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Cardiovascular Function, Cortical Thickness and Cognitive Performance in Middle-aged Hispanic Adults

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Cardiovascular Function, Cortical Thickness and Cognitive Performance in Middle-aged Hispanic Adults

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Abstract

Cardiovascular Function, Cortical Thickness and Cognitive Performance in Middle-aged Hispanic Adults

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Background: Alzheimer's disease (AD) prevalence has grown 68% in that timeframe, and has risen to the sixth leading cause of death in the United States. Hispanics are at increased risk of acquiring cardiovascular risk factors that contribute to AD pathology and are minimally 1.5 times more likely at any age to be diagnosed with AD. Identifying the roots of this ethnic disparity can lead to more effective personalized health interventions. **Aim:** To compare indices of vascular health to measures of gray matter integrity in middle-aged Hispanic and Caucasian adults. As a secondary outcome, we will examine these health statuses in relation to cognitive function. **Methods:** Sixty subjects in Caucasian (n=30) and Hispanic (n=30) groups were matched across racial classification by age, gender, years of education, and cognitive status. Participants' arterial stiffness (carotid-femoral pulse-wave velocity and β-stiffness index), arterial wave reflection (augmentation index), endothelial function (flow-mediated dilation), and atherosclerosis (carotid arterial wall intima-media thickness) were characterized. Magnetic resonance imaging (MRI) estimated cortical thickness in *a priori* cortical

regions of interest known to be susceptible to vascular risk factors. Cognitive function was assessed with a comprehensive cognitive battery covering the domains of global cognitive function, language function, visuo-spatial abilities, memory function and attention-executive function. **Results:** Carotid-femoral pulse wave velocity (cfPWV) ($p=0.02$), Carotid artery β-stiffness index ($p=0.01$), and augmentation index (Aix) ($p=0.05$) were significantly greater in Hispanics than in Caucasians. Carotid intima-media thickness (IMT) and flow-mediated dilation (FMD) were not different between the groups. Hispanics exhibited thinner left inferior frontal gyrus (LIFG) cortical thickness ($p=0.04$) with concurrently lower language ($p=0.02$), memory ($p=0.03$), and attention-executive functioning ($p=0.02$). **Conclusion:** Hispanics exhibited significantly greater cfPWV, Aix, and β-stiffness index as well as selective cortical thinning of the LIFG. Additionally, language, working memory and attention-executive domains of cognition were lower in the Hispanic group compared to their age-, gender-, education- and cognitive status-matched Caucasian counterparts. These results may form a basis for future investigations that aim to explain the increased prevalence and earlier onset of symptoms of AD in the Hispanic population through cardiovascular health.

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INTRODUCTION

Although the overall mortalities from heart disease, stroke, and prostate cancer have declined between the years 2000 and 2010, Alzheimer's disease (AD) prevalence has grown 68% in that timeframe, and has risen to the sixth leading cause of death in the United States **(Thies, 2013)**. Almost a million new AD diagnoses will be expected annually by 2050 **(Thies, 2013)**. People aged 65 years and older are the largest growing segment of the population and this cohort is expected to double by 2030, comprising 20% of the total population **(CDC, 2007)**. The cost of dementias was $203 billion in 2012, and this economic burden will continue to rise as the population ages **(Thies, 2013)**.

The Hispanic population will constitute the largest proportion (20%) of all minority groups **(US Census, 2008)**. Hispanics are 3 times more likely than Caucasians at ages 55-64 years to exhibit cognitive impairment **(Thies, 2013)**. Additionally, Hispanics typically present with symptoms on average 6.8 years earlier in life than Caucasians **(Clark, 2005)**. Identifying the roots of this ethnic disparity can lead to more effective personalized health interventions. Such disparities may be found in the prevailing theory of AD pathogenesis, the vascular hypothesis. The vascular hypothesis of AD is that cerebral perfusion declines during the normal aging process, but worsens with the accumulation of vascular risk factors, creating a critically attained threshold of cerebral hypoperfusion (CATCH) that result in a faster cognitive and functional decline **(de la Torre, 2012; Kume 2011, Solfrizzi, 2004).** US-born Mexican Americans are more likely to develop high blood pressure, metabolic dysfunction, and inflammation risk factors than Caucasians **(Crimmins, 2007)**. Many of these risk factors overlap with those buttressing the vascular hypothesis of AD and negatively impact cognition **(den Heijer, 2005, Leritz, 2009)** even at subclinical levels **(Kennedy 2009, Leritz, 2010, 2011)**

making early identification and prevention critical. Indeed the Hispanic population has increased prevalence of AD and likelihood of developing precursors with earlier symptom onset. Therefore, targeted study of AD pathology in Hispanics is of the utmost importance. Despite the approximately 73,000 articles published on AD in the last two decades **(de la Torre, 2012)**, to our knowledge, no group has rigorously investigated the relationship of indices of cardiovascular health and gray matter in relation to cognitive function in Hispanics.

Accordingly, the aim of the present study was to compare indices of vascular health to measures of gray matter integrity in middle-aged Hispanic and Caucasian adults. As a secondary outcome, we will examine these health statuses in relation to cognitive function. In order to comprehensively address these objectives, we characterized a variety of participants' vascular functions, including arterial stiffness via pulse wave velocity and β-stiffness index, arterial wave reflection via augmentation index, endothelial function via flow-mediated dilation (FMD), and atherosclerosis via carotid arterial wall intima-media thickness. Magnetic resonance imaging (MRI) was used to estimate cortical thickness in *a priori* cortical regions of interest (ROI) known to be susceptible to vascular risk factors **(Leritz, 2011)** to detect early gray matter morphological changes. To assess cognitive function, participants completed a comprehensive cognitive battery. We hypothesized that the Hispanic population would have greater arterial stiffness with reduced cortical thickness in specific brain regions related to cardiovascular disease. These phenotypes were expected to relate to cognitive performance and race was expected to moderate this relationship.

