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The Effects of Age and Metabolic Status on Cognitive Performance

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Clinical Psychology

by

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ABSTRACT OF THE DISSERTATION

The Effects of Age and Metabolic Status on Cognitive Performance

by

Lori Haase

Doctor of Philosophy in Clinical Psychology

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Metabolic syndrome is a constellation of vascular and metabolic risk factors that frequently occur in combination, including obesity, raised triglycerides, reduced HDL cholesterol, raised blood pressure, and raised fasting plasma glucose, with the presence of 3 out of 5 risk factors constituting a diagnosis of metabolic syndrome. Metabolic syndrome is associated with increased rates of mortality and increased risk for developing dementia. Changes in brain structure and cognitive functioning have been reported within the literature. However, research examining cognitive performance in individuals with metabolic syndrome is limited, inconclusive and focuses primarily on older cohorts. As such, the effect of metabolic syndrome on cognitive functioning earlier in the lifespan is unclear. This study aimed to investigate

cognitive performance in young, middle-aged, and older adults with multiple metabolic and vascular risk factors in a sample of 91 community dwelling participants.

The following tests were administered: Dementia Rating Scale, Mini-Mental State Exam, reading subtest from the Wide Ranged Achievement Test-4, Digit Span from the Wechsler Memory Scale-III, Boston Naming Test-2 (BNT), Brief Visuospatial Memory Test-Revised (BVMT-R), California Verbal Learning Test-II (CLVT-II), and several tests from the D-KEFS (Trail Making Test, Verbal Fluency, Design Fluency, and Color-Word Interference Test).

As expected, older adults performed more poorly than young and middle-aged adults on measures of information processing speed, attention, memory, and executive functioning. Individuals with metabolic syndrome self-report greater disinhibited eating relative to normal controls. Additionally, individuals with metabolic syndrome performed more poorly on figural memory and figural fluency. These findings suggest that aspects of higher-order, executive functions of visuospatial processing are impaired in metabolic syndrome.

Given that individuals with metabolic syndrome had significantly greater self-reported disinihibited eating and performed more poorly on higher-order measures of visuospatial processing (e.g., memory, initiation, planning, multitasking, inhibition), future studies aimed at investigating potential causal relationships between metabolic syndrome, disinhibited eating, and executive dysfunction may provide insight into effective intervention targets to delay or prevent metabolic syndrome. Last, results indicated that incorporating measures of visuospatial abilities in future studies would

improve the characterization of cognitive declines in individuals with metabolic syndrome.

I. INTRODUCTION

Metabolic Syndrome

Cardiovascular disease (CVD) and type 2 diabetes mellitus (DM) are global epidemics. CVD is the number one cause of death, with mortality rates accounting for 29.2% or 16.7 million global deaths [World Health Organization (WHO), 2006; 2010]. In 2010, in the United States alone, total healthcare expenditure for CVD was estimated to exceed $503.2 billion (Loyd-Jones et al., 2010). Approximately 23.6 million US children and adults have diabetes mellitus (DM), which is estimated to cost $174 billion (Centers for Disease Control and Prevention (CDC, 2008). The number of individuals with DM is projected to increase 165% by the year 2050 (Boyle et al., 2001). Ninety percent of DM cases are classified as Type 2, which accounts for 6.8% or 4 million global deaths [International Diabetes Federation (IDF), 2010]. The presence of type 2 DM not only increases the risk for CVD (Hu et al., 2002), but CVD is also the leading cause of death in these individuals (CDC, 2008; for a review Nesto, 2004). Given the global burden of CVD and type 2 DM, the early diagnosis and intervention of those at risk are major health initiatives.

Metabolic syndrome is a constellation of vascular and metabolic risk factors that are directly related to the development of CVD and increase the risk of developing type 2 DM (Eckel, Grundy, & Zimmet 2005; Grundy et al., 2005; IDF, 2006). These vascular and metabolic risk factors frequently occur in combination, and taken together, increase CVD morbidity rates more than the individual components alone (Isomaa et al., 2001; Lakka et al., 2002). Middle-aged and older adults

with metabolic syndrome are three to four times more likely to have coronary heart disease, stroke, and mortality (Isomaa et al., 2001; Kurl et al., 2006; Lakka et al., 2002; Ninomiya et al., 2004). Furthermore, individuals with metabolic syndrome are at increased risk for polycystic ovary syndrome, fatty liver, gallstones, asthma, sleep disturbances, and cancer [Executive Summary of the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); ATP III, 2001]. The primary goal in diagnosing metabolic syndrome is to identify those individuals at risk for CVD and type 2 DM, and to target those individuals with risk reduction interventions (i.e., pharmacological interventions, weight reduction, increased physical activity; Eckel et al., 2005).

Definition of Metabolic Syndrome

There have been several proposed definitions for metabolic syndrome, all of which have included the same core components [i.e., obesity, insulin resistance, dyslipidemia (high triglycerides and low HDL cholesterol), and hypertension] with various modifications in the details of their criteria. In 1998, the WHO set forth the first definition of metabolic syndrome (Alberti & Zimmet, 1998; WHO, 1999). Shortly thereafter, the European Group for the Study of Insulin Resistance proposed a definition (Balkau & Charles, 1999). And, in 2001, Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III, 2001) revised the definition outlined by WHO, making modifications aimed at improving its clinical utility.

Over the following years, there was an abundance of studies investigating metabolic syndrome and it became clear that the definition of metabolic syndrome could be further improved in terms of its diagnostic sensitivity. Therefore, the IDF proposed a new set of diagnostic criteria (IDF, 2006). According to the IDF (2006), for an individual to carry the diagnosis of metabolic syndrome they must have central obesity (operationally defined as body mass index (BMI) >30kg/m^2 or waist circumference ≥ to 94 cm for males and 80 cm for females). Additionally, individuals must have two of the following symptoms: (1) raised triglycerides (≥ 150 mg/dL) or currently receiving treatment for dyslipidemia; (2) reduced HDL cholesterol (< 40 mg/dL in males and < 50 mg/dL in females) or currently receiving treatment for dyslipidemia; (3) raised blood pressure (BP; systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg) or treatment of diagnosed hypertension; and (4) raised fasting plasma glucose (≥ 100 mg/dL) or previous diagnosis of type 2 diabetes.

Previous studies demonstrated significant ethnic discrepancies between obesity cut-points and the risk of CVD, resulting in under diagnosis of metabolic syndrome within specific ethnicities (Lear, Chen, Frohlich, & Birmingham, 2002; Tan, Ma, Wai, Chew, & Tai, 2004; WHO, 2004). Therefore, in order to improve diagnostic sensitivity and move towards an international definition of metabolic syndrome, the IDF outlined ethnic specific values for waist circumference. Recognition of ethnic differences enhances the definition of metabolic syndrome by making it applicable to clinical practice worldwide, better identifies those as risk for CVD, and improves the estimation of prevalence rates.

However, more recently, a joint statement was released, proposing modifications to the current IDF criteria for metabolic syndrome (Alberti et al., 2009), which more closely resembles that put forth by ATP III. The representatives concluded that abdominal obesity should no longer be a prerequisite for metabolic syndrome, but rather, it should be 1 of the 5 possible components of the original IDF criterion, with the presence of ≥ 3 of 5 constituting a metabolic syndrome diagnosis. This modification is partly influenced by mounting evidence which suggests that while obesity is present in the majority of those with metabolic syndrome, there are individuals who are non-obese and still are at increased risk for CVD and type 2 DM (Dvorak, DeNino, Ades, & Poehlman, 1999; Ruderman, Chisholm, Pi-Sunyer, & Schneider, 1998).

Prevalence rates of Metabolic Syndrome

Prevalence rates of metabolic syndrome have proven difficult to estimate. Not only do the prevalence rates of the individual risk factors of metabolic syndrome vary among populations, but metabolic syndrome varies as a result of differences in genetics, diet, smoking, physical activity, and so forth (Cameron, Shaw, & Zimmet, 2004). Furthermore, prevalence rates of metabolic syndrome are likely to be underestimated given that there is no internationally recognized definition (Eckel et al., 2005). Despite these measurement difficulties, it is estimated that 20-25 percent of the world's population meets criteria for metabolic syndrome (IDF, 2006). Within the United States, age-adjusted prevalence rates of metabolic syndrome were estimated to be 23.7% or 47 million individuals in 2002 (Ford, Giles, & Dietz, 2002). Between

2003 and 2006, prevalence rates were estimated to be approximately 34% of the population (Loyd-Jones et al., 2010).

Several demographic variables have been shown to influence prevalence rates. Specifically, there are clear differences in prevalence rates among ethnicities (Ford et al., 2002; Park et al., 2003). Compared to non-Hispanic Caucasian Americans, Mexican Americans had the highest age-adjusted prevalence rates (31.9%; Ford et al., 2002). In a recent review of the literature, Cameron, Shaw & Zimmet (2004) reported gender differences in prevalence rates of metabolic syndrome, with the most discrepant being in India (8% of men and 46% of women diagnosed with metabolic syndrome). Prevalence rates are also highly age-dependent. Based on data collected within the United States between 2003 to 2006, by the National Health and Nutrition Examination Survey, 20.3% of men age 20-39, 40.8% age 40-59, and 51.5% age 60 and older, met criteria for metabolic syndrome (Loyd-Jones et al., 2010). For women, 15.6% age 20-39, 37.2% age 40-59, and 54.4% age 60 and older met criteria for metabolic syndrome (Loyd-Jones et al., 2010). These findings suggest that prevalence rates are increasing over time, and that middle-aged and older adults are particularly at risk for developing metabolic syndrome. Prevalence rates also increase with increasing weight status (Park et al., 2003). Park et al. (2003) found that metabolic syndrome was present in 4.6%, 22.4% and 59.6% of normal-weight, overweight and obese men, and that a similar distribution could be observed in women. Estimates of metabolic syndrome are likely to increase in parallel with the rising rates of obesity (Must et al., 1999; WHO, 2006), the growing population of older adults (CDC, 2003), and increasing environmental risk factors (i.e., sedentary lifestyle, increase consumption of

high caloric foods; Briefel, & Johnson, 2004; Hu, 2003; Popkin & Duffey, 2010). Increasing rates of metabolic syndrome will invariably increase the number of individuals with CVD and type 2 DM, and the associated global healthcare expenditure. Therefore, it is important to elucidate the effects of metabolic syndrome in order to target effective interventions.

Primary Mechanisms of Metabolic Syndrome

While there is no single pathogenesis associated with metabolic syndrome, several risk factors have been identified including insulin resistance, obesity, atherogenic dyslipidemia, inflammation, raised blood pressure, and raised plasma glucose (Grundy et al., 2005; Eckel et al., 2005). However, insulin resistance and obesity are thought to be the primary pathologic mechanisms of metabolic syndrome (Abbasi, Brown, Lamendola, McLaughlin, & Reaven, 2002; Alberti et al. 2009; Eckel, 2005; IDF, 2006; Shen et al., 2003) and will be discussed in greater detail.

Obesity refers to excessive total body fat and has increased in US adults from 15% in the 1970s to 31% in 2000 (Flegal, Carroll, Ogden, & Johnson, 2002). It is estimated that by 2015, roughly 2.3 million adults will be overweight (BMI >25) and more than 700 million will be obese (BMI >30; WHO, 2006). This dramatic increase in obesity is related to the interaction between genetic predisposition and environmental factors such as decreased energy expenditure, increased energy intake, and the increased availability of high-fat, palatable foods (Hill & Peters, 1998; Lindqvist, de la Cour, Stegmark, Hakanson, & Erlanson-Albertsson, 2005; Ravussin & Bouchard, 2000; Swimburn, Sacks, & Ravussin, 2009). Obesity in middle age decreases life expectancy and increases the risk for mortality (Adams et al., 2006;

Peeters et al., 2003; Yan et al., 2006). In addition, obesity is associated with multiple medical conditions including CVD, type 2 DM, insulin resistance, dyslipidemia, hypertension, gallstone disease, osteoarthritis, and cancer (Eckel et al., 2005; Han, van Leer, Seidell, & Lean, 1995; Must et al., 1999; Pi-Sunyer, 2002). Approximately 58% of DM can be attributed to increased body mass index (International Obesity Task Force, 2006). As would be expected, being obese increases the risk of developing metabolic syndrome (Lemieux et al., 2000; Zimmet, Alberti, & Shaw, 2005). The relationship between obesity and metabolic syndrome is linked to central/abdominal obesity (Carr et al., 2004). Abdominal obesity, in particular, visceral obesity, is commonly found in individuals with insulin resistance (Carr et al., 2004; Evans, Hoffman, Kalkhoff, & Kissebah, 1984; Grundy et al., 2005) and is directly related to the amount of insulin secretion within the body (Figlewicz, 2003; Polonsky et al., 1988). Shockingly, over 50% of US adults have abdominal obesity (Li, Ford, McGuire, & Mokad, 2007), putting them at increased risk for multiple vascular and metabolic risk factors. However, it should be noted that a subset of normal weight individuals are still at an increased risk for CVD and type 2 DM (Dvorak et al., 1999; Ruderman et al., 1998), which may be explained by genetic (e.g., first-degree relative of type 2 DM) and environmental risk factors (e.g. sedentary lifestyle; Ruderman et al., 1998).

Insulin is a hormone that is produced in the pancreas and transported throughout the body and central nervous system. Insulin is linked to food intake/regulation, energy homeostasis, and neuronal growth/survival (Plum, Schubert, & Bruning, 2005; Wozniak, Rydzewski, Baker, & Raizada, 1993). Insulin resistance is

a condition in which body cells become less sensitive to the hormone insulin [National Diabetes Information Clearinghouse (NIDCD), 2008]. The primary role of insulin in the body is to regulate glucose metabolism. The body's defense to insulin resistance is to increase the output of insulin. When this mechanism fails, glucose (hyperglycemia) and insulin (hyperinsulinemia) build up within the blood and increase the risk for type 2 DM (NDIC, 2008). These elevated conditions can exist within the body for years prior to the development of type 2 DM, resulting in long-term exposure to potentially toxic levels of insulin and glucose within the blood (Cole, Astell, Green & Sutherland, 2007). The exact mechanism of insulin resistance is unknown, however, obesity and age are thought to be major risk factors (Cole et al., 2007). The role of insulin resistance in CVD was first described by Reaven (1988). Since that time, insulin resistance has been found to be an independent predictor of CVD, type 2 DM, glucose intolerance, dyslipidemia, hypertension, and mortality in men and women (Abbasi et al., 2002; DECODE Study Group, 2004; Haffner, Mykkanen, Festa, Burke, & Stern, 1990; Kendall & Harmel, 2002; Reaven, 1988). In fact, 95.2% of people with multiple vascular and metabolic risk factors are insulin resistant (Bonora et al., 1998).

Vascular risk factors over the lifespan

The presence of multiple vascular risk factors and metabolic syndnrome has been documented in young adults (Gupta, et al., 2009; Juonala et al., 2004). The short- and long-term deleterious effects of developing these conditions in young adulthood are unknown. In middle-aged adults, the presence of multiple metabolic risk factors increases the risk of CVD and mortality (Lakka et al., 2002), and is associated with cognitive decline and the risk of developing dementia (See below). Relative to

younger cohorts, older adults (>65 years of age) are at an increased risk of CVD and type 2 DM (Loyd-Jones, et al., 2010). In fact, the majority of CVD and coronary deaths occur in individuals age 65 and older, with older adults accounting for 81% of deaths from coronary heart disease and 86% of stroke deaths (Loyd-Jones et al., 2010; ATP III, 2001). Between 2010 and 2050, a 336% increase in type 2 DM will occur among individuals age 75 and older (Boyle et al., 2001); these individuals are 2 to 4 times more likely to die from heart disease and stroke (CDC, 2008).

Obesity and physical inactivity also increase with age (Doshi, Polsky, & Chang, 2007; Loyd-Jones, et al., 2010). Obesity in middle-aged and older adults is associated with increased risk for mortality (Adams et al., 2006) and CVD (Harris et al., 1997). In particular, abdominal obesity in older adults is associated with increased blood pressure and increases the risk of hypertension and stroke (Cassano, Segal, Vokonas, & Weis, 1990; Folsom, Prineas, Kaye, & Munger, 1990).

In summary, metabolic syndrome can develop in young adults and the prevalence rates increase with increasing age (Ford et al., 2002). The population of older adults is projected to increase from 12.4% in 2000 to 19.6% in 2030 (CDC, 2003). As such, the aging population constitutes a subset of individuals who will likely place the greatest demand on the healthcare system, and personal/family and public resources (CDC, 2003). Elucidating the effects of metabolic syndrome in young, middle-aged, and older adults may help to inform future research aimed at reducing the risk of developing metabolic syndrome, CVD, and type 2 DM.

Neuroimaging and Cognition

Normal Aging

Structural Changes. The normal aging process is associated with changes in brain structure and function. In particular, the frontal, subcortical, and mesial temporal areas are most susceptible to structural changes in healthy aging (Allen, Bruss, Brown, & Damasio, 2005; Jernigan et al., 1991; Raz et al., 2005; Walhoved et al., In Press). Greater age-related structural changes occur within anterior brain regions relative to posterior regions (Head et al., 2004). Of note, even modest cerebral changes in healthy older adults are associated with declines in cognitive function (Cook et al., 2002; DeCarli et al., 1995; de Groot et al., 2005).

Cognitive Decline. Age-related changes in cognitive function have been reported in individuals as early as the second decade of life (Salthouse, 2009). In older adults, cognitive decrements associated with normal aging occur most commonly on measures of information processing speed, memory, and executing function (Hultsch, MacDonald, & Dixon, 2002; Schonknecht, Pantel, Kruse, & Schroder, 2005; van Hooren et al., 2007).

Functional Neuroimaging. With the advent of functional neuroimaging, neural mechanisms of cognition in healthy aging, neurologic and psychiatric disease processes are being elucidated. Functional magnetic imaging (fMRI) measures changes in metabolism (regional rate and volume of blood, relative to the amount of oxygen in the blood), termed BOLD (Blood Oxygenation Level Dependent), as an indirect measure of neuronal activity (Buxton, & Frank, 1997; Ogawa, Lee, Kay, & Tanks, 1990; Papanicolaou, 1998). Normal aging is associated with changes in cerebrovasculature (e.g., arteriosclerosis) and decreases in resting cerebral blood flow, rate of oxygen consumption, and vascular reactivity (D'Esposito, Deouell, &

Gazzaley, 2003), all of which can alter the BOLD signal and therefore, influence the interpretation of data. Nevertheless, functional changes within the aging brain have been observed and are associated with cognitive performance. In particular, previous studies have shown that in healthy older adults, better cognitive performance is associated with increased activation in the bilateral frontal lobes (Cabeza, 2002; Grady, McIntosh, & Craik, 2005; Eyler et al., 2011), which is in contrast to younger adults who typically demonstrate lateralized neural activity; these changes are thought to reflect age-related compensatory mechanisms such that greater brain activation is associated with better performance on these types of tasks.

Individuals with Vascular Risk Factors

Structural changes. Normal age related changes in brain structure and function are influenced by the presence of vascular risk factors. Cerebral atrophy and white matter abnormalities have been found in individuals with hypertension (de Leeuw et al., 2002; Heijer et al., 2003; Kennedy and Raz 2009), type 2 DM (de Bresser et al., 2010; Yau et al., 2009), and obesity (Jagust, Harvey, Mungas, & Haan, 2005; Taki et al., 2008). Kennedy and Raz (2009) reported accelerated age-related reduction in white matter in individuals with controlled hypertension. Interestingly, while healthy age-related changes were associated with white matter damage in anterior brain regions, hypertension was associated with white matter damage that also extended to posterior brain regions. Moreover, previous research has shown that abnormalities in insulin are associated with the development of neurofibrillary tangles and amyloid plaques, the characteristic neuropathological changes found in Alzheimer's disease (Cole et al., 2007; Luchsinger, 2008; Plum et al., 2005).

Cognitive Decline. Obesity, type 2 DM, hyperinsulinemia, and high blood pressure in middle-aged adults is associated with cognitive decline (Dey, Misra, Desai, Mahapatra, & Padma, 1997; Elias, Elias, Robbins, & Budge, 2004; Knopman et al., 2001; Launer, Masaki, Petrovitch, Foley, & Halvik, 1995; Sabia, Kivimaki, Shipley, Marmot, & Singh-Manoux, 2009; Ryan and Geckle, 2000; Young, Mainous, & Carnemolla, 2006). In addition, obesity in adolescence and in older adults is associated with impaired executive functioning (e.g., decision-making, impaired cognitive flexibility, and impulsivity; Batterink, Yokum, & Stice, 2010; Fergenbaum et al., 2009; Mobbs, Crepin, Thiery, Golay, & Van der Liden, 2010; Pauli-Pott, Albayrak, Hebebrand, & Pott, 2010; Pignatti et al., 2006). Taken together, these results suggest that impairment in cognitive functioning in individuals with vascular risk factors can occur early in the lifespan.

Several vascular and metabolic risk factors have been consistently associated with cognitive decline in older adults (for a review see Kloppenborg, van den Berg, Kappelle, & Bissels, 2008; Stampfer, 2006). Specifically, obesity (Dore, Elias, Robbins, Budge, & Elias, 2008; Fergenbaum et al., 2009; Gorospe & Dave, 2007), insulin resistance (Abbatecola et al., 2004; Geroldi et al., 2005), type 2 DM (Biessels, ter Baak, Erkelens, & Hijman, 2001; Hassing et al., 2004, Helzner et al., 2009;Yeung, Fischer, & Dixon, 2009), hypertension (Bucur & Madden, 2010), and hyperlipidema (Bennet et al., 2007; Helzner et al., 2009; Moroney et al., 1999; Yaffe, Barrett-Conner, Lin, & Grady, 2002) are associated with cognitive decline and increase the risk for dementia. Individuals with vascular and metabolic risk factors demonstrate cognitive decrements, that are above and beyond those reported in healthy aging, on measures of

information processing speed, memory, and executive functioning (van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009). Given that the domains of cognition affected by the presence of vascular risk factors are the same as those reported in healthy aging, vascular and metabolic risk factors are thought to accelerate natural aging and disease processes.

