STRUCTURAL NEURAL CORRELATES OF METABOLIC SYNDROME

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ABSTRACT OF THE THESIS

Structural Neural Correlates of Metabolic Syndrome
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The metabolic syndrome (MetS) is a cluster of risk factors that together increase the risk of developing cardiovascular disease and diabetes relative to the risk associated with each individual component alone. It is estimated that 34% of Americans over the age of 20 meet criteria for MetS, and the prevalence of MetS is estimated to climb to 45% in adults who are 60 years of age or older. Previous research has shown MetS and its individual components are associated with lower cognitive function and increased risk for future cognitive decline and dementia in both middle-aged and older adults.

The present study used archival structural MRI data to investigate differences in cortical thickness and subcortical volumes between adults with and without MetS. A total of twenty-six middle age and older age adults with and without MetS (n = 14, n = 12, respectively) were included in the present study. Clinical data were acquired prior to the imaging session and included measurements of body mass index, waist circumference, and blood pressure. T-1 weighted structural MRI scans were processed using the Freesurfer image analysis suite, which allows for the study of cortical and subcortical anatomy via cortical reconstruction and volumetric segmentation. It was hypothesized that (1) Adults with MetS would have smaller values for cortical thickness and subcortical volume in brain areas related to executive functioning, memory, taste and reward processing, regulation of food intake and appetite, and behavioral inhibition, (2) Cortical and subcortical measurements would be negatively associated with measures of adiposity, and (3) Cortical and subcortical measurements would be negatively associated with metabolic risk factor burden.

Analyses of covariance revealed group differences in cortical thickness in structures of the medial temporal lobe, controlling for age and gender. The MetS group had smaller values for cortical thickness in the left entorhinal cortex, left parahippocampal gyrus, left temporal pole, and right temporal pole. Correlation analyses revealed a number of significant relationships between clinical data and cortical thickness in these medial temporal structures. Both measures of adiposity and metabolic risk factor burden were negatively associated with cortical thickness in these areas. Further, exploratory analyses showed cortical thickness in medial temporal structures was negatively associated with the presence of hypertension and diabetes.

The principal finding of the present study was that adults with MetS had smaller values for cortical thickness in medial temporal lobe structures relative to metabolically healthy adults. The medial temporal lobe is implicated in early Alzheimer’s disease pathology and its structures are important to memory function. In group comparisons, the largest effect size was seen in the left entorhinal cortex, an area suggested to be the first site of neuropathological changes seen in Alzheimer’s disease. Given the established connections
between medial temporal lobe atrophy and cognitive decline and dementia, our findings suggest that middle-age and older adults with MetS may be at increased risk for cognitive decline and future dementia.
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INTRODUCTION

METABOLIC SYNDROME

The metabolic syndrome (MetS) is characterized by various risk factors for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) and has been shown to negatively impact cognition and accelerate cerebral atrophy in normal aging (Yates, Sweat, Yau, Turchiano, & Convit, 2012). Individuals with MetS are twice as likely to develop CVD over the next 5-10 years compared to individuals without MetS. In addition, those with MetS are five times more at risk for T2DM (Alberti et al., 2009). While there has been debate about the clinical criteria for diagnosing MetS (Alberti et al., 2009), the National Cholesterol Education Program Third Adult Treatment Panel guidelines specify that individuals must meet at least three of the following criteria for diagnosis: (1) elevated waist circumference (WC); (2) hypertriglyceridemia; (3) low high-density lipoprotein (HDL) cholesterol; (4) high blood pressure, and (5) elevated fasting glucose (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001) (Table 1). It is estimated that 34% of Americans over the age of 20 meet criteria for MetS (Ervin, 2009). While MetS is seen in young adults, the prevalence of MetS rises with age and body mass index (BMI) (Ervin, 2009). It is estimated that the prevalence of MetS climbs to 45% in individuals who are 60 years of age or older (Ford, Giles, & Dietz, 2002). More recently, a European study found that in its sample of 1,183 participants aged 65-88 years, 36.3% met criteria for MetS. Closer examination of the participants with MetS revealed the prevalence of the individual components of MetS in the sample: 51.7% had abdominal obesity, 62.8% were hypertensive, 31.2% had high triglyceride levels, 35.5% had low HDL cholesterol, and 24.1% were hyperglycemic (Dik et al., 2007). The rising prevalence of MetS, due in part to increasing rates of obesity and sedentary lifestyles, has made MetS both a public health and a clinical concern (Alberti et al., 2009).

Cardiovascular risk factors associated with MetS, such as hypertension and diabetes, are thought to contribute to the development of Alzheimer’s disease (AD) and vascular dementia (Gregg et al., 2000; Kalmijn, Feskens, Launer, Stijnen, & Kromhout, 1995; Launer, 2002; Yaffe, Barrett-Connor, Lin, & Grady, 2002). Research on MetS and the individual
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Table 1. Criteria for Clinical Diagnosis of the Metabolic Syndrome

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<tr>
<td>Elevated waist circumference</td>
<td>Population and country-specific definitions</td>
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<tr>
<td>Elevated triglycerides (drug treatment for</td>
<td>≥ 150 mg/dL (1.7 mmol/L)</td>
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<td>elevated triglycerides is an alternate indicator)</td>
<td></td>
</tr>
<tr>
<td>Reduced HDL-C (drug treatment for reduced HDL-C is</td>
<td>&lt;40 mg/dL (1.0 mmol/L) in males</td>
</tr>
<tr>
<td>an alternate indicator)</td>
<td></td>
</tr>
<tr>
<td>Elevated blood pressure (antihypertensive drug</td>
<td>Systolic ≥130 and/or Diastolic ≥85</td>
</tr>
<tr>
<td>treatment in a patient with a history of</td>
<td></td>
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<td>hypertension is an alternate indicator)</td>
<td></td>
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<tr>
<td>Elevated fasting glucose (drug treatment of</td>
<td>≥100 mg/dL</td>
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<td>elevated glucose is an alternate indicator)</td>
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Abbreviations: HDL-C = high-density lipoprotein cholesterol.

components of MetS support that the syndrome is a risk factor for cognitive impairment in middle-aged and older adults (Dik et al., 2007; Yaffe et al., 2004), and increases risk for dementia (Kalmijn et al., 2000; Kivipelto et al., 2001; Kivipelto et al., 2005; Launer et al., 2000; Raffaitin et al., 2009; Skoog et al., 1996; Vanhanen et al., 2006).

**Obesity**

It is estimated that two-thirds of American adults are overweight and roughly a third of American adults meet the World Health Organization criterion for obesity (Ogden et al., 2006). Obesity is associated with a number of health conditions such as diabetes, CVD, and some types of cancer (Kopelman, 2000). Obesity has a detrimental effect on life expectancy either by causing or aggravating health conditions like coronary heart disease, T2DM, hypertension, sleep apnea, and stroke (Kopelman, 2000; Olshansky et al., 2005). These health conditions related to obesity are thought to alter brain structure and cognitive function
In recent years, obesity has gained additional attention as research has shown obesity to be related to both risk for AD and cerebral atrophy through longitudinal computerized topography (CT) and cross-sectional magnetic resonance imaging (MRI) studies (Gustafson, Lissner, Bengtsson, Björkelund, & Skoog, 2004; Gustafson, Rothenberg, Blennow, Steen, & Skoog, 2003; Ho et al., 2010; Kalmijn et al., 2000).

Overweight and obesity are characterized by abnormal or excessive adipose tissue that is potentially damaging to health. Historically, BMI has been a popular measure used to define obesity. BMI is an index of weight-to-height ratio and is calculated by dividing weight by the square of height (kg/m$^2$). According to the World Health Organization, overweight is defined as a BMI greater than or equal to 25, and obesity is defined as a BMI greater or equal to 30 (World Health Organization, 2014). BMI is a useful population-measure of obesity and is easy to interpret due to the fact that age and gender do not affect its calculation. However, the BMI does not always give an accurate picture of an individual’s adiposity and risk for cardiovascular and metabolic diseases. BMI is limited in that it does not illustrate differential fat distribution within the body. This limitation is problematic in that different fat compartments within the body do not equally contribute to metabolic risks (Fox et al., 2007). Despite the limitations of the BMI, in the past decade, numerous studies have shown that elevated BMI is significantly associated with future cognitive decline, increased risk for dementia, decreased global and regional brain volumes, and cortical thinning.

Abdominal obesity is associated with several of the risk factors that define MetS. Abdominal obesity can be defined by anthropometric measures, including waist circumference (WC), waist-to-hip ratio, waist-to-height ratio, or radiographic (e.g., CT or MRI) quantifications of abdominal obesity. Visceral adipose tissue (VAT), a radiographic measure of abdominal obesity, is associated with increased markers of inflammation and vascular and metabolic abnormalities (Bacha, Saad, Gungor, Janosky, & Arslanian, 2003; Despres & Lemieux, 2006; Despres, Moorjani, Ferland, et al., 1989; Despres, Moorjani, Tremblay, et al., 1989; Ross, Freeman, Hudson, & Janssen, 2002). In contrast to the BMI, measures of abdominal obesity both address the importance of body fat distribution, and recognize gender-related differences in topological distribution of body fat (Goodman-Gruen & Barrett-Connor, 1996; Lovejoy & Sainsbury, 2009). Measures of abdominal obesity and
body fat distribution have been shown to better predict risk for cardiovascular and metabolic diseases than BMI, which suggests that viscerally obese individuals may be at the greatest risk for developing MetS, CVD, and T2DM (Dalton et al., 2003; Zhu et al., 2004).

