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The Metabolic Syndrome, Neuropsychological Process Scores, and Mild Cognitive Impairment in Ethnic and Racial Minorities

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requirements for the degree Doctor of Philosophy

in

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by

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The Dissertation of Jacquelyn Szajer is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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VITA

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ABSTRACT OF DISSERTATION

The Metabolic Syndrome, Neuropsychological Process Scores,
and Mild Cognitive Impairment
in
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by

Jacquelyn Szajer

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University of California San Diego, 2020

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Rationale: Ethnic/racial minorities have increased prevalence of Alzheimer's disease (AD) and other dementias and may differ from the non-Hispanic White population in terms of risk factors and disease manifestation. The metabolic syndrome (MetS) is a modifiable risk factor for vascular-related cognitive decline and AD, and prevalence varies across ethnic/racial groups. Neuropsychological process scores used in conjunction with total scores have been shown to help detect subtle cognitive changes predictive of Mild Cognitive Impairment and dementia; however, this has not been well-studied in minorities

or MetS. The present study examined relationships between MetS, process scores, and future cognitive function in a racially/ethnically diverse sample from the Framingham Heart Study.

Design: Participants included 258 middle-aged and 155 older Black/African American, Hispanic, and Asian American adults. 32% met criteria for MetS (n = 130), with similar rates across ethnicity/race groups. Repeated measures and univariate analyses of covariance were used to examine group differences in total and process error scores on neuropsychological tests of memory and executive function. Relationships between baseline process errors, exam 2 total scores, MCI status were explored using regression. It was predicted that MetS would be associated with increased process errors, and process errors would be predictive of future cognitive declines.

Results: MetS interacted with ethnicity/race to predict Logical Memory immediate recall. Among the Black/African American group, those with MetS scored higher than controls. The trend was in the opposite direction among the Hispanic and Asian American groups; however, the effect was not significant. MetS did not predict any other cognitive outcome. Across groups, multiple baseline Trails B sequencing errors were associated with a 10x higher likelihood of progression to MCI at exam 2, controlling for inter-exam interval, age, Trails B total scores, WRAT reading scores, sex, and MetS. No other process errors predicted future cognitive status.

Conclusions: Present results suggest Trails B process errors may be useful indicators of risk for cognitive decline among minority groups. Future research investigating potential mediating effects of genetic risk for AD in clinical and more

socioeconomically diverse samples is warranted in order to determine whether these results are generalizable to larger populations.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia in the United States. AD is associated with increasing health care costs, reduced quality of life, and prevalence rates that are projected to nearly triple by 2050. Deaths from AD increased by 89% between 2000 and 2014 while those from heart disease – the current number one cause of death – have declined (Alzheimer's Association, 2017).

Ethnic and racial minorities have higher prevalence and incidence rates of AD, with studies showing that, on average, older Black/African American adults have twice the risk and older Hispanic adults have one and a half times the risk of receiving an AD diagnosed relative to older non-Hispanic White adults (Dilworth-Anderson et al., 2008; Harwood & Ownby, 2000; Manly & Mayeux, 2004; Steenland et al., 2016). Asian American older adults have been shown to have the lowest rates of AD and related dementias (ADRD) relative to five other ethnic/racial groups, including Hispanics, Blacks/African Americans, Pacific Islanders, American Indian/Alaska Native, as well as non-Hispanic Whites (Mayeda et al., 2016). Although, prior research has demonstrated historically higher rates of vascular dementias among Asian Americans (Still et al., 1990). While research suggests that genetic risk for AD differs by race/ethnicity, genetic differences alone have not accounted for the significant differences in prevalence rates among these groups (Chin et al., 2011; Yaffe et al., 2013).

Mild cognitive impairment (MCI) is thought to represent the intermediary stage between normal cognitive function and dementia (Petersen et al., 1999; Petersen & Morris,

2005), and is characterized by mild but quantifiable changes in neurocognitive function that do not significantly impair daily functional abilities. MCI is associated with greater risk for future functional decline and worsening cognitive impairment (Wadley et al., 2007), and roughly 50% of those diagnosed with MCI will progress to dementia within 3-4 years (Petersen et al., 1999). MCI prevalence rates are typically estimated to be between 10-20% among adults over the age of 65 (Lopez et al., 2003; Petersen et al., 2010). However, research has reported higher rates of MCI among minority groups. For example, individuals of Black/African American decent have been found to have increased rates of MCI compared to non-Hispanic White individuals, even after controlling for education and literacy (Manly et al., 2008; Sachs-Ericsson & Blazer, 2005). Research has also reported ethnic/racial variance in age of diagnosis. For example, studies from Project FRONTIER (Facing Rural Obstacles to health Now Through Intervention, Education & Research) and TARCC (Texas Alzheimer's Research & Care Consortium) including between 400-600 Mexican American participants has found that this ethnic group received diagnoses of MCI and AD at significantly younger ages than the non-Hispanic White group, controlling for education level, genetic risk for AD, and sex, with diagnoses of MCI occurring as early as age 50 in the Mexican American group versus age 64 in the non-Hispanic White group (O'Bryant et al., 2013).

Given elevated rates of MCI and ADRD in ethnic/racial minority groups, it is critical to identify early markers of risk for ADRD in these groups to facilitate the ability to implement early interventions aimed at targeting modifiable risk factors and delaying progression of cognitive declines.

Vascular Risk for MCI and ADRD: Metabolic Syndrome (MetS)

Vascular disease has long been linked with increased risk for MCI and ADRD and represents a modifiable target for early intervention and prevention efforts. Research has posited that the presence of multiple vascular conditions carries even greater risk for ADRD, with studies reporting post-mortem cerebrovascular and inflammatory changes as well as increased AD-specific pathology in those with multiple ante-mortem vascular risk factors (Luchsinger et al., 2005; Whitmer et al., 2005). Many ethnic and racial minority groups are at increased risk vascular disease, highlighting the need to study their potential contribution to increased rates of ADRD in these groups.

Metabolic syndrome (MetS) refers to the clustering of commonly co-occurring metabolic and vascular conditions within an individual, including diabetes, insulin resistance, and raised fasting plasma glucose, increased triglycerides, hyperlipidemia and decreased high density lipoprotein cholesterol (HDL-C), central adiposity, and hypertension, (Alberti et al., 2009) . MetS has been shown to increase risk for major vascular disease over and above the sum of risk conferred by each condition alone (Golden et al., 2002; Sattar et al., 2003) and has also been associated with an increased risk for MCI and ADRD in cross sectional (Crichton et al., 2012; Misiak et al., 2012; Profenno et al., 2010; Raffaitin et al., 2009; Vanhanen et al., 2006; Watts et al., 2013) as well as longitudinal research (Hughes et al., 2017; Lin et al., 2014; Tortelli et al., 2017). Prospective studies have demonstrated this is particularly true when MetS occurs during middle age (Kalmijn et al., 2000), highlighting the importance of understanding early

contributions of the syndrome to risk for cognitive decline later in life.

There are a number of clinical definitions for MetS. The International Diabetes Federation (IDF) criteria focuses on the importance of central obesity and insulin resistance as causative factors in the syndrome (Alberti et al., 2005, 2006). The IDF definition of MetS specifies that a person must have central obesity (defined using waist circumference) plus two of the following four factors: (1) raised triglycerides defined as ≥ 150 mg/dL or having a specific treatment for lipid abnormality (2) reduced HDL cholesterol defined as < 40 mg/dL in males and < 50 mg/dL in females, or having a specific treatment for lipid abnormality (3) elevated blood pressure defined as a systolic BP ≥ 130 or a diastolic BP ≥ 85 mm Hg, or having had treatment of previously diagnosed hypertension (4) elevated fasting plasma glucose defined as ≥ 100 mg/dL or previously diagnosed type 2 diabetes.

Insulin resistance and obesity are highly comorbid cerebrovascular conditions that have been posited as significant driving forces behind the pathophysiological processes leading to MetS (Abbasi et al., 2002; Alberti et al., 2009; Després & Lemieux, 2006). Insulin resistance is the core component of Type 2 Diabetes Mellitus (T2DM), or insulin-resistant diabetes. Diabetes mellitus generally refers to a cluster of chronic metabolic conditions characterized by abnormalities in the use and/or production of insulin resulting in increased blood glucose levels (hyperglycemia). Individual risk factors for MetS (e.g., hypertension, dyslipidemia, and obesity) are common comorbidities in T2DM. Accordingly, MetS is highly common among individuals with T2DM and there is a 5-fold increased risk for developing T2DM among those with MetS (Stern et al., 2004).

Independent of MetS, epidemiological evidence has demonstrated higher incidence of clinically diagnosed AD in those with insulin resistance (Irie et al., 2008; Luchsinger et al., 2001; Peila et al., 2001). Insulin resistance has also been implicated as a risk factor for MCI (Roberts, Knopman, Geda, et al., 2014) cognitive impairments across the lifespan and for dementia in old age (Biessels et al., 2006, 2008; Marseglia et al., 2016, 2018; Ryan et al., 2016). Insulin resistance and diabetes have also been linked to cognitive decline and dementia risk across ethnic groups (Bangen et al., 2015; Mayeda et al., 2013, 2014; Noble et al., 2012).

Obesity, characterized by elevated adiposity, is an independent risk factor for cardiovascular and cerebrovascular diseases such as cerebrovascular accidents (i.e., strokes) and T2DM. There are currently approximately two billion obese adults worldwide and 42% of Americans are predicted to be obese by 2030 (Finkelstein et al., 2012). Obesity is typically defined by a body mass index (BMI) of greater than or equal to 30. However, the BMI cutoff criteria may not be an ideal predictor of cardiometabolic abnormalities, as research has demonstrated that many patients classified as "obese" do not show abnormal metabolic risk factor profiles (Després & Lemieux, 2006).

As with insulin resistance, obesity has been independently associated with increased risk for MCI and ADRD (Gustafson et al., 2003; Nilsson & Nilsson, 2009; Sabia et al., 2009). Several cross-sectional and prospective studies have also demonstrated increased future risk of ADRD in association with obesity in middle age (Kivipelto et al., 2005; Razay & Vreugdenhil, 2005; Whitmer et al., 2005, 2008; Xu et al., 2011)

MetS Risk and Prevalence

Approximately one-third of the adult U.S. population has MetS (Heiss et al., 2014). Epidemiological studies have reported increases in MetS prevalence for every sociodemographic group in the U.S. since 1990, with more than a third of all US adults having met the IDF definition and criteria for metabolic syndrome by 2012 (Moore et al., 2017). Epidemiological studies have shown MetS varies by sex, with women at a 25% increased risk of MetS compared to men (Campbell et al., 2016). This is particularly true when using IDF criteria due to higher rates of abdominal obesity in women. Prevalence rates of MetS have also been shown to increase with age, with middle aged adults (ages 40-59) having a three times greater likelihood and older adults (ages 60 and up) having more than four times greater likelihood of having MetS than young adults (Devers et al., 2016; Ervin, 2009; Hildrum et al., 2007; Lechleitner, 2008). This is of particular concern considering age is the greatest risk factor for MCI and AD, and MetS during middle age has been associated with increased risk for cognitive decline and dementia.

Epidemiological studies have demonstrated ethnic and racial variance in the prevalence of MetS, with a greater prevalence of MetS being consistently demonstrated in Hispanic and Black/African American groups relative to non-Hispanic White groups (Gaillard, 2017; Gurka et al., 2014). Data from the National Health and Nutrition Examination Survey (NHANES) collected between 2007–2012 indicated odds ratios of 0.77 for Black/African American men, 1.20 for Black/African American women, 1.04 for Mexican American men, and 1.20 for Mexican American women, relative to their non-Hispanic White counterparts (Moore et al., 2017). This is especially noteworthy in the

context of increased risk for ADRD an in these ethnic/racial groups. Rates of MetS may also be more prevalent in Asian American than non-Hispanic White groups, despite lower BMI and rates of obesity (Palaniappan et al., 2011). However, this is only when obesity is not required for a diagnosis of MetS, as with the IDF criteria.

Rates of MetS factors have also been show to vary among ethnic/racial minority groups. For example, studies have shown that Black/African American men tend to maintain normal triglyceride levels even in the presence of cardiovascular disease, referred to as the *African American triglyceride paradox* (Sumner & Cowie, 2008; Yu et al., 2012), which could explain why Black/African American men are *less* likely than non-Hispanic White men and women to meet criteria for MetS (Goran, 2008; Moore et al., 2017; Osei & Gaillard, 2017). Among Hispanic groups, epidemiological evidence has shown higher prevalence rates of insulin resistance and diabetes relative to other ethnic and racial groups (Carrion et al., 2011; Goran, 2008). Interestingly, Hispanic groups have been shown to have lower risk for cardiovascular related mortality despite similar socioeconomic status-based risks for CV disease as Black/African American groups, a phenomenon referred to as the *Hispanic health paradox* (Schneiderman et al., 2014; Yaffe et al., 2007a). A caveat to this paradox, however, is that while Hispanic groups are living longer, increasing age and high rates of diabetes and insulin resistance have contributed to an increased risk for and prevalence of ADRD among older Hispanic adults (Bangen et al., 2015; Blaum et al., 2007; Fitten et al., 2014; Luchsinger et al., 2015; Zeki Al Hazzouri et al., 2013). Diabetes is also associated with greater percent decreases in independent activities of daily living (IADLs) and activities of daily living among Hispanic older adults, a requirement for a

diagnosis of major (versus mild) neurocognitive disorders (Blaum et al., 2007).

Neural Correlates of MetS

MetS and its cerebrovascular risk factors have been shown to negatively impact brain structure and function, contributing to neuropathological processes that increase risk for MCI and ADRD (Bokura et al., 2010; Cavalieri et al., 2010; Muller et al., 2010; Segura et al., 2009; Yates et al., 2012). Suggested mechanisms for the effects of MetS on the brain and cognition include neuroinflammation, dysfunction in vascular reactivity, abnormal brain lipid metabolism and oxidative stress (Yates et al., 2012). Notably, neuroimaging studies have linked MetS to structural changes, including volume loss in the hippocampus and frontal lobes, as early as adolescence, (Yates et al., 2012), highlighting the lifespan effects vascular disease can have on the brain.

