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Diffusion Tensor Imaging and Neuropsychological Performance in Insulin Resistant Individuals

Elizabeth M. Lane
University of Missouri-St. Louis, emskc2@gmail.com

DIFFUSION TENSOR IMAGING AND NEUROPSYCHOLOGICAL PERFORMANCE IN INSULIN RESISTANT INDIVIDUALS

by

ELIZABETH M. LANE
M.A., Psychology, University of Missouri – Saint Louis, 2009
B.A., Psychology, University of Missouri – Saint Louis, 2007

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Advisory Committee

Robert H Paul, Ph.D.
Chairperson

Berit Brogaard, D.M.Sci, Ph.D.
Committee Member

Steve Bruce, Ph.D.
Committee Member

Michael Griffin, Ph.D.
Committee Member

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Abstract

The current study sought to understand the relationships between insulin resistance (IR) diffusion tensor imaging (DTI), and neuropsychological measures. It was hypothesized that IR would have a negative impact upon both DTI and neuropsychological tests. It was predicted that white matter in the uncinate fasciculus would be the most severely impacted, and that this would in turn affect processes of executive function and memory.

Aim: The purpose of the study was to determine the impact of IR on white matter brain integrity among cognitively normal older adults using DTI and neuropsychological test performance.

Background: The prevalence of IR has increased with the growing incidence of obesity and older aged adults. IR is associated with an increased risk for dementia, particularly vascular dementia. Studies specifically focused on the effects of IR on cognitive function have reported impairments in memory (Bruehl, Sweat, & Hassenstab, 2010), and executive function (Abbatecola, Paolisso, & Lamponi, 2004) among otherwise healthy individuals with clinically-defined IR. Neuroimaging studies have revealed that IR is related to the development of stroke in the subcortical white matter (Kario, Matsuo, Kobayashi, Hoshide, & Shimada, 2001), and increased atherosclerosis (Park & Kwon, 2008). While the exact mechanism of damage to the white matter is unknown, reduction of insulin transport in the brain (Segura et al., 2009) and atherosclerosis and arterial stiffness (Kario et al., 2001) have been suggested as possible causes of small vessel disease in IR. Despite the relationships between IR and brain integrity noted above, few studies have investigated the impact of IR on the brain by combining neuroimaging and comprehensive neuropsychological batteries among otherwise

healthy adults, and no studies have examined the microstructural integrity of the brain specific to IR using DTI.

Hypothesis: Older individuals with IR would exhibit compromised DTI metrics including fractional anisotropy (FA) and mean diffusivity (MD) in the uncinate fasciculus, and perform significantly worse on tests of memory and executive function.

Methods: Forty-six individuals between the ages of 53-79 years were evaluated for IR using drawn blood. The QUICKI algorithm was utilized to determine IR level. All individuals underwent a 3 Tesla DTI scan and a neuropsychological battery. MD and FA were calculated for the uncinate fasciculus.

Results: After controlling for education, IR status was significant for list learning ($p<.006$). However, IR was not significant for DTI scalar metrics of the uncinate fasciculus or measures of executive function.

Conclusion: These findings indicate IR has negative consequences for tasks that involve learning, but not with measures of executive function. Future studies are necessary to investigate the relation of IR to other white matter tracts in the brain.

Diffusion Tensor Imaging and Neuropsychological Performance in Insulin Resistant Individuals

Background and Significance

The population is rapidly aging and dementia is becoming an increasing public health concern. It is estimated that 16 million individuals in the U.S. will have dementia by the year 2050 (Hebert, Scherr, Bienias, Bennett, & Evans, 2003), and current treatment options are only minimally effective. Many of the pathological brain changes associated with abnormal cognitive aging occur years before the onset of dementia. Several of the risk factors for abnormal cognitive aging are modifiable and are associated with poor cardiovascular health, including obesity, type 2 diabetes mellitus (DM; Luchsinger, Tang, Stern, Shea, & Mayeux, 2001) and metabolic syndrome (MetS; Luchsinger, Tang, Shea, & Mayeux, 2004). Given that these factors are modifiable and pathological changes begin much earlier than the onset of dementia, it is imperative to identify early risk factors for abnormal cognitive aging.

The purpose of the study was to determine the impact of insulin resistance (IR) on brain integrity among older adults using diffusion tensor imaging (DTI) and neuropsychological performance. It was predicted that IR would be a metabolic biomarker for abnormalities on DTI and neuropsychological tests. Secondarily, the study examined the relation between the individual aspects of MetS and DTI scalar metrics to determine whether MetS would be a better correlate of DTI indices and cognitive performance rather than IR alone.

Insulin has many metabolic actions including stimulation of glucose uptake and suppression/regulation of hepatic glucose production and lipolysis (Ferrannini et al., 2007). IR is characterized by reduced cellular sensitivity to circulating insulin, and a failure of insulin to bind to insulin receptors or propagate a proper signal through the

insulin receptor embedded in the membrane of fat and muscle cells. Consequently, the glucose transporter GLUT-4 is not embedded into the cell membrane and glucose fails to enter the cells and hence accumulates in the blood. When glucose accumulates in the blood, the pancreas responds by producing more insulin as a protective mechanism against hyperglycemia and lipolysis; the end result is hyperinsulinemia. In the majority of participants with IR, pancreatic beta-cells (which produce insulin) fail and insulin secretion is unable to increase further, leading to metabolic decompensation, hyperglycemia, and DM (Sesti, 2006). Pancreatic beta-cell failure is manifested by development of impaired fasting glucose (blood glucose >100mg/dl), which increases risk of DM (DeFronzo, Ralph, Ferrannini, 1991).

The prevalence of IR is increasing with the growing incidence of obesity and older aged adults (Abbatecola et al., 2004). IR is etiologically linked to obesity (Ferrannini, 1997; Petersen & Shulman, 2006), and is a precursor to the development of DM (Sesti, 2006). Notably, IR has been linked to both cognitive deficits in executive function and memory (Abbatecola et al., 2004; Hassenstab, Sweat, Bruehl, & Convit, 2010), and atherosclerosis and white matter lesions on structural imaging (Kario et al., 2001; Park et al., 2008). The increasing prevalence of IR as a result of mounting levels of obesity and DM in industrialized nations makes the study of its consequences imperative and relevant. This is particularly true since IR is in most cases preventable and reversible (Balkau et al., 2008; Torjesen et al., 1997). It is also important to note that IR does not exist in isolation; it is intimately linked to MetS, which now affects almost half of people over the age of 60 (Segura et al., 2009). MetS represents a cluster of risk factors for cardiovascular disease (CVD) and DM. Currently, the most updated criteria to define MetS are from the harmonization effort between the International Diabetes Federation, National Heart, Lung, and Blood Institute, American

Heart Association, World Heart Federation, International Atherosclerosis Society, and the International Association for the Study of Obesity developed in 2009 (Alberti et al., 2009). These criteria state that 3 out of the 5 following must be present for a diagnosis of MetS: 1) abdominal obesity: waist circumference >102cm in males and >88cm in females; 2) triglycerides: ≥150 mg/dl; 3) HDL cholesterol: <40 mg/dl in males and <50 mg/dl in females; 4) blood pressure: ≥130/85 mmHg; and/or 5) fasting glucose: ≥100 mg/dl.

Insulin is present in the brain. Insulin enters the brain through insulin receptor-mediated active transport across the blood-brain-barrier. In addition to brain glucose utilization, insulin is also involved in neuroendocrine, metabolic, neurotropic, and neuromodulatory activities (Erol, 2008). Insulin receptors are located in the hippocampus, olfactory bulb, hypothalamus, amygdala, septum, substantia nigra, basal ganglia, and cerebral cortex including the frontal lobe (Watson & Craft, 2006). Many studies have illustrated the importance of insulin in normal cognitive function, particularly in the areas of memory (Bruehl et al., 2010; Convit, Wolf, Tarshish, & de Leon, 2003) and executive function (Abbatecola et al., 2004; Hassenstab et al., 2010). While the brain produces a modest amount of insulin, the majority of the insulin in the brain originates in the periphery and passes into the brain (Banks, 2004).

Impaired insulin in the brain is associated with increased production of amyloid beta and tau proteins in cerebrospinal fluid (Cole & Frautschy, 2007; Watson, Peskind, & Asthana, 2003), oxidative stress, and mitochondrial dysfunction (Erol, 2008). IR is also associated with arterial stiffness, placing individuals at increased risk for CVD (Stehouwer, Henry, & Ferreira, 2008). Hyperinsulinemia and even mild hyperglycemia are independent risk factors for silent stroke on magnetic resonance imaging (MRI) for individuals with impaired fasting glucose (Kwon et al., 2006).

IR and DM increase the risk of both Alzheimer's disease and vascular dementia (VaD). IR is a precursor to the development of DM. The risk of dementia is particularly high in individuals with IR and carriers of APOE4 alleles (Craft et al., 2003; Irie et al., 2008; Luchsinger, 2008). Studies have also discovered that individuals with DM have higher incidences of large artery disease (Kim, Lee, Kang, Yoon, & Roh, 2008) and deep white matter lesions (Manschot et al., 2007). IR independent of diabetes is also a risk factor for dementia (Pasquier, Boulogne, Leys, & Fontaine, 2006). A large population-based study reported that individuals with IR in the absence of DM had a greater risk for subcortical VaD (Geroldi, Frisoni, & Paolisso, 2005). Additionally, a longitudinal study of healthy middle-aged individuals reported that individuals with IR at 50 years of age were more likely to later develop VaD (Rönnemaa et al., 2008).