**Blood Pressure, Inflammation, and Hyperglycemia**

In addition to obesity, several other components of MetS and inflammation have been associated with cognitive decline, increased risk of dementia, and cerebral atrophy. Elevated blood pressure, particularly systolic blood pressure, has been associated with cerebral atrophy, poor cognitive performance, and risk for dementia (Kivipelto et al., 2001; Raz, Rodrigue, & Acker, 2003; Taki et al., 2004; Ward, Carlsson, Trivedi, Sager, & Johnson, 2005). Insulin resistance and diabetes have been strongly linked to obesity (Haslam & James, 2005). Both MRI and neuropsychological findings have implicated hyperglycemia and related conditions such as T2DM in worsening cerebral atrophy and cognitive dysfunction. In the Framingham Offspring study, diabetes, fasting glucose, and insulin resistance were all inversely related to total brain volume (Tan et al., 2011). More recently, diabetes and insulin resistance have been reported to contribute to the inverse association between VAT and total brain volume suggesting that they are mediators in this relationship (Debette et al., 2010). With regard to cognition, hyperglycemia has been identified as the most important MetS component contributing to the relationship between MetS and cognition (Dik et al., 2007). In addition, T2DM has been linked to higher odds of having AD (Irie et al., 2008; Leibson et al., 1997). Similar to obesity, T2DM is thought to increase risk for dementia by inducing cerebral atrophy, which is thought to increase risk for future AD neuropathology (Raji et al., 2010).

While inflammation is not one of the recognized clinical components defining the MetS, obesity is strongly related to inflammatory markers such as C-reactive protein and fibrinogen (Pou et al., 2007). High levels of inflammation increase the risk for future diabetes and heart disease, and thus have been hypothesized to be a mechanism for the detrimental effects associated with MetS. In the Framingham Offspring study, higher levels of inflammation predicted greater risk of dementia, and various inflammatory markers were negatively related to total brain volume (Jefferson et al., 2007; Schmidt et al., 2002). In studies of cognition and MetS, a significant interaction has been reported between
inflammation levels and MetS wherein persons with both MetS and high inflammation were at the most increased risk for cognitive impairment (Dik et al., 2007; Yaffe et al., 2004). Taken together, prior research suggests that several components of MetS and inflammation play a role in the relationships between MetS and cognitive and cerebral detriments.

**Metabolic Syndrome, Obesity, and Cognition**

Understanding the relationship between MetS and its individual components and cognition is vital as cognitive impairment is related to brain tissue atrophy, a measure of disease progression in neurodegenerative disorders. Research has shown that atrophy, particularly in the medial temporal lobe, is correlated with and predictive of cognitive impairment in healthy elderly participants and participants genetically at risk for early-onset AD (Rusinek et al., 2003). Similarly, brain atrophy has been suggested to mediate the relationship between diabetes and cognition and may explain the association between diabetes and AD (Roberts et al., 2014). Metabolic syndrome and its individual components have been reported to have a negative effect on cognitive functioning in a number of adult studies and across the lifespan (Bokura, Nagai, Oguro, Kobayashi, & Yamaguchi, 2010; Cavalieri et al., 2010; Hassenstab, Sweat, Bruehl, & Convit, 2010; Komulainen et al., 2007; Muller et al., 2007; Schuur et al., 2010; Segura & Jurado, 2009; Smith, Hay, Campbell, & Trollor, 2011). More specifically, MetS has been reported to negatively affect memory, visuospatial abilities, executive functioning, processing speed, and general cognitive functioning (Bokura et al., 2010; Cavalieri et al., 2010; Hassenstab et al., 2010; Komulainen et al., 2007; Muller et al., 2010; Schuur et al., 2010; Segura et al., 2009). Despite these findings in several studies, some studies have not found significant relationships between MetS and cognitive functioning (Haley et al., 2010; Tournoy et al., 2010).

**Metabolic Syndrome, Obesity and Cognition in Middle Age**

The effect of obesity and MetS in midlife on cognition is critical to study, considering the rapidly growing elderly population. Past studies of obesity in middle age adults, both cross-sectional and longitudinal, have found that higher midlife BMI was associated with lower cognitive performance in multiple domains (Cournot et al., 2006; Wolf et al., 2007). More recently, in a study of BMI over the adult life course, cognitive scores for tests of
memory and executive function in late midlife were associated with measures of BMI in early adulthood (25 years old), early midlife, and late midlife. In more stringent analyses adjusted for age, sex, and education, chronic obesity was associated with lower scores on the mini mental state examination, and tests of memory and executive function (Sabia, Kivimaki, Shipley, Marmot, & Singh-Manoux, 2009).

Similar to studies of obesity and cognition, several studies have shown that having MetS in midlife has been associated with lower cognitive performance. In one study, persistent MetS was associated with lower cognitive performance (Akbaraly et al., 2010). Similarly, a study of MetS in people in their late fifties to early seventies found that those with MetS performed worse on cognitive tests assessing memory and executive functioning compared to people without the syndrome (Cavalieri et al., 2010). Further analysis showed that this effect was only seen in men, but not in women. In addition, the presence of more MetS components was associated with worse cognitive performance in men. Consistent with past studies, cognitive dysfunction was most pronounced in males with MetS who also had high inflammation as measured by high-sensitivity C-reactive protein (hs-CRP) (Cavalieri et al., 2010; Dik et al., 2007; Yaffe et al., 2004). Together, these studies demonstrate that obesity and MetS are associated with cognitive deficits in middle age.

**Metabolic Syndrome, Obesity and Cognition in Old Age**

Similar to studies of the relationship between cognition and MetS in midlife, research on MetS in older adults has demonstrated that MetS is associated with cognitive impairment and risk of cognitive decline. In a study of adults over seventy years old, Yaffe et al. (2004) found that older adults with MetS were more likely to develop cognitive impairment over a four year period relative to older adults without MetS. In elders with MetS, the number of MetS components was not significantly associated with risk of cognitive decline. Overall, this study demonstrated that MetS in older adults is significantly associated with risk of cognitive decline, and that this relationship may be modified by inflammation (Yaffe et al., 2004). A later study of older adults (ages 65-88) supported the previous findings in the Yaffe et al. (2004) study and concluded that people with MetS had worse cognitive performance on all measures compared to people without MetS, and that this effect was strongest in people with high inflammation. Of all the individual components of MetS, hyperglycemia was found
to be the most important factor driving the relationship between MetS and cognitive performance (Dik et al., 2007).

In a review of MetS and cognitive disorders in the elderly, Yaffe (2007) investigated whether a diagnosis of MetS or the individual components of MetS were more important in identifying risk for cognitive decline. After reviewing three individual studies of elderly populations of varying ethnicities, Yaffe concluded that the additive effect of the factors that define MetS is associated with greater risk for cognitive decline than any individual component of the disorder alone. However, there was some evidence that impaired glucose control may be as important as a diagnosis of MetS on risk for cognitive decline (Yaffe, 2007; Yaffe et al., 2007; Yaffe et al., 2004).

The relationship between obesity and cognitive impairment in older adults appears to be more complex than the relationship reported in MetS research. Research among obese older adults has shown obesity to be both protective and detrimental to cognition. In a review of cognitive performance in obese old adults between 65-95 years old, Smith et al. (2011) found that there was a negative relationship between obesity and cognition in cross-sectional studies where the mean participant age was less than 73 (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003; Jeong, Nam, Son, Son, & Cho, 2005; Nilsson & Nilsson, 2009; Walther, Birdsell, Glisky, & Ryan, 2010). However, in two studies where the mean age exceeded 73 years old, the opposite association was present where obesity was positively associated with cognitive performance (Kuo et al., 2006; Nilsson & Nilsson, 2009). Prospective studies in older adults have also revealed mixed findings. In some studies of older adults, risk for age-related cognitive decline tended to increase with increased body weight (Cournot et al., 2006; Elias et al., 2003; Wolf et al., 2007), while in other studies obesity either predicted higher cognitive performance or less cognitive decline at follow-up (Han et al., 2009). These mixed findings both in cross-sectional and prospective studies may stem from the use of the BMI measure to measure adiposity. BMI is particularly limited in older adults because of changes in body composition. Another explanation for the mixed results may be a survival effect in the elderly.

From these studies of MetS in older adults, it is apparent that MetS has an adverse effect on cognitive function. It seems that the presence of MetS more accurately predicts cognitive decline compared to the individual components of the syndrome alone. However,
inflammation has been identified as a possible modifier in the relationship between MetS and cognition, and there is some evidence for the role of hyperglycemia or impaired glucose control in this relationship.

**Metabolic Syndrome, Obesity, and Risk for Dementia**

The relationship between MetS and its individual components and dementia is gravely important. Dementia is the combination of memory disorders and deficits in cognitive functioning that significantly impacts activities of daily living. Cognitive impairment can include impairment of abstract thinking or judgment, or other deficits in higher cortical function. It is estimated that 18% of people over the age of 75 have dementia. Although dementia is most common in older people, it is not part of normal aging. Of the dementia subtypes, the most common form of dementia is AD, which accounts for roughly 60-70% of dementia cases, followed by vascular dementia (Duthey, 2013). As the elderly population rapidly grows, the number of people with dementia will inevitably grow. High BMI and obesity, particularly in midlife, has been found to be a risk factor for dementia and AD (Fitzpatrick et al., 2009; Gorospe & Dave, 2007; Gustafson et al., 2003; Kalmijn et al., 2000; Kivipelto et al., 2005; Rosengren, Skoog, Gustafson, & Wilhelmsen, 2005; Whitmer, Gunderson, Barrett-Connor, Quesenberry, & Yaffe, 2005; Whitmer et al., 2008). Studies of MetS and its components have similarly shown that metabolic and cardiovascular risk factors in midlife and old age increase the risk for future dementia (Kalmijn et al., 2000; Kivipelto et al., 2001; Kivipelto et al., 2005; Launer et al., 2000; Raffaitin et al., 2009; Skoog et al., 1996; Vanhanen et al., 2006). While several studies have demonstrated that midlife obesity and MetS components increase the risk for dementia in later years, the effect of midlife overweight on risk for dementia is less certain (Fitzpatrick et al., 2009; Kivipelto et al., 2005; Whitmer et al., 2005; Whitmer et al., 2008).