The specific effects of MetS on brain morphology in middle age have been relatively under-studied, however, MetS in adults under the age of 60 is associated with greater risk of ischemic stroke, subcortical white matter lesions, periventricular white matter hyperintensities, and changes in brain metabolism (Bokura et al., 2008; Yates et al., 2012). A recent study investigating the effects of MetS and relative contribution of individual MetS risk factors on cortical thickness in middle age and older adults (ages 32-79) also reported significant negative effects of MetS on cortical thickness in clusters within the left inferior parietal, rostral middle frontal, lateral occipital and right precentral cortices; no effects of age were found (Schwarz et al., 2018). Reduced cortical thickness has also been reported in the entorhinal cortex in association with MetS in middle aged adults (McIntosh et al., 2017).

Functional brain changes have also been reported. For example, middle aged adults with MetS were found to have reduced brain response (relative to healthy controls) during pleasantness evaluation of sweet and bitter tastes in brain regions involved in higher-level cognitive processing (Green et al., 2015). Similar findings have been reported in binge-eating behaviors (Filbey et al., 2012; Tsuchiya & Adolphs, 2007) and those with increased body mass index (Blum et al., 2012), highlighting the link between brain function, diet and health.

Neural correlates of individual MetS factors.

The neurological correlates of MetS on the brain may be driven, at least in part, by its individual factors, which have been shown to exert individual neurological effects that contribute to cognitive decline and risk for MCI and ADRD. Insulin resistance and diabetes have been linked to increased cortical and subcortical infarctions, greater volume of white matter hyperintensities, and decreased hippocampal and whole brain volume (Roberts, Knopman, Przybelski, et al., 2014). Shared biological and CSF-based pathways to AD and diabetes have been posited as potential mechanisms for the link between insulin resistance and risk for MCI and ADRD (Crane et al., 2013; de la Monte, 2014; Hoscheidt et al., 2016; Kim & Feldman, 2015; Sridhar et al., 2015). For example, common pathogenic factors in both AD and diabetes include brain insulin resistance and oxidative stress (de la Monte & Wands, 2008), chronic hyperglycemia, hyperinsulinemia, acute hypoglycemic episodes, microvascular disease, and fibrillary deposits (in both the brain and in the pancreas), inflammation, obesity, and dyslipidemia (Sridhar et al., 2015). PET neuroimaging studies have shown evidence of changes in glucose metabolism within the

posterior cingulate, parietal, temporal, and prefrontal cortex in middle aged and young adults at genetic risk for AD (Reiman et al., 2004), highlighting how insulin-related disorders might play a role in the disease process.

Obesity has been associated with neuropathology in older adults that is linked to risk for ADRD, including reductions in cortical thickness (Gustafson, Lissner, et al., 2004) and microvascular changes in white matter (Gustafson, Steen, et al., 2004; Walther et al., 2010). Functional brain changes in reward processing have also been demonstrated in obesity that have important implications for reward-based behaviors such as eating in the absence of hunger and binge-eating that cause and maintain obesity (Babbs et al., 2013; Blum et al., 2017; de Araujo et al., 2012; Filbey et al., 2012; Gearhardt et al., 2014; Wang et al., 2002). For example, reduced reward response in the caudate nucleus and nucleus accumbens, regions that serve as part of the mesolimbic dopaminergic reward pathway, has been demonstrated in obese older adults after consuming and while rating a pleasant taste relative to water (Green et al., 2011). Decreased reward response has also been demonstrated in overweight adolescent females in response to more complex, high fat content foods, such as a milk shake relative to a flavorless liquid (Gearhardt et al., 2011; Stice et al., 2008).

Decreased reward response in obesity has been theorized to represent a "Reward Deficiency syndrome" (RDS). RDS refers to a predisposition to seek rewarding stimuli and engage in rewarding behaviors to compensate for inefficient or deficient DA functioning, and has been reported in association with decreased availability of striatal D2 receptors seen in obesity (Blum et al., 1996). The release of dopamine via dopaminergic pathways,

such as the mesolimbic pathway, is known to play a role in behavioral motivation, reward, pleasure, learning, and reinforcement (Blum et al., 2012). Accordingly, RDS is thought to contribute to the development and maintenance of obesity influencing behaviors such as disinhibited and impulsive eating (Wang, Volkow, & Fowler, 2002).

Neuropsychological Correlates of MetS

Findings are mixed regarding whether there are neuropsychological profiles that can be reliably attributed to MetS or its individual factors. Reasons for inconsistency in the literature include variability in sample demographics, individual MetS risk factors examined, the criteria used to define MetS, and methods for defining and measuring cognitive impairment (Crichton et al., 2012; Watts et al., 2013). Studies of the effects of MetS on neuropsychological performance have also largely focused on cross-sectional, clinical, older-adult samples (Dik et al., 2007; Razay et al., 2007; Vanhanen et al., 2006) , with little research on MetS in middle age, when the earliest neurocognitive changes are likely to occur.

One cross-sectional study of MetS in middle age reported that an increased number of MetS risk factors was negatively associated with performance on paragraph recall (WMS-R: logical memory), short- and long-delay recall of a word list (CVLT), and visual paired associates learning, as well as overall intellectual functioning (Hassenstab et al., 2010). Cross-sectional research has also demonstrated executive dysfunction on several measures including the Frontal Assessment Battery, in neurologically intact middle aged and older adults (Bokura et al., 2010). However, findings regarding the effects of MetS on cognitive function in middle age have been inconsistent. For example, a study including

3,369 European men found no association between MetS in middle age and performance on tests of visual memory, recognition memory, and digit-symbol substitution (Tournoy et al., 2010). A separate study also failed to find significant differences between middle aged adults with MetS and controls on visual memory (McIntosh et al., 2017). The same study conducted a path analytic mediation model of the effects of the number of MetS risk factors on visual memory performance with left entorhinal cortical (EC) thickness as a mediator in middle age. Results indicated that MetS was significantly related to left EC thickness, which in turn was related significantly to total immediate visual memory (e.g., learning), but not delayed recall scores, which are most predictive of dementia (McIntosh et al., 2017).

Research findings on MetS and cognitive function in aging also vary widely, with some studies reporting no effects of MetS on cognition in older adults (Overman et al., 2017), and others reporting mediating effects of variables such as comorbid chronic conditions (Foong et al., 2017). However, relatively consistent findings have been demonstrated across several cognitive domains. For example, decreased processing speed and visuoconstruction has been reported in older patients with MetS (Segura et al., 2009). MetS has also been associated with executive dysfunction (Bokura et al., 2010; Falkowski et al., 2014; Schuur et al., 2010). Deficits in executive function are particularly noteworthy as they have been linked to unhealthy eating habits and poor exercise and nutrition behaviors (Calvo et al., 2014; Joseph et al., 2011).

Notably, the studies mentioned above were comprised of primarily non-Hispanic White groups, and few studies have examined ethnic/racial variance in MetS in the context

of neuropsychological function. Among those that have included significant proportions of subjects from ethnic/racial minority groups, findings suggest that MetS and its individual factors may be associated with changes in cognitive function as early as middle age. For example, one study of diverse, rural community-dwelling middle aged and older adults (*n* = 395; mean age = 61 years), comprised of 37% Hispanic and 53% non-Hispanic White adults, reported that MetS was associated with impairments on measures of trail making, clock drawing, and several other executive function tests (Falkowski et al., 2014). Research from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) has also reported associations between indicators of cerebrovascular disease such as arterial stiffness and compromised blood flow and lower cognitive function among middle-aged and older diverse Hispanics (Tarraf et al., 2017).

As with studies in non-Hispanic White samples, most research in ethnically/racially diverse samples has focused solely on aging samples. Research from the Northern Manhattan Study (NOMAS), which includes over 1000 older adults from a largely Hispanic multi-ethnic urban community, has found that baseline MetS predicted cognitive function across multiple domains (memory, language, motor, executive function) at 10-year follow-up, with blood pressure being the most predictive individual factor for all cognitive domains except memory, after controlling for age, gender, ethnicity/race, education, smoking, alcohol, and risk factor treatment variables (Levin et al., 2014). Longitudinal research in a multiethnic sample of older adults from the Washington Heights-Inwood Columbia Aging Project has also reported that baseline CV risk factors (composite score including smoking, stroke, heart disease, diabetes, hypertension, and

central obesity) were associated with lower baseline performance on general cognitive processing, memory, and executive functioning measures among Black women and Hispanic men. However, CV risk factors were not related to decline in cognition over time. CV risk factors were not associated with cognition in Hispanics after adjustment for medications, (Schneider et al., 2015). A study examining the effects of MetS on cognitive change scores in a sample of older Hispanic adults enrolled in the Sacramento Area Latino Study of Aging (SALTA) reported that Hispanic adults with MetS had significantly worse 3-year change scores on the Modified Mini-Mental State Examination (a cognitive screener) and the Delayed Word-List Recall verbal memory test (Yaffe et al., 2007a).

Inconsistent findings regarding the neuropsychological correlates of MetS could be due, in part, to varying methods for assessing cognitive function. For instance, research investigating cognitive decline in MetS has widely used abbreviated and or/screening measures of cognitive function not sensitive to preclinical cognitive decline (Hishikawa et al., 2016). Studies have also used widely varying methods for identifying and labeling latent variables to represent cognitive domains measured by tests and scores used in their research, making it almost impossible to determine the specific neuropsychological domains and specific abilities are influenced by MetS (Crichton et al., 2012). Studies that *have* examined more comprehensive measures of cognitive function across multiple domains (e.g., memory, executive functioning, and attention) generally have not used standardized neuropsychological tests and have focused primarily on non-Hispanic White and older adult samples. Research in middle aged and ethnically/racially diverse samples, using standardized neuropsychological tests and methods for identifying MCI and ADRD

are needed.

Neuropsychological correlates of individual MetS factors.

Individual MetS factors have also been independently linked to neurocognitive changes. Insulin resistance and diabetes have been linked to cognitive decline and dementia risk across multiple ethnic groups (Bangen et al., 2015; Mayeda et al., 2013, 2014; Noble et al., 2012). For example, diabetes is associated with greater percent decreases in independent activities of daily living (IADLs) and activities of daily living among Hispanic older adults (Blaum et al., 2007). In primarily White samples, studies have shown differences in memory as a function of insulin and glucose dysfunction in AD (Watson & Craft, 2004) and other neurodegenerative disease (Craft & Watson, 2004). Diabetes has also been associated with poorer performance on measures of processing speed, verbal and visual memory, motor functioning, and executive functions, (Bottiroli et al., 2014; Palta et al., 2014), including cognitive control and inhibition (Frazier et al., 2015).

Obesity has also been linked to significant neurocognitive deficits (Joseph et al., 2011; Smith et al., 2011), with research reporting impairment on neuropsychological tests and process measures of executive function associated with frontal lobe dysfunction (Yang et al., 2018). These deficits have been demonstrated early in life. For example, deficits on tests of mental flexibility and inhibitory control efficiency have been shown in overweight/obese, as compared to normal weight young adults using go/no go tasks (Gunstad et al., 2007; Jasinska et al., 2012). Less efficient inhibitory control in overweight young adults has also been demonstrated on a stop-signal task and on the Simon task

(Sellaro & Colzato, 2017), which measures problem solving and decision making capacity in the context of stimulus induced response conflict. Notably, studies of obesity have linked executive dysfunction such as impulsivity and risky decision making to weight gain and dysfunctional eating behaviors, such as eating in the absence of hunger, binge eating, and emotionally-motivated eating (Filbey et al. 2012; Gearheardt et al. 2011). Visuoconstruction performance has also been shown to be impaired in obesity(Sargénius et al., 2017). As with MetS, however, findings have varied due to factors ranging from study population (e.g., hospital in-patient, outpatient, to epidemiological population-level sampling) to measure of obesity used. For example, a study on obesity measured using BMI demonstrated effects on attention/processing speed, and interactions with age influencing executive functioning, but no effects of BMI or interaction effects on memory or language functioning (Stanek et al., 2013).

Hypertension has also been associated with cognitive changes. For example, epidemiological research from the Framingham Heart Study has also reported that comorbid obesity and hypertension at baseline examination were associated with decreased cognitive function over time across domains of learning, memory, executive functioning, and abstract reasoning (Elias et al., 2003). The effects of hypertension on memory, concentration, visual retention, verbal fluency, and the Mini-Mental State Examination, a screener for cognitive impairment have also been reported in healthy aging (Paran et al., 2003). Hypertension has also been linked to declines in memory performance during midlife, but only in carriers of the Apolipoprotein-e (ApoE) gene ε4 allele, a known genetic risk factor for Alzheimer's disease (Oberlin et al., 2015).

Measuring Subtle Cognitive Decline in Metabolic Syndrome

Subtle cognitive decline refers to mild changes in cognition that occur prior to more frank impairments that can be easily measured with standard neuropsychological tests. These subtle changes can signal warning of risk for MCI and ADRD, enabling earlier intervention and prevention efforts. Accordingly, determining whether MetS is associated with subtle changes in cognition and characterizing these changes could aid in earlier identification of those with MetS who are most at risk for MCI and ADRD.

Research has operationalized subtle cognitive declines using neuropsychological total (e.g., achievement) scores on six neuropsychological tests of language (Category fluency, 30-item Boston Naming Test), attention (Trail Making Test, Parts A & B) and memory (Rey Auditory Verbal Learning Test 30-minute delayed free recall and recognition; Edmonds et al., 2015) . Studies have also shown cognitive discrepancy measures derived from total scores are useful in detecting subtle cognitive declines on executive function measures in normally-functioning older adults (Fine et al., 2008). Additional work has identified three different subtypes of subtle cognitive declines, including an executive, memory, and multi-domain subtype (Toledo et al., 2015), highlighting the utility of studying subtle declines in cognition across multiple domains.

