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Structural and cognitive correlates of body mass index in healthy older adults

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Abstract

Background: Obesity, commonly measured with body mass index (BMI), is associated with numerous deleterious health conditions and has been identified as a potential modifier of alterations in brain integrity related to old age. Prior research has suggested that white matter integrity observed using diffusion tensor imaging (DTI) is altered in relation to high BMI, but the integrity of specific white matter tracts remains poorly understood. Additionally, no studies have examined fractional anisotropy (FA) of white matter tract integrity in conjunction with neuropsychological evaluation associated with elevated BMI among older adults. The purpose of the present study was to examine white matter tract integrity and cognitive performance associated with elevated BMI in advanced age.

Hypotheses: Elevated BMI would be independently associated with lower white matter integrity in tracts connecting frontal and temporal brain regions, and would be associated with poorer cognitive performance in tests of executive function, processing speed, and memory. Second, there would be evidence for a BMI by age interaction relating to measures of white matter integrity and cognitive performance.

Methods: Sixty two healthy older adults aged 51 to 81 were evaluated with magnetic resonance imaging (MRI) and neuropsychological evaluation. Associations were examined between BMI, tract-based FA, and cognitive ability in domains of executive function, processing speed, and memory. Hierarchical linear regression analyses were utilized to determine the impact of BMI on FA and cognitive function after accounting for the influence of demographic variables, followed by a test for the interaction of BMI and age on FA and cognitive indices. Secondary analyses were conducted to assess the

sensitivity of DTI diffusivity metrics to elevated BMI, and to relate tract FA to cognitive performance.

Results: Initial analyses showed that increased age was related more strongly to cognitive performance than FA by tract. After controlling for these initial relationships, elevated BMI was associated with lower FA in the uncinate fasciculus ($p = .01$), though there was no evidence of an age by BMI interaction relating to FA in this tract. No relationships between cognition and BMI were observed after controlling for demographic variables. Secondary analyses did not suggest that DTI diffusivity metrics provide unique information about microstructural tract integrity related to high BMI.

Conclusions: Elevated BMI is associated with altered integrity of the uncinate fasciculus. This white matter tract connects frontal and temporal lobes and is involved in memory function. There was no evidence of an age by BMI interaction on FA of the UF, and BMI did not relate to cognitive performance in this study. Future studies should examine measures of cardiovascular health and systemic inflammation to identify factors influencing relationships between BMI and white matter tract integrity.

Structural and Cognitive Correlates of Body Mass Index in Healthy Older Adults

The purpose of this study was to examine the impact of body mass index (BMI) on the integrity of white matter tracts using diffusion tensor imaging (DTI) and neuropsychological function in a sample of healthy older adults. It was hypothesized that elevated BMI would be independently associated with decreased white matter integrity in tracts connecting to frontal and temporal brain regions. It was also hypothesized that individuals with elevated BMI would exhibit poorer cognitive performance in tests of executive function, processing speed, and memory. Finally, it was hypothesized that age and BMI would interact to exhibit an additive association with white matter integrity and cognitive function in metrics shown to be altered in relation to high BMI.

Obesity has become an increasingly prevalent health concern in recent decades, especially in the United States and other Western cultures (Baskin, Ard, Franklin, & Allison, 2005; Flegal, Carroll, Ogden, & Curtin, 2010). Recent estimates indicate that nearly a third of adults in the United States are classified as obese (Flegal et al., 2010). As a result, a high percentage of individuals are at increased risk for chronic obesity-related health conditions, including diabetes, cardiovascular disease, and high cholesterol (Malnick & Knobler, 2006). If uncorrected, these obesity-related consequences can contribute to decreased quality of life, increased cost of health care, and increased mortality (Sturm, 2002).

One of the most common methods to quantify body composition is BMI. BMI (defined as weight in kilograms divided by height in meters squared) provides a quick but relatively accurate standardized assessment of body weight, and is highly correlated with body fat percentage (Flegal et al., 2009). Research has shown that individuals in the

overweight (25.0 – 29.9 kg/m^2) and obese (≥ 30.0 kg/m^2) BMI ranges experience significantly more health problems than normal-weight individuals, and individuals at the extreme ends of the BMI spectrum (i.e. underweight and obese) experience the highest number of adverse health consequences (Grundy, Brewer, Cleeman, Smith, & Lenfant, 2004; Malnick & Knobler, 2006). In addition to its utility as an epidemiological index of obesity, BMI has been widely used to examine alterations in brain integrity related to obesity. Several studies have described significant relationships between BMI, neuroimaging metrics, and measures of cognitive performance (Gunstad et al., 2007; Gunstad et al., 2008; van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009).

Evidence suggests that high BMI is related to poor cognitive performance. A recent meta-analysis described a negative association between BMI and executive function, processing speed, and memory performance (van den Berg et al., 2009). In addition, several studies have demonstrated poor cognitive performance in relation to high BMI independent of age (Cournot et al., 2006; Gunstad, Paul, Cohen, Tate, & Gordon, 2006; Gunstad et al., 2007; Sabia, Kivimaki, Shipley, Marmot, & Singh-Manoux, 2009). Some studies have demonstrated better cognitive performance with high BMI (Gunstad, Lhotsky, Wendell, Ferucci, & Zonderman, 2010; Kuo et al., 2006; Ward, Carlsson, Trivedi, Sager, & Johnson, 2005), though these include population-based designs and liberal inclusion criteria that limit application of findings to a sample of healthy older adults. Overall, while research suggests elevated BMI is associated with cognitive difficulties in adulthood, few studies have examined this relationship in healthy older adults.

Several neuroimaging techniques have been employed to investigate brain tissue characteristics associated with BMI. Morphometric approaches with structural magnetic resonance imaging (MRI) have been utilized to examine changes in brain volume linked to BMI. Many of these studies have reported smaller volumes of gray and white matter in obese individuals compared to normal-weight individuals, especially in frontal and temporal structures (Gunstad et al., 2008; Ho et al., 2011; Raji et al., 2010; Ward et al., 2005). A few studies have reported larger brain volume in relation to high BMI (Haltia et al., 2007; Taki et al., 2008; Walther, Birdsill, Glisky, & Ryan, 2010), but varying sample demographics and group comparisons of these studies may explain these discrepant findings. Further, few studies have incorporated cognitive assessment along with neuroimaging metrics to examine cognitive status in association with white matter tract integrity. Though these volumetric approaches are valuable for assessing the amount of regional tissue composition in the brain, they are limited with regard to quantification of the structural integrity of these tissues, and are unable to provide information regarding neuronal integrity within brain matter.

A neuroimaging approach incorporating DTI may provide distinct detail about the integrity of neuronal microstructure within the brain not captured by other methods. The advantage of DTI over other neuroimaging sequences is the opportunity to quantify microstructural characteristics of white matter (Basser & Pierpaoli, 1996). These measurements are obtained by calculating the rate that water diffuses along a gradient within an identified neural tract. In intact neurons, the movement of water along the fibers is directionally restricted, whereas damaged neurons permit more random, non-directional diffusion. Fractional anisotropy (FA) is a commonly used DTI metric that

measures the ratio of water diffusion that is anisotropic, or directional, in a voxel. Different pathological processes, such as edema and cellular neuropathology, are theorized to negatively affect the integrity and organizational properties of white matter in the brain leading to alterations in FA of affected tissues (Assaf & Pasternak, 2008; Medina et al., 2006). DTI diffusivity metrics, including axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD), the latter which is an average of the former two measures, may provide additional information about white matter integrity. However, the utility of these measures to provide unique information about white matter integrity associated with BMI not captured by FA has not been established.

Past research has exhibited the sensitivity of DTI to white matter abnormalities associated with changes in BMI. For example, Bettcher et al. (2013) recently reported lower FA values in the corpus callosum and cingulate associated with elevated BMI after accounting for the potential influence of vascular and inflammatory markers. Other studies have also described a significant negative impact of BMI on similar brain regions (Stanek et al., 2011; Xu, Li, Lin, Sinha, & Potenza, 2011). For example, Xu et al. (2011) reported decreased FA in the corpus callosum and fornix associated with BMI. Researchers interpreted these findings to suggest that obesity-related biological processes such as leptin- and fatty acid-driven inflammation vary across brain regions. Other research has suggested that obesity is associated with altered DTI diffusivity indices in the corpus callosum (Mueller et al., 2011). These findings are supported by a recent proton magnetic resonance spectroscopy study reporting myelin alterations and structural damage to neurons in frontal white matter, potentially leading to decreased frontal lobe connectivity and function (Gazdzinski, Kornak, Weiner, & Meyerhoff, 2008).

Collectively, these studies demonstrate the sensitivity of DTI to the deleterious impact of BMI on white matter microstructure, but integrity of specific white matter tracts remains less understood.

While many studies suggest that high BMI relates to lower white matter integrity and cognitive performance across the lifespan (Gunstad et al., 2006; Gunstad et al., 2007; Sabia et al., 2009; Stanek et al., 2011), few studies have examined these measures in a healthy older adult sample. This dearth of research represents an important avenue for further exploration due to the effects of physiological aging processes on brain integrity regardless of BMI (Keller, 2006). The aging process is likely driven by progressive disruptions in normal cellular processes (e.g., oxidative stress, inflammation, vascular difficulties) that contribute to brain dysfunction (Floyd & Hensley, 2002; Sohal, 2002). While increased age has been identified as a primary risk factor for the development of neurodegenerative diseases such as Alzheimer's (Keller, 2006; Lindsay et al., 2002), evidence suggests that normal aging processes also lead to diffuse disruptions in brain tissue volume and integrity (Yankner, Lu, & Loerch, 2008). Accordingly, otherwise healthy older adults exhibit cognitive and neural characteristics that differ from those of young healthy adults (Keller, 2006). Although recent research has aimed to clarify neuroimaging and neurocognitive correlates of age-related brain disruption, the progression of these age-related alterations in brain integrity varies between individuals (Raz et al., 2005; Raz & Rodrigue, 2006).