**Metabolic Syndrome and Dementia in Middle Age**

A handful of studies have examined whether MetS and its associated cardiovascular risk factors are associated with risk of dementia. One prospective study of Japanese-American men found that those with a cluster of metabolic cardiovascular risk factors in midlife had increased risk of vascular dementia, but not AD, 25 years later (Kalmijn et al.,
In another population-based study, Kivipelto et al. (2001) investigated the association between midlife high blood pressure and serum cholesterol concentrations and AD in later life. Prior longitudinal studies have shown high blood pressure tends to precede AD (Launer et al., 2000; Skoog et al., 1996). The study revealed that both raised systolic blood pressure and high serum cholesterol concentration in midlife significantly increased the risk of developing AD in later life, even when controlling for other vascular risk factors. Further, the presence of both raised systolic blood pressure and high cholesterol was associated with greater risk than either of the risk factors independently (Kivipelto et al., 2001). In addition to high total cholesterol level and high systolic blood pressure, midlife obesity has also been shown to be a significant risk factor for dementia. The clustering of these factors in middle age, high total cholesterol, high systolic blood pressure, and midlife obesity, increased the risk of dementia additively. Further, relative to people with none of these risk factors, obese persons with both high cholesterol and high blood pressure were roughly six times more likely to develop dementia 21 years later (Kivipelto et al., 2005).

Several other studies have focused on the impact of midlife obesity on risk for dementia independently of other cardiovascular risk factors (Fitzpatrick et al., 2009; Gorospe & Dave, 2007; Gustafson et al., 2003; Rosengren et al., 2005; Whitmer et al., 2005; Whitmer et al., 2008). These studies have reported that both global obesity and central obesity in middle age increase the risk of dementia in old age, controlling for comorbid conditions. A recent meta-analysis of prospective studies found that underweight, overweight, and obese BMI were all linked to an increased risk for dementia relative to normal BMI subjects. Underweight and obese populations appeared to be at greater risk for dementia relative to overweight persons (Anstey, Cherbuin, Budge, & Young, 2011). Recently, a Swedish twin study found that relative to persons with normal BMI, people who were overweight or obese at midlife were at greater risk for developing dementia, with obese people being at the greatest risk. The study reported that people with dementia or AD were 70% more likely to be overweight at midlife compared to controls. People who were obese at midlife were even more likely to develop AD or vascular dementia in the future. Co-twin matched case-control analyses attenuated these relationships suggesting that familial factors contribute to the relationship between increased adiposity in middle age and dementia (Xu et al., 2011). Together, these prospective and longitudinal studies show that both obesity and
vascular risk factors in midlife significantly increase the risk for dementia. Furthermore, some studies have reported that clusters of metabolic and cardiovascular risk factors increase the risk for dementia additively (Kivipelto et al., 2001; Kivipelto et al., 2005).

**Metabolic Syndrome and Dementia in Old Age**

The association between MetS or metabolic risk factors and dementia has also been studied in older adults. One population-based study found that AD was more prevalent in elderly women (69-78 years old) with MetS relative to women without MetS, but this finding was not present in men. This gender inconsistency may be attributed to sample limitations; there were less men with MetS than women with MetS in the study (104 vs. 314, respectively), and there were limited numbers of men with AD (N = 13). Even when controlling for apolipoprotein 4 (ε4) phenotype, education, age, and total cholesterol, and excluding diabetic subjects, MetS was significantly related to AD (Vanhanen et al., 2006). In a similar study of persons over the age of 65, having MetS increased the risk of developing vascular dementia over the next four years, controlling for sociodemographic variables and ε4 status (Raffaitin et al., 2009). Of the individual components of MetS, high triglyceride level was the only component significantly predictive of all-cause and vascular dementia. In addition, diabetes was significantly associated with all-cause and vascular dementia, while impaired fasting glucose was not significantly associated with risk of dementia (Raffaitin et al., 2009). The small literature on this subject suggests that MetS in late life is associated with developing dementia, including both AD and vascular dementia.

Research on MetS, obesity, and the individual components of MetS has consistently demonstrated that the presence of these health conditions as early as midlife can negatively impact cognitive functioning and increase risk for future dementia. These findings demonstrate the importance of cardiovascular and metabolic health for cognitive functioning and susceptibility to neurodegenerative disease.

**Metabolic Syndrome and the Brain: Imaging Studies of Cerebral Atrophy**

Gray matter (GM), characterized by dense populations of neuronal cell bodies, has been a central focus of imaging studies investigating the impact of obesity and its associated cardiovascular and metabolic factors on the brain. GM volume and cortical thickness are
used as a marker of brain atrophy, or shrinkage of the brain. Cerebral atrophy, or brain volume loss, is a part of normal aging, but this process can be accelerated by vascular factors and neurodegenerative disease (Blatter et al., 1995; Fotenos, Snyder, Girton, Morris, & Buckner, 2005; Jernigan et al., 1991; Kantarci & Jack, 2003). In both neurodegenerative and cerebrovascular diseases, brain atrophy is an indicator of disease progression (Jouvent, Viswanathan, & Chabriat, 2010). Cerebral atrophy is a detrimental process that contributes to cognition decline and dementia (De Leon et al., 1997; Visser, Verhey, Hofman, Scheltens, & Jolles, 2002; Wegiel et al., 1999). The investigation of cerebral atrophy is crucial in MetS as vascular risk factors commonly exhibited by individuals with MetS, such as hypertension, hypercholesterolemia, and diabetes, have all been found to increase risk for dementia or atrophy in elderly populations (Aliev, Obrenovich, Smith, & Perry, 2003; Heijer et al., 2003; Kivipelto et al., 2002; Leibson et al., 1997; Meyer et al., 1999; Ott et al., 1999; Schnaider Beeri et al., 2004; Togo, Katsuse, & Iseki, 2004).

Cerebral atrophy has not been studied specifically in MetS, however a number of studies in the past decade have reported that obesity, typically defined by BMI, is associated with decreased local or global brain volumes (Brooks et al., 2013; Gustafson et al., 2004; Kurth et al., 2012; Maayan, Hoogendoorn, Sweat, & Convit, 2011; Pannacciulli et al., 2006; Raji et al., 2010; Taki et al., 2008; Walther et al., 2010; Ward et al., 2005). This trend has been observed in middle aged and older adults, as well as young adults and adolescents.

**Cerebral Atrophy and Obesity: Imaging Studies of Young Adults**

Within the last five years, MRI studies have been conducted examining the effects of obesity on young adults. Yokum, Ng, and Stice (2012) used MRI to identify differences in global brain volume and regional gray matter volumes in regions associated with taste, reward, and inhibition among lean, overweight, and obese young females (M age = 18.4, S.D. = 2.8). Furthermore, the study examined whether brain volumes in these regions predicted increases in BMI a year later. Group analyses found significant differences in global GM volume between obese and overweight, and obese and lean individuals, but not overweight and lean individuals, suggesting that the association between BMI and GM is nonlinear. Contrary to the original hypotheses, the study did not observe significant correlations between BMI and GM volume in a priori regions associated with reward
(caudate, putamen), taste (postcentral gyrus, insula), and inhibitory control (inferior, middle, and superior frontal gyri). However, the study reported GM reductions in the bilateral superior frontal gyri and the left middle frontal gyrus that were correlated with subsequent increases in BMI at follow-up suggesting that decreased GM volume in regions implicated in inhibitory control may increase risk for future weight gain. In another MRI study, structural MRI and neuropsychological tests were used to assess the relationship between obesity, executive function, disinhibition, and brain volume in lean and obese adolescents (14-21 years old). Compared to lean participants, obese participants had significantly lower orbitofrontal (OFC) volumes, and there was a nonsignificant statistical trend for decreased frontal lobe gray matter volumes in obese participants. The OFC has been implicated in food reward processing, in addition to behavioral inhibition, and has reciprocal connections to limbic areas and the hypothalamus (Kringelbach, 2005). Further, the study reported the obese group performed worse on cognitive measures of executive function. Disinhibition, as measured by the three-factor eating questionnaire (TFEQ) was correlated with BMI, Stroop color-word score, and OFC volume (Maayan et al., 2011). Taken together, these studies of adolescents and young adults show that obesity is linked to GM reductions in brain regions associated with impulse control and inhibition, and food reward, including the frontal gyri and the OFC.

Beyond adolescence, MRI studies have also investigated brain abnormalities related to obesity in young adults in their twenties through early forties. In a voxel-based morphometric analysis of young adults in their mid-twenties to early forties, Pannacciulli et al. (2006) studied regional differences in brain structure between obese and lean adults. After controlling for confounders such as age and sex, the study reported that the obese group had significantly lower GM density in several areas including the post-central gyrus, frontal operculum, putamen, middle frontal gyrus, and the cerebellar cortex (Pannacciulli et al., 2006). The post-central gyrus and frontal operculum are involved in taste processing (Haase, Cerf-Ducastel, & Murphy, 2009). The putamen, part of the dorsal striatum, has been shown to be important in feeding-related reward in animals and humans (Pannacciulli et al., 2006). Further, human studies have linked dopamine levels in the dorsal striatum to food reward (Small, Jones-Gotman, & Dagher, 2003). The prefrontal cortex is thought to be involved more specifically in decisions about stopping eating in addition to its roles in inhibition and
goal-directed behavior. The cerebellum, which has direct connections to the hypothalamus, has been associated with feeding behavior (Tataranni et al., 1999). Overall, the study provided evidence that obesity is associated with abnormalities in brain areas implicated in taste, reward, behavioral control, and feeding behavior in young adults.