Evidence also suggests that neuropsychological process measures, indices of the behaviors and strategies employed over time to achieve the solution to a problem (Kaplan, 1988), add value to total scores in terms of detecting early, subtle changes that occur before typical neuropsychological criteria for a diagnosis of MCI or AD are met (Crocco et

al., 2014; Hankee et al., 2013; Libon et al., 2011; Loewenstein et al., 2004; Thomas, Edmonds, et al., 2018; Thomas, Eppig, et al., 2018). Process scores include aspects of cognitive processing such as strategy use, measures of cognitive skill trade-off (e.g., sacrificing speed for accuracy), and error measures such as intrusions, repetitions, false-positives, confabulations, set-losses, sequencing errors, and perseverative responses. Investigation of subtle cognitive declines across total scores as well as process measures in ethnic/racial groups with MetS may provide critical information about early cognitive changes that signal warning of dementia and AD risk in these groups, allowing modifiable risk factors such as MetS to be targeted for effective prevention efforts.

Purpose of the Present Study

As pharmaceutical treatments to slow the progression of AD and other dementias are developed, it is critical to identify demographically appropriate, early indicators of who among those with modifiable risk factors, such as MetS, will go on to develop ADRD. Research on prodromal neuroimaging and plasma biomarkers is promising but still inconclusive, and as noted, neuropsychological assessment remains the gold standard for diagnosis of a neurocognitive disorder. MetS-related neuropathology may be associated with subtle changes in neuropsychological function that occur prior to more marked deficits seen in ADRD. Characterizing cognitive changes associated with MetS and how these might vary across racial/ethnic groups is an important step in understanding who with the syndrome is at risk for later developing MCI and ADRD.

While a handful of studies have demonstrated differences in cognitive function in

association with MetS in diverse samples, they have typically used non-standardized, less sensitive tests of cognition, and have focused on largely non-Hispanic White, aging samples. Given brain imaging findings in ethnic and racial minorities with MetS risk factors as early as childhood and theorized reciprocal relationships between MetS, brain function, and behavior, it is reasonable to expect subtle cognitive changes would exist prior to frank cognitive impairments that warrant a diagnosis of MCI or of ADRD. The potential clinical impact of subtle cognitive declines in neuropsychological function in MetS is wide reaching. Early cognitive impairments have the potential to increase behaviors that contribute directly to MetS such as overconsumption of rewarding foods and sub-optimal metabolic and vascular medication use patterns. Understanding how these changes vary by ethnicity is critical to individualizing treatment and intervention plans.

Accordingly, the aims of the present study were as follows: (1) To characterize MetS in the FHS OMNI cohorts and examine relationships between MetS and neuropsychological test performance and (2) To characterize process error scores in the FHS OMNI cohorts and explore the extent to which process errors represent subtle cognitive decline and are predictive of future cognitive function in an ethnically and racially diverse, non-clinical, epidemiological sample of middle aged and older adults. It was predicted that MetS would be associated with increased process errors and that process errors at baseline examination would be predictive of future cognitive declines. Given ethnic/racial variation in MetS and its individual factors, it was hypothesized that ethnicity/race would moderate MetS effects on cognition.

METHODS

The Framingham Heart Study

The Framingham Heart Study (FHS) is a longitudinal, epidemiological study from the National Heart, Lung, and Blood Institute (then, the National Heart Institute) conducted in collaboration with Boston University. The study began in 1948 and is the longest-running, multigenerational study in medical history. FHS was originally focused on the residents of Framingham, MA, a city approximately 20 miles west of Boston. The general goal of the study at its inception was to identify common factors and characteristics that contribute to cardiovascular disease across time. To date, the FHS has over 14,000 participants spanning three generations, including parents, children, spouses, and grandchildren. Longitudinal data on medical history, physical health, cognitive function and laboratory exams (e.g., blood panels) are collected approximately every two to six years.

FHS OMNI Cohorts.

The OMNI waves of the FHS were implemented to reflect increasing diversity of the Framingham, MA community in the 1990's and consists of individuals of Black/African American, Hispanic, Asian, Indian, Pacific Islander and Native American origins, who at the time of enrollment were residents of Framingham and the surrounding areas. Data collection occurred at two separate intervals, resulting in two OMNI cohorts. As reported by the FHS, total sample size of the OMNI1 cohort is 506. Total current sample size of the OMNI2 cohort is 410 (data collection is ongoing).

The current study included data from a subset of the OMNI cohorts (n = 879 after

excluding subjects), described in detail below (see Participants section).

FHS Baseline Physical Exam And Laboratory Data.

Baseline physical exam and laboratory data were available for all participants (*n* = 852). This included variables comprising risk factors for MetS: waist circumference, BMI, fasting plasma glucose, HDL cholesterol, LDL cholesterol, triglycerides, systolic and diastolic blood pressure.

FHS Neuropsychological Evaluations.

Participants without cognitive data (*n* = 372) and those tested in Spanish (*n* = 27) were excluded from main analyses. We also excluded pariticpants who met criteria for MCI at baseline (*n* = 40; See MCI section below). Cross-sectional neuropsychological data were included from 413 participants. Performance over time was evaluated at two exam dates (baseline, T2). Years between exams 1 and 2 ranged from 1 – 16, with an average of 6.78 years (standard error = .20), and over 70% of the sample ranging from 5-7 years. Longitudinal data were available for 153 participants. (See the Participants section below for demographics of the sample.) Of note, sample sizes varied for each across cognitive tests and domains due to missing data. (See Data Analysis section below for description of and descriptive statistics for cognitive variables.

FHS neuropsychological battery

The comprehensive neuropsychological battery used in the FHS consists of well-validated, standardized and widely used neuropsychological tests spanning all cognitive domains. Select tests from the battery that were used in the current study are described below.

Verbal academic achievement was measured using the Wide Range Achievement Test-3 (WRAT-3) Reading subtest, a measure of single word oral reading abilities and estimate of premorbid function.

Memory was assessed using the Logical Memory (LM) and Visual Reproduction (VR) subtests of the Wechsler Memory Scales (WMS). Logical Memory is a measure of verbal memory for contextual information. Participants listen to verbally administered stories and are asked to repeat them immediately and after a 20-30 minute delay. Total scores are derived for immediate memory, delayed memory, and recognition memory performance. Process measures are derived for the number of related and unrelated confabulations and number of intrusions. Visual Reproduction is a measure of figural (visual) memory. Participants are shown a series of 5 pages for ten seconds with 1 or 2 simple figures on each page and asked to reproduce the figure(s) from memory immediately and then again after a 20-30 minute delay. Total scores are derived for immediate memory, delayed memory, and recognition memory performance.

Executive function was measured using the Trail Making Test (Trails B), a measure of visuomotor set switching from the Expanded Halstead Reitan Battery, as well as the Digit Span (Digits Backward), a measure of auditory working memory.

Visuospatial functioning was assessed using the Hooper Visual Organization Test (HVOT), Clock Drawing Test (Clock), and the Block Design subtest from the WAIS. The HVOT is a measure of visual organization and integration. Clock is a measure of visual conceptualization and simple figure reproduction. Block Design is a measure of basic and complex visuoconstruction abilities.

Participants

Sex

The overall sample was 42.6% male (*n* = 363) and 57.4% female (*n* = 489). The sample of participants with available cognitive data was 40.9% male (*n* = 169) and 59.1% female (*n* = 244).

Ethnicity/Race

Ethnicity/race was determined based on self-report across all exam dates. Participants were excluded if they reported multiple ethnicity/race groups (i.e., any combination of Black/African American, Asian American, or Hispanic, and anyone reporting mixed race), if they declined to report race, or if they were inconsistent in their reporting across years. We also excluded participants reporting Indian, Pacific Islander and Native American ethnicities due to very low subject numbers (< 10 per group). After exclusion of subjects, the overall sample was 26.3% Asian American (*n* = 215), 31.5% Black/African American (*n* = 258) and 42.2% Hispanic (*n* = 346). The Asian American group consisted of 107 men and 64 women, the Black/African American group consisted of 97 men and 151 women, and the Hispanic group consisted of 129 men and 204 women. The sample of those with cognitive data was 29.1% Asian American (*n* = 120), 35.4% Black/African American (*n* = 146) and 35.6% Hispanic (*n* = 147).

Age At Baseline Exam

Participants younger than 40 were excluded due to low sample sizes (*n* = 22). Participants ranged in age from 40-85 years. Average age of the overall sample was 56.93

years (SE = .46). Average age of the sample with available cognitive data was 57.27 years (SE = .45).

Participants with available cognitive data were also categorized into middle aged (*n* = 258; range = 40-59 years) and older adult (*n* = 155; range = 65-85 years) groups. Average age was 51.34 years (SE = .31) among the middle aged group and 66.99 years (SE = .47) among the older adult group. The Asian American group consisted of 70 middle aged and 50 older adults. The Black/African American group consisted of 80 middle aged and 66 older adults. The Hispanic group consisted of 108 middle aged and 39 older adults.

Age at Exam 2

Among participants who received a second neuropsychological evaluation, age ranged from 46-84 years. The average age was 63.02 years (SE = .59) and there were of 60 middle aged and 93 older adults. The Asian American group consisted of 20 middle aged and 22 older adults. The Black/African American group consisted of 18 middle aged and 44 older adults. The Hispanic group consisted of 22 middle aged and 27 older adults.

Literacy and Education Level

Only those with available cognitive data had data for WRAT-3 word reading. The average WRAT-3 word reading score was 47.89 (SE = .32), 48.46 (SE = .38) for the MetS group, 46.72 (SE = .68) for the control group, 48.41 (SE = .60) for the Asian American group, 48.10 (SE = .41) for the Black/African American group, and 47.28 (SE = .76) for the Hispanic group.

Education level was categorized according to those reporting: not having graduated high school; having graduated high school; having completed some college; and having a

college degree. Of the OMNI cohort subjects with available cognitive data, 61.7% reported they were college graduates (n = 266), 17.9% reported completing some college (n = 77), 9.3% were high school graduates (n = 40), and 11.1% reported they did not graduate high school (n = 48). Among the Asian American group, 106 reported having a college degree, 98 reported having completed some college, five reported having graduated high school, and three subjects reported not having graduated high school. Among the Black/African American group, 30 reported having a college degree, 33 reported having completed some college, sixteen reported having graduated high school, and 28 subjects reported not having graduated high school. Among the Hispanic group, 95 reported having a college degree, 30 reported having completed some college, eight reported having graduated high school, and 3 subjects reported not having graduated high school.

MetS

MetS status was determined using the IDF criteria (i.e., central obesity or BMI greater than 30, plus two out of four of: elevated blood pressure, reduced HDL cholesterol, high triglycerides, impaired fasting glucose), measured at baseline physical examination. Ethnic-specific criteria were used for waist circumference, which specify a cutoff of 90cm for Asian American males (versus 94cm for males of all other ethnicities). Cutoffs for females are the same across ethnic groups. A 2-level categorical variable was derived to code those who did and did not meet criteria for IDF MetS. The number of MetS risk factors an individual has was also analyzed as an ordinal variable ranging from 0-5.

MCI

MCI status was determined using the Jak and Bondi (Jak/Bondi) actuarial

neuropsychological MCI criteria (Bondi et al., 2014; Jak et al., 2009). In summary: to derive Jak/Bondi MCI scores, total test scores across the neuropsychological battery were standardized based on age, education, and sex-adjusted scores using a neurologically normal (i.e., free from history of stroke, brain injury, seizures, learning disorder) subsample of the current study's participants. Participants were classified as having MCI if their scores on more than one measure within one or two cognitive domains fell below -1 SD (relative to the norms derived using the neurologically normal group). Those who met criteria for MCI at baseline (n = 40) were excluded (as noted above).

Data Analysis

Primary aims and hypotheses were tested using repeated measures and univariate analyses of variance as well as logistic and multiple regression analyses. Significant interactions and multivariate effects were examined using univariate simple effects tests and Bonferroni pairwise comparisons. Age and ethnicity/race were included as covariates in all analyses given known group differences in neuropsychological test performance. Time between exams was controlled for in all longitudinal analyses. Research indicates that quality of education (as indexed by literacy measures such as the WRAT-3 Word Reading) is a better predictor of neuropsychological test performance than education level in ethnic and racial minority groups (Manly, Schupf, Tang, & Stern, 2005), Given the ethnic/racial minority composition of the present sample, WRAT-3 Word Reading (WRAT) scores were included as a covariate all analyses. WRAT scores were available for 268 participants (Range = 18-57; μ = 47.87, SE = .33, Std. Dev. = 5.36).

Neuropsychological Measures

Primary outcome variables of interest were derived from the total test scores (i.e., the raw score on a test generally indicating the number of correct responses or total time on a test) and process error scores at baseline and T2.

Total scores.

Standardized composite scores (z-scores) were derived for tests of memory (WMS-III LM and VR delayed memory), executive function (Trails B, Digit Span Backward), and visuospatial functioning (HVOT, Clock, Block Design). See Table 1 (below) for descriptive statistics.

Table 1. *Descriptive statistics for composite total scores.*

	N	Min	Max	Mean	Std. Error	Std. Deviation
Memory Composite	349	-2.39	1.62	.05	.04	.67
EF Composite	349	-3.16	1.67	.02	.04	.75
Visuospatial Composite	339	-3.75	1.63	.13	.05	.85

Executive function and memory are the two most common domains tested in the assessment of ADRD. Within these domains, LM and Trails B are two of the most frequently used in ADRD test batteries. Thus, the bulk of analyses focused on standardized total scores (z-scores) and process error scores on two individual tests, Total scores included LM immediate and delayed recall scores, and Trails B total time to completion. Trails B time to completion scores were reversed for direct comparison with other tests. See Table 2 (below) for descriptive statistics.

Table 2. *Descriptive statistics for individual total scores.*

	N	Min	Max	Mean	Std. Error	Std. Deviation
LM Immediate Recall	346	2.00	19.00	11.34	.19	3.61
LM Delayed Recall	346	.00	19.00	10.19	.20	3.64
Trails B	342	-10.00	-.47	-1.67	.07	1.24

Logical Memory process error scores.

LM error scores included confabulation errors, defined as recall of information that was not explicitly part of the original story (e.g., "she was poor"), and intrusion errors, defined as recall of information that had been previously mentioned by the examinee, but was not part of the original story (e.g., "she was a server, just like I am"). Errors were categorized by FHS in two ways for immediate recall using the qualifiers "related" and "unrelated", and four ways for delayed recall using the qualifiers "new, related," "old, related," "new unrelated," and "old unrelated". The initial approach to analyzing process errors on Logical Memory was derived from (Libon et al., 2015), which focused on related and unrelated errors, while collapsing across new and old errors, and immediate and delayed recall trials. Related errors referred to confabulations and intrusions that were *related* to the story details (e.g., "they were starving," "she was poor," "she was a single parent"). Accordingly, unrelated errors we not related to story details (e.g., "she was a server, like me," "she went to the library," "the kids were at school," "her boss was mean").