Few studies have examined the impact of IR on cognitive function. IR is a major component of MetS and studies of the latter report an increased prevalence of cognitive deficits among individuals with the condition (Dik et al., 2007). Studies specifically focused on the effects of IR on cognitive function have reported impairments in memory (Bruehl et al., 2010) and executive function (Abbatecola et al., 2004) among otherwise healthy individuals with clinically-defined IR. Neuroimaging studies have revealed that IR is related to the development of stroke in the subcortical white matter (Kario et al., 2001) and increased atherosclerosis (Park et al., 2008). While the exact mechanism of damage to the white matter is unknown, reduction of insulin transport in the brain (Segura et al., 2009), atherosclerosis and arterial stiffness (Kario et al., 2001) have been suggested as possible causes of small vessel disease in IR. Despite the relationships between IR and brain integrity noted above, few studies have investigated the impact of IR on the brain by combining neuroimaging and neuropsychological batteries among otherwise healthy adults. Several studies have investigated the link

between cognitive deficits and MetS (Petersen & Shulman, 2006; Sesti, 2006), but few have explored the specific impact of IR on the brain even though IR has a pathogenic role in MetS. The present study examined the microstructural integrity of the brain specific to IR using DTI in conjunction with neuropsychological tests.

Results from Di Bonito et al. (2007) indicate that IR is predictive of impaired performance on the Mini Mental State Exam (MMSE), a test of general cognitive function. Additionally, when the different aspects of MetS were entered into a regression analysis, only IR and age remained significant predictors of cognitive decline on the MMSE. IR has also been associated with worse performance on a measure of executive function (i.e., Trail Making Test; Abbatecola et al., 2004). Other studies have indicated that IR is associated with impaired memory performance (Bruehl et al., 2010; Hassenstab et al., 2010), and hippocampal atrophy in cognitively normal elderly (Convit et al., 2003) and in rats (Stranahan et al., 2008). Additionally, IR increases the risk of cognitive impairment associated with the disease in individuals with HIV (Valcour et al., 2006). These studies clearly demonstrate a relationship between IR and deficits in cognitive function. However, previous studies have used incomplete batteries for assessment of cognitive function and none were examined in the context of DTI indices of white matter integrity. The current study aimed to clarify the relation of IR to neuropsychological function by providing information about the specific role of IR to white matter integrity and neuropsychological performance. This study integrated novel and sensitive neuroimaging measures of white matter integrity and neuropsychological performance to characterize the relationships between IR and brain integrity.

Few studies have examined the microstructural integrity of the brain on DTI among otherwise healthy individuals with IR. DTI is a method of MRI that measures the anisotropic movement of water diffusion along brain fibers, providing information

about the integrity of the microstructure of the nerve tracts. Because the myelinated axons of healthy neurons are linear, water diffuses more quickly along the length of axons than it does across the width of the axons. Water will diffuse in a linear matter along healthy neuronal fibers, whereas it the anisotropic diffusion will increase when a fiber tract has been damaged. MD measures the rate of diffusion and FA measures the degree of anisotropy providing information about the directionality of tracts. Studies across multiple disease states indicate that DTI indices are more sensitive to white matter neuropathology than standard volumetric MRI techniques (Basser & Pierpaoli, 2011; Conturo et al., 1999; Xu et al., 2010).

A study among individuals with DM revealed that increased IR correlates with reductions in FA (Yau et al., 2009). Another study that investigated the impact of MetS revealed significantly lower FA and apparent diffusion coefficient in the uncinate fasciculus, corpus callosum, and longitudinal fasciculus in older individuals with MetS versus healthy individuals with no apparent CVD risks (Segura et al., 2009). Relatedly, studies using structural MRI have reported subcortical white matter lesions specific to individuals with IR (Kario et al., 2001). While the exact mechanism of damage to the white matter is unknown, reduction of insulin transport in the brain (Segura et al., 2009) and atherosclerosis and arterial stiffness (Kario et al., 2001) have been suggested as possible causes of small vessel disease associated with IR. There is an association with IR and the white matter integrity of the brain, however, this relationship needs to be investigated more deeply in order to determine whether IR plays a significant role in white matter damage among otherwise healthy individuals.

In order to compare results with previous studies that have investigated the impact of MetS on DTI (Segura et al., 2009), the uncinate fasciculus was included as the region of interest in the primary analysis for the current study. The uncinate

fasciculus is a white matter tract that connects the orbital gyrus in the frontal lobe with the anterior portion of the temporal lobe. The tract also contains cholinergic fibers from the basal nucleus of Meynert. The uncinate fasciculus is believed to play a role in memory performance and decision making (Sasson, Doniger, Pasternak, & Assaf, 2010). Damage to this area has been implicated in individuals with Alzheimer's disease (Kiuchi, Morikawa, Taoka, & Nagashima, 2009; Morikawa et al., 2009) and mild cognitive impairment (Kiuchi et al., 2009). It was therefore hypothesized that this white matter tract would be preferentially impacted by IR, and DTI metrics of tract integrity within the uncinate fasciculus would correlate with poorer performance on tests of memory and executive function.

Summary

The current study integrated IR, cognitive function, and DTI. IR is becoming increasingly common due to rising obesity rates and number of individuals over the age of 60. Both age and obesity are factors known to increase the risk for IR and CVD. Studies suggest that individuals with DM experience deficits in memory and executive function, as well as being more likely to become demented later in life. While IR is pathologically related to DM, there is evidence pointing towards earlier consequences in cognitive function and later life risks for dementia due to IR. If in fact IR does impact the brain before an individual reaches the stage of DM, then it is important to investigate the specific role of IR since it is not only preventable, but also reversible. As of yet, few studies have investigated the role of IR and cognitive function relating to measurements of DTI; the current study investigated these relations.

Approach

The present study investigated the unique contribution of IR on the brain as assessed utilizing DTI and neuropsychological tests. A serum measure of IR was

added to the final year of an existing longitudinal study investigating microstructural brain integrity, genetic markers of vascular health and inflammation, and neuropsychological performance among otherwise healthy older adults (the parent study did not include any focus on IR). The blood draw was taken within a month of the DTI scan and neuropsychological test administration. Twenty-four individuals with IR were compared to 22 individuals without IR on DTI and neuropsychological tests. It was predicted that individuals with IR would exhibit compromised subcortical white matter integrity of the uncinate fasciculus on DTI and perform significantly worse on tests of executive function and memory compared to those without IR.

Research Design Considerations

An important design consideration focused on whether there would be a sufficient number of individuals with IR in the parent study. Previous reports have estimated that approximately 50% of individuals will eventually become IR in their lifetime (Eddy, Schlessinger, Kahn, Peskin, & Schiebinger, 2009). Additionally, these numbers increase as individuals age (Abbatecola et al., 2004; Stolk, Breteler, & Ott, 1997). Individuals in the parent study are believed to be representative of the population; therefore, similar numbers of IR were expected in this sample. To provide more confidence, health history information was examined from the baseline visit of the parent study to determine the frequency of risk factors for IR. The preliminary data indicated that there were sufficient numbers of individuals in the sample that would be IR. Specifically, 35% of the sample had high cholesterol or was treated for high cholesterol, 35% had high blood pressure or was being treated for high blood pressure, and 67% was overweight or obese. These numbers are nearly identical to the numbers in other studies (Ford & Giles, 2003). Based on these data, it was believed that there

would be an adequate number of individuals with IR and that the sample is representative of the population.

A second design consideration was the decision to investigate IR independently rather than all components of MetS as a whole. It appears that IR is present in the majority of individuals with MetS (Bonora et al., 1998). When examined independently from other risk factors for CVD, IR is the most important single factor in predicting cardiovascular events (Eddy et al., 2009; Zavaroni et al., 1989). It can also be present when other components of MetS are absent, such as normal glycaemia (Bonora et al., 1998; Zavaroni et al., 1989). Additionally, several studies have shown that IR plays an independent role in cognitive function (Abbatecola et al., 2004; Bruehl et al., 2010; Hassenstab et al., 2010; Stolk et al., 1997). Based on these factors, it was determined that IR may be a unique contributing factor to changes in the brain and cognitive status. As such, IR served as an independent critical variable in primary analyses in the present study while MetS was examined in secondary analyses.

The final design consideration focused on the choice of the IR test to be used for the proposed study. The hyperinsulinemic euglycemic glucose clamp is considered to be the gold standard for testing IR (Katz et al., 2000); however, this method is time consuming, expensive, and invasive and is therefore impractical to perform in the proposed study. In response to IR, plasma glucose and insulin progressively rise, and an increase in either of these parameters is suggestive of IR. A variety of methods take advantage of this relationship to quantify IR, including homeostasis model assessment and the Quantitative Insulin Sensitivity Check Index (QUICKI method). The QUICKI method uses a ratio of fasting blood glucose and insulin to derive an index of insulin sensitivity. Insulin sensitivity = 1/ [log fasting insulin level (micro units per milliliter)] + [log fasting glucose level (milligrams per deciliter)] (Katz et al., 2000). The QUICKI was

elected for use in this study because it is easy to perform, requires only a single blood draw, and is inexpensive. Furthermore, this method is highly correlated with the gold standard euglycemic hyperinsulin clamp method (r = .80-.90; Muniyappa & Quon, 2007).

Participants

A total of 46 cognitively normal older adults individuals were included in the present study (mean age = 64 years; 74% female). Table 1 includes summary details for the study sample. Thirty-four of the individuals in the study were recruited from an ongoing longitudinal study of cognitive aging. DTI data and neuropsychological evaluations were utilized from the final year of the longitudinal study with the addition of a fasting blood draw. Twelve additional participants were recruited using the same methods used in the longitudinal study. Protocol administration to the new recruits was identical to the protocol administration for the individuals from the final year of the longitudinal study. T-tests were performed to compare the two cohorts on demographic factors and dependent variables to determine if they differed on any of the measures. The newly recruited individuals had a significantly higher BMI (M = 30.59 vs. 26.37), were younger (M = 58.42 vs. 65.97), and there were more females than the original cohort (91.7% female vs. 67.6% female). However, the groups did not differ in education level or on the QUICKI measurement dependent variable. Overall, the IR group included 24 individuals (71% female) and the non-IR group was comprised of 22 individuals (77%). Sample details for the two groups are summarized in Table 2.