Adding to the literature in this age group, Smucny et al. (2012) examined GM volume differences between obese-prone (OP) and obese-resistant (OR) young to middle age adults. OR adults were self-described as “naturally thin people” meaning they had difficulty gaining weight and spent little effort maintaining their lean bodies, had no familial history of obesity, had never been overweight, and exercised fewer than three hours per week. In contrast, OP adults were self-described as “people who struggle with their weight,” and had both a familial history of obesity and self-reported history of weight fluctuations. Further, OP adults were recruited to have a BMI between 20-30 kg/m² and were overweight on average. Investigating OP adults as opposed to already obese adults is advantageous in that structural differences observed may precede future weight gain and obesity and thus these structural changes could either help explain the neural mechanisms of obesity or be used to predict obesity risk. MRI analyses showed OP adults had decreased GM volume in the insula, medial orbitofrontal cortex, and the cerebellum when controlling for body fat mass. These significant findings suggest that people prone to obesity exhibit structural brain differences in areas implicated in taste and reward processing, and in areas associated with feeding behavior.

Collectively, MRI studies of obesity in young adults spanning adolescence through adults in their forties demonstrate that obese and obese-prone adults have decreased regional GM volumes relative to lean and normal weight individuals in areas associated with inhibitory control, taste and reward processing, and feeding behavior. Despite some unique findings reported in each study, there were some trends in the regional volume differences. Obese individuals tended to have decreased volumes in prefrontal and frontal areas associated with behavioral inhibition and other cognitive functions, such as the middle frontal gyrus and the OFC, and the cerebellum.
Cerebral Atrophy and Obesity: Imaging Studies of Middle-Age Adults

Imaging studies of the effects of obesity and vascular and metabolic risk factors on brain structure in middle-aged adults are needed. Only a handful of studies have examined the impact of obesity and vascular risk factors on brain structure in middle-aged adults (Debette et al., 2010; Ward et al., 2005). Ward et al. (2005) investigated the effects of obesity as measured by BMI and cardiovascular factors on global brain volume in cognitively healthy middle-aged men and women (aged 40-66). The study found that both age and BMI were negatively associated with brain volume in a linear regression analysis. BMI continued to be significantly associated with brain volume when controlling for age suggesting accelerated brain atrophy in middle-age individuals with elevated BMI. Cardiovascular risk factors, including hypertension and hypercholesterolemia, were not associated with brain volume in this sample (Ward et al., 2005).

In another study of middle-age adults, Debette et al. (2010) investigated relationships between various measures of obesity and MRI-markers of brain aging, including total brain volume, temporal horn volume, white matter hyperintensity volume, and brain infarcts. Temporal horn volume was used as a substitute for hippocampal volume due to difficulty classifying hippocampal volume. The study utilized both anthropometric (BMI, WC, waist-to-hip ratio) and radiographic measures of obesity. The study found that all measures of adiposity were negatively correlated with total brain volume, controlling for age, sex, and vascular risk factors such as systolic blood pressure, smoking, diabetes mellitus, history of cardiovascular disease, and physical activity index. The relationship between CT-based quantifications of abdominal obesity and total brain volume was the most robust finding, and was found to exist independent of BMI and insulin resistance. However, there were no enduring significant relationships between anthropometric or CT-based abdominal fat measures and temporal horn volume, white matter hyperintensity volumes, or brain infarcts. In addition to replicating past findings of reduced total brain volume in obese individuals, Debette et al. (2010) demonstrated that some measures of adiposity are better than others in describing the relationship between obesity and cerebral atrophy, particularly radiographic measures of abdominal obesity and waist-to-hip ratio.
Cerebral Atrophy and Obesity: Imaging Studies of Older Adults

Despite a relative shortage of MRI-based imaging studies of obesity in middle-age adults, more research has been conducted in older adults. Jagust, Harvey, Mungas, and Haan (2005) studied the relationship between central adiposity, as measured by waist-to-hip ratio, and structural brain abnormalities associated with cognitive dysfunction and dementia, including decreased hippocampal volume. In a sample of adults 60 years and older, the study reported a negative association between waist-to-hip ratio and hippocampal volume, controlling for age. This relationship held significant after adjusting for BMI, total cholesterol, fasting blood glucose, and insulin levels or systolic blood pressure. The results of this study of central obesity in older adults suggest a link between elevated waist-to-hip ratio and structural brain abnormalities seen in neurodegenerative diseases such as AD.

Raji et al. (2010) investigated the relationships between brain atrophy and obesity and T2DM in a sample of elderly individuals who remained cognitively normal for at least five years post-imaging. In agreement with past studies, the study reported elevated BMI was associated with lower brain volumes in overweight and obese people. Despite normal cognitive functioning, elderly individuals had BMI-associated atrophy in brain areas targeted by neurodegeneration such as the hippocampus, and frontal lobes. Relative to subjects with normal BMI, obese subjects had decreased GM in the frontal lobes, anterior cingulate gyrus, hippocampus, and thalamus. Across all subjects, regional GM volumes most strongly related to BMI included the OFC, the hippocampus, and subcortical structures including the putamen, globus pallidus, and thalamus. Bivariate analyses between regional brain volumes and fasting plasma insulin showed high insulin levels were negatively correlated with brain volumes in the splenium of the corpus callosum, the OFC, and the hippocampus. Participants diagnosed with T2DM showed atrophy in various brain regions including the frontal lobes, prefrontal cortex, genu and splenium of the corpus callosum, middle cingulate gyrus, superior parietal lobule, the occipital lobes, the cerebellum, and the basal ganglia (caudate, putamen, and globus pallidus). In multiple regression analysis controlling for T2DM and fasting plasma insulin, BMI continued to be negatively associated with GM volumes in the OFC, anterior cingulate gyrus, medial temporal lobe and subcortical white matter (WM) (Raji et al., 2010). The results suggest that obesity and T2DM are related to volume loss in
brain regions associated with taste (OFC, thalamus), reward (OFC, putamen), and areas targeted by neurodegeneration (hippocampus, frontal lobes).

Similarly, Walther et al. (2010) studied the relationship between BMI and regional GM and WM volumes in older females (ages 52-92) with and without controlling for hypertension. Consistent with past research, the study reported an inverse relationship between BMI and GM volumes. Specifically, controlling for hypertension, higher BMI was significantly associated with atrophy in left orbitofrontal, right inferior frontal and precentral gyri, the parahippocampal, fusiform, and lingual gyri, and right cerebellar regions. The finding that GM differences were attenuated when controlling for hypertension suggests that hypertension contributes to atrophy in the brain. Another study investigated late-life obesity in a sample of normal weight and obese seventy-five year olds who maintained a stable weight over the previous five years. Consistent with other studies, obese people had significantly smaller global and regional GM volumes. Exploratory whole brain uncorrected analysis showed that obese people had GM volume reductions in the bilateral supplementary motor area, bilateral dorsolateral prefrontal cortex (DLPFC), left inferior frontal and postcentral gyri, controlling for T2DM and education. However, more stringent regional analyses corrected for family-wise error only demonstrated significant GM atrophy in the left DLPFC (Brodmann Area 9) in obese participants, an area that has been linked to appetite regulation and executive functioning, especially working memory (Brooks et al., 2013; Le et al., 2009).

Studies of obesity and comorbid conditions in older adults have shown trends for reduced GM volumes in frontal brain regions and areas affected by neurodegeneration. Several of these brain regions are associated with executive functioning and memory, reward processing, and regulation of food intake and appetite.

**Cerebral Atrophy and Obesity: Imaging Studies Across the Lifespan**

A handful of studies have investigated the relationship between obesity and structural brain differences across the lifespan. In a study of BMI and GM volume in healthy subjects (ages 12-81), results indicated a significant negative correlation between total gray matter volume and BMI in men, controlling for age, alcohol intake, history of hypertension, and diabetes mellitus. Specifically, the analyses revealed negative correlations between BMI and
regional GM volumes in the bilateral medial temporal lobes, anterior lobe of the cerebellum, occipital lobe, frontal lobe, precuneus, and midbrain, while the opposite relationship was observed for volumes of the bilateral inferior frontal gyri, posterior lobe of the cerebellum, frontal lobes, temporal lobes, thalami, and caudate heads (Taki et al., 2008). Positive correlations between BMI and GM regions are not well understood and have not been widely reported in other studies. These positive relationships may illustrate the obesity paradox, and may be due in part to the use of BMI as a measure of obesity. The obesity paradox refers to phenomena wherein obesity seemingly serves a protective factor in some chronic medical conditions. For example, elderly patients with a number of chronic diseases and elevated BMI have demonstrated lower all-cause and cardiovascular mortality than normal-weight counterparts suffering from the same diseases (Hainer & Aldhoon-Hainerova, 2013). Some argue that the obesity paradox exists because of the use of BMI when investigating health consequences of obesity instead of body fat distribution (Hamdy, Porramatikul, & Al-Ozairi, 2006). Thus, it is possible that the findings in this study were due to use of BMI, which is not necessarily an indicator of metabolic health. Interestingly, there were no significant findings for women in this study while differences have since been observed in studies of females alone (Walther et al., 2010; Yokum et al., 2012). This unexpected gender effect may have been due to differences in fat distribution (e.g., visceral versus subcutaneous fat) between men and women in the study. It is possible that the men in the study had more visceral fat than the women, which is more strongly associated with MetS than other types of fat.