Examination of the distributions of related v. unrelated errors indicated that most participants committed at least one related error (n = 285; 91% of those with cognitive

data), while only 12 participants did not. In contrast, only 27 participants made an unrelated error. Examination of the distributions of errors by error type revealed 285 participants committed at least one confabulation error, while only 7 participants made an intrusion error. Thus, analysis of LM errors was focused on related confabulation errors. See Table 3 (below) for descriptive statistics.

Trails B process error scores.

Trails B (TB) process errors broken down by FHS into self-corrected and examiner-corrected errors. Only 28 subjects committed self-corrected errors. Thus, analyses focused on examiner corrected errors. Overall, 109 participants made an examiner-corrected error on TB.

Three error types were coded by FHS for TB: sequencing errors, set loss errors, and perceptual errors. While sequencing and set-loss errors are traditional aspects of the scoring of the Trail Making Test, perceptual errors are not. Further, only 19 subjects in the current sample committed perceptual errors. Thus, analyses focused on set loss and sequencing errors. Overall, 44 subjects made set-loss errors (14% of those with cognitive data) and 88 (28% of those with cognitive data) made sequencing errors. This is in line with previous research reporting that 26% of cognitively normal participants made at least one error on Trails B (Ruffolo et al., 2000). See Table 3 (below) for descriptive statistics.

Table 3. *Descriptive statistics for LM and Trails B (TB) errors*

	N	Min	Max	Mean	Std. Error	Std. Deviation
LM Confabulation Errors	267	0	18	4.28	.18	2.96
LM Intrusion Errors	248	0	3	.06	.02	.31
TB Set Loss Errors	205	0	11	.24	.06	.92
TB Sequencing Errors	205	0	6	.53	.07	1.05

RESULTS

The first aim of the present study is two-fold: (1) to characterize MetS and (2) to examine relationships between MetS and neuropsychological test performance in the FHS OMNI cohorts.

MetS in the FHS OMNI Cohorts

Among participants with available health-related data, (n = 879), 28.7% (n = 259) met IDF criteria for MetS and the average number of MetS factors was 1.99 (SE = .04). Similar proportions of each ethnic/race group met IDF criteria for MetS: 31.6% of the Asian American group (n = 68), 27.5% of the Black/African American group (n = 71), and 30.6% of the Hispanic group (n = 114).

Among those who received a neuropsychological evaluation (n = 413), 31.5% (n = 130) met IDF criteria for MetS and the average number of MetS factors was 2.05 (SE = .06). Rates of MetS were similar across the Asian American group (n = 44), the Black/African American group (n = 39), and the Hispanic group (n = 47), and all groups had similar average number of MetS factors.: Asian American group average = 2.05 (SE = .09) , Black/African American group average = 1.90 (SE = .07) , Hispanic group average = 2.08 (SE = .06) . Chi^2 analyses supported that there were no significant ethnic/race group differences in the number of subjects that met criteria for MetS or in the number of MetS factors ($p > .05$).

In terms of other demographics, the average age of the MetS group was 59.4 years (SE = .82), and the control group was 56.2 years (SE = .54). Chi^2 analyses indicated that

the MetS group differed significantly from the control group in terms of the ratio of middle aged to older adults, X^2 (1, 413) = 8.36, p = .004. The MetS group had a relatively even ratio of middle aged (n = 68) to older adults (n = 62), while the control group was comprised of a greater proportion of middle aged (n = 190) than older adults (n = 93). Overall, a middle aged participant was more likely to be in the control group. Chi^2 analyses also indicated that the MetS group differed significantly from the control group in terms of the ratio of males to females, X^2 (1, 413) = 38.53, p < .001. Males were more likely to meet criteria for MetS (n = 82) than females (n = 48). Chi^2 analyses suggested there were no differences between the MetS and control groups in terms of education level (p > .51). WRAT-3 word reading scores were also similar across groups (MetS group average = 46.72, SE = .68; Control group average = 48.46, SE = .38). There were also no differences between the MetS and control groups in terms of frequency of participants with MCI, either at baseline (p > .96) or second exam (p > .88)

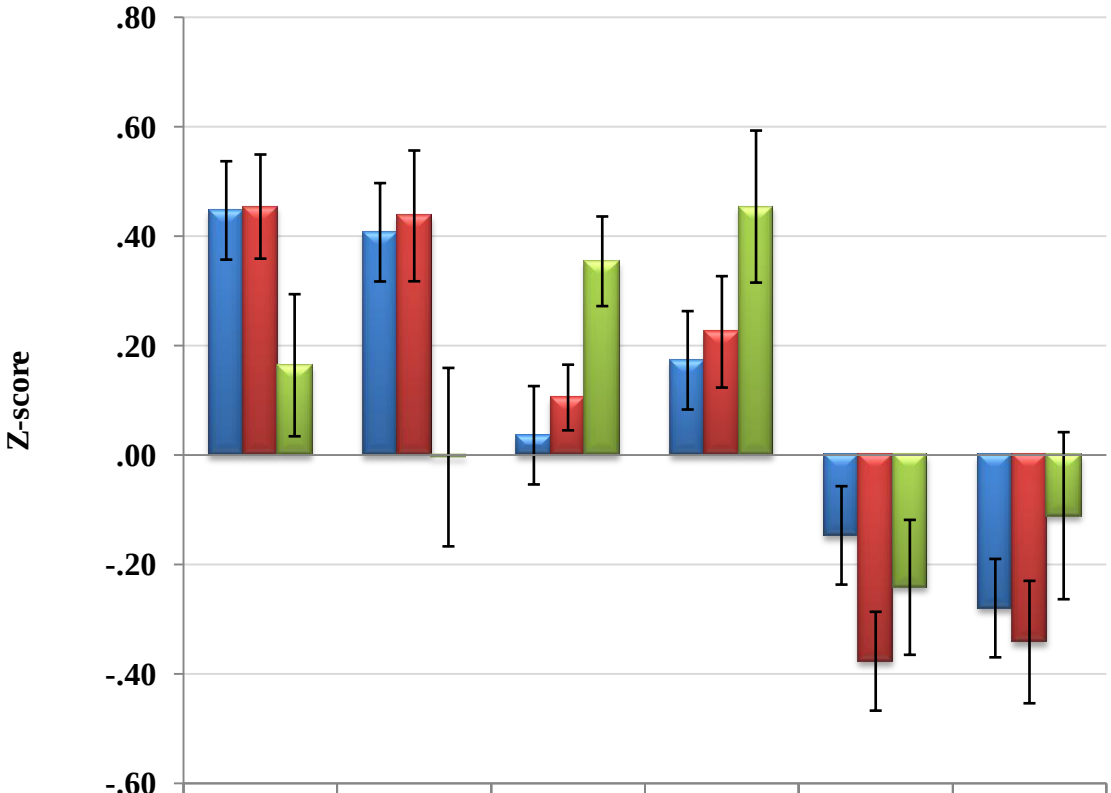
MetS and Neuropsychological Test Performance

The second aspect of this study's first aim was to examine relationships between MetS and neuropsychological test performance in the FHS OMNI cohorts.

Composite Total Test Scores

A repeated measures ANCOVA was conducted to examine group differences in memory, EF, and visuospatial composite total scores. Neuropsychological domain ("domain") served as the repeated measure, ethnicity/race and IDF MetS group were

included as independent factors, and age and WRAT reading scores were included as covariates. (See Figure 1.)



	Asian		Black/African American		Hispanic	
	Control	MetS	Control	MetS	Control	MetS
Memory	.45	.41	.04	.17	-.15	-.28
EF	.45	.44	.11	.23	-.38	-.34
VSP	.16	.00	.35	.45	-.24	-.11

Figure 1. *Bar chart and table depicting memory, EF, and visuospatial composite total scores within MetS and ethnicity/race groups*

Within subject effects of domain.

Box's Test of the equality of covariance matrices and Mauchly's test of sphericity indicated that the assumptions were violated (*p's* < .001). Thus, a Greenhouse-Geisser correction for degrees of freedom was used. Results revealed a significant within-subject

interaction between domain and ethnicity/race, $F(3.56, 456.15) = 8.07$, $p < .001$, *partial eta squared* (η^2) = .06. The main effect of domain was also significant, $F(1.78, 456.15) = 4.75$, $p = .01$, $\eta^2 = .02$. No other within-subject effects were significant (p's ranged from .06-.85).

Post hoc pairwise comparisons were conducted using a Bonferroni correction for multiple comparisons to test the effects of ethnicity/race within domain. Results indicated that the effect of ethnicity/race was significant across each domain (see Table 4 below). For the domains of memory and EF, the Asian American group scored significantly higher than the Black/African American group, which scored significantly higher than the Hispanic group. In the visuospatial domain, however, the Black/African American group performed significantly higher than both the Asian group and Hispanic group. The difference between the Asian American and Hispanic groups was not significant.

Table 4. *Bonferroni pairwise comparisons of ethnicity/race group marginal means on composite total scores*

		Memory			Executive Function			Visuospatial		
Bonferroni Group Comparisons		Mean Diff	Std. Error	Sig.	Mean Diff	Std. Error	Sig.	Mean Diff	Std. Error	Sig.
Asian	Black/AA	.319*	.092	.002	.282*	.096	0.011	-.324*	.132	.044
	Hispanic	.671*	0.1	.000	.808*	.104	.000	.256	.145	.234
Black/AA	Asian	-.319*	.092	.002	-.282*	.096	0.011	.324*	.132	.044
	Hispanic	.352*	.089	.000	.526*	.093	.000	.580*	.13	.000
Hispanic	Asian	-.671*	0.1	.000	-.808*	.104	.000	-.256	.145	.234
	Black/AA	-.352*	.089	.000	-.526*	.093	.000	-.580*	.13	.000

*. The mean difference is significant
AA = African American

Between-Subject effects on total composite scores.

Levene's test indicated that error variances were not equal across groups for the memory and EF total score composites (p's = .045 and .02). Thus, a more stringent p-value

was used to interpret between subject effects ($p < .01$). Results revealed significant between-subject main effects of age, $F(1, 256) = 72.12$, $p < .001$, $\eta^2 = .22$, WRAT, $F(1, 256) = 53.76$, $p < .001$, $\eta^2 = .17$, and ethnicity/race group, $F(2, 256) = 28.18$, $p < .001$, $\eta^2 = .18$ on composite scores across domains. Effects of MetS and ethnicity/race*MetS were not significant (p's = .77 and .42).

Across ethnicity/race group and domain, scores decreased with age and increased with WRAT word reading scores. Bonferroni pairwise comparisons were used to test the simple effects of ethnicity/race on composite total tests scores (see Table 5). Results indicated that across domains, the Hispanic group performed significantly worse than both the Asian American and Black/African American groups. The Asian American and Black/African American groups did not significantly differ from one another.

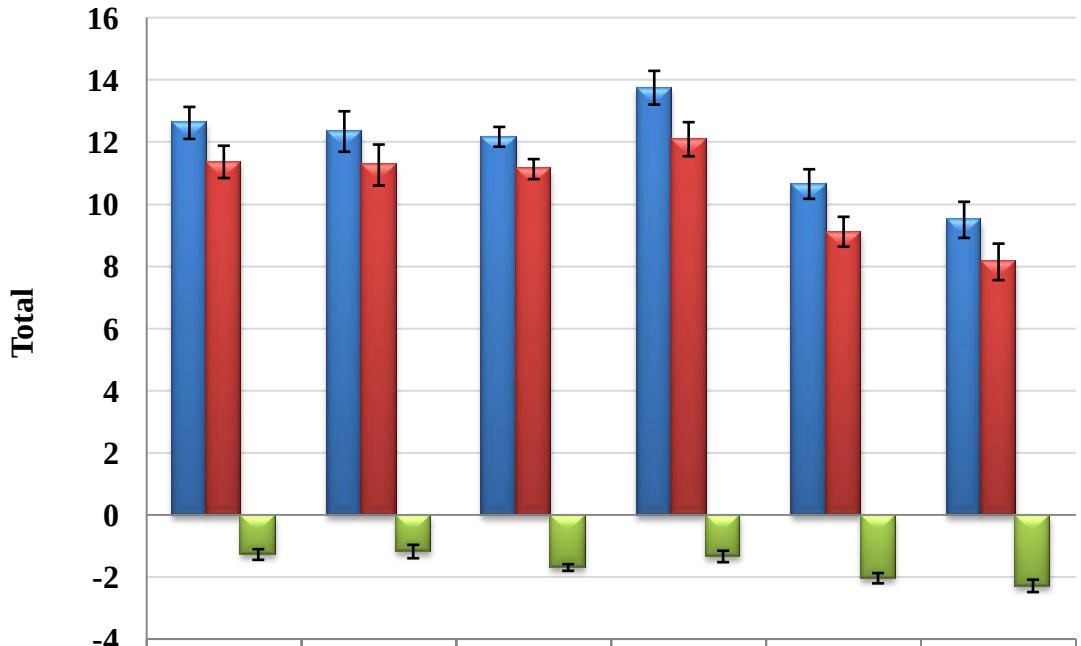
Table 5. *Bonferroni pairwise comparisons of ethnicity/race group marginal mean composite total scores across domains*

Bonferroni Group	Comparisons	Mean Difference in z-scores	Std. Error	Sig.
Asian American	Black/African American	.093	.076	.664
	Hispanic	.567*	.083	.000
Black/ African American	Asian	-.093	.076	.664
	Hispanic	.474*	.075	.000
Hispanic	Asian	-.567*	.083	.000
	Black/African American	-.474*	.075	.000

*. The mean difference is significant

Individual Total Test Scores

See Figure 2 (below) for group mean total test scores.