The study protocol was approved by the University of Missouri – Saint Louis Internal Review Board prior to commencement of data collection. Written informed consent was obtained from all individuals before participation in the study.

Inclusion / Exclusion

Inclusion: 1) age over 50 years. Exclusion: 1) any history of alcohol or drug abuse according to DSM-IV criteria; 2) psychiatric illnesses that would confound the analysis of the study, including current severe depression, bipolar, schizophrenia, personality disorders; 3) confounding neurological medical conditions, such as Parkinson's disease, progressed stages of eating disorders, multiple sclerosis, thyroid disease, diabetes, epilepsy, stroke; 4) genetic disorders, such as Huntington's disease; 5) blood borne illnesses (HIV, Hepatitis); 6) cancer in the last 10 years or a history of radiation treatment; 7) head injury defined as LOC >5 minutes and post-traumatic amnesia; 8) history of learning disabilities; 9) contraindications for MRI (ferrous metallic implants, claustrophobia, body size too large to fit in the scanner); 10) uncorrected impairment in hearing, vision, or hand movement; 11) diagnosis of dementia; 12) developmental disabilities; and, 13) history of gastric bypass surgery.

Physiological Measures

IR was measured using the QUICKI method. Fasting levels of glucose and insulin were assessed through a standard blood draw and lab analyses after fasting for at least 8 hours. QUICKI is a fasting blood draw algorithm: QUICKI = 1/ (log insulin + log glucose in mg/dL). Individuals were considered IR when their QUICKI index was below 0.35 (Katz et al., 2000). Blood was collected using the coordinating services at the University Health Services at the University of Missouri – St. Louis. Due to the fact that this was a fasting blood draw, cognitive testing was performed on a separate day or after the participant had eaten a meal to ensure validity of the cognitive data.

Total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, HbA1c, and C-reactive protein were also collected with the serum samples and were analyzed using standard lab methods. These measures were investigated as part of the secondary analyses.

Other physiological measures for secondary analyses included other components of MetS, such as, 1) average blood pressure taken 3 times during a study visit; 2) waist circumference measured directly above the iliac crest of the upper hip bone; 3) body mass index using measured height and weight; and 4) hip circumference measured at the greatest protrusion.

Neuropsychological Evaluation

The neuropsychological battery was designed to be focused on executive function and memory as these domains are known to be sensitive to IR, as well as cognitive functions subserved by the uncinate fasciculus. The uncinate fasciculus represented the region of interest for the DTI analysis. Additionally, a complete battery encompassing all cognitive domains was utilized to provide secondary data for exploratory analyses.

Executive Function was assessed using Trail Making B, Letter Number Sequencing from the Wechsler Adult Intelligence Scale-IV (WAIS-IV), Color-Word Interference from the Delis Kaplan Executive Function System (DKEFS), Paced Auditory Serial Addition Test (PASAT), FAS Verbal Fluency, and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Figure Copy. These measures are described below.

Trail Making B measures cognitive flexibility. The participant was presented with a sheet of paper with circles containing numbers and letters. The participant must connect the numbers and letters in an alternating ascending order as quickly as possible. A practice trial was presented before the actual timed task. Time to completion was the outcome measure.

Letter Number Sequencing from the WAIS-IV is a measure of attention and working memory. The participant was read a string of numbers and letters mixed in

random order. They were required to put the numbers and letters in ascending order, with numbers first in numerical order followed by the letters in alphabetical order. Total correct was the dependent measure.

The DKEFS Color-Word Interference test is a test of response inhibition. There are 4 trials overall, but only Trial 3 was used for the present study as Trial 3 is the primary measure of response inhibition. The participant was presented with a page with color names printed in different color ink. The participant was required to name the color of ink the letters are printed in, and not read the word. Time to completion was the outcome variable on each trial.

The PASAT is an auditory test of attention, rate of information processing, and working memory. The primary objective is to add a newly presented auditory number to a previously presented auditory number. There are 4 trials with 50 numbers each that are played aloud from a recording to the participant. Each trial increases in difficulty by shortening the latency between the previously presented auditory number and the new auditory number. The participant was asked to speak all answers aloud. The primary outcome variable was percent of the number correct divided by the number presented.

FAS Verbal Fluency is a test of lexical fluency. The participant was given 60 seconds to generate as many words as they could that began with each of the letters “f”, “a”, and “s”. The participant must name only words that begin with the letter presented to them, with the exclusion of words that are names of people, place, or numbers. The total number of words generated across all three trials was the primary outcome measure.

Visuospatial ability and planning will be tested using Figure Copy with total score as the outcome variable. For this task, the participant was presented with a complex figure that they were required to copy to a sheet of paper while viewing the figure.

Memory was assessed using subtests from the RBANS (Randolph, 1998). List Learning, Story Memory, List Recall, Story Recall, Figure Recall, and List Recognition were included as part of the memory analyses.

Immediate recall was tested using List Learning with number remembered as the outcome variable. Participants were presented 4 times with a list of 10 words that they repeated immediately following the administration of the list of words.

Semantic memory was tested using Story Memory with total correct as the outcome variable. A short story was presented to the participant and they were required to repeat details of the story as accurately as possible. Two trials were completed and accuracy across both recall trials served as the dependent variable.

Long-term memory was tested using List Recall with total correct as the outcome variable. List recall required the participant to recall the words from the list learning trial after a delay with several nonverbal tests administered in the interval.

Story Recall measures semantic memory with total score as the dependent measure. It requires the participant to recall the story that was read to them earlier, with as much detail as possible. Several distractor tasks that do not interfere with language are performed in the interval. The primary outcome measure was number of correct information.

Figure Recall tests visuospatial memory and planning. After a delay with several tests in the interval, participants were asked to draw as much of the previously presented figure as they could remember. Total score was the outcome variable.

Recognition was assessed using List Recognition with total score as the dependent variable. Participants were presented with 20 words that may or may not have been on the list learning portion, and they were required to answer either “yes” or “no” about whether those words were on the list.

Supplemental Battery. The executive and memory tests described above were analyzed to address the specific aims of the study. The supplemental battery was administered after the core battery and was used for exploratory analyses. The supplemental battery includes the RBANS, Mini Mental State Exam (MMSE), Montreal Cognitive Assessment test (MoCA), Grooved Pegboard test, and Trail Making A. These tests are described briefly below.

The RBANS is a 30 minute battery that encompasses primary domains of cognitive function. The primary aims of the study only utilize the memory components of the battery, but the entire test was given for the study. Other secondary measures for the study within the RBANS battery included Line Orientation, Semantic Fluency, Naming, Coding, and Digit Span. Line Orientation is a visuospatial task that presents the participant with an array of lines from a point of origin and 2 target lines that they must identify with the lines in the array. The dependent variable was the number of lines correct. Semantic Fluency is a language task that requires the participant to provide as many words as possible that fall under a semantic category in 60 seconds. The number of appropriate words was the dependent variable. Picture Naming is a language task that presents the participant with 10 pictures that they must then name. Correct answers on the 10 items were the dependent variable. Coding is a visual processing and attention task that requires the participant to fill in numbers that match corresponding shapes from a key during a 90 second interval. The dependent variable was number completed correctly within the time period. Finally, Digit Span is an attention and working memory test. The participant is presented with a string of numbers that they must repeat back in the same order. The dependent variable was the number correct.

The MMSE is a brief measure of global cognitive function. The MMSE is widely used as a screening tool for dementia. The MMSE briefly examines several areas of function, including orientation, naming, learning, memory, working memory, semantic ability, visuospatial ability, and repetition. The dependent variable was total score out of possible points.

The MoCA is a recently developed screen for general cognitive impairment (Nasreddine et al., 2005). The test consists of 13 tasks organized into 8 cognitive domains including Visuospatial/Executive Function, Naming, Memory, Attention, Language, Abstraction, Delayed Recall, and Orientation. The dependent variable was total score out of 30 possible points.

The Grooved Peg Board test is a test of fine motor skills. The participant was required to fit pegs into a board that has holes for the pegs with the notches in different directions. Both hands are tested, one at a time, with the dominant hand being tested first and the nondominant hand tested second. Time to completion for each hand was the dependent variable.

The Trail Making A is a test of attention and visual scanning. The participant was presented with a page with numbers in a random order and they are required to draw a continuous line connecting the lowest number to the highest number as quickly as possible. Time to completion was the dependent variable.

DTI

Consistent with the ongoing longitudinal study for which most participants were recruited, all neuroimaging took place at Washington University Mallinckrodt Institute of Radiology. A Siemens 3T Magnetom Allegra head-only scanner was used for all scans (Siemens Healthcare, Erlangen, Germany). The Allegra is capable of gradient speeds

with a slew rate of up to 400 T/m/ms for a maximum effective amplitude of 40 mT/m on all 3 axes. Participants were in the scanner for less than 1 hour.

Axial DTI images were collected with a custom single-shot echo-planar tensor-encoded pulse sequence. The TE=86.2 ms and TR=7.82 s, with 64 contiguous 2.0 mm slices for each contrast. There was a 128 x 128 acquisition matrix with a 256 x 256 FOV (isotropic 2.0 x 2.0 2.0 mm voxels). Diffusion gradients were applied in 31 non-collinear diffusion-encoded directions with a b magnitude of 996 s/mm^2, and including 24 main directions. The scan was repeated twice in order to average the signal, equaling 72 total acquisitions.

FSL Flirt (mutual information metric; Jenkinson, Bannister, Brady, & Smith, 2002) was used to register each participant's DWI images to the B_0 image for motion correction. Tensors and FA values were calculated with Diffusion Toolkit's dti_recon (Wang, Benner, Sorensen, & Wedden, 2007) from the DWIs, b values, and diffusion-encoding vectors. Using one seed per voxel, reconstructions of continuous white matter fiber bundles were created from the tensor field using a continuous tracking (FACT) algorithm (Mori, Crain, Chacko, & Van Zijl, 1999). Tracts were stopped when the FA threshold reached ≤0.15 or the step angle was ≥35 degrees. Additionally, tracts that were shorter than 10 mm long were excluded from the analyses.