Studies utilizing MRI have demonstrated that gray matter volume steadily declines with age, while white matter volume follows an inverse U-shape with age (Ge et al., 2002; Giorgio et al., 2010). Researchers have suggested that onset of white matter

decline is more indicative of aging processes than gray matter decline (Ge et al., 2002). For example, gray matter volume decline beginning in the third decade may signify brain maturation via nonpathologic neuronal pruning processes, while white matter decline accelerates at middle to older age upon accumulation of focal lesions and disruption to myelin and axonal properties. Generally, it is thought this age-related atrophy affects brain tissue in an anterior to posterior pattern (Brickman et al., 2006; Coffey et al., 1992; McDowell, Xi, Lindsay, & Tuokko, 2004; Raz et al., 1997; Salat, Kaye, & Janowsky, 1999). While volumetric analyses provide insight into patterns of brain aging, researchers have suggested that age-related changes to white matter lead to decreased connectivity between regions with potential to impact gray matter structure and cognitive function later in life (Brickman et al., 2006). As a result, examination of white matter may provide a more accurate assessment of brain health status across the aging trajectory.

Many studies have demonstrated the sensitivity of DTI to age-related alterations in white matter integrity. Results of these studies generally describe lower FA in relation to older age, implying that the compositional properties of white matter decrease with age (Pfefferbaum, Adalsteinsson, & Sullivan, 2005; Pfefferbaum et al., 2000; Salat et al., 2005). These cross-sectional findings have been supported by longitudinal analyses, which have demonstrated that changes to measures of white matter integrity are detectable in as little as one to two years after baseline examination in older adults (Barrick, Charlton, Clark, & Markus, 2010). Yet, it is still unclear if increased age has a preferential impact on the integrity of frontal white matter, due to variability in affected regions in studies of older adults. For example, several DTI studies have demonstrated age-related decreases in frontal white matter integrity compared to posterior brain regions

(Pfefferbaum et al., 2000; Salat et al., 2005; Sullivan et al., 2001), while others have failed to detect notable differences between frontal areas and other regions (Barrick et al., 2010; Bennett, Madden, Vaidya, Howard, & Howard, 2010). This inconsistency in the literature is likely due to individual factors, including genetic, vascular, and inflammatory mechanisms that are independently associated with white matter integrity (Bennett & Madden, 2013).

Disruptions in white matter microstructural integrity using DTI have been linked to poor cognitive performance in older individuals. Cognitive difficulties can be explained in part by white matter connectivity, which has an important role in rapid communication between distant brain areas (Brickman et al., 2006; Davatzikos & Resnick, 2002). Sasson, Doniger, Pasternak, Tarrasch, and Assaf (2012) demonstrated that higher integrity in frontal and temporal white matter, as well as several prominent white matter tracts, was generally related to better cognitive performance. Specifically, domains of processing speed, memory, and complex executive functions are most frequently shown to be diminished in advanced age (Ownby, 2010; Sasson et al., 2012). These findings coincide with cognitive aging theories that postulate interactions between frontal lobe functions, functions mediated by speed of processing, and memory processes as determinants of overall age-related cognitive health (Jacobs et al., 2013; Salthouse, Atkinson, & Berish, 2003; West, 1996). The degree to which these cognitive functions are impaired, however, is difficult to predict accurately and likely hinges on a number of additional variables (Brickman et al., 2006; Jacobs et al., 2013). Body mass is one factor that may alter the expression of aging processes on brain structure and cognitive function.

Although the exact mechanism by which BMI affects the brain is not fully understood, elevated body mass may have a compounding effect on the cascade of biological processes related to aging, thereby potentially playing an important role in age-related brain variability (Doherty, 2003). Consequences of advanced age have been linked to multiple physiological processes, and researchers have identified processes including oxidative stress and vascular aging processes such as vascular inflammation, endothelial cell dysfunction, and arterial stiffness as primary factors contributing to age-related outcomes (Ungvari, Kaley, de Cabo, Sonntag, & Csiszar, 2010). Although these factors partially interact with each other, each are responsible for unique outcomes that can impact cellular metabolism, atherosclerosis, and cerebral hypoperfusion, resulting in increased risk of ischemic stroke and white matter damage (Sierra, Coca, & Schiffrin, 2011). Obesity and physical health behaviors can have a modifying effect on several of these processes, influencing the degree to which vascular aging mechanisms are expressed and altering their effects on the brain as a result (Ungvari et al., 2010). For example, obesity is independently associated with endothelial dysfunction, hypertension, and cerebrovascular disease (Malnick & Knobler, 2006; Sierra, Coca, & Schiffrin, 2011), which may lead to additive expression of age-related physiology.

The mechanism by which obesity impacts aging physiology likely involves a sequence of metabolic processes initiated by adipocytes. In general, adipocytes that comprise fat tissue release leptin into the bloodstream which initiates a cascade of inflammatory response mechanisms (Mathieu, Lemieux, & Despres, 2010; Wisse, 2004). Adipose tissue quantities are elevated in individuals with high BMI, leading to an overabundance of leptin in the bloodstream which then triggers increased release of

cytokines and inflammatory proteins (Considine et al., 1996; Thalmann & Meier, 2007; Wisse, 2004). These inflammatory markers, if present in elevated quantities for long periods of time, have a detrimental impact on the cellular integrity of brain tissue, particularly oligodendrocytes that comprise white matter (Griffin, 2006; Roth, Ramírez, Alarcón, & Von Bernhardi, 2005). While causal factors responsible for the relationship between obesity and brain tissue degradation have not been fully explored, evidence suggests that high body mass is linked to detrimental effects on the brain independent of age (Bruce-Keller, Keller, & Morrison, 2009; Jagust, 2007). Taken together, these factors may contribute to a physiological model of brain tissue loss leading to neurocognitive decline, but the observable impact of BMI on microstructural brain integrity and the resulting disruptions in cognitive ability remain poorly understood.

Recent work incorporating novel tractography indices of white matter integrity as a function of BMI has demonstrated that the length of white matter fiber bundles is a sensitive measure to BMI in healthy older adults, and provides a basis for the current study (Bolzenius et al., 2013). In this study, measures of fiber bundle length (FBL) by lobe were analyzed in relation to BMI after accounting for the effects of age. FBL is a novel DTI tractography metric of white matter integrity assessing the average length of white matter fibers within a given white matter tract or region. Results of this study revealed that while age exerted a robust effect on FBL in several lobes of the brain, BMI was independently associated with FBL in the temporal lobe. These findings indicate that temporal white matter integrity may be among the earliest impacted by obesity-related processes. This study however, did not investigate focal brain regions thought to be related to cognitive performance, and to what degree tract integrity relates to

variations in cognition. Incorporating measures of white matter integrity in addition to cognitive assessment has potential to yield important information about cognitive difficulties associated with BMI, and if these difficulties are related to alterations in brain microstructure. In addition, examination of these variables in a healthy older adult sample may clarify the role of body weight as a modifier of age-related alterations in brain integrity.

Results of this study and existing neuroimaging studies have implicated temporal and frontal lobe structures as areas most likely to exhibit alterations associated with high BMI (Gazdzinski et al., 2008; Raji et al., 2010; Verstynen et al., 2012). While the scope of tract selection in these studies is limited, some results have identified alterations in anisotropy and diffusivity in white matter tracts connecting to temporal and frontal regions. Specifically, select association fibers (i.e. superior longitudinal fasciculus (SLF) and cingulate) have exhibited alterations associated with high BMI (Marks, Katz, Styner, & Smith, 2011; Verstynen et al., 2012; Xu et al., 2011). Evidence from the cognitive aging literature suggests that deterioration of these white matter fibers may impact cognitive function. Posterior sections of the corpus callosum (subdivided into midposterior corpus callosum (mpCC) and posterior corpus callosum (pCC)) as well as the uncinate fasciculus (UF) have been associated with poor performance in measures of memory, executive function, and processing speed in aging individuals (Fujie et al., 2008; Turken et al., 2008; Voineskos et al., 2012). Since these cognitive domains are frequently impacted in high BMI individuals (Cournot et al., 2006; Gunstad et al., 2007; Sabia et al., 2009), exploration of cognitive ability in conjunction with neuroanatomical

correlates represents an important investigation into brain-behavior relationships associated with high BMI.

Public Health Relevance. Obesity is a major modifiable risk factor for cardiovascular, metabolic, and neurologic difficulties, yet rates have spiked in recent decades among the general public (Baskin et al., 2005). Individuals with high BMI tend to experience greater rates of cognitive difficulties and affective symptoms compared to normal-weight counterparts (Cserjési, Luminet, Poncelet, & Lénárd, 2009; Gunstad et al., 2007). Additionally, elevated BMI has been identified as a risk factor for development of neurodegeneration such as Alzheimer's disease, independent of comorbid cardiovascular problems (Gustafson et al., 2003; Whitmer et al., 2008). Given the increasing life expectancy of the general public, reports predict rates of Alzheimer's disease will rise steeply in coming decades (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007). As a result, it is essential to identify modifiable factors that could mitigate the burden of these diseases on our public health system. Examining these factors in an older adult sample will provide important information regarding cognitive and white matter characteristics that may identify predispositional qualities for eventual cognitive decline and neuropathology.