REVIEW OF LITERATURE

DEMENTIA

Dementia is a disease that encompasses many subsets that all present in characteristic decline in memory and cognitive function that leads to a loss of independent function **(Plassman, 2007)**. Although there are many subcategories of dementia, Alzheimer's Disease (AD) is undoubtedly the most common form, accounting for an estimated 60-80% of cases **(Thies 2013)**. Individuals who have the disease suffer progressively worse symptoms as pathology accumulates. Early symptoms of AD include apathy and depression with later symptoms of impaired judgment, disorientation, confusion, and difficulty speaking or walking. Ultimately the disease can result in mortality with respiratory infection as the most common immediate cause **(Mölsä, 1986)**. The presentation of symptoms is determined by the amount of accumulated pathology within the individual **(Stern, 2002)**. While brain and cognitive reserve have been hypothesized to delay the presentation of AD symptoms **(Stern, 2002)**, there is no cure for the disease. Sadly, one is unlikely to be found with our present technologies, simply because dead neurons cannot be restored to their original state **(de la Torre, 2010)**. The prevalence of this debilitating disease is rising with some populations more vulnerable than others.

ALZHEIMER'S DISEASE PREVALENCE AND RISK

The prevalence of AD has grown 68% from years 2000 through 2010 and has risen to the sixth leading cause of death in the United States **(Thies, 2003)**. The number of new AD diagnoses is rapidly increasing. An estimated 411,000 new cases of AD were diagnosed in 2000 with a projected one million made annually by 2050 **(Herbert, 2001)**. The greatest independent risk factor known for AD is age. The segment of the U.S. population 65 years and older is

expected to double by 2030 and comprise 20% of the total population **(CDC, 2007)**. Hispanics will constitute the largest minority group of this segment, representing 20% of the elder population. This growth is of great concern, as Hispanics are three times more likely than whites to exhibit cognitive impairment between the ages of 55-64 and 1.6 times at ages 85 and older. From these and other data, the Alzheimer's Association estimates that older Hispanics are at least 1.5x more likely than whites to develop AD and other forms of dementia at any age. Additionally, Hispanics typically present with symptoms on average 6.8 years earlier in life **(Clark 2005)**. Determining the root of the disparate prevalence of AD is of the utmost importance for designing effective individualized interventions for all populations.

DISPARITY ROOTED IN GENETICS?

The development of AD is definitively multi-factorial, stemming from genetic predisposition, environmental influence and vascular risk factor clustering. The apolipoprotein E (ApoE) gene represents a genetic factor that increases an individual's risk for developing AD. One form of the ApoE gene is inherited from each parent. Those who inherit the e4 polymorphism from one parent have a heighted risk of AD, and those who inherit the e4 from both parents have even further risk. The prevalence of this particular polymorphism is 13.1% and 14.2% in Caucasians and Hispanics respectively **(Tang 1998)**. When the deleterious e4 genotype of ApoE is inherited from one parent, whites had 3.2 times increased likelihood of developing AD compared to 2.2 times in Hispanics **(Farrer, 1997)**. Therefore, the passing of this gene is likely not the root of the disparity in AD prevalence and onset of symptoms between Caucasians and Hispanics. Ostensibly, it is more probable that differential pathology accumulated throughout the lifespan accounts for observed prevalence differences.

DISPARATE RISK FACTOR ACCUMULATION

Epidemiological data from the National Health and Nutrition Examination Survey (NHANES) III reported ethnic differences in metabolic syndrome risk factors. Metabolic syndrome is the possession of multiple metabolic abnormalities that are associated with greater risk for developing insulin resistance, cardiovascular disease and all cause mortality **(Mozumdar, 2011)**. These metabolic maladies include central obesity (waist circumference: >102 cm and >88; men and women respectively), dyslipidemia (triglycerides ≥150 mg/dl; HDL men <40 mg/dl; women <50 mg/dl), hypertension (≥130/≥85 mm Hg), and elevated fasting glucose (≥110 mg/dl) **(Mottillo, 2010)**. According to NHANES III, Mexican Americans had the highest prevalence of Metabolic Syndrome among any demographic from 1999-2006 of 36.6% for men and 42.65% for women after adjusting for age **(Mozumdar, 2011)**. Similarly, in a separate study, Mexican Americans were found more likely to develop blood pressure, metabolic, and inflammation risk factors than Caucasians after accounting for age and gender **(Crimmins, 2007)**. Importantly, these differences disappear when adjusting for education and socioeconomic status, suggesting that environmental factors may be critical. Nonetheless, when placing the differences of cardiovascular and metabolic risk factor accumulation in context with proposed models of AD pathogenesis, racial prevalence differences of AD may be explainable.

VASCULAR HYPOTHESIS OF ALZHEIMER'S DISEASE

The vascular hypothesis of AD asserts that accumulation of vascular risk factors such as hypertension, hyperlipidemia and metabolic syndrome exacerbates an already declining cerebral perfusion that occurs with aging **(de la Torre, 2012)**. These risk factors can exist silently in cognitively intact individuals for decades before symptoms are expressed. These risk factors individually and synergistically disturb hemodynamics leading to a critically attained threshold of cerebral hypoperfusion (CATCH) **(de la Torre, 2000).** Once CATCH is reached, clearance of

harmful toxins that can traumatically affect neurons is limited, leading to neuronal dysfunction. A schematic of nuanced progression to dementia by ethnicity is proposed in Figure 1. With cardiovascular and cognitive health undeniably linked, potentially any risk factor or disease state that limits cerebral perfusion could contribute to dementia through the vascular hypothesis model. While each risk factor merits individual investigation, their resulting effect of disrupted hemodynamics proximal toa compromised cerebral autoregulation will be discussed.

INDICES OF CARDIOVASCULAR FUNCTION

Major indices of cardiovascular function that reflect cardiovascular function and help govern hemodynamics that are highly related to risk factor accumulation are arterial stiffness, blood pressure wave reflection, and β-stiffness. Other measures of interest that reflect atherosclerosis and vessel function are carotid intima-media thickness (cIMT) and flow-mediated dilation (FMD).

