula), hunger modulation (OFC), and the dopaminergic reward response (caudate) (Chechlacz et al., 2009). Further, activation in subcortical reward areas (i.e., basal ganglia structures) were positively related to self-report of emotional eating and negatively associated with dietary self-care, which the authors suggest may be related to the need for diabetics to follow such a restrictive diet.

The MetS and T2DM groups reported more disinhibited eating on self-report measures. Dietary modification is one of the primary treatments for T2DM (Franz et al., 2003), suggesting that this group may be very cognizant of the amount of carbohydrates they regularly consume. Additionally, although they report more disinhibited eating than the healthy control group, individuals with T2DM may be attempting to adhere to a relatively restrictive diet; possibly to a greater degree than the other groups in the analysis. Although details about specific dietary habits are beyond the scope of this study, a sweet taste may be more reinforcing to an individual who attempts to minimize consumption of carbohydrates/sweets after chronic overexposure.

After a 700 kcal preload, diabetics in the current study had an increased fMRI response during pleasantness evaluation of the bitter taste in a region encompassing the postcentral gyrus and the insula, but decreased response during pleasantness evaluation of the sweet taste when compared with the more insulin sensitive groups.

In contrast, the MetS group exhibited the opposite pattern, demonstrating a greater response to the sweet taste when sated.

Insulin receptors are present throughout the brain, especially in the olfactory bulb, hippocampus, and hypothalamus (Corp et al., 1986; Marks, Porte, Stahl, & Baskin, 1990; Plum et al., 2005; Unger et al., 1989), and there is also evidence that insulin receptors are also found in lower concentrations in the cortex (Werther et al., 1987). Leptin is a hormone secreted by white adipose tissue that is involved in energy regulation and glucose metabolism through its action on the CNS. Insulin and leptin circulate in proportion to body fat mass (Considine et al., 1996; Hoffler et al., 2009; Jeanrenaud, 1978), and function in the CNS to decrease the subjective experience of reward through their action on the dopaminergic reward system (Figlewicz, 2003a; Figlewicz & Benoit, 2009; Figlewicz, Evans, Murphy, Hoen, & Baskin, 2003; Figlewicz & Sipols, 2010). Intracerebroventricular insulin and leptin administration results in blocked conditioned place preference to a high-fat diet in rats (Figlewicz et al., 2004), and decreased lever presses for self-administration of sucrose (Figlewicz, Bennett, Naleid, Davis, & Grimm, 2006), suggesting that when functioning properly, they serve to reduce food intake and promote weight loss.

Insulin action in the CNS related to the control of food intake is likely very complex (Anthony et al., 2006). Anthony and colleagues reported that insulin administration is associated with increased glucose metabolism in the ventral striatum and prefrontal cortex, but reduced metabolism in the amygdala and hippocampus. Additionally, during a visual task, the BOLD response is significantly reduced during

infusion of insulin compared to suppression of endogenous insulin (Seaquist et al., 2007).

Certain regions of the insula are modulated by hunger (Haase et al., 2009; Small et al., 2001). Given the role of insulin and leptin in modulating reward during the physiological state of satiety (i.e., suppressing the reward response to reduce/terminate energy intake), it was hypothesized that the healthy control group would have less activation of hunger-modulated taste processing regions after a preload than the individuals with varying degrees of insulin-resistance (i.e., the MetS and T2DM groups). The healthy control group and the MetS group demonstrated the hypothesized pattern; the control group had a reduced response, relative to the MetS group, in the insula/postcentral gyrus during pleasantness evaluation of sucrose. This pattern may represent dysfunction in insulin and/or leptin CNS action, and a reduction in modulation of reward value during a physiological state where further energy consumption may be disadvantageous. Further, inadequate modulation of reward signaling may result in continued energy consumption during satiety in the daily life of this group.

The results in the T2DM group during pleasantness evaluation of sweet taste in the physiological state of satiety are more difficult to interpret. This group demonstrated greater responses in the insula/postcentral gyrus during evaluation of bitter relative to the sweet taste. There is the possibility that increased attention to and adequate control of glucose levels in T2DM may be reflected in the similarities between the control group and the T2DM group's pattern of response in the insula/postcentral gyrus to sweet taste in the satiety condition (decreased response

relative to the group with MetS). However, this interpretation is highly speculative. Further studies examining brain response to pleasant food-related stimuli during satiety, and investigating relationships between fMRI activation and plasma glucose, insulin, and leptin levels are warranted to increase understanding of the current findings.

There is a small body of literature on taste function in diabetes mellitus, which suggests a generalized reduction in taste sensitivity in diabetic individuals (Settle, 1986, 1991). Several studies have documented significantly higher taste detection thresholds (i.e., the lowest concentration at which an individual can clearly *detect* a taste from water) in diabetics for sucrose, glucose, sodium chloride, citric acid, and quinine sulfate (Hardy, Brennand, & Wyse, 1981; Khobragade, Wakode, & Kale, 2012; Perros, MacFarlane, Counsell, & Frier, 1996), and higher recognition thresholds (i.e., the lowest concentration at which an individual can clearly *identify* a taste) for sucrose, sodium chloride, quinine sulfate, and urea in participants with T2DM when compared to healthy control subjects (Hardy et al., 1981; Niewoehner, Allen, Boosalis, Levine, & Morley, 1986; Perros et al., 1996). Further, the length of time with a diagnosis of diabetes and diabetes-related complications (such as peripheral neuropathy) are linked to poorer taste recognition ability in insulin-dependent (i.e., Type I) diabetes (Abbasi, 1981; Le Floch et al., 1989).

Phenylthiocarbamide (PTC) is detected as an extremely bitter taste to some individuals, classified as “tasters”, but is either tasteless or only slightly bitter to others, who are classified as “nontasters” (Cohen & Ogdon, 1949; Fox, 1932; Hall, Bartoshuk, Cain, & Stevens, 1975; Harris & Kalmus, 1949). Some studies suggest

that diabetics have decreased sensitivity to PTC (Ali, Khan, Mahtab, Khan, & Muhibullah, 1994), and that there is a higher proportion of PTC nontasters in the diabetic population (Rao & Sisodia, 1970; Terry & Segall, 1947). However, other studies do not support this (Akesson, 1959; Harris, Kalmus, & Trotter, 1949) and it is hypothesized that any differences in the proportion of nontasters in diabetics may actually be due to general decreased taste sensitivity in this population (Settle, 1991).

The most well established finding related to taste function in diabetes, is elevated glucose taste thresholds (Khobragade et al., 2012; Perros et al., 1996; Settle, 1991). It has been hypothesized that this may be due to: (a) elevated blood glucose; (b) hyperinsulinemia; and/or (c) generally reduced taste sensitivity. Settle (1991) argues that glucose insensitivity may actually be just the first symptom of a taste abnormality that eventually progresses to affect other taste qualities (glucose → other sweet stimuli → salty stimuli → all taste stimuli).

The participants with T2DM in the present study did not demonstrate elevated taste thresholds compared to the other groups. However, the sample was very small, and this effect may be small in the population, suggesting the need for a large sample size to detect any differences. The decreased activation to sucrose in the satiety condition could be conceptualized as being related to potential decreases in overall taste function. However, this wouldn't explain the pattern of results in the group with T2DM during the hunger condition (reduced activation in the bitter taste condition, relative to the sweet taste condition).

Implications and Future Directions

The results from the present investigation and from several previous studies suggest altered neural processing of pure taste (Green et al., 2011) and flavor (Stice, Spoor, Bohon, & Small, 2008; Stice, Spoor, Bohon, Veldhuizen, et al., 2008) stimuli in obesity. Taste and flavor (taste, olfaction, texture, temperature, etc) represent stimuli attached to the receipt of a food reward. In addition to blunted brain responses in reward regions after consuming food (or a food-related stimulus), obese individuals may be sensitized to conditioned cues of high calorie foods. Viewing pictures of high calorie foods has been used to investigate alterations in neural or attentional responses to food, and research in this area has implications for increased understanding of altered appetite, cravings, and anticipation/planning of food intake in this population. Obese participants demonstrate increased activation of dopaminergic reward (nucleus accumbens, striatum), motivation (anterior cingulate, orbitofrontal cortex), limbic (amygdala, hippocampus), and interoceptive (insula) regions relative to lean individuals in response to pictures of energy dense foods (Killgore & Yurgelun-Todd, 2005; Rothemund et al., 2007; Scharmuller, Ubel, Ebner, & Schienle, 2012; Schienle, Schafer, Hermann, & Vaitl, 2009; Stoeckel et al., 2008). There is also evidence of deficient amygdala-OFC and amygdala-nucleus accumbens connectivity in obese individuals (Stoeckel et al., 2009), and decreased frontal activation in obese individuals, likely related to weaker inhibitory control (Batterink, Yokum, & Stice, 2010). Visual attention bias for high calorie foods is greater in obese participants and is associated with increased consumption of snack food in a research environment (Werthmann et al., 2011).

To date, research on CNS taste function and brain responses to anticipation and receipt of food reward in individuals with MetS and T2DM is very limited. The results of the current study suggest that middle-aged and older adults with MetS and T2DM respond differentially to taste stimuli when hungry and after a meal. Differential processing of food-related stimuli in individuals with high levels of adipose tissue and metabolic and vascular abnormalities has significant implications for increased understanding of the neural underpinnings of eating behavior in these individuals. Hormonal signaling of long and short-term energy stores (e.g., leptin, insulin, ghrelin, PYY, etc.) is disrupted in individuals with MetS, and there are potentially significant structural changes in the brains of middle-aged and older adults with multiple cerebrovascular risk factors. Alterations in nutrient signaling and structural brain changes in these populations are likely related to the observed functional differences in CNS processing of taste stimuli, and this will be important to investigate in future studies. Future research on relationships among these variables is warranted in order to better conceptualize and develop interventions for overeating in these disorders.

The current study provides the first evidence of altered fMRI of brain responses in MetS and T2DM to pleasant and aversive taste stimuli during pleasantness evaluation. The results suggest that middle-aged and older adults with MetS and T2DM demonstrate differential processing of taste stimuli during pleasantness evaluation when compared to middle-aged and older adults who do not have as many vascular and metabolic abnormalities. The subjective experience of food reward plays a crucial role in eating behavior. Therefore, elucidating any

differences in neural correlates of taste and reward in these populations may lead to more effective pharmaceutical and behavioral interventions.

Chapter 4, in part, is currently being prepared for submission for publication of the material. Green, E; Jacobson, A; Haase, L; Murphy, C. The dissertation author was the primary investigator and author of this material.

References

Abbasi, A. A. (1981). Diabetes: diagnostic and therapeutic significance of taste impairment. *Geriatrics, 36*(12), 73-78.