In a similar study of BMI and brain volume in adults across the lifespan (ages 17-79), it was hypothesized that obese adults would show reduced brain volumes in several regions, including frontal and temporal regions, relative to normal weight and overweight individuals. In this sample, it should be noted that individuals were screened for medical conditions such as hypertension, diabetes, and cardiac disease. After adjusting for age, analyses revealed that obese individuals had reduced whole brain volumes and total gray matter volume relative to normal weight and overweight participants. Though multivariate analyses failed to show significant group differences, univariate analyses showed that obese individuals had significantly reduced GM volumes in parietal and temporal regions, and there was a nonsignificant trend for reduced volume in the occipital and temporal lobes ($p = .05; p = .07$) (Gunstad et al., 2008). The results of this study contribute to the growing evidence that
obesity may be related to structural brain changes, specifically cerebral atrophy, across the lifespan independent of diabetes and hypertension.

More recently, Kurth et al. (2012) studied the relationships between both BMI and WC and GM volume in healthy subjects between 18-80 years of age. It was hypothesized that WC would be a better predictor of atrophy relative to BMI given evidence that waist circumference is more closely linked to metabolic factors. Similar to some studies, participants did not have high blood pressure (less than 140/90 mm Hg) and had no reported history of diabetes or lipid disorder (Gunstad et al., 2008). The study reported significant negative correlations between GM volume and BMI and waist circumference in the hypothalamus, the cerebellum, and the prefrontal, anterior temporal and inferior parietal cortices. For both measures of obesity, the most robust finding was volume reduction in the hypothalamus. Within the frontal lobe, reductions were seen in the OFC, frontal pole, anterior parts of inferior and superior frontal gyri, and dorsomedial prefrontal cortices. Within the temporal lobe, in addition to the hypothalamus, there were significant differences in the middle and superior temporal gyri. These correlations tended to be more robust for WC compared to BMI, and there were additional significant findings for WC in the insula, the globus pallidus, and the inferior parietal lobe including the angular and supramarginal gyri. Further, there was a significant gender-by-waist circumference interaction where the findings were stronger for females.

Studies of obesity across the lifespan have similarly found evidence of decreased GM volume in obese populations. While there were some contradictory findings in which elevated BMI was associated with greater GM regional volumes in men (Taki et al., 2008), most studies reported findings that support the relationship between obesity and decreased GM volumes. Collectively, structural imaging studies of obesity and components of MetS have reported decreased volumes in brain regions involved in executive functioning and memory (OFC, dorsolateral prefrontal cortex, and medial temporal lobe), taste (OFC, insula, frontal operculum, thalamus) and reward (OFC, putamen) processing, behavioral inhibition (frontal areas), and appetite regulation (cerebellum, hypothalamus, dorsolateral prefrontal cortex).
**SIGNIFICANCE AND PURPOSE OF THE PROPOSED STUDY**

Structural MRI studies investigating the effects of obesity and/or cardiovascular risk factors on cerebral atrophy across the lifespan have shown that these factors tend to be associated with decreased gray matter. While there have been mixed findings regarding which brain regions are impacted by these medical conditions, it is evident that obesity and cardiovascular issues are linked to cerebral atrophy and cognitive impairment. These findings are greatly concerning as cerebral atrophy may predispose people to accelerated cognitive decline or increased risk for dementia. The evidence linking MetS, obesity, and cardiovascular risk factors to GM atrophy and dementia risk suggests that health care costs will rise due to obesity-related dementia, and that caretakers and other healthcare providers will face additional nonfinancial and emotional burdens.

Despite the numerous studies on the effects of obesity and its comorbidities on brain atrophy, cognitive dysfunction, and risk for dementia, no study has investigated the effect of metabolic syndrome on cerebral atrophy in adults to our knowledge. The purpose of the study is to investigate structural differences in cortical volumes and thicknesses and subcortical volumes in middle-aged and older adults with metabolic syndrome. Relationships between structural MRI findings and cognitive performance on neuropsychological measures will be investigated elsewhere.

**SPECIFIC AIMS**

**Aim #1:** To examine structural differences in cortical thickness and subcortical volume between adults with and without MetS.

**Hypothesis:** It is hypothesized that adults with MetS will have smaller measures of cortical thickness and subcortical volume in brain areas related to executive functioning, memory, taste and reward processing, regulation of food intake and appetite, and behavioral inhibition.

**Aim #2:** To investigate relationships between cortical thickness and subcortical volume measurements, and measures of adiposity.

**Hypothesis:** It is hypothesized that cortical and subcortical measurements will be negatively associated with measures of adiposity.

**Aim #3:** To investigate relationships between cortical thickness and subcortical volume measurements, and metabolic risk factor burden.

**Hypothesis:** It is hypothesized that cortical and subcortical measurements will be negatively associated with metabolic risk factor burden.
METHODS

PARTICIPANTS

Twenty-six middle-aged and older adults (aged 44-98 years old) were recruited from the San Diego community, Kaiser Permanente, and the UCSD Bariatric and Metabolic Institute. Participants who met less than three of five clinical criteria for MetS were assigned to the healthy control group (n = 12). The MetS group (n = 14) included participants who met the clinical criteria for MetS (see Table 1); these participants had at least three of the five conditions specified in clinical guidelines. All participants gave informed consent and were compensated for their participation after each study visit.

PROCEDURE

For the purposes of this structural imaging study, participants completed two study sessions. During the first visit, participants underwent procedures to determine MetS status, and were screened for exclusionary criteria. During the second visit, the structural MRI data were acquired at the UCSD Keck Center for functional MRI.

Screening Session

In the screening session, participants were screened for the following exclusionary criteria: ageusia, anosmia, recent upper respiratory infection or allergies, left-handedness, history of traumatic brain injury with at least five minutes loss of consciousness, and contraindications for MRI (e.g., metal in mouth and/or body). For more detailed information regarding the procedures used to determine ageusia and anosmia, see Murphy, Gilmore, Seery, Salmon, and Lasker (1990).

MetS status was determined using the International Diabetes Federation (IDF) guidelines for clinical diagnosis of MetS (Alberti et al., 2009). Participants in the MetS group had at least three of the following conditions: elevated waist circumference, elevated triglycerides, decreased HDL cholesterol levels (or treatment for HDL cholesterol), elevated systolic and/or diastolic blood pressure (or antihypertensive drug treatment), or elevated fasting glucose (or T2DM diagnosis in lieu of elevated fasting glucose). Specific cutoffs for these criteria are specified in Table 1. Height and weight were measured using a stadiometer.
and digital scale. Using these measurements, BMI was calculated by dividing the participant’s weight (kilograms) by height (meters) squared. Waist circumference (WC) was measured at the midpoint between the top of the hip bone (iliac crest) and the lowest point of the ribcage. Blood pressure was measured while participants were seated using an electronic blood pressure monitor. The average of three consecutive blood pressure readings was calculated and used in analyses. For participants recruited from Kaiser Permanente or the UCSD Bariatric and Metabolic Institute without a diagnosis of hyperlipidemia, HDL cholesterol levels and triglycerides were determined with CardioChek Triglyceride and HDL Cholesterol Strips after a 12-hour fast. Additionally, all participants completed a self-report questionnaire to report any current medications being used to treat hypertension, dyslipidemia, or T2DM, and the International Physical Activity Questionnaire (IPAQ) to measure physical activity.

**Magnetic Resonance Imaging**

Magnetic resonance imaging data were collected at the UCSD Center for Functional Magnetic Resonance Imaging.

**MRI Acquisition**

High-resolution T1-weighted IRSPGR scans were obtained on a 3T GE Discovery MR750 scanner with the following parameters: field of view (FOV) = 24 cm, slice thickness = 1.2 mm, resolution 0.9375x0.9375x1.2 mm³, echo time (TE) = 3 ms, Locs per slab = 170, flip angle = 8°. The T1-weighted IRSPGR sequence was collected using an image-based prospective motion correction technique (PROMO) in real time (Brown et al., 2010; White et al., 2010).

**Gray Matter Data**

T1-weighted structural scans were processed using the Freesurfer image analysis suite, version 5.2.0 (http://surfer.nmr.mgh.harvard.edu). Freesurfer allows the study of cortical and subcortical anatomy. Briefly, the cortical reconstruction and volumetric segmentation process includes removal of non-brain tissue, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures, and reconstruction of the boundary between cortical gray and white matter (Fischl
Participants were included in imaging analyses if Freesurfer’s automated process successfully produced global brain measures, cortical thickness, and subcortical volumes without error. Each subject’s post-processing outputs were manually inspected for reconstruction accuracy in the Talairach transform, skull strip, white and pial surfaces, and segmentations. After inspection, it was decided that manual edits were not required. Region of interest (ROI) cortical thickness and subcortical volume estimates were extracted from automatic surface parcellation labels using the Desikan/Killiany Atlas (Desikan et al., 2006)

**STATISTICAL ANALYSES**

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, version 21).

**Demographics and Clinical Data**

Two-tailed independent sample t-tests and chi-square analyses were conducted on age, gender, education, BMI, WC, and physical activity to examine group differences in demographics and clinical data. Additionally, chi-square analyses were used to examine differences in metabolic profiles and medications. Participants were excluded from all analyses if any demographic data exceeded more than two standard deviations from the mean of the group (N = 1).

**Structural MRI Analyses**

Structural MRI analyses investigated group differences in cortical thickness and subcortical volume in a priori ROIs, and examined relationships between MRI measurements and clinical data such as measures of adiposity, metabolic risk factor burden, and presence of individual criterion of MetS.