Neuroimaging: Obesity. Obesity is associated with environmental risk factors, such as increased energy intake of palatable foods, i.e., foods rich in fat (Swinburn, Sacks, & Ravussin, 2009). Energy intake, consumption and termination, is regulated by complex interactions of peptides throughout the body and the brain (Erlanson-Albertsson, 2005). However, research suggests that this system is easily nullified in the presence of highly palatable, energy dense foods and decreased physical activity (Berthoud, 2004; Erlanson-Albertsson, 2005). At the central processing level, consumption of highly palatable food activates the reward network, which overrides the relatively weak homeostatic satiety signals within the brain, resulting in over consumption. Consistent with this hypothesis, functional neuroimaging studies have found that obese individuals demonstrate abnormal activation within regions that process reward contingencies and memory processes (e.g., dorsal and ventral striatum, prefrontal cortices, mesial temporal lobes; Green et al., 2011; DelParigi, Chen, Salbe, Reiman, & Tatarani, 2005; Gautier et al., 2001; Stice, Spoor, Bohon, Veldhuizen, & Small, 2008; Volkow et al., 2009). In obese individuals, deactivation within the prefrontal cortices is correlated with impulsivity and reduced memory performance (Volkow et al., 2009). Disruption of reward networks is further supported by the fact that obese individuals also have lower dopamine receptor availability within the

striatum, which is negatively associated with BMI (Wang et al., 2001). Altered neural activity in obese individuals has been localized within the caudate and nucleus accumbens (Green et al., 2011) and within the middle insula and the hippocampus (DelParigi et al., 2004), suggesting possible regions within the brain responsible for the development of obesity. Similar neural networks have been implicated in drug addiction (Kelley & Berridge, 2002; Wang, Volkow, Thanos, & Fowler, 2004). Taken together, these findings suggest that the disruption within the reward network in obese individuals may be the underlying neural mechanism of obesity. Despite the alarming rate of obese individuals, current treatments targeting energy intake and expenditure are relatively ineffective over long-term periods. Therefore, understanding the neural mechanisms of reward in the obese population will help to create targeted interventions aimed at effective, long-term weight reduction.

Neuroimaging: Insulin Resistance. As discussed earlier, insulin is a hormone that is found throughout the body and central nervous system, and is directly associated with food intake/regulation and energy homeostasis (Plum et al., 2005; Wozniak et al., 1993). The greatest densities of insulin receptors within the brain are localized within the hypothalamus, hippocampus, olfactory bulb, striatum, and cerebellum (Plum et al., 2005; Wozniak et al., 1993; Figlewicz, 2003; Figlewicz, Patterson, Zavosh, Brot, & Szot, 1999). Changes in insulin are thought to impact hypothalamic neuropeptides, resulting in changes in food intake (Plum et al., 2005). The amount of insulin within the brain is negatively correlated with the amount of fat in the body, and as would be expected, insulin signaling within the brain of obese individuals is reduced (Kaiyala, Prigeon, Kahn, Woods, & Schwartz, 2000).

Decreased insulin signaling is also associated with reduced reward (Figelwicz & Sipols, 2010). A recent neuroimaging experiment found that administration of insulin resulted in increased blood glucose metabolism within the ventral striatum and prefrontal cortex, and decreased metabolism within the amygdala, hippocampus, and cerebellum (Anthony et al., 2006). However, in insulin resistant men, there was significantly less activation within the ventral striatum, a region implicated in reward processing, suggesting multiple mechanisms contributing to obesity in insulin resistance (Anthony et al., 2006). In addition to the role that insulin plays in energy homeostasis, insulin resistance may be one of the mechanisms that contribute to the cognitive decrements found in type 2 DM (Luchsinger, 2008).

Neuroimaging: Type 2 DM. Deficits in memory have been consistently reported in type 2 DM and are associated with hippocampal atrophy (Bruehl et al., 2009; Gold et al., 2007; Manschot et al., 2006). Impaired performance on measures of memory and executive function in type 2 DM have also been linked to reduced functional connectivity between the hippocampus and the default mode network, suggesting the potential for more widespread neuropathological changes in type 2 DM (Zhou et al., 2010). Given these data, it is therefore not surprising that individuals with type 2 DM are impaired on measures of attention, executive function, information processing speed, and memory, with performance correlated with structural brain abnormalities (e.g., infarcts, atrophy; Manschot et al., 2006). This seemingly global cognitive decline likely reflects an interaction between age, duration of exposure to insulin resistance and hyperinsulinemia, and length of time since type 2 DM diagnosis (Cole et al., 2007; Plum et al., 2005).

Neuroimaging: Hypertension. Approximately 50 million Americans have high blood pressure, with 50% of individuals ages 60-69 years meeting criteria for high blood pressure (Chobainian et al., 2003). As blood pressure increases, so does the risk for stroke, ischemic heart disease, and CVD (Chobainian et al., 2003; Seshadri, et al., 2001). Previous research in hypertensive patients has consistently found a negative relationship between white matter abnormalities and performance on measures of executive functioning, memory, attention, and psychomotor speed, in middle age and older adults (Hanneddottir et al., 2009, Raz, Rodrigue, & Acker, 2003; Sierra et al., 2004, van Swieten et al., 1991). In fact, significant atrophy and white matter hyperintensities within the frontal lobes and decreased performance on measures of executive functioning are present in individuals with controlled hypertension (Raz et al., 2003). In addition, it has been documented that hypertensive patients also have disruption in regional cerebral blood flow within the fontal cortex and basal ganglia that is associated with reduced cognitive performance (Fujishima, Ibayashi, Fujii, & Mori, 1995).

In summary, based on the aforementioned experiments, it is clear that vascular and metabolic risk factors are directly related to structural and functional brain changes, and declines in cognitive performance. Given that these risk factors often occur in combination, resulting in metabolic syndrome, elucidating their combined effect on brain structure and function is important for characterizing metabolic disease and creating effective interventions.

Metabolic Syndrome

Structural Changes. Compared to normal aged-related structural changes, individuals with metabolic syndrome are more likely to have a history of stroke (Kurl et al., 2006; Ninomiya et al., 2004) and white matter hyperintensities (Park et al., 2007). Metabolic syndrome is an independent risk factor for silent brain infarction, periventricular hyperintensities, and subcortical white matter lesions (Bokura, Yamaguchi, Ijima, Nagai, & Oguro, 2008; Kwon et al., 2006, 2009; Park et al., 2008). Older adults with metabolic syndrome show greater age-related anterior - posterior white matter degeneration relative to healthy older adults (Segura et al., 2009b). In the aforementioned studies, metabolic syndrome was found to be an independent predictor of structural deterioration, accounting for more variance than the individual components of the syndrome. For example, Kwon et al (2009) found that the number of metabolic syndrome risk factors was positively associated with the number of silent brain infarctions.

Cognitive Decline. The structural brain changes in individuals with metabolic syndrome (e.g., silent brain infarction) are associated with cognitive decrements (Vermeer et al., 2003). Metabolic syndrome, as a whole, accounts for a greater amount of cognitive decline above and beyond the individual risk factors (Ho et al., 2008; Yaffe, 2007) and is associated with poorer cognitive performance (van den Berg et al., 2008; Gatto et al., 2008; Komulainen et al., 2007; Yaffe, Weston, Blackwell, & Krueger, 2009). These findings suggest that the cluster of risk factors that together constitute metabolic syndrome, above and beyond its individual components, contribute to impaired cognition.

The majority of studies examining cognitive performance in individuals with metabolic syndrome have focused primarily on older adults. In particular, in three different prospective studies, metabolic syndrome was found to be associated with declines in global cognitive function, in Caucasian-, African-, and Latino-Americans (Yaffe et al., 2004; 2007), and in Chinese older adults (Ho, Niti, Yap, Kua, & Ng, 2008). Yaffe and colleagues (2004; 2007) demonstrated that those with high levels of serum markers of inflammation had significantly greater declines in cognitive performance than those without inflammation, suggesting one potential mechanism for cognitive decline. Cross-sectional studies examining more specific aspects of cognitive function have revealed poorer performance in metabolic syndrome relative to controls on measures of information processing speed (Dik et al., 2007; Segura et al., 2009; van den Berg et al., 2008), attention (van den Berg et al., 2008), verbal memory (Dik et al., 2007; Komulainen 2007), executive functioning (e.g. fluency and inhibition) (Segura et al., 2009a; van den Berg et al., 2008), and fluid intelligence (Dik et al., 2007). However, variability of the pattern of cognitive decline in metabolic syndrome is clearly present within the literature. Within the same experiments, there were reportedly no significant differences between individuals with metabolic syndrome and healthy controls on measures of global cognitive function and information processing speed (Komulainen et al., 2007), learning (Gatto et al., 2008), memory (Gatto et al., 2008; Segura et al., 2009a; van den Berg et al., 2008;), language (Gatto et al., 2008; van den Berg et al., 2008), and executive function (Gatto et al., 2008; Segura et al., 2009; van den Berg et al., 2008). Interestingly, metabolic syndrome in the oldest old (85+ years of age), is not associated with significant

declines in cognitive performance (Laudisio et al., 2008; van den Berg et al., 2007). These findings suggest that some aspects of metabolic syndrome may be protective later in life (e.g. abdominal obesity).

Despite the increased risk of multiple cardiovascular risk factors in young adulthood relative to adolescents (Gupta, et al., 2009), the effect of metabolic disease on cognitive function within this cohort has yet to be examined.

However, obese persons have been found to report significantly more disinhibited eating than their normal weight counterparts (Harden et al., 2009; Maayan et al., 2011; Mobbs et al., 2010). In addition, in obese adolescents, disinhibited eating is associated executive dysfunction, and had reduced orbitofrontal cortex volumes than non-obese adolescents (Maayan et al., 2011). In addition, the investigation of cognitive function in middle-aged adults with metabolic syndrome is limited. In a 10-year follow up study of cognitive performance of middle-age individuals with metabolic syndrome, those who consistently met criteria for metabolic syndrome performed significantly poorer than those with non-persistent metabolic syndrome and those without any history of metabolic syndrome, on measures of memory, verbal fluency, reasoning, and vocabulary (Akbaraly et al., 2010). No significant differences were found on a measure of general cognitive function (MMSE).

To date, little is known about the relative impact of metabolic syndrome on cognition at various points in the lifespan. The literature suggests that the time span in which an individual with metabolic syndrome is assessed and the number of years an individual meets criteria for metabolic syndrome may contribute to cognitive decline and the variability in cognitive deficits reported in the literature. Understanding the

effects of metabolic syndrome on cognition in young, middle-aged, and older adults would help to document the age at which changes in cognition first appear in metabolic syndrome and may provide support for initiating targeted interventions earlier in the lifespan.

Risk of Dementia

Obesity, hypertension, and high cholesterol in middle age are associated with an increased risk for dementia (Kivipelto et al., 1997; 2001). The presence of hyperinsulinemia, hyperglycemia, diabetes, hypertension, and hyperlipidemia in older adults are also associated with an increased risk of developing Alzheimer's disease (Kuusisto et al., 1997; Luchsinger & Mayeux, 2004; Qiu, Winnblad, & Fratiglioni, 2005). However, the strongest evidence for an underlying mechanism of vascular risk factors and Alzheimer's disease comes from research on DM and hyperinsulinemia (Luchsinger & Mayeux, 2004). Insulin resistance is implicated in the neuropathologic changes in Alzheimer's disease (Cole et al., 2007; Frolich et al., 1998; Gasparini, Netzer, Greengard, & Xu, 2002; Luchsinger, 2008;) More specifically, hyperinsulinemia within the brain is associated with increase tau phosphorylation, increased beta-amyloid deposition, hypoglycemia, and desensitization to toxins (for a review see Cole et al., 2007; Luchsinger, 2008). The dysregulation of insulin signaling within the brain may be an underlying neural mechanism of Alzheimer's disease. CVD and type 2 DM are also associated with the development of MCI (Solfrizzi et al., 2004), vascular dementia (Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006; Knopman, Rocca, Cha, Edland, & Kokmen, 2002; Leys, Pasquire, & Parneti, 1999)

and Alzheimer's disease (Biessels et al., 2006; Esiri, Nagy, Smith, Barneston, & Smith, 1999; Jellinger & Mitter-Ferstl, 2003; Snowdon et al., 1997; Stampfer, 2006;).

Research examining the relationship between metabolic syndrome and dementia has produced mixed results. A case-control study of 50 consecutive individuals with probable Alzheimer's disease found that metabolic syndrome was associated with a 3-fold increase in the risk for Alzheimer's disease (Razay, Vreugdenhil, & Wilcock, 2007). Cross-sectional studies have shown associations between metabolic syndrome and an increased risk for Alzheimer's disease (Vanhanen, et al., 2006) and vascular dementia (Solfrizzi et al., 2010). In a prospective study, Yaffe, Weston, Blackwell, and Krueger (2009) found that metabolic syndrome is associated with greater cognitive impairment at a 4-year follow-up. A prospective study of Japanese-American elderly men found that metabolic risk factors, present at middle age, increased the risk of developing vascular dementia, but not Alzheimer's disease, 25 years later (Kalmijn et al., 2000). Conversely, a more recent prospective study failed to find an association between metabolic syndrome and overall dementia, Alzheimer's disease, and vascular dementia, at a 3.5-year follow-up (Forti et al., 2010). Variability in the association between metabolic syndrome and dementia in both cross-sectional and prospective designs is likely influenced by the definition of metabolic syndrome employed, time-window of assessment, and environmental differences among cohorts.

Prevalence rates of dementia increase dramatically with advancing age (Lobo et al., 2000). It is therefore not surprising that with the growing cohort of older adults, worldwide estimates of individuals diagnosed with dementia are projected to reach

81.1 million by 2040 (Ferri et al., 2005). In 2010, the health care costs of those with dementia were expected to exceed $172 billion (Alzheimer's Association, 2010). Given that there are few disease modifying interventions for dementia, elucidating the relationship between cognitive decline and metabolic syndrome may suggest avenues to pursue for targeted interventions aimed at delaying or preventing this syndrome, cognitive decline, and the progression to dementia (Middleton & Yaffe, 2009).

Aims of the Current Study

The aim of the proposed experiment is to examine the potential differences in cognitive performance in young, middle-aged and older adults with and without vascular and metabolic risk factors, using a comprehensive neuropsychological battery. The tests administered were chosen in order to measure a broad array of neurocognitive abilities, with specific emphasis on measures of information processing speed, attention, memory, and executive function.

Significance of the Current Study

CVD and DM are global epidemics. Metabolic syndrome is a cluster of vascular and metabolic risk factors (obesity, hypertension, dyslipidemia, hyperglycemia) that frequently occur in combination, and increase the risk for CVD, type 2 DM, and dementia. The pathological changes associated with obesity and insulin resistance are considered the underlying mechanisms of metabolic syndrome. Changes in brain structure (e.g., cerebral atrophy and white matter abnormalities) are present in individuals with metabolic syndrome. Research investigating the changes in cognitive functioning in individuals with metabolic syndrome is inconclusive and focuses primarily on older cohorts**.** As such, the effect of metabolic status on cognitive

functioning in young adults and middle aged adults, and potential differences in cognitive functioning among young, middle-aged, and older adults are unclear.

Metabolic syndrome is associated with an increased risk of dementia. Older adults represent a cohort that is particularity at risk for the development of obesity, type 2 DM, metabolic syndrome, and dementia. Given the projected increase in population estimates of older adults, it is important to understand the health consequences of metabolic syndrome in this growing cohort. In addition, there is currently no treatment for dementia and there are few modifiable risk factors of dementia. Therefore, metabolic syndrome is of particular interest because elucidating the underlying mechanisms of this syndrome may help to inform future treatment avenues to pursue to alter the course of cognitive decline and delay the progression to dementia.

Hypotheses

The following are the specific hypotheses of the current study:

Hypothesis 1. It was hypothesized that there would be significant differences in cognitive functioning among age groups. In particular, the older adult sample would perform significantly poorer relative to young and middle-age adults on measures of information processing speed, memory, and executive functioning (e.g., cognitive switching, fluency). In addition, it was hypothesized that there would be no significant differences in cognitive performance between middle-aged and young adults.

Hypothesis 2. Overall, the literature examining the effect of metabolic syndrome on cognitive functioning has been inconsistent. Several studies have found significant differences in cognitive performance on measures of information

processing speed, verbal memory, and aspects of executive functioning. As such, it was hypothesized that individuals with metabolic syndrome would perform significantly poorer relative to normal controls on measures of information processing speed, memory, and executive functioning. Fewer studies and more inconsistencies have been reported within the literature with regard to cognitive performance in metabolic syndrome on measures of attention, learning and cognitive switching. Therefore, it was hypothesized that differences in performance on these measures between individuals with metabolic syndrome and normal controls will be small and may not reach statistical significance.

Hypotheses 3. To date, studies examining cognitive functioning in metabolic syndrome have focused on older adults; therefore, it is not clear whether changes in cognition will be observed in younger adults at risk for metabolic syndrome, nor is it clear if significant differences will be observed between middle-aged and older adults. However, given that the aging process and metabolic syndrome are both associated with changes in information processing speed, memory and executive functioning, it was hypothesized that if the current study found an interaction between age group and metabolic status, it would be within these domains. More specifically, middle-aged and older adults would perform significantly poorer on information processing speed, memory, and executive functioning relative to young, middle-aged, and older adults without metabolic syndrome and young adults at risk with metabolic syndrome. It was also hypothesized that young adults at risk with metabolic syndrome will be significantly more disinhibited relative to young, middle-aged, and older adults without metabolic syndrome.

II. METHODS

Participants

Participants for the current study included young adults (18-35 years of age, n = 31), middle-aged adults (45-54 years of age, n = 28), and older adults (65-86 years, n =32). Groups were matched for age and education. Participants were excluded if they were left-handed, or had a positive history of head injury with loss of consciousness > 5 minutes, substance use disorders, and neurological or psychiatric diseases. The total study sample consisted of 91 participants; the sample consisted of the following ethnicities: 83% Caucasian, 11% Hispanic, 3.3% Asian, and 2.2% African American.

Metabolic Criteria

The following inclusion criteria were used to determine metabolic status. According to the International Diabetes Federation (IDF; 2006) and subsequent modification (Alberti et al., 2009), for an individual to carry the diagnosis of metabolic syndrome they must have ≥ 3 of 5 of the following risk factors: central obesity, operationally defined as body mass index (BMI) >30kg/m^2 or waist circumference ≥ to 94 cm for males and 80 cm for females; raised triglycerides (≥ 150 mg/dL) or currently receiving treatment for dyslipidemia; reduced HDL cholesterol (< 40 mg/dL in males and < 50 mg/dL in females) or currently receiving treatment for dyslipidemia; raised blood pressure (BP; systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg) or treatment of diagnosed hypertension; and raised fasting plasma glucose (≥ 100 mg/dL) or previous diagnosis of type 2 diabetes. Ethnic specific vales of waist circumference were employed as outlined by the IDF (IDF, 2006); in particular, for

the present study, ethnic specific values were applied to Asian Americans, which was 3.3% of the current sample.

Blood pressure, height, weight, waist circumference, and systolic/diastolic blood pressures were measured. Calculations were performed for pulse pressure (systolic – diastolic blood pressure) and BMI (kg/m^2). Participants' self-reported a diagnosis and/or current treatment for raised triglycerides, reduced HDL, and type 2 DM.

Assessment

A broad range of neurocognitive measures were administered for the present experiment in order to provide a comprehensive assessment of cognitive functioning and to allow for the examination of domain specific composite scores, that is, the average of two or more test scores that require similar cognitive abilities (specified below).

As discussed earlier, there are inconsistencies within the literature regarding cognitive changes associated with metabolic syndrome, with a number of studies documenting no significant differences of cognitive performance between healthy individuals and those with metabolic syndrome (for review see Crichton et al., 2011). One reason for this inconsistency may be due to the failure to detect subtle cognitive changes on single tests above and beyond cognitive changes associated with normal aging, particularly in individuals whose cognitive performance is not expected to be in the clinically impaired range. There have been a number of studies that have used cognitive discrepancy analysis to detect subtle cognitive changes (Jacobson et al., 2009; Fine et al., 2008; Wetter et al., 2006; Bondi et al., 2008). Cognitive discrepancy

analysis allows for the comparison of subtle cognitive changes that might not be detected by examining mean differences in raw scores. In particular, cognitive discrepancy analysis consists of the subtraction of standardized scores of one cognitive task from another. Tests are selected a priori based on evidence that one task is likely to be more affected than another. In addition, cognitive discrepancy scores can also be used to examine asymmetric or dissimilar domains such as verbal relative to visuospatial abilities (Wilde et al., 2001; Finton et al., Jacobson et al., 2005). Given the inconsistency within the metabolic syndrome literature and the fact that these individuals are at risk for the development of Alzheimer's disease, the discrepancy analyses in the present experiment were based on previous studies investigating cognitive performance in individuals at risk for Alzheimer's disease (Jacobson et al., 2009; Fine et al., 2008; Wetter et al., 2006; Bondi et al., 2008) and those specified and normed in the D-KEFs manual (Delis et al., 2001).

The following neurocognitive measures were administered as part of a larger test battery:

Mini-Mental State Exam (MMSE). The MMSE is a brief measure of cognition (Folstein, Folstein, & McHugh, 1975). It is commonly administered to older adults as a screen for cognitive impairment and to track changes in cognition over time.

Dementia Rating Scale (DRS). The DRS is a global measure of cognition that can be administered to older adults with known or suspected dementia (Mattis, 1976). A global measure of cognition/dementia severity is calculated based on the

individual's cognitive abilities. Domains of cognition assessed include attention, initiation and perseveration, construction, conceptualization, and memory.

The total scores from the MMSE (Folstein et al., 1975) and DRS (Mattis, 1976) were used to exclude those whose scores enter the clinically impaired range, which is less than 24 for the MMSE and less than 130 for the DRS.

Wide Range Achievement Test-4 (WRAT-4). The WRAT-4 is a measure of basic academic skills that assesses Reading, Spelling, and Arithmetic (Wilkinson & Robertson, 2006). For the present experiment, the participants were administered the Reading subtest. The Reading subtest measures letter identification and word recognition. During the administration of the Reading subtest, participants were asked to verbally read a series of words. If the participant obtained a score of less than 5, they were asked to read a series of letters; the test was discontinued after 10 consecutive failed responses. The summary score from the WRAT-4 Reading subtest, in combination with self-report of highest level of education obtained at the time of testing, was used as an estimate of premorbid intellectual functioning and the quality of education (Manly, Jacobs, Touradji, Small, & Stern 2002).

Digit Span from the Wechsler Memory Scale - third edition (DS). The DS is a measure of auditory attention (Wechsler, 1997). During the administration of the DS, the examiner read a sequence of digits and the participant was asked to repeat the digits in the same order (forward) and, in a separate condition, in reverse order (backward). The test was discontinued after the participant failed to correctly repeat both trials of an item. DS total was used as a measure of attention.