Summary

It is estimated that nearly one-third of adults in the United States are classified as obese based on BMI values (Flegal et al., 2010). Elevated BMI is associated with a variety of metabolic and cardiovascular health conditions that exert negative influences on the brain tissue integrity and cognitive function, and may be a source of age-related variability in cognitive function (Grundy et al., 2004; Gunstad et al., 2007; Gunstad et al.,

2008; Malnick & Knobler, 2006; Stanek et al., 2011; van den Berg et al., 2009). These adverse consequences are frequently reported in studies assessing cognitive, behavioral, or health outcomes, but few studies use DTI in conjunction with neuropsychological assessment to investigate the impact of BMI status on white matter microstructural integrity and cognition. Neuroimaging evidence suggests that elevated BMI is associated with structural abnormalities that contribute to cognitive difficulties observed in individuals with high BMI (Bettcher et al., 2013; Gazdzinski et al., 2008; Mueller et al., 2011; Stanek et al., 2011; Xu et al., 2011), yet the extent to which BMI impacts age-related variability in brain integrity remains unclear. The primary purpose of this study was to investigate the relationship between BMI and both white matter integrity and cognition in older adults using DTI and neuropsychological indices. I hypothesized that while age would strongly relate to DTI measures, elevated BMI would be independently associated with lower white matter integrity in fiber tracts connecting to frontal and temporal lobes (i.e. SLF, UF, cingulate, mpCC, and pCC). Additionally, I hypothesized that increased BMI would be associated with poorer cognitive performance in tests of executive function, processing speed, and memory after controlling for covariates.

Approach

This study analyzed the impact of BMI on white matter integrity using DTI in a sample of healthy older adults to identify markers of obesity-related processes in the brain. Measures of white matter tract integrity, neuropsychological performance, and demographic and health information were acquired as part of a larger longitudinal study of cognitive aging (R01 NS052470; PI: Paul). Demographic and health history information were collected at the initial cognitive appointment that occurred within one

month of neuroimaging procedures for the majority of participants. BMI was calculated by a trained research assistant as part of the cognitive assessment portion of the parent study.

Research Design Considerations

The first consideration was the use of BMI to quantify body weight rather than another method of quantifying body composition. While imaging methods such as dual-energy X-ray absorptiometry are able to make precise assessments of body tissue composition (Svendsen, Haarbo, Hassager, & Christiansen, 1993), they are more invasive and time-consuming than measurements of easily-gathered physical characteristics (e.g., height, weight) and as a result are less practical methods for body composition assessment. Although other anthropometric measures such as waist circumference or waist-stature ratio have been used to varying extents in epidemiological and neurological research (e.g., Janssen, Katzmarzyk, & Ross, 2004; Gunstad et al., 2010), BMI has long served as the metric for standardized population-based obesity estimates (Malnick & Knobler, 2006; Mokdad, Marks, Stroup, & Gerberding, 2004) and has been shown to be consistently associated with various negative health conditions in older adults (Patterson, Frank, Kristal, & White, 2004). Additionally, it has been reported that anthropometric variables of BMI, waist circumference, and waist-stature are more highly correlated with each other than with body fat percentage as observed with dual-energy X-ray absorptiometry (Flegal et al., 2009). There also does not appear to be much difference in the predictive value of these metrics for health conditions. For example, Bosy-Westphal et al. (2006) reported that BMI, waist circumference, and body fat percentage equally predicted metabolic risk factors, while Wildman, Mackey, Bostom, Thompson, and

Sutton-Tyrrell (2003) did not find notable differences between different anthropometric measures with regard to cardiovascular conditions. Further, Waldstein and Katzel (2006) did not report notable differences between BMI and waist circumference on cognitive performance in domains of executive function and psychomotor speed. As a result, in the absence of tools to measure actual body fat percentage (i.e. X-ray techniques), BMI is the most optimal method of body weight quantification for the present study.

Another consideration was measuring BMI on a continuum rather than stratified by BMI category (i.e. underweight, normal, overweight, or obese). While many studies examine group differences between BMI categories, there is evidence for a U-shaped relationship between the BMI scale and health outcomes in population-based studies (Malnick & Knobler, 2006). The advantage of collapsing BMI categories into a continuous variable is the greater potential to identify alterations in outcome measures that do not fit closely with epidemiological BMI category cutoffs. Also, as the current sample contains no underweight (BMI < 18.5) and few obese (BMI ≥ 30.0; $n = 7$) participants, the ability to detect significant effects comparing these groups would be notably limited. Therefore, the choice was made to analyze BMI on a continuous scale to identify the impact of BMI on white matter across the entire range of values.

The final consideration was the selection of DTI metrics to use in the proposed study. Alterations in FA have been observed in relation to high BMI (Stanek et al., 2011; Verstynen et al., 2012; Xu et al., 2011), while the few studies examining MD tend to show higher MD concomitant with lower FA (Xu et al., 2011). Additional measures of AD and RD, which together comprise MD, are theorized to provide information about the microstructural integrity of axons and myelin, respectively (Verstynen et al., 2012).

Studies have demonstrated positive covariation between FA and AD, and inverse covariation between FA and both MD and RD associated with BMI status (Verstynen et al., 2012; Xu et al., 2011). While AD, RD, and MD may provide further detail regarding tract integrity, their utility above and beyond FA as measures of specific neuronal processes relative to BMI has not been established, and it has been suggested that these measures may not accurately reflect neuronal characteristics in the absence of physical tissue analysis (Wheeler-Kingshott & Cercignani, 2009). As a result, inclusion of variables that exhibit multicollinearity with each other may increase familywise error rate while not significantly contributing to study findings. Therefore, the decision was made to not examine AD, RD, and MD as primary outcome variables, though these measures will be included in secondary analyses and represent avenues for further exploration of white matter integrity.

Participants

A total of 62 individuals between the ages of 51 and 81 (M = 62.40, SD = 8.44) were included in the study. Participants were recruited from the local community in addition to the Research Participant Registry of the Washington University Institute of Clinical and Translational Sciences. Demographics and health history were obtained as part of cognitive assessment procedures at the University of Missouri – St. Louis, while MRI scans were acquired at Washington University in St. Louis. This included assessment of BMI as well as blood pressure, which was computed into a measure of pulse pressure (defined as systolic minus diastolic blood pressure averaged across three time points during cognitive assessment). This was included to assess the relative contribution of blood pressure at time of testing to white matter and cognitive variables,

as pulse pressure is sensitive to differences in cognitive performance (Dahle, Jacobs, & Raz, 2009). Approval was obtained from both the UMSL and Washington University Institutional Review Board (IRB) and all participants provided informed consent for participation in all study procedures.

Inclusion/Exclusion Criteria

All participants were required to be fluent English speakers to participate in the study protocol. Individuals with a self-reported history of medical conditions with potential to impact cognitive function (e.g., thyroid disease) were excluded. Also, individuals with a history of neurological disease (e.g., dementia, multiple sclerosis, Parkinson's disease), treatment-dependent diabetes, significant head injury (defined as loss of consciousness greater than five minutes), alcohol or drug abuse, or MRI contraindication (e.g., claustrophobia) were not considered for inclusion. Individuals were excluded if they reported a current diagnosis of a DSM Axis I psychiatric condition (e.g., schizophrenia) with the exception of treated depression. Preliminary data from the Depression Anxiety Stress Scales (Lovibond & Lovibond, 1995) were examined to assess presence of current depressive symptoms, and did not reveal notable affective symptoms in this sample. The Mini-Mental State Examination (MMSE) was used to screen for current symptoms of dementia, excluding individuals with scores below 24.

DTI

MRI scan acquisitions were obtained using a head-only Magnetom Allegra 3T MRI scanner. During the duration of data acquisition, all hardware, software, acquisition protocols, and pulse sequences remained unchanged to ensure quality assurance of neuroimaging data. Structural MRI data were obtained utilizing T1-weighted

magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence, T2-weighted turbo spin echo (TSE), and T2-weighted fluid-attenuated inversion recovery (FLAIR). An initial pilot sample from the same parent study was used to establish slice coverage and field of view parameters. Total scan time was limited to less than one hour.

To obtain diffusion weighted images, a custom single-shot multislice echo-planar tensor-encoded pulse sequence was used, with 31 non-collinear diffusion gradient directions comprising the 24 main direction used for data processing (diffusion weighting of b = 996 s/mm^2) and 5 baseline I_0 acquisition sequences (b = 0 s/mm^2). To ensure whole brain coverage, acquisition parameters (TE = 86.2 ms, TR = 7.82 s) were optimized across 64 contiguous 2.0 mm slices for each contrast. Additional imaging parameters included a 128 x 128 acquisition matrix with 256 x 256 mm field of view (isotropic 2.0 x 2.0 x 2.0 mm voxels). Each participant's diffusion weighted images and diffusion-encoding vectors were registered via affine registration to the first I_0 volume with the mutual information metric of FSL FLIRT to correct for motion in the scanner and eddy current artifacts (Jenkinson, Bannister, Brady, & Smith, 2002). Brain tissue was extracted with the FSL Brain Extraction Tool. To identify specific white matter tracts, the Johns Hopkins University (JHU) DTI atlas along with International Consortium for Brain Mapping (ICBM) lobe atlas were mapped to each participant through affine registration to the FA image with mutual information (Wakana et al., 2007). The corpus callosum was segmented into five different subsections – of which the two most posterior sections are examined in this study – based on established anatomical connections to distinct cortical areas (Rosas et al., 2010). Tracts of interest (SLF, UF, cingulate, mpCC, and pCC; see Figure 1) were segmented using custom software,

including neuronal structures if the corresponding structure on the JHU atlas contains at least 80% of its arc length. Scan data were averaged with two scan repeats (total of 72 acquisitions). Raw (k-space) data were saved, stored, then reconstructed floating-point diffusion weighted images using a custom method of image reconstruction. DTI scalar metrics (i.e. FA) in white matter tracts were recorded and computed from the diffusion tensor. Additional measures of AD, RD, and MD were computed for use in secondary analyses.