	Control	MetS	Control	MetS	Control	MetS
	Asian		Black/African American		Hispanic	
LMi	12.62	12.34	12.17	13.75	10.65	9.50
LMd	11.36	11.26	11.13	12.09	9.12	8.15
Trails B	-1.27	-1.17	-1.69	-1.33	-2.03	-2.28

Figure 2. *Bar chart depicting LMi, LMd, and Trails B (reversed) total scores within MetS and ethnicity/race groups.*

Logical Memory immediate recall.

A univariate ANCOVA was conducted to examine group differences in Logical Memory immediate recall (LMi) scores, with age and WRAT reading scores included as covariates. Levene's test of equality of error variances was not significant (p = .69), indicating that the assumption of homogeneity of error variance across groups was met. The ethnicity/race*MetS interaction was significant, $F(2, 258) = 4.30$, p = .02, η^2= .03. The main effect of MetS was not significant (p = .91), however, the main effect of ethnicity/race was significant, $F(2, 258) = 17.56$, $p < .001$, η^2= .12. Significant main effects

were also found for age, $F(1, 258) = 6.65$, $p = .01$, $\eta^2 = .03$, and WRAT, $F(1, 258) = 13.39$, $p < .001$, $\eta^2 = .05$, such that across ethnicity/race and MetS groups, scores increased with WRAT word reading scores and decreased with age.

Post hoc simple effects tests were conducted to examine the effects of IDF MetS status on LMi within ethnicity/race groups, controlling for age and WRAT scores. See Figure 2 (below). Results revealed that the effect of MetS was only significant within the Black/African American group, $F(1, 127) = 6.19$, $p = .02$, $\eta^2 = .05$, among which the IDF MetS group scored significantly higher than the control group (see Figure 2).

In addition to MetS, WRAT scores significantly predicted LMi in the Black/African American group, $F(1, 127) = 7.15$, $p = .008$, $\eta^2 = .05$, with higher WRAT scores being correlated with higher LMi scores. Age was not significant ($p = .13$). While MetS was not significant in the Asian American and Hispanic groups (p's = .79 and .21), the general relationship between MetS and LMi scores was in the predicted direction: those with MetS scored lower than controls. Among the Asian American group, only age was a significant predictor of LMi score, $F(1, 56) = 8.62$, $p = .005$, $\eta^2 = .13$, with older age being associated with lower scores. WRAT scores were not significant ($p = .29$). Among the Hispanic group, only WRAT scores significantly predicted LMi scores, $F(1, 71) = 12.65$, $p = .001$, $\eta^2 = .15$. Higher WRAT scores were associated with higher LMi scores.

Logical Memory delayed recall.

A univariate ANCOVA was conducted to examine group differences in Logical Memory delayed recall (LMd) scores, with age and WRAT reading scores included as covariates. Levene's test of equality of error variances was not significant ($p = .63$),

indicating that the assumption of homogeneity of error variance across groups was met. The main effect of MetS and the interaction between ethnicity/race and MetS were not significant (p's = .94 and .14). Significant main effects were found for ethnicity/race, $F(2, 258) = 19.02$, $p < .001$, $\eta^2 = .13$, age, $F(1, 258) = 4.15$, $p < .05$, $\eta^2 = .02$, and WRAT, $F(1, 258) = 18.63$, $p < .001$, $\eta^2 = .07$. Across ethnicity/race and MetS groups, scores increased with WRAT word reading scores and decreased with age. Post hoc Bonferroni pairwise comparisons were conducted to examine the significant effect of ethnicity/race on LMd scores. Results indicated that the Hispanic group scored significantly lower than both the Asian and Black/African American groups (see Table 6).

Table 6. *Bonferroni pairwise comparisons of ethnicity/race group marginal mean differences in LMd total scores*

Bonferroni Group Comparisons		Mean Difference	Std. Error	Sig.
Asian	Black/ African American	-.299	.528	1.000
	Hispanic	2.682*	.573	.000
Black/ African American	Asian	.299	.528	1.000
	Hispanic	2.981*	.507	.000
Hispanic	Asian	-2.682*	.573	.000
	Black/ African American	-2.981*	.507	.000

*. The mean difference is significant

Trails B time to completion.

A univariate ANCOVA was conducted to examine group differences in Trails B total (i.e., time to completion) scores, with age and WRAT reading scores included as covariates. Results indicated significant effects of ethnicity/race, $F(2, 257) = 12.99$, $p < .001$, $\eta^2 = .09$, age, $F(1, 257) = 26.22$, $p < .001$, $\eta^2 = .09$, and WRAT, $F(1, 257) = 34.16$, $p < .001$, $\eta^2 = .12$. The main effect of MetS and the interaction between ethnicity/race and

MetS were not significant (*p*'s = .64 and .19). Across ethnicity/race and MetS groups, scores increased with WRAT word reading scores and decreased with age. Post hoc Bonferroni pairwise comparisons were conducted to examine the significant effect of ethnicity/race on Trails B total scores. Results indicated that the Hispanic group scored significantly lower than both the Asian American and Black/African American groups (see Table 7, Figure 2).

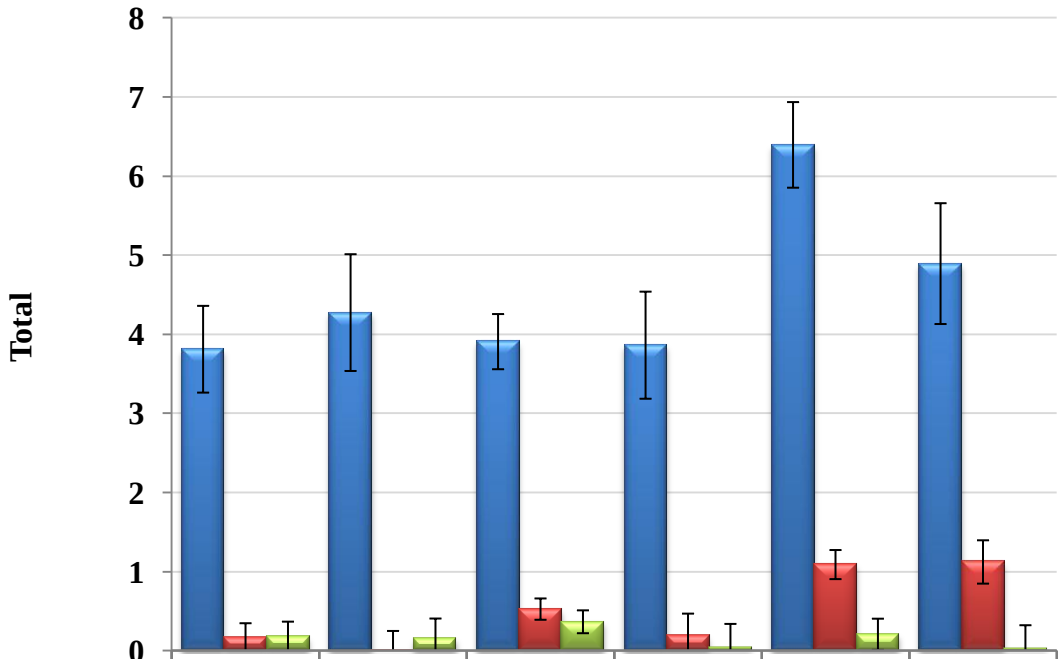
Table 7. *Bonferroni pairwise comparisons of ethnicity/race group marginal mean differences in Trails B total scores*

Bonferroni Group Comparisons		Mean Difference	Std. Error	Sig.
Asian	Black/ African American	.288	.174	.299
	Hispanic	.934*	.190	.000
Black/ African American	Asian	-.288	.174	.299
	Hispanic	.646*	.171	.001
Hispanic	Asian	-.934*	.190	.000
	Black/ African American	-.646*	.171	.001

*. The mean difference is significant

Process Error Scores

The second aim of the study was to characterize process error scores in the FHS OMNI cohorts and explore the extent to which process errors represent subtle cognitive decline and are predictive of future cognitive function. See Figure 3 below for group means.



	Asian		Black/African American		Hispanic	
	Control	MetS	Control	MetS	Control	MetS
Confabs	3.81	4.27	3.91	3.86	6.39	4.89
Sequencing	.17	.02	.53	.19	1.09	1.12
Set Losses	.18	.16	.37	.04	.21	.03

Figure 3. *Bar chart and table depicting average LM confabulations, Trails B sequencing errors, and Trails B set loss errors within MetS and ethnicity/race groups. Standard error bars represent standard errors of each group mean.*

Logical Memory errors.

A univariate ANCOVA was conducted to examine between subject effects of MetS and race/ethnicity on LM confabulation errors, with age and WRAT included as covariates. Results indicated significant main effects of age, $F(1, 187) = 5.90$, $p = .016$, $\eta^2 = .03$, and ethnicity/race, $F(2, 187) = 4.67$, $p = .01$, $\eta^2 = .05$. The interaction between ethnicity/race and MetS, and the main effects of WRAT and IDF MetS were not significant (p's = .45, .44, .29).

Post hoc Bonferroni pairwise comparisons were conducted to examine the significant effect of ethnicity/race on LM confabulations. Results indicated that the Hispanic group made significantly more confabulation errors than the Asian group. The Black/African American group committed fewer confabulations than the Hispanic group and more than the Asian group; however, this effect was not significant (see Table 8 below, Figure 3 above).

Table 8. *Bonferroni pairwise comparisons of ethnicity/race group marginal mean differences in LM confabulations*

Bonferroni Group Comparisons		Mean Difference	Std. Error	Sig.
Asian	Black/ African American	.16	.60	1.00
	Hispanic	-1.60*	.66	.05
Black/ African American	Asian	-.16	.60	1.00
	Hispanic	-1.76*	.61	.01
Hispanic	Asian	1.60*	.66	.05
	Black/ African American	1.76*	.61	.01

*. The mean difference is significant

Trails B errors.

Univariate ANCOVAs were conducted to examine the between subject effects of MetS and race/ethnicity on Trails B (TB) sequencing and set loss errors, with age and WRAT included as covariates.

TB sequencing errors.

ANCOVA results indicated a significant main effect of ethnicity/race, $F(2, 136) = 10.88$, $p < .001$, $\eta^2 = .14$. The interaction between ethnicity/race and MetS, and the main effects of age, WRAT and IDF MetS were not significant (p's = .71, .30, .42, .40).

For the main effect of ethnicity/race, post-hoc Bonferroni pairwise comparisons of marginal means indicated that the Hispanic group made significantly more sequencing errors than the Asian and Black/African American groups. The difference between the Asian and Black/African American groups was not significant (see Table 9 and Figure 3 for marginal means and pairwise comparisons).

Table 9. *Bonferroni pairwise comparisons of ethnicity/race group marginal mean differences in TB sequencing errors*

Bonferroni Group Comparisons		Mean Difference	Std. Error	Sig.
Asian	Black/ African American	-.27	.22	.66
	Hispanic	-1.01*	.22	.00
Black/ African American	Asian	.27	.22	.66
	Hispanic	-.75*	.23	.00
Hispanic	Asian	1.01*	.22	.00
	Black/ African American	.75*	.23	.00

*. The mean difference is significant

TB set loss errors.

ANCOVA results indicated a significant main effect of age, $F(1, 136) = 4.75$, $p = .03$, $\eta^2 = .03$, such that set loss errors increased with age. The interaction between ethnicity/race and MetS, and main effects of ethnicity/race, IDF MetS, and WRAT were not significant (p's = .80, .94, .37, .66).

Process errors as predictors of future total test scores and progression to MCI

The second aim of the present study was to explore whether neuropsychological process scores predict future decline. Multiple and logistic regression analyses were used

to determine whether process error scores at baseline (exam 1) predicted (a) standardized total scores at exam 2, and (b) progression to MCI at exam 2. Significant results were followed up with stepwise multiple regression including baseline age, WRAT reading scores, MetS status, sex, and ethnicity/race.

Exam 2 Logical Memory Total Scores

None of the baseline LM or TB error scores (confabulations, sequencing errors, and set loss errors) were significant predictors of exam 2 LM immediate recall (*p*'s = .28-.83). Confabulations and set loss errors were not significant predictors of LM delayed recall at time 2 (*p*'s = .36 and .70), however, TB sequencing errors approached significance (β = -.68, p = .05, R^2 = .03).

Exam 2 Trails B Total Score

Baseline confabulations and set loss errors were not significant (*p's* = .64 and .09), however, sequencing errors significantly predicted Trails B total score (β = -.29, p = .01, R^2 = .05) such that baseline sequencing errors were associated with lower scores on Trails B. Stepwise analyses revealed that this effect was significant over and above age, WRAT reading scores, MetS status, and sex, (β = -.24, t = -2.27, p = .03, R^2 = .14). However, adding ethnicity/race to the model nullified the significant effects of sequencing errors (*p* now = .27). R^2 = 18 for the final "full model" containing all variables. Across models, WRAT reading score was also significant predictor of TB total score at T2, including when ethnicity/race was included in the model, (Full model: β = -.05, t = -2.27, p = .03). Age, MetS status, and sex were not significant (*p's* = .34, .35, and .74).

A follow-up test of ethnicity/race group differences in TB scores at T2 indicated significant group differences, $F(2, 176) = 4.92$, $p = .008$, such that the Asian American Group performed significantly higher than the Hispanic group (see Table 10 for pairwise comparisons).

Table 10. *Bonferroni pairwise comparisons of ethnicity/race group marginal mean differences in TB total score at T2*

Bonferroni Group Comparisons		Mean Difference	Std. Error	Sig.
Asian	Black/ African American	.33	.26	.63
	Hispanic	-.85*	.27	.01
Black/ African American	Asian	-.33	.26	.63
	Hispanic	.52	.26	.15
Hispanic	Asian	-.85*	.27	.01
	Black/ African American	-.52	.26	.15

Progression to MCI

Forty-two participants met criteria for MCI at the second exam (*n* for controls = 111). Chi^2 analyses indicated that the MCI and control group significantly differed in terms of ethnicity/race $X^2(2) = 17.82$, $p < .001$. The MCI group was primarily comprised of participants in the Hispanic group. See Table 11 for frequencies.

Table 11. *Frequencies of self-reported ethnicity/race within MCI groups and in total*

	Asian American	Black/African American	Hispanic	Total
Control	33	54	24	111
MCI	9	8	25	42
Total	42	62	42	153

The groups also significantly differed in self-reported education level, $X^2(3) =$

14.95, p = .002. A greater percentage of the control group reported having graduated college (66%) than in the MCI group (50%). Further, a greater percentage of the MCI group reported not having graduated high school (21%) than in the control group (3%). See Table 12 for frequencies.