Boston Naming Test-2 (BNT). The BNT-2 is a 60-item measure of verbal confrontation naming (Kaplan, Goodglass, & Weintraub, 2001). During the administration of the test, black and white drawings of common objects were presented and the participant was asked to provide the name of the object. Items were presented sequentially with increasing difficulty. A response was considered correct if the participant provided the appropriate name within the first 20 seconds or within 20 seconds after the stimulus cue was provided. If the participant failed to provide the correct name after the stimulus cue was provided, the item was scored incorrect and the phonemic cue was given. Testing began at item 30, if the participant missed one of the first 8 items, the examiner reversed until 8 consecutive items were identified. The test was discontinued after 8 failed attempts to name the object.

Delis-Kaplan Executive Function System (D-KEFS). The D-KEFS is a comprehensive set of tests aimed at assessing higher-level cognitive functions (Delis, Kaplan, & Kramer, 2001). The following subtests were administered as part of the present experiment: Trail Making Test, Verbal Fluency, Design Fluency, and Color-Word Interference Test.

D-KEFS Trail Making Test (TMT). Cognitive flexibility is the primary executive functioning skill measured in the TMT (Delis et al., 2001). There are 5 conditions of the TMT: Visual Scanning, Number Sequencing, Letter Sequencing, Number-Letter Switching, and Motor Speed. The Motor Speed condition required that the participant trace over a dotted line as quickly as possible; time to completion was used as a measure of motoric functioning. The Number Sequencing condition required that the participant draw a line connecting numbers in sequential order; time to

completion was used as a measure of information processing speed. The Number-Letter Switching condition required that the participant switch back and forth between connecting numbers and letters in sequential order; time to completion was used as a measure of cognitive flexibility.

D-KEFS Verbal Fluency. The Verbal Fluency subtest measures verbal response generation and cognitive flexibility (Delis et al., 2001). There are three main conditions: Letter Fluency, Category Fluency, and Category Switching. For all conditions, the participant had 60 seconds to complete the task. In the Letter condition, the participant was asked to generate as many words as they could that begin with a specific letter (F, A, and S); total correct responses over the three tails was used as a measure of fluency. During the Category condition, the participant was asked to generate as many words as they could that belong to a specific semantic category (animals and boy's names); total correct responses from the two trials was used as a measure of fluency. In the Category Switching condition, the participant was asked to generate words, switching between two difference semantic categories (fruits and pieces of furniture); total responses was used as a measure of cognitive flexibility.

D-KEFS Design Fluency. The Design Fluency subtest measures non-verbal response generation, inhibition, and cognitive flexibility (Delis et al., 2001). There are three main conditions: Filled Dots, Empty Dots, and Switching. For the purposes of the present experiment, the Filled Dot and Empty Dot conditions were used as a measure of fluency. During the Filled Dot condition, the participant was presented with rows of boxes containing only filled dots and was asked to connect the dots using only 4 straight lines. In the Empty Dot condition, the participant was presented with

rows of boxes containing 5 empty dots and 5 filled dots and was asked to connect only empty dots, which requires the inhibition of the previous task (Filled Dot). In the Switching condition, the participant was asked to connect dots, switching between empty and filled dos; number of total switches was used as a measure of cognitive flexibility.

D-KEFS Color-Word Interference Test (CWIT). The primary executive functioning abilities that are measured in the CWIT are inhibition of an overlearned response and cognitive flexibility (Delis et al., 2001). On 4 separate conditions, the examinee is asked to name the color of patches (Color Naming), read the names of colors presented in black ink (Word Reading), name the color of the ink that words are presented in and not read the words (Inhibition), and switch back and forth between naming the color of the ink that words are presented in and reading names of words presented in incongruent colors (Inhibition/Switching). Time to completion for the Color Naming condition will be used as a measure of information processing speed. The time to completion for the Inhibition condition will be used as a measure of impulsivity. Last, time to completion for the Inhibition/Switching condition will be used as a measure of cognitive flexibility.

California Verbal Learning Test-II (CVLT-II). The CVLT-II is a measure of verbal learning and memory (Delis, Kramer, Kaplan, & Ober, 2000). During the learning trials (Trials 1-5), the participant was verbally presented with a list of 16 words, which fall into 4 different semantic categories, and was asked to immediately recall all of the words. An interference list was then presented, consisting of 16 words that fall into 4 different semantic categories, followed by a short delay free recall

condition, where the participant was asked to recall from memory all of the items remembered, and a cued recall condition, where the participant was provided with 4 difference semantic cues. After a 20-mintue delay, the participant was asked to freely recall the words (long-delay free-recall) and was then prompted with cues (long-delay cued recall). Total Recall across Trials 1-5 was used as a measure of learning and long-delay free recall was used as a measure of delayed memory.

Brief Visuospatial Memory Test-Revised (BVMT-R). The BVMT-R is measure of visual learning and memory (Benedict, 1997). During the learning conditions, the participant was presented with a stimulus card, containing six geometric designs, for 10 seconds, and was instructed to study the designs on the stimulus card. Immediately following the removal of the stimulus card, the participant was asked to draw the designs that they remembered. After a 25-minute delay, the participant was asked to produce the designs again. To assess recognition memory the examinee was presented with 12 stimulus cards and instructed to respond "yes" to the designs previously presented and "no" to novel designs. For the learning and memory trials, each item was awarded two points if it was accurately drawn and in the correct location, 1 point was award if only one of the criteria is met, and 0 points were awarded if neither criterion was met or if no designs were drawn. Total correct responses across all three learning trials was used as a measure of visual learning. Total correct responses for the delayed condition was used as a measure of delayed memory.

Self-Report Questionnaires

Self-report questionnaires were administered to assess mood and impulsive personality traits. Specifically, the Beck Depression Inventory – Second Edition (Beck, Steer, & Brown, 1996) was used to screen for depressive symptoms; the State Trait Anxiety Inventory (Spielberger, Gorsuch, & Luschene, 1970) was used to screen for anxiety symptoms; The Three-Factor Eating Questionnaire (Srunkard & Messick, 1985) was used to assess food intake-behavior, including disinhibition; and the Barratt Impulsiveness Scale (BIS; Patton, Stanford, & Barratt, 1995) was used to assess for impulsiveness. The percentage of stroke risk was assessed using the Stroke Risk Assessment Test (D'Agostino, Wolf, Belanger, & Kannel, 1994).

Procedures

Participants were part of an ongoing NIH-funded fMRI research study (RO1-AG04085-25) aimed at investigating the relationship among chemosensory and cognitive processes in healthy aging and metabolic disease. Participants received monetary compensation for their participation. The Institutional Review Boards at San Diego State University and the University of California, San Diego have given approval for the experiment.

The current study was part of a larger neuroimaging study that consisted of four separate testing sessions. In the first session, the participant was screened for chemosensory functioning, general cognitive functioning, and metabolic status. Functional magnetic resonance imaging (fMRI) scans were conducted in the second and third sessions. During the fourth session, neuropsychological measures were administered. Total testing time for each participant was approximately 8 hours; each testing session lasted approximately 2 hours. Neuropsychological tests were

administered in accordance with the published manuals. The instruments were administered by two doctoral students in clinical psychology (one being the first author) and two additional research assistants (one being a NIMH- Career Opportunities in Research (COR) Scholar) in the SDSU Lifespan Human Senses Laboratory. All testers and scorers were trained in accordance with the published manuals. Tests were scored twice by two different scorers. After the data were entered into a spreadsheet, the accuracy was checked by two different research assistants.

Statistical Methods

Given that the aim of the present study was to examine the effect of age group and metabolic status and the interaction between age group and metabolic status, the individual measures were analyzed using both raw and age-corrected standardized scores. However, for the composite scores, discrepancy scores, and asymmetric scores, age-corrected standardized scores were employed for generaliziability. It should be noted that the Boston Naming Test corrects for age and education and that no significant differences in education were found among age groups or metabolic status for the current study. Z-score transformations were performed [(age-corrected standardized score – mean)/standard deviation], in order to combine test scores with different metrics, as outlined below.

Composite Scores. In order to create domain specific composite scores, the following age-corrected z-scores were averaged: (1) *Attention*: digit span total from the Wechsler Memory Scale 3rd edition and the attention subscale from the DRS; (2) *Information Processing Speed (IPS)*: Number and Letter sequencing conditions from the Trail Making Test (TMT); (3) *Learning*: CVLT-II (Total Trials 1-5) and BVMT-R

(Total Trials 1-3); (4) *Memory*: delayed recall conditions of the CVLT-II and BVMT-R; (5) *Fluency*: letter condition of the Verbal Fluency Test and the Filled Dot and Empty Dot conditions of the Design Fluency Test from the D-KEFS; (6) *Cognitive Switching:* Category Switching condition of the Verbal Fluency Test, Number-Letter Switching condition from the TMT, Switching condition from the Design Fluency, and the Inhibition/Switching condition of the CWIT from the D-KEFS; (7) *Language*: WRAT-4 Reading subtest, Boston Naming Test, and Category condition from the Verbal Fluency.

Contrast Scores. Contrast scores were computed using age-corrected standardized scores as follows: (1) **Cognitive Switching:** Trails Switching: Trail Making Test switching condition minus the average of the number and letter conditions, Verbal Switching: Verbal Fluency switching condition minus the category condition, Design Switching: Design Fluency switching condition minus the empty dot condition; and CWIT Switching: switching condition minus the average of the color naming and word reading conditions (2) **Memory**: Verbal Memory: CVLT-II long-delay free recall condition minus WRAT-4 reading and Figural Memory: BVMT long-delay free recall condition minus the construction; and (3) Semantic: Boston Naming test minus WRAT-4 Reading.

Asymmetric Scores. In order to examine potential asymmetric effects, absolute values were computed, from the age-corrected standardized scores, based on differences between variables, as follows: (1) Learning: CVLT-II total trials 1-5 minus BVMT total trials 1-3; Memory: CVLT-II long-delay free recall minus BVMT long-delay free recall; Fluency: Verbal Fluency letter condition minus Design Fluency

empty dot condition; and Switching: Verbal Fluency switching minus Design Fluency switching.

Data Screening

Prior to analysis, all variables were screened for normality of distribution and outliers. Normality of distribution was analyzed using the following statistics: Shapiro-Wilk, skewness, and kurtosis. Shapiro-Wilk analysis indentified several variables as being non-normally distributed including: composite scores (information processing speed, cognitive switching, memory), contrast scores (trails switching, verbal memory), and lateralized scores (learning, memory, fluency, and switching). With regard to kurtosis, one composite score (cognitive switching) and one lateralized score (learning) were significantly peaked, whereas, no variables were identified as being skewed. In addition, all analyses were screened for violations of homogeneity of variance using Levene's Test of Equality of Error Variances. The following scores violated homogeneity of variance: BMI, percent stroke risk, BDI, STAI (state anxiety). All analyses were conducted using parametric statistics; however, variables found to have non-normal distributions and/or violations of homogeneity of variance were re-analyzed using non-parametric statistics (i.e., Mann-Whitney U test); however, the results of the non-parametric analyses were unchanged, most likely due to the robustness of ANOVA. As such, for consistency and interpretation ease, parametric analyses used for interpretation in the current study.

In order to investigate the hypotheses outlined by the current study, statistical analyses, described below, were conducted. An alpha level of $p = .05$ was used for all

analyses in order to achieve a balance between small sample size and Type I and Type II errors.

Demographic Information

For continuous variables, three separate between subjects multivariate analysis of variance (MANOVA) were performed to examine the relationship between age group and metabolic status and 1) *Demographic Characteristics:* education, MMSE and DRS; 2) *Body Measurements*: weight (lbs), height (cm), body mass index (BMI), waist circumference, systolic blood pressure, diastolic blood pressure, pulse pressure, and percentage of stroke risk; and 3) *Self-Report Measurements*: BDI, STAI (state and trait indices), TFEQ (cognitive restraint, disinhibition, hunger), and BIS (first order factors: attention, motor, self control, cognitive complexity, perseverance, cognitive instability). Newman-Keuls Multiple Range tests were used to probe the significant interactions at an alpha of .05. For dichotomous variables, Pearson's chi-square analyses were performed to examine potential associations between metabolic status and age group for metabolic criteria [waist circumference, BMI, raised blood pressure, raised triglycerides, reduced HDL cholesterol, diabetes] and gender.

Cognitive Functioning

Analysis of variance (ANOVA) tests were conducted to examine potential associations of age group and metabolic status with cognitive functioning for the composite scores, contrast scores, and lateralized scores among age group and metabolic status. Newman-Keuls Multiple Range tests were used to probe the significant effects at an alpha of .05.

Individual Measure Analysis. In order to determine which individual measures were significantly related age group, metabolic status, and the interaction between metabolic status and age group, ANOVA tests were run separately on the raw and age-corrected standardized scores. In particular, the following indices were examined: CVLT-II total trials 1-5 and long-delay free recall; BVMT total trials 1-3 and delay; digit span; BNT; WRAT-4 reading; verbal fluency: letter, category, category switching, set-loss errors; design fluency: filled dots, empty dots, switching, set-loss errors and repetitions; trail making test: number, letter, number-letter switching; and color-word interference test: color naming, word reading, inhibition, inhibition/switching, inhibition errors, and inhibition/switching errors.

Discrepancy Scores. Contrast scores were created based on the age-corrected standardized scores for Verbal Fluency: Verbal Fluency switching condition minus the category condition; Design Fluency: average of the filled and empty dot condition and switching condition minus the average of the filled and empty dot conditions; Trail Making Test: average of the number and letter conditions, and switching condition minus the average of the number and letter conditions; and CWIT: average of the color naming and word reading conditions, and switching condition minus the average of the color naming and word reading conditions. Significant effects with more than two means were followed up with Newman-Keuls multiple range tests at an alpha of .05.

Exploratory analyses. As a follow-up to the main analysis, the raw data and standardized data were re-analyzed without the young adult cohort in order to examine the effect of metabolic syndrome on cognitive performance between middle-age and

older adults. The young adult cohort was removed given that we did not anticipate significant declines in cognitive performance other than disinhibition.

III. RESULTS

A total of a 91 individuals participated in the study. Participants were classified as young (age 18-35), middle-age (age 45-54), and older (age 65-86) adults. Based on the metabolic syndrome criteria outlined above, individuals were classified as either having metabolic syndrome or as normal controls (See Table 1). For the young adult metabolic cohort, all participants met criteria for obesity. As previously discussed, prevalence of metabolic syndrome in young adults is estimated to be 20.3% and 15.6% for male and females, respectively (Loyd-Jones et a., 2010). For the present young adult metabolic cohort, 14.3% of participants met full criteria (3 out of 5 risk factors), 21.4% met partial criteria (2 out of 5 risk factors), and 64.3% were classified as only obese. Obesity is associated with increased risk for the development of metabolic syndrome over the lifespan. As such, for the purpose of the present manuscript the metabolic young cohort will be operationally defined as obese with additional risk factors.

Demographic Information

Demographic Characteristics. There were no significant effects of age group, metabolic status, or interactions between metabolic status and age group for years of education, MMSE, or DRS (Table 1). Cross tabulation analyses were conducted to investigate whether gender was significantly related to metabolic status and age group. Statistical significance was evaluated with Person's chi square test ($p < 0.01$). As expected, there was no significant difference in the proportion of males and females among age groups and metabolic status

Body Measurements. There were significant differences in body measurements for metabolic status [$F(1,88) = 8.00$, $p < .001$, $\eta^2 = .72$] and age group ([$F(2,88) = 16.00$, $p < .001$, $\eta^2 = .43$]; Table 2); however, there were no significant interactions between age group and metabolic status. For the main effect of metabolic status, there were significant differences between individuals with metabolic syndrome and controls for weight, BMI, and waist circumference ($p < .01$; Figure 1). Individuals with metabolic syndrome had significantly greater weight, BMI, and waist circumference relative to controls. For the main effect of age group, there were significant differences for weight, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, pulse pressure, and percent stroke risk ($p < .01$; Figure 2). Significant differences were follows, weight (lbs): middle-aged adults weighed significantly more than young and older adults; BMI: middle-aged adults had significantly greater BMI than young and older adults; waist circumference: middle-aged adults had significantly greater waist circumference than young and older adults; systolic blood pressure: older adults had significantly greater systolic blood pressure than young and middle-aged adults; diastolic blood pressure: middle-aged adults had significantly greater diastolic blood pressure than young and older adults; pulse pressure: older adults had significantly greater pulse pressure than young and middle-aged adults; stroke risk: older adults had significantly greater stroke risk than young and middle-aged adults.

Self-Report Measurement*s*. There were significant differences in self-report measurements for metabolic status [$F(1,84) = 13$, $p < .02$, $\eta^2 = .30$], Table 3); however, there were no significant differences for age group and there was no

significant interaction between age group and metabolic status. For the main effect of metabolic status, there were significant differences between individuals with metabolic syndrome and controls for the TFEQ: disinhibition and TFEQ: hunger ($p < .01$; Figure 3); individuals with metabolic syndrome had significantly greater self-reported disinhibited eating and hunger.

Metabolic Criteria. Cross tabulation analyses were conducted to investigate whether metabolic criteria were significantly related to metabolic status and age group. Statistical significance was evaluated with Person's chi square test ($p < 0.01$). As expected, the proportion of individuals who were classified as meeting the metabolic criterion for waist circumference, BMI, raised blood pressure, raised triglycerides, reduced HDL, and DM was significantly different between metabolic status groups (metabolic and normal controls). Moreover, as expected, the proportion of individuals who were classified meeting criteria for waist circumference, BMI, raised triglycerides, reduced HDL, and DM was not significantly different among age groups; suggesting that age is independent from these metabolic criteria (Table 4). However, the presence of high blood pressure was associated with age group.

Table 1: Demographic Characteristics of Participants

	Age Group & Metabolic Status					
Variable	Young Control (n=17)	Young Metabolic (n=14)	Middle-age Control (n=15)	Middle-age Metabolic (n=13)	Older Control (n=13)	Older Metabolic (n=19)
Age	22.69 (2.24)	24.10 (3.63)	50.13 (2.92)	50.77 (2.80)	72.25 (5.67)	71.61 (6.29)
Education	15.25 (1.39)	14.30 (2.21)	14.80 (2.11)	15.31 (2.36)	14.67 (2.46)	15.00 (2.61)
Gender (% Male)	41.2	42.9	46.7	38.5	69.2	36.8
MMSE	29.56 (1.03)	29.20 (.79)	29.33 (.90)	28.85 (1.95)	29.00 (.74)	28.44 (1.29)
DRS	141.25 (2.08)	140.60 (1.43)	141.27 (2.37)	141.31 (1.93)	140.83 (1.90)	141.94 (2.46)

Note. MMSE = Mini-mental Status Examination; DRS = Dementia Rating Scale

Table 2: Body Measurements of Participants

	Age Group & Metabolic Status					
Variable	Young Control	Young Metabolic	Middle-age Control	Middle-age Metabolic	Older Control	Older Metabolic
Weight (lbs)	151.54 (30.84)	228.55 (29.67)	161.70 (27.61)	255.22 (40.17)	160.73 (25.67)	193.21 (38.83)
Height (cm)	172.57 (12.23)	171.64 (7.29)	171.20 (9.40)	168.88 (7.56)	172.84 (13.89)	164.60 (9.65)
BMI	22.86 (2.57)	35.01 (3.56)	24.85 (2.73)	39.89 (6.39)	24.71 (2.73)	32.28 (6.54)
Waist Circumference (cm)	80.69 (10.54)	108.22 (6.59)	91.11 (13.33)	119.70 (11.27)	90.24 (9.39)	107.04 (13.05)
Systolic Blood Pressure	121.06 (14.05)	126.81 (7.03)	124.59 (21.21)	135.77 14.01)	144.81 (21.92)	138.34 (16.56)
Diastolic Blood Pressure	71.05 (10.70)	72.65 (5.34)	76.60 (13.07)	82.41 (8.28)	74.85 (11.90)	72.13 (9.72)
Pulse Pressure	50.01 (11.33)	54.15 (7.72)	47.99 (14.68)	53.33 (10.42)	69.96 (15.08)	66.19 (18.77)
Stroke Risk (%)	2.59 (1.58)	2.92 (1.04)	3.00 (1.51)	5.08 (3.95)	11.58 (4.81)	15.11 (10.28)

Note. BMI = body mass index; lbs = pounds, cm = centimeters

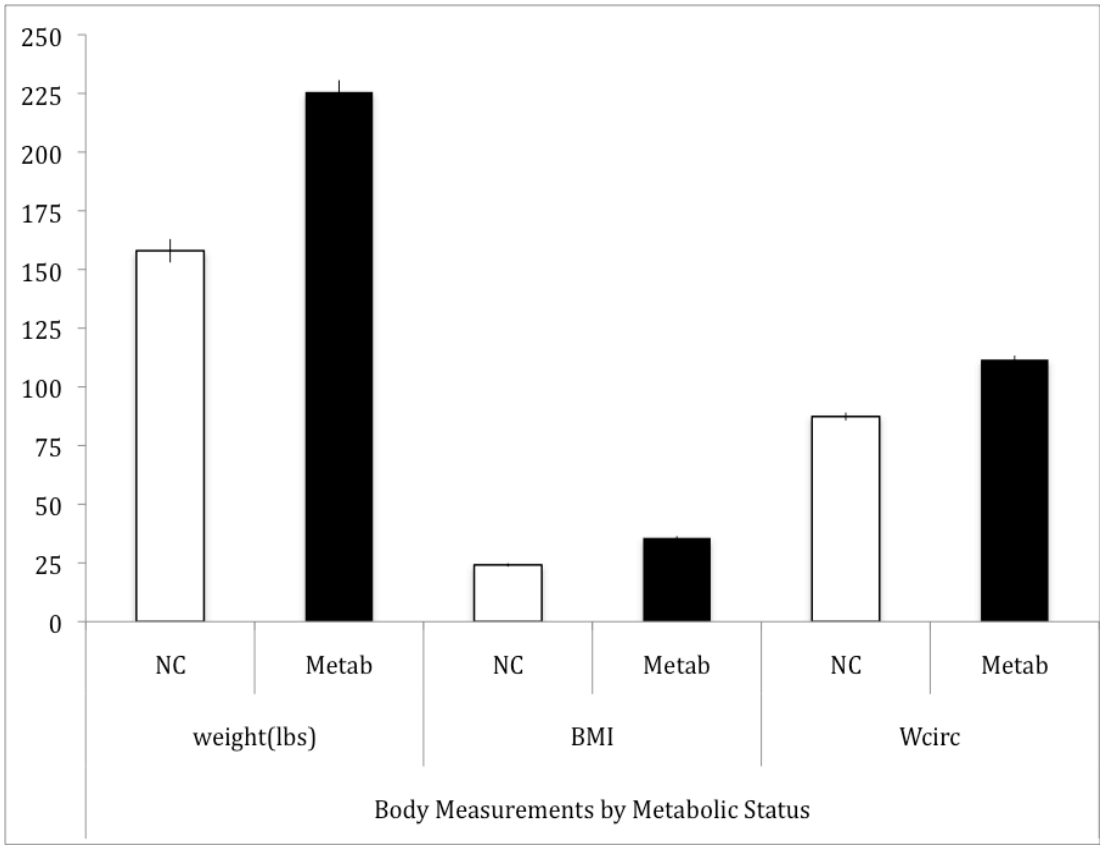

Figure 1: Body Measurements for Participants by Metabolic Status
Note. NC = normal controls; Metab = Metabolic Status; BMI = body mass index; Wcirc = waist circumference; error bars = standard errors.