Scalar metrics of DTI (FA and MD) in the white matter were recorded and computed from the diffusion tensor. Right and left FA and MD for the uncinate fasciculus was included for primary analyses in order to contrast results obtained from the proposed study with the extant literature on DTI abnormalities associated with MetS (e.g., Segura et al., 2009).

Neuroimaging quality control Weekly quality control scans to assess coil sensitivity and long-term stability were performed. Participant head movement was

restrained using specialized foam pads and tape, and images were visually inspected for motion and/or other artifacts after each sequence was run. DTI quality control was supported using the vacuum-filled head stabilizer, and by examining the unwarping procedure to identify images where registration detects misalignment larger than 2mm in any direction.

Statistical Analysis

The primary aims of the study were to compare individuals with IR and those with no evidence of IR on DTI of the uncinate fasciculus and neuropsychological tests, and to determine if these factors are related. The independent variables for these measurements were an IR group versus a non-IR group. The dependent variables were FA and MD of the uncinate fasciculus on DTI, and raw scores from the neuropsychological tests.

Aim 1. Compare the microstructural integrity of the brain on DTI in individuals with IR to those with no evidence of IR in an otherwise healthy older population of individuals.

Demographic factors, such as age, sex, and education, were examined using t-tests to determine if there was a significant difference between the IR groups. The IR group had significantly lower education (M = 14.88 years) than the non-IR group (M = 16.18 years). Therefore, education was included as a covariate in a MANCOVA analysis to determine if IR individuals had compromised MD and FA in the uncinate fasciculus compared to those without IR.

Aim 2. Determine if individuals with IR perform worse on tests of memory and executive function than those with no evidence of IR in an older population of individuals.

As above, education was included as a covariate in these analyses since education differed between groups. Separate MANCOVAs were computed to contrast the two groups on neuropsychological tests of memory and executive function. Executive measures (FAS, Trails B, DKEFS Color Word, PASAT) were included as dependent variables in the first MANCOVA to determine if the IR group performed differently than the non-IR group. Similarly, performances on the RBANS memory measures were included as dependent variable in a separate MANCOVA with group assignment of IR status entered as the independent variables.

Aim 3. Determine whether IR mediates the relationship between DTI indices and neuropsychological performance in this population.

Since Aim 1 did not reveal any significant results, Aim 3 was not pursued in this context. Additionally, the secondary analyses did not reveal significant findings to pursue this aim.

Secondary Analysis. The analyses for aims 1 and 2 were repeated comparing individuals that met the criteria for MetS versus those who did not on cognitive tests and DTI metrics of the uncinate fasciculus. Additionally, the analyses were repeated for each of the individual variables of MetS, including waist circumference, triglycerides, HDL cholesterol, blood pressure, and glucose, in order to investigate if other MetS-related variables had an impact on FA and MD in the uncinate fasciculus and tests of memory and executive function. Groups were assigned according to the established MetS cut-offs, and used as dependent variables. Analyses were not performed for the positive triglyceride groups or the positive HDL groups, because each of these samples only had 3 individuals with high enough levels to qualify for the cut-off. FA and MD of the uncinate fasciculus and cognitive tests of memory and executive function were the independent variables. Demographic variables were assessed as covariates, including

age, education, gender, and race. The only demographic variable that was significant for the MetS variables was the relation between glucose and age ($r^2 = 0.31$; $p = 0.04$).

The False Discovery Rate (FDR) method was used on all primary analyses to control for multiple comparisons that included 104 comparisons between and within groups (Benjamini & Hochberg, 1995). After the correction, the significance cut-off was set at $p < 0.006$.

Finally, exploratory correlation analyses were conducted in order to investigate the relation of the metabolic, imaging, and cognitive variables to one another. Scatter plots were utilized to assess for outliers prior to analysis.

Power Analysis

Power was based on work conducted by Segura et al. (2009). In this study FA was examined among 19 older adults with MetS ranging in age from 50-80. The effect sizes for the DTI indices were medium ($r^2 = 0.54$ for the right uncinate fasciculus, $r^2 = 0.59$ for the left uncinate fasciculus). Further, the t values comparing individuals with and without MetS were highly significant (t's = 3.8, 4.3). Based on these data, it was anticipated that inclusion of 25 individuals per group in the current study would provide power of at least .90 to detect significant differences in DTI indices. Aim 2 was not as well powered as the first aim, and was based on previous studies of individuals diagnosed with IR. Bruehl et al. (2010) previously reported a significant impact of IR on memory and executive function with a larger sample (IR = 38, non-IR = 54) than what was included for the current study (IR = 24, non-IR = 22).

Results

Aim 1. MANCOVA was used to investigate the first aim of the study to determine whether individuals with IR differed from individuals without IR on MD and FA DTI metrics of the uncinate fasciculus. Box's Test of Equality of Covariance Matrices was

used to assess the assumption that covariance matrices were equal across the dependent variable groups, and was found to be non-significant ($p = 0.45$). Additionally, Levene's Test of Equality of Error Variances was not significant for any of the FA or MD measures. Based on the outcome of the two statistics, it was determined that all assumptions of MANCOVA had been met. Wilk's Lambda failed to show a significant difference between IR groups on DTI measures of FA and MD in the uncinate fasciculus ($F(4,36) = 0.89$; $p = 0.481$). The test of between subject effects also showed no significant differences between the groups on the individual metrics (see Table 3).

Aim 2. MANCOVA was used to determine whether there was a difference between IR groups on measures of memory and executive function. The first MANCOVA compared the IR groups on tests of executive function. There was no statistically significant difference on executive function as evidenced by Wilk's Lambda ($F(7,24) = 1.11$; $p = 0.391$). There were no significant results for Levene's Test of Equality of Error Variances, so the uncorrected model was used for between subject effects. There were no significant differences between IR and non-IR on any of the individual tests of executive function (see Table 4).

The second MANCOVA investigated the difference between IR and non-IR individuals on tests of memory. All assumptions were met for the multivariate statistic, but Wilk's Lambda failed to be significant between the groups after the FDR was applied ($F(6,37) = 2.77$; $p = 0.025$). Levene's Test of Equality of Error Variances was significant for RBANS List Recognition, and the corrected model was assessed for this test when looking at between subjects effects. The Levene's Test was not significant for the other memory measures, and therefore, the uncorrected model was used for these tests of between subject effects. Individuals with IR performed worse than individuals without IR on the RBANS List Learning test ($F(1,45) = 8.41$; $p = 0.006$; see Table 5).

Secondary Aims.

Of the 46 individuals in the study, 15 met the criteria for having MetS (i.e., positive for meeting 3 or more of the 5 conditions of the syndrome). Of note, all of the individuals with MetS were also IR. Details for this sample are in Table 6.

Secondary Aim 1. A MANOVA was used to determine if there was a significant difference in FA and MD DTI measures of the uncinate fasciculus between individuals with and without MetS. Wilk's Lambda for the MANOVA did not reveal a significant overall difference between the two groups ($F(4,37) = 1.54$; $p = 0.212$). Additionally, none of the individual factors survived the FDR correction (see Table 7).

Further analyses were conducted to explore the individual relations between the variables that make up MetS. FA and MD in the uncinate fasciculus were compared between individuals who met the criteria for high blood pressure and those who did not meet the criteria. Box's Test of Equality of Covariance Matrices was significant ($p = 0.05$), and Pillai's Trace was used as the omnibus test in the MANOVA. The results between the groups did not reveal a significant relation for the DTI measures ($F4,37) = 1.68$; $p = 0.175$). Additionally, none of the between subjects factors survived the FDR correction (see Table 8).

The MANOVAs comparing DTI measures in the uncinate fasciculus for glucose or waist circumference were not significantly different. Between subject tests also did not show any significant differences on the individual measures (see Table 8).

Secondary Aim 2. Separate MANOVAs were conducted to determine if individuals with MetS differed from individuals without MetS on tests of memory and executive function. Wilk's Lambda did not show a significant difference between the groups on measures of executive function ($F(7,25) = 1.67$; $p = 0.163$). Additionally,

none of the individual tests survived the FDR correction for multiple comparisons (see Table 9).

Wilk's Lambda approached the threshold for significance at the corrected FDR level on memory tests between individuals between individuals with MetS and those without MetS ($F(6,38) = 3.44$; $p = 0.008$; see Table 10). Levene's Test of Equality of Error Variances was significant for RBANS List Recognition, and therefore the corrected model was used in the between subjects assessment for this test. RBANS List Learning was the only memory measure that was significantly different between the groups, with individuals with MetS performing worse than those without MetS ($F(1,45) = 9.64$; $p = 0.003$).

Separate MANOVAs were conducted to determine if there were differences between individuals on tests of executive function on the individual criteria for MetS. Wilk's Lambda was not significant for individuals with high blood pressure compared to those without on tests of executive function ($F(7,25) = 0.76$, $p = 0.625$). Additionally, none of the individual comparisons survived the FDR cut-off (see Table 11).

The MANOVA comparing individuals with high vs. normal glucose failed to show a significant difference on executive function measures between groups ($F(7,24) = 1.18$, $p = 0.353$). The between subjects effects indicated that individuals with high glucose approached the cut-off for significance for worse performance on the second trial of the PASAT compared to individuals with normal glucose levels ($F(1,33) = 7.77$; $p = 0.009$; see Table 11).

The MANOVA comparing executive function and waist circumference did not reveal any significant overall differences between groups ($F(7,25) = 0.99$; $p = 0.460$). Additionally, the between subject effects for each of the tests of executive function did

not reveal any significant difference between groups on the individual tests (see Table 11).