Abbasi, F., Brown, B. W., Jr., Lamendola, C., McLaughlin, T., & Reaven, G. M. (2002). Relationship between obesity, insulin resistance, and coronary heart disease risk. *J Am Coll Cardiol, 40*(5), 937-943.

Adeli, K., Taghibiglou, C., Van Iderstine, S. C., & Lewis, G. F. (2001). Mechanisms of hepatic very low-density lipoprotein overproduction in insulin resistance. *Trends Cardiovasc Med, 11*(5), 170-176.

Adrian, T. E., Ferri, G. L., Bacarese-Hamilton, A. J., Fuessl, H. S., Polak, J. M., & Bloom, S. R. (1985). Human distribution and release of a putative new gut hormone, peptide YY. *Gastroenterology, 89*(5), 1070-1077.

Air, E. L., Benoit, S. C., Blake Smith, K. A., Clegg, D. J., & Woods, S. C. (2002). Acute third ventricular administration of insulin decreases food intake in two paradigms. *Pharmacol Biochem Behav, 72*(1-2), 423-429.

Akesson, H. O. (1959). Taste sensitivity to phenyl-thio-urea in tuberculosis and diabetes mellitus. *Ann Hum Genet, 23*, 262-265.

Alberti, K. G., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., et al. (2009). Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation, 120*(16), 1640-1645.

Alberti, K. G., Zimmet, P., & Shaw, J. (2005). The metabolic syndrome--a new worldwide definition. *Lancet, 366*(9491), 1059-1062.

Alberti, K. G., & Zimmet, P. Z. (1998). Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med, 15*(7), 539-553.

Ali, S. G. M., Khan, A. K. A., Mahtab, H., Khan, A. R., & Muhibullah, M. (1994). Association of Phenylthiocarbamide Taste Sensitivity with Diabetes-Mellitus in Bangladesh. *Human Heredity, 44*(1), 14-17.

Ansell, B. J. (2000). Cholesterol, stroke risk, and stroke prevention. *Curr Atheroscler Rep, 2*(2), 92-96.

Anthony, K., Reed, L. J., Dunn, J. T., Bingham, E., Hopkins, D., Marsden, P. K., et al. (2006). Attenuation of insulin-evoked responses in brain networks controlling appetite and reward in insulin resistance: the cerebral basis for impaired control of food intake in metabolic syndrome? *Diabetes, 55*(11), 2986-2992.

Arner, P. (2001). Free fatty acids - do they play a central role in type 2 diabetes? *Diabetes Obes Metab, 3 Suppl 1*, 11-19.

ATP. (2002). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation, 106*(25), 3143-3421.

Bacha, F., Saad, R., Gungor, N., Janosky, J., & Arslanian, S. A. (2003). Obesity, regional fat distribution, and syndrome X in obese black versus white adolescents: race differential in diabetogenic and atherogenic risk factors. *J Clin Endocrinol Metab, 88*(6), 2534-2540.

Badre, D., & D'Esposito, M. (2007). Functional magnetic resonance imaging evidence for a hierarchical organization of the prefrontal cortex. *Journal of Cognitive Neuroscience, 19*(12), 2082-2099.

Bartoshuk, L. M., Duffy, V. B., Green, B. G., Hoffman, H. J., Ko, C. W., Lucchina, L. A., et al. (2004). Valid across-group comparisons with labeled scales: the gLMS versus magnitude matching. *Physiol Behav, 82*(1), 109-114.

Baskin, D. G., Figlewicz, D. P., Woods, S. C., Porte, D., Jr., & Dorsa, D. M. (1987). Insulin in the brain. *Annu Rev Physiol, 49*, 335-347.

Batterink, L., Yokum, S., & Stice, E. (2010). Body mass correlates inversely with inhibitory control in response to food among adolescent girls: an fMRI study. *Neuroimage, 52*(4), 1696-1703.

Baura, G. D., Foster, D. M., Porte, D., Jr., Kahn, S. E., Bergman, R. N., Cobelli, C., et al. (1993). Saturable transport of insulin from plasma into the central nervous system of dogs in vivo. A mechanism for regulated insulin delivery to the brain. *J Clin Invest, 92*(4), 1824-1830.

Bays, H. E., Bazata, D. D., Clark, N. G., Gavin, J. R., 3rd, Green, A. J., Lewis, S. J., et al. (2007). Prevalence of self-reported diagnosis of diabetes mellitus and associated risk factors in a national survey in the US population: SHIELD (Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes). *BMC Public Health, 7*, 277.

Beason-Held, L. L., Moghekar, A., Zonderman, A. B., Kraut, M. A., & Resnick, S. M. (2007). Longitudinal changes in cerebral blood flow in the older hypertensive brain. *Stroke, 38*(6), 1766-1773.

Beaver, J. D., Lawrence, A. D., van Ditzhuijzen, J., Davis, M. H., Woods, A., & Calder, A. J. (2006). Individual differences in reward drive predict neural responses to images of food. *J Neurosci, 26*(19), 5160-5166.

Beckstead, R. M., Morse, J. R., & Norgren, R. (1980). The nucleus of the solitary tract in the monkey: projections to the thalamus and brain stem nuclei. *J Comp Neurol, 190*(2), 259-282.

Beevers, G., Lip, G. Y., & O'Brien, E. (2001). ABC of hypertension: The pathophysiology of hypertension. *BMJ, 322*(7291), 912-916.

Berridge, K. C. (1996). Food reward: brain substrates of wanting and liking. *Neurosci Biobehav Rev, 20*(1), 1-25.

Berridge, K. C. (2009). 'Liking' and 'wanting' food rewards: brain substrates and roles in eating disorders. *Physiol Behav, 97*(5), 537-550.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res Brain Res Rev, 28*(3), 309-369.

Berthoud, H. R. (2002). Multiple neural systems controlling food intake and body weight. *Neurosci Biobehav Rev, 26*(4), 393-428.

Berthoud, H. R., & Morrison, C. (2008). The brain, appetite, and obesity. *Annu Rev Psychol, 59*, 55-92.

Bewick, G. A. (2012). Bowels control brain: gut hormones and obesity. *Biochem Med (Zagreb), 22*(3), 283-297.

Blum, K., Noble, E. P., Sheridan, P. J., Montgomery, A., Ritchie, T., Jagadeeswaran, P., et al. (1990). Allelic association of human dopamine D2 receptor gene in alcoholism. *JAMA, 263*(15), 2055-2060.

Bogdanovic, N., Bretillon, L., Lund, E. G., Diczfalusy, U., Lannfelt, L., Winblad, B., et al. (2001). On the turnover of brain cholesterol in patients with Alzheimer's disease. Abnormal induction of the cholesterol-catabolic enzyme CYP46 in glial cells. *Neurosci Lett, 314*(1-2), 45-48.

Bokura, H., Yamaguchi, S., Iijima, K., Nagai, A., & Oguro, H. (2008). Metabolic syndrome is associated with silent ischemic brain lesions. *Stroke, 39*(5), 1607-1609.

Breteler, M. M., van Swieten, J. C., Bots, M. L., Grobbee, D. E., Claus, J. J., van den Hout, J. H., et al. (1994). Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. *Neurology, 44*(7), 1246-1252.

Brief, D. J., & Davis, J. D. (1984). Reduction of food intake and body weight by chronic intraventricular insulin infusion. *Brain Res Bull, 12*(5), 571-575.

Brown, M. S., & Goldstein, J. L. (1986). A receptor-mediated pathway for cholesterol homeostasis. *Science, 232*(4746), 34-47.

Brown, T. T., Kuperman, J. M., Erhart, M., White, N. S., Roddey, J. C., Shankaranarayanan, A., et al. (2010). Prospective motion correction of high-resolution magnetic resonance imaging data in children. *Neuroimage, 53*(1), 139-145.

Brownlee, M. (1995). Advanced protein glycosylation in diabetes and aging. *Annu Rev Med, 46*, 223-234.

Burgess, P. W., Dumontheil, I., & Gilbert, S. J. (2007). The gateway hypothesis of rostral prefrontal cortex (area 10) function. *Trends in Cognitive Sciences, 11*(7), 290-298.

Burguera, B., Couce, M. E., Long, J., Lamsam, J., Laakso, K., Jensen, M. D., et al. (2000). The long form of the leptin receptor (OB-Rb) is widely expressed in the human brain. *Neuroendocrinology, 71*(3), 187-195.

Cabanac, M. (1971). Physiological role of pleasure. *Science, 173*(4002), 1103-1107.

Carmelli, D., Swan, G. E., Reed, T., Wolf, P. A., Miller, B. L., & DeCarli, C. (1999). Midlife cardiovascular risk factors and brain morphology in identical older male twins. *Neurology, 52*(6), 1119-1124.

Carmichael, S. T., & Price, J. L. (1996). Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. *J Comp Neurol, 371*(2), 179-207.

Carvalheira, J. B., Ribeiro, E. B., Araujo, E. P., Guimaraes, R. B., Telles, M. M., Torsoni, M., et al. (2003). Selective impairment of insulin signalling in the hypothalamus of obese Zucker rats. *Diabetologia, 46*(12), 1629-1640.

Cavada, C., Company, T., Tejedor, J., Cruz-Rizzolo, R. J., & Reinoso-Suarez, F. (2000). The anatomical connections of the macaque monkey orbitofrontal cortex. A review. *Cereb Cortex, 10*(3), 220-242.

Cavdar, S., San, T., Aker, R., Sehirli, U., & Onat, F. (2001). Cerebellar connections to the dorsomedial and posterior nuclei of the hypothalamus in the rat. *J Anat, 198*(Pt 1), 37-45.

Cerf-Ducastel, B., Haase, L., & Murphy, C. (2012). Effect of Magnitude Estimation of Pleasantness and Intensity on fMRI Activation to Taste. *Chemosens Percept, 5*(1), 100-109.

Cerf-Ducastel, B., & Murphy, C. (2001). fMRI activation in response to odorants orally delivered in aqueous solutions. *Chem Senses, 26*(6), 625-637.

Chechlacz, M., Rotshtein, P., Klamer, S., Porubska, K., Higgs, S., Booth, D., et al. (2009). Diabetes dietary management alters responses to food pictures in brain regions associated with motivation and emotion: a functional magnetic resonance imaging study. *Diabetologia, 52*(3), 524-533.

Chen, G., Saad, Z. S., Britton, J. C., Pine, D. S., & Cox, R. W. (2013). Linear mixed-effects modeling approach to FMRI group analysis. *Neuroimage, 73*, 176-190.

Chikama, M., McFarland, N. R., Amaral, D. G., & Haber, S. N. (1997). Insular cortical projections to functional regions of the striatum correlate with cortical cytoarchitectonic organization in the primate. *J Neurosci, 17*(24), 9686-9705.

Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo, J. L., Jr., et al. (2003). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA, 289*(19), 2560-2572.