There were no significant MCI group differences in age, sex, employment status, or marital status (p's = .29-.62).

Table 12. *Frequencies of self-reported education levels within MCI groups and in total*

	Less than HS	HS Grad	Some College	College Grad	Total
Control	3	12	23	73	111
MCI	9	4	8	21	42
Total	12	16	31	94	153

Logistic regression analyses were conducted to explore the relationship between baseline Logical Memory and Trails B error scores and Jak/Bondi MCI status at exam 2. Significant results were followed up with stepwise multiple regression including age, Trails B total scores, WRAT reading scores, sex, and MetS status (entered in that order). All analyses controlled for time between exams 1 and 2, which was not a significant predictor of MCI status in any model (all p's > .05).

Results indicated that baseline LM confabulation and TB Set Loss error scores were not significant predictors of conversion to MCI status at time 2 (p's > .05). However, increased TB Sequencing errors significantly predicted MCI status at time 2 [Log Likelihood = 118.88, Cox & Snell R^2 = .08; B = .64, S.E. = .24, Wald(1) = 7.16, p = .007; odds ratio = 1.90].

Stepwise analyses revealed that this effect was significant over and above age, Trails B total scores, WRAT reading scores, sex, and MetS status [Log Likelihood = 75.56, Cox & Snell R^2 = .17; B = .66, S.E. = .28, Wald(1) = 5.42, p = .02; odds ratio = 1.93].

The only model where sequencing errors was not significant was when Trails B total scores were added to the model including age and sequencing errors (p = .07). In this model, Trails B total scores were significant [Log Likelihood = 105.32, Cox & Snell R^2 = .13; $B_{TrailsB}$ = -.50, S.E. = .23, Wald(1) = 4.80, p = .03; odds ratio = .61]. Notably, however, when WRAT reading scores were added in the next step, sequencing errors was again the only significant predictor [Log Likelihood = 75.78, Cox & Snell R^2 = .17; B = .65, S.E. = .27, Wald(1) = 5.60 , p = .02; odds ratio = 1.92]. See Figure 4 for MCI group means.

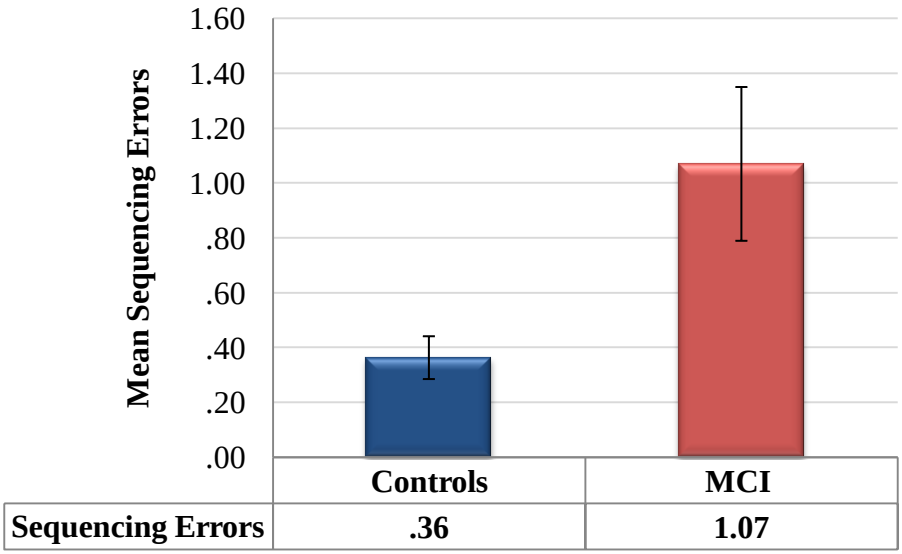


Figure 4. *Bar chart depicting average number of Trails B Sequencing errors by MCI status at exam 2*

Categorizing Error Scores

Given the non-normal distribution of error scores, longitudinal analyses with significant effects of error variables were re-analyzed using categorized error variables to ensure valid findings. For each test, error scores were categorized into 0 errors, 1 error, and 2 or more errors (i.e., a 3-level error variable) in accordance with previous studies of process errors on LM and Trails B (Ashendorf et al., 2008; Thomas, Edmonds, et al., 2018; Thomas, Eppig, et al., 2018). Variables were also created to represent the contrasts: 0 versus 1 or more errors (i.e. 1+ errors), and 0 or 1 versus 2 or more errors (i.e. 2+ errors). See Figure 5 below for frequencies.

TB Total Score and Sequencing Errors.

Multiple regression analyses resulted in similar findings as when using the quantitative variable. The 3-level variable significantly predicted Trails B total score (β = -.99, t = -4.16, $p < .001$, R^2 = .13). Stepwise analyses revealed that this effect was significant over and above age, WRAT reading scores, MetS status, and sex (β = -.49, t = -3.40, p = .001, R^2 = .19).

1+ sequencing errors also significantly predicted Trails B total score (β = -.99, t = -4.16, $p < .001$, R^2 = .13). Stepwise analyses revealed that this effect was also significant over and above age, WRAT reading scores, MetS status, and sex (β = -.89, t = -4.14, $p < .001$, R^2 = .23).

2+ sequencing errors significantly predicted Trails B total score (β = -.72, t = -1.99, p = .049, R^2 = .04). Stepwise analyses revealed that this effect was significant over and above age, MetS status, and sex ((β = -.73, t = -2.00, p = .048, R^2 = .05). However, when

WRAT reading was included in the model, only WRAT scores were significant (β = .05, *t* = 2.06, *p* = .042, R^2 = .12).

MCI and Sequencing Errors.

Logistic regression analyses indicated that the 3-level error variable significantly predicted MCI at exam 2 [Log Likelihood = 113.06, Cox & Snell R^2 = .07; B = .82, S.E. = .31, Wald(1) = 7.11, *p* = .008; odds ratio = 2.28]. Stepwise follow-up analyses were identical to those conducted using the quantitative variable: this effect was significant over and above inter-exam interval, age, Trails B total scores, WRAT reading scores, sex, and MetS status [Log Likelihood = 79.92, Cox & Snell R^2 = .16; B = .90, S.E. = .41, Wald(1) = 4.76, *p* = .03; odds ratio =2.46].

Results also showed that 2+ TB sequencing errors at baseline significantly predicted progression to MCI at the second exam [Log Likelihood = 109.89, Cox & Snell R^2 = .09; B = 2.06, S.E. = .66, Wald(1) = 9.64, *p* = .002; odds ratio =7.87]. Stepwise follow-up analyses were identical to those conducted using the quantitative variable: this effect was significant over and above inter-exam interval, age, Trails B total scores, WRAT reading scores, sex, and MetS status [Log Likelihood = 73.11, Cox & Snell R^2 = .19; B = 2.33, S.E. = .83, Wald(1) = 7.88, *p* = .005; odds ratio = 10.23]. Having 1+ TB sequencing error did not increase odds of progression (*p* = .08).

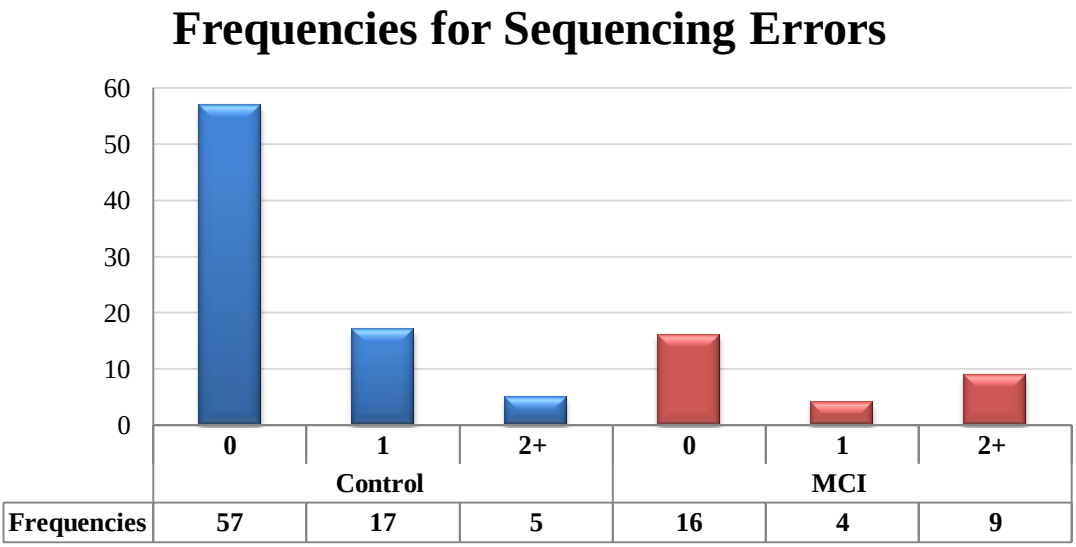


Figure 5. *Bar chart and table depicting frequencies of participants in the MCI and control groups that made 0, 1, and 2+ Trails B Sequencing errors.*

Additional Analyses

Exploring MetS

The present study's hypotheses regarding main and interaction effects of MetS were not supported. One possible explanation is that the use of the IDF criteria to determine MetS may have excluded those who would meet criteria for MetS using different definitions. For example, the IDF requirement of central obesity for a MetS diagnosis could result in under-diagnosis among certain ethnic groups, such as Asian American groups who tend to have lower rates of central obesity despite high rates of other vascular diseases, such as hypertension and hyperlipidemia. Thus, exploratory ANCOVA models were run using alternative measures of MetS.

First, we used an alternative set of criteria to determine MetS status in order to explore whether results would vary based on the criteria used to diagnose MetS. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)

criteria for MetS do not specify a particular factor that must be present but require that an individual meet the cutoffs for at least three of the five MetS factors. Thirty-three percent (versus 29%) of the entire sample met criteria for ATP MetS. Within ethnic/race groups, 34.3% of the Asian American group (versus 30.3%), 30.6% of the Black/African American group (versus 27.8%), and 35.4% of the Hispanic group (versus 31.2%) met criteria for ATP MetS. Results of the ANCOVA's echoed those for IDF-MetS criteria: ATP MetS status was not predictive of cognitive function across any models (p's ranged from .07-.78) and there were no changes to any previously described results. The one exception was that the interaction between MetS and ethnicity/race was no longer significant ($p = .07$).

Second, we analyzed MetS risk in terms of "MetS burden", quantified based on the number of MetS factors a participant met criteria for. Number of MetS factors ranged from 0-5, with an average of 2.05 (standard error = .06). Overall, results were highly comparable to those found when using IDF MetS. No significant main or interaction effects were found for # factors with one exception: an interaction between ethnicity/race and # factors predicted scores on LM immediate recall. Post hoc tests of the effects of # factors within each ethnic/race group revealed that the effect was only significant for the Hispanic group, $F(1, 56) = 6.76$, $p = .01$, , $\eta^2 = .09$: more MetS factors were associated with lower scores on immediate recall. The effect approached significance for the Black/African American group ($p = .06$), but was in the opposite direction: more MetS factors were associated with higher scores on immediate recall (similar to results with IDF MetS). The effect was not significant in the Asian American group ($p = .33$).

An additional possible explanation for the lack of IDF- MetS effects in the current study was the exclusion of participants who met criteria for MCI at baseline exam, which may have diminished power to detect the presence of subtle cognitive changes in the MetS group. Thus, analyses were re-run including these excluded subjects. A total of 35 participants with MetS who met criteria for MCI at baseline were excluded from original analyses (thus the majority of those excluded for an MCI diagnosis at baseline exam had MetS). After including these participants, the *n's* for the models increased by 20-30 participants and accordingly, there was a marginal increase in power for several significant effects in some of the models (e.g., a *p*-value of > .001 vs. .004). However, all results of the ANCOVA's echoed those found when those with MCI at baseline were excluded from analyses. In other words, inclusion of those with MCI at baseline did not elucidate effects of MetS on cognition. Inclusion of these participants also introduced a confound for significant effects that were found (i.e., it would not be possible to determine whether MCI status was driving effects).

Exploring Sociodemographic Moderators

Given the highly prevalent main effects of ethnicity/race found in the present study, sociodemographic differences between ethnic/racial groups at the time of testing were explored as possible moderators in models with significant ethnicity/race effects. Sociodemographic variables available included education level, age group, sex, employment status, and marital status.

Education level and WRAT scores.

Research has long shown that relationships between cognitive performance and

ethnicity/race are often accounted for by differences in educational background and attainment. We re-ran models with significant ethnicity/race effects to further explore the possible role of education in the present findings including (1) WRAT scores as a moderator rather than solely as an independent covariate, and (2) reported education level in place of and in addition to WRAT reading scores as moderators.

When the ethnicity/race*WRAT interaction was included as a moderator, ethnicity/race was no longer a significant predictor of Trails B total scores, LM confabulations, or TB sequencing errors (p's = .08, .84, .54). For LMi, the effect of ethnicity/race remained significant (p = .004), as did the effects of age, WRAT scores, and the ethnicity/race*MetS interaction (p's = .01, .01, .02). (Simple effects tests of the effects of MetS status within ethnicit/race groups were the same as those found in the original model. See above.) However, the ethnicity/race*WRAT interaction was also significant, $F(2, 256) = 4.24$, p = .016, η^2 = .03, suggesting the effects of ethnicity/race on LMi scores were moderated by WRAT scores. Simple effects tests indicated that the effect of WRAT scores on LMi was significant within the Black/African American group, $F(1, 126) = 4.77$, p = .031, η^2= .04, as well as the Hispanic group, $F(1, 70) = 8.36$, p = .005, η^2= .11, but not the Asian American group (p > .05). For LMd, the effect of ethnicity/race remained significant, as did the effects of age, and WRAT scores (p's = .03, .04, .001) after inclusion of the ethnicity/race*WRAT interaction, which was not significant (p = .07). Thus, all significant ethnicity/race effects disappeared when the ethnicity/race*WRAT interaction was included in models for every cognitive outcome except for LM total scores.