**CORTICAL THICKNESS AND SUBCORTICAL VOLUMES**

Analysis of Covariance (ANCOVA) was conducted to examine group differences in global brain measures, cortical thickness, and subcortical volumes. In all analyses, age and gender were included as covariates. For global brain measures, estimated intracranial volume (ICV) was also controlled for in volumetric analyses. Similarly, estimated ICV values were
used to adjust subcortical volumes to control for the effect of head size on subcortical volumes. Analyses of global brain measures were performed to allow us to test the specificity of our findings. Regional cortical and subcortical analyses were selected a priori and examined brain regions involved in memory (hippocampus, medial temporal lobe, middle temporal gyrus, precuneus), and reward (lateral OFC, putamen, insula, caudate, nucleus accumbens). Brain regions demonstrating significant group differences were further investigated in correlational analyses exploring relationships between structural MRI measures and clinical data.

**Relationships Between Gray Matter and Measures of Adiposity**

One-tailed partial bivariate Pearson correlations between cortical thickness measures and different measures of adiposity (e.g., BMI, WC) were performed, controlling for age and gender.

**Relationships Between Gray Matter and Metabolic Risk Factor Burden**

One-tailed partial bivariate Pearson correlations between cortical thickness measures and metabolic risk factor burden were performed, controlling for age and gender. Metabolic risk factor burden was determined by summing the total number of MetS criteria a participant met as specified in the clinical criteria for MetS. Metabolic risk factor burden ranged from 0-4. While there are actually five clinical criteria for MetS, we combined criteria for low HDL cholesterol and high triglyceride levels into one criterion (referred to as dyslipidemia) due to lack of more detailed clinical data in all subjects.

**Relationships Between Gray Matter and Hypertension, Dyslipidemia, and Diabetes Mellitus**

One-tailed partial bivariate Pearson correlations were conducted between cortical thickness measures and individual criterion for MetS diagnosis. Participants were dichotomized into groups based on whether or not they met clinical criteria for MetS for the following medical conditions: high blood pressure, dyslipidemia (low HDL cholesterol and/or elevated triglycerides), and T2DM.
RESULTS

DEMOGRAPHICS AND CLINICAL DATA

There were no significant differences \( p > 0.05 \) between the MetS and control groups in gender (36% males in MetS and 50% males in control; \( \chi^2 = 0.540 \)), age, education, mini mental status exam (MMSE), or physical activity (Table 2). As expected, there were significant group differences in BMI, waist circumference (WC), and metabolic risk factor burden \( p < 0.001 \). Additionally, there were group differences in number of people who met criterion for abdominal obesity, high blood pressure, dyslipidemia, and T2DM. Further, there were group differences in medications taken for the treatment of dyslipidemia and T2DM (Table 3).

| Table 2. Demographic and Clinical Data of MetS and Control Groups |
|-------------------|-------------------|------|------|
|                   | MetS Mean (SD)    | Control Mean (SD) | t    | p    |
| Age               | 55.50 (9.61)      | 63.08 (12.15)     | 1.777| 0.088|
| Intelligence      | 119.00 (17.26)    | 111.73 (17.57)    | -0.928| 0.366|
| Education         | 14.11 (2.69)      | 15.33 (3.23)      | 1.057| 0.301|
| MMSE              | 29.00 (1.18)      | 28.67 (1.87)      | -0.551| 0.586|
| BMI*              | 37.56 (6.86)      | 25.17 (2.86)      | -5.822| <0.001|
| WC*               | 120.13 (12.25)    | 89.97 (8.61)      | -7.346| <0.001|
| Risk factor burden* | 3.14 (0.77)    | 0.75 (0.45)       | -8.254| <0.001|
| Physical activity | 1804.36 (1844.10) | 2848.25 (2378.59)| 1.260| 0.220|

*\( p < 0.001 \)

MRI ANALYSES

Analyses on global brain measures revealed no differences between the MetS and control groups in total GM, cortical GM, subcortical GM, cortical WM, and mean thickness, controlling for age and gender (Table 4).
Table 3. Metabolic Profiles for MetS and Control Groups

<table>
<thead>
<tr>
<th>Meets criteria for:</th>
<th>MetS (%)</th>
<th>Control (%)</th>
<th>χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>14 (100)</td>
<td>2 (16.7)</td>
<td>18.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>14 (100)</td>
<td>6 (50)</td>
<td>9.10</td>
<td>0.003</td>
</tr>
<tr>
<td>Dyslipidemia*</td>
<td>9 (64.3)</td>
<td>1 (8.3)</td>
<td>8.55</td>
<td>0.003</td>
</tr>
<tr>
<td>Insulin resistance (T2DM)</td>
<td>7 (50)</td>
<td>0 (0)</td>
<td>8.21</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Current medications:

<table>
<thead>
<tr>
<th>Current medications</th>
<th>MetS (%)</th>
<th>Control (%)</th>
<th>χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>High blood pressure</td>
<td>6 (42.9)</td>
<td>2 (16.7)</td>
<td>2.08</td>
<td>0.149</td>
</tr>
<tr>
<td>Dyslipidemia*</td>
<td>6 (42.9)</td>
<td>1 (8.3)</td>
<td>3.91</td>
<td>0.048</td>
</tr>
<tr>
<td>Insulin resistance (T2DM)</td>
<td>7 (50)</td>
<td>0 (0)</td>
<td>8.21</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Meets criteria for low HDL cholesterol and/or elevated triglycerides.

Table 4. Global Brain Measures of MetS and Control Groups

<table>
<thead>
<tr>
<th></th>
<th>MetS</th>
<th>Control</th>
<th>F_{1,22}</th>
<th>p</th>
<th>\eta_p^2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (S.D.)</td>
<td>Mean (S.D.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICV (cm³)</td>
<td>1458135 (191815)</td>
<td>1551985 (174696)</td>
<td>2.684</td>
<td>0.116</td>
<td>0.109</td>
</tr>
<tr>
<td>Total GM (cm³)*</td>
<td>562866 (57552)</td>
<td>574120 (69114)</td>
<td>0.059</td>
<td>0.810</td>
<td>0.003</td>
</tr>
<tr>
<td>Cortical GM (cm³)*</td>
<td>414739 (47652)</td>
<td>426057 (51481)</td>
<td>0.162</td>
<td>0.692</td>
<td>0.008</td>
</tr>
<tr>
<td>Subcortical GM (cm³)*</td>
<td>52073 (4578)</td>
<td>53064 (5921)</td>
<td>0.349</td>
<td>0.561</td>
<td>0.016</td>
</tr>
<tr>
<td>Cortical white matter (cm³)*</td>
<td>456866 (49926)</td>
<td>449386 (64152)</td>
<td>1.491</td>
<td>0.236</td>
<td>0.066</td>
</tr>
<tr>
<td>Mean thickness (mm)</td>
<td>2.35 (0.086)</td>
<td>2.37 (0.14)</td>
<td>1.736</td>
<td>0.201</td>
<td>0.073</td>
</tr>
</tbody>
</table>

*ICV controlled for in analyses.

A priori ROI analyses revealed important differences between the MetS and control groups in cortical thickness estimates (Table 5). ROI cortical thickness analyses in memory areas (medial temporal lobe, middle temporal gyrus, precuneus cortex) revealed significant cortical thinning in the MetS group compared to the control group in the left medial temporal lobe (F_{1,22} = 8.447, p = 0.008, \eta_p^2 = 0.277), and a trend for lower cortical thickness in the
Table 5. Structural Differences in Cortical Thickness Between MetS Groups

<table>
<thead>
<tr>
<th></th>
<th>F(1,22)</th>
<th>p</th>
<th>η_p²</th>
</tr>
</thead>
<tbody>
<tr>
<td>L entorhinal cortex</td>
<td>7.219</td>
<td>0.013</td>
<td>0.247</td>
</tr>
<tr>
<td>L parahippocampal</td>
<td>4.995</td>
<td>0.036</td>
<td>0.185</td>
</tr>
<tr>
<td>gyrus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L temporal pole</td>
<td>5.252</td>
<td>0.032</td>
<td>0.193</td>
</tr>
<tr>
<td>R temporal pole</td>
<td>4.333</td>
<td>0.049</td>
<td>0.165</td>
</tr>
<tr>
<td>L medial temporal</td>
<td>8.447</td>
<td>0.008</td>
<td>0.277</td>
</tr>
<tr>
<td>lobe</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

right medial temporal lobe (F(1,22) = 3.771, p = 0.065, η² = 0.146). Further analyses of the individual structures of the medial temporal lobes showed significant cortical thinning in the MetS group compared to the control group in the left entorhinal cortex (F(1,22) = 7.219, p = 0.013, η_p² = 0.247), left parahippocampal gyrus (F(1,22) = 4.995, p = 0.036, η_p² = 0.185), left temporal pole (F(1,22) = 5.252, p = 0.032, η_p² = 0.193), and right temporal pole (F(1,22) = 4.333, p = 0.049, η_p² = 0.165) (Table 5). There were no significant group differences in cortical thickness in frontal areas related to reward and executive functioning (lateral OFC), or inhibitory control (frontal gyr). Further, there were no volumetric differences in brain regions implicated in appetite regulation (cerebellar regions, frontal areas), and there were no statistically significant group differences found in ROI subcortical volume analyses in reward (putamen, insula, caudate, nucleus accumbens) or memory (hippocampus) regions (p > 0.05).