Christoff, K., & Gabrieli, J. D. E. (2000). The frontopolar cortex and human cognition: Evidence for a rostrocaudal hierarchical organization within the human prefrontal cortex. *Psychobiology, 28*(2), 168-186.

Clark, N. G., Fox, K. M., & Grandy, S. (2007). Symptoms of diabetes and their association with the risk and presence of diabetes: findings from the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD). *Diabetes Care, 30*(11), 2868-2873.

Cohen, J., & Ogdon, D. P. (1949). Taste blindness to phenyl-thio-carbamide and related compounds. *Psychol Bull, 46*(6), 490-498.

Considine, R. V., Sinha, M. K., Heiman, M. L., Kriauciunas, A., Stephens, T. W., Nyce, M. R., et al. (1996). Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med, 334*(5), 292-295.

Cooper, S. J., & Al-Naser, H. A. (2006). Dopaminergic control of food choice: contrasting effects of SKF 38393 and quinpirole on high-palatability food preference in the rat. *Neuropharmacology, 50*(8), 953-963.

Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., et al. (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science, 261*(5123), 921-923.

Corp, E. S., Woods, S. C., Porte, D., Jr., Dorsa, D. M., Figlewicz, D. P., & Baskin, D. G. (1986). Localization of 125I-insulin binding sites in the rat hypothalamus by quantitative autoradiography. *Neurosci Lett, 70*(1), 17-22.

Couillard, C., Bergeron, N., Prud'homme, D., Bergeron, J., Tremblay, A., Bouchard, C., et al. (1998). Postprandial triglyceride response in visceral obesity in men. *Diabetes, 47*(6), 953-960.

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res, 29*(3), 162-173.

Critchley, H. D., & Rolls, E. T. (1996). Hunger and satiety modify the responses of olfactory and visual neurons in the primate orbitofrontal cortex. *J Neurophysiol, 75*(4), 1673-1686.

Cummings, D. E., & Overduin, J. (2007). Gastrointestinal regulation of food intake. *J Clin Invest, 117*(1), 13-23.

Dai, W., Lopez, O. L., Carmichael, O. T., Becker, J. T., Kuller, L. H., & Gach, H. M. (2008). Abnormal regional cerebral blood flow in cognitively normal elderly subjects with hypertension. *Stroke, 39*(2), 349-354.

Davis, C., Strachan, S., & Berkson, M. (2004). Sensitivity to reward: implications for overeating and overweight. *Appetite, 42*(2), 131-138.

de Groot, J. C., de Leeuw, F. E., Oudkerk, M., van Gijn, J., Hofman, A., Jolles, J., et al. (2000). Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. *Ann Neurol, 47*(2), 145-151.

De Groot, J. C., De Leeuw, F. E., Oudkerk, M., Van Gijn, J., Hofman, A., Jolles, J., et al. (2002). Periventricular cerebral white matter lesions predict rate of cognitive decline. *Ann Neurol, 52*(3), 335-341.

de Leeuw, F. E., de Groot, J. C., Oudkerk, M., Witteman, J. C., Hofman, A., van Gijn, J., et al. (2002). Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain, 125*(Pt 4), 765-772.

DeCarli, C., Miller, B. L., Swan, G. E., Reed, T., Wolf, P. A., Garner, J., et al. (1999). Predictors of brain morphology for the men of the NHLBI twin study. *Stroke, 30*(3), 529-536.

Degen, L., Oesch, S., Casanova, M., Graf, S., Ketterer, S., Drewe, J., et al. (2005). Effect of peptide YY3-36 on food intake in humans. *Gastroenterology, 129*(5), 1430-1436.

Despres, J. P. (2006). Is visceral obesity the cause of the metabolic syndrome? *Ann Med, 38*(1), 52-63.

Despres, J. P., Moorjani, S., Ferland, M., Tremblay, A., Lupien, P. J., Nadeau, A., et al. (1989). Adipose tissue distribution and plasma lipoprotein levels in obese women. Importance of intra-abdominal fat. *Arteriosclerosis, 9*(2), 203-210.

Despres, J. P., Moorjani, S., Tremblay, A., Ferland, M., Lupien, P. J., Nadeau, A., et al. (1989). Relation of high plasma triglyceride levels associated with obesity and regional adipose tissue distribution to plasma lipoprotein-lipid composition in premenopausal women. *Clin Invest Med, 12*(6), 374-380.

Despres, J. P., Nadeau, A., Tremblay, A., Ferland, M., Moorjani, S., Lupien, P. J., et al. (1989). Role of deep abdominal fat in the association between regional adipose tissue distribution and glucose tolerance in obese women. *Diabetes, 38*(3), 304-309.

Di Francesco, V., Zamboni, M., Dioli, A., Zoico, E., Mazzali, G., Omizzolo, F., et al. (2005). Delayed postprandial gastric emptying and impaired gallbladder contraction together with elevated cholecystokinin and peptide YY serum levels sustain satiety and inhibit hunger in healthy elderly persons. *Journals of Gerontology Series a-Biological Sciences and Medical Sciences, 60*(12), 1581-1585.

Di Francesco, V., Zamboni, M., Zoico, E., Mazzali, G., Dioli, A., Omizzolo, F., et al. (2006). Unbalanced serum leptin and ghrelin dynamics prolong postprandial satiety and inhibit hunger in healthy elderly: another reason for the "anorexia of aging". *Am J Clin Nutr, 83*(5), 1149-1152.

Diagnosis and classification of diabetes mellitus. (2012). *Diabetes Care, 35 Suppl 1*, S64-71.

Dietrichs, E. (1984). Cerebellar autonomic function: direct hypothalamocerebellar pathway. *Science, 223*(4636), 591-593.

Dietrichs, E., & Haines, D. E. (1984). Demonstration of hypothalamo-cerebellar and cerebello-hypothalamic fibres in a prosimian primate (Galago crassicaudatus). *Anat Embryol (Berl), 170*(3), 313-318.

Dietrichs, E., Wiklund, L., & Haines, D. E. (1992). The hypothalamo-cerebellar projection in the rat: origin and transmitter. *Arch Ital Biol, 130*(3), 203-211.

Dik, M. G., Jonker, C., Comijs, H. C., Deeg, D. J., Kok, A., Yaffe, K., et al. (2007). Contribution of metabolic syndrome components to cognition in older individuals. *Diabetes Care, 30*(10), 2655-2660.

Dreher, J. C., Meyer-Lindenberg, A., Kohn, P., & Berman, K. F. (2008). Age-related changes in midbrain dopaminergic regulation of the human reward system. *Proc Natl Acad Sci U S A, 105*(39), 15106-15111.

Drewnowski, A. (1998). Energy density, palatability, and satiety: implications for weight control. *Nutr Rev, 56*(12), 347-353.

Egan, B. M., Zhao, Y., & Axon, R. N. (2010). US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. *JAMA, 303*(20), 2043-2050.

Elshourbagy, N. A., Liao, W. S., Mahley, R. W., & Taylor, J. M. (1985). Apolipoprotein E mRNA is abundant in the brain and adrenals, as well as in the liver, and is present in other peripheral tissues of rats and marmosets. *Proc Natl Acad Sci U S A, 82*(1), 203-207.

Ervin, R. B. (2009). Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003-2006. *Natl Health Stat Report*(13), 1-7.

Faurion, A., Cerf, B., Van De Moortele, P. F., Lobel, E., Mac Leod, P., & Le Bihan, D. (1999). Human taste cortical areas studied with functional magnetic resonance imaging: evidence of functional lateralization related to handedness. *Neurosci Lett, 277*(3), 189-192.

Figlewicz, D. P. (2003a). Adiposity signals and food reward: expanding the CNS roles of insulin and leptin. *American Journal of Physiology-Regulatory Integrative and Comparative Physiology, 284*(4), R882-R892.

Figlewicz, D. P. (2003b). Adiposity signals and food reward: expanding the CNS roles of insulin and leptin. *Am J Physiol Regul Integr Comp Physiol, 284*(4), R882-892.

Figlewicz, D. P., Bennett, J., Evans, S. B., Kaiyala, K., Sipols, A. J., & Benoit, S. C. (2004). Intraventricular insulin and leptin reverse place preference conditioned with high-fat diet in rats. *Behav Neurosci, 118*(3), 479-487.

Figlewicz, D. P., Bennett, J. L., Naleid, A. M., Davis, C., & Grimm, J. W. (2006). Intraventricular insulin and leptin decrease sucrose self-administration in rats. *Physiol Behav, 89*(4), 611-616.

Figlewicz, D. P., & Benoit, S. C. (2009). Insulin, leptin, and food reward: update 2008. *American Journal of Physiology-Regulatory Integrative and Comparative Physiology, 296*(1), R9-R19.

Figlewicz, D. P., Evans, S. B., Murphy, J., Hoen, M., & Baskin, D. G. (2003). Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat. *Brain Research, 964*(1), 107-115.

Figlewicz, D. P., & Sipols, A. J. (2010). Energy regulatory signals and food reward. *Pharmacol Biochem Behav, 97*(1), 15-24.

Finger, T. E., Bottger, B., Hansen, A., Anderson, K. T., Alimohammadi, H., & Silver, W. L. (2003). Solitary chemoreceptor cells in the nasal cavity serve as sentinels of respiration. *Proc Natl Acad Sci U S A, 100*(15), 8981-8986.

Finger, T. E., & Kinnamon, S. C. (2011). Taste isn't just for taste buds anymore. *F1000 Biol Rep, 3*, 20.

Folstein, M. F., Robins, L. N., & Helzer, J. E. (1983). The Mini-Mental State Examination. *Arch Gen Psychiatry, 40*(7), 812.

Ford, E. S. (2005a). Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. *Diabetes Care, 28*(11), 2745-2749.

Ford, E. S. (2005b). Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. *Diabetes Care, 28*(7), 1769-1778.

Ford, E. S., Li, C., & Zhao, G. (2010). Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US. *J Diabetes, 2*(3), 180-193.

Fox, A. L. (1932). The Relationship between Chemical Constitution and Taste. *Proc Natl Acad Sci U S A, 18*(1), 115-120.

Frank, S., Laharnar, N., Kullmann, S., Veit, R., Canova, C., Hegner, Y. L., et al. (2010). Processing of food pictures: influence of hunger, gender and calorie content. *Brain Res, 1350*, 159-166.

Frank, S., Linder, K., Kullmann, S., Heni, M., Ketterer, C., Cavusoglu, M., et al. (2012). Fat intake modulates cerebral blood flow in homeostatic and gustatory brain areas in humans. *Am J Clin Nutr, 95*(6), 1342-1349.

Frank, S., Wilms, B., Veit, R., Ernst, B., Thurnheer, M., Kullmann, S., et al. (2013). Altered brain activity in severely obese women may recover after Roux-en Y gastric bypass surgery. *Int J Obes (Lond)*.