Separate MANOVAs were conducted to determine if there were differences between individuals on tests of memory on the individual criteria for MetS. A MANOVA was performed comparing individuals with high blood pressure to those without on memory measures. The Wilk's Lambda did not show a significant difference comparing blood pressure and memory measures ($F(6,38) = 1.57$, $p = 0.184$). Additionally, there were no significant differences between blood pressure groups on the individual memory measures (see Table 12).

A MANOVA was performed that compared individuals with high glucose to those with normal glucose level on tests of memory. All assumptions of normality were met and not violated according to Box's Test of Equality of Covariance Matrices and Levene's Test of Equality of Error Variances. Wilk's Lambda failed to show a significant difference between the two groups on the memory measures ($F(6,37) = 1.77$, $p = 0.133$). Levene's Test of Equality of Error Variances was significant for List Recognition, and therefore, the corrected model was used in the between subject effects. All other memory measures were in compliance of normality. Furthermore, there were no differences between groups on the individual memory tests (see Table 12.)

A MANOVA was performed comparing memory measures between individuals with larger waist circumference with those with lower waist circumference. Box's Test of Equality of Covariance Matrices was significant, so Pillai's Trace was used as the omnibus test. Pillai's Trace failed to show a significant difference between the waist circumference groups ($F(6,38) = 1.83$, $p = 0.119$). When investigating differences on the individual memory tests between groups, Levene's Test was significant for RBANS

List Recognition. Therefore, the corrected model was used for this particular memory test on the between subject effects. Levene's was not significant for the other memory measures, and the uncorrected statistics were utilized. Furthermore, the between subject comparisons for waist circumference and the individual memory measures did not reveal significant results after the FDR correction (see Table 12).

Tertiary Aims. There were several significant relations in the exploratory correlations between metabolic factors with cognitive and DTI variables. Table 13 is a correlation table with significant values for all metabolic factors related to FA for the major fiber tracts in the brain. Table 14 is a correlation table of significant values between metabolic factors and MD in the major fiber tracts in the brain. Table 15 displays the significant values between metabolic factors and the RBANS tests. Finally, Table 16 shows the significant values for metabolic factors and all other cognitive tests. Waist and hip circumference were most often associated with MD of the various tracts in the brain. Systolic and Diastolic blood pressure were most often associated with FA metrics of various white matter tracts.

Discussion

The primary aim of this study was to determine if individuals with IR have compromised brain white matter tracts and changes in cognitive function. The findings indicate that individuals with IR perform worse on a learning measure than individuals that are not IR, but there were no differences in performance on other memory or executive function measures specific to IR. Additionally, there were no significant differences between the groups on DTI integrity measures of the uncinate fasciculus, a white matter tract of the brain thought to play a role in memory function (Diehl et al., 2008). Secondary analyses of MetS and the various individual metabolic markers revealed additional significant relationships with tests of memory and executive function.

DTI Metrics

Findings from the current study do not support the initial aim of the study suggesting that individuals with IR would have reduced integrity of the uncinate fasciculus, as there were no differences between IR individuals and non-IR individuals. Previous studies have indicated reduced integrity of the uncinate fasciculus in individuals with MetS (Segura et al., 2010). These studies suggested that IR is the underlying driving factor in MetS, but this hypothesis has not been investigated independently in this context. The Segura et al. 2010 study did not differentiate between individual aspects of MetS, but rather used the syndrome as a whole to differentiate between groups and the relation to the uncinate fasciculus. We were unable to reproduce the Segura et al. 2010 results in the current study when investigating MetS as a syndrome. To further explore the relationship between MetS and the uncinate fasciculus, independent analyses were performed with each of the factors that are included in the diagnosis of MetS with the cutoff for each factor used to represent each group. However, none of the individual factors were significantly related to white matter integrity of the uncinate fasciculus.

To further classify the relation of the independent variables involved in MetS and their relation to the uncinate fasciculate, exploratory correlation analyses were performed allowing each factor to be treated as a continuous variable rather than having a cutoff. The secondary analyses indicated a medium-sized correlation between both fasting serum glucose and blood pressure with FA of both the right and left uncinate fasciculus. Furthermore, glucose had a medium-sized relation to compromised MD in the right and left uncinate fasciculus. These findings suggest the possibility that glucose or blood pressure could be related to MetS and white matter integrity in the uncinate fasciculus. Additionally, the cutoff scores used to classify an individual as having MetS

may not fully capture the underlying pathological process taking place, which may be much earlier than indicated. Longitudinal studies with larger sample sizes are necessary to confirm these findings, and determine if either glucose or blood pressure, or both factors together, are underlying the relation between metabolic factors and reduction in the integrity of the uncinate fasciculus. Additional studies are necessary to further classify the relation of IR to other white matter tracts in the brain.

Previous research indicates that there is an association of subcortical infarcts related to IR (Kario et al., 2001). Many of the long association fibers in the brain lie along the sensitive vascular watershed areas of the brain, including the cingulum, superior longitudinal fasciculus, and fronto-occipital fasciculus (Chui, 2007). It is possible that since IR is strongly related to vascular health, the long association fibers along the watershed areas may be preferentially impacted by an interaction between IR and small vessel disease in the brain. Exploratory correlation analyses revealed that the QUICKI was related to lower MD in the right cingulum, and therefore has a possible negative impact on this brain structure. However, FA in the temporal portion of the superior longitudinal fasciculus was higher as IR increased, indicating possibly reduced integrity of this tract due to IR. Further studies are needed in order to determine the exact relationship between IR and FA of the temporal region of the superior longitudinal fasciculus. Additionally, increased level of insulin showed a positive relationship with increased FA in the left cingulate gyrus and the right inferior longitudinal fasciculus. These findings are contradictory to what would be expected in individuals that are IR, and are perhaps spurious. A possible explanation is that increased levels of circulating insulin are compensating for the loss in insulin sensitivity. It is also possible that the peripheral measurements of circulating levels of insulin do not accurately reflect central levels of the hormone. Additionally, previous studies have reported differences between

central and peripheral levels of insulin due to loss of active transport of insulin across the blood brain barrier in IR individuals (Banks, 2004). Further studies are necessary to confirm these findings and determine whether central versus peripheral levels of insulin and insulin sensitivity relate to white matter integrity.

There were similar contradictory results for several other exploratory metabolic markers and DTI measures. Most notably, waist circumference and BMI had negative correlations with several of the MD measures of tract integrity, indicating that as these metabolic markers increased the integrity of the fiber tracts was improved. The tracts implicated were the anterior thalamic radiation, cingulate gyrus, superior longitudinal fasciculus in the temporal lobe, and the inferior longitudinal fasciculus. Additionally, these 2 measures were related to more MD measures than any of the other metabolic markers. High BMI and large waist circumference have consistently been shown to be related to CVD, DM, and increased mortality rates (Janssen, 2002). A possible explanation for the relationships in the current study is that the relation is not linear between disease burden and metabolic markers. Previous studies have indicated that BMI that is too low or too high is related to increases in mortality (Allison, Faith, Heo, & Kotler, 1997). Given that the sample of individuals used in the current study included a healthy group of older individuals, it is possible that the sample did not include individuals on the outlying extremes to explain the associations in the current study. Additionally, increased hip circumference was related to increased integrity in these same fiber tracts. This finding is not necessarily inconsistent with previous research indicating that increased hip circumference can actually be beneficial and protective, but additional confirmatory studies are necessary. Previous studies have reported a lower incidence of CVD and heart disease in individuals with larger hip circumference (Heitmann, Frederiksen, & Lissner, 2004). Future research with large samples that are

more representative of all older individuals will be necessary in order to determine the relation of BMI and waist circumference to white matter integrity.

In additional exploratory correlation analyses, blood pressure was related to FA in several white matter tracts. Increased blood pressure was related to lower FA integrity of the uncinate fasciculus, anterior thalamic radiation, and inferior fronto-occipital fasciculus. Previous research indicates that high blood pressure is associated with reduced microvascular function (Serne et al., 1999). Studies have also reported positive relationships between increased blood pressure positive and silent cerebral infarcts (Kario et al., 2001). Another study indicated that high blood pressure was related to cerebrovascular lesions (Bokura, Yamaguchi, Iijima, Nagai, & Oguro, 2008). Additionally, previous research has indicated that high blood pressure is associated with white matter hyperintensities, an indication of small vessel disease (Gunstad et al., 2005). High blood pressure may therefore have a negative impact on the white matter via small vessel disease, but confirmatory studies are necessary.

Interestingly, the exploratory analyses indicated that increased glucose was related to decreased integrity of the forceps minor on both FA and MD measurements. Previous studies have indicated that the forceps minor is impacted by age-related changes (Burzynska et al., 2010). These results indicate that increased glucose levels could perpetuate the aging effects seen in the forceps minor, however this relationship still remains uninvestigated. Future studies should focus on ascertaining the factors related to the integrity of the forceps minor.

Caution should be taken in the interpretation and conclusions drawn from the correlational associations in this study, as they were exploratory in nature. Further studies are necessary to confirm these findings. Additionally, limitations exist in tract based DTI measurements of white matter integrity, the first of which is crossing fibers of

different white matter tracts. FA measurement is particularly sensitive to the problem of crossing fibers, since reductions in FA may indicate fibers crossing rather than actual reductions in tract integrity (Jones, Knösche, & Turner, 2012). Additionally, in the present study white matter tracts of interest were derived with the use of a white matter map, and were not based solely on the individual's own anatomy. Therefore, more complex structures, such as the uncinate fasciculus, are not as easily derived and may contain error. Some of these factors may also account for the contradictory results between some of the metabolic factors and white matter tracts mentioned previously. Future studies employing methods such as diffusion spectrum imaging that can address these issues will be able to help clarify these relationships.