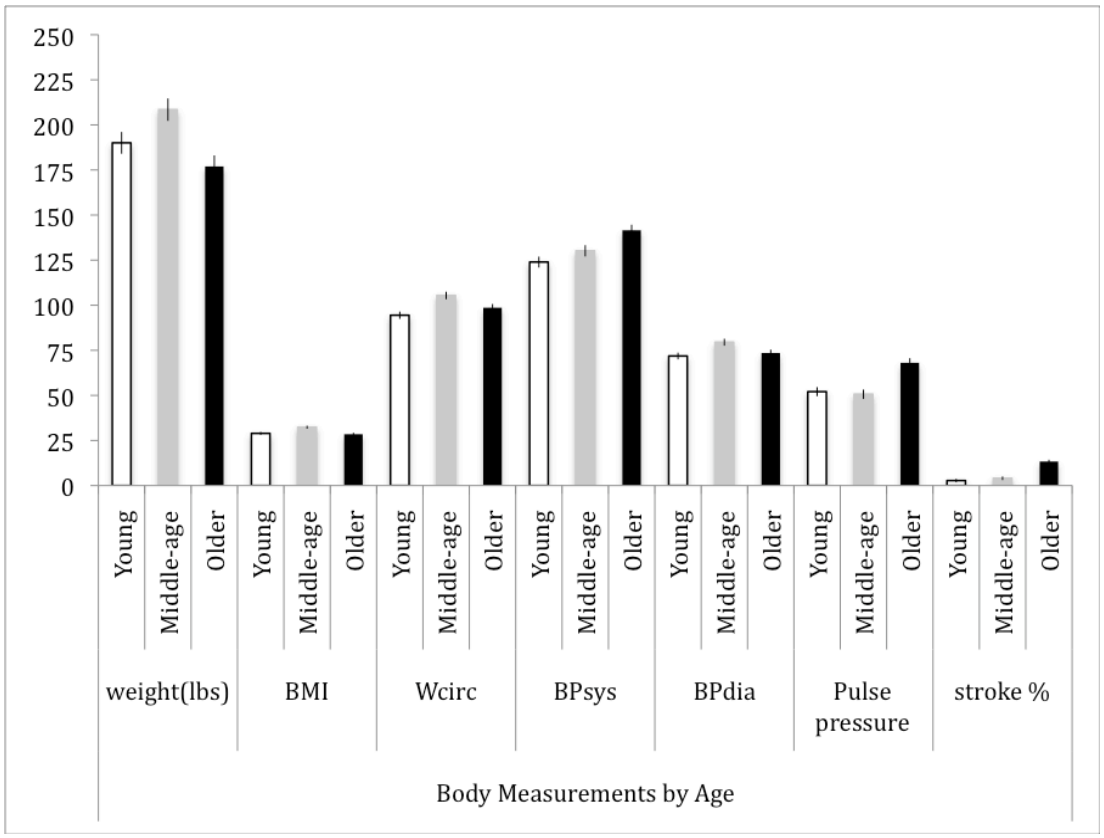

Figure 2: Body Measurements for Participants by Age Group
Note. BMI = body mass index; Wcirc = waist circumference; BPsys: systolic blood pressure; BPdai = diastolic blood pressure

Table 3: Self-Report Measurements of Participants

	Age Group & Metabolic Status					
Variable	Young Control	Young Metabolic	Middle-age Control	Middle-age Metabolic	Older Control	Older Metabolic
BDI	5.06 (3.88)	5.80 (4.87)	8.07 (11.98)	10.69 (8.24)	4.70 (3.71)	8.58 (7.89)
STAI: State	28.82 (6.42)	28.60 (5.48)	32.27 (13.55)	32.23 (8.17)	27.50 (6.77)	32.47 (10.30)
STAI: Trait	34.29 (7.19)	33.50 (7.53)	34.60 (12.54)	33.38 (8.87)	30.80 (7.45)	34.42 (9.66)
TFEQ: Cognitive Restraint	8.76 (4.48)	9.80 (5.01)	9.60 (5.23)	8.85 (4.54)	10.30 (5.27)	10.84 (3.59)
TFEQ: Disinhibition	4.88 (3.04)	6.00 (2.45)	3.87 (4.17)	10.31 (3.01)	5.30 (3.92)	6.47 (3.50)
TFEQ: Hunger	3.71 (2.37)	4.40 (3.75)	3.33 (3.04)	6.69 (3.09)	3.20 (3.22)	5.26 (3.16)
BIS: Attention	9.76 (2.61)	9.70 (2.21)	9.40 (1.64)	10.46 (1.81)	8.80 (2.30)	10.53 (2.48)
BIS: Motor	13.71 (2.26)	13.70 (3.06)	14.27 (3.67)	16.23 (2.77)	14.50 (2.68)	13.26 (2.81)
BIS: Self-control	12.06 (3.85)	10.70 (2.50)	13.47 (3.20)	14.08 (3.77)	10.00 (3.16)	11.63 (3.29)
BIS: Cognitive Complexity	11.06 (1.52)	10.50 (2.64)	11.60 (3.02)	12.08 (2.36)	12.30 (2.63)	11.05 (3.14)
BIS: Preservative	7.12 (1.41)	6.70 (1.64)	8.13 (2.03)	8.69 (2.40)	7.30 (1.34)	7.68 (1.95)
BIS: Cognitive Instability	5.88 (1.80)	6.30 (1.77)	5.67 (1.18)	5.54 (1.61)	5.10 (1.60)	6.11 (2.05)
BIS: First order factor	59.53 (8.35)	57.60 (8.82)	62.53 (10.32)	67.08 (10.62)	58.00 (8.63)	60.26 (9.39)

Note. BDI = Beck Depression Inventory-II; STAI = State Trait Anxiety Inventory; TFEQ = Three-Factor Eating Questionnaire; BIS = Barratt Impulsiveness Scale

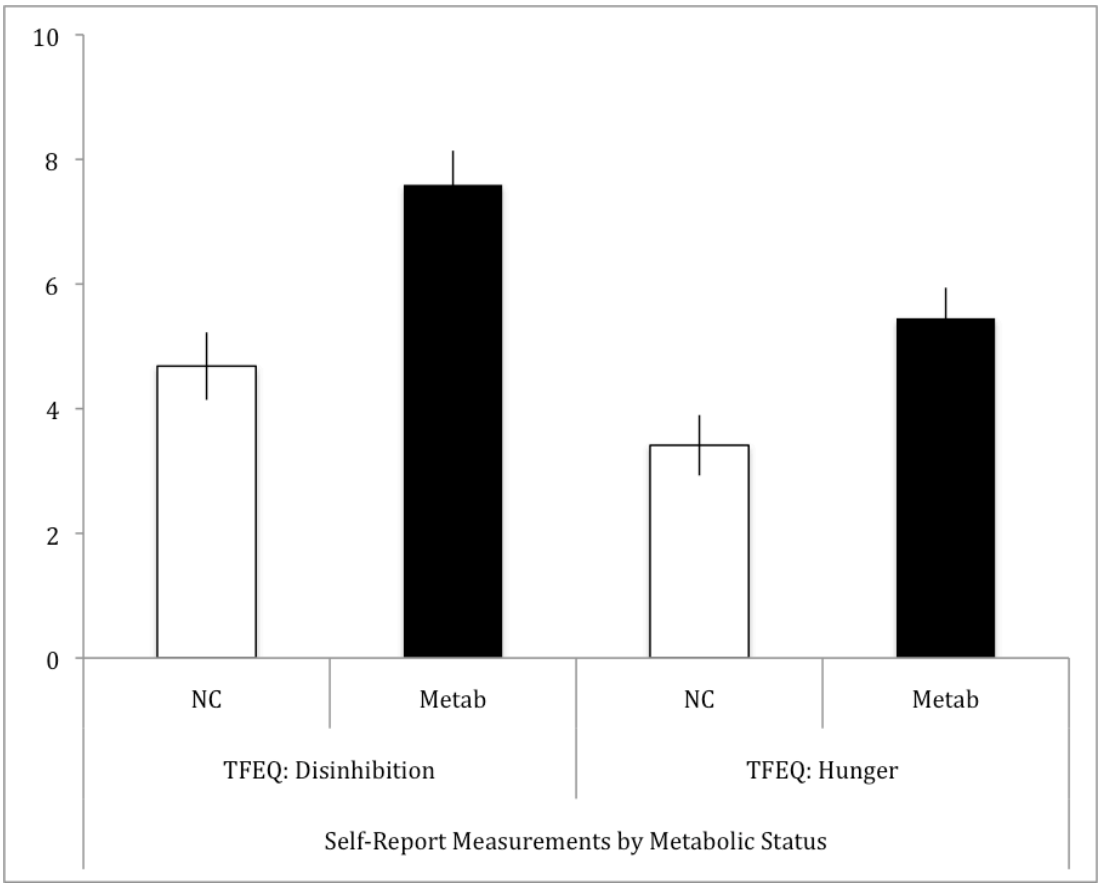

Figure 3: Self-Report Measurements for Participants by Metabolic Status
Note. NC = normal controls; Metab = Metabolic Status; TFEQ = three-factor eating questionnaire

Table 4: Percentage of Participants Meeting Metabolic Criteria

	Age Group		
Variable	Young	Middle- Age	Older
Waist Circumference	64.5	75.0	81.3
BMI	45.2	46.4	37.5
Raised Blood Pressure	29.0	60.7	93.8
Raised Triglycerides	32.3	50.0	56.3
Reduced HDL	32.3	50.0	56.3
Diabetes	3.2	17.9	21.9

Note. BMI = body mass index; HDL = high-density lipoprotein

Cognitive Functioning

Hypothesis 1. Relationship Between Age Group and Cognitive Functioning

Table 5 summarizes the age-corrected means, standard deviations, F-values, partial eta squares, and significance of each combined score (composite, contrast, lateralized) for age group and metabolic status. For composite scores there was a main effect of age group for language; older adults performed significantly better on measures of language than young and middle-age adults. Additionally, there were several main effects of age group for the contrast scores including verbal switching, verbal memory, and semantic. For the verbal switching contrast, middle-aged adults performed significantly better than young and older adults on the verbal fluency category switching condition than the category condition. For the verbal memory contrast, middle-aged adults performed significantly better on CVLT-II LDFR than WRAT-4 Reading, relative to young and older adults. For the semantic memory contrast, older adults performed significantly better on the BNT than WRAT-4 Reading, relative to young adults.

Individual Measures.

Table 6 summarizes the age-corrected means, standard deviations, F-values, partial eta squares, and significance of each standardized score for young, middle-aged, and older adults. There were main effects of age group for CVLT-II learning, verbal fluency set loss, design fluency set loss errors, trail making test, number condition, and trail making, number+letter condition. For CVLT-II learning, middle-aged and older adults performed significantly better on CVLT-II learning than young adults. For the BNT, older adults performed significantly better than young and

middle-aged adults. For verbal fluency and design fluency set loss conditions, young adults made significantly fewer set loss errors than middle-aged and older adults. For TMT number condition and number+letter contrast, older adults were significantly faster than young adults. There were no other significant effects of age group for the individual measures.

Table 7 summarizes the raw score (uncorrected for age) means, standard deviations, F-values, partial eta squares, and significance for young, middle-aged, and older adults. Figures 4-8 depict significant effects. There were several main effects of age group including CVLT-II Total 1-5 and LDFR; BVMT- Total 1-3 and delay; digit span; verbal fluency switching and set loss errors; design fluency filled dot condition, empty dot, and switching conditions; trail making test number, letter, and number letter conditions; and color-word interference test inhibition and inhibition/switching conditions. For the CVLT-II Total 1-5, young adults and middle-aged adults performed significantly better than older adults; CVLT-II LDFR, young adults and middle-aged adults performed significantly better than older adults; BVMT- Total 1-3, young adults performed better than middle-aged and older adults; and BVMT- delay, young adults performed better than older adults (Figure 4). For the digit span, young adults performed better than older adults; verbal fluency switching, young adults and middle-aged adults performed significantly better than older adults; and verbal fluency set loss errors, older adults made significantly more set loss errors than young adults (Figure 5). For the design fluency filled dot condition, young adults and middle-aged adults performed significantly better than older adults; design fluency empty dot condition, middle-aged adults performed significantly better than older adults; design

fluency switching, young adults performed significantly better than middle-aged and older adults (Figure 6). For the trail making test number, letter, and number/letter switching conditions, older adults were significantly slower than young and middle-aged adults (Figure 7). For the color-word interference test inhibition condition, older adults were significantly slower than young and middle-aged adults; and color word interference test inhibition/switching condition, older adults were significantly slower than young adults (Figure 8).

Table 5: Combined Score Means and Standard Deviations of Cognitive Performance for Age Group and Metabolic Status

	Age Group and Metabolic Status							
	Young Control	Young Metabolic	Middle-age Control	Middle-age Metabolic	Older Control	Older Metabolic		
Composite Scores	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	Partial Eta Squared
IPS	.12 (.20)	.05 (.22)	.11 (.21)	.15 (.22)	.49 (.22)	.11 (.18)	-	_
Attention	.77 (.14)	.50 (.15)	.53 (.15)	.62 (.16)	.71 (.16)	.75 (.13)	_	_
Learning	.06 (.23)	-.04 (.26)	.34 (.25)	.23 (.27)	.56 (.27)	.23 (.22)	_	_
Memory	.08 (.24)	-.29 (.26)	.55 (.25)	.32 (.27)	.54 (.27)	.10 (.22)	_	_
Fluency	.33 (.21)	.55 (.23)	.72 (.23)	.59 (.24)	1.07 (.24)	.49 (.20)	_	_
Cognitive Set-Shifting	.42 (.17)	.43 (.18)	.64 (.18)	.50 (.19)	.56 (.19)	.40 (.16)	_	_
Language	.39 (.17)	.46 (.19)	.34 (.18)	.42 (.19)	1.04 (.19)	.90 (.16)	$F^1 = 6.85^{**}$ $F^2 = .00$ $F^3 = .26$	$\eta^2 = .14$ $\eta^2 = .00$ $\eta^2 = .01$
Contrast Scores								
Trails switching	-.49 (.20)	-.12 (.22)	-.49 (.22)	-.46 (.23)	-.46 (.23)	-.61 (.19)	_	_
Verbal switching	-.12 (.26)	-.57 (.29)	.36 (.28)	.26 (.30)	-.41 (.30)	-.54 (.25)	$F^1 = 4.32^{*}$ $F^2 = .997$ $F^3 = .25$	$\eta^2 = .09$ $\eta^2 = .01$ $\eta^2 = .01$
Design switching	.29 (.20)	-.21 (.22)	-.36 (.21)	-.10 (.22)	-.59 (.22)	.25 (.19)	$F^1 = .92$ $F^2 = 1.28$ $F^3 = 5.38^{**}$	$\eta^2 = .02$ $\eta^2 = .02$ $\eta^2 = .11$
CWIT switching	.22 (.20)	.29 (.22)	.29 (.21)	.21 (.23)	.08 (.23)	.04 (.19)	_	_
Verbal memory	-.64 (.32)	-.68 (.35)	.25 (.34)	.23 (.36)	-.52 (.36)	-.70 (.30)	$F^1 = 4.31^{*}$ $F^2 = .08$ $F^3 = .03$	$\eta^2 = .09$ $\eta^2 = .00$ $\eta^2 = .00$
Figural memory	-.02 (.27)	-.37 (.30)	.58 (.29)	.03 (.31)	.66 (.31)	.16 (.26)	$F^1 = 2.56$ $F^2 = 3.99^{*}$ $F^3 = .07$	$\eta^2 = .06$ $\eta^2 = .05$ $\eta^2 = .00$
Semantic	-1.22 (.31)	-.64 (.35)	-.45 (.33)	-.26 (.36)	.26 (.36)	.16 (.30)	$F^1 = 5.97^{**}$ $F^2 = .65$ $F^3 = .55$	$\eta^2 = .12$ $\eta^2 = .01$ $\eta^2 = .01$
Asymmetric Scores								
Learning	1.02 (.18)	.67 (.20)	1.10 (.19)	.89 (.21)	1.06 (.21)	.96 (.17)	_	_
Memory	.75 (.19)	1.13 (.21)	.64 (.20)	.89 (.22)	.79 (.22)	.90 (.18)	_	_

Table 5: Continued

	Age Group and Metabolic Status							
	Young Control	Young Metabolic	Middle-age Control	Middle-age Metabolic	Older Control	Older Metabolic		
Fluency	1.08 (.19)	.95 (.21)	.96 (.20)	1.41 (.22)	.98 (.22)	1.02 (.18)	_	_
Switching	1.04 (.19)	.93 (.21)	.85 (.20)	1.08 (.22)	.95 (.22)	.93 (.18)	_	_

Note. IPS = information processing speed; CWIT = color-word interference test; ** = p<.01; * = p<.05; F1 = main effect of age group; F2 = main effect of metabolic status; F3 = interaction between age group and metabolic status

Table 6: Standardized Score Means and Standard Deviations of Cognitive Performance for the Main Effect of Age Group

	Age Group				
	Young	Middle-age	Older		
Standardized Scores	Mean(SD)	Mean(SD)	Mean(SD)	F	Partial Eta Squared
CVLT 1-5	50.97 (1.89)	56.65 (1.99)	56.91 (1.89)	3.11*	.07
CVLT LDFR	-.02 (.21)	.64 (.22)	.28 (.21)	_	_
BVMT 1-3	49.23 (2.10)	49.10 (2.20)	51.05 (2.09)	_	_
BVMT Delay	48.06 (1.97)	52.29 (2.07)	53.61 (1.97)	_	_
Digit Span	11.98 (.53)	11.24 (.56)	12.14 (.53)	_	_
BNT	47.14 (2.10)	50.51 (2.24)	60.95 (2.01)	11.70**	.22
WRAT-4 Reading	109.62 (2.40)	106.09 (2.52)	114.29 (2.42)	_	_
Verbal Fluency					
Letter	11.08 (.65)	11.88 (.68)	12.15 (.64)	_	_
Category	12.73 (.56)	12.02 (.59)	12.78 (.56)	_	_
Switch	11.81 (.60)	12.93 (.63)	11.35 (.60)	_	_
Set loss	12.20 (.39)	10.98 (.41)	10.01 (.39)	7.89**	.16
Design Fluency					
Filled	11.31 (.56)	11.55 (.59)	12.01 (.56)	_	_
Empty	11.07 (.52)	12.09 (.55)	12.04 (.52)	_	_
Filled + Empty	11.45 (.50)	12.13 (.53)	12.28 (.50)	_	_
Switching	11.85 (.48)	11.42 (.51)	11.73 (.48)	_	_
Set Loss	12.42 (.43)	10.90 (.45)	9.94 (.43)	8.44**	.17
Repetitions	11.38 (.41)	10.51 (.43)	10.12 (.41)	_	_

Table 6: Continued

	Age Group				
	Young	Middle-age	Older		
Trail Making Test					
Number	11.19 (.40)	11.62 (.41)	12.71 (.39)	3.94*	.09
Letter	10.75 (.42)	11.50 (.44)	12.16 (.42)	_	_
Number + Letter	11.63 (.44)	12.24 (.46)	13.26 (.43)	3.57*	.08
Number-Letter Switching	10.86 (.43)	11.08 (.45)	11.46 (.43)	_	_
Color Word Interference Test					
Color	9.47 (.48)	9.92 (.51)	10.95 (.48)	_	_
Reading	10.34 (.47)	10.17 (.50)	10.73 (.47)	_	_
Color + Reading	10.22 (.43)	10.40 (.45)	11.12 (.43)	_	_
Inhibition	10.99 (.47)	11.16 (.49)	10.96 (.47)	_	_
Inhibition Switching	10.58 (.46)	11.41 (.49)	11.40 (.47)	_	_
Inhibition Error	10.33 (.46)	10.71 (.48)	11.18 (.47)	_	_
Inhibition Switching Error	10.91 (.33)	10.84 (.34)	11.31 (.34)	_	_
Contrasts					
Trails Switching	9.23 (.47)	8.73 (.49)	8.02 (.47)	_	_
Verbal Switching	10.68 (.53)	10.67 (.55)	10.99 (.52)	_	_
Design Switching	10.41 (.44)	9.35 (.46)	9.48 (.44)	_	_
Color Word Interference Switching	10.36 (.39)	11.01 (.41)	9.99 (.39)	_	_

Note. CVLT = California Verbal Learning Test 2; LDFR = long-delay free recall; BVMT = Brief Visuosptial Memory Test; BNT = Boston Naming Test; WRAT-4 = Wide Range Achemient Test 4; ** = p<.01; * = p<.05.