Franken, I. H., & Muris, P. (2005). Individual differences in reward sensitivity are related to food craving and relative body weight in healthy women. *Appetite, 45*(2), 198-201.

Franz, M. J., Bantle, J. P., Beebe, C. A., Brunzell, J. D., Chiasson, J. L., Garg, A., et al. (2003). Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care, 26 Suppl 1*, S51-61.

Fudge, J. L., Breitbart, M. A., Danish, M., & Pannoni, V. (2005). Insular and gustatory inputs to the caudal ventral striatum in primates. *J Comp Neurol, 490*(2), 101-118.

Fujishima, M., Ibayashi, S., Fujii, K., & Mori, S. (1995). Cerebral blood flow and brain function in hypertension. *Hypertens Res, 18*(2), 111-117.

Gautier, J. F., Chen, K., Salbe, A. D., Bandy, D., Pratley, R. E., Heiman, M., et al. (2000). Differential brain responses to satiation in obese and lean men. *Diabetes, 49*(5), 838-846.

Gautier, J. F., Chen, K., Uecker, A., Bandy, D., Frost, J., Salbe, A. D., et al. (1999). Regions of the human brain affected during a liquid-meal taste perception in the fasting state: a positron emission tomography study. *Am J Clin Nutr, 70*(5), 806-810.

Gautier, J. F., Del Parigi, A., Chen, K. W., Salbe, A. D., Bandy, D., Pratley, R. E., et al. (2001). Effect of satiation on brain activity in obese and lean women. *Obesity Research, 9*(11), 676-684.

Geliebter, A., Ladell, T., Logan, M., Schneider, T., Sharafi, M., & Hirsch, J. (2006). Responsivity to food stimuli in obese and lean binge eaters using functional MRI. *Appetite, 46*(1), 31-35.

Gilbert, S. J., Frith, C. D., & Burgess, P. W. (2005). Involvement of rostral prefrontal cortex in selection between stimulus-oriented and stimulus-independent thought. *European Journal of Neuroscience, 21*(5), 1423-1431.

Glendinning, J. I., Yiin, Y. M., Ackroff, K., & Sclafani, A. (2008). Intragastric infusion of denatonium conditions flavor aversions and delays gastric emptying in rodents. *Physiol Behav, 93*(4-5), 757-765.

Gomez, J. M., Maravall, F. J., Gomez, N., Navarro, M. A., Casamitjana, R., & Soler, J. (2003). Interactions between serum leptin, the insulin-like growth factor-I system, and sex, age, anthropometric and body composition variables in a healthy population randomly selected. *Clinical Endocrinology, 58*(2), 213-219.

Green, B. G., Dalton, P., Cowart, B., Shaffer, G., Rankin, K., & Higgins, J. (1996). Evaluating the 'labeled magnitude scale' for measuring sensations of taste and smell. *Chemical Senses, 21*(3), 323-334.

Green, B. G., Shaffer, G. S., & Gilmore, M. M. (1993). Derivation and Evaluation of a Semantic Scale of Oral Sensation Magnitude with Apparent Ratio Properties. *Chemical Senses, 18*(6), 683-702.

Green, E., Jacobson, A., Haase, L., & Murphy, C. (2011). Reduced nucleus accumbens and caudate nucleus activation to a pleasant taste is associated with obesity in older adults. *Brain Res, 1386*, 109-117.

Green, E., Jacobson, A., Haase, L., & Murphy, C. (2012). Can age-related CNS taste differences be detected as early as middle age? Evidence from fMRI. *Neuroscience*.

Green, E., & Murphy, C. (2012). Altered processing of sweet taste in the brain of diet soda drinkers. *Physiol Behav*.

Grundy, S. M. (2004). Obesity, metabolic syndrome, and cardiovascular disease. *J Clin Endocrinol Metab, 89*(6), 2595-2600.

Grundy, S. M., Cleeman, J. I., Daniels, S. R., Donato, K. A., Eckel, R. H., Franklin, B. A., et al. (2005). Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation, 112*(17), 2735-2752.

Guo, Z., Viitanen, M., Fratiglioni, L., & Winblad, B. (1996). Low blood pressure and dementia in elderly people: the Kungsholmen project. *BMJ, 312*(7034), 805-808.

Guthoff, M., Grichisch, Y., Canova, C., Tschritter, O., Veit, R., Hallschmid, M., et al. (2010). Insulin modulates food-related activity in the central nervous system. *J Clin Endocrinol Metab, 95*(2), 748-755.

Haase, L., Cerf-Ducastel, B., Buracas, G., & Murphy, C. (2007). On-line psychophysical data acquisition and event-related fMRI protocol optimized for

the investigation of brain activation in response to gustatory stimuli. *J Neurosci Methods, 159*(1), 98-107.

Haase, L., Cerf-Ducastel, B., & Murphy, C. (2009). Cortical activation in response to pure taste stimuli during the physiological states of hunger and satiety. *Neuroimage, 44*(3), 1008-1021.

Haase, L., Green, E., & Murphy, C. (2011). Males and females show differential brain activation to taste when hungry and sated in gustatory and reward areas. *Appetite, 57*(2), 421-434.

Hall, M. J., Bartoshuk, L. M., Cain, W. S., & Stevens, J. C. (1975). PTC taste blindness and the taste of caffeine. *Nature, 253*(5491), 442-443.

Hallschmid, M., Higgs, S., Thienel, M., Ott, V., & Lehnert, H. (2012). Postprandial administration of intranasal insulin intensifies satiety and reduces intake of palatable snacks in women. *Diabetes, 61*(4), 782-789.

Hannesdottir, K., Nitkunan, A., Charlton, R. A., Barrick, T. R., MacGregor, G. A., & Markus, H. S. (2009). Cognitive impairment and white matter damage in hypertension: a pilot study. *Acta Neurol Scand, 119*(4), 261-268.

Hardy, S. L., Brennand, C. P., & Wyse, B. W. (1981). Taste thresholds of individuals with diabetes mellitus and of control subjects. *J Am Diet Assoc, 79*(3), 286-289.

Harris, H., & Kalmus, H. (1949). The measurement of taste sensitivity to phenylthiourea. *Ann Eugen, 15*(1), 24-31.

Harris, H., Kalmus, H., & Trotter, W. R. (1949). Taste sensitivity to phenylthiourea in goitre and diabetes. *Lancet, 2*(6588), 1038.

Hass, N., Schwarzenbacher, K., & Breer, H. (2007). A cluster of gustducin-expressing cells in the mouse stomach associated with two distinct populations of enteroendocrine cells. *Histochem Cell Biol, 128*(5), 457-471.

Hass, N., Schwarzenbacher, K., & Breer, H. (2010). T1R3 is expressed in brush cells and ghrelin-producing cells of murine stomach. *Cell Tissue Res, 339*(3), 493-504.

Hegele, R. A. (2009). Plasma lipoproteins: genetic influences and clinical implications. *Nat Rev Genet, 10*(2), 109-121.

Heijer, T., Skoog, I., Oudkerk, M., de Leeuw, F. E., de Groot, J. C., Hofman, A., et al. (2003). Association between blood pressure levels over time and brain atrophy in the elderly. *Neurobiol Aging, 24*(2), 307-313.

Heni, M., Kullmann, S., Ketterer, C., Guthoff, M., Bayer, M., Staiger, H., et al. (2013). Differential effect of glucose ingestion on the neural processing of food stimuli in lean and overweight adults. *Hum Brain Mapp*.

Hettes, S. R., Gonzaga, W. J., Heyming, T. W., Nguyen, J. K., Perez, S., & Stanley, B. G. (2010). Stimulation of lateral hypothalamic AMPA receptors may induce feeding in rats. *Brain Res, 1346*, 112-120.

Heverin, M., Bogdanovic, N., Lutjohann, D., Bayer, T., Pikuleva, I., Bretillon, L., et al. (2004). Changes in the levels of cerebral and extracerebral sterols in the brain of patients with Alzheimer's disease. *J Lipid Res, 45*(1), 186-193.

Ho, A. J., Raji, C. A., Becker, J. T., Lopez, O. L., Kuller, L. H., Hua, X., et al. (2010). Obesity is linked with lower brain volume in 700 AD and MCI patients. *Neurobiol Aging, 31*(8), 1326-1339.

Hofer, D., Puschel, B., & Drenckhahn, D. (1996). Taste receptor-like cells in the rat gut identified by expression of alpha-gustducin. *Proc Natl Acad Sci U S A, 93*(13), 6631-6634.

Hoffler, U., Hobbie, K., Wilson, R., Bai, R., Rahman, A., Malarkey, D., et al. (2009). Diet-induced obesity is associated with hyperleptinemia, hyperinsulinemia, hepatic steatosis, and glomerulopathy in C57Bl/6J mice. *Endocrine, 36*(2), 311-325.

Hogan, D. B., Ebly, E. M., & Rockwood, K. (1997). Weight, blood pressure, osmolarity, and glucose levels across various stages of Alzheimer's disease and vascular dementia. *Dement Geriatr Cogn Disord, 8*(3), 147-151.

Hsiung, G. Y., Sadovnick, A. D., & Feldman, H. (2004). Apolipoprotein E epsilon4 genotype as a risk factor for cognitive decline and dementia: data from the Canadian Study of Health and Aging. *CMAJ, 171*(8), 863-867.

Iso, H., Jacobs, D. R., Jr., Wentworth, D., Neaton, J. D., & Cohen, J. D. (1989). Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med, 320*(14), 904-910.

Israeli-Korn, S. D., Masarwa, M., Schechtman, E., Abuful, A., Strugatsky, R., Avni, S., et al. (2010). Hypertension increases the probability of Alzheimer's disease and of mild cognitive impairment in an Arab community in northern Israel. *Neuroepidemiology, 34*(2), 99-105.

Jacobson, A., Green, E., & Murphy, C. (2010). Age-related functional changes in gustatory and reward processing regions: An fMRI study. *Neuroimage, 53*(2), 602-610.

Jarvik, G. P., Wijsman, E. M., Kukull, W. A., Schellenberg, G. D., Yu, C., & Larson, E. B. (1995). Interactions of apolipoprotein E genotype, total cholesterol level, age, and sex in prediction of Alzheimer's disease: a case-control study. *Neurology, 45*(6), 1092-1096.

Jeanrenaud, B. (1978). Hyperinsulinemia in obesity syndromes: its metabolic consequences and possible etiology. *Metabolism, 27*(12 Suppl 2), 1881-1892.

Jick, H., Zornberg, G. L., Jick, S. S., Seshadri, S., & Drachman, D. A. (2000). Statins and the risk of dementia. *Lancet, 356*(9242), 1627-1631.

Jobst, E. E., Enriori, P. J., & Cowley, M. A. (2004). The electrophysiology of feeding circuits. *Trends Endocrinol Metab, 15*(10), 488-499.