Neuropsychological Evaluation

All cognitive testing was completed following the demographic and health history portion of study participation. Specific tests were selected to represent cognitive domains known to be affected by BMI status. As a result, the proposed study focused on measures of executive function, processing speed, and memory. A preliminary principal components analysis revealed that measures of executive function and processing speed related well to each other, with memory measures comprising an additional factor. This observed correlation between executive function and processing speed is in line with results of cognitive aging research and is likely driven by underlying changes in white matter (Jacobs et al., 2013).

Executive function was assessed using Trails B from the Trail Making Test (TMT; AITB, 1944), Trial 4 of the Color-Word Interference Test (CWIT) of the Delis-Kaplan Executive Function System (D-KEFS; Delis, 2001), and Letter Number Sequencing (LNS) from the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997). Trails B requires participants to draw lines connecting alternating numbers and letters in a sequential order. Trial 4 of the CWIT is an advanced task of response

inhibition and set shifting requiring participants to name the color of ink in which a word is printed (i.e. the word "blue" depicted in red ink). A portion of these words are printed within a box, and participants must read the word if contained inside a box but name the ink color if not contained inside a box. LNS requires participants to listen to a string of both letters and numbers, then mentally sequence numbers in order first followed by letters in alphabetical order. The task sequences lengthen as participants answer correctly, and the difficulty of responding correctly rises accordingly. Time to completion was the outcome measure for Trails B and CWIT Trial 4, and total number correct was the outcome measure for LNS.

Processing speed was assessed using Trails A from the TMT, Trial 1 from the CWIT, and Coding from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, Tierney, Mohr, & Chase, 1998). Trails A requires participants to draw lines that sequentially connect circles numbered 1 through 25 as quickly as possible. Trial 1 of the CWIT requires participants to name patches of ink color as quickly as possible. Coding presents participants with rows of boxes. In the top half of each box is a number, and participants must fill in the bottom half of each box with the corresponding symbol according to a given key. Time to completion served as the outcome measure for Trails A and Trial 1 of the CWIT, and total number of correct responses within 90 seconds served as the outcome measure for Coding.

Domains of immediate and delayed memory were assessed using subtests of the RBANS. Immediate memory was assessed using List Learning and Story Memory subtests, and delayed memory was assessed using List Recall and Story Recall. The List Learning subtest presents participants with a list of ten semantically unrelated words,

repeated across four separate trials, each trial followed by immediate recall. List Recall occurs approximately 20 minutes after initial presentation, at which time participants are instructed to freely recall as many words as possible in the original list. Story Memory involves a story being presented twice to participants, both followed by immediate recall, followed by Story Recall that requires participants to freely recall the story after a delay of approximately 20 minutes. Number correct served as the outcome measure for each of the RBANS subtests.

Statistical Analyses

Prior to statistical computation, data were screened for outliers by computing standardized z-scores for all dependent variables in SPSS 21. Demographic and health variables significantly associated with white matter integrity or cognitive ability were identified using Pearson's correlation coefficients (i.e., age, years of education, pulse pressure) or independent samples t-tests (i.e. sex). White matter indices were collapsed across hemispheres since prior BMI studies have not reported unilateral differences in FA in white matter regions of interest (Bettcher et al., 2013; Verstynen et al., 2012). Weighted FA values (raw FA multiplied by overall tract length to jointly assess both length and integrity of the tract) by tract served as the primary white matter outcome variable. Cognitive test raw scores served as outcome variables for neuropsychological evaluation analyses. Statistical significance was determined using the false discovery rate (FDR) method, which provides a stepwise correction method that assesses significance based on the number of comparisons made (Benjamini & Hochberg, 1995).

Aim 1 Analysis. To determine the association between BMI and microstructural integrity of white matter tracts in the brain using DTI.

Demographic and health variables, including age, sex, years of education, and pulse pressure, were examined using bivariate correlations or independent samples t-tests to determine if differences in these variables were significantly associated with FA by tract. Variables identified in this preliminary step were entered in the first step of a hierarchical linear regression model, and FA for each tract was entered in the second step. Additionally, age and BMI variables were mean-centered and factored to create an interaction term, and were utilized to determine the interaction between age and BMI on FA in tracts exhibiting significant alterations associated with BMI.

Aim 2 Analysis. To investigate the association between BMI and cognitive performance in domains of executive function, processing speed, and memory.

Similar to Aim 1, preliminary analyses were first computed to identify demographic and health variables that were significantly associated with cognitive test scores. These variables were entered into step one of a hierarchical regression model, and cognitive test raw scores in domains of executive function, processing speed, and memory were entered into step two. Additionally, mean-centered age and BMI variables were used to determine if cognitive tests exhibiting main BMI effects showed evidence for an interaction.

Secondary Analyses. Secondary analyses were completed to address two goals. The first goal was to examine the association between BMI and white matter integrity in DTI metrics of AD, RD, and MD. Demographic and health variables demonstrating significant association with diffusivity indices in tracts of interest were entered into step one of a hierarchical regression, with BMI entered into step two. The second goal was to identify relationships between white matter integrity and cognitive test performance.

Partial correlation analyses were utilized to examine relationships between DTI indices and cognitive test raw scores, controlling for age.

Power Analyses

Power for Aim 1 was based on data from a previous study incorporating similar DTI dependent variables in healthy adults across the lifespan (Stanek et al., 2011). Effect sizes of group comparisons in this study were shown to be in the moderate to large range. Using equivalent f^2 effect size norms for a linear regression analysis, a moderate to large effect size was estimated, resulting in a required sample of 42 to achieve 80% power. Power for Aim 2 was based on data from a recent study on cognitive outcomes associated with BMI (Gunstad et al., 2007). Group comparisons in this study equated to small to moderate effect sizes. Assuming a moderate f^2 effect size for analysis resulted in a required sample of 52 to achieve 80% power. While these previous studies represent the most directly comparable investigations to the present study, no studies have utilized the complete set of neuroimaging and cognitive metrics proposed in this study. Additionally, the lack of statistics reported in similar studies and varying analytic methods led to incompatibility when translating to current study analyses.

Results

Preliminary and Demographic Analyses

The final sample was comprised of 62 participants (20 males, 42 females) completing DTI and cognitive evaluation components of the study. Data were screened for univariate normality using Q-Q plots and outliers were identified using standardized z-scores among all dependent variables. Results of these analyses concluded that data did not violate assumptions of normality. Outliers were identified at $|z| \geq 3$ and removed in a

pairwise fashion from analyses. Participant demographics were characterized using descriptive statistics and compared to dependent variables using Pearson's correlation coefficients (i.e. age, years of education, pulse pressure) or independent samples t-tests (i.e. sex). See Table 1 for characterization statistics regarding demographic/health status.

Aim 1

Preliminary examination of demographic and health variables did not reveal significant relationships between age and tract FA. Rather, FA of the cingulate significantly varied by sex ($t(59) = 3.703$, $p < .001$) and years of education was significantly related to FA of the pCC ($r(53) = .294$, $p < .05$). After controlling for these associations, significant alterations in FA related to BMI were observed in the UF. Specifically, higher BMI was associated with lower FA in the UF ($F(1, 60) = 6.981$, $p = .01$, $\beta = -.323$), which explained 10.4% of the variance. The test for an interaction between age and BMI in FA was not significant after adding the interaction term to the model ($F(1, 58) = 2.653$, $p > .05$), providing no support for the presence of an interactive effect of age and BMI relating to FA of the UF (Figures 2-6).

Aim 2

Initial analysis of demographic and health variables suggested that age and pulse pressure were most commonly associated with cognitive performance. Results indicated there were no significant associations between BMI and cognitive performance after controlling for demographic and health variables. Accordingly, no test for interaction effects between age and BMI was computed due to the lack of a main effect of BMI on cognitive performance. See Table 3 for full details of Aim 2 results.

Secondary Analyses

Secondary Aim 1. Similar to Aim 1, a series of hierarchical regression analyses were computed to determine the association between BMI and DTI scalar metrics of AD, RD, and MD in selected tracts of interest. Preliminary analyses showed that in addition to age, sex had the most frequent associations with these diffusivity metrics in tracts of interest. After controlling for these variables and correcting for FDR, no significant relationships were observed between BMI and white matter tract integrity. Prior to FDR correction, significant associations were observed between BMI and white matter integrity of the UF and mpCC. In the UF, higher BMI was associated with lower AD ($F(1, 59) = 5.458$, $p < .05$, $\beta = -.291$) and lower MD ($F(1, 59) = 3.992$, $p < .05$, $\beta = -.252$), which explained 8.5% and 6.3% of the variance, respectively. In the mpCC, higher BMI was associated with higher RD ($F(1, 51) = 5.513$, $p < .05$, $\beta = .312$) and higher MD ($F(1, 50) = 5.379$, $p < .05$, $\beta = .306$), which explained 9.8% and 17.5% of the variance, respectively. Detailed results from this analysis are presented in Table 4.

Secondary Aim 2. Partial correlation analyses controlling for age were used to examine relationships between FA and cognitive test performance. Although some moderate magnitude correlations were observed between FA and cognitive performance, none remained significant after correcting for FDR. As a result, cognitive functions tested in this study did not relate to integrity of white matter tracts independent of age. Detailed results of this analysis are presented in Tables 5-7.

Discussion

The primary objective of this study was to determine if BMI was associated with alterations in white matter integrity and cognitive performance in a sample of healthy older adults. Results indicated that elevated BMI was independently associated with

lower FA in the UF. No relationships were observed between BMI and cognitive performance in domains of executive function, processing speed, or memory. There was no evidence for an interactive relationship between age and BMI on white matter integrity or cognitive performance. Secondary analyses including AD, RD, and MD did not provide strong support for the sensitivity of these metrics to BMI, as initial relationships were negated by FDR correction.