Table 7: Raw Score Means and Standard Deviations of Cognitive Performance for the Main Effect of Age Group

	Age Group				
	Young	Middle-age	Older		
Raw Scores	Mean(SD)	Mean(SD)	Mean(SD)	F	Partial Eta Squared
CVLT 1-5	53.30 (1.85)	53.10 (1.90)	46.80 (1.83)	4.04*	.09
CVLT LDFR	11.99 (.62)	12.54 (.63)	9.89 (.61)	5.15**	.11
BVMT 1-3	27.46 (1.11)	23.43 (1.17)	21.10 (1.11)	8.35**	.16
BVMT Delay	10.31 (.40)	9.51 (.42)	8.75 (.40)	3.81*	.08
Digit Span	19.98 (.70)	18.58 (.73)	17.23 (.70)	3.89*	.08
BNT	53.86 (1.30)	54.67 (1.36)	57.20 (1.30)	_	_
WRAT-4 Reading	63.56 (.91)	64.05 (.95)	64.71 (.90)	_	_
Verbal Fluency					
Letter	40.76 (2.22)	43.99 (2.33)	42.38 (2.22)	_	_
Category	44.97 (1.48)	43.80 (1.55)	40.51 (1.48)	_	_
Switch	15.04 (.51)	15.82 (.54)	13.06 (.51)	7.54**	.15
Set loss	.50 (.30)	1.29 (.32)	2.14 (.30)	7.28**	.15
Design Fluency					
Filled	11.28 (.62)	11.43 (.65)	9.22 (.62)	3.91*	.08
Empty	12.25 (.63)	12.75 (.66)	10.50 (.63)	3.43*	.08
Filled + Empty	23.53 (1.15)	24.18 (1.20)	19.72 (1.14)	4.33*	.09
Switching	9.82 (.47)	8.34 (.49)	7.04 (.46)	9.00**	.18
Set Loss	1.58 (.48)	2.18 (.51)	3.17 (.48)	_	_
Repetitions	3.81 (.78)	5.73 (.82)	4.65 (.76)	_	_
Trails Making Test					
Number	25.66 (2.13)	29.75 (2.24)	38.96 (2.13)	10.23**	.19
Letter	26.54 (2.32)	31.12 (2.44)	41.55 (2.31)	10.99**	.21

Table 7: Continued

	Age Group				
	Young	Middle-age	Older		
Number + Letter	52.20 (4.00)	60.86 (4.20)	80.54 (3.99)	13.13**	.24
Number-Letter Switching	60.51 (5.73)	76.36 (6.02)	103.01 (5.71)	14.08**	.25
Color Word Interference Test					
Color	28.68 (1.21)	29.68 (1.18)	31.36 (1.12)	_	_
Reading	21.45 (.88)	22.36 (.92)	23.98 (.87)	_	_
Color + Reading	50.13 (1.83)	52.04 (1.92)	55.34 (1.8)	_	_
Inhibition	46.69 (2.58)	52.85 (2.71)	68.06 (2.58)	18.13**	.29
Inhibition Switching	53.55 (3.76)	60.42 (3.95)	68.42 (3.75)	3.92*	.08
Inhibition Error	1.30 (.39)	.89 (.41)	1.50 (.40)	_	_
Inhibition Switching Error	1.12 (.34)	1.16 (.36)	1.99 (.35)	_	_
Contrasts					
Trails Switching	8.31 (4.61)	15.50 (4.84)	22.49 (4.60)	_	_
Verbal Switching	-29.93 (1.30)	-27.98 (1.37)	-27.45 (1.30)	_	_
Design Switching	-2.42 (.50)	-4.41 (.53)	-3.46 (.50)	3.76*	.08
Color Word Interference Switching	3.43 (3.28)	8.38 (3.44)	13.08 (3.27)	_	_

Note. See Table 6 for abbreviations. ** = p<.01; * = p<.05.

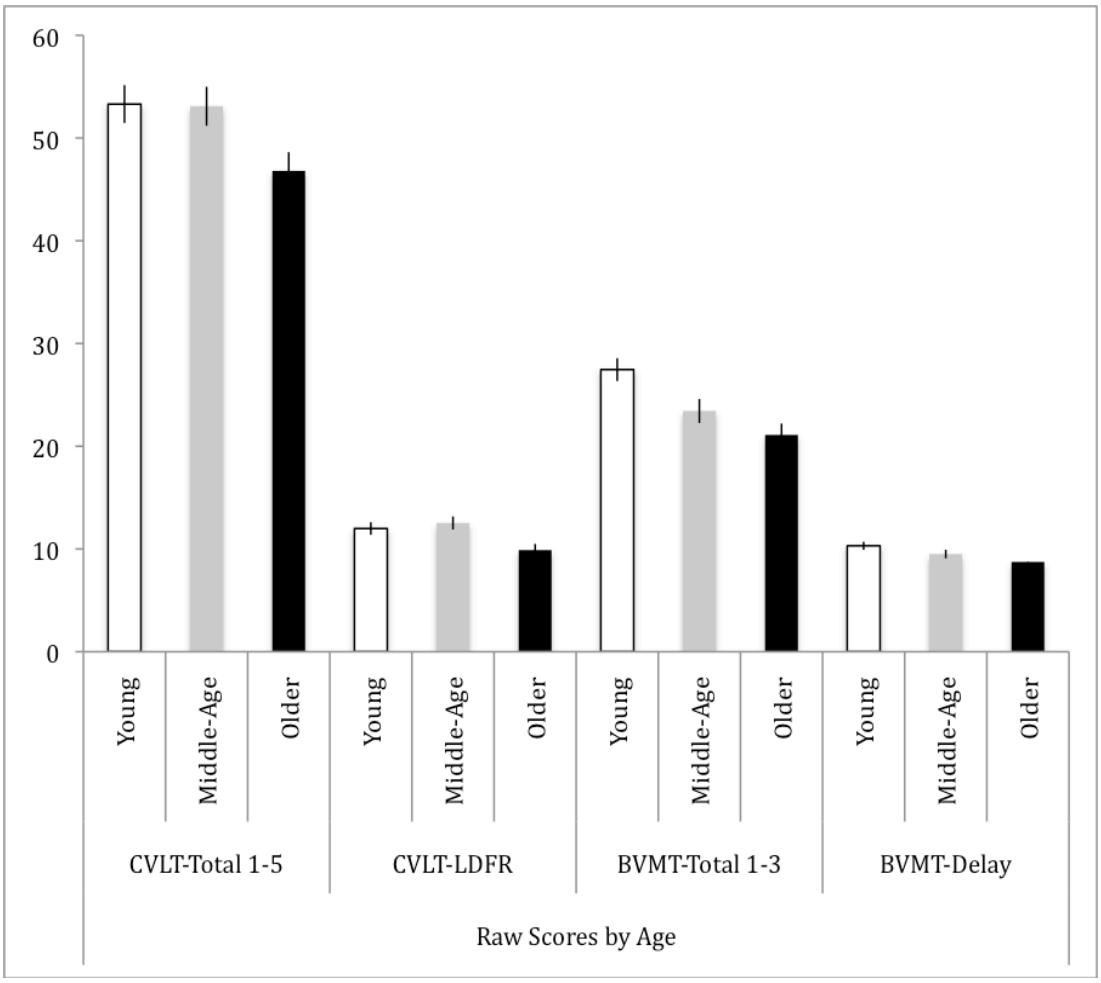

Figure 4: Raw Scores: Significant Effects of Age Group
Note. CVLT = California Verbal Learning Test; LDFR = long-delay free recall; BVMT = Brief Visuosptial Memory Test

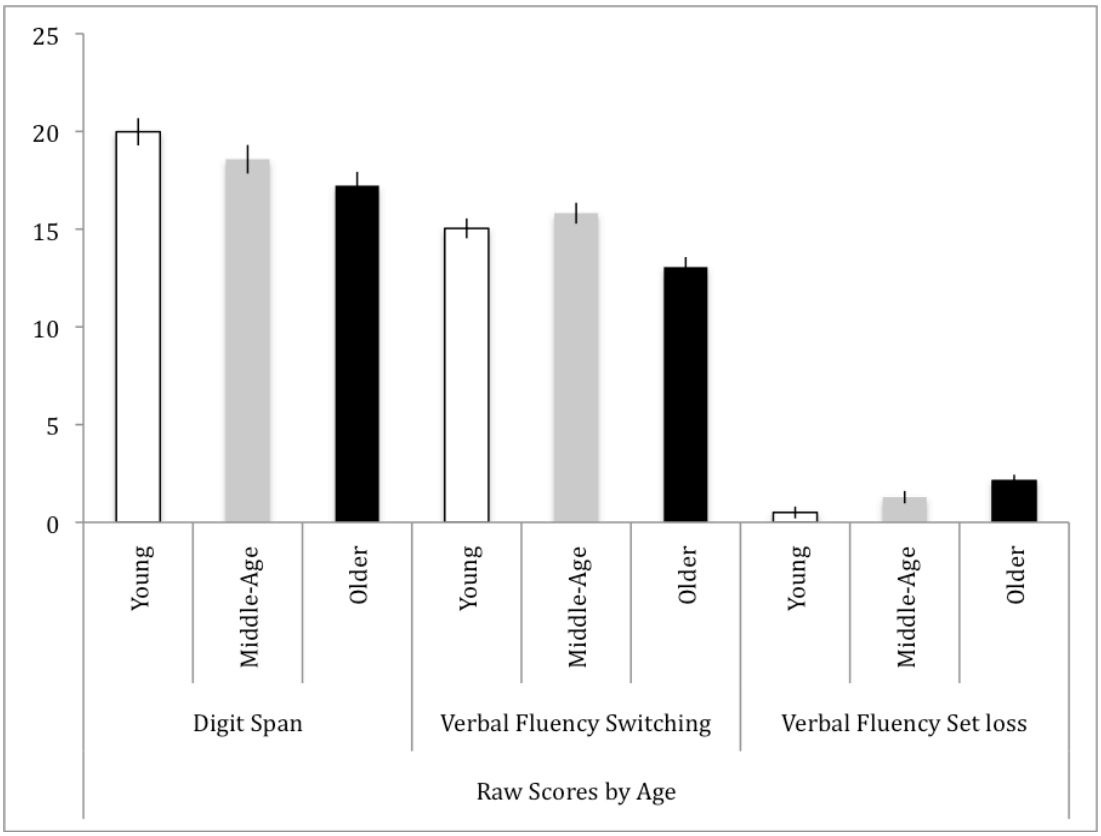

Figure 5: Raw Scores: Significant Effects of Age Group

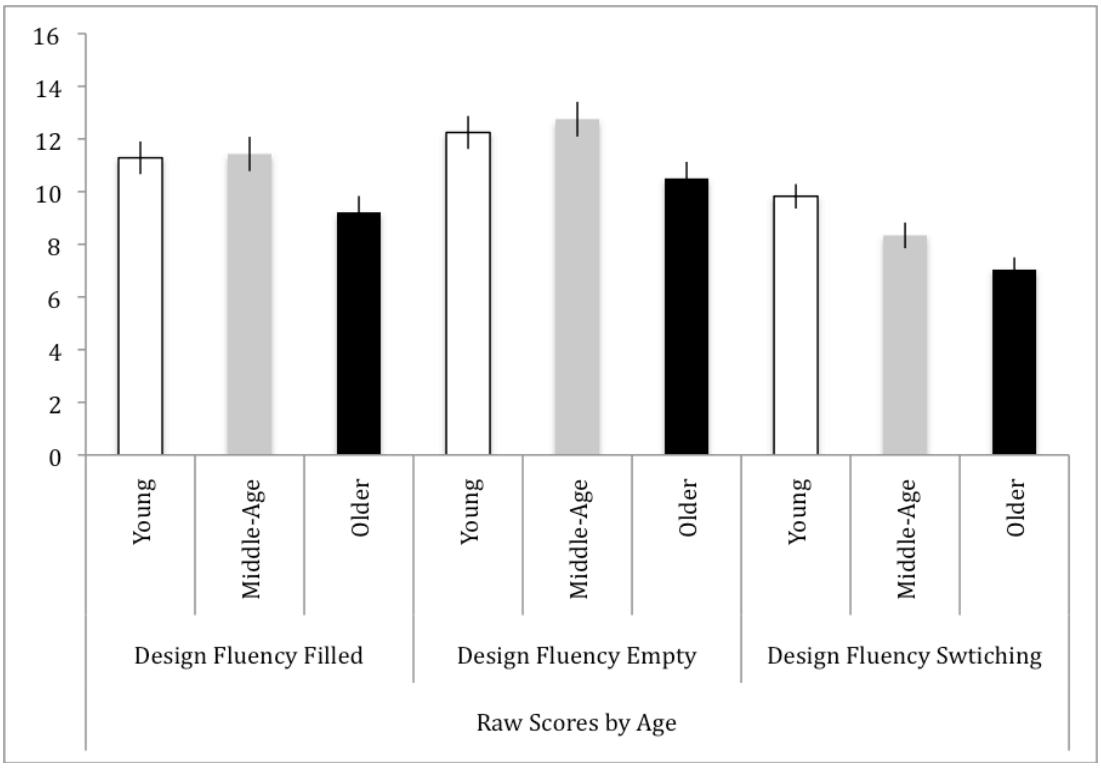

Figure 6: Raw Scores: Significant Effects of Age Group

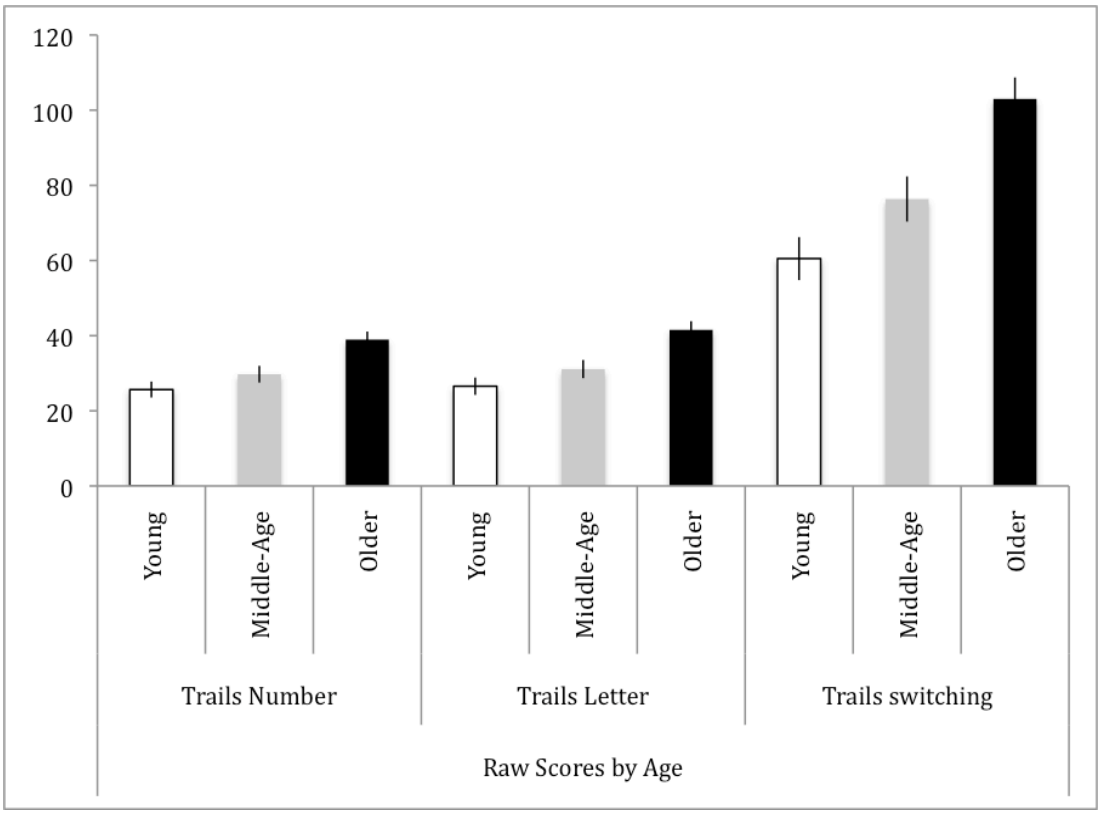

Figure 7: Raw Scores: Significant Effects of Age Group
Note. Trails = trail making test

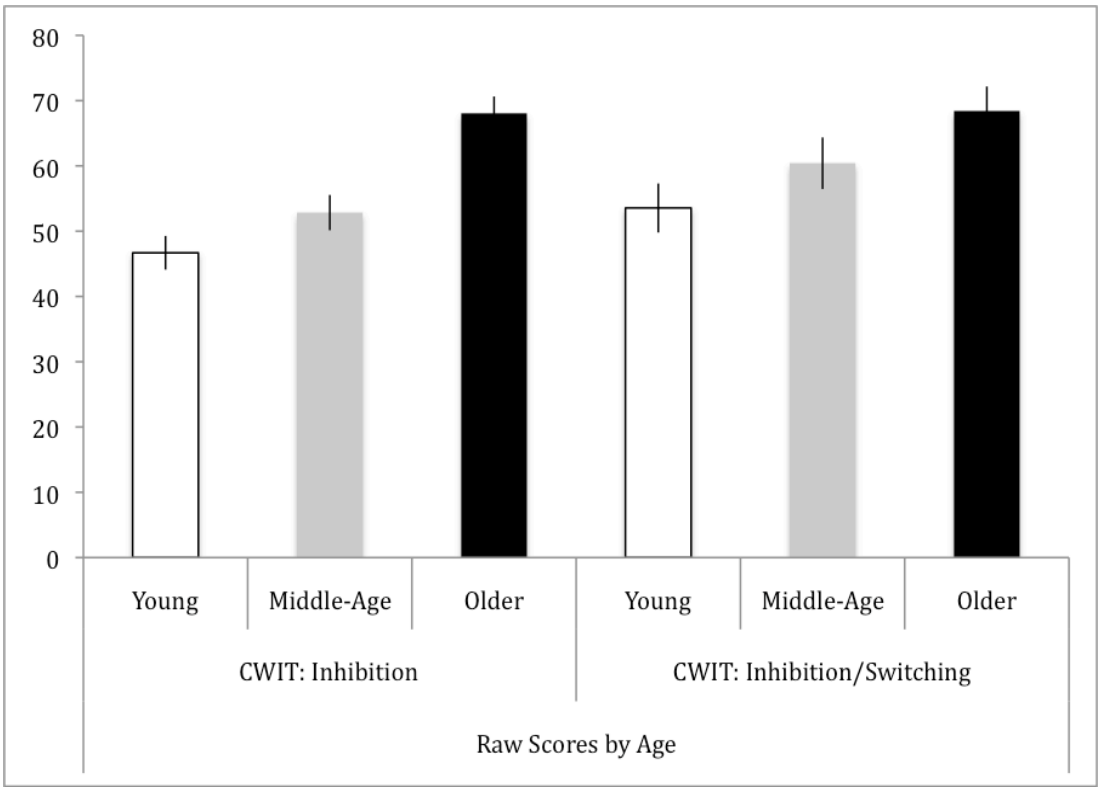

Figure 8: Raw Scores: Significant effects of Age Group
Note. CWIT = color-word interference test

Hypothesis 2. Relationship Between Metabolic Status and Cognitive Functioning

Table 5 summarizes the age-corrected means, standard deviations, F-values, partial eta squares, and significance of each combined score (composite, contrast, lateralized) for age group and metabolic status. For the contrast scores, there was a main effect of status for figural memory. Normal controls performed significantly better on the BVMT long-delay free recall than the DRS construction subscale relative to individuals with metabolic syndrome (Figure 9). There were no other significant main effects for metabolic status.

Individual Measures. Table 8 summarizes the age-corrected means, standard deviations, F-values, partial eta squares, and significance of each standardized score for individuals with and without metabolic syndrome. There were no significant main effects of metabolic status for the individual measures.

Table 9 summarizes the raw score (uncorrected for age) means, standard deviations, F-values, partial eta squares, and significance of each standardized score for individuals with and without metabolic syndrome. Consistent with the standardized data, there were no significant main effects of metabolic status for the individual measures.

Table 8: Standardized Score Means and Standard Deviations of Cognitive Performance for the Main Effect of Metabolic Status

	Metabolic Status			
	Control	Metabolic		
Standardized Scores	Mean(SD)	Mean(SD)	F	Partial Eta Squared
CVLT 1-5	55.44 (1.57)	54.25 (1.57)	_	_
CVLT LDFR	.45 (.18)	.15 (.18)	_	_
BVMT 1-3	50.97 (1.74)	48.61 (1.74)	_	_
BVMT Delay	53.31 (1.64)	49.32 (1.64)	_	_
Digit Span	11.98 (.44)	11.59 (.44)	_	_
BNT	52.85 (1.77)	52.88 (1.74)	_	_
WRAT-4 Reading	111.29 (2.00)	108.71 (2.00)	_	_
Verbal Fluency				
Letter	11.65 (.54)	11.76 (.53)	_	_
Category	12.16 (.46)	12.85 (.46)	_	_
Switch	12.20 (.50)	11.86 (.50)	_	_
Set loss	11.25 (.33)	10.88 (.32)	_	_
Design Fluency				
Filled	12.06 (.47)	11.18 (.46)	_	_
Empty	12.18 (.43)	11.29 (.43)	_	_
Filled + Empty	12.36 (.42)	11.55 (.42)	_	_
Switching	11.64 (.40)	11.69 (.40)	_	_
Set Loss	11.29 (.36)	10.88 (.36)	_	_
Repetitions	10.61 (.34)	10.72 (.34)	_	_
Trails Making Test				
Number	12.06 (.33)	11.61 (.33)	_	_
Letter	11.82 (.35)	11.12 (.350)	_	_

Table 8: Continued

	Metabolic Status			
	Control	Metabolic		
Number + Letter	12.70 (.36)	12.06 (.36)	_	_
Number-Letter Switching	11.33 (.35)	10.94 (.35)	_	_
Color Word Interference Test				
Color	10.45 (.40)	9.78 (.40)	_	_
Reading	10.58 (.39)	10.25 (.39)	_	_
Color + Reading	10.85 (.36)	10.31 (.36)	_	_
Inhibition	11.56 (.39)	10.52 (.39)	_	_
Inhibition Switching	11.33 (.38)	10.93 (.39)	_	_
Inhibition Error	11.16 (.39)	10.32 (.38)	_	_
Inhibition Switching Error	11.09 (.27)	10.94 (.27)		
Contrast				
Trails Switching	8.64 (.39)	8.68 (.39)	_	_
Verbal Switching	10.64 (.44)	10.93 (.43)	_	_
Design Switching	9.35 (.37)	10.15 (.37)	_	_
Color Word Interference Switching	10.48 (.33)	10.43 (.33)	_	_

Note. See Table 6 for abbreviations.
** = p<.01; * = p<.05.