Joseph, J. A., Roth, G. S., & Strong, R. (1990). The striatum, a microcosm for the examination of age-related alterations in the CNS: a selected review. *Rev Biol Res Aging, 4*, 181-199.

Kaasinen, V., Vilkman, H., Hietala, J., Nagren, K., Helenius, H., Olsson, H., et al. (2000). Age-related dopamine D2/D3 receptor loss in extrastriatal regions of the human brain. *Neurobiol Aging, 21*(5), 683-688.

Kalmijn, S., Feskens, E. J., Launer, L. J., Stijnen, T., & Kromhout, D. (1995). Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. *Diabetologia, 38*(9), 1096-1102.

Kalmijn, S., Foley, D., White, L., Burchfiel, C. M., Curb, J. D., Petrovitch, H., et al. (2000). Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study. *Arterioscler Thromb Vasc Biol, 20*(10), 2255-2260.

Karhunen, L. J., Lappalainen, R. I., Vanninen, E. J., Kuikka, J. T., & Uusitupa, M. I. (1997). Regional cerebral blood flow during food exposure in obese and normal-weight women. *Brain, 120 (Pt 9)*, 1675-1684.

Kern, W., Benedict, C., Schultes, B., Plohr, F., Moser, A., Born, J., et al. (2006). Low cerebrospinal fluid insulin levels in obese humans. *Diabetologia, 49*(11), 2790-2792.

Khobragade, R. S., Wakode, S. L., & Kale, A. H. (2012). Physiological taste threshold in type 1 diabetes mellitus. *Indian J Physiol Pharmacol, 56*(1), 42-47.

Kilander, L., Nyman, H., Boberg, M., Hansson, L., & Lithell, H. (1998). Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. *Hypertension, 31*(3), 780-786.

Killgore, W. D., & Yurgelun-Todd, D. A. (2005). Body mass predicts orbitofrontal activity during visual presentations of high-calorie foods. *Neuroreport, 16*(8), 859-863.

Killgore, W. D., & Yurgelun-Todd, D. A. (2007). Positive affect modulates activity in the visual cortex to images of high calorie foods. *Int J Neurosci, 117*(5), 643-653.

Kitagawa, K. (2010). Cerebral blood flow measurement by PET in hypertensive subjects as a marker of cognitive decline. *J Alzheimers Dis, 20*(3), 855-859.

Kivipelto, M., Helkala, E. L., Laakso, M. P., Hanninen, T., Hallikainen, M., Alhainen, K., et al. (2002). Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. *Ann Intern Med, 137*(3), 149-155.

Kivipelto, M., Helkala, E. L., Laakso, M. P., Hanninen, T., Hallikainen, M., Alhainen, K., et al. (2001). Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ, 322*(7300), 1447-1451.

Kivipelto, M., Laakso, M. P., Tuomilehto, J., Nissinen, A., & Soininen, H. (2002). Hypertension and hypercholesterolaemia as risk factors for Alzheimer's disease: potential for pharmacological intervention. *CNS Drugs, 16*(7), 435-444.

Koechlin, E., & Summerfield, C. (2007). An information theoretical approach to prefrontal executive function. *Trends Cogn Sci, 11*(6), 229-235.

Korf, E. S., White, L. R., Scheltens, P., & Launer, L. J. (2004). Midlife blood pressure and the risk of hippocampal atrophy: the Honolulu Asia Aging Study. *Hypertension, 44*(1), 29-34.

Kurth, T., Everett, B. M., Buring, J. E., Kase, C. S., Ridker, P. M., & Gaziano, J. M. (2007). Lipid levels and the risk of ischemic stroke in women. *Neurology, 68*(8), 556-562.

Kuusisto, J., Koivisto, K., Mykkanen, L., Helkala, E. L., Vanhanen, M., Hanninen, T., et al. (1997). Association between features of the insulin resistance syndrome and Alzheimer's disease independently of apolipoprotein E4 phenotype: cross sectional population based study. *BMJ, 315*(7115), 1045-1049.

Kwon, H. M., Kim, B. J., Lee, S. H., Choi, S. H., Oh, B. H., & Yoon, B. W. (2006). Metabolic syndrome as an independent risk factor of silent brain infarction in healthy people. *Stroke, 37*(2), 466-470.

Kwon, H. M., Kim, B. J., Park, J. H., Ryu, W. S., Kim, C. K., Lee, S. H., et al. (2009). Significant association of metabolic syndrome with silent brain infarction in elderly people. *J Neurol, 256*(11), 1825-1831.

Lakka, H. M., Laaksonen, D. E., Lakka, T. A., Niskanen, L. K., Kumpusalo, E., Tuomilehto, J., et al. (2002). The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA, 288*(21), 2709-2716.

Landahl, S., Bengtsson, C., Sigurdsson, J. A., Svanborg, A., & Svardsudd, K. (1986). Age-related changes in blood pressure. *Hypertension, 8*(11), 1044-1049.

Launer, L. J., Masaki, K., Petrovitch, H., Foley, D., & Havlik, R. J. (1995). The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. *JAMA, 274*(23), 1846-1851.

Launer, L. J., Ross, G. W., Petrovitch, H., Masaki, K., Foley, D., White, L. R., et al. (2000). Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiol Aging, 21*(1), 49-55.

Le Floch, J. P., Le Lievre, G., Sadoun, J., Perlemuter, L., Peynegre, R., & Hazard, J. (1989). Taste impairment and related factors in type I diabetes mellitus. *Diabetes Care, 12*(3), 173-178.

Leddy, J. J., Epstein, L. H., Jaroni, J. L., Roemmich, J. N., Paluch, R. A., Goldfield, G. S., et al. (2004). Influence of methylphenidate on eating in obese men. *Obes Res, 12*(2), 224-232.

Leroith, D. (2012). Pathophysiology of the metabolic syndrome: implications for the cardiometabolic risks associated with type 2 diabetes. *Am J Med Sci, 343*(1), 13-16.

Lewis, S. J., Rodbard, H. W., Fox, K. M., & Grandy, S. (2008). Self-reported prevalence and awareness of metabolic syndrome: findings from SHIELD. *Int J Clin Pract, 62*(8), 1168-1176.

Li, G., Higdon, R., Kukull, W. A., Peskind, E., Van Valen Moore, K., Tsuang, D., et al. (2004). Statin therapy and risk of dementia in the elderly: a community-based prospective cohort study. *Neurology, 63*(9), 1624-1628.

Liu, Y., Gao, J. H., Liu, H. L., & Fox, P. T. (2000). The temporal response of the brain after eating revealed by functional MRI. *Nature, 405*(6790), 1058-1062.

Lloyd-Jones, D., Adams, R., Carnethon, M., De Simone, G., Ferguson, T. B., Flegal, K., et al. (2009). Heart disease and stroke statistics--2009 update: a report from

the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation, 119*(3), 480-486.

Longstreth, W. T., Jr., Manolio, T. A., Arnold, A., Burke, G. L., Bryan, N., Jungreis, C. A., et al. (1996). Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke, 27*(8), 1274-1282.

Lusis, A. J. (2000). Atherosclerosis. *Nature, 407*(6801), 233-241.

Lusis, A. J., & Pajukanta, P. (2008). A treasure trove for lipoprotein biology. *Nat Genet, 40*(2), 129-130.

MacIntosh, C. G., Andrews, J. M., Jones, K. L., Wishart, J. M., Morris, H. A., Jansen, J. B., et al. (1999). Effects of age on concentrations of plasma cholecystokinin, glucagon-like peptide 1, and peptide YY and their relation to appetite and pyloric motility. *Am J Clin Nutr, 69*(5), 999-1006.

Malik, S., McGlone, F., Bedrossian, D., & Dagher, A. (2008). Ghrelin modulates brain activity in areas that control appetitive behavior. *Cell Metab, 7*(5), 400-409.

Manolio, T. A., Kronmal, R. A., Burke, G. L., Poirier, V., O'Leary, D. H., Gardin, J. M., et al. (1994). Magnetic resonance abnormalities and cardiovascular disease in older adults. The Cardiovascular Health Study. *Stroke, 25*(2), 318-327.

Marette, A., Mauriege, P., Marcotte, B., Atgie, C., Bouchard, C., Theriault, G., et al. (1997). Regional variation in adipose tissue insulin action and GLUT4 glucose transporter expression in severely obese premenopausal women. *Diabetologia, 40*(5), 590-598.

Marks, J. L., Porte, D., Jr., Stahl, W. L., & Baskin, D. G. (1990). Localization of insulin receptor mRNA in rat brain by in situ hybridization. *Endocrinology, 127*(6), 3234-3236.

Martel, P., & Fantino, M. (1996). Influence of the amount of food ingested on mesolimbic dopaminergic system activity: a microdialysis study. *Pharmacol Biochem Behav, 55*(2), 297-302.

Mathy, I., Dupuis, M. J., Pigeolet, Y., & Jacquerye, P. (2003). [Bilateral ageusia after left insular and opercular ischemic stroke]. *Rev Neurol (Paris), 159*(5 Pt 1), 563-567.

Matsuda, M., & DeFronzo, R. A. (1999). Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care, 22*(9), 1462-1470.

Matsuda, M., Liu, Y., Mahankali, S., Pu, Y., Mahankali, A., Wang, J., et al. (1999). Altered hypothalamic function in response to glucose ingestion in obese humans. *Diabetes, 48*(9), 1801-1806.

Mattis, S. (1976). Mental status examination for organic mental syndrome in the elderly patient. In L. Bellack & T. B. Karusu (Eds.), *Geriatric psychiatry* (pp. 77-121). New York: Grune & Stratton.

McGowan, M. K., Andrews, K. M., Fenner, D., & Grossman, S. P. (1993). Chronic intrahypothalamic insulin infusion in the rat: behavioral specificity. *Physiol Behav, 54*(5), 1031-1034.

McKinney, J. S., & Kostis, W. J. (2012). Statin Therapy and the Risk of Intracerebral Hemorrhage: A Meta-Analysis of 31 Randomized Controlled Trials. *Stroke*.

Meigs, J. B., Wilson, P. W., Nathan, D. M., D'Agostino, R. B., Sr., Williams, K., & Haffner, S. M. (2003). Prevalence and characteristics of the metabolic syndrome in the San Antonio Heart and Framingham Offspring Studies. *Diabetes, 52*(8), 2160-2167.

Molander, L., Gustafson, Y., & Lovheim, H. (2010a). Longitudinal associations between blood pressure and dementia in the very old. *Dement Geriatr Cogn Disord, 30*(3), 269-276.

Molander, L., Gustafson, Y., & Lovheim, H. (2010b). Low blood pressure is associated with cognitive impairment in very old people. *Dement Geriatr Cogn Disord, 29*(4), 335-341.

Moroney, J. T., Tang, M. X., Berglund, L., Small, S., Merchant, C., Bell, K., et al. (1999). Low-density lipoprotein cholesterol and the risk of dementia with stroke. *JAMA, 282*(3), 254-260.