DTI Metrics

Findings from the present study provide support for the first primary aim predicting a significant association between lower FA and elevated BMI after controlling for contributing factors. A significant inverse relationship was observed between FA in the UF and BMI, consistent with hypotheses and results of previous studies (Bettcher et al., 2013; Stanek et al., 2011; Verstynen et al., 2012; Xu et al., 2011). However, data did not indicate an interaction between age and BMI with regard to FA in the UF. Significantly lower FA in the UF associated with high BMI is a novel finding, as very few studies have examined the UF in relation to BMI. The UF connects the orbital gyrus region of the frontal lobe to the anterior temporal lobe, and is shown to be involved in memory performance (Fujie et al., 2008; Sasson et al., 2012). Lower FA in the UF is consistent with hypotheses of the present study as well as prior research revealing lower white matter integrity in the temporal lobe (Bolzenius et al., 2013). Overall, these results suggest that elevated BMI has a negative impact on the directionality of water diffusion in the UF resulting in abnormal tract integrity observed with DTI. Additional studies are needed to confirm this relationship in a similar sample of healthy older adults and to determine if these alterations persist or exacerbate over time.

To further evaluate the underlying diffusion characteristics of white matter tracts in the present study, secondary analyses were conducted examining associations between BMI, AD, RD, and MD. None of the white matter tracts exhibited significant associations with BMI after controlling for confounding variables and correcting for FDR, but a few modest preliminary relationships are noted. Consistent with the results of Aim 1, alterations in diffusivity in the UF were observed. Altered diffusivity was also observed in the mpCC. Within the UF, high BMI was associated with lower AD and MD, suggesting that water diffusion was generally lower in this tract. By contrast, high BMI was associated with higher RD and MD in the mpCC, which may be a result of rapid water diffusion away from axons in this tract. These findings are partially consistent with prior research demonstrating that FA positively relates to AD but negatively relates to RD and MD in white matter regions associated with BMI (Verstynen et al., 2012; Xu et al., 2011). The global decrease in UF diffusivity has not been reported in existing literature, but increased diffusivity in the mpCC is consistent with research by Xu et al. (2011). It has been suggested that both lowered FA and MD may be indicative of early axonal dysfunction related to ischemic lesions (Burzynska et al., 2010) or age-related changes to cellular membrane density and glial cell activation (Beach, Walker, & McGeer, 1989; Beaulieu, 2002). However, since none of these relationships survived FDR correction, it is possible that these conflicting relationships between BMI and AD, RD, and MD do not represent genuine alterations in white matter microstructure or cellular processes. As a result, while AD, RD, and MD have potential to provide unique information regarding white matter microstructural integrity, these results do not suggest

that these measures substantially contributed to assessment of white matter integrity in this study.

Overall, results from this study are consistent with previous studies suggesting that white matter tract integrity is altered in relation to high BMI, but regional alterations vary between studies. For example, Xu et al. (2011) reported that while FA tends to decrease in relation to high BMI, alterations in AD, RD, and MD are bidirectional depending on the tract of interest. Researchers observed negative relationships between BMI and both FA and AD in the body of the corpus callosum as well as between MD and RD in the fornix and splenium of the corpus callosum, but AD in the SLF was positively related to BMI. The authors suspected these conflicting relationships were due to biological processes related to BMI that impact white matter integrity differently depending on the particular brain region. Factors involved in cellular metabolism and inflammation, such as free fatty acids and leptin, likely have some role in this relationship (Bettcher et al., 2013; Mueller et al., 2011; Xu et al., 2011). This assumption remains untested at this point, as serum concentrations of vascular and inflammatory markers were not obtained in the present study. Few studies have investigated relationships between the UF and BMI, and therefore the exact mechanism of BMI-related pathophysiology in this tract remains unknown. Future studies should seek to build upon existing DTI findings and assess inflammatory markers with potential to impact white matter integrity and cognitive performance.

Conclusions from the present study are consistent with the majority of studies examining the relationship between BMI and brain tissue integrity in healthy older adults. Aging has been associated with a gradual decrease in white matter integrity and cognitive

performance, though the progression of age-related decline is variable between individuals (Jacobs et al., 2013; Ownby, 2010; Pfefferbaum, Adalsteinsson, & Sullivan, 2005; Pfefferbaum et al., 2000; Salat et al., 2005; Sasson et al., 2012). Obesity has been identified as a potential modifier of age-related alterations in brain tissue integrity (Doherty, 2003; Ungvari et al., 2010), but few studies have assessed relationships between white matter integrity and BMI in a group of healthy older adults. Results of the current study are consistent with findings from prior assessment using DTI tractography in this sample (Bolzenius et al., 2013), which revealed associations between high BMI and decreased mean fiber bundle length in the temporal lobe, independent of age. Present study results extend these findings by identifying a negative impact of high BMI on UF integrity. Interestingly, while age has been shown in prior research to relate to white matter integrity (Bolzenius et al., 2013; Pfefferbaum et al., 2000; Salat et al., 2005), current study findings did not suggest that age was strongly related to white matter integrity of these tracts. Further, while some studies have identified an interaction between age and BMI on DTI metrics (Stanek et al., 2011), no evidence for an interaction was observed in this study. This discrepancy may be explained by age range differences between studies, as Stanek et al. (2011) surveyed adults across the lifespan (i.e. ages 21 to 86) while the present study sampled strictly older adults. This over-representation of young adults may have led to significant interactions attributable to brain changes throughout adulthood, whereas this variability was limited in the current study. Collectively these findings suggest that elevated BMI is independently associated with modified brain tissue integrity in healthy older adults. Further studies are needed to

establish consistency of affected brain regions and to identify cellular mechanisms linked to these alterations.

Cognitive Evaluation

Results of this study do not support the second aim of the study predicting poorer cognitive performance in domains of executive function, processing speed, and memory associated with high BMI. Preliminary analyses identified significant relationships between age and cognitive function, such that increased age was related to poorer cognitive performance in most neuropsychological tests. After controlling for these preliminary relationships, there was no evidence of an association between BMI and cognitive ability in any cognitive test. A recent meta-analysis suggested that a relationship exists between BMI and cognition, particularly in tests of executive function, processing speed, and memory (van den Berg et al., 2009), though the effects are usually small to moderate and vary between studies.

One potential factor influencing this variability between current study results and prior findings is the age range of study samples. Research has shown that advanced age has independent negative effects on performance in these cognitive domains (Ownby, 2010; Sasson et al., 2012), but performance may vary based on individual factors such as white matter abnormalities and cardiovascular conditions (Brickman et al., 2006; Jacobs et al., 2013). The majority of studies have revealed negative relationships between BMI and cognition across the adult lifespan (Cournot et al., 2006; Gunstad et al., 2006; Gunstad et al., 2007; Sabia et al., 2009; Waldstein & Katzel, 2006), though some studies report positive relationships between BMI and cognition (Gunstad et al., 2010; Kuo et al., 2006; Ward et al., 2005). Differences between study designs and neuropsychological

battery selection likely have a role in these reported discrepancies between studies. For example, studies reporting better cognitive performance with high BMI did not recruit a cognitively intact cohort (Kuo et al., 2006) or a strictly healthy older adult sample (Gunstad et al., 2010; Ward et al., 2005). Therefore, despite some inconsistency across studies, the majority of literature suggests that high BMI is negatively associated with cognitive ability (Cournot et al., 2006; Gunstad et al., 2006; Gunstad et al., 2007; Sabia et al., 2009; van den Berg et al., 2009), though this hypothesis was not supported in the present study.

Another aim of this study was to explore the relationship between white matter integrity and cognitive test scores. To this end, tract FA was correlated with cognitive test raw scores to identify the degree of relationship between underlying brain microstructure and objective cognitive ability, controlling for age. Results did not reveal significant relationships between DTI indices and cognitive test scores after correcting for FDR, indicating that integrity of white matter tracts did not relate to cognitive ability in this sample. Existing research has suggested that white matter tracts analyzed in the present study are related to cognitive ability (Fujie et al., 2008; Voineskos et al., 2012), but results of the present study did not support this assumption. Also, the lack of relationship between DTI indices, cognition, and factors other than age may have attenuated most of the variability necessary to produce strong correlations between these measures. Still, given the associations between these white matter regions and cognitive function described by prior studies (Marks et al., 2011; Turken et al., 2008; Voineskos et al., 2012), it is possible that stronger brain-behavior relationships would be revealed in a larger sample.

The lack of significant relationships between BMI and cognitive performance in the present study may be due to several possibilities. While some previous studies indicate BMI is negatively related to cognition in older adults (Elias et al., 2003; Waldstein & Katzel, 2006), it is possible that a larger number of participants at the high ends of the age and BMI scales would have revealed more significant relationships with brain structure. At present, however, these data do not suggest that a significant relationship between BMI and cognition would have existed with a larger number of participants. Specifically, standardized β values of BMI with cognition are negligible, indicating that potentially low power to detect significant relationships was limited by effect size rather than sample size. Evidence also suggests that alterations to white matter microstructure precede cognitive changes (Brickman et al., 2006; Medina et al., 2006), suggesting that longitudinal assessment of these individuals may reveal long-term cognitive changes associated with altered DTI metrics. Repeated assessments of these participants are needed to fully evaluate this assumption and to assess if this lack of significant findings holds true over time in these older adults.