Table 9: Raw Score Means and Standard Deviations of Cognitive Performance for the Main Effect of Metabolic Status

	Metabolic Status			
	Control	Metabolic		
Raw Scores	Mean(SD)	Mean(SD)	F	Partial Eta Squared
CVLT 1-5	51.29 (1.50)	50.84 (1.53)	_	_
CVLT LDFR	11.48 (.50)	11.47 (.51)	_	_
BVMT 1-3	24.69 (.92)	23.30 (.92)	_	_
BVMT Delay	9.93 (.33)	9.11 (.33)	_	_
Digit Span	18.71 (.58)	18.49 (.58)	_	_
BNT	54.29 (1.08)	56.20 (1.08)	_	_
WRAT-4 Reading	64.77 (.75)	63.44 (.75)	_	_
Verbal Fluency				
Letter	42.2 (1.85)	42.55 (1.84)	_	_
Category	41.93 (1.23)	44.26 (1.26)	_	_
Switch	14.80 (.42)	14.48 (.42)	_	_
Set loss	1.19 (.25)	1.43 (.25)	_	_
Design Fluency				
Filled	11.10 (.52)	10.19 (.52)	_	_
Empty	12.38 (.52)	11.29 (.52)	_	_
Filled + Empty	23.47 (.95)	21.48 (.95)	_	_
Switching	8.39 (.39)	8.41 (.36)	_	_
Set Loss	2.04 (.40)	2.58 (.40)	_	_
Repetitions	4.78 (.65)	4.67 (.64)	_	_
Trails Making Test				
Number	30.03 (1.77)	32.88 (1.77)	_	_
Letter	31.82 (1.93)	34.32 (1.92)	_	_

Table 9: Continued

	Metabolic Status			
	Control	Metabolic		
Number + Letter	61.85 (3.33)	67.20 (3.32)	_	_
Number-Letter Switching	75.80 (4.76)	84.12 (4.74)	_	_
Color Word Interference Test				
Color	29.21 (.93)	30.61 (.93)	_	_
Reading	22.07 (.73)	23.13 (.73)	_	_
Color + Reading	57.28 (1.52)	53.73 (1.51)	_	_
Inhibition	53.14 (2.15)	58.59 (2.14)	_	_
Inhibition Switching	60.08 (3.13)	61.51 (3.12)	_	_
Inhibition Error	.92 (.33)	1.53 (.32)	_	_
Inhibition Switching Error	1.31 (.29)	1.54 (.28)	_	_
Contrast				
Trails Switching	13.95 (3.83)	16.92 (3.82)	_	_
Verbal Switching	-27.13 (1.08)	-29.77 (1.08)	_	_
Design Switching	-3.99 (.42)	-2.88 (.42)	_	_
Color Word Interference Switching	8.81 (2.72)	7.78 (2.71)	_	_

Note. See Table 6 for abbreviations.
** = p<.01; * = p<.05.

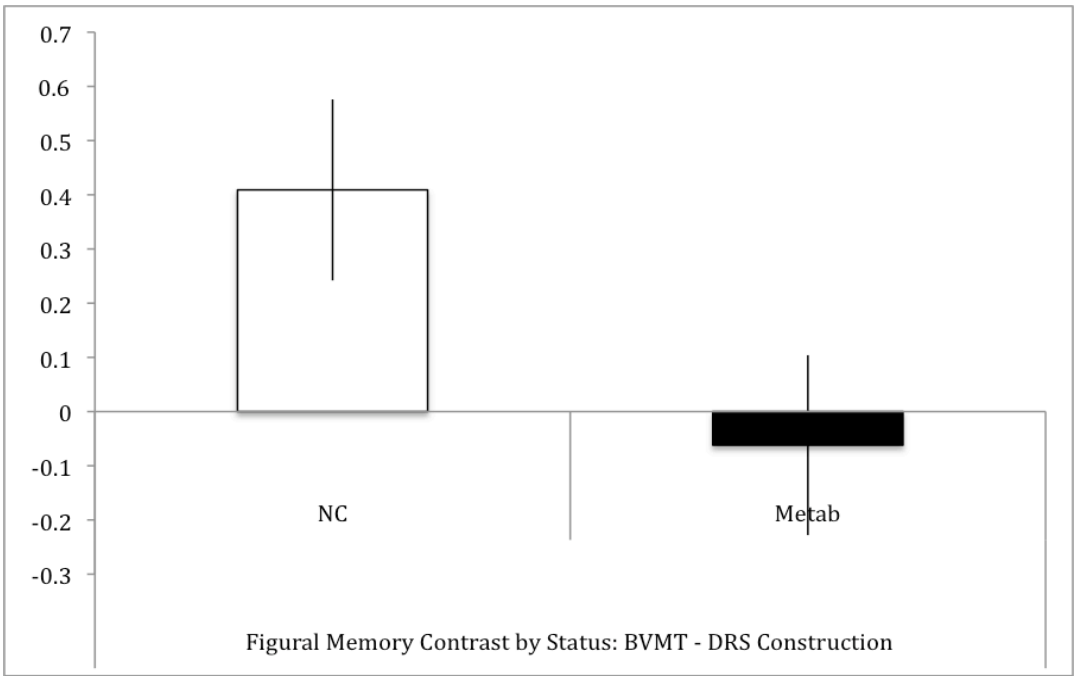

Figure 9: Standardized Data: Significant Effects of Metabolic Status
Note. BVMT = Brief Visuospatial Memory Test; DRS = Dementia Rating Scale

Hypothesis 3. Interaction Between Metabolic Status and Age Group for Cognitive Functioning

Table 5 summarizes the age-corrected means, standard deviations, F-values, partial eta squares, and significance of each combined score (composite, contrast, lateralized) for age group and metabolic status. There were no significant interactions between age group and metabolic status for the composite scores or the lateralized scores. However, for the contrast scores, there was a significant interaction between age group and metabolic status for design switching. Older adults with metabolic syndrome performed significantly better than older normal controls on higher-order figural switching condition than the lower-order figural fluency. Additionally, young controls performed significantly better than older controls on higher-order figural switching condition than the lower-order figural fluency. There were no other significant interactions between metabolic status and age group.

Individual Measures. Table 10 summarizes the age-corrected means, standard deviations, F-values, partial eta squares, and significance of each standardized score for young, middle-aged, and older adults with and without metabolic syndrome. Figures 10-12 depict significant effects. There were interactions between age group and metabolic status for design fluency filled dots, design fluency filled+empty dots, and design fluency contrast. Newman Keuls Multiple Range test failed to find significant effects for design fluency filled dots and filled +empty dots. However, simple effects analysis, demonstrated significant mean differences for the design fluency filled dot and filled +empty dots conditions between older adult controls and older adults with metabolic syndrome ($p<.05$), where older controls performed

significantly better than older adults with metabolic syndrome. For the design contrast, Newman-Keuls Multiple Range Test demonstrated that older adults with metabolic syndrome performed significantly better than older controls on higher-order figural switching condition than the lower-order figural fluency. Additionally, young controls performed significantly better than older controls on higher-order figural switching condition than the lower-order figural fluency.

Table 11 summarizes the raw score (uncorrected for age) means, standard deviations, F-values, partial eta squares, and significance of each standardized score for young, middle-aged, and older adults with and without metabolic syndrome (Figure 13). Similar to the standardized data, there was a significant interaction between age group and metabolic status for the design fluency filled dot condition. Newman Keuls Multiple Range test demonstrated that older adults with metabolic syndrome performed significantly poorer than middle-aged controls and young adults with metabolic syndrome.

Table 10: Standardized Score Means and Standard Deviations of Cognitive Performance for the Interaction Between Metabolic Status and Age Group

	Age Group & Metabolic Status							
	Young Control	Young Metabolic	Middle-age Control	Middle-age Metabolic	Older Control	Older Metabolic		
Standardized Scores	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	Partial Eta Squared
CVLT 1-5	50.94 (2.54)	51.00 (2.80)	57.60 (2.71)	55.69 (2.91)	57.77 (2.91)	56.05 (2.40)	_	_
CVLT LDFR	.18 (.28)	-.21 (.31)	.67 (.30)	.62 (.32)	.50 (.32)	.05 (.27)	_	_
BVMT 1-3	50.18 (2.82)	48.29 (3.11)	49.27 (3.00)	48.92 (3.22)	53.46 (3.22)	48.63 (2.67)	_	_
BVMT Delay	49.82 (2.65)	46.29 (2.92)	54.27 (2.83)	50.31 (3.03)	55.85 (3.03)	51.37 (2.51)	_	_
Digit Span	12.53 (.71)	11.43 (.79)	10.87 (.76)	11.62 (.82)	12.54 (.82)	11.74 (.68)	_	_
BNT	46.00 (2.82)	48.29 (3.11)	49.71 (3.11)	51.31 (3.23)	62.85 (3.23)	59.05 (2.67)	_	_
WRAT-4 Reading	112.24 (3.23)	107.00 (3.56)	106.33 (3.44)	105.85 (3.69)	115.31 (3.69)	113.28 (3.14)	_	_
Verbal Fluency								
Letter	10.94 (.87)	11.21 (.96)	11.53 (.92)	12.23 (.99)	12.46 (.99)	11.84 (.82)	_	_
Category	12.24 (.75)	13.21 (.83)	11.80 (.80)	12.23 (.86)	12.46 (.86)	13.11 (.71)	_	_
Switch	12.12 (.81)	11.50 (.89)	12.93 (.86)	12.92 (.92)	11.54 (.92)	11.16 (.76)	_	_
Set loss	12.47 (.53)	11.93 (.58)	11.73 (.56)	10.23 (.60)	9.54 (.60)	10.47 (.50)	_	_
Design Fluency								
Filled	10.47 (.75)	12.14 (.83)	12.33 (.80)	10.77 (.86)	13.39 (.86)	10.63 (.71)	4.16*	.09
Empty	10.65 (.70)	11.50 (.77)	12.80 (.75)	11.39 (.80)	13.08 (.80)	11.00 (.66)	_	_
Filled + Empty	10.82 (.67)	12.07 (.74)	12.80 (.72)	11.46 (.77)	13.46 (.77)	11.11 (.64)	3.44*	.08
Switching	11.71 (.65)	12.00 (.71)	11.60 (.69)	11.23 (.74)	11.62 (.74)	11.84 (.61)	_	_
Set Loss	12.77 (.58)	12.07 (.64)	11.33 (.62)	10.46 (.66)	9.77 (.66)	10.11 (.55)	_	_
Repetitions	11.82 (.55)	10.93 (.60)	9.93 (.58)	11.08 (.63)	10.08 (.63)	10.16 (.52)	_	_
Trails Making Test								
Number	10.94 (.53)	11.43 (.59)	11.93 (.57)	11.31 (.61)	13.31 (.61)	12.11 (.50)	_	_
Letter	11.29 (.57)	10.21 (.63)	12.00 (.61)	11.00 (.65)	12.15 (.65)	12.16 (.54)	_	_

Table 10: Continued

	Age Group & Metabolic Status							
	Young Control	Young Metabolic	Middle-age Control	Middle-age Metabolic	Older Control	Older Metabolic		
Standardized Scores	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	Partial Eta Squared
Number + Letter	11.77 (.58)	11.50 (.64)	12.87 (.62)	11.62 (.67)	13.46 (.67)	13.05 (.55)	_	_
Number-Letter Switching	10.29 (.57)	11.43 (.63)	11.93 (.61)	10.23 (.65)	11.77 (.65)	11.16 (.54)	_	_
Color Word Interference Test								
Color	9.59 (.65)	9.36 (.72)	10.07 (.69)	9.77 (.74)	11.69 (.74)	10.21 (.62)	_	_
Reading	10.47 (.64)	10.21 (.70)	9.80 (.68)	10.54 (.73)	11.46 (.73)	10.00 (.60)	_	_
Color + Reading	10.29 (.58)	10.14 (.63)	10.33 (.61)	10.46 (.66)	11.92 (.66)	10.32 (.55)	_	_
Inhibition	11.35 (.63)	10.64 (.70)	11.93 (.67)	10.39 (.72)	11.39 (.72)	10.53 (.60)	_	_
Inhibition Switching	10.94 (.62)	10.21 (.68)	11.20 (.66)	11.62 (.71)	11.85 (.71)	10.94 (.60)	_	_
Inhibition Error	10.88 (.62)	9.79 (.68)	11.33 (.66)	10.08 (.71)	11.25 (.74)	11.11 (.58)	_	_
Inhibition Switching Error	10.88 (.44)	10.93 (.48)	11.07 (.47)	10.62 (.50)	11.33 (.52)	11.28 (.42)	_	_
Contrast								
Number + Letter	11.77 (.58)	11.50 (.64)	12.87 (.62)	11.62 (.67)	13.46 (.67)	13.05 (.55)	_	_
Number-Letter Switching	10.29 (.57)	11.43 (.63)	11.93 (.61)	10.23 (.65)	11.77 (.65)	11.16 (.54)	_	_

Note. See Table 5 for abbreviations.
** = p<.01; * = p<.05.

Table 11: Raw Score Means and Standard Deviations of Cognitive Performance for the Interaction Between Metabolic Status and Age Group

	Age Group & Metabolic Status							
	Young Control	Young Metabolic	Middle-age Control	Middle-age Metabolic	Older Control	Older Metabolic		
Raw Scores	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	Partial Eta Squared
CVLT 1-5	53.53 (2.43)	53.08 (2.78)	54.20 (2.59)	52.00 (2.78)	46.15 (2.78)	47.44 (2.36)	_	_
CVLT LDFR	12.29 (.81)	11.69 (.93)	12.53 (.86)	12.54 (.93)	9.62 (.93)	10.17 (.79)	_	_
BVMT 1-3	28.06 (1.50)	26.86 (1.65)	23.87 (1.59)	23.00 (1.71)	22.15 (1.71)	20.05 (1.42)	_	_
BVMT Delay	10.47 (.54)	10.14 (.59)	9.93 (.57)	9.08 (.62)	9.39 (.62)	8.11 (.51)	_	_
Digit Span	20.82 (.94)	19.14 (1.03)	18.00 (.99)	19.15 (1.07)	17.31 (1.07)	17.16 (.89)	_	_
BNT	52.29 (1.75)	55.43 (1.92)	52.80 (1.86)	56.54 (1.99)	57.77 (1.99)	56.63 (1.65)	_	_
WRAT-4 Reading	64.77 (1.22)	62.36 (1.34)	64.40 (1.30)	63.69 (1.39)	65.15 (1.39)	64.26 (1.15)	_	_
Verbal Fluency								
Letter	40.24 (2.99)	41.29 (3.29)	43.13 (3.18)	44.85 (3.41)	43.23 (3.41)	41.53 (2.82)	_	_
Category	43.59 (1.99)	46.36 (2.19)	43.13 (2.12)	44.46 (2.27)	39.08 (2.27)	41.95 (1.88)	_	_
Switch	15.29 (.69)	14.79 (.76)	15.87 (.73)	15.77 (.78)	13.23 (.78)	12.89 (.65)	_	_
Set loss	.29 (.41)	.71 (.45)	.73 (.43)	1.85 (.47)	2.54 (.47)	1.74 (.39)	_	_
Design Fluency								
Filled	10.35 (.84)	12.21 (.92)	12.40 (.89)	10.46 (.96)	10.54 (.96)	7.90 (.79)	3.77 *	.082
Empty	11.71 (.84)	12.79 (.93)	13.73 (.89)	11.77 (.97)	11.69 (.97)	9.32 (.80)	_	_
Filled + Empty	22.6 (1.54)	25.00 (1.70)	26.13 (1.64)	22.23 (1.76)	22.31 (1.76)	17.21 (1.46)	3.51 *	.076
Switching	9.65 (.63)	10.00 (.69)	8.60 (.67)	8.08 (.71)	6.92 (.71)	7.16 (.59)	_	_
Set Loss	1.24 (.65)	1.93 (.72)	1.67 (.69)	2.69 (.74)	3.23 (.74)	3.11 (.61)	_	_
Repetitions	2.82 (1.04)	4.79 (1.15)	7.07 (1.11)	4.39 (1.19)	4.46 (1.19)	4.84 (.99)	_	_
Trails Making Test								

Table 11: Continued

	Age Group & Metabolic Status							
	Young Control	Young Metabolic	Middle-age Control	Middle-age Metabolic	Older Control	Older Metabolic		
Raw Scores	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	Partial Eta Squared
Number	26.53 (2.87)	24.79 (3.16)	27.80 (3.05)	31.69 (3.28)	35.77 (3.28)	42.16 (2.71)	_	_
Letter	25.29 (3.12)	27.79 (3.44)	28.00 (3.32)	34.23 (3.57)	42.15 (3.57)	40.95 (2.95)	_	_
Number + Letter	51.82 (5.38)	52.57 (5.93)	55.80 (5.73)	65.92 (6.15)	77.92 (6.15)	83.11 (5.09)	_	_
Number-Letter Switching	64.59 (7.70)	56.43 (8.48)	64.27 (8.20)	88.46 (8.81)	98.54 (8.81)	107.47 (7.28)	_	_
Color Word Interference Test								
Color	28.65 (1.51)	28.71 (1.66)	29.20 (1.60)	30.15 (1.72)	29.77 (1.72)	32.95 (1.43)	_	_
Reading	21.18 (1.18)	21.71 (1.30)	22.80 (1.26)	21.92 (1.35)	22.23 (1.35)	25.74 (1.16)	_	_
Color + Reading	49.82 (2.46)	50.43 (2.71)	52.00 (2.61)	52.08 (2.81)	52.00 (2.81)	58.68 (2.32)	_	_
Inhibition	44.88 (3.47)	48.50 (3.83)	49.00 (3.70)	56.69 (3.97)	65.54 (3.97)	70.58 (3.28)	_	_
Inhibition Switching	52.18 (5.06)	54.93 (5.57)	60.07 (5.39)	60.77 (5.78)	68.00 (5.78)	68.84 (4.78)	_	_
Inhibition Error	.88 (.52)	1.71 (.57)	.47 (.55)	1.31 (.59)	1.42 (.62)	1.58 (.49)	_	_
Inhibition Switching Error	1.18 (.46)	1.07 (.51)	.93 (.49)	1.39 (.53)	1.83 (.55)	2.16 (.44)	_	_
Contrast								
Trails Switching	12.77 (6.19)	3.86 (6.83)	8.47 (6.59)	22.53 (7.08)	20.62 (7.08)	24.37 (5.86)	_	_
Verbal Switching	-28.29 (1.75)	-31.57 (1.93)	-27.27 (1.86)	-28.69 (2.00)	-25.85 (2.00)	-29.05 (1.66)	_	_
Design Switching	-2.06 (.67)	-2.79 (.74)	-5.13 (.72)	-3.69 (.77)	-4.77 (.77)	-2.15 (.64)	2.86	.06
Color Word Interference Switching	2.35 (4.41)	4.50 (4.85)	8.07 (4.69)	8.69 (5.04)	16.00 (5.04)	10.16 (4.17)	_	_

Note. See Table 5 for abbreviations.
** = p<.01; * = p<.05.

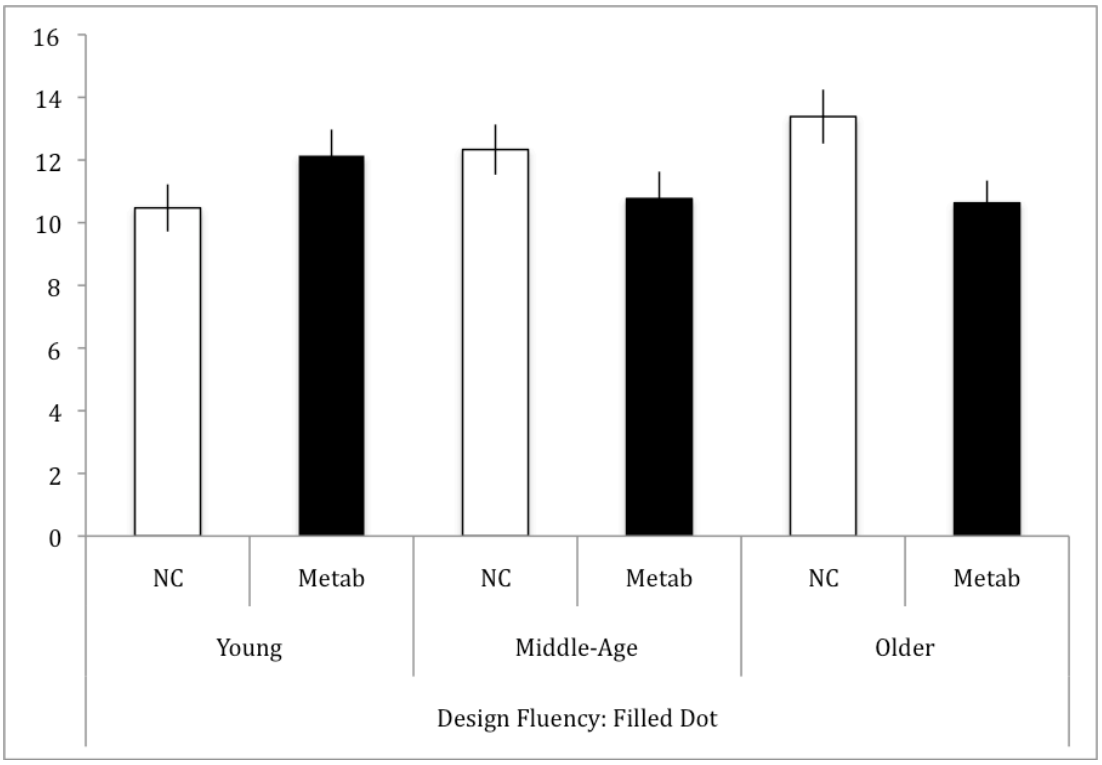

Figure 10: Standardized Data: Significant Interactions Between Metabolic Status and Age Group

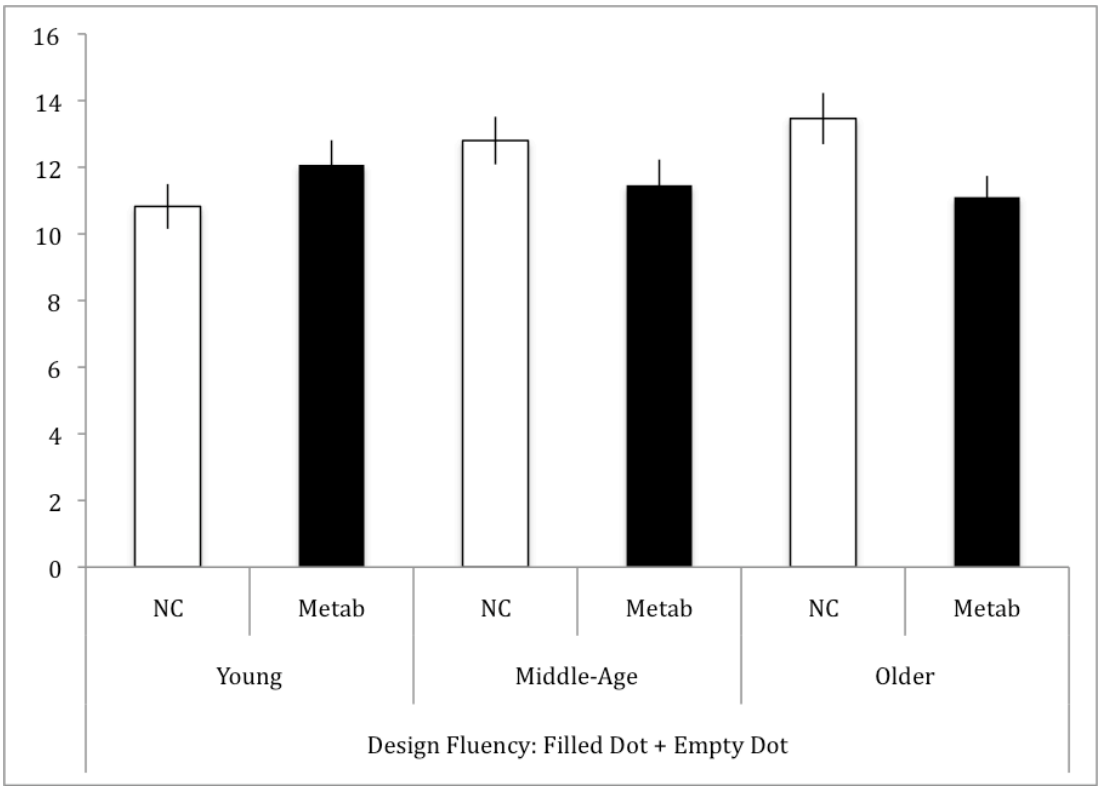

Figure 11: Standardized Data: Significant Interactions Between Metabolic Status and Age Group