ARTERIAL STIFFNESS. The stiffness of a central segment of the vasculature can be assessed by measuring carotid-femoral pulse wave velocity (cfPWV). This value is determined by detecting the transit time of a pulse wave over a measured distance from sites at the carotid and femoral arteries **(Rhee, 2008)**. Increases in arterial stiffness can compound the reflection of the incident pressure wave.

AUGMENTATION INDEX. Reflected pressure waves stem from reflection points throughout the arterial tree. With aging the reflected pressure waves occur earlier in the cardiac cycle, augmenting central systolic blood pressure and decreasing diastolic pressure **(Rhee, 2008)**. This phenomenon effectively widens the pulse pressure and exposes vessels to greater pulsatility. An

assessment of this reflected wave form is the augmentation index (AIx) which is calculated as the difference between the peak systolic pressure and the first shoulder of the incident wave expressed as a percentage of the pulse pressure **(Rhee, 2008)**.

BETA-STIFFNESS. Distending pressure plays a crucial role in determining lumenal diameter. An alternative measure of arterial stiffness accounts for this relationship by calculating arterial compliance independent of blood pressure called the β-stiffness index. To conduct this measure, B-mode ultrasound is used to capture vessel diameter 2-3 centimeters proximal to the carotid artery bulb and is coupled with beat-to-beat pulse pressures obtained from applanation tonometry on the contralateral carotid artery. β-stiffness is then calculated from diameter and pressure values attained over ten cardiac cycles with the equation $\beta=\ln(SBP/DBP)\times D/\Delta D$ where SBP and DBP are systolic and diastolic blood pressure and D is diameter **(Rhee, 2008)**.

ATHEROSCLEROSIS. An early indicator of atherosclerosis in the carotid artery is cIMT. This marker is also obtained from images recorded by high-resolution B-mode ultrasound also taken 2-3 centimeters proximal to the carotid artery bulb. From these images, electronic calipers can trace the thickness of the intima and media of the near vessel wall during diastole over the course of multiple cardiac cycles, yielding an average cIMT.

ENDOTHELIAL FUNCTION. The function of vascular endothelium also largely determines the diameter of a vessel. Flow-mediated dilation (FMD) is a non-invasive ultrasound method that is proposed as a marker of endothelial function. To perform FMD, the diameter of the brachial artery is measured with specialized software from images captured with a high-resolution

ultrasound probe before and after reactive hyperemia induced by five minutes of forearm cuff occlusion **(Uehata, 1997)**. The difference of the pre and post diameter is expressed as a percentage of the baseline value.

CARDIOVASCULAR FUNCTION AND COGNITION

Each measure described above has been independently linked to cognition and AD pathology. A study examining the relationship between arterial and cognition determined that increased cfPWV was associated with lower Mini-Mental Examination Score (MMSE), a measure of global cognitive function **(Zhong, 2014)**. Furthering arterial stiffness as an indicator of AD pathology, PWV was associated with β-amyloid deposition in the brains, a hallmark AD pheonotype of very elderly adults **(Hughes, 2013)**. Furthermore, multiple studies using cfPWV were able predict cognitive decline **(Poels, 2007; Benetos, 2011)**, and find associations with domains of cognition including psychomotor speed (Watson 2011), verbal learning, and memory **(Waldstein, 2008)** at various ages. The relationship between arterial stiffness and cognitive decline is wonderfully summarized in a systematic review and meta-analysis by Pase et al. 2012. The AIx and β-stiffness index have similarly been investigated in relation to cognition. AIx was shown to be an independent predictor of speed of memory, although did not affect working memory or attention **(Pase, 2010).** β-stiffness index has been proposed as a potential risk factor for dementia **(Mororvic, 2009; Jurasic, 2009)**.

Similarly, severe cIMT was associated with decreased MMSE scores in one study **(Xiang, 2013)** and poor cognitive performance in visuospatial skills and speed, verbal memory and verbal fluency domains in another **(Lopez-Oloriz, 2013)**. Finally, endothelial dysfunction measured by FMD is associated with mild cognitive impairment, maintenance of ability to perform activities of daily living yet exhibit cognitive decline, **(Tremblay, 2013)** measured on

the MMSE (**Vendemiale, 2013).** A different investigation showed that higher FMD predicted better executive function (**Smith, 2011**). Reduced diameter of vessels perfusing the brain may explain these observed relations of decreased cardiovascular and cognitive function. Plaque or clot formation measured with cIMT is indicated by greater thickness and typically localizes to bends and branches of the arterial tree. These buildups serve to narrow the vasculature **(de la Torre, 2009)**. Further limiting vessel diameter is endothelial dysfunction as measured by FMD. According to Poiseuille's Law, flow through a conduit is proportional to the radius of the vessel to the fourth power. Therefore, any alterations in a vessel's diameter from narrowing or loss of endothelial function could dramatically reduce blood flow to the brain.

MIDLIFE RISK IDENTIFICATION

Over 73,000 research articles have been published on the topic of AD, yet to this day, there is no known pharmaceutical or lifestyle intervention known to reverse the effects of AD and restore cognitive health (**de la Torre, 2012**). If in fact the vascular hypothesis model correctly describes the pathogenesis of dementia and AD, by the time symptomatic AD has set in, it's pathology is likely irreversible. As a result, a turning point in its mitigation may be early identification of the previously discussed risk factors during midlife. Detection of modifiable risk factors and adverse cardiovascular health indices could appropriately identify individuals at heightened risk for subsequent AD diagnosis.

At midlife, these risk factors are identifiable, yet CATCH may not be reached. At this critical time point, pharmaceutical or lifestyle interventions such as diet and exercise may protect against, slow or even stop the progress of non-genetic related disease. A cross-sectional study support this idea in which aerobic fitness was associated with higher memory performance (**Tarumi, 2013**). A case-control study in which exercise measures were obtained on average 31

years prior to the onset of dementia found that light and regular exercise was associated with reduced odds of dementia diagnosis compared to being sedentary (odds ratio [OR] =0.63, 95% confidence interval [CI], 0.43–0.91 and OR=0.34, 95% CI, 0.16–0.72 respectively) **(Andel, 2008)**. These data are encouraging that ameliorating risk factors identified in midlife through interventions such as aerobic exercise may stem the rise of AD.