Cognitive Measures

IR individuals performed significantly worse on a verbal learning measure, when compared to individuals that were not IR. On average, IR individuals performed almost 3 points lower overall on the RBANS List Learning measure. This finding is consistent with previous studies that showed that IR is related to memory tests, including learning indices (Hassenstab et al., 2010). Previous studies have also reported differences between individuals with IR and those who are not IR on other memory measures such as Paragraph Recall and Delayed Recall (Awad, Gagnon, & Messier, 2004; Bruehl et al., 2010). The current study failed to reveal a significant relationship between IR status and other forms of memory. Additionally, the analyses comparing individuals with MetS to those without MetS maintained the same relation with List Learning while failing to show a relation to the other memory measures. These results suggest that insulin resistance may be an important factor in successful performance on list learning tasks.

Analysis of the individual metabolic biomarkers failed to indicate associations with memory performance. Previous studies have indicated that low HDL cholesterol is

related to decline in List Learning and Recall measures beginning as early as midlife (Singh-Manoux, Gimeno, Kivimaki, Brunner, & Marmot, 2008). The current sample contained a very small amount of individuals below the cutoff for what is considered to be low HDL (n = 3), and future studies will need to investigate a wider spectrum of HDL cholesterol in order to decipher the full relationship of HDL to memory measures. Low HDL has been linked to severity of AD (Merched, Xia, Visvikis, Serot, & Siest, 2000), as well as increased risk of stroke in the elderly, particularly if the individual has DM (Hayashi et al., 2009). Furthermore, studies indicate that IR and DM increase the risk for developing AD (Rönnemaa et al., 2008), a disease that has the hallmark feature of memory loss. Given that IR and the associated risk factors are modifiable, it may offer an opportunity to buffer the effects of memory decline and reduce risk of AD.

Additional exploratory correlation analyses of the memory measures and other metabolic markers revealed possible relationships between RBANS List Recognition and QUICKI, fasting glucose, and hip circumference. All three markers had a positive correlation with List Recognition, meaning that as the biomarker increased, so did performance on the List Recognition task. For fasting glucose, this relation counters what is commonly shown in other studies (Tournoy, Lee, & Pendleton, 2010). IR is not commonly associated with List Recognition in other studies, but is related to other types of memory (Hassenstab et al., 2010). The relation between larger hip circumference and better performance on the Recognition task is supported by previous research that suggests that a larger hip circumference may have metabolically protective features (Seidell, Pérusse, Després, & Bouchard, 2001). It should be noted that results related to the RBANS List Recognition task should be taken with caution. The sample was a group of older individuals with healthy cognitive function, and recognition tasks do not show age-related decline in previous studies (Craik & McDowd, 1987). Therefore, there

was a very low amount of variability in performance between individuals, and the measurement overall showed a ceiling effect of performance. Future studies should investigate these relations within samples that show variability and decline on List Recognition tasks in order to determine the significance of these relationships.

There were no detectable differences on executive function measures between IR and non-IR individuals in the study. Additionally, there were no differences between IR groups on the individual executive function measures. Previous studies have reported decreased performance on measures of executive function in IR (Abbatecola et al., 2004; Bruehl et al., 2010). It is possible that the current study did not have a sufficient number of individuals to detect differences between the IR groups on executive function measures. In an attempt to buffer the lack of power for this particular aim, the PASAT was added to the battery of measures. The PASAT has been shown in other populations with demyelinating diseases to be sensitive to abnormalities in the white matter tracts (Audoin et al., 2005). However, the analyses failed to detect differences even on the PASAT between IR groups. Additionally, the PASAT is extremely challenging for individuals, and has a high dropout rate. As such, there were fewer individuals that completed the entire task (N = 33), further adding to the lack of power for this particular aim. A previous study investigating white matter tracts and executive measures in DM individuals also failed to find an association with the PASAT measure, so it is possible that this measure is not sensitive to changes associated with IR (Kodl et al., 2008). When the aspects of MetS were considered individually, there was a trend towards individuals with high glucose having significantly lower performance on the second trial of the PASAT, although this association failed to meet the cut-off when corrected for multiple comparisons. The exploratory correlation analyses with the various biomarkers and the PASAT suggest that performance on the

task may decrease as blood pressure, BMI, waist circumference, hip circumference, and triglycerides increase. Future studies with larger samples are necessary to determine whether these measures serve as reliable biomarkers for performance on executive function measures like the PASAT.

Analyses of executive measures using MetS as a whole failed to indicate significant differences between groups on executive measures. Additionally, none of the individual aspects of MetS were associated with executive function measures when the MetS cutoffs were used. These findings are contradictory to previous reports showing differences between these groups (Segura et al., 2009), but we may be underpowered to replicate previous findings.

A curious finding from the exploratory correlation analyses was the relation of Letter-Number Sequencing to several of the metabolic markers. The results indicate that as CRP, waist circumference, and BMI increases so does performance on Letter-Number Sequencing, a task of working memory. This finding is in the opposite direction of what is expected, since increased scores on Letter-Number Sequencing indicate better performance. Distributions for these factors all fall within the normal range and all have an adequate sample size. Possibilities for this finding may represent spurious findings. Additionally, there was a correlation between increased hip circumference and performance on the Letter-Number Sequencing task. This finding is consistent with the theory that increase hip circumference may provide metabolically protective effects on cognitive function (Seidell et al., 2001).

Vascular Mechanisms

IR is associated with arterial stiffness, placing individuals at increased risk for cerebrovascular disease (Stehouwer et al., 2008). Hyperinsulinemia and even mild hyperglycemia are independent risk factors for individuals with impaired fasting glucose

for silent stroke on MRI (Kwon et al., 2006). IR in turn impairs cerebrovascular functions and contributes to vasoconstricted arteries, (Miller, 2002) atherosclerotic plaque accumulation, (Park, Hong, Sung, & Jung, 2008) white matter hyperintensities, (Last, Alsop, & Abduljalil, 2007) and increased stroke risk (Abbott, Donahue, Macmahon, Reed, & Yano, 1968). Additionally, white matter in the brain is especially vulnerable to unhealthy vascular response due to the location of the border zones for the major arteries being located in the white matter (Chui, 2007).

One possible mechanism for damage to the blood vessels by IR is indicated from recent animal studies showing that impaired insulin secretion is associated with a reduction in cerebrovascular dilation due to decreased activation of nitric oxide (NO; Katakam, Snipes, Steed, & Busija, 2012) and damage to neurons because of an augmented response of reactive oxygen species (Busija & Miller, 2004). Insulin impacts the endothelium of blood vessels via two pathways, including the phosphatidylinositol 3-kinase (PI3-K) pathway and the mitogen-activated protein kinase (MAPK) pathway (Muniyappa & Quon, 2007). The PI3-K pathway acts as a vasodilator by releasing NO, while the MAPK pathway acts to vasoconstrict blood vessels. Only the PI3-K pathway becomes resistant to the effect of insulin, resulting in a loss of vasodilation (Erdös, Snipes, Kis, Miller, & Busija, 2004). Additionally, since the MAPK pathway is sensitive to insulin, there is compounded vasoconstriction effect. It is possible that cerebrovascular damage resulting from the vasoconstrictive impact of IR is contributing to the proliferation of age-related cognitive decline and dementia.

Other mechanisms

Impaired insulin in the brain is associated with increased production of amyloid beta and tau proteins in cerebrospinal fluid, (Cole & Frautschy, 2007; G. Watson et al., 2003) oxidative stress, and mitochondrial dysfunction (Erol, 2008). These factors are

most often related to gray matter changes in the brain, with the hippocampus being a primary target (Van den Berg, De Craen, Biessels, Gussekloo, & Westendorp, 2006)(West, Coleman, Flood, & Troncoso, 1994). Glucose has been indicated as one of the primary metabolic factors related to cortical changes due to the large number of receptors found in the hippocampus and frontal lobes (Awad et al., 2004). Further studies that follow individuals over a long period of time are necessary to ascertain the exact relationships and mechanisms that underlie changes over time.

Glucagon-like peptide (GLP-1) is an antihyperglycemic hormone that induces insulin secretion from the pancreas after eating and in the presence of glucose (Salcedo, Tweedie, Li, & Greig, 2012). Additionally, GLP-1 suppresses glucagon secretion from the liver (Nauck, Vardarli, Deacon, Holst, & Meier, 2011). GLP-1 may have a positive effect on beta-cell synthesis of insulin by increasing beta cell adaption and survival (Yusta et al., 2006). GLP-1 agonists are now starting to be used as supplemental medications for DM. There have been several benefits noted in individuals taking GLP-1 agonist in animal studies leading to the investigation of these agents as treatment in AD (Perry & Greig, 2004). A promising finding is that GLP-1 agonists may reduce the severity of IR by improving insulin sensitivity (Parlevliet, De Leeuw van Weenen, Romijn, & Pijl, 2010). Other studies suggest that insulin affects GLP-1 and that IR may result in defective GLP-1 secretion (Nauck et al., 2011). GLP-1 also regulates cardiovascular function via reduction in nitric oxide synthase and reactive oxygen species (Cabou, Vachoux, Campistron, Drucker, & Burcelin, 2011; Lerche et al., 2008). Additionally, a high-fat diet leads to brain GLP-1 signaling that induces hyperinsulinemia and IR (Knauf et al., 2008). Due to the cost and invasiveness involved with the measurement of GLP-1, it was not included in the present study.

However, it is important that future studies determine whether GLP-1 could provide relief from the complications associated with IR.

An additional consideration for future studies is the involvement of stress hormones, such as cortisol, in the relation to IR. There are several overlapping factors between increased cortisol levels and IR, such as central obesity, hypertension, elevated lipids, and IR (Corry & Tuck, 2001). Cortisol can block the actions of insulin on glucose uptake (HOLMÄNG & BJÖRNTORP, 1992). Additionally, both cortisol and insulin have been related to declarative memory measures and hippocampal volume (Convit, 2005). Further studies are indicated in order to ascertain the relationship underlying insulin to cortisol.