Morris, M. C., Evans, D. A., Bienias, J. L., Tangney, C. C., Bennett, D. A., Aggarwal, N., et al. (2003). Dietary fats and the risk of incident Alzheimer disease. *Arch Neurol, 60*(2), 194-200.

Murphy, C., & Cain, W. S. (1980). Taste and olfaction: independence vs interaction. *Physiol Behav, 24*(3), 601-605.

Murphy, C., Cain, W. S., & Bartoshuk, L. M. (1977). Mutual action of taste and olfaction. *Sens Processes, 1*(3), 204-211.

Murphy, C., Gilmore, M. M., Seery, C. S., Salmon, D. P., & Lasker, B. R. (1990). Olfactory thresholds are associated with degree of dementia in Alzheimer's disease. *Neurobiol Aging, 11*(4), 465-469.

Murphy, K. G., & Bloom, S. R. (2006). Gut hormones and the regulation of energy homeostasis. *Nature, 444*(7121), 854-859.

Murphy, S., Xu, J., & Kochanek, K. (2012). Deaths: Preliminary data for 2010. *Statistics Reports* Retrieved May 26, 2012, from http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_04.pdf

Niewoehner, C. B., Allen, J. I., Boosalis, M., Levine, A. S., & Morley, J. E. (1986). Role of zinc supplementation in type II diabetes mellitus. *Am J Med, 81*(1), 63-68.

Noble, E. P., Blum, K., Ritchie, T., Montgomery, A., & Sheridan, P. J. (1991). Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. *Arch Gen Psychiatry, 48*(7), 648-654.

Noble, E. P., Noble, R. E., Ritchie, T., Syndulko, K., Bohlman, M. C., Noble, L. A., et al. (1994). D2 dopamine receptor gene and obesity. *Int J Eat Disord, 15*(3), 205-217.

Norgren, R. (1990). Gustatory System. In G. Paxinos (Ed.), *The Human Nervous System* (pp. 845-861). San Diego: Academic Press.

Notkola, I. L., Sulkava, R., Pekkanen, J., Erkinjuntti, T., Ehnholm, C., Kivinen, P., et al. (1998). Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease. *Neuroepidemiology, 17*(1), 14-20.

O'Doherty, J., Rolls, E. T., Francis, S., Bowtell, R., McGlone, F., Kobal, G., et al. (2000). Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. *Neuroreport, 11*(4), 893-897.

O'Regan, C., Wu, P., Arora, P., Perri, D., & Mills, E. J. (2008). Statin therapy in stroke prevention: a meta-analysis involving 121,000 patients. *Am J Med, 121*(1), 24-33.

Obici, S., Feng, Z., Karkanias, G., Baskin, D. G., & Rossetti, L. (2002). Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats. *Nat Neurosci, 5*(6), 566-572.

Okereke, O., Hankinson, S. E., Hu, F. B., & Grodstein, F. (2005). Plasma C peptide level and cognitive function among older women without diabetes mellitus. *Arch Intern Med, 165*(14), 1651-1656.

Ott, A., Stolk, R. P., Hofman, A., van Harskamp, F., Grobbee, D. E., & Breteler, M. M. (1996). Association of diabetes mellitus and dementia: the Rotterdam Study. *Diabetologia, 39*(11), 1392-1397.

Pannacciulli, N., Del Parigi, A., Chen, K. W., Le, D. S. N. T., Reiman, E. M., & Tataranni, P. A. (2006). Brain abnormalities in human obesity: A voxel-based morphometric study. *Neuroimage, 31*(4), 1419-1425.

Pannacciulli, N., Ortega, E., Koska, J., Salbe, A. D., Bunt, J. C., & Krakoff, J. (2007). Glucose response to an oral glucose tolerance test predicts weight change in non-diabetic subjects. *Obesity (Silver Spring), 15*(3), 632-639.

Papassotiropoulos, A., Lutjohann, D., Bagli, M., Locatelli, S., Jessen, F., Buschfort, R., et al. (2002). 24S-hydroxycholesterol in cerebrospinal fluid is elevated in early stages of dementia. *J Psychiatr Res, 36*(1), 27-32.

Park, K., Yasuda, N., Toyonaga, S., Tsubosaki, E., Nakabayashi, H., & Shimizu, K. (2008). Significant associations of metabolic syndrome and its components with silent lacunar infarction in middle aged subjects. *J Neurol Neurosurg Psychiatry, 79*(6), 719-721.

Pasquet, P., Frelut, M. L., Simmen, B., Hladik, C. M., & Monneuse, M. O. (2007). Taste perception in massively obese and in non-obese adolescents. *Int J Pediatr Obes, 2*(4), 242-248.

Patton, H. D., & Ruch, T. C. (1946). The relation of the foot of the pre- and postcentral gyrus to taste in the monkey and chimpanzee. *Fed Proc, 5*(1 Pt 2), 79.

Peila, R., Rodriguez, B. L., White, L. R., & Launer, L. J. (2004). Fasting insulin and incident dementia in an elderly population of Japanese-American men. *Neurology, 63*(2), 228-233.

Perros, P., MacFarlane, T. W., Counsell, C., & Frier, B. M. (1996). Altered taste sensation in newly-diagnosed NIDDM. *Diabetes Care, 19*(7), 768-770.

Petrovitch, H., White, L. R., Izmirilian, G., Ross, G. W., Havlik, R. J., Markesbery, W., et al. (2000). Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia aging Study. *Neurobiol Aging, 21*(1), 57-62.

Plum, L., Schubert, M., & Bruning, J. C. (2005). The role of insulin receptor signaling in the brain. *Trends Endocrinol Metab, 16*(2), 59-65.

Porte, D., Jr., Baskin, D. G., & Schwartz, M. W. (2002). Leptin and insulin action in the central nervous system. *Nutr Rev, 60*(10 Pt 2), S20-29; discussion S68-84, 85-27.

Porte, D., Jr., Baskin, D. G., & Schwartz, M. W. (2005). Insulin signaling in the central nervous system: a critical role in metabolic homeostasis and disease from C. elegans to humans. *Diabetes, 54*(5), 1264-1276.

Posner, H. B., Tang, M. X., Luchsinger, J., Lantigua, R., Stern, Y., & Mayeux, R. (2002). The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. *Neurology, 58*(8), 1175-1181.

Pritchard, T. C., Hamilton, R. B., Morse, J. R., & Norgren, R. (1986). Projections of thalamic gustatory and lingual areas in the monkey, Macaca fascicularis. *J Comp Neurol, 244*(2), 213-228.

Qiu, C., von Strauss, E., Winblad, B., & Fratiglioni, L. (2004). Decline in blood pressure over time and risk of dementia: a longitudinal study from the Kungsholmen project. *Stroke, 35*(8), 1810-1815.

Ramnani, N., & Owen, A. M. (2004). Anterior prefrontal cortex: Insights into function from anatomy and neuroimaging. *Nature Reviews Neuroscience, 5*(3), 184-194.

Rao, G. N., & Sisodia, P. (1970). Diabetes and phenylthiocarbamide (PTC) tasting ability. *J Assoc Physicians India, 18*(6), 577-581.

Raz, N. (2000). In F. I. M. Craik & T. A. Salthouse (Eds.), *The handbook of aging and cognition* (Vol. 2nd edition, pp. 1-90). Mahwah, NJ: Erlbaum.

Raz, N., Rodrigue, K. M., & Acker, J. D. (2003). Hypertension and the brain: vulnerability of the prefrontal regions and executive functions. *Behav Neurosci, 117*(6), 1169-1180.

Razay, G., Vreugdenhil, A., & Wilcock, G. (2007). The metabolic syndrome and Alzheimer disease. *Arch Neurol, 64*(1), 93-96.

Rea, T. D., Breitner, J. C., Psaty, B. M., Fitzpatrick, A. L., Lopez, O. L., Newman, A. B., et al. (2005). Statin use and the risk of incident dementia: the Cardiovascular Health Study. *Arch Neurol, 62*(7), 1047-1051.

Reaven, G. M. (1988). Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes, 37*(12), 1595-1607.

Refolo, L. M., Pappolla, M. A., LaFrancois, J., Malester, B., Schmidt, S. D., Thomas-Bryant, T., et al. (2001). A cholesterol-lowering drug reduces beta-amyloid pathology in a transgenic mouse model of Alzheimer's disease. *Neurobiol Dis, 8*(5), 890-899.

Reitz, C., Tang, M. X., Manly, J., Mayeux, R., & Luchsinger, J. A. (2007). Hypertension and the risk of mild cognitive impairment. *Arch Neurol, 64*(12), 1734-1740.

Reynolds, C. A., Gatz, M., Prince, J. A., Berg, S., & Pedersen, N. L. (2010). Serum lipid levels and cognitive change in late life. *J Am Geriatr Soc, 58*(3), 501-509.

Rigamonti, A. E., Pincelli, A. I., Corra, B., Viarengo, R., Bonomo, S. M., Galimberti, D., et al. (2002). Plasma ghrelin concentrations in elderly subjects: comparison with anorexic and obese patients. *J Endocrinol, 175*(1), R1-5.

Rockwood, K., Kirkland, S., Hogan, D. B., MacKnight, C., Merry, H., Verreault, R., et al. (2002). Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. *Arch Neurol, 59*(2), 223-227.

Roger, V. L., Go, A. S., Lloyd-Jones, D. M., Benjamin, E. J., Berry, J. D., Borden, W. B., et al. (2012). Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation, 125*(1), e2-e220.

Rolls, B. J., Rolls, E. T., Rowe, E. A., & Sweeney, K. (1981). Sensory specific satiety in man. *Physiol Behav, 27*(1), 137-142.

Rolls, E. T. (2007). Understanding the mechanisms of food intake and obesity. *Obes Rev, 8 Suppl 1*, 67-72.

Rolls, E. T., Murzi, E., Yaxley, S., Thorpe, S. J., & Simpson, S. J. (1986). Sensory-specific satiety: food-specific reduction in responsiveness of ventral forebrain neurons after feeding in the monkey. *Brain Res, 368*(1), 79-86.

Rolls, E. T., Scott, T. R., Sienkiewicz, Z. J., & Yaxley, S. (1988). The responsiveness of neurones in the frontal opercular gustatory cortex of the macaque monkey is independent of hunger. *J Physiol, 397*, 1-12.

Rolls, E. T., Sienkiewicz, Z. J., & Yaxley, S. (1989). Hunger Modulates the Responses to Gustatory Stimuli of Single Neurons in the Caudolateral Orbitofrontal Cortex of the Macaque Monkey. *Eur J Neurosci, 1*(1), 53-60.

Rolls, E. T., Yaxley, S., & Sienkiewicz, Z. J. (1990). Gustatory responses of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. *J Neurophysiol, 64*(4), 1055-1066.