BRAIN REGIONS ASSOCIATED WITH CARDIOVASCULAR RISK FACTORS

Clearly there an association exists between cardiovascular and cognitive health. While the exact mechanisms by which each risk factor may confer reduced cognitive function are unknown, they appear to preferentially target specific regions of the brain. A cross-sectional assessment of cortical thickness across ages 43-83 identified which specific regions exhibit structural changes in relation to cardiovascular and metabolic risk factors and are outlined in Tables 1 and 2 for the left and right hemispheres respectively **(Leritz, 2011)**. Accordingly, other groups buttressed these findings showing hypertension is related to cortical atrophy in regions related to AD **(den Heijer, 2005)**. Type-2 diabetes also appears related to reduced cortical thickness in the medial temporal lobe of patients with AD **(Biessels, 2006)**, supporting the idea that acquired insulin insensitivity is deleterious to brain structure. It is argued that even at subclinical levels, these risk factors negatively impact brain structure and function in specific processing regions **(Leritz, 2009)**. Not only do these associations exist, with advancing age, the presence of hypertension and dyslipidemia accelerated declines in cerebral perfusion and cortical atrophy in a four-year longitudinal follow-up study **(Meyer, 1999)**. The accumulation of cardiovascular and metabolic risk factors disrupts normal brain function in specific brain regions, and their continued presence places individuals on the fast track to cognitive decline and dementia. The regions associated cardiovascular function are responsible for many domains of

cognition including global function, crystalized intelligence, information processing, visuo-spatial processing, executive function, memory and attention. Damages to these areas may confer cognitive impairment and symptomatic AD. Therefore, further investigation characterizing the relationship of each risk factor to specific brain regions and cognitive performance is of merit.

GRAY MATTER INTEGRITY MEASUREMENT BY CORTICAL THICKNESS

Gray matter volume is defined as the amount of grey matter that lies between the grey-white interface and the pia mater **(Winkler, 2010)**. Cortical thickness is a validated measure of gray matter, as the two are highly associated. To measure cortical thickness, magnetic resonance imaging (MRI) conducts T_1 – weighted anatomical scans of the entire brain using a high-resolution spoiled gradient echo sequence (256 x 256 matrix, field of view = 24 x 24 cm^2, 1mm slice thickness, 0 gap). From MRI scans, regions of interest can be targeted by creating spheres 5 mm in diameter around a central coordinate for the chosen regions according to the Talairach and Tournoux atlas **(Seo, 2007)** using specialized software **(Du, 2007)**. Using this method, examination of brain regions associated cardiovascular and metabolic risk factors can be accomplished.

DOMAINS OF COGNITIVE FUNCTION AND ASSESSMENT

Beyond quantifying gray matter integrity as a metric of brain structure, cognitive function can be assessed through the use of cognitive tests directed at specific domains of cognition. The major domains of cognition include global cognitive function, intelligence, language, memory, executive function, and attention. Each of these domains are susceptible to aging and AD. The MMSE is a measure of global cognitive function as it incrporates questions taxing multiple cognitive domains. The Weschler Adult Intelligence Scale (WASI) also has many subtests and

is composed of questions testing verbal comprehension, perceptual reasoning, and working memory. Verbal fluency can be tested by having an individual name as many words as possible that begin with a certain letter, or within a category such as animals. Memory can be assessed when a subject is asked to repeat a successively longer string of numbers with immediate or delayed recall in a test known as the Digit Span. When reciting the numbers in reverse order, executive function is challenged. Another way to assess executive function is the Trails Making Test (TMT). The TMT is comprised of a two tasks, A and B. In Trails A, an individual draw a line connecting 25 encircled numbers sequentially shown on a sheet of paper. For Trails B, the same task is performed except the person must alternate between numbers and letters (e.g., 1, A, 2, B, 3, C, etc.) **(Tombaugh, 2004)**. The California Verbal Learning Test (CVLT) has multiple components that tax many cognitive domains including attention, memory, language, and visuospatial. Each of the above stated tests can serve to identify impairments in specific domains of cognition that may be affected by AD.

INTEGRATED APPROACH FOR AD PREVENTION

Dementia and AD is a deadly debilitating public health problem affecting more people every year. With the discovery of a cure to AD unlikely, the prevention of AD pathology is the best defense. Cardiovascular and metabolic risk factors are key contributors to the vascular dementia model explaining AD pathogenesis. The Hispanic population has both increased and growing prevalence of AD. Compounding this problem, Hispanics have elevated risk of developing AD precursors with earlier symptom onset. An integrated approach of examining indices of cardiovascular function in relation to brain structure and cognitive function in this population is of the utmost importance. Such studies should be performed on adults during midlife when risk factors may be present but can still be ameliorated by individualized

intervention. Future investigations should examine the effects of lifestyle interventions such as diet and exercise in relation to cardiovascular function, gray matter integrity and cognitive function.

METHODS

PARTICIPANTS

One hundred and two community dwelling adults aged 40-60 years were recruited through local newspaper and online advertisements. Of the 102 subjects, only those with complete cardiovascular and gray matter imaging data were included. Self-identifying second generation Hispanic participants were targeted for recruitment to generate a state representative sample of demographic characteristics for that population. Subjects were then matched across racial classification by age, gender, years of education, and cognitive status to reduce between group heterogeneity and possible confounding covariates. Matching scheme resulted in the inclusion of 60 total subjects in Caucasian (n=30) and Hispanic (n=30) groups. All participants completed a health history questionnaire reporting existing and past medical conditions and treatments. Individuals were excluded for reporting existing cardiovascular disease (e.g., coronary artery disease, angina pectoris, myocardial infarction, heart failure, and cardiac surgery), neurological disease (e.g., stroke, Parkinson's disease, and clinically significant traumatic brain injury), or contraindications to Magnetic Resonance Imaging. Participants with metabolic syndrome risk factors (e.g., hypertension, dyslipidemia, diabetes mellitus) were included. The local institutional review board approved the study, and informed consent was obtained from all participants.