Conclusion

The primary findings of the current study indicate that IR is related to List Learning, but not executive function or white matter integrity of the uncinate fasciculus. Secondary analyses revealed that MetS is also related to List Learning performance, but not to executive function or white matter integrity. Exploratory correlations revealed several other significant relationships between metabolic biomarkers and DTI white matter integrity and cognitive function that require further analysis. Given that the metabolic markers are modifiable risk factors, future studies should focus on creating programs and studies that focus on changing these factors in a positive direction.

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Table 1. Study Sample Characteristics (N = 46)

	Mean (SD)	Minimum	Maximum
Age, years	64.00 (7.07)	53	79
Education, years	15.50 (2.21)	12	20
BMI	27.47 (5.81)	16.16	41.33
Diastolic Blood Pressure	125.82 (16.93)	92.60	158.30
Systolic Blood Pressure	74.86 (9.81)	56.60	103.70
Waist Circumference (cm)	97.98 (14.11)	74.00	124.50
Hip Circumference (cm)	109.53 (12.14)	83.00	136.00
QUICKI	0.3556 (0.04)	0.2686	0.4537
Insulin	10.09 (9.69)	2	46
Glucose	94.57 (11.59)	75	140
HbA1c	5.55 (0.32)	4.80	6.30
Total Cholesterol	197.65 (33.01)	128	271
HDL	65.15 (16.60)	32	110
LDL	113.52 (26.71)	67	191
Triglycerides	94.72 (44.24)	41	274
C-reactive Protein	0.211 (0.26)	0.012	1.261

Table 2. IR Group Characteristics (IR = 24; non-IR = 22)

	Mean (SD)		Minimum		Maximum	
	IR	non-IR	IR	non-IR	IR	non-IR
Age, years	64.54 (6.90)	63.41 (7.37)	54	53	78	79
Education, years	14.88 (2.44)	16.18 (1.74)	12	12	20	20
BMI	30.46 (5.53)	24.20 (4.18)	20.94	16.16	41.33	34.20
Diastolic Blood Pressure	131.59 (11.69)	119.52 (19.61)	108.00	92.60	158.30	158.00
Systolic Blood Pressure	78.40 (10.13)	71.01 (7.99)	64.30	56.60	103.70	86.00
Waist Circumference (cm)	105.79 (11.32)	89.45 (11.85)	77.50	74.00	124.50	115.00
Hip Circumference (cm)	115.50 (11.16)	103.02 (9.71)	96.50	83.00	136.00	122.50
QUICKI	0.3232 (0.02)	0.3908 (0.02)	0.2686	0.3623	0.3583	0.4537
Insulin	15.33 (11.05)	4.36 (1.26)	6	2	48	6
Glucose	99.50 (12.15)	89.18 (8.25)	81	75	140	106
HbA1c	5.69 (0.31)	5.39 (0.24)	5.20	4.80	6.30	5.80
Total Cholesterol	197.33 (36.46)	198.00 (29.65)	128	146	271	242
HDL	60.42 (14.38)	70.32 (17.54)	32	43	100	110
LDL	115.71 (29.13)	111.14 (24.26)	67	77	191	156
Triglycerides	106.04 (49.69)	82.36 (34.65)	41	43	274	154
C-reactive Protein	0.241 (0.20)	0.179 (0.31)	0.012	0.012	0.720	1.261

Table 3. Comparison of IR and non-IR on FA and MD of the Uncinate Fasciculus

	IR Mean (SD)	non-IR Mean (SD)	F	p
Left Uncinate FA	0.353 (0.02)	0.364 (0.02)	2.83	0.101
Right Uncinate FA	0.364 (0.02)	0.375 (0.02)	3.06	0.088
Left Uncinate MD	$7.3x10^{-4}$ ($3.1x10^{-5}$)	$7.2x10^{-4}$ ($2.4x10^{-5}$)	0.77	0.387
Right Uncinate MD	$7.5x10^{-4}$ ($4.5 x10^{-5}$)	$7.4x10^{-4}$ ($3.2x10^{-5}$)	0.71	0.405

Table 4. Comparison of IR and non-IR on Measures of Executive Function

	IR Mean (SD)	non-IR Mean (SD)	F	p
Trails B	79.25 (31.91)	79.25 (40.15)	0.91	0.665
Color-Word Interference	57.75 (11.10)	50.82 (9.18)	2.68	0.112
Letter Fluency	41.88 (13.49)	48.53 (16.07)	1.04	0.315
PASAT Trial 1, %	88.84 (7.03)	87.16 (10.25)	0.19	0.667
PASAT Trial 2, %	84.32 (7.99)	87.79 (8.72)	0.70	0.409
PASAT Trial 3, %	84.10 (8.63)	87.98 (8.13)	1.82	0.187
PASAT Trial 4, %	86.31 (10.31)	88.96 (8.34)	0.23	0.638

Table 5. Comparison of IR and non-IR on Memory Measures

	IR Mean (SD)	non-IR Mean (SD)	F	p
List Learning	28.13 (3.94)	30.91 (3.58)	8.41*	0.006*
Story Memory	16.17 (2.99)	17.68 (2.87)	2.71	0.107
List Recall	6.52 (1.93)	6.72 (2.41)	0.22	0.642
List Recognition	19.78 (0.42)	19.55 (0.80)	1.52	0.120
Story Recall	8.65 (2.10)	9.50 (1.85)	0.82	0.371
Figure Recall	13.87 (2.97)	14.32 (3.03)	0.05	0.830

*$p < 0.006$

Table 6. MetS Group Characteristics (MetS = 14, non-MetS = 32)

	Mean (SD)		Minimum		Maximum	
	MetS	non	MetS	non	MetS	non
Age, years	65.79 (6.78)	63.22 (7.16)	54	53	78	79
Education, years	15.64 (2.50)	15.44 (2.11)	12	12	20	20
BMI	30.80 (4.82)	26.01 (5.67)	23.90	16.16	40.07	41.33
Diastolic Blood Pressure	136.04 (12.58)	121.34 (16.78)	108.00	92.60	158.30	158.00
Systolic Blood Pressure	80.14 (11.34)	72.55 (8.22)	64.30	56.60	103.70	90.66
Waist Circumference (cm)	107.79 (7.79)	93.69 (14.19)	94	74	123	125
Hip Circumference (cm)	117.18 (8.70)	106.19 (12.01)	105	83	133	136
QUICKI	0.3216 (.03)	0.3704 (0.04)	0.2686	0.2815	0.3583	0.4537
Insulin	15.86 (12.69)	7.56 (6.86)	6	2	46	38
Glucose	103.86 (12.69)	90.50 (8.45)	91	75	140	114
HbA1c	5.76 (0.32)	5.45 (0.27)	5.30	4.80	6.30	6.10
Total Cholesterol	193.21 (38.77)	199.59 (30.64)	128	146	246	271
HDL	63.14 (16.02)	66.03 (16.97)	32	43	100	110
LDL	109.07 (28.98)	115.47 (25.90)	67	77	162	191
Triglycerides	105.36 (56.50)	90.06 (37.79)	41	43	274	190
C-reactive Protein	0.192 (0.21)	0.220 (0.28)	0.012	0.01	0.720	1.26

Table 7. Comparison of MetS and non-MetS on FA and MD of the Uncinate Fasciculus

	MetS Mean (SD)	non-MetS Mean (SD)	F	p
Left Uncinate FA	0.349 (0.02)	0.364 (0.02)	5.22	0.028
Right Uncinate FA	0.361 (0.02)	0.374 (0.02)	4.19	0.047
Left Uncinate MD	$7x10^{-4}$ ($3.5x10^{-5}$)	$7x10^{-4}$ ($2.3x10^{-5}$)	2.17	0.149
Right Uncinate MD	$8x10^{-4}$ ($5.1x10^{-5}$)	$7x10^{-4}$ ($3.0x10^{-5}$)	3.14	0.084

Table 8. Comparison of Individual MetS Components by Diagnostic Cutoff on FA and MD of the Uncinate Fasciculus

	MetS Mean (SD)	non-MetS Mean (SD)	F	p
Blood Pressure (MetS = 22, non-Mets = 20)				
Left Uncinate FA	0.352 (0.02)	0.366 (0.02)	5.46	0.025
Right Uncinate FA	0.364 (0.18)	0.376 (0.02)	3.75	0.060
Left Uncinate MD	$7.3x10^{-4}$ ($3.0x10^{-5}$)	$7.2x10^{-4}$ ($2.5x10^{-5}$)	0.47	0.499
Right Uncinate MD	$7.5x10^{-4}$ ($4.3x10^{-5}$)	$7.4x10^{-4}$ ($3.5x10^{-5}$)	0.16	0.691
Glucose (MetS = 13, non-MetS = 29)				
Left Uncinate FA	0.354 (0.02)	0.361 (0.02)	0.29	0.594
Right Uncinate FA	0.358 (0.01)	0.375 (0.02)	3.07	0.088
Left Uncinate MD	$7.4x10^{-4}$ ($3.4x10^{-5}$)	$7.2x10^{-4}$ ($2.3x10^{-5}$)	3.80	0.058
Right Uncinate MD	$7.6x10^{-4}$ ($5.3x10^{-5}$)	$7.4x10^{-4}$ ($2.9x10^{-5}$)	2.82	0.101
Waist Circumference (MetS = 27, non-MetS = 15)				
Left Uncinate FA	0.357 (0.02)	0.362 (0.02)	0.47	0.498
Right Uncinate FA	0.369 (0.02)	0.370 (0.02)	0.03	0.854
Left Uncinate MD	$7.3x10^{-4}$ ($2.8x10^{-5}$)	$7.3x10^{-4}$ ($2.8x10^{-5}$)	0.02	0.890
Right Uncinate MD	$7.5x10^{-4}$ ($4.2x10^{-5}$)	$7.4x10^{-4}$ ($3.5x10^{-5}$)	0.31	0.580