Mechanisms of Aging and Obesity

Findings from the present study are partially consistent with results of previous studies on brain tissue composition and cognitive function associated with BMI. Consistent with previous studies, the role of advanced age in relation to cognition was supported in this study, though age did not relate strongly to tract integrity. The detrimental effects of aging are thought to be manifested by a gradual acceleration of several physiological processes. For example, age-related changes in vascular system integrity have been linked to oxidative stress via production of reactive oxygen species

(ROS; Ungvari et al., 2010). This effect has in turn been shown to promote development of cardiovascular conditions such as coronary heart disease and stroke, along with endothelial cell dysfunction resulting in increased permeability of the blood-brain barrier. Additionally, ROS can also work in synchrony with inflammatory proteins, such that oxidative stress promotes release of inflammatory proteins, which themselves lead to exacerbation of oxidative stress. Evidence suggests that if prolonged, this cascade can lead to chronic atherosclerosis, arterial stiffness, and other cardiovascular diseases (Sierra, Coca, & Schiffrin, 2011).

Individually, each of these processes have been linked to cardiovascular outcomes resulting in impaired efficiency of cellular metabolism, atherosclerosis, and cerebral hypoperfusion (Sierra, Coca, & Schiffrin, 2011). Together, the gradual activation of one or more of these processes can lead to further activation of other vascular aging mechanisms, resulting in increased risk for ischemic stroke that may lead to damage to deep white matter tissues. While differences in white matter FA have been linked to age (Barrick et al., 2010), results of the present study did not show a significant relationship between age and tract FA. By contrast, age was strongly related to cognitive performance in this study. This finding is consistent with existing literature (Brickman et al., 2006), as age is noted to be a chief risk factor for decreased cognitive ability, cognitive impairment, and neurodegenerative disease (Keller, 2006; Lindsay et al., 2002).

Outcomes of previous studies have indicated that obesity and other physical health characteristics may have an important role in several age-related physiological processes, and may modify the severity of vascular aging expression in affecting brain health (Ungvari et al., 2010). These studies suggest that obesity has independent effects

on several of these processes, potentially exacerbating age-related disruption of endothelial cell function, hypertension, and development of cerebrovascular disease (Malnick & Knobler, 2006; Sierra, Coca, & Schiffrin, 2011). Although the relationship between these physiological mechanisms of cellular pathology and high BMI are still being evaluated, the increase in adipocytes that accompanies an increase in BMI may trigger further cellular pathology.

Leptin, a key neuromodulator involved in feeding behaviors, is released during satiety primarily by adipocytes (Harvey, Shanley, O'Malley, & Irving, 2005). Individuals in normal-weight ranges tend to have low quantities of adipocytes, resulting in regulated levels of leptin (Wisse, 2004). In addition to the role of leptin in hunger and satiety, it also is involved with activation of the inflammatory response, as well as cognition (Harvey et al., 2005; Wisse, 2004). It has been theorized that in obesity, the elevated level of leptin released by the high quantity of adipocytes is inefficiently recognized by the brain, leading to chronically elevated leptin levels, and as a result, pro-inflammatory cytokines (Considine et al., 1996; Harvey et al., 2005; Wisse, 2004). These cytokines have been linked to dystrophic neurite growth via hyperphosphorylated tau proteins and neurofibrillary tangles (Griffin, 2006). Increased formation of dystrophic neurites has been shown to trigger synthesis of β-amyloid precursor protein (APP), which alters intracellular calcium concentrations via constant positive feedback between APP and pro-inflammatory interleukin (IL-1 and IL-6) and S100β cytokines (Griffin, 2006; Mrak, Sheng, & Griffin, 1996). If these cellular processes continue unmitigated, they can result in astrogliosis and premature apoptosis (Griffin, 2006). Together, these changes to cellular physiology have been linked to alterations to white matter integrity by disrupting

normal oligodendrocyte function (Roth et al., 2005). While this cascade of physiological processes represents a potential mechanism of white matter disruption associated with high BMI, these markers were not obtained in the current study, and therefore it remains unclear to what degree these processes are altered in this sample of healthy older adults. Similar studies, however, have demonstrated the potentially impactful role of vascular and inflammatory markers influencing white matter integrity (Bettcher et al., 2013), but additional studies are needed to confirm this relationship.

Conclusions

Results of the current study are partially consistent with previous studies suggesting that high BMI is associated with disruptions to white matter tract microstructure and cognitive performance. Findings indicate that high BMI is significantly associated with lower FA in the UF, though there was no evidence of an interaction between BMI and age relating to tract integrity. These white matter alterations were observed in the absence of significant relationships between BMI and cognitive performance, indicating that altered white matter microstructure may be observable prior to lower cognitive performance in relation to BMI.

Some important limitations of the current study should be mentioned. It remains unknown if additional white matter tract or cognitive associations with BMI would have been observed in a slightly older sample, as the average age of the current sample (M = 62.40) is still relatively young compared to average age of onset of mild cognitive impairment and Alzheimer's disease, both of which are more common after age 65 (Lopez et al., 2003). Further, inclusion of additional cognitive constructs may have revealed cognitive scores significantly associated with BMI, providing a more

comprehensive assessment of brain integrity. Finally, the range of BMI values of the current sample may not have been fully representative of the older adult population, given the underrepresentation of individuals in the obese BMI classification (i.e. BMI ≥ 30.0). This is likely an artifact of study inclusion due to MRI compatibility, but as a result, the ability of study conclusions to be generalized to a population that is more inclusive of obese individuals is limited.

Overall, this is one of the first studies to combine both DTI measurement and cognitive performance in relation to BMI in healthy older adults. Results indicate that high BMI is related to lower tract integrity but not cognitive performance in this sample. Future studies are needed to investigate the relationship between BMI and brain tissue integrity, and how this may relate to changes in cognitive performance over time. Examination of additional white matter structures such as the anterior thalamic radiation and forceps minor, and collecting blood markers of inflammatory factors related to obesity are necessary to further clarify these relationships, particularly in older adult samples.

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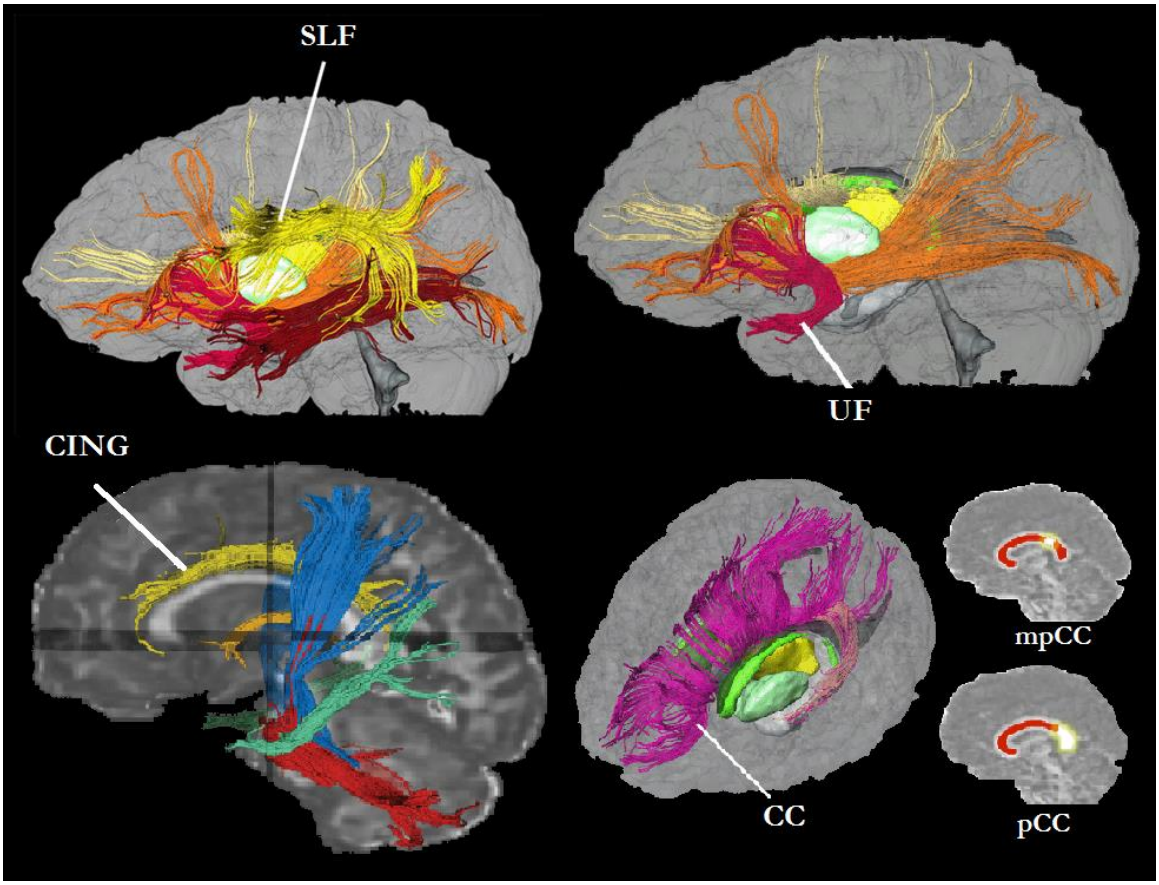
Figure 1. White matter tracts of interest



Note: SLF = superior longitudinal fasciculus (in yellow); UF = uncinate fasciculus (in red); CING = cingulate gyrus (in yellow); mpCC = midposterior corpus callosum; pCC = posterior corpus callosum

Figure 2. Relationship between BMI and FA in the superior longitudinal fasciculus