COGNITIVE ASSESSMENT

All participants completed a comprehensive cognitive battery covering five cognitive domains. These domains included global cognitive functioning, language function, visual-spatial abilities, memory functions and attention-executive functions **(Haley, 2007)**. Global cognitive function was measured by the Mini-Mental State Exam (MMSE) and Wescher Abbreviated Scale of Intelligence (WASI-IQ). Language function was determined from the Category Fluency for Animals (Animals) and Speed and Capacity of Learning Processing (SCOLP) test. Visual-spatial

skills were measured by the Complex Figure Test (CFT) copy. The California Verbal Learning Test (CVLT) and Complex Figure Test (CFT) immediate recall, delayed recall, and recognition discrimination measured memory. Attention-executive functions were assessed by Trail Making Test A and B and the Controlled Oral Word Association Test (COWAT).

VASCULAR FUNCTION ASSESSMENT

All vascular function measures were completed after an overnight fast of at least 8 h having abstained from caffeine, alcohol consumption, and exercise. All measurements were taken after participants completed >15 min of supine rest in a quiet comfortable laboratory setting.

ARTERIAL STIFFNESS. Carotid-femoral (cfPWV) was recorded as previously described (VP-2000; Omron Healthcare, Bannockburn, IL) (**Cortez-Cooper, 2003)**. CfPWV was obtained using arterial applanation tonometry incorporating an array of 15-micropiezoresistive transducers placed on the carotid and femoral arteries and calculated from carotid-to-femoral artery distance divided by transit time. The transit time was determined from the time delay between proximal and distal "foot" waveforms. The arterial path length was twice measured as the straight distance between the carotid and femoral measurement sites over the body surface using a non-elastic tape measure. As a secondary metric of arterial wave reflection and arterial stiffness, augmentation index (Aix) was calculated as pressure from the shoulder to the late peak of the pulse waveform divided by the pulse pressure (ΔP/PP) **(Brown, 1999)**.

Images of the common carotid artery were captured using an iE 33 Ultrasound System equipped with a high-resolution linear-array transducer (Philips, Bothell, Washington) (Tanaka et al. 2002). A B-mode longitudinal image of the common carotid artery 1-2 cm proximal to the carotid bulb was acquired perpendicularly to the vessel so the near and far wall interfaces were

clearly visible. All ultrasound-derived images were saved in DICOM format and analyzed later with computerized image-analysis software (Vascular Research Tool Carotid Analyzer, Medical Imaging Applications, Coralville, IA). In concert with acquired carotid artery images, simultaneous recordings of pulse pressure waveforms from the contralateral common carotid artery were obtained using applanation tonometery (VP-2000; Omron Healthcare) **(Tanaka, 2000)**. Subsequently, β-stiffness index was calculated using the equations described in detail elsewhere **(O'Rourke, 2002; Laurent, 2006)** in which $\beta=\ln(SBP/DBP)\times D/\Delta D$; where SBP is the systolic blood pressure, DBP is the diastolic blood pressure, and D is carotid lumen diameter (**RHEE, 2008)**.

INTIMA-MEDIA THICKNESS. Carotid artery images obtained during the arterial stiffness measurement were analyzed with computerized image-analysis software (Vascular Research Tool Carotid Analyzer, Medical Imaging Applications, Coralville, IA). The distance between the leading edge of the intima-lumen interface and leading edge of the media-adventitia interface of the far wall was defined as the intima-media thickness (IMT). An average of at least 10 measurements resulted in the final IMT value. A single investigator blinded to subject characteristics performed all image analyses.

ENDOTHELIAL FUNCTION. Brachial artery FMD was used to assess endothelial function **(Vita, 2002)**. A B-mode Doppler ultrasound machine (iE 33 Ultrasound System, Philips, Bothell, WA) with a custom transducer-holding device was used to measure brachial artery diameters and blood flow velocity. Brachial artery images were obtained in a longitudinal orientation located 5–10 cm proximal to the antecubital fossa. Following baseline measurements, a blood pressure

cuff placed on the ipsilateral forearm distal to the elbow was inflated to 100 mmHg above baseline systolic blood pressure for 5 min using a rapid cuff inflator (E20, Hokanson, Bellevue, WA). Ultrasound-derived blood velocity and diameter data were saved as DICOM format and transferred to a computer using a digital image viewing software (Access Point 2004, Freeland Systems; Westminster, CO) for later analyses. The same investigator blinded to subject identity analyzed all ultrasound brachial images using image analysis software (Vascular Research Tool Brachial Analyzer, Medical Imaging Applications, Coralville, IA).

FMD was expressed as the percent change in brachial artery diameters recorded during the pre and post occlusion phases and was calculated using the equation: ((maximum diameter – baseline diameter)/baseline diameter)*100. The average of 10 end-diastolic brachial artery diameters before blood flow occlusion was used for baseline diameters, and the average of three peak end-diastolic diameters during the reperfusion phase was used for maximum brachial artery diameter.

NEUROIMAGING DATA ACQUISITION

MRI data for each participant was acquired in a single session on a 3T GE Signa Excite MRI scanner equipped with a standard head coil. T_1 – weighted anatomical scans of the entire brain were collected using a high-resolution spoiled gradient echo sequence (256 x 256 matrix, field of view = 24 x 24 cm^2, 1mm slice thickness, 0 gap).

Scans were processed using the default settings in the Freesurfer Imaging Analysis Suite (v.4.5; http://surfer.nmr.mgh.harvard.edu), described in detail elsewhere **(Fischl and Dale, 2000).** Cortical thickness was extracted and analyzed from *apriori* ROIs to expand upon published coordinates emperically shown to be related to cardiovascular risk factors **(Leritz, 2011)**: bilateral superior temporal gyri, bilatertal inferior frontal gyri, bilateral anterior cingulate

gyri, bilateral middle occipital, bilateral anterior cingulate gyri, bilateral inferior parietal, bilateral middle frontal, bilateral cingulate, bilateral supramarginal and orbital frontal cortex. Each ROI was selected based on their published association with cerebraovascular health, Their location coordinates are summarized in Table 2. Spherical ROIs, 5 mm in diameter, were automatically created around the central coordinate for the chosen regions according to the Talairach and Tournoux atlas **(SEO, 2007)** using the Analysis of Functional NeuroImages (AFNI) software **(Du, 2007)**.