Roman, G. C., Erkinjuntti, T., Wallin, A., Pantoni, L., & Chui, H. C. (2002). Subcortical ischaemic vascular dementia. *Lancet Neurol, 1*(7), 426-436.

Rosenbaum, M., Sy, M., Pavlovich, K., Leibel, R. L., & Hirsch, J. (2008). Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. *J Clin Invest, 118*(7), 2583-2591.

Ross, R., Freeman, J., Hudson, R., & Janssen, I. (2002). Abdominal obesity, muscle composition, and insulin resistance in premenopausal women. *J Clin Endocrinol Metab, 87*(11), 5044-5051.

Rothemund, Y., Preuschhof, C., Bohner, G., Bauknecht, H. C., Klingebiel, R., Flor, H., et al. (2007). Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. *Neuroimage, 37*(2), 410-421.

Rozin, P. (1982). "Taste-smell confusions" and the duality of the olfactory sense. *Percept Psychophys, 31*(4), 397-401.

Rubinsztein, D. C., & Easton, D. F. (1999). Apolipoprotein E genetic variation and Alzheimer's disease. a meta-analysis. *Dement Geriatr Cogn Disord, 10*(3), 199-209.

Ruhl, C. E., & Everhart, J. E. (2001). Leptin concentrations in the United States: relations with demographic and anthropometric measures. *American Journal of Clinical Nutrition, 74*(3), 295-301.

Ruitenberg, A., Skoog, I., Ott, A., Aevarsson, O., Witteman, J. C., Lernfelt, B., et al. (2001). Blood pressure and risk of dementia: results from the Rotterdam study and the Gothenburg H-70 Study. *Dement Geriatr Cogn Disord, 12*(1), 33-39.

Saper, C. B., Chou, T. C., & Elmquist, J. K. (2002). The need to feed: homeostatic and hedonic control of eating. *Neuron, 36*(2), 199-211.

Sbarbati, A., Merigo, F., Benati, D., Tizzano, M., Bernardi, P., Crescimanno, C., et al. (2004). Identification and characterization of a specific sensory epithelium in the rat larynx. *J Comp Neurol, 475*(2), 188-201.

Scharmuller, W., Ubel, S., Ebner, F., & Schienle, A. (2012). Appetite regulation during food cue exposure: A comparison of normal-weight and obese women. *Neuroscience Letters, 518*(2), 106-110.

Schienle, A., Schafer, A., Hermann, A., & Vaitl, D. (2009). Binge-Eating Disorder: Reward Sensitivity and Brain Activation to Images of Food. *Biological Psychiatry, 65*(8), 654-661.

Schneider, S. M., Al-Jaouni, R., Caruba, C., Giudicelli, J., Arab, K., Suavet, F., et al. (2008). Effects of age, malnutrition and refeeding on the expression and secretion of ghrelin. *Clinical Nutrition, 27*(5), 724-731.

Schulingkamp, R. J., Pagano, T. C., Hung, D., & Raffa, R. B. (2000). Insulin receptors and insulin action in the brain: review and clinical implications. *Neurosci Biobehav Rev, 24*(8), 855-872.

Scott, T. R., & Verhagen, J. V. (2000). Taste as a factor in the management of nutrition. *Nutrition, 16*(10), 874-885.

Scott, T. R., Yaxley, S., Sienkiewicz, Z. J., & Rolls, E. T. (1986). Gustatory responses in the nucleus tractus solitarius of the alert cynomolgus monkey. *J Neurophysiol, 55*(1), 182-200.

Seaquist, E. R., Chen, W., Benedict, L. E., Ugurbil, K., Kwag, J. H., Zhu, X. H., et al. (2007). Insulin reduces the BOLD response but is without effect on the VEP during presentation of a visual task in humans. *J Cereb Blood Flow Metab, 27*(1), 154-160.

Serra-Prat, M., Fernandez, X., Burdoy, E., Mussoll, J., Casamitjana, R., & Puig-Domingo, M. (2007). The role of ghrelin in the energy homeostasis of elderly people: A population-based study. *Journal of Endocrinological Investigation, 30*(6), 484-490.

Settle, G. (1986). Diabetes mellitus and the chemical senses. In H. L. Meiselman & R. S. Rivlin (Eds.), *Clinical measurement of taste and smell* (pp. 487-513). New York: MacMillan Publishing Company.

Settle, G. (1991). The chemical senses in diabetes mellitus. In T. V. Getchell, R. L. Doty, L. M. Bartoshuk & J. Snow (Eds.), *Smell and Taste in Health and Disease* (pp. 829-843). New York: Raven Press.

Shah, N. S., Vidal, J. S., Masaki, K., Petrovitch, H., Ross, G. W., Tilley, C., et al. (2012). Midlife blood pressure, plasma beta-amyloid, and the risk for Alzheimer disease: the Honolulu Asia Aging Study. *Hypertension, 59*(4), 780-786.

Sherwood, N. E., Jeffery, R. W., French, S. A., Hannan, P. J., & Murray, D. M. (2000). Predictors of weight gain in the Pound of Prevention study. *Int J Obes Relat Metab Disord, 24*(4), 395-403.

Shobab, L. A., Hsiung, G. Y., & Feldman, H. H. (2005). Cholesterol in Alzheimer's disease. *Lancet Neurol, 4*(12), 841-852.

Siep, N., Roefs, A., Roebroeck, A., Havermans, R., Bonte, M. L., & Jansen, A. (2009). Hunger is the best spice: An fMRI study of the effects of attention, hunger and calorie content on food reward processing in the amygdala and orbitofrontal cortex. *Behavioural Brain Research, 198*(1), 149-158.

Sierra, C., & Coca, A. (2006). White matter lesions and cognitive impairment as silent cerebral disease in hypertension. *ScientificWorldJournal, 6*, 494-501.

Simon, S. A., de Araujo, I. E., Gutierrez, R., & Nicolelis, M. A. (2006). The neural mechanisms of gustation: a distributed processing code. *Nat Rev Neurosci, 7*(11), 890-901.

Skoog, I., Andreasson, L. A., Landahl, S., & Lernfelt, B. (1998). A population-based study on blood pressure and brain atrophy in 85-year-olds. *Hypertension, 32*(3), 404-409.

Skoog, I., Lernfelt, B., Landahl, S., Palmertz, B., Andreasson, L. A., Nilsson, L., et al. (1996). 15-year longitudinal study of blood pressure and dementia. *Lancet, 347*(9009), 1141-1145.

Small, D. M., Jones-Gotman, M., & Dagher, A. (2003). Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. *Neuroimage, 19*(4), 1709-1715.

Small, D. M., & Prescott, J. (2005). Odor/taste integration and the perception of flavor. *Exp Brain Res, 166*(3-4), 345-357.

Small, D. M., Zatorre, R. J., Dagher, A., Evans, A. C., & Jones-Gotman, M. (2001). Changes in brain activity related to eating chocolate: from pleasure to aversion. *Brain, 124*(Pt 9), 1720-1733.

Smeets, P. A., de Graaf, C., Stafleu, A., van Osch, M. J., & van der Grond, J. (2005). Functional MRI of human hypothalamic responses following glucose ingestion. *Neuroimage, 24*(2), 363-368.

Smeets, P. A., Vidarsdottir, S., de Graaf, C., Stafleu, A., van Osch, M. J., Viergever, M. A., et al. (2007). Oral glucose intake inhibits hypothalamic neuronal activity more effectively than glucose infusion. *Am J Physiol Endocrinol Metab, 293*(3), E754-758.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23 Suppl 1*, S208-219.

Sobel, N., Prabhakaran, V., Hartley, C. A., Desmond, J. E., Zhao, Z., Glover, G. H., et al. (1998). Odorant-induced and sniff-induced activation in the cerebellum of the human. *J Neurosci, 18*(21), 8990-9001.

Solomon, A., Kivipelto, M., Wolozin, B., Zhou, J., & Whitmer, R. A. (2009). Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. *Dement Geriatr Cogn Disord, 28*(1), 75-80.

Spitz, M. R., Detry, M. A., Pillow, P., Hu, Y., Amos, C. I., Hong, W. K., et al. (2000). Variant alleles of the D2 dopamine receptor gene and obesity. *Nutr Res, 20*(3), 371-380.

Stanley, B. G., Ha, L. H., Spears, L. C., & Dee, M. G., 2nd. (1993). Lateral hypothalamic injections of glutamate, kainic acid, D,L-alpha-amino-3-hydroxy-5-methyl-isoxazole propionic acid or N-methyl-D-aspartic acid rapidly elicit intense transient eating in rats. *Brain Res, 613*(1), 88-95.

Stanley, B. G., Willett, V. L., 3rd, Donias, H. W., Dee, M. G., 2nd, & Duva, M. A. (1996). Lateral hypothalamic NMDA receptors and glutamate as physiological mediators of eating and weight control. *Am J Physiol, 270*(2 Pt 2), R443-449.

Stice, E., Spoor, S., Bohon, C., & Small, D. M. (2008). Relation between obesity and blunted striatal response to food is moderated by TaqIA A1 allele. *Science, 322*(5900), 449-452.

Stice, E., Spoor, S., Bohon, C., Veldhuizen, M. G., & Small, D. M. (2008). Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. *J Abnorm Psychol, 117*(4), 924-935.

Stoeckel, L. E., Kim, J., Weller, R. E., Cox, J. E., Cook, E. W., & Horwitz, B. (2009). Effective connectivity of a reward network in obese women. *Brain Research Bulletin, 79*(6), 388-395.

Stoeckel, L. E., Weller, R. E., Cook, E. W., 3rd, Twieg, D. B., Knowlton, R. C., & Cox, J. E. (2008). Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *Neuroimage, 41*(2), 636-647.

Strader, A. D., & Woods, S. C. (2005). Gastrointestinal hormones and food intake. *Gastroenterology, 128*(1), 175-191.

Stunkard, A. J., & Messick, S. (1985). The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *J Psychosom Res, 29*(1), 71-83.

Swan, G. E., DeCarli, C., Miller, B. L., Reed, T., Wolf, P. A., & Carmelli, D. (2000). Biobehavioral characteristics of nondemented older adults with subclinical brain atrophy. *Neurology, 54*(11), 2108-2114.

Szczypka, M. S., Kwok, K., Brot, M. D., Marck, B. T., Matsumoto, A. M., Donahue, B. A., et al. (2001). Dopamine production in the caudate putamen restores feeding in dopamine-deficient mice. *Neuron, 30*(3), 819-828.

Tai, K., Feinle-Bisset, C., Horowitz, M., Wishart, J. M., & Chapman, I. M. (2010). Effects of nutritional supplementation on the appetite and energy intake responses to IV cholecystokinin in older adults. *Appetite, 55*(3), 473-477.