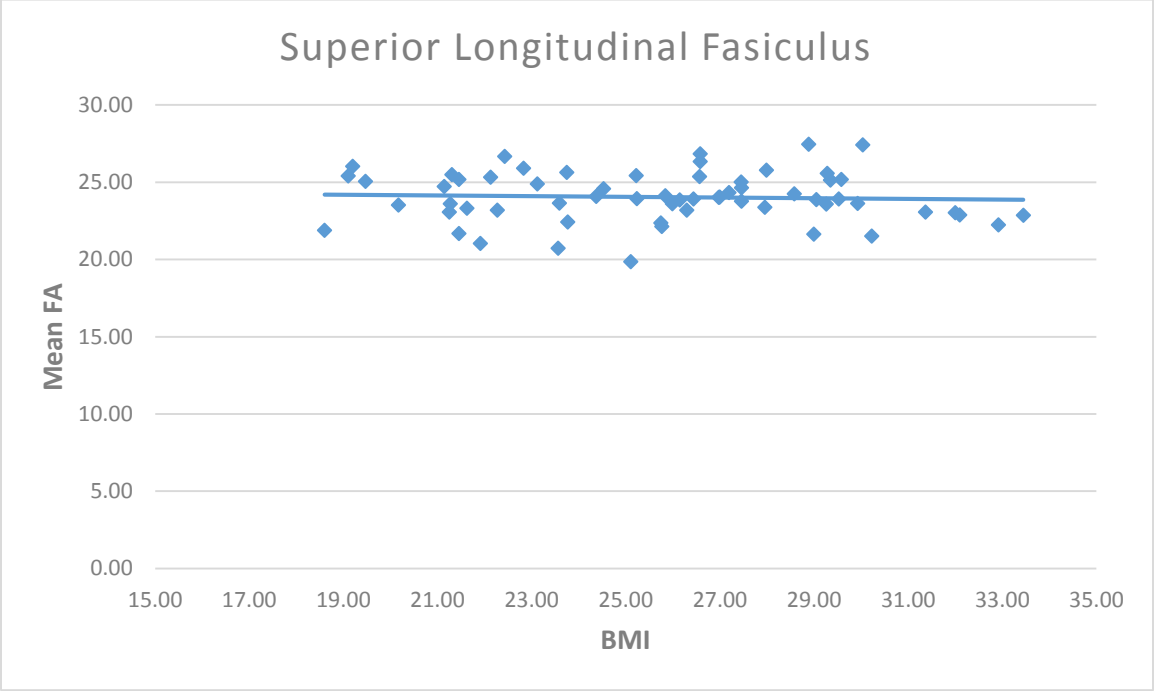


Figure 3. Relationship between BMI and FA in the uncinate fasciculus

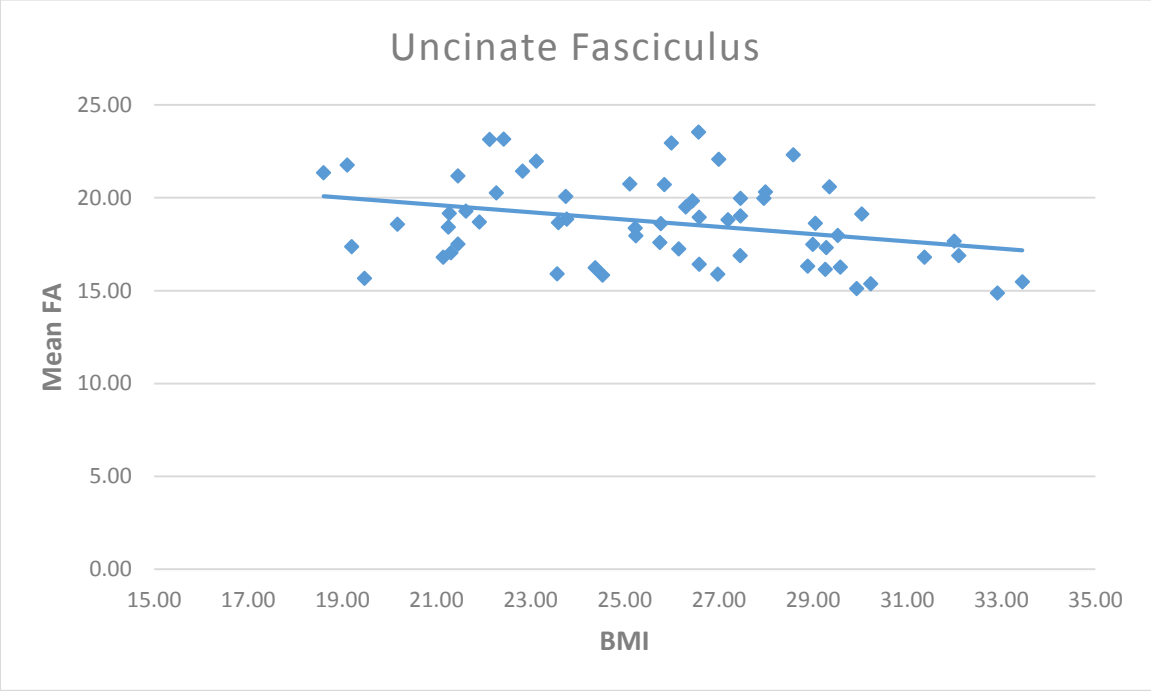


Figure 4. Relationship between BMI and FA in the cingulate

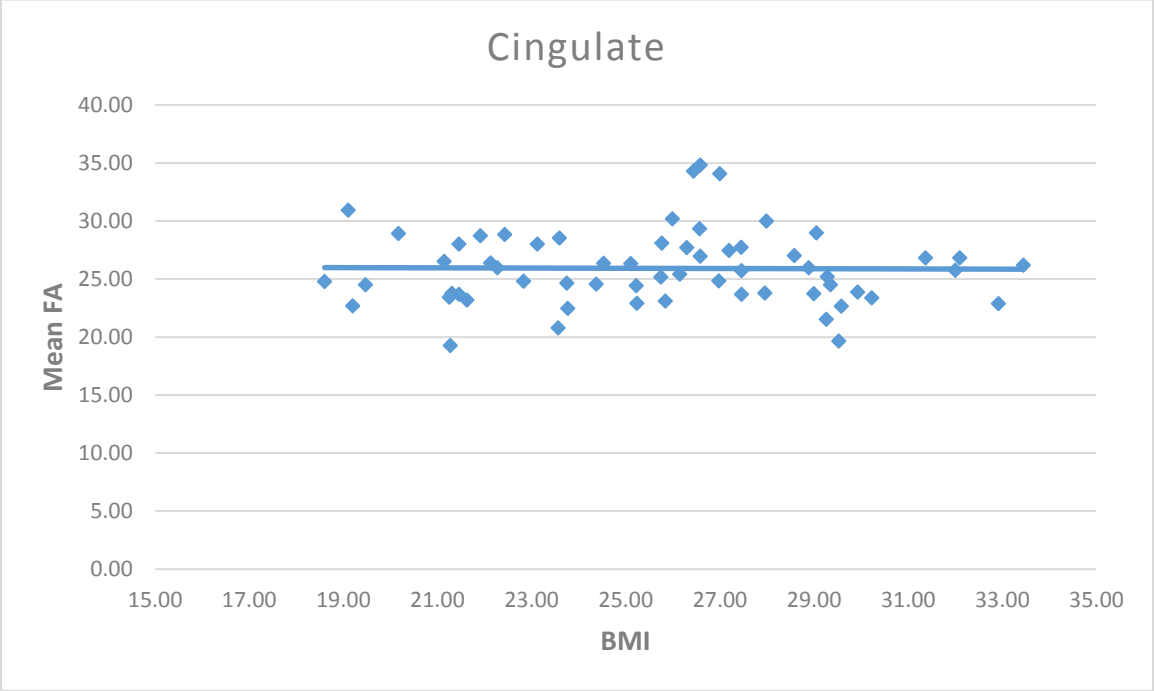


Figure 5. Relationship between BMI and FA in the midposterior corpus callosum

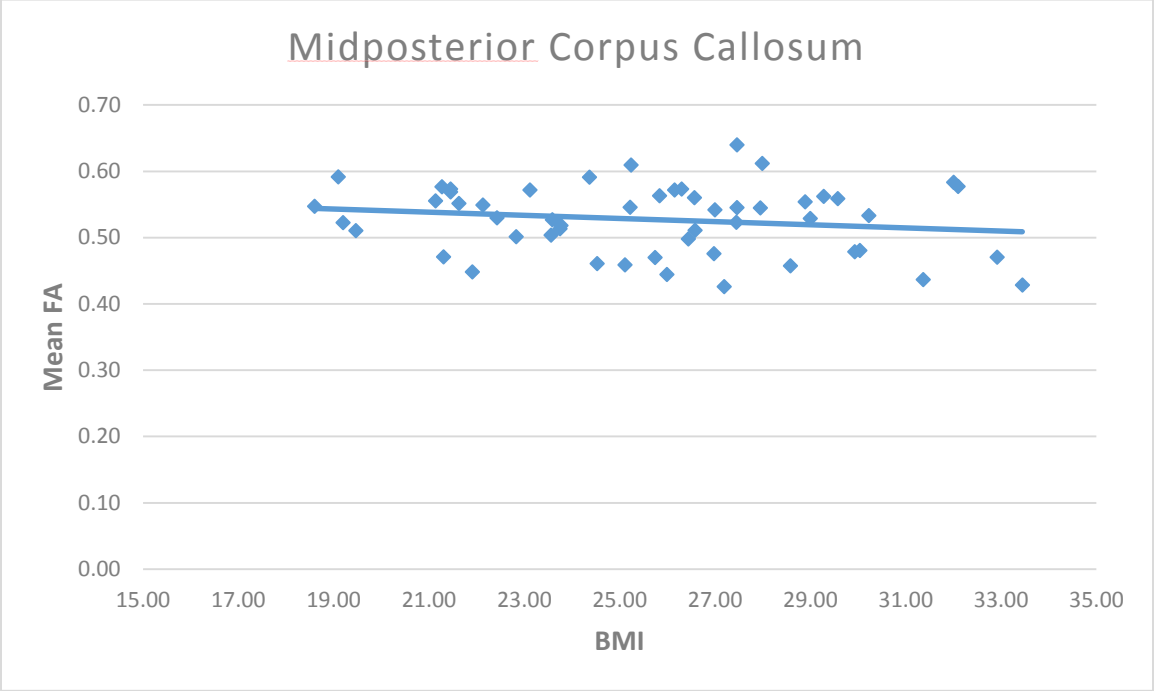


Figure 6. Relationship between BMI and FA in the posterior corpus callosum

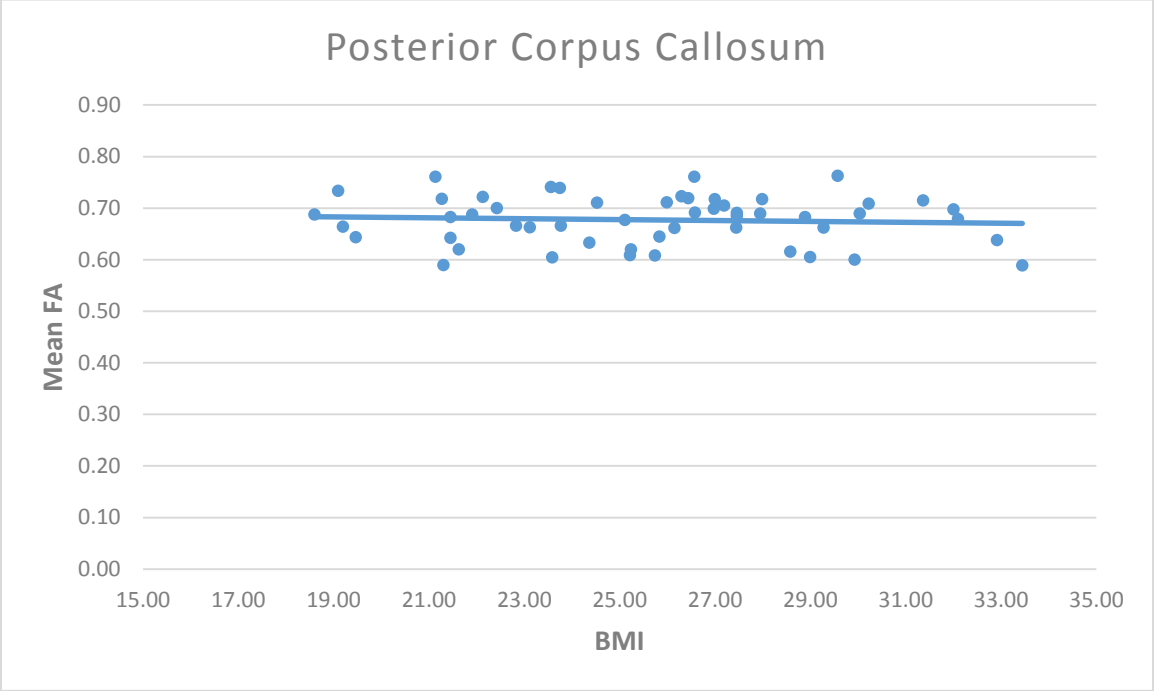


Table 1. Study sample characteristics

N=62 (20 males, 42 females)

Variable	Mean	SD	Min	Max
Age, years	62.40	8.44	51	81
Education, years	15.23	2.49	12	20
BMI	25.74	3.72	18.60	33.45
Pulse Pressure	50.53	9.97	32	72
MMSE	28.7	1.42	24	30

Table 2. Hierarchical regression results for FA by tract

Superior Longitudinal Fasciculus	β	R^2	ΔR^2	ΔF	Sig. ΔF
[1]BMI	-.049	.002	.002	.143	.707
Uncinate Fasciculus	β	R^2	ΔR^2	ΔF	Sig. ΔF
[1]BMI*	-.323	.104	.104	6.981	.010
Cingulate	β	R^2	ΔR^2	ΔF	Sig. ΔF
[1]Sex	-.439	.189	.189	13.714	<.001
[2]BMI	-.051	.191	.002	.187	.667
Midposterior Corpus Callosum	β	R^2	ΔR^2	ΔF	Sig. ΔF
[1]BMI	-.174	.030	.030	1.584	.214
Posterior Corpus Callosum	β	R^2	ΔR^2	ΔF	Sig. ΔF
[1]Education	.292	.086	.086	4.809	.033
[2]BMI	-.066	.091	.005	.241	.626

Superscript denotes the regression step number into which each variable was entered
*BMI significant at $p < .05$

Table 3. Hierarchical regression results for cognitive test scores

Executive Function		β	R^2	ΔR^2	ΔF	Sig. ΔF
Trails B	[1]Age	.219	.122	.122	3.817	.028
	[1]Pulse Pressure	.203				
	[2]BMI	-.049	.130	.008	.535	.468
DKEFS #4	[1]Age	.339	.127	.127	8.127	.006
	[2]BMI	.148	.148	.021	1.396	.243
Letter Number	[1]Age	-.208	.048	.048	2.894	.094
	[2]BMI	-.079	.054	.006	.371	.545

Processing Speed		β	R^2	ΔR^2	ΔF	Sig. ΔF
Coding	[1]Age	-.500	.249	.249	19.536	<.001
	[2]BMI	.009	.249	.000	.006	.941
Trails A	[1]Age	.305	.130	.130	4.260	.019
	[1]Pulse Pressure	.102				
	[2]BMI	-.042	.132	.002	.111	.740
DKEFS #1	[1]Age	.461	.243	.243	9.141	<.001
	[1]Pulse Pressure	.030				
	[2]BMI	.093	.251	.008	.628	.431

Memory		β	R^2	ΔR^2	ΔF	Sig. ΔF
List Learning	[1]Age	-.131	.118	.118	3.883	.026
	[1]Sex	.286				
	[2]BMI	-.039	.120	.002	.094	.760
Story Memory	[1]Pulse Pressure	-.264	.061	.061	3.825	.055
	[2]BMI	.094	.069	.008	.527	.471
List Recall	[1]BMI	-.024	.001	.001	.035	.852
Story Recall	[1]BMI	.040	.002	.002	.094	.760

Superscript denotes the regression step number into which each variable was entered