STATISTICAL ANALYSES

Shapiro–Wilk test indicated a normal (Gaussian) distribution for all continuous variables. Descriptive statistics were calculated for demographics, vascular and cognitive variables. Independent samples *t*-tests were performed with race as a categorical variable defining groups. Levene's test indicated equal variance for all outcomes in both groups. Univariate linear regression examined the association between vascular indices and cortical thickness within each *a priori* ROI. The decision to not adjust models for typical covariates was based on subject matching between groups. Moderation analyses were performed using Preacher and Hayes' macro to assess the interaction of race and vascular functions on each significant *a priori* ROI. To be considered significant, both the race and interaction terms had to reach the level of $p<0.05$. Data are presented as mean ± SD. All data were analyzed using SPSS statistical analysis software version 22.0 (SPSS Statistics, IBM, Armonk, NY, USA).

RESULTS

SUBJECT CHARACTERISTICS. Sample descriptive characteristics are reported in Table 3. Group matching resulted in no significant differences in any participant descriptive characteristics with the exception of height (p=0.01). Blood pressure and blood cholesterol levels were not different between the groups. Carotid artery β-stiffness index, pulse wave velocity, and augmentation index were significantly greater in Hispanics than in Caucasians. Carotid IMT and FMD were not different between the groups.

CORTICAL THICKNESS. Cortical thicknesses of each *a priori* region of interest (ROI) is presented in Table 4. Mean cortical thickness was not different between the groups in most ROI examined. However, the Hispanic cohort exhibited significant thinning of the left inferior frontal gyrus (LIFG).

COGNITIVE BATTERY. No group difference was observed in MMSE score (Table 5). Global cognitive function was lower in the Hispanic group on the WASI Vocabulary and FSIQ Total. Language difficulties were further reflected in the SCOLP tests as Hispanics performed worse on errors and spot the word subtests. In cognitive domains largely independent of language processing, the Hispanic group exhibited lower working memory on the CVLT delayed recall and lower performance in the attention-executive domain with the Digit Span. No differences were found on remaining cognitive tests.

RACE INTERACTION. Univariate regression revealed that PWV, IMT, and FMD did not predict left inferior frontal gyrus (LIFG) thickness. As shown in Figure 3, carotid AI did not predict

LIFG thickness in Caucasians, but did so in Hispanics (p=0.04). The interaction term between AIx and race was not significant but was trending (p=0.099). As depicted in Figure 4, β-stiffness index was a significant predictor of LIFG thickness in Caucasians (p=0.02) but not in Hispanics (p=0.90). The interaction term of race and β-stiffness did not reach statistical significance.

DISCUSSION

The present study compared measurements of vascular health and gray matter integrity across middle-aged Caucasian and Hispanic adults. The primary finding was significantly elevated pulse wave velocity, arterial wave reflection, β-stiffness accompanied by selective cortical atrophy in the left inferior frontal gyrus in the Hispanic adults.. Additionally, working memory and attention-executive domains of cognition were lower in the Hispanic group compared to their age-, education- and MMSE-matched Caucasian counterparts.. The present findings further support the vascular hypothesis of dementia where compromised cardiovascular health, changes in cortical morphology, and impairment of cognitive function are concurrently present. These results may form a basis for future investigations that help explain the increased prevalence and earlier onset of symptoms of AD in the Hispanic population.

Cardiovascular risk factors have been hypothesized to disturb arterial hemodynamics leading to chronic brain hypoperfusion, reduced energy substrate delivery which can lead to neuronal death, and ultimately cognitive dysfunction **(de la Torre, 2012)**. Even at subclinical levels, these risk factors confer impairments to brain structure and function in specific processing regions **(den Heijer, 2005; Leritz, 2009)**. This model is reinforced by an investigation that demonstrated lower arterial stiffness was associated with occipitoparietal perfusion and enhanced cognitive function in middle-aged adults (**Tarumi, 2013)**. Additionally, chronic brain hypoperfusion has been linked to cortical microinfarcts **(Okamoto, 2012)** that lead to cognitive impairment **(Kövari, 2007; Arvanitakis Z, 2011).** Hispanics have increased susceptibility to acquiring these risk factors that occurs prior to neurodegeneration and cognitive impairment **(Vermeer, 2003).** With no present cure to AD, identification and management of these risk

factors through lifestyle and pharmacological interventions is essential, especially in the Hispanic population who exhibit heightened vulnerability.

The LIFG is critical to executive function and inhibitory control. The LIFG is related to the recall of semantic information, for example deciding which part of a word's definition is appropriate in context **(Thompson-Schill, 1999)**. Not only does the LIFG work to select the correct semantic information, it aids in its retrieval **(Hirshorn, 2006)**. Dyslipidemia is associated with reduced cortical thickness of the LIFG **(Leritz, 2011)**. In a study using a Go/NoGo task, patients with LIFG lesions made more false alarm errors than healthy controls and performed worse when response inhibition was most difficult **(Swick, 2008)**. While the changes in LIFG thickness were not significantly associated with the observed differences in cognitive function in the present study, this region appears related to the working memory and attention-executive domains. Maintaining the structural integrity of this region may delay the onset of semantic recall errors.

Undoubtedly, the greatest strength of the current investigation was the cohort of apparently healthy middle-aged Hispanic adults. Matching participants across ethnicities also enabled isolation of vascular function, gray matter morphology, and cognitive function from the influence of differential covariates between the groups. With participant matching, there were no group differences in key confounding factors, including the number of metabolic risk factors. Despite their equivalent health and global cognitive statuses, the Hispanic group demonstrated significantly worse vascular health, selective cortical atrophy, and domain specific cognitive impairment.