Partial bivariate correlations performed between measures of cortical thickness in medial temporal lobes structures and clinical data (BMI, WC, risk factor burden) revealed a number of significant relationships (Table 6). Relationships between cortical thickness and clinical measures of adiposity (BMI, WC) were investigated in the left medial temporal lobe (Figure 1), left entorhinal cortex (Figure 2), left parahippocampal gyrus (Figure 3), left temporal pole (Figure 4), and right temporal pole (Figure 5). BMI was negatively associated with cortical thickness in the left entorhinal cortex, left parahippocampal gyrus, left temporal pole, and the right temporal pole. Similarly, WC was negatively associated with cortical thickness in the left entorhinal cortex, left parahippocampal gyrus, and the right temporal pole.
Table 6. Partial Bivariate Correlations Between Cortical Thickness and Measures of Obesity and Metabolic Risk Factor Burden

<table>
<thead>
<tr>
<th></th>
<th>BMI</th>
<th>Waist circumference</th>
<th>Risk factor burden</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>p</td>
<td>R</td>
</tr>
<tr>
<td>L entorhinal cortex</td>
<td>-0.655</td>
<td>&lt;0.001</td>
<td>-0.595</td>
</tr>
<tr>
<td>L parahippocampal cortex</td>
<td>-0.574</td>
<td>0.002</td>
<td>-0.467</td>
</tr>
<tr>
<td>L temporal pole</td>
<td>-0.405</td>
<td>0.025</td>
<td>-0.326</td>
</tr>
<tr>
<td>R temporal pole</td>
<td>-0.624</td>
<td>0.001</td>
<td>-0.509</td>
</tr>
<tr>
<td>L medial temporal lobe</td>
<td>-0.649</td>
<td>&lt;0.001</td>
<td>-0.570</td>
</tr>
</tbody>
</table>

Figure 1. Left: Partial correlation plots showing the negative associations between body mass index (BMI) and waist circumference (WC) residualized values and cortical thickness of the left medial temporal lobe (MTL) after controlling for age and gender. Right: Three-dimensional representation of the left MTL.

Figure 2. Left: Partial correlation plots showing the negative associations between body mass index (BMI) and waist circumference (WC) residualized values and cortical thickness of the left entorhinal cortex after controlling for age and gender. Right: Three-dimensional representation of the left entorhinal cortex.
Figure 3. Left: Partial correlation plots showing the negative associations between body mass index (BMI) and waist circumference (WC) residualized values and cortical thickness of the left parahippocampal gyrus after controlling for age and gender. Right: Three-dimensional representation of the left parahippocampal gyrus.

Figure 4. Left: Partial correlation plots showing the negative associations between body mass index (BMI) and waist circumference (WC) residualized values and cortical thickness of the left temporal pole after controlling for age and gender. Right: Three-dimensional representation of the left temporal pole.

Figure 5. Left: Partial correlation plots showing the negative associations between body mass index (BMI) and waist circumference (WC) residualized values and cortical thickness of the right temporal pole after controlling for age and gender. Right: Three-dimensional representation of the right temporal pole.
In addition, relationships between cortical thickness and metabolic risk factor burden were examined in these medial temporal structures. Metabolic risk factor burden was negatively associated with all significant MRI findings: left entorhinal cortex, left parahippocampal gyrus, left temporal pole, and right temporal pole. However, with the exception of the left temporal pole, the strongest associations between clinical data and MRI findings were seen with body mass index.

Exploratory analyses were conducted to investigate the relationship between cortical thickness of medial temporal structures and individual MetS criterion (Table 7). Partial bivariate analyses showed high blood pressure, or use of antihypertensives to treat high blood pressure, was negatively associated with cortical thickness in the left entorhinal cortex, left parahippocampal gyrus, left temporal pole, and the left medial temporal lobe. Similarly, T2DM was negatively correlated with left entorhinal cortex, left parahippocampal gyrus, bilateral temporal pole, and left medial temporal lobe cortical thickness. There were no significant associations detected between dyslipidemia and cortical thickness.

**Table 7. Partial Bivariate Correlations Between Cortical Thickness and MetS Criteria**

<table>
<thead>
<tr>
<th></th>
<th>Hypertension</th>
<th></th>
<th>Dyslipidemia</th>
<th></th>
<th>T2DM</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>p</td>
<td>R</td>
<td>p</td>
<td>R</td>
<td>p</td>
</tr>
<tr>
<td>L entorhinal cortex</td>
<td>-0.441</td>
<td>0.015</td>
<td>-0.072</td>
<td>0.368</td>
<td>-0.472</td>
<td>0.010</td>
</tr>
<tr>
<td>L parahippocampal</td>
<td>-0.369</td>
<td>0.038</td>
<td>-0.197</td>
<td>0.178</td>
<td>-0.523</td>
<td>0.004</td>
</tr>
<tr>
<td>L temporal pole</td>
<td>-0.408</td>
<td>0.024</td>
<td>-0.148</td>
<td>0.246</td>
<td>-0.479</td>
<td>0.009</td>
</tr>
<tr>
<td>R temporal pole</td>
<td>-0.314</td>
<td>0.068</td>
<td>-0.139</td>
<td>0.258</td>
<td>-0.521</td>
<td>0.005</td>
</tr>
<tr>
<td>L medial temporal lobe</td>
<td>-0.487</td>
<td>0.008</td>
<td>-0.149</td>
<td>0.244</td>
<td>-0.575</td>
<td>0.002</td>
</tr>
</tbody>
</table>
DISCUSSION

This study examined structural brain differences in middle-aged and older adults with MetS. The principal finding of this study was that the MetS group had significantly smaller measures of cortical thickness in the left medial temporal lobe compared to the control group. Additionally, cortical thicknesses in structures of the medial temporal lobe were negatively associated with clinical measures of adiposity, metabolic risk factor burden, and presence of T2DM and hypertension. Studies that have investigated associations between obesity and individual metabolic risk factors and cortical atrophy of temporal areas are consistent with these findings. While several studies have examined the effects of obesity, hypertension, and diabetes mellitus on brain structure, to our knowledge no study has examined the impact of MetS, a clustering of cardiovascular and metabolic risk factors, on brain structure.

GROUP COMPARISONS: STRUCTURAL DIFFERENCES IN METABOLIC SYNDROME

Between-group analyses revealed that the MetS group had significant cortical thinning in the left medial temporal lobe, and the right temporal pole relative to the control group. Within the left medial temporal lobe, the MetS showed reduced cortical thicknesses in the entorhinal cortex, the parahippocampal gyrus, and the left temporal pole. The strongest finding was present in the left entorhinal cortex. There were no group differences in global brain measures ($p > 0.05$), which allow us to better comment on the specificity of our findings. There were no group differences in cortical thickness in hypothesized frontal regions. Additionally, there were no group differences found in hypothesized subcortical regions.

Medial Temporal Lobe

The structures of the medial temporal lobe play an important role in establishing long-term memory (declarative memory) (Squire & Zola-Morgan, 1991), which is known to be one of the first functions affected in AD (Weiner et al., 2013). Consistent with memory complaints, the medial temporal lobe is considered to be the site of the first pathological changes seen in AD (Braak, Alafuzoff, Arzberger, Kretzschmar, & Del Tredici, 2006; Braak
This study showed that middle-aged and older adults with MetS had smaller estimates of cortical thickness in the left medial temporal lobe compared to healthy controls. Magnetic resonance imaging is emerging as a potential tool to quantify atrophy in the medial temporal lobe structures affected in the early stages of AD (Fennema-Notestine et al., 2009). Cross-sectional MRI studies have shown the structures of the medial temporal lobe are vulnerable to atrophy in both normal aging and AD (Rusinek et al., 2003). In some studies, atrophy of the medial temporal lobe predicted conversion to AD in subjects in the prodromal stage of the disease known as mild cognitive impairment (MCI) (Fennema-Notestine et al., 2009; Killiany et al., 2002). Similarly, atrophy of the medial temporal lobe structures has been reported to discriminate between normal controls, MCI, and AD (Shi, Liu, Zhou, Yu, & Jiang, 2009).

In normally aging individuals, accelerated atrophy rates in the medial temporal lobe have been found to predict future memory decline (Rusinek et al., 2003). Similarly, BMI and T2DM have been associated with decreased volumes and measures of atrophy in the medial temporal lobe in cognitively healthy individuals (Gustafson et al., 2004; Korf et al., 2007; Taki et al., 2008).

**Entorhinal Cortex**

The MetS group showed the most cortical thinning in the left entorhinal cortex relative to the control group. The entorhinal cortex has been suggested to be the first site of neuropathological changes in AD. It is hypothesized that AD begins in the entorhinal cortex, and then spreads to the hippocampus and eventually to the cortex (Braak & Braak, 1995). The involvement of the entorhinal cortex in early AD pathology has been confirmed by histopathologic studies (Braak & Braak, 1991). Consistent with this view of AD pathology, Du et al. (2004) found a higher rate of atrophy in the entorhinal cortex compared to the hippocampus in AD patients suggesting that the entorhinal cortex is affected by neurodegenerative processes prior to the hippocampus. Neuroimaging studies have consistently demonstrated the involvement and importance of the entorhinal cortex in MCI and AD. MRI studies in mild AD and AD populations have consistently reported volume loss in the entorhinal cortex (Atiya, Hyman, Albert, & Killiany, 2003; Du et al., 2001). Similarly, longitudinal MRI studies of AD have found increased rates of atrophy in the entorhinal.
cortex relative to other brain structures (Du et al., 2003; Schott et al., 2003). Atrophy in the entorhinal cortex has been reported to reflect the progression of AD; structural measures of the entorhinal cortex have been reported to discriminate between patients with AD and controls, and between subjects with MCI and controls, and to predict conversion to AD in research populations (Atiya et al., 2003; Kantarci & Jack, 2003; Teipel, Meindl, Grinberg, Heinsen, & Hampel, 2008; Younes, Albert, & Miller, 2014). Imaging studies have also found relationships between entorhinal cortex measures and cognition; measures of entorhinal cortex atrophy and entorhinal cortex volume have been shown to correlate with neuropsychological measures in MCI and AD patients (Di Paola et al., 2007; Li et al., 2012). Similarly, Velayudhan et al. (2013) reported baseline entorhinal cortex thickness was associated with cognitive decline over one year in AD patients. Our finding in the entorhinal cortex may help us understand the connection between MetS and increased risk for cognitive decline and dementia. Recently, Younes et al. (2014) reported significant morphometric changes in the entorhinal cortex 8-10 years prior to clinical symptom onset in subjects with symptomatic and preclinical AD, while significant changes in the hippocampus were noticed later approximately 2-4 years prior to onset. The cortical thinning seen in the MetS group may suggest that middle age and older adults with MetS experience accelerated atrophy that resembles the trajectory seen in early AD.