Given significant ethnicity/race group differences in self-reported education level,

education level was explored in place of and in addition to WRAT word reading scores.

For LMi total scores, univariate ANCOVA results indicated that the effect of education level was significant $F(1, 338) = 13.06$, $p < .001$, $\eta^2 = .04$. The main effect of ethnicity/race remained significant, $F(2, 338) = 5.18$, $p = .006$, $\eta^2 = .03$. The interaction between ethnicity/race and education level was not significant ($p = .21$). Age remained a significant predictor of LMi scores, $F(1,338) = 9.35$, $p = .002$, $\eta^2 = .03$. The effect of MetS was not significant ($p = .17$).

For LMd total scores, univariate ANCOVA results revealed that the effect of education level was significant $F(1, 336) = 17.88$, $p < .001$, $\eta^2 = .05$. The main effect of ethnicity/race remained significant, $F(2, 336) = 3.68$, $p = .03$, $\eta^2 = .02$. The interaction between ethnicity/race and education level was not significant ($p = .48$). Age remained a significant predictor of LMi scores, $F(1,336) = 7.87$, $p = .005$, $\eta^2 = .02$. The effect of MetS was not significant ($p = .64$).

For TB total scores, the main effect of education level was significant $F(1, 334) = 29.12$, $p < .001$, $\eta^2 = .08$. The main effect of ethnicity/race was not significant ($p = .29$). The interaction between education level and ethnicity/race was not significant ($p > .39$). MetS was not significant ($p = .25$), but age was significant $F(1, 334) = 24.27$, $p < .001$, $\eta^2 = .06$.

For LM confabulation errors, education level, ethnicity/race, and their interaction were not significant (*p's* between .48 and .99). MetS and age were also not significant (*p's* = .6 and .12).

For TB sequencing errors, the main effects of education level, ethnicity/race and the interaction between ethnicity/race and education level were not significant (*p's* >.05). MetS was not significant ($p = .25$), but age was significant $F(1, 197) = 4.19$, $p = .04$, $\eta^2 = .02$.

Thus, across all measures except for LMi, the effects of ethnicity/race were no longer significant after inclusion of education level in the models.

When both education level and WRAT scores were included in the models, neither education level nor WRAT was a significant predictor of process error scores (*p*'s > .05). Ethnicity/race remained a significant predictor of all process error scores. For LMi total scores, WRAT and ethnicity/race, but not education level, were significant predictors (WRAT, $p = .006$, $\eta^2 = .03$; ethnicity/race, $p = .002$, $\eta^2 = .05$). When interactions were included in the model, the interaction between ethnicity/race and WRAT was significant, $F(2, 255) = 3.12$, $p = .046$, $\eta^2 = .02$. Post hoc tests of the simple effects of WRAT within each ethnicity/race group indicated that the effect of WRAT scores on LMi was significant within the Black/African American group, $F(1, 126) = 4.77$, $p = .031$, $\eta^2 = .04$, as well as the Hispanic group, $F(1, 70) = 8.36$, $p = .005$, $\eta^2 = .11$.

For total scores on Trails B, both education level and WRAT were highly significant (*p*'s < .001, education level $\eta^2 = .10$, WRAT $\eta^2 = .06$), while ethnicity/race was no longer significant ($p = .32$). When interactions were included in the model, the main effect of WRAT remained highly significant ($p < .001$, $\eta^2 = .06$) and the main effect of ethnicity/race was no longer significant ($p = .28$). The interaction between WRAT and ethnicity/race was not significant ($p = .46$).

Baseline age group.

Baseline age group (middle vs. old age) was also explored as an alternative to the quantitative age variable. Chi^2 analyses indicated that there were significant ethnicity/race group differences in age group, $X^2(2) = 12.13$, $p = .002$. Frequencies revealed the Hispanic group had a greater proportion of middle aged adults ($n = 108$; older $n = 39$), than the Black/African American group (middle $n = 80$; older $n = 66$), and the Asian American group (middle $n = 70$; older $n = 50$).

When controlling for ethnicity/race, MetS status, and WRAT scores, the interaction between age group and ethnicity/race was not a significant predictor of any total or process error scores (p's ranged from .12-.99). Age group was a significant predictor of TB total scores ($p = .008$, $\eta^2 = .03$), but not LMi or LMd total scores, TB sequencing errors or TB set loss errors (p's > .05). Consistent with previous findings, ethnicity/race remained a significant predictor of LMi ($p = .002$, $\eta^2 = .05$), LMd ($p < .001$, $\eta^2 = .07$), and TB total scores ($p < .001$, $\eta^2 = .06$), as well as TB sequencing errors ($p < .001$, $\eta^2 = .14$), but not LM confabulation errors or TB set loss errors (p's > .05). WRAT scores remained predictive of total but not process scores (p's all <.001).

Thus, age did not moderate effects of ethnicity/race and using the dichotomous age group variable was less predictive than age in years, which predicted all cognitive outcomes.

Sex.

Participant sex was also explored as a possible moderator of ethnicity/race effects. Chi^2 analyses indicated that there were no significant ethnicity/race group differences in

sex (p = .27). Overall, participant sex was not found to have significant main effects and it did not significantly interact with ethnicity/race to predict any total or process error scores (p's ranged from .21-.98). Consistent with previous findings, when controlling for sex, age, MetS status, and WRAT scores, ethnicity/race remained a significant predictor of LMi (p < .001, η^2 = .09), LMd (p < .001, η^2 = .12), and TB total scores (p < .001, η^2 = .09), LM confabulation errors (p =.049, η^2 = .03), and TB sequencing errors (p < .001, η^2 = .15), but not TB set loss errors (p > .05).

Thus, sex did not moderate effects of ethnicity/race, was not predictive of cognitive outcomes, and did not alter results.

Employment status.

Self-reported employment status was also explored as a possible moderator of ethnicity/race effects. Employment status was categorized as employed (n = 243) and unemployed (n = 102). Detailed information about employment history was not available. Chi^2 analyses indicated that there were no significant ethnicity/race group differences in employment status (p = .27). Among the Asian group, 73 subjects reported being employed and 29 reported being unemployed. Among the Black/African American group, 96 subjects reported being employed and 40 subjects reported being unemployed. Among the Hispanic group, 74 subjects reported being employed and 33 subjects reported being unemployed.

Overall, employment status was not found to have significant main effects and it did not significantly interact with ethnicity/race to predict any total or process error scores (p's ranged from .19-.88). Consistent with previous findings, ethnicity/race remained a

significant predictor of LMi, LMd, and TB total scores (p's < .001, η^2's = .08, .10 and .09), as well as LMi confabulation errors (p = .03, η^2= .04), and TB sequencing errors (p = .004, η^2= .08) when controlling for employment status, MetS status, and WRAT scores.

Thus, employment status did not moderate effects of ethnicity/race, was not predictive of cognitive outcomes, and did not alter results.

Marital status.

Marital status was also explored as a possible moderator of ethnicity/race effects. Marital status categories included: never married (n = 29), married (n = 251), and no longer married (i.e., widowed, divorced, or separated; n = 69). Chi^2 analyses indicated that there were significant ethnicity/race group differences in marital status, $X^2(2) = 40.89$, p < .001. Frequencies revealed that while the vast majority of all groups reported being married, the Black/African American and Hispanic groups were more likely to report being divorced, separated, or widowed. Among the Asian group, three subjects reported never having been married, 97 subjects reported being married and six reported they were no longer married. Among the Black/African American group, nineteen subjects reported never having been married, 81 reported being married and 36 reported they were no longer married. Among the Hispanic group, seven subjects reported never having been married, 73 reported being married and 27 reported they were no longer married.

Overall, marital status was not found to have significant main effects and it did not significantly interact with ethnicity/race to predict any total or process error scores (all p's > .05). Ethnicity/race remained a significant predictor of LMi (p = .001, η^2 = .05) and TB total scores (p = .02, η^2 = .03), but was no longer a significant predictor of LMi , TB

sequencing or set loss errors (all p's > .05) when controlling for marital status, age, MetS status, and WRAT scores.

Thus, marital status did not moderate effects of ethnicity/race and was not predictive of cognitive outcomes, but it shared enough variance with ethnicity/race that ethnicity/race was no longer a significant predictor of LMi and TB process errors.

DISCUSSION

The present study had two primary aims. The first was to characterize MetS in the FHS OMNI cohorts and examine relationships between MetS and neuropsychological test performance. The second was to characterize process error scores in the FHS OMNI cohorts and determine whether process were predictive of future cognitive function. Across these aims, it was predicted that MetS would be associated with increased process errors and that process errors at baseline examination would be predictive of future cognitive declines. Given ethnic/racial variation in risk for MetS and cognitive impairment, it was hypothesized that ethnicity/race would moderate MetS effects on cognition. Hypotheses about MetS were not supported; however, baseline process errors were found to predict future test performance and were associated with increased likelihood of an MCI diagnosis at the second exam**.**

Metabolic Syndrome

Regarding the first aim, approximately 30% of the FHS OMNI cohorts met IDF criteria for MetS and participants had an average of two MetS factors. Males and older adults were more likely to meet criteria for MetS, however, the MetS and control groups did not differ in terms of ethnicity/race, education level, WRAT word reading scores, or rates of MCI (at baseline and exam 2). Rates of MetS were only increased by several percentage points when the ATP-III criteria were used. Using ATP-III MetS and number of MetS factors as explanatory variables in place of IDF MetS did not change results.

Equivalent rates of MetS across ethnicity/race groups were unexpected given the requirement of central obesity for an IDF-MetS diagnosis and epidemiologically lower rates of obesity in Asian American groups. Exploration of rates of obesity (determined using ethnicity-specific waist-circumference cutoffs) revealed that a significantly greater proportion of the Asian American group was obese relative to the Black/African American and Hispanic groups, $X^2(2) = 10.77$, $p = .005$. Based on waist-circumference, frequencies indicated that 62% of the Asian American group, 38% of the Black/African American group, and 34% of the Hispanic group was obese. However, there was no difference in rates of obesity across ethnic/race groups when BMI was used ($p = .24$). Based on BMI, frequencies indicated that 33% of the Asian American group, 26% of the Black/African American group, and 37% of the Hispanic group was obese. This is in line with research showing that adiposity rates in Asian American groups are higher than measures such as BMI suggest (Deurenberg et al., 1997; Deurenberg & Deurenberg-Yap, 2003; He et al., 2001). It is also in accordance with findings suggesting rates of MetS are higher in Asian American than in non-Hispanic White groups (Palaniappan et al., 2011). This study used a variation of both the IDF and NCEP AT P-III criteria to define MetS: they removed the obesity criterion entirely (in order to avoid circularity when analyzing the association between obesity and MetS), and required that participants meet criteria for two out of the four remaining MetS factors. Using these criteria, they found that rates of MetS where higher in Asian American that non-Hispanic White groups, and this was true for participants across a wide range BMI's, despite lower overall rates of obesity in the Asian American group.

In accordance with the homogeneity of MetS rates across ethnicity/race and MCI groups, MetS was not independently related to and did not interact with ethnicity/race to predict neuropsychological test performance. These results held when analyses were run using number of MetS factors and an alternative definition of MetS (ATP-III), suggesting that the criteria used to define MetS in the present study does not explain the present findings. The sole exception was a significant interaction between MetS and ethnicity/race that accounted for marginal variance in scores on LM immediate recall even after controlling for WRAT reading scores, age, education level, sex, employment status, and marital status. Results suggested that the Black/African American MetS subgroup performed significantly *better* than the control group (see Figure 2, page 33). The effect was not significant within the Asian American and Hispanic groups, but the trend was the opposite: control groups performed better than MetS groups. This result was unexpected and contrary to the current study's hypotheses and studies showing cognitive impairments in MetS (Bokura et al., 2010; Falkowski et al., 2014; Hassenstab et al., 2010; Segura et al., 2009). Moreover, the practical difference between the group means was marginal, at best (i.e., a difference of two words recalled, on average). Thus, any interpretation should be made with caution as this finding is likely aberrant.

The overall lack of a relationship between MetS and cognitive function in the present study is contrary to the present study's hypotheses and numerous past studies showing cognitive deficits in MetS among diverse groups. For example, previous research has shown an effect of MetS on tests of executive function, including Trail Making, clock drawing, and other executive function tests in a sample of rural, community dwelling

middle aged and older adults (average age = 61.3 years) with MetS that was 40% Hispanic (Falkowski et al., 2014). Research from the Sacramento Area Latino Study of Aging has also demonstrated worse three-year change scores on a cognitive screener (modified Mini Mental State Exam) and on a test of delayed recall of a word-list among Hispanics with MetS (Yaffe et al., 2007b). Studies in non-Hispanic White adults have also show impaired processing speed and visuoconstruction among older patients (Segura et al., 2009), as well as executive dysfunction among community dwelling older adults (Schuur et al., 2010) and in neurologically intact middle aged and older adults with MetS (Bokura et al., 2010). Poorer performance on tests of memory have also been reported in middle aged and older adults with MetS, including on story recall (WMS-R: Logical Memory), short- and long-delay recall on CVLT, and visual paired associates learning, (Bokura et al., 2010; Hassenstab et al., 2010).

One possible explanation for the overall lack of significant effects of MetS in the present study is that these effects may be mediated by unmeasured factors, such as genetic risk for dementia. For example, research in non-Hispanic Whites cohorts of FHS has shown that genetic risk for AD (i.e., ApoE, ε4 allele carrier status) mediates the effects of MetS on cognition over time such that MetS was only predictive of change over time in those *without* the ApoE ε4 allele (Bangen et al., 2019). Similarly, findings from the Multi-Ethnic Study of Atherosclerosis showed that baseline metabolic factors (fasting glucose and blood pressure) were associated with worse performance on cognitive measures (Digit Span and Digit Symbol Coding and a cognitive screener), and this effect was stronger for those *without* the ApoE ε4 allele and did not differ by ethnicity/race (Hughes et al., 2017).

These findings suggest that the effects of Mets may not be a strong enough determinant of cognitive function in those with genetic risk for AD. Neuroimaging research has also suggested that the relationship between MetS and cognition is mediated by brain changes (McIntosh et al., 2017). Future studies examining genetic risk for AD (e.g., ApoE), brain structure, and brain function, as mediators and moderators of the relationships between MetS and cognition over time are warranted.