Unfortunately, our modest sample size limited the statistical power to detect vascular mediation of impaired cognition or racial moderation of the relationships between vascular

health, gray matter morphology, and cognitive function. Although there was a significant relation between the number of metabolic syndrome components and decreased cortical thickness, this relationship was not significantly mediated by any measure of vascular function, nor moderated by race (data not shown). Therefore, we could not determine if the causation of cognitive impairment from cortical atrophy that can induce impaired vascular health is unique to the Hispanic population.

The present investigation examined the relation of indices of vascular health and gray matter morphology in middle-aged Hispanic and matched Caucasian adults. In spite of the fact that both Hispanics and Caucasians were matched for key variables, Hispanics exhibited significantly greater arterial stiffness, arterial wave reflection, and β-stiffness index as well as selective cortical thinning of the LIFG. However, ethnicity was not found as a moderator of the relationship between vascular function, gray matter integrity, and cognitive function. Future investigation into the physiological mechanisms behind the increased prevalence of AD in Hispanics is necessary, given enhanced susceptibility to cardiovascular risk factors in this population. Determining which risk factors are most commonly acquired in Hispanics and what impact each risk factor confers to vascular outcomes, brain structure, and cognitive function is vital.

APPENDIX A - TABLES

Table 1: Left hemisphere regions associated with cardiovascular risk factors with listed Talaraich coordinates

Risk Factor	Area	X	Y	Z
HTN	Superior Temporal	-51	17	0
Cholest	Inferior Frontal	-44	24	2
Gluc	Anterior Cingulate (perigenual)	-2	36	7
Cholest/Gluc	Middle Occipital	-35	-76	16
HTN	Anterior Cingulate (middle)	-1	26	21
Cholest	Inferior Parietal	-48	-24	25
HTN/Cholest	Middle Frontal	-37	-29	26
Cholest	Cingulate	-6	28	31
HTN	Supramarginal	-51	-48	31

HTN = Hypertension; Cholest = Cholesterol; Gluc = Glucose.

Table 2: Right hemisphere regions associated with cardiovascular risk factors with listed Talaraich coordinates.

Risk Factor	Area	X	Y	Z
Gluc	OFC	7	29	-20
HTN	Superior Temporal	51	17	0
Cholest	Inferior Frontal	44	24	2
Cholest/Gluc	Middle Occipital	35	-76	16
HTN	Anterior Cingulate (middle)	1	26	21
Cholest	Inferior Parietal	48	-24	25
HTN/Cholest	Middle Frontal	37	-29	26
Cholest	Cingulate (high)	6	28	31
HTN	Supramarginal	51	-48	31

HTN = Hypertension; Cholest = Cholesterol; Gluc = Glucose.

Table 3. Selected subject characteristics

		Caucasian	Hispanic	*p*-value
Descriptive	Male/Female (n)	14/16	14/16	-
	Age (years)	49.0 ± 5.2	48.4 ± 5.3	0.66
	Education (years)	15.5 ± 2.3	15.2 ± 2.3	0.61
	Mini Mental State Examination (score)	28 ± 1	27 ± 2	0.13
	Height (cm)	172 ± 8	166 ± 10	0.01
	Body mass (kg)	85.4 ± 17.4	85.1 ± 19.9	0.94
	BMI (kg/m^2)	28.7 ± 5.4	30.7 ± 6.8	0.21
	Systolic Blood Pressure (mmHg)	124 ± 16	125 ± 14	0.82
	Diastolic Blood Pressure (mmHg)	75 ± 10	75 ± 11	0.90
	Blood glucose (mg/dl)	108 ± 29	116 ± 41	0.43
	LDL-cholesterol (mg/dl)	118 ± 34	108 ± 32	0.30
	HDL-cholesterol (mg/dl)	45 ± 17	48 ± 13	0.56
	Triglyceride (mg/dl)	167 ± 85	155 ± 114	0.67
	Total cholesterol (mg/dl)	204 ± 54	187 ± 38	0.17
	Metabolic Syndrome Components (n)	2.5 ± 1.5	2.5 ± 1.5	0.96
Vascular	Pulse wave velocity (cm/s)	1034 ± 178	1178 ± 264	0.02
	Augmentation index (%)	13 ± 17	22 ± 15	0.05
	Beta-stiffness index (AU)	6.33 ± 2.36	8.10 ± 2.04	0.01
	Carotid intima media thickness (mm)	0.59 ± 0.13	0.58 ± 0.13	0.84
	Flow-mediated dilation (%)	5.3 ± 4.0	5.1 ± 3.8	0.85

Data are means ±SD. BMI=body mass index

Table 4. Mean cortical thicknesses of each *a priori Regions of interest*

		Talairach Coordinates			Caucasian (n=30)	Hispanic (n=30)	
					Mean Thickness (mm)	Mean Thickness (mm)	
		X	Y	Z			*p*-value
Left	Superior Temporal	-51	17	0	2.37 ± 0.08	2.35 ± 0.08	0.35
	Inferior Frontal	-44	24	2	2.55 ± 0.27	2.41 ± 0.25	0.04
	Anterior Cingulate	-2	36	7	2.25 ± 0.58	2.17 ± 0.46	0.57
	Middle occipital	-35	-76	16	2.33 ± 0.31	2.31 ± 0.34	0.81
	Anterior Cingulate	-1	26	21	1.56 ± 0.78	1.27 ± 0.69	0.14
	Inferior Parietal	-48	-24	25	2.63 ± 0.47	2.66 ± 0.50	0.89
	Middle Frontal	-37	-29	26	2.11 ± 0.26	2.11 ± 0.27	0.95
	Cingulate	-6	28	31	3.07 ± 0.64	2.78 ± 0.63	0.08
	Supramarginal	-51	-48	31	2.44 ± 0.33	2.59 ± 0.26	0.07
Right	Orbitofrontal Cortex	7	29	-20	2.38 ± 0.08	2.35 ± 0.07	0.20
	Superior Temporal	51	17	0	2.61 ± 0.58	2.55 ± 0.47	0.70
	Inferior Frontal	44	24	2	2.49 ± 0.25	2.49 ± 0.35	0.94
	Middle Occipital	35	-76	16	2.35 ± 0.25	2.34 ± 0.22	0.86
	Anterior Cingulate	1	26	21	0.47 ± 0.34	0.60 ± 0.55	0.26
	Inferior Parietal	48	-24	25	2.57 ± 0.44	2.54 ± 0.42	0.78
	Middle Frontal	37	-29	26	1.97 ± 0.63	1.96 ± 0.46	0.97
	Cingulate	6	28	31	3.06 ± 0.46	3.04 ± 0.47	0.84
	Supramarginal	51	-48	31	2.48 ± 0.31	2.49 ± 0.34	0.92

Data are means±SD.