**Parahippocampal Gyrus and Temporal Pole**

The parahippocampal gyrus is consistently found to be vulnerable to increased rates of atrophy in MCI and AD (Julkunen et al., 2010; Wang et al., 2009). This structure is known to be important to memory encoding and retrieval (Yao, Hu, Zhao, & Liang, 2011). Similar to the entorhinal cortex, pathologic studies have found the parahippocampal gyrus is affected in the early stages of AD (Braak & Braak, 1991). In one MRI study, the left parahippocampal gyrus and bilateral superior temporal poles were found to show promising diagnostic value in differentiating normal controls and AD patients (Hanggi, Streffer, Jancke, & Hock, 2011). Parahippocampal volume differences between patients with AD and normal controls have been demonstrated in several studies (Ikeda et al., 1994; Jack et al., 1997; Kesslak, Nalcioglu, & Cotman, 1991). Recently, Yao, Hu, Liang, Zhao, and Jackson (2012) investigated cross-sectional and longitudinal changes in atrophy between MCI and normal
controls. Normal controls showed atrophy in the left parahippocampal gyrus, right superior temporal gyrus, and the right superior temporopolar area over two years, consistent with previous MRI findings of atrophy in normal aging (Convit et al., 2000; Ohnishi, Matsuda, Tabira, Asada, & Uno, 2001). However, at both timepoints, MCI patients had significant cortical thinning in the parahippocampal gyrus, superior, middle, and inferior temporal gyrus, and the middle temporopolar area compared to controls. While atrophy of the parahippocampal gyrus and right superior temporal gyrus were seen in normal aging, these same regions showed higher rates of atrophy in MCI individuals (Yao et al., 2012).

Studies of normally aging adults have found relationships between measures of adiposity and volumes of parahippocampal and temporopolar regions. In a study of older females, Walther et al. (2010) reported negative associations between medial temporal lobe structures, including the parahippocampal gyrus, and BMI with and without controlling for hypertension. In another study of relationships between gray matter and adiposity, WC was negatively correlated with GM in the temporopolar region (Kurth et al., 2012). In our study, we found that the MetS group had cortical thinning in the left parahippocampal gyrus and bilateral temporal poles, which have been shown to be subject to higher rates of atrophy in MCI and AD relative to normal aging, and to be associated with measures of adiposity in adults (Hanggi et al., 2011; Kurth et al., 2012; Walther et al., 2010; Yao et al., 2012).

**Nonsignificant Findings**

Contrary to our hypotheses, we did not observe statistically significant group differences in cortical thickness in frontal regions such as the lateral OFC. A number of studies have found OFC volume reductions in obese or obese-prone persons relative to normal controls (Maayan et al., 2011; Smucny et al., 2012). Further, some studies have reported a relationship between OFC volumes and BMI in older adults and across the lifespan (Kurth et al., 2012; Raji et al., 2010). In addition, we did not observe significant group differences in cortical thickness in the middle temporal gyri or the precuneus. However there was a nonsignificant trend for smaller measures of cortical thickness in the precuneus in the MetS group compared to control group.

We did not find statistically significant differences in hippocampus volumes, an important structure of the medial temporal lobe that is affected by neurodegenerative
disorders and normal aging. In older adults, BMI and waist-hip ratio have been shown to be associated with decreased hippocampal volumes (Jagust et al., 2005; Raji et al., 2010). In the present sample, the lack of significant findings in the hippocampus may be due to the age of participants; our sample included both middle age and older adults while other studies reporting significant hippocampal findings have not included middle age adults. Additionally, in this sample we did not find significant differences in subcortical volumes related to taste and reward such as the structures of the basal ganglia (putamen, caudate, nucleus accumbens, pallidum) or insula.

**RELATIONSHIPS BETWEEN CLINICAL DATA AND MRI FINDINGS**

Partial correlation analyses revealed significant negative associations between clinical data (BMI, WC, risk factor burden), and cortical thickness. With the exception of the left temporal pole, each MRI finding was significantly associated with all three clinical measures. The correlations with the largest values were present in the left entorhinal cortex and the right temporal pole.

Exploratory analyses showed both hypertension and diabetes mellitus were negatively associated with cortical thickness in the left medial temporal lobe. Diabetes was significantly related to cortical thickness in all medial temporal lobe structures analyzed, while hypertension was associated with all structures with the exception of the right temporal pole. The association reported between diabetes mellitus and medial temporal lobe thickness is supported by previous findings showing associations between diabetes mellitus and medial temporal lobe atrophy (den Heijer et al., 2003; Korf et al., 2007). Similarly, previous literature supports the relationships found between blood pressure and brain structure; untreated hypertension has been reported to predict greater hippocampal atrophy in nondemented elderly subjects (den Heijer et al., 2005; Korf, White, Scheltens, & Launer, 2004), and blood pressure has been shown to attenuate the relationship between obesity and brain volume (Walther et al., 2010). When examining the effect of diabetes and hypertension together, one study reported an interaction between diabetes and hypertension on cortical atrophy where diabetes was associated with cortical atrophy in hypertensive participants, but not normotensive participants (Schmidt et al., 2004).
POTENTIAL MARKERS FOR DEMENTIA

In addition to markers of cerebral atrophy, there are a number of other promising markers for dementia. Measures of olfactory function such as odor identification tests are a promising tool to aid AD diagnosis (Graves et al., 1999; Morgan, Nordin, & Murphy, 1995); recently, one study reported performance on an odor identification test predicted conversion from MCI to AD (Conti et al., 2013). Similarly, gene dose of apolipoprotein E type 4 allele is strongly related to risk for late-onset AD (Corder et al., 1993). Cerebrospinal fluid protein biomarkers, such as the 42 amino acid form of β-amyloid, also demonstrate promising clinical utility as a biomarker for AD (Blennow, 2004). Despite the encouraging value of these markers of atrophy, olfactory measures, and genetic markers in predicting risk for dementia, currently none of these indicators can be used independently for clinical diagnosis. Given the complex nature of dementia, it is likely that in the future a number of these tools will be used together to diagnosis dementia.

STRENGTHS AND LIMITATIONS

One strength of the present study included high-resolution T1-weighted imaging data with an image-based prospective motion correction technique (PROMO) in real time (White et al., 2010). Prospective motion correction has been shown to improve subjective image and Freesurfer subcortical volumetric segmentation and cortical surface reconstruction quality in high-resolution MRI scans (Brown et al., 2010). Another strength of this study is the use of cortical thickness as a marker of atrophy. The present study is one of the few studies that have used cortical thickness to investigate brain structure differences associated with obesity and comorbid conditions (Hassenstab et al., 2012; Marques-Iturria et al., 2013; Tchistiakova, Anderson, Greenwood, & MacIntosh, 2014). Most MRI studies of obesity and comorbid conditions have used voxel-based morphometry. Cortical thickness has been shown to be precise and sensitive to changes in cortical morphology (Julkunen et al., 2009; Yao et al., 2012). However, our study also had several limitations. The greatest limitation to the present study is the small sample size. Given this limitation, we were unable to explore the contribution of each metabolic and cardiovascular risk factor to structural brain differences seen in the MetS group while controlling for other factors. However, in exploratory analyses, we explored correlations between MetS criteria and significant MRI findings, which gave
some insight into the role of each factor in the structural differences observed. Another limitation of the study is the lack of more detailed clinical information, such as triglycerides, HDL cholesterol, and fasting glucose levels. Such information would provide more powerful analyses and would eliminate the need to rely on participant self-reports. In addition, it would be helpful to follow these participants longitudinally in order to determine whether/which participants develop MCI.

**FUTURE DIRECTIONS**

The present study demonstrated significant structural brain differences in middle-age and older adults with MetS in regions consistently implicated in early AD pathology. Future studies should attempt to replicate the findings presented here with larger sample sizes. A larger sample size would allow for more powerful statistical analyses. Similarly, a large sample size would allow investigators to assess whether the accumulation of metabolic and cardiovascular risk factors has a greater impact on brain structure than any individual risk factor alone as has been shown in studies investigating the relationship between metabolic and cardiovascular factors and risk for dementia (Kivipelto et al., 2001; Kivipelto et al., 2005).

**CONCLUSION**

As the elderly population grows and obesity continues to be an international health epidemic, the incidence of dementia is likely to increase. While all participants in our study performed within normal limits on the MMSE and DRS, we found smaller measures of cortical thickness in the MetS group in bilateral structures of the medial temporal lobe, an area implicated in early AD pathology. Most importantly, we found that the MetS group had cortical thinning in the left entorhinal cortex, which has been suggested to be the first site of neuronal alterations in AD. Given the established connections between medial temporal lobe atrophy and cognitive decline and dementia, our findings suggest that middle-age and older adults with MetS may be at increased risk for cognitive decline and future dementia. Understanding the effect of MetS on brain structure is vital as it may help to elucidate a connection between MetS and dementia.
REFERENCES


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