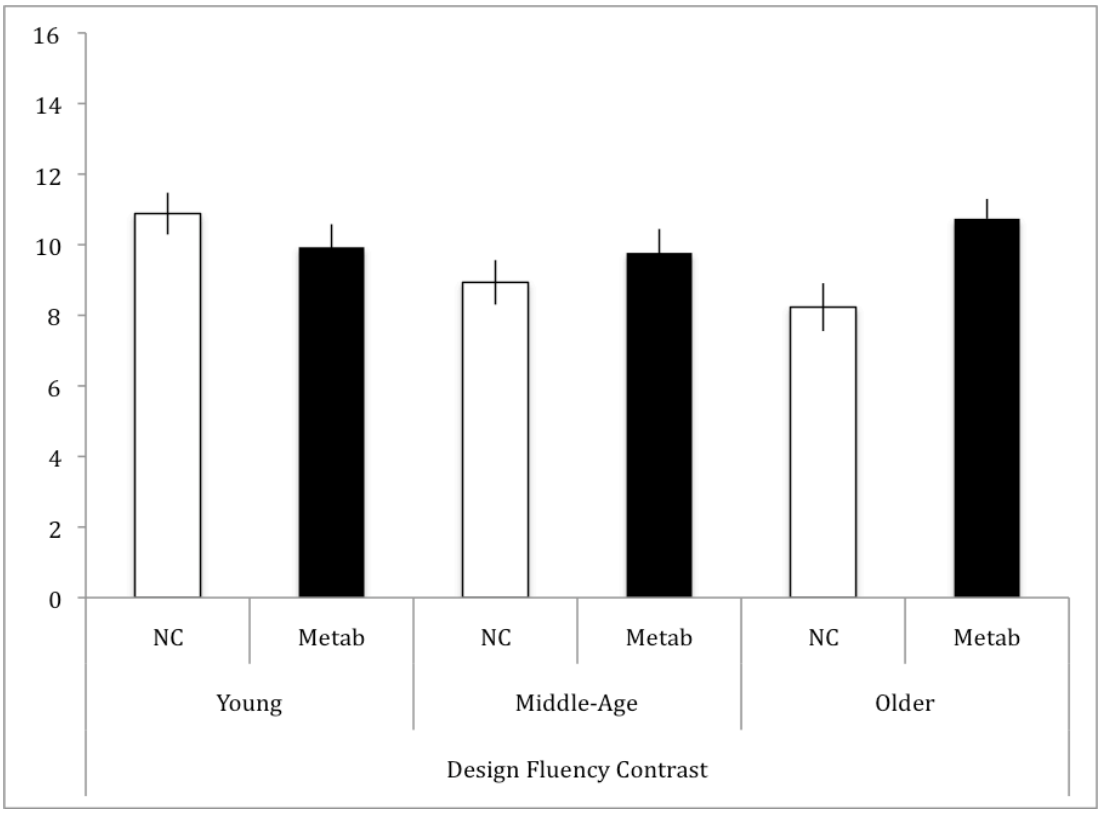

Figure 12: Standardized Data: Significant Interactions Between Metabolic Status and Age Group

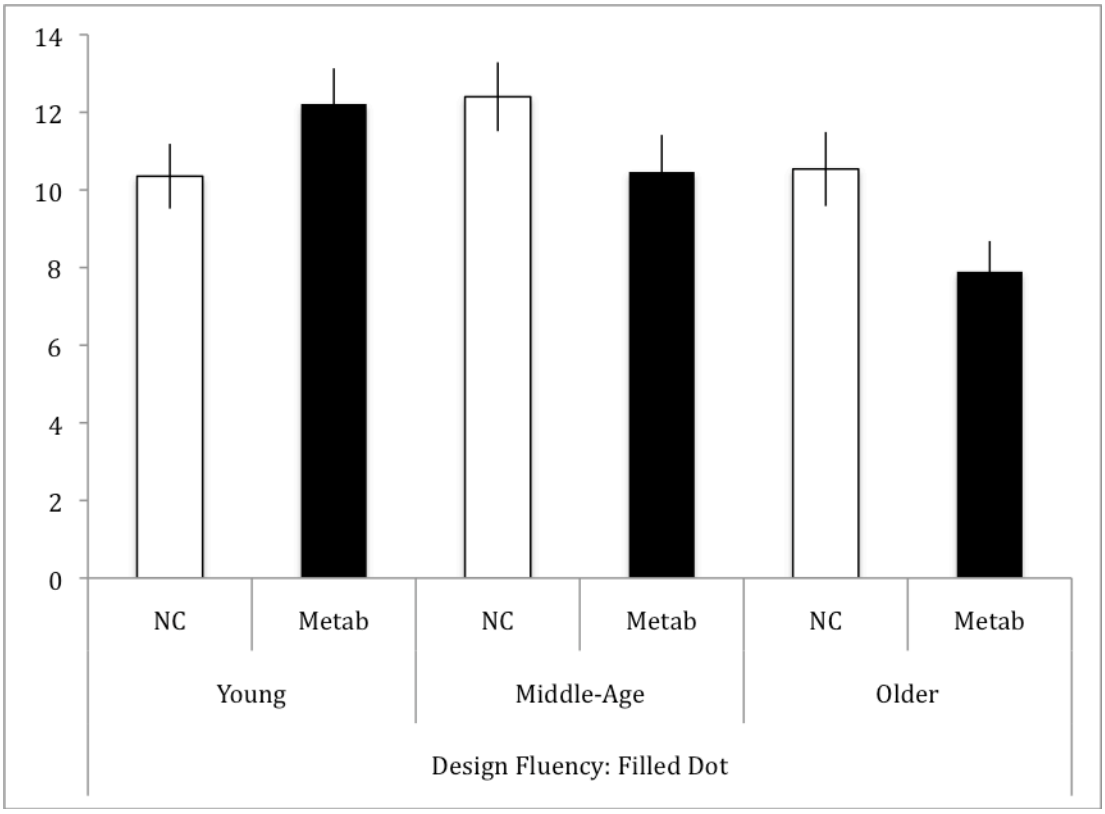

Figure 13: Raw Scores: Significant Interactions Between Metabolic Status and Age Group

Exploratory Analyses

The standardized data (Table 12) and raw score data (Table 13) were re-analyzed without the young. For the standardized data, there were significant effects for age group for BNT and WRAT-4 Reading. The standardized scores for older adults were significantly higher than middle-aged adults on both tasks. For the raw score data, there were significant effects of age group for the CVLT-II Total 1-5 and LDFR, verbal fluency switching, design fluency filled dot and empty dot conditions, trail making test number, letter, and number letter switching conditions, and color-word interference test inhibition condition (Tables 14-16). For all measures middle-aged adults performed better than older adults.

There were significant effects of metabolic status on the standardized scores for design fluency, filled dot condition, empty dot condition, filled+empty dot condition, and design contrast (Table 12, Figure 17). For design fluency filled dot and empty dot conditions and filled+empty dots, controls had significantly better than individuals with metabolic syndrome. For the design contrast, middle-aged and older adults with metabolic syndrome had significantly higher contrast scores than middle-aged and older controls on higher-order figural switching condition than the lower-order figural fluency. There was a significant interaction between metabolic status and age group for the verbal switching contrast. However, Newman Keuls Multiple Range Test failed to demonstrate significant differences. In addition, simple effects analysis failed to find significant differences.

Similar to the standardized data, there were significant effects of metabolic status on raw scores for the design fluency filled dot, empty dot, and filled+empty

conditions, where controls performed significantly better than individuals with metabolic syndrome (Figure 18) and for the design contrast, where middle-aged and older adults with metabolic syndrome had significantly higher contrast scores than middle-aged and older controls on higher-order figural switching condition than the lower-order figural fluency.

Table 12: Standardized Score Means and Standard Deviations of Cognitive Performance for the Interaction Between Metabolic Status and Middle-Aged and Older Adults

	Age Group and Metabolic Status					
	Middle-Age Control	Middle-Age Metabolic	Older Control	Older Metabolic	F	Partial Eta Sigma
BNT	49.71 (3.16)	51.31 (3.28)	62.85 (3.28)	59.05 (2.71)	$F^1 = 11.23$** $F^2 = .13$ $F^3 = .75$	$\eta^2 = .17$ $\eta^2 = .00$ $\eta^2 = .01$
WRAT-4 Reading	106.33 (3.58)	105.85 (3.84)	115.31 (3.84)	113.28 (3.27)	$F^1 = 5.08$* $F^2 = .12$ $F^3 = .05$	$\eta^2 = .09$ $\eta^2 = .00$ $\eta^2 = .00$
Design Fluency						
Filled	12.33 (.86)	10.77 (.92)	13.39 (.92)	10.63 (.76)	$F^1 = .28$ $F^2 = 6.19$* $F^3 = .47$	$\eta^2 = .01$ $\eta^2 = .10$ $\eta^2 = .01$
Empty	12.80 (.79)	11.39 (.85)	13.08 (.85)	11.00 (.70)	$F^1 = .01$ $F^2 = 4.75$* $F^3 = .17$	$\eta^2 = .00$ $\eta^2 = .08$ $\eta^2 = .00$
Filled + Empty	12.80 (.77)	11.46 (.83)	13.46 (.83)	11.11 (.69)	$F^1 = .04$ $F^2 = 5.57$* $F^3 = .42$	$\eta^2 = .00$ $\eta^2 = .09$ $\eta^2 = .01$
Contrast						
Verbal Switching	11.27 (.71)	10.08 (.76)	10.15 (.76)	11.84 (.63)	$F^1 = .21$ $F^2 = .12$ $F^3 = 4.04$*	$\eta^2 = .00$ $\eta^2 = .00$ $\eta^2 = .07$
Design Switching	8.93 (.65)	9.77 (.70)	8.23 (.70)	10.74 (.58)	$F^1 = .04$ $F^2 = 6.52$* $F^3 = 1.63$	$\eta^2 = .00$ $\eta^2 = .10$ $\eta^2 = .03$

Note. See Table 6 for abbreviations.
** = $p<.01$; * = $p<.05$.

Table 13: Raw Score Means and Standard Deviations of Cognitive Performance for the Interaction Between Metabolic Status and Middle-Aged and Older Adults

	Age Group and Status					
	Middle-Age Control	Middle-Age Metabolic	Older Control	Older Metabolic	F	Partial Eta Sigma
CVLT 1-5	54.20 (2.83)	52.00 (3.03)	46.15 (3.03)	47.44 (2.58)	$F^1 = 4.80^*$ $F^2 = .03$ $F^3 = .37$	$\eta^2 = .080$ $\eta^2 = .000$ $\eta^2 = .007$
CVLT LDFR	12.53 (.92)	12.54 (.98)	9.62 (.98)	10.17 (.84)	$F^1 = 8.05^{**}$ $F^2 = .09$ $F^3 = .09$	$\eta^2 = .128$ $\eta^2 = .002$ $\eta^2 = .002$
Verbal Fluency						
Switch	15.87 (.76)	15.77 (.81)	13.23 (.81)	12.89 (.67)	$F^1 = 12.91^{**}$ $F^2 = .08$ $F^3 = .02$	$\eta^2 = .187$ $\eta^2 = .001$ $\eta^2 = .000$
Design Fluency						
Filled	12.40 (.92)	10.46 (.99)	10.54 (.99)	7.89 (.82)	$F^1 = 5.60^*$ $F^2 = 5.98^*$ $F^3 = .14$	$\eta^2 = .091$ $\eta^2 = .097$ $\eta^2 = .003$
Empty	13.73 (.95)	11.77 (1.02)	11.69 (1.02)	9.32 (.84)	$F^1 = 5.46^*$ $F^2 = 5.10^*$ $F^3 = .05$	$\eta^2 = .089$ $\eta^2 = .083$ $\eta^2 = .001$
Filled + Empty	26.13 (1.74)	22.23 (1.87)	22.23 (1.87)	17.21 (1.55)	$F^1 = 6.41^*$ $F^2 = 6.41^*$ $F^3 = .10$	$\eta^2 = .103$ $\eta^2 = .103$ $\eta^2 = .002$
Trails Making Test						
Number	27.80 (3.50)	31.69 (3.76)	35.77 (3.76)	42.16 (3.11)	$F^1 = 6.79^*$ $F^2 = 2.11$ $F^3 = .12$	$\eta^2 = .108$ $\eta^2 = .036$ $\eta^2 = .002$
Letter	28.00 (3.72)	34.23 (3.99)	42.15 (3.99)	40.95 (3.30)	$F^1 = 7.70^{**}$ $F^2 = .45$ $F^3 = .98$	$\eta^2 = .121$ $\eta^2 = .008$ $\eta^2 = .017$
Number + Letter	55.80 (6.53)	65.92 (7.01)	77.92 (7.01)	83.11 (5.80)	$F^1 = 8.86^{**}$ $F^2 = 1.34$ $F^3 = .14$	$\eta^2 = .137$ $\eta^2 = .023$ $\eta^2 = .002$
Number-Letter Switching	64.27 (9.50)	88.46 (10.20)	98.54 (10.20)	107.474 (8.44)	$F^1 = 7.69^{**}$ $F^2 = 2.97$ $F^3 = .63$	$\eta^2 = .121$ $\eta^2 = .050$ $\eta^2 = .011$
Color Word Interference						
Inhibition	49.00 (4.30)	56.69 (4.62)	65.54 (4.62)	70.58 (3.82)	$F^1 = 12.21^{**}$ $F^2 = 2.14$ $F^3 = .09$	$\eta^2 = .179$ $\eta^2 = .037$ $\eta^2 = .002$
Contrast						
Design Switching	-5.13 (.76)	-3.69 (.82)	-4.77 (.82)	-2.16 (.68)	F1 = 1.51 F2 = 6.88* F3 = .57	$\eta 2 = ..026$ $\eta 2 = .109$ $\eta 2 = .010$

Note. See Table 6 for abbreviations.
** = p<.01; * = p<.05.

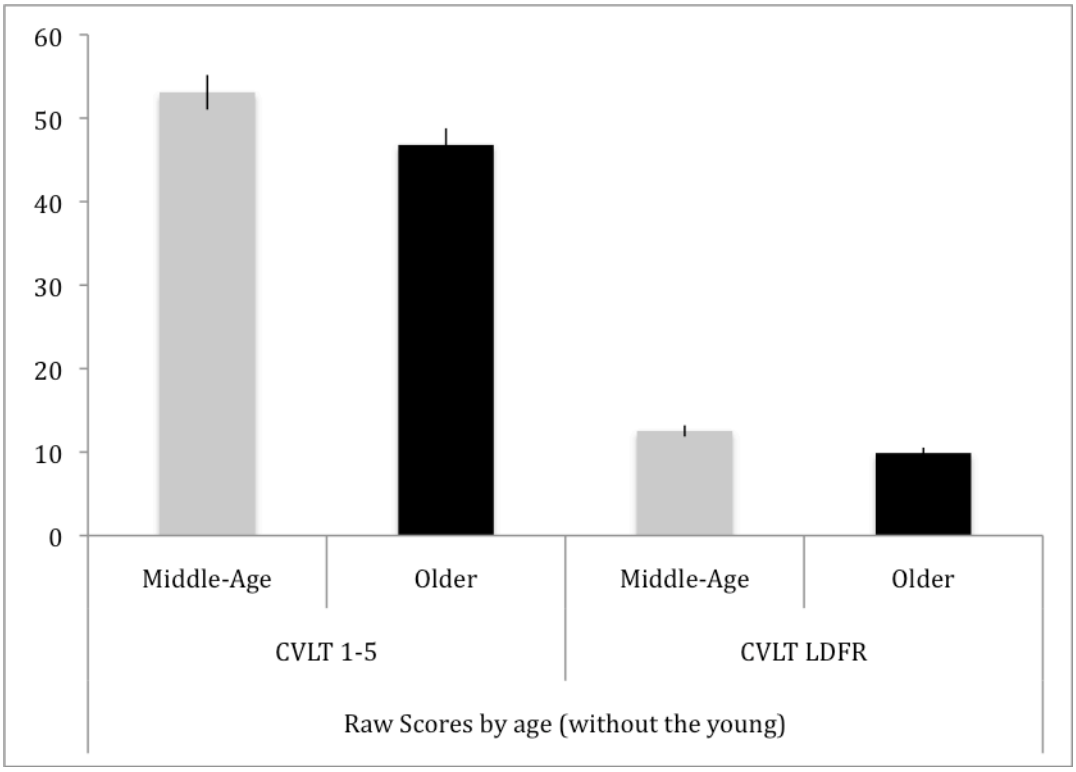

Figure 14: Raw Scores: Significant Effect of Age Group for Middle-Age and Older Adults

Note. CVLT 1-5 = California Verbal Learning Test-II, total trials 1-5; CVLT LDFR = California Verbal Learning Test-II, long-delay free recall.

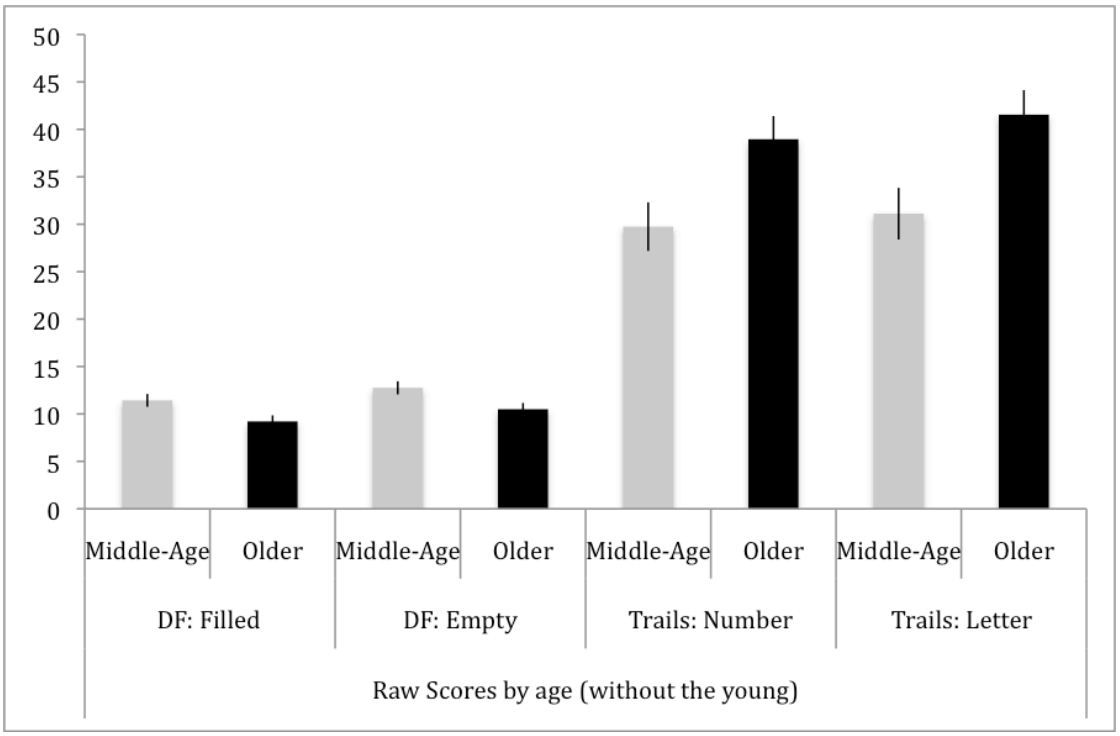

Figure 15: Raw Scores: Significant Effect of Age Group for Middle-Age and Older Adults

Note. DF = design fluency; Trails: trail making test

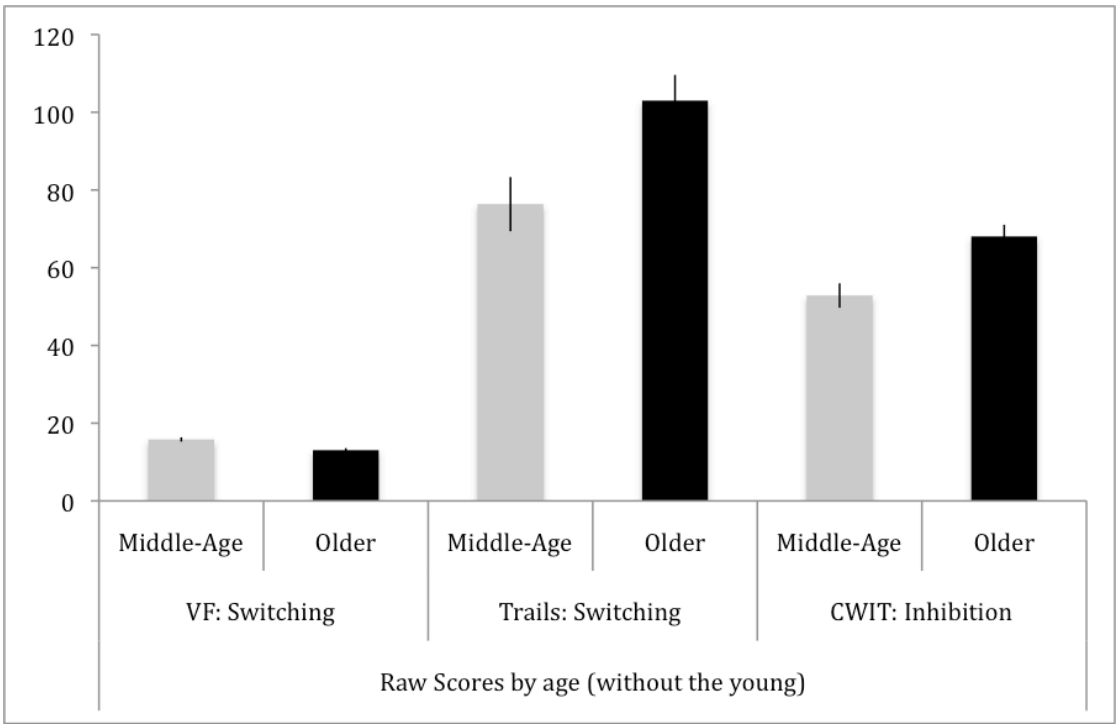

Figure 16: Raw Scores: Significant Effect of Age Group for Middle-Age and Older Adults