Table 5. Cognitive Function

Domain	Caucasian Mean ± SD	Hispanic Mean ± SD	*p-value*
Global cognitive functioning			
Mini Mental State Examination	28.4 ± 1.4	27.8 ± 1.9	0.13
WASI Matrix reasoning	27.3 ± 3.4	25.1 ± 3.6	0.83
WASI FSIQ Total	117.6 ± 12.2	109.2 ± 11.3	0.01
Language			
WASI Vocabulary	68.0 ± 7.7	62.9 ± 9.5	0.02
Speed and Capacity of Learning Processing			
Comprehension	57.5 ± 11.9	51.3 ± 14.0	0.07
Errors	0.9 ± 1.7	2.0 ± 2.2	0.04
Spot the Word	50.9 ± 4.6	48.0 ± 5.0	0.03
Visual–spatial			
Complex Figure Test (CFT-Copy)	29.7 ± 4.4	29.5 ± 4.3	0.86
Memory			
California Verbal Learning Test (CVLT)			
Immediate recall	11.4 ± 3.2	10.1 ± 2.7	0.09
Delayed recall	11.7 ± 3.3	10.8 ± 3.0	0.27
Recognition discrimination	3.5 ± 2.4	3.0 ± 0.8	0.25
Complex Figure Test (CFT)			
Immediate recall	17.1 ± 5.5	14.8 ± 6.0	0.14
Delayed recall	16.8 ± 5.1	13.8 ± 5.9	0.03
Recognition discrimination	19.6 ± 4.3	19.8 ± 2.6	0.82
Attention-executive			
Trail Making Test A, Time (Trails AT)	35 ± 12.3	32.1 ± 10.5	0.32
Trail Making Test B, Time (Trails BT)	77.9 ± 31.8	72.9 ± 29.1	0.53
Controlled Oral Word Association Test (COWAT)	35.4 ± 12.0	36.7 ± 8.1	0.63
WAIS-III Digit Span Subtest (Digit Span)	17.9 ± 3.9	15.5 ± 3.8	0.02

APPENDIX B - FIGURES

Figure Legends

Figure 1: Proposed model depicting the differences of dementia pathogenesis in Caucasians and Hispanics.

Figure 2: Augmentation index significantly predicts left inferior frontal cortex thickness in Hispanics but not in Caucasians. Open circles represent individual cases of the Hispanic cohort while the dashed line represents the group's line of best fit. Closed circles represent individual cases of the Caucasian cohort while the full line represents the group's line of best fit.

Figure 3: β-stiffness significantly predicts left inferior frontal cortex thickness in Caucasians but not in Hispanics. Open circles represent individual cases of the Hispanic cohort while the dashed line represents the group's line of best fit. Closed circles represent individual cases of the Caucasian cohort while the full line represents the group's line of best fit.

Figure 1.

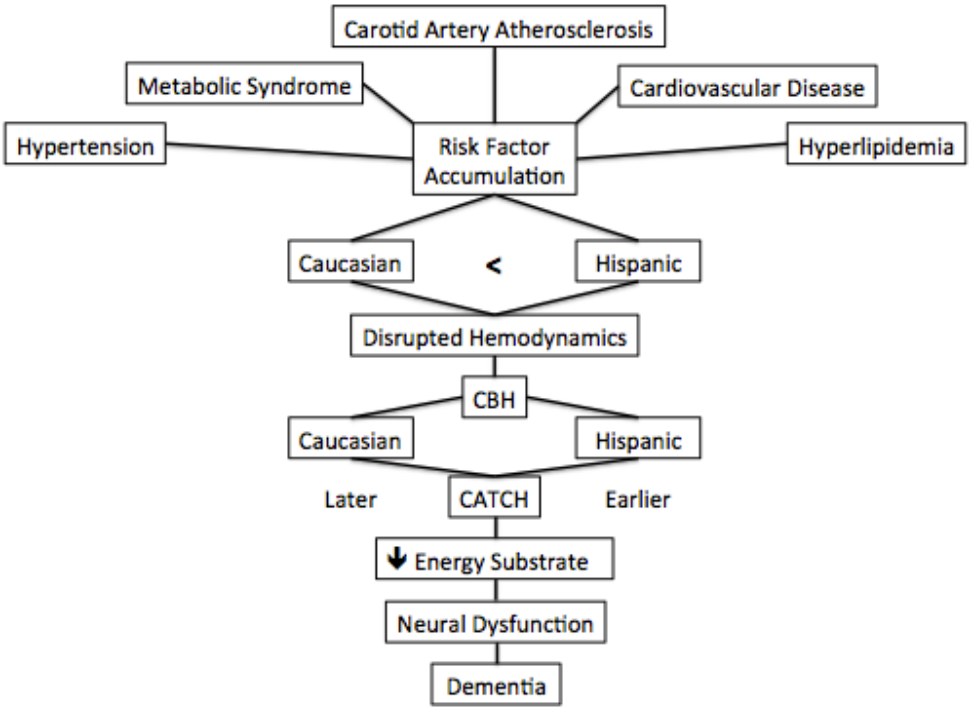

Carotid Artery Atherosclerosis
Metabolic Syndrome
Cardiovascular Disease
Hypertension
Risk Factor Accumulation
Hyperlipidemia
Caucasian
<
Hispanic
Disrupted Hemodynamics
CBH
Caucasian
Hispanic
Later
CATCH
Earlier
Energy Substrate
Neural Dysfunction
Dementia

Figure 2.