Table 9. Comparison of MetS and non-MetS on Measures of Executive Function

	MetS Mean (SD)	non-MetS Mean (SD)	F	p
Trails B	84.58 (44.98)	71.00 (29.29)	1.11	0.301
Color-Word Interference	59.67 (11.48)	51.05 (8.87)	5.82	0.022
Letter Fluency	41.83 (14.47)	51.05 (8.87)	1.01	0.324
PASAT Trial 1, %	88.15 (7.93)	87.88 (9.36)	0.01	0.933
PASAT Trial 2, %	82.19 (7.62)	88.34 (8.21)	4.51	0.042
PASAT Trial 3, %	83.97 (9.81)	87.32 (7.60)	1.20	0.282
PASAT Trial 4, %	86.87 (11.14)	88.14 (8.32)	0.14	0.713

Table 10. Comparison of MetS and non-MetS on Memory Measures

	MetS Mean (SD)	non-MetS Mean (SD)	F	p
List Learning	26.85 (3.18)	30.56 (3.80)	9.64*	0.003*
Story Memory	16.62 (2.36)	17.03 (3.25)	0.17	0.688
List Recall	5.92 (1.44)	6.91 (2.35)	1.96	0.168
List Recognition	19.92 (0.28)	19.56 (0.72)	3.08	0.064
Story Recall	9.15 (1.28)	9.03 (2.25)	0.03	0.855
Figure Recall	14.15 (2.41)	14.06 (3.21)	0.01	0.927

*$p < 0.006$

Table 11. Comparison of Individual MetS Components by Diagnostic Cutoff on Measures of Executive Function

	MetS Mean (SD)	non-MetS Mean (SD)	F	p
Blood Pressure (MetS = 20, non-MetS = 13)				
Trails B	78.95 (40.51)	71.31 (27.66)	0.35	0.556
Color-Word Interference	55.45 (10.60)	52.23 (10.71)	0.72	0.402
Letter Fluency	40.80 (10.59)	52.23 (18.41)	5.15	0.030
PASAT Trial 1, %	88.45 (6.99)	87.25 (11.21)	0.15	0.705
PASAT Trial 2, %	86.41 (7.72)	85.63 (9.74)	0.07	0.798
PASAT Trial 3, %	86.18 (8.55)	85.97 (8.71)	0.01	0.945
PASAT Trial 4, %	87.12 (9.98)	88.53 (8.44)	0.18	0.677
Glucose (MetS = 12, non-MetS = 21)				
Trails B	76.08 (10.73)	75.86 (44.47)	0.19	0.669
Color-Word Interference	57.58 (8.01)	52.24 (11.55)	0.69	0.412
Letter Fluency	43.67 (17.41)	46.24 (13.86)	0.18	0.674
PASAT Trial 1, %	85.54 (10.75)	89.37 (7.29)	1.89	0.179
PASAT Trial 2, %	80.34 (8.77)	89.40 (6.34)	7.77	0.009
PASAT Trial 3, %	84.27 (8.92)	87.15 (8.25)	0.80	0.379
PASAT Trial 4, %	88.02 (10.16)	87.48 (9.01)	0.01	0.933
Waist Circumference (MetS = 23, non-MetS = 10)				
Trails B	76.57 (38.09)	74.50 (31.39)	0.02	0.881
Color-Word Interference	55.30 (11.36)	51.60 (8.55)	0.85	0.364
Letter Fluency	44.04 (15.27)	48.20 (14.83)	0.53	0.474

PASAT Trial 1, %	89.87 (7.00)	83.62 (11.03)	3.88	0.058
PASAT Trial 2, %	86.71 (7.99)	84.70 (9.67)	0.39	0.537
PASAT Trial 3, %	86.43 (8.70)	85.33 (8.33)	0.12	0.736
PASAT Trial 4, %	86.10 (9.82)	89.24 (8.22)	0.40	0.532

Table 12. Comparison of Individual MetS Components by Diagnostic Cutoff on Memory Measures

	MetS Mean (SD)	non-MetS Mean (SD)	F	p
Blood Pressure (MetS = 25, non-MetS = 20)				
List Learning	28.60 (4.06)	30.60 (3.68)	2.93	0.094
Story Memory	17.20 (3.25)	16.55 (2.68)	0.52	0.476
List Recall	6.36 (2.22)	6.95 (2.09)	0.83	0.368
List Recognition	19.60 (0.71)	19.75 (0.55)	0.61	0.441
Story Recall	9.36 (1.66)	8.70 (2.36)	1.21	0.277
Figure Recall	14.36 (3.15)	13.75 (2.79)	0.46	0.501
Glucose (MetS = 13, non-MetS = 32)				
List Learning	27.62 (3.33)	30.25 (4.02)	2.34	0.134
Story Memory	16.77 (2.39)	16.97 (3.25)	0.00	0.956
List Recall	6.31 (1.70)	6.75 (2.33)	0.06	0.801
List Recognition	19.92 (0.28)	19.56 (0.72)	1.63	0.079
Story Recall	9.31 (1.49)	8.97 (2.19)	0.85	0.362
Figure Recall	14.54 (2.15)	13.91 (3.27)	0.18	0.673
Waist Circumference (MetS = 28, non-Mets = 17)				
List Learning	28.68 (3.97)	30.82 (3.73)	3.23	0.079
Story Memory	16.89 (2.85)	16.94 (3.33)	0.00	0.959
List Recall	6.46 (1.97)	6.88 (2.47)	0.39	0.534
List Recognition	19.82 (0.39)	19.41 (0.87)	4.71	0.036
Story Recall	8.89 (1.87)	9.35 (2.23)	0.55	0.462

Figure Recall	14.00 (2.67)	14.24 (3.51)	0.07	0.800

Table 13. Significant Correlations Between Metabolic Factors and FA of Fiber Tracts

	QUIKI	Insulin	Glucose	Diastole	Systole	BMI	Waist	Hip
RAntThal				-0.44	-0.45	-0.40	-0.31	
LCingGyr		0.37		-0.32	-0.35			
LCingHip					0.33			
ForMin			-0.32					
LInfFro				-0.32				
RInfFro				-0.37	-0.31			
RInfLon		0.37						
RSupLonT	-0.32							0.31
LUnc			-0.37	-0.45	-0.32			
RUnc			-0.39	-0.38				

$p < .05$

Note: RAntThal = Right anterior thalamic radiation; LCingGyr = Left cingulate gyrus; LCingHip = Left cingulum – hippocampus; ForMin = Forceps minor; LInfFro = Left inferior fronto-occipital fasciculus; RInfFro = Right inferior fronto-occipital fasciculus; RInfLon = Right inferior longitudinal fasciculus; RSupLonT = Right superior longitudinal fasciculus (temporal only); LUnc = Left uncinate fasciculus; RUnc = Right uncinate fasciculus

Table 14. Significant Correlations Between Metabolic Factors and MD of Fiber Tracts

	QUIKI	Glucose	HbA1c	HDL	CRP	BMI	Waist	Hip
LAntThal					-0.33	-0.48	-0.46	-0.45
LCingGyr	0.33					-0.34	-0.34	-0.35
RCingGyr						-0.32	-0.30	-0.34
LCingHip		0.41	0.33					
ForMaj				-0.34				
ForMin		0.35						
RInfFro							-0.32	
RInfLon								
LSupLonT				-0.40			-0.30	-0.33
RSupLonT						-0.32	-0.32	-0.38
LSupLon								0.31
LUnc		0.34						
RUnc		0.32						

$p < .05$

Note: LAntThal = Left anterior thalamic radiation; LCingGyr = Left cingulate gyrus; RCingGyr = Right cingulate gyrus; LCingHip = Left cingulum – hippocampus; ForMaj = Forceps major; ForMin = Forceps minor; RInfFro = Right inferior fronto-occipital fasciculus; RInfLon = Right inferior longitudinal fasciculus; LSupLonT = Left superior longnitudinal fasciculus (temporal only); RSupLonT = Right superior longitudinal fasciculus (temporal only); LSupLon = Left superior longitudinal fasciculus; LUnc = Left uncinate fasciculus; RUnc = Right uncinate fasciculus

Table 15. Significant Correlations Between Metabolic Factors and RBANS Subtests

	QUIKI	Insulin	Glucose	HbA1c	HDL	Waist	Hip	Cholest
List Learn	0.32	-0.37		-0.34	0.32			
Line Orient								-0.34
Digit Span						0.29		
Coding				-0.30				
List Recall					0.33			
List Recog	-0.39		0.30				0.30	

$p < .05$

Note: Cholest = Cholesterol; List Learn = List Learning; Line Orient = Line Orientation; List Recog = List Recognition

Table 16. Significant Correlations Between Metabolic Factors and Cognitive Measures

	Ins	Gluc	A1c	CRP	Diast	Syst	BMI	Wais	Hip	Trig
MOCA	-0.30	-0.39					-0.31		-0.36	
PegND					0.36					
TMA		0.51	0.30							
CW3		0.30								
LNS				0.33			0.39	0.38	0.38	
P1					-0.36	-0.37				
P2		-0.32					-0.37	-0.38	-0.32	-0.37
P3					-0.47	-0.44		-0.32		-0.34

$p < .05$

Note: Ins = Insulin; Gluc = Glucose; A1c = HbA1c; CRP = C-reactive protein Diast = Diastolic pressure; Syst = Systolic pressure; Wais = Waist circumference, Hip = Hip circumference; Trig = Triglycerides; MOCA = Montreal Cognitive Assessment; PegND = Grooved pegs – non-dominant hand; TMA = Trail Making Test A; CW3 = Color-Word Interference, trial 3; LNS = WAIS-III Letter-Number Sequencing; P1 = PASAT Trial 1; P2 = PASAT Trial 2; P3 = PASAT Trial 3