Note. VF = verbal fluency; Trails: trail making test; CWIT: color-word interference test

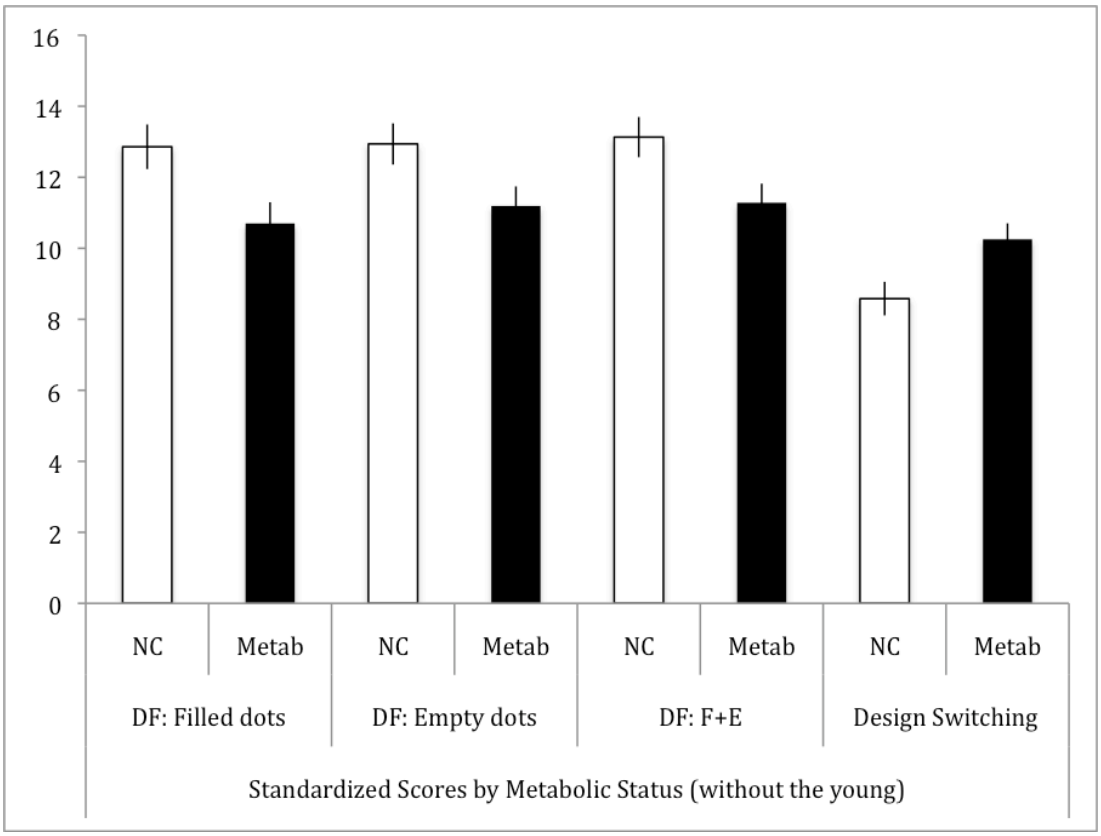

Figure 17: Standardized Scores: Significant Effect of Metabolic Status for Middle-Age and Older Adults

Note. NC = normal controls; Metab = metabolic; DF = Design Fluency; F+E = filled plus empty dot conditions

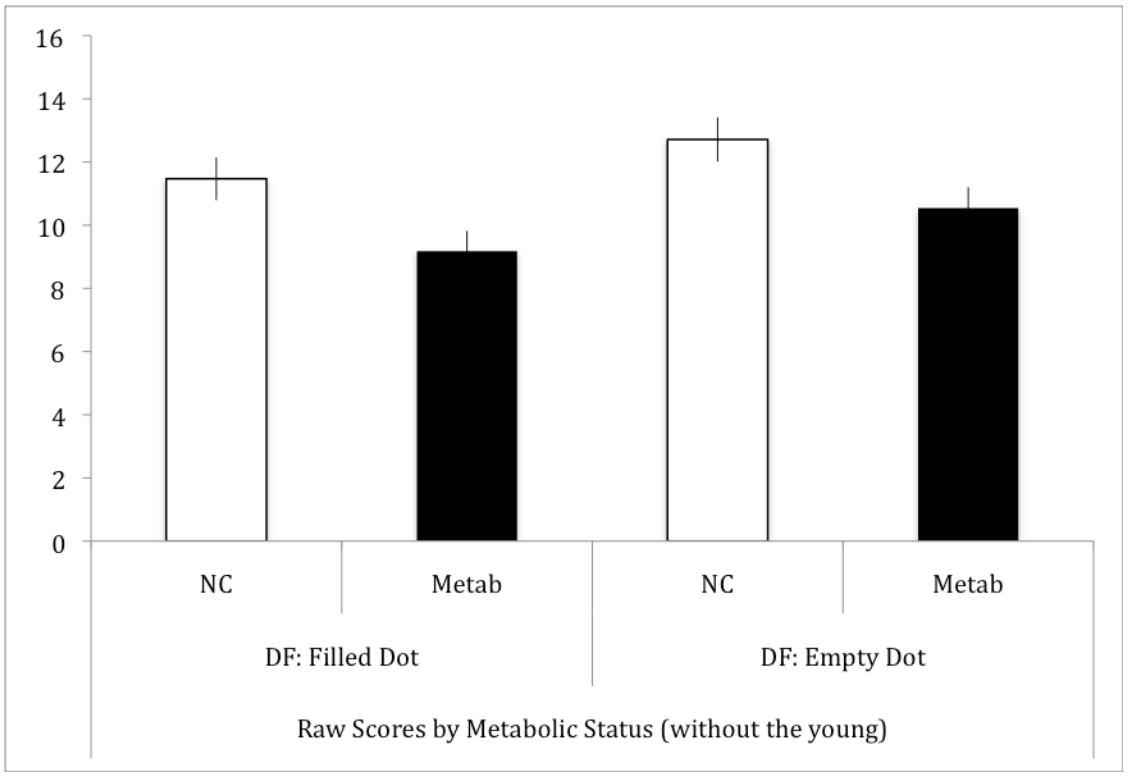

Figure 18: Raw Score: Significant Effect of Metabolic Status for Middle-Age and Older Adults

Note. NC = normal controls; Metab = metabolic; DF = Design Fluency

IV. DISCUSSION

The primary aim of the current study was to investigate differences in cognitive functioning among young adults (classified as normal or at risk for metabolic syndrome), middle-aged (classified as normal or metabolic syndrome), and older adults, (classified as normal or metabolic syndrome).

Demographic Characteristics of Participants

For the present cohort, individuals with metabolic syndrome weighed significantly more and had greater BMIs and waist circumferences than controls; however, there were no significant differences in systolic blood pressure (Table 2, Figure 1). Irrespective of metabolic status, the middle-aged cohort weighed significantly more and had greater BMIs, waist circumferences, and diastolic blood pressure than young and older adults, whereas, older adults had significantly greater systolic blood pressure, pulse pressure, and percent stroke risk than young and middle-aged adults (Table 2, Figure 2). There were no significant interactions between age group and metabolic status for body measurements.

Individuals with metabolic syndrome rated themselves as more disinhibited and hungry than controls, regardless of age, on the Three-Factor Eating Questionnaire, a self-report measure of eating behavior (Table 3, Figure 3). To date, there have been no previous studies that have examined disinhibition in metabolic syndrome. However, obese persons have been found to report significantly more disinhibited eating than their normal weight counterparts (Harden et al., 2009; Mobbs et al., 2010). Disinhibition increases likelihood of weight gain and living a sedentary lifestyle (Bryant et al., 2010; Hays et al., 2002), which contribute to the development of

metabolic syndrome (Hu, 2003). A recent study found that obese adolescents had higher ratings of disinhibited eating, performed lower on tests of executive function, and had reduced orbitofrontal cortex volumes than non-obese adolescents (Maayan et al., 2011). The current study suggests that individuals with metabolic syndrome are significantly higher in self-reported disinhibited eating behaviors than the control group, which has been previously associated with declines in executive functioning and structural brain changes.

As expected, the proportion of individuals who met criteria for the vascular and metabolic risk factors that constitute metabolic syndrome (e.g., BMI, raised blood pressure) was significantly different between controls and individuals with metabolic syndrome. Moreover, with the exception of raised blood pressure, there were no significant differences in the proportion of individuals who met criteria for the vascular risk factors among young, middle-aged, and older adults, suggesting that age is independent from most metabolic criteria (Table 4). The percentage of participants who had raised blood pressure (BP; systolic BP $\geq$ 130 or diastolic BP $\geq$ 85 mm Hg) and/or were prescribed hypertensive medication was 29% of young adults, 60% of middle-aged adults, and 94% of older adults. Therefore, it is not surprising that older adults had significantly higher systolic blood pressure compared to young and middle-aged adults.

Age Group Effects on Cognitive Performance

The results, from the raw score analysis, indicated that there were multiple main effects of age group on cognitive performance (Table 7, Figures 4-8). As hypothesized, older adults performed more poorly than young adults on measures of

information processing speed, verbal and figural memory (learning and delayed recall), and executive functioning (cognitive switching, verbal set-loss errors). Age related cognitive decline on measures of information processing speed, memory, and executive functioning have been consistently documented (Van der Elst et al., 2006; Grady & Craik, 2001; Hultsh et al., 2002; Finkel et al., 2007; Schonkencht et al., 2005; van Hooren et al., 2007; Wilson et al., 2002; for review see Drag & Bieliauskas, 2009). In addition to changes in cognition, healthy aging is also associated overall brain volume reductions, with the greatest reduction in brain volume occurring the frontal and parietal regions (Resnick et al., 2003; Resnick Lamar, & Driscoll, 2007). Of note, the present study showed age group effects across all measures of cognitive set-shifting and failed to find significant age group effects for the corresponding lower-order component processes. Task demands of cognitive set-shifting are independent from the lower-order components (Wecker et al., 2005), have been shown to predict future cognitive decline (Clark et al., 2012), and are dependent on frontal lobe functioning.

In addition to the hypothesized age group effects, older adults also performed more poorly than young adults on measures of auditory attention (digit span), and inhibition (Color-Word Interference Test – inhibition condition), both of which have been implicated in normal age related declines (Tse et al., 2010; Collette et a., 2009; Hasher et al., 1991; Stevens, et al., 2008; for review see Drag & Bieliauskas, 2009). However, there are reports of intact simple attention in normal aging (Berardi et al., 2001).

There were no significant differences in cognitive performance between young and middle-aged adults, suggesting that these two cohorts were more similar in their cognitive performance relative to older adults. Results demonstrated several differences between middle-aged and older adults. In particular, Newman-Keuls Multiple Range Test revealed that older adults performed more poorly than middle-aged adults on measures of information processing speed, learning, memory, and cognitive set-shifting. To date, few studies have examined differences in performance on cognitive functioning between middle-age and older adults. In general research suggests that the greatest changes in cognitive functioning are typically observed in individuals over 60 years of age, with relatively intact cognitive functioning in middle-age adults (Treitz, Heyder, & Daum, 2007; Nilsson, 2003). However, there is evidence to suggest that declines in complex attentional abilities (divided attention and switching) begin in middle age (Georgiou-Karistianis et al., 2006). The present study contributes to the literature on aging and provides evidence for declines in specific areas of cognitive functioning in older adults relative to young and middle-aged adults.

A number of studies examining cognitive decline in metabolic syndrome reported higher systolic blood pressure as the primary component of metabolic syndrome, independently associated with poor cognitive outcomes (Gatto, et al., 2008; Creavin et al., 2012). Chronic, uncontrolled hypertension is associated with declines in executive functioning and information processing speed in older adults (Bucur & Madden, 2010). However, structural brain changes are found even in those with medication-controlled hypertension (Raz et al., 2003). It is interesting to note that for the age group effects, the largest effect sizes were on measures of executive

functioning and processing speed. Given that 94% of older adults meet criteria for high blood pressure and older adults had significantly higher systolic blood pressure, the potential interaction between hypertension and old age cannot be completely ruled out.

Metabolic Status Effects on Cognitive Performance

There was a main effect of metabolic status for the figural memory contrast (Figure 9). Normal controls performed significantly better than individuals with metabolic syndrome on the contrast examining BVMT delayed recall condition minus the DRS construction subscale. Recent reports suggest that individuals with metabolic syndrome demonstrate declines on measures of figural working memory (Raffaitin et al., 2011) while maintaining intact 2-dimensional visuoconstructional abilities (van den Berg et al., 2008). Moreover, figural memory decline has been reported in individuals with dyslipidemia (Ancelin et al., 2012; Ward et al., 2010). Taken together, this suggests that individuals with metabolic syndrome show greater declines in higher-order visuospatial abilities (figural memory) relative to lower-order visuospatial abilities (simple 2-dimensional construction).

In addition, as part of the exploratory analyses, which examined the effect of age group and metabolic syndrome on cognitive performance without the young cohort, middle-age and older adults with metabolic syndrome were found to perform significantly poorer than controls on several design fluency conditions (filled dot, empty dot, and filled+empty dot; Figure 13). The design fluency filled and empty dot conditions from the D-KEFs require intact basic motor skills, visual attention, visual perceptual, and constructional skills (Delis, Kaplan, & Kramer, 2001). These measures

also require intact aspects of executive functioning including initiation, multitasking (drawing while maintaining the rules), planning, inhibition of previous responses, and inhibition of rules from the first condition. It is interesting that, in the present cohort, individuals with metabolic syndrome rated themselves as more disinhibited than controls; however, there were no significant correlations between self-reported disinhibition and performance on the design fluency nor were the effects modified when controlling for self-reported disinhibition (data not presented). Given the task demands of the design fluency test, these findings provide further evidence for declines in higher-order visuospatial abilities in individuals with metabolic syndrome.

With regard to neural correlates of cognitive decline in metabolic syndrome, low levels of HDL has been associated with declines on the BVMT and reduced grey matter volume in the bilateral temporal poles, middle temporal gyrus, temporal-occipital gyri and left superior temporal gyrus/parahippocampal region (Ward et al., 2010). Performance on the design fluency empty dot condition is associated with bilateral frontal, temporal, and parietal lobe volumes (Kramer et al., 2007). In addition, a recent study reported that, prior to controlling for the component processes from the design fluency (filled and empty conditions), performance on the set-shifting condition was associated with volumes of bilateral frontal, parietal, temporal and occipital regions, whereas, after controlling for the component processes, the set-shifting was associated with the frontal-parietal gray matter regions (Pa et al., 2010). Taken together, the aforementioned studies provide some hypotheses regarding which brain regions may be associated with declines on figural memory and figural fluency tasks in metabolic syndrome including bilateral temporal and occipital regions.

Clinically, changes in memory and executive functioning are associated with declines in activities of daily living and medication adherence (Arlt et al., 2008; Grigsby et al., 1998; Johnson, Lui & Yaffe, 2007; Stoehr et al., 2008). In addition, comorbidity of vascular risk factors is also associated with functional decline (Stuck et al., 1999) and declines in one's ability to manage vascular risk factors (Munshi et al., 2006). Taken together, this suggests that an individual with metabolic syndrome may be at risk for poor medication compliance, which may also contribute to the maintenance of metabolic syndrome and by extension, an increased risk of the development of dementia.

Interestingly, there was no significant effect of metabolic status on measures of verbal memory and verbal fluency. Declines in verbal memory and verbal fluency in metabolic syndrome have been inconsistently reported within the literature (Komulainen et al., 2007; Raffaitin et al., 2011; Segura et al., 2009; Benedict et al., 2011). The inconsistency within the literature on changes in cognitive performance in individuals with metabolic syndrome is likely influenced by a number of variables including how the cognitive domains are operationally defined and measured (Crichton et al., 2011), time-course of the risk factors (Akbaraly et a., 2010), and whether or not the metabolic and vascular risk factors are controlled or uncontrolled via medication and/or exercise (Ligthart et al., 2010; Bosma et al., 2002). In addition, given that the diagnosis of metabolic syndrome requires that an individual meet 3 or 5 different criteria, various combinations of vascular risk may have differential effects on cognitive performance; there is considerable variability within the literature

regarding which single or combination of metabolic and vascular risk factors account for changes in cognition (for a review see Crichton et al., 2011).

To our knowledge, this is the first study to investigate the effect of metabolic syndrome on figural fluency performance. For the present cohort, the results suggest that individuals with metabolic syndrome may demonstrate preferential decline in higher-order visuospatial abilities. Additional experiments, with larger cohorts that incorporated figural fluency measures would provide additional support for the present results.

Metabolic Status and Age Group Effects on Cognitive Performance

There was a significant interaction between age group and metabolic status on the design fluency contrast; specifically, the design fluency switching minus the combined filled dot and empty dot conditions. This contrast allows for the separation of the figural set-shifting, which requires cognitive flexibility, from the component processes of figural fluency, described above. Interestingly, older adults with metabolic syndrome performed significantly better than older controls on the design fluency switching condition relative to the design fluency condition. Given that there was no significant effect of metabolic status for on the design fluency switching condition, this finding may be driven by the poor performance on the lower order components. However, this finding may also suggest intact figural set-shifting in metabolic syndrome, after controlling for the cognitive demands required for the fluency only conditions, which declined in the metabolic group compared to controls. There were no significant differences as a function of metabolic status for cognitive set-shifting on the verbal fluency test, the trail making test, or the color-word

interference test. The design fluency switching condition has been found to be more sensitive to cognitive set-shifting than the other measures of switching in the D-KEFS battery (Pa et al., 2010).

There were also significant interactions between age group and metabolic status for the filled dot and filled+empty dot conditions. However, Newman-Keuls Multiple Range Test failed to find statistically significant mean differences, which may be related to power, given that the effects were significant once the young adults were removed from the analysis. In support of this hypothesis, simple effects analysis was run to test the hypothesis that older controls would perform better than the older metabolic group and the middle-age controls would perform better than the middle-age metabolic group. As expected older controls performed better than older adults with metabolic syndrome; however, this effect did not reach statistical significance for the middle age group, although visual inspection of the data suggests a trend (Figure 9). These findings are in line with the exploratory analysis that indicated a main effect of metabolic status on design fluency, that is, middle-aged and older adults with metabolic syndrome performed poorer on the empty and filled do conditions of the design fluency test.

Declines in executive functioning in metabolic syndrome have been reported in the literature (Bokura et al., 2010; Cavalieri et al., 2010; Segura et al., 2009; Gatto et al., 2008). However, it should be noted that within these experiments executive functioning was assessed with either screening measures or was defined as a latent variable combining multiple processes such as novel problem solving, cognitive set-shifting, inhibition, and fluency. Based on the literature, it is difficult to determine

which executive functioning processes are affected in metabolic syndrome. In fact, in a recent review of the literature on cognitive performance in metabolic syndrome, one of the primary criticisms, to date, is the "lack of standardized nomenclature for cognitive variables" (Crichton et al., 2011). As such, the present study adds to the literature by investigating the effects of metabolic syndrome on individual tests of cognitive functioning. However, future studies are warranted with larger sample sizes.

While little is known about the impact of multiple vascular risk factors on cognition in young adulthood, obesity has been consistently associated with declines in executive functioning (Batterink et al., 2010; Fergenbaum et al., 2009; Mobbs et al., 2010; Pauli-Pott et al., 2010; Pignatti et al., 2006). In the present study there was no effect of obesity on cognitive performance in young adults. As such, further investigation of cognitive decline associated with obesity and multiple vascular risk factors in this cohort is warranted.

Limitations

There are several limitations of the current study. Our young adult cohort was comprised of obese individuals who are at risk for the development of metabolic syndrome. Thus the present results may underestimate the effect of metabolic syndrome on cognitive functioning in young adults.

As discussed in the introduction, individuals with persistent metabolic syndrome over a 10-year period demonstrate poorer cognitive performance on measures of memory, verbal fluency, reasoning, and vocabulary (Akbaraly et al., 2010). In the current study, the duration of time that an individual met criteria for

metabolic syndrome is unknown, and could underestimate significant differences in cognition in a number of domains.

The participants in the present study were part of a larger experiment aimed at examining the neural correlates of reward processing in metabolic syndrome. Participants had to meet certain physical criteria in order to be eligible for fMRI scanning. In particular, they had to be right-handed, weigh less than 300lbs, and have waist circumferences that would fit comfortably inside the bore of the MRI scanner. Moreover, the present cohort had a high level of education and was comprised of mostly Caucasian individuals from middle-class socioeconomic status. As such, this cohort may represent a healthier subset of metabolic syndrome. Last, the sample size in the present study was small and future studies with larger samples are warranted to fully characterize the cognitive changes associated with metabolic syndrome.

Conclusions

In summary, the results of the present study provide further evidence for age related declines in cognitive functioning on measures of information processing speed, attention, memory, and executive functioning. The present study demonstrated that individuals with metabolic syndrome self-report greater levels of disinhibited eating than controls, which is associated with cognitive decline and may have implications for the development and maintenance of metabolic syndrome. The present study also provides additional evidence that declines in figural memory are associated with metabolic syndrome and provides the first evidence of declines in figural fluency in metabolic syndrome. These findings suggest that aspects of higher-order, executive functions of visuospatial processing are impaired in metabolic syndrome.

Interestingly, older adults with metabolic syndrome performed significantly better on the design fluency switching condition than the design fluency lower order components (filled and empty dot conditions) relative to controls; suggesting intact cognitive set-shifting abilities in this domain.

Given that individuals with metabolic syndrome had significantly greater self-reported disinihibited eating and performed more poorly on executive aspects of visuospatial processing (e.g., memory initiation, planning, multitasking, inhibition), future studies aimed at investigating potential causal relationships between metabolic syndrome and disinhibited eating and executive dysfunction may provide insight into effective intervention targets to delay or prevent metabolic syndrome. Last, incorporating measures of visuospatial abilities in future studies would improve the characterization of cognitive declines in individuals with metabolic syndrome.

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