Another possible explanation is that the generally high education levels reported by participants in the present sample may be associated with cognitive reserve that masks the effects of MetS. This is supported by recent research that reported no association between MetS and MCI in a large sample of high socioeconomic status mostly non-Hispanic White older adults (Martinez-Miller et al., 2019). Future studies should aim to include samples with lower SES and/or education levels.

Given ethnic/racial variance in risk for individual MetS risk factors, it is possible that individual risk factors are more explanatory of cognitive function within or across ethnic/racial minority groups. For example, research in a large cohort of European older male adults reported that diabetes and glycemia, but not MetS, were associated with cognitive decline (Overman et al., 2017; Tournoy et al., 2010). Another study that included a multiethnic elderly cohort (but did not account for ethnicity/race in analyses) similarly reported that diabetes and hyperinsulinemia, but not MetS, were associated with an increased dementia risk (Muller et al., 2007).

Finally, it is also possible that the relatively young age of the sample at baseline prevented detection of MetS-related changes in cognition (e.g., 62% of the sample was

middle aged at baseline). However, the MetS group consisted of a greater percentage of older adults (n = 62; middle age n = 68) than the control group (n = 93; middle age n = 190). Further, the sample for longitudinal analyses was comprised of 61% older adults and still, no effects of MetS were found. Thus, it is unlikely that age of the sample can explain the lack of effects of MetS on cognition in the present study.

Process Errors, Future Test Performance, and Risk for MCI

Regarding the second aim, 28% of the sample met criteria for MCI at exam 2, commensurate with studies in the primarily non-Hispanic white FHS cohorts that have reported rates of roughly 30% (Jak et al., 2016). Those reporting Hispanic ethnicity were by far most likely to be diagnosed with MCI at exam 2. The control group was also more likely to report having graduated college, while the MCI group was more likely to report not having graduated high school. Rates of those reporting having completed high school and some college were similar across groups, and there were no group differences in age, sex, employment status, or marital status.

Memory confabulation errors were not predictive of any cognitive outcome. This is in contrast with research previously reporting associations between memory errors and risk for MCI and AD. For example, memory process scores, such as word-list recall intrusion errors, have been shown to predict progression from normal cognitive function to MCI and from MCI to early AD, even after accounting for standard achievement scores (i.e., total scores) and CSF biomarkers (Thomas et al., 2018). Although there were high rates of confabulation errors, it is possible that these errors were related to unmeasured

factors (e.g., test administration and scoring, sociodemographic factors) rather than actual cognitive changes, particularly given the young age of the present sample at baseline (e.g., most were middle-aged). It is also possible that rates of confabulation errors are inherently higher in certain ethnic/racial minority groups. Future studies of process errors in these groups including lifespan populations are warranted.

Baseline sequencing errors on Trails B were associated with lower performance on Trails B at exam 2 and, most notably, were also found to be associated with an increased likelihood of progression to MCI and at exam 2. In particular, those who made two or more sequencing errors at baseline had a 10 times greater likelihood of progression to MCI at exam 2 relative to those who made 0 or 1 error. Baseline Trails B set loss errors were not predictive of any cognitive outcome; however, this is likely due to overall low commission of set loss errors across the entire sample. This finding ethnically/racially diverse sample expands upon previous studies in primarily non-Hispanic White samples showing process scores aid in the detections of preclinical changes in cognition that signal risk for MCI and dementia (Crocco et al., 2014; Hankee et al., 2013; Libon et al., 2011; Loewenstein et al., 2004; Thomas, Edmonds, et al., 2018; Thomas, Eppig, et al., 2018). Another study that focused specifically on trails B sequencing errors reported that using Trails B error scores in tandem with time to completion resulted in equal or slightly improved classification rates of MCI and AD (Ashendorf et al., 2008). This study found that the optimal cutoff for diagnostic classification was greater than or equal to one error. Future studies including diverse samples with more severe cognitive declines and/or

dementia diagnoses would permit analysis of whether Trails B errors are predictive of progression from MCI to dementia in minority groups.

Trails B errors have also been linked to important neurocognitive and functional outcomes related to ADRD. For example, research has reported that Trails B sequencing errors, but not measures of visual scanning or cognitive flexibility, predict IADLs in Parkinson's disease (Higginson et al., 2013). Studies of overall Trails B process errors (i.e. without specifying error type) have also reported associations with fitness to drive in the elderly, with a suggested cutoff of more than 3 errors on Trails B to determine fitness (Molnar et al., 2009, 2012; Molnar & Simpson, 2010; Roy & Molnar, 2013). However, studies have also suggested that time scores may be more useful than TB error measures in determine driving fitness in cognitively impaired populations (Dobbs & Shergill, 2013; Duncanson et al., 2018). More research is needed in sociodemographically and ethnically/racially diverse samples.

Measures of trail making have long been shown to be sensitive to acquired brain injury and cognitive decline and used in batteries for the diagnosis of dementia (Reitan & Wolfson, 1994). Increased time to completion on Trails B can be due to any number of factors ranging from deficits in visual scanning to executive deficits leading to slower or impaired set-shifting. Errors on trail making tests are largely attributed to executive dysfunction ranging from impulsivity, deficits in working memory, or inability to monitor errors and maintain accuracy while prioritizing speed. In accordance with these links to executive function, numerous studies suggest that Trails B errors are associated with frontal dysfunction. Research using voxel-based lesion-behavior mapping reported that

number of Trails B errors, but not completion time, predicted lesion location in the right frontal lobe (Kopp et al., 2015). Similarly, a study reported that Trails B errors were more useful than time to completion in accurately categorizing patients based on specific lesion type: Patients who made more than 1 error on Trails B all had frontal lobe lesions (versus non-frontal lesions or normal brain structure), those with dorsolateral frontal lesions made the most errors, and those with inferior medial damage had relatively normal Trails B performance (Stuss et al., 2001). Research in the FHS Offspring cohort has also linked Trails B errors to measures of frontal lobar volume, as well as total brain volume and volume of large white matter hyperintensities (Hankee et al., 2013).

Notably, vascular disease has been widely associated with declines in frontal lobe function. Research on Trails B errors in the FHS Offspring cohort reported higher Framingham Stroke Risk Profile scores at baseline were associated with significantly more Trails B errors 10-15 years later, while associations with traditional (total) scores were not significant (Nishtala et al., 2014). CV risk factors were highly prevalent in the current sample of minorities. Thus, while MetS status was not significant in the present study, the relationship between Trails B sequencing errors and future cognition found in the present study may be reflective of underlying cerebrovascular changes, particularly given that most of the participants in the present study had at least one vascular condition.

Sociodemographic Considerations

Ethnicity/race independently predicted all cognitive outcomes except for set loss errors over and above age, WRAT reading scores, MetS status, sex, marital status, and

employment status. In terms of process scores, Hispanic participants were most likely to make memory (confabulation) and executive function (sequencing) errors at baseline, and were also most likely to have an MCI diagnosis at exam 2.

Importantly, however, education level accounted for and WRAT scores moderated the effects of ethnicity in all models except for total scores on logical memory (i.e., the significant effects of ethnicity/race disappeared when the Race*WRAT interaction and when education level were included in models). Outside of ethnicity/race, WRAT reading scores and education level independently predicted total scores (higher WRAT scores were associated with better performance) but not process scores. These findings are in line with long standing research showing ethnic/racial group differences in neuropsychological test performance are due in large part to differences in quality of education (Manly et al., 2003, 2005), as well as research in Black/African American and non-Hispanic White groups that has reported cross-sectional race group differences on memory and EF composite scores were significant over and above vascular risk factors (e.g., hypertension, diabetes, hypercholesterolemia) but mediated by education quality (Carvalho et al., 2015). Quality of education has also been shown to attenuate the effects of race/ethnicity and on memory and executive function test scores over and above *years* of education in both English and Spanish speakers (Brewster et al., 2014).

Previous research in the primarily non-Hispanic White, highly educated Offspring cohort of FHS has reported that errors on Trails B varied significantly with education level such that those with lower education made more errors (Hankee et al., 2013). However, neither education level nor WRAT scores predicted process errors in the present study.

This may suggest that process errors are less influenced by socioeconomic variables than standardized total test scores in this ethnically/racially diverse sample. Future studies investigating predictors of process errors in ethnic/racial minority groups are warranted.

Strengths, Limitations, and Future Directions

Overall, the current study has some notable strengths and its findings add to a long history of important results produced by the highly respected FHS. First, to the authors' knowledge this is the first study to characterize process error score performance across memory and executive function measures in diverse minority groups with varying risk for AD and other dementias. Accordingly, the opportunity to analyze neuropsychological process scores alongside standardized primary/total scores allowed for more in-depth analysis of cognitive function and classification of MCI status in this large minority sample. Another strength was the inclusion of a large proportions of middle-aged adults of different ethnic/racial minority backgrounds, which adds valuable information to a literature base focused primarily on non-Hispanic White older adults. An additional strength was the use of the Jak and Bondi actuarial neuropsychological MCI criteria, which have been shown to diagnose MCI more accurately than conventional Petersen/Winblad criteria, as typified in large scale studies like the Alzheimer's Disease Neuroimaging Initiative (Bondi et al., 2014). However, the FHS Offspring cohort was used as the basis for forming the normative group due to smaller sample sizes in the OMNI cohorts. The present study also did not stratify by ethnicity/race when creating the Jak/Bondi MCI scores based on the neurologically normal sample (i.e. we did not create separate norms for

each ethnic/race group). Studies have long shown that the use of standardized or demographically corrected test scores that are not specific to ethnic/racial group membership leads to over-pathologizing of minorities (Heaton et al., 1996; Manly et al., 1998). As such, MCI may have been overestimated in this minority sample, and future work should directly examine the utilization of standardized scores by racial/ethnic-specific subgroups in MCI diagnosis.

As with all studies, there are a number of limitations that should be noted about the present research. The first is that we were limited in our ability to analyze profiles of process error scores due to missing data and low error commission for some variables (e.g., intrusion errors on LM, set loss errors on Trails B). Another limitation of the current study was the lack of a non-Hispanic White control group, which would have allowed us to determine whether the current findings are specific to certain ethnic/racial minority groups or generalize to the larger majority population. In relation, criteria for determining ethnic/racial group membership were limited to self-reported ethnicity/race, and did not incorporate additional information about relevant cultural variables (e.g., nationality, generations/years in U.S.). Thus, we cannot say with certainty that the present findings would generalize to other samples of these minority groups, nor can we determine the nature of the ethnic/race group difference (e.g., are they related to biological/genetic ethnic/racial factors, or purely environmental). Future studies may wish to include additional sociodemographic or ethnic/racial background information to further classify minority groups.

An additional limitation is the previously discussed high level of education of the sample, with most reporting having at least some college education. Thus, those with low education levels may have been underrepresented and results may not generalize to broader populations of the presently included ethnic/racial groups. A final and related limitation to note is that the MCI group was comprised primarily of those who reported Hispanic ethnicity, who also happened to be most likely to report the lowest levels of education. Accordingly, replication of these findings is necessary to determine whether they generalize beyond this ethnic minority group. Future studies including broader ranges of education levels across ethnic/racial groups are warranted.

Additional suggestions for future studies include examining the effects of individual risk factors (including variables such as onset, course, treatments, and severity), which may contribute information regarding how ethnic/racial differences in patterns of MetS factors are related to risk for cognitive decline and the development of AD and other dementias. As mentioned earlier, genetic risk for AD has been shown to influence the effects of MetS and other vascular risk factors on cognition. Future studies examining the potential effect of ApoE genotype on relationships between MetS and cognition among minority groups are warranted.

In relation, future studies linking demographic group differences in process scores to other early markers of AD and other dementias, such as CSF biomarkers, are also warranted. Particularly as recent research has reported that CSF biomarkers for AD (β-amyloid [Aβ42, Aβ40], total and phosphorylated tau [t-tau and p-tau_{181}], endothelial dysfunction, α-synuclein, and neurofilament light chain) may vary between Blacks/African

American and non-Hispanic White groups. For example, a recent study reported that after controlling for demographic differences, AD genetic risk, and cognitive function, older Black/African American participants had lower CSF levels of p-tau$_{181}$, t-tau, and Aβ40 than White participants, despite similar levels of Aβ42, white matter hyperintensity volume, and hippocampal volume. Cognitively impaired Black/African American participants also had lower CSF t-tau/Aβ42 and p-tau$_{181}$/Aβ42 than cognitively impaired White participants (Howell et al., 2017). However, another recent study of similar AD biomarkers among Blacks/African American and non-Hispanic White groups reported an interaction between ApoE genotype and CSF tau levels such that only those with ApoE ε4allele showed racial differences in p-tau$_{181}$ and t-tau (Morris et al., 2019). Of note, this study was limited by systematic differences in recruitment of each race group and both studies have relatively small sample sizes considering claims about race group differences at the molecular level. Accordingly, further study is required before AD biomarkers such as CSF tau can be applied as indicators of risk in minority groups, highlighting the important role that neuropsychological assessment will continue to play in the diagnosis of AD and other dementias.

Conclusions

As the population continues to age, identifying the earliest cognitive changes in those at risk for cognitive decline and dementia across ethnic and racial groups is pivotal to the ability to implement early interventions aimed at delaying progression of cognitive declines. The present study contributes to a growing body of literature suggesting that

process errors are useful indicators of risk for neurocognitive decline in aging and should be considered in addition to standardized total scores in the context of clinical interpretation. Results indicated that executive function errors, in particular, were predictive of increased risk for MCI in ethnic/racial minority groups, over and above total test scores and important sociodemographic predictors such as age and quality of education. Studies have demonstrated links between cerebrovascular disease, frontal lobe changes, and Trails B errors. While metabolic syndrome was not predictive of neurocognitive outcomes, notably high rates of certain risk factors for cerebrovascular disease in the present sample (e.g., 60% of the Asian American group was obese) suggest that further exploration of the links between individual cerebrovascular risk factors and process scores is warranted. Future research investigating potential mediating effects of genetic risk for AD in clinical and more socioeconomically diverse samples is also warranted to determine whether these results are generalizable to larger populations.

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