Taki, Y., Kinomura, S., Sato, K., Inoue, K., Goto, R., Okada, K., et al. (2008). Relationship between body mass index and gray matter volume in 1,428 healthy individuals. *Obesity (Silver Spring), 16*(1), 119-124.

Tataranni, P. A., Gautier, J. F., Chen, K., Uecker, A., Bandy, D., Salbe, A. D., et al. (1999). Neuroanatomical correlates of hunger and satiation in humans using positron emission tomography. *Proc Natl Acad Sci U S A, 96*(8), 4569-4574.

Terry, M. C., & Segall, G. (1947). The association of diabetes and taste-blindness. *J Hered, 38*(5), 135-137.

Thompson, J., Thomas, N., Singleton, A., Piggott, M., Lloyd, S., Perry, E. K., et al. (1997). D2 dopamine receptor gene (DRD2) Taq1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. *Pharmacogenetics, 7*(6), 479-484.

Tizzano, M., Gulbransen, B. D., Vandenbeuch, A., Clapp, T. R., Herman, J. P., Sibhatu, H. M., et al. (2010). Nasal chemosensory cells use bitter taste signaling to detect irritants and bacterial signals. *Proc Natl Acad Sci U S A, 107*(7), 3210-3215.

Toth, P. P. (2003). Reverse cholesterol transport: high-density lipoprotein's magnificent mile. *Curr Atheroscler Rep, 5*(5), 386-393.

Towell, A., Muscat, R., & Willner, P. (1988). Behavioural microanalysis of the role of dopamine in amphetamine anorexia. *Pharmacol Biochem Behav, 30*(3), 641-648.

Travers, J. B. (1988). Efferent projections from the anterior nucleus of the solitary tract of the hamster. *Brain Res, 457*(1), 1-11.

Triantafyllidi, H., Arvaniti, C., Lekakis, J., Ikonomidis, I., Siafakas, N., Tzortzis, S., et al. (2009). Cognitive impairment is related to increased arterial stiffness and microvascular damage in patients with never-treated essential hypertension. *Am J Hypertens, 22*(5), 525-530.

Unger, J., McNeill, T. H., Moxley, R. T., 3rd, White, M., Moss, A., & Livingston, J. N. (1989). Distribution of insulin receptor-like immunoreactivity in the rat forebrain. *Neuroscience, 31*(1), 143-157.

Unger, J. W., Livingston, J. N., & Moss, A. M. (1991). Insulin receptors in the central nervous system: localization, signalling mechanisms and functional aspects. *Prog Neurobiol, 36*(5), 343-362.

van der Laan, L. N., de Ridder, D. T., Viergever, M. A., & Smeets, P. A. (2011). The first taste is always with the eyes: a meta-analysis on the neural correlates of processing visual food cues. *Neuroimage, 55*(1), 296-303.

van Swieten, J. C., Geyskes, G. G., Derix, M. M., Peeck, B. M., Ramos, L. M., van Latum, J. C., et al. (1991). Hypertension in the elderly is associated with white matter lesions and cognitive decline. *Ann Neurol, 30*(6), 825-830.

Vanhanen, M., Koivisto, K., Kuusisto, J., Mykkanen, L., Helkala, E. L., Hanninen, T., et al. (1998). Cognitive function in an elderly population with persistent impaired glucose tolerance. *Diabetes Care, 21*(3), 398-402.

Vanhanen, M., Koivisto, K., Moilanen, L., Helkala, E. L., Hanninen, T., Soininen, H., et al. (2006). Association of metabolic syndrome with Alzheimer disease: a population-based study. *Neurology, 67*(5), 843-847.

Volkow, N. D., Gur, R. C., Wang, G. J., Fowler, J. S., Moberg, P. J., Ding, Y. S., et al. (1998). Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. *Am J Psychiatry, 155*(3), 344-349.

Volkow, N. D., Logan, J., Fowler, J. S., Wang, G. J., Gur, R. C., Wong, C., et al. (2000). Association between age-related decline in brain dopamine activity and impairment in frontal and cingulate metabolism. *Am J Psychiatry, 157*(1), 75-80.

Volkow, N. D., Wang, G. J., & Baler, R. D. (2011). Reward, dopamine and the control of food intake: implications for obesity. *Trends Cogn Sci, 15*(1), 37-46.

Volkow, N. D., Wang, G. J., Telang, F., Fowler, J. S., Goldstein, R. Z., Alia-Klein, N., et al. (2009). Inverse Association Between BMI and Prefrontal Metabolic Activity in Healthy Adults. *Obesity, 17*(1), 60-65.

Vul, E., Harris, C., Winkielman, P., & Pashler, H. (2009). Puzzlingly High Correlations in fMRI Studies of Emotion, Personality, and Social Cognition. *Perspectives on Psychological Science, 4*(3), 274-290.

Wang, G. J., Volkow, N. D., Logan, J., Pappas, N. R., Wong, C. T., Zhu, W., et al. (2001). Brain dopamine and obesity. *Lancet, 357*(9253), 354-357.

Wang, G. J., Volkow, N. D., Thanos, P. K., & Fowler, J. S. (2009). Imaging of brain dopamine pathways: implications for understanding obesity. *J Addict Med, 3*(1), 8-18.

Wen, Y. Q., Zhu, J. N., Zhang, Y. P., & Wang, J. J. (2004). Cerebellar interpositus nuclear inputs impinge on paraventricular neurons of the hypothalamus in rats. *Neurosci Lett, 370*(1), 25-29.

Werther, G. A., Hogg, A., Oldfield, B. J., McKinley, M. J., Figdor, R., Allen, A. M., et al. (1987). Localization and characterization of insulin receptors in rat brain and pituitary gland using in vitro autoradiography and computerized densitometry. *Endocrinology, 121*(4), 1562-1570.

Werthmann, J., Roefs, A., Nederkoorn, C., Mogg, K., Bradley, B. P., & Jansen, A. (2011). Can(not) take my eyes off it: attention bias for food in overweight participants. *Health Psychol, 30*(5), 561-569.

White, N., Roddey, C., Shankaranarayanan, A., Han, E., Rettmann, D., Santos, J., et al. (2010). PROMO: Real-time prospective motion correction in MRI using image-based tracking. *Magn Reson Med, 63*(1), 91-105.

Whitmer, R. A., Sidney, S., Selby, J., Johnston, S. C., & Yaffe, K. (2005). Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology, 64*(2), 277-281.

WHO. (2012). Obesity and overweight factsheet. Retrieved May 30, 2012, from http://www.who.int/mediacentre/factsheets/fs311/en/

Williams, V. J., Leritz, E. C., Shepel, J., McGlinchey, R. E., Milberg, W. P., Rudolph, J. L., et al. (2012). Interindividual variation in serum cholesterol is associated with regional white matter tissue integrity in older adults. *Hum Brain Mapp*.

Wollmer, M. A., Streffer, J. R., Lutjohann, D., Tsolaki, M., Iakovidou, V., Hegi, T., et al. (2003). ABCA1 modulates CSF cholesterol levels and influences the age at onset of Alzheimer's disease. *Neurobiol Aging, 24*(3), 421-426.

Wolozin, B., Kellman, W., Ruosseau, P., Celesia, G. G., & Siegel, G. (2000). Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. *Arch Neurol, 57*(10), 1439-1443.

Wu, S. V., Rozengurt, N., Yang, M., Young, S. H., Sinnett-Smith, J., & Rozengurt, E. (2002). Expression of bitter taste receptors of the T2R family in the

gastrointestinal tract and enteroendocrine STC-1 cells. *Proc Natl Acad Sci U S A, 99*(4), 2392-2397.

Xu, J., Kochanek, K., & Tejada-Vera, B. (2009). *Deaths: Preliminary data for 2007.* Hyattsville, MD: National Center for Health Statistics.

Yaffe, K., Barrett-Connor, E., Lin, F., & Grady, D. (2002). Serum lipoprotein levels, statin use, and cognitive function in older women. *Arch Neurol, 59*(3), 378-384.

Yamada, M., Kasagi, F., Sasaki, H., Masunari, N., Mimori, Y., & Suzuki, G. (2003). Association between dementia and midlife risk factors: the Radiation Effects Research Foundation Adult Health Study. *J Am Geriatr Soc, 51*(3), 410-414.

Yaxley, S., Rolls, E. T., & Sienkiewicz, Z. J. (1988). The responsiveness of neurons in the insular gustatory cortex of the macaque monkey is independent of hunger. *Physiol Behav, 42*(3), 223-229.

Yaxley, S., Rolls, E. T., & Sienkiewicz, Z. J. (1990). Gustatory responses of single neurons in the insula of the macaque monkey. *J Neurophysiol, 63*(4), 689-700.

Yokum, S., Ng, J., & Stice, E. (2012). Relation of regional gray and white matter volumes to current BMI and future increases in BMI: a prospective MRI study. *Int J Obes (Lond), 36*(5), 656-664.

Young, S. E., Mainous, A. G., 3rd, & Carnemolla, M. (2006). Hyperinsulinemia and cognitive decline in a middle-aged cohort. *Diabetes Care, 29*(12), 2688-2693.

Zahniser, N. R., Goens, M. B., Hanaway, P. J., & Vinych, J. V. (1984). Characterization and regulation of insulin receptors in rat brain. *J Neurochem, 42*(5), 1354-1362.

Zamboni, M., Zoico, E., Fantin, F., Panourgia, M. P., Di Francesco, V., Tosoni, P., et al. (2004). Relation between leptin and the metabolic syndrome in elderly women. *Journals of Gerontology Series a-Biological Sciences and Medical Sciences, 59*(4), 396-400.

Zandi, P. P., Sparks, D. L., Khachaturian, A. S., Tschanz, J., Norton, M., Steinberg, M., et al. (2005). Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. *Arch Gen Psychiatry, 62*(2), 217-224.

Zhang, Y., Tuomilehto, J., Jousilahti, P., Wang, Y., Antikainen, R., & Hu, G. (2012). Total and High-Density Lipoprotein Cholesterol and Stroke Risk. *Stroke*.

Zhu, J. N., & Wang, J. J. (2008). The cerebellum in feeding control: possible function and mechanism. *Cell Mol Neurobiol, 28*(4), 469-478.

Zhu, J. N., Zhang, Y. P., Song, Y. N., & Wang, J. J. (2004). Cerebellar interpositus nuclear and gastric vagal afferent inputs reach and converge onto glycemia-sensitive neurons of the ventromedial hypothalamic nucleus in rats. *Neurosci Res, 48*(4), 405-417.

Zierath, J. R., Livingston, J. N., Thorne, A., Bolinder, J., Reynisdottir, S., Lonnqvist, F., et al. (1998). Regional difference in insulin inhibition of non-esterified fatty acid release from human adipocytes: relation to insulin receptor phosphorylation and intracellular signalling through the insulin receptor substrate-1 pathway. *Diabetologia, 41*(11), 1343-1354.