Table 4. Hierarchical regression results for secondary DTI indices

Superior Longitudinal Fasciculus		β	R^2	ΔR^2	ΔF	Sig. ΔF
AD	[1]Age	.262	.072	.072	4.687	.034
	[2]BMI	.054	.075	.003	.185	.668
RD	[1]Age	.310	.176	.176	6.322	.003
	[1]Sex	-.216				
	[2]BMI	.092	.185	.009	.594	.444
MD	[1]Age	.281	.147	.147	5.096	.009
	[1]Sex	-.202				
	[2]BMI	.073	.152	.005	.354	.554

Uncinate Fasciculus		β	R^2	ΔR^2	ΔF	Sig. ΔF
AD	[1]BMI*	-.291	.085	.085	5.458	.023
RD	[1]BMI	-.208	.043	.043	2.672	.107
MD	[1]BMI*	-.252	.063	.063	3.992	.050

Cingulate		β	R^2	ΔR^2	ΔF	Sig. ΔF
AD	[1]Sex	-.394	.152	.152	10.424	.002
	[2]BMI	-.046	.154	.002	.139	.710
RD	[1]Age	.283	.204	.204	7.284	.002
	[1]Sex	-.327				
	[2]BMI	-.085	.211	.007	.497	.484
MD	[1]Sex	-.394	.152	.52	10.379	.002
	[2]BMI	-.048	.154	.002	.153	.697

Midposterior Corpus Callosum		β	R^2	ΔR^2	ΔF	Sig. ΔF
AD	[1]Age	.308	.175	175	5.211	.009
	[1]Pulse Pressure	.067				
	[2]BMI	.258	.237	.062	3.869	.055
RD	[1]BMI*	.312	.098	.098	5.513	.023
MD	[1]Age	.222	.086	.086	4.793	.033
	[2]BMI*	.306	.175	.089	5.379	.025

Posterior Corpus Callosum		β	R^2	ΔR^2	ΔF	Sig. ΔF
AD	[1]BMI	.019	.000	.000	.019	.891
RD	[1]Age	.414	.270	.270	9.242	<.001
	[1]Education	-.277				
	[2]BMI	-.031	.271	.001	.059	.809
MD	[1]Age	.426	.177	.177	10.939	.002
	[2]BMI	-.027	.177	.000	.041	.839

Superscript denotes the regression step number into which each variable was entered
*BMI significant at $p < .05$ prior to FDR correction

Table 5. Partial correlations between FA and executive function controlling for age

Tract	Trails B	DKEFS #4	Letter Number
Superior Longitudinal Fasciculus	-.012	.035	.101
Uncinate Fasciculus	-.177	.131	.070
Cingulate	-.131	.194	.142
Midposterior Corpus Callosum	-.005	.103	-.276
Posterior Corpus Callosum	-.201	.187	-.077

Table 6. Partial correlations between FA and processing speed controlling for age

Tract	Coding	Trails A	DKEFS #1
Superior Longitudinal Fasciculus	.195	-.188	-.305*
Uncinate Fasciculus	.158	-.224	.133
Cingulate	.079	-.147	-.122
Midposterior Corpus Callosum	.107	-.277	.088
Posterior Corpus Callosum	.115	.080	.053

*significant at $p < .05$ prior to FDR correction

Table 7. Partial correlations between FA and memory controlling for age

Tract	List Learning	Story Memory	List Recall	Story Recall
Superior Longitudinal Fasciculus	-.201	.057	-.114	.202
Uncinate Fasciculus	-.135	-.065	-.134	-.091
Cingulate	-.061	.090	-.023	.107
Midposterior Corpus Callosum	-.321*	-.321*	-.025	-.192
Posterior Corpus Callosum	-.130	.102	.019	.160

*significant at $p < .05$ prior to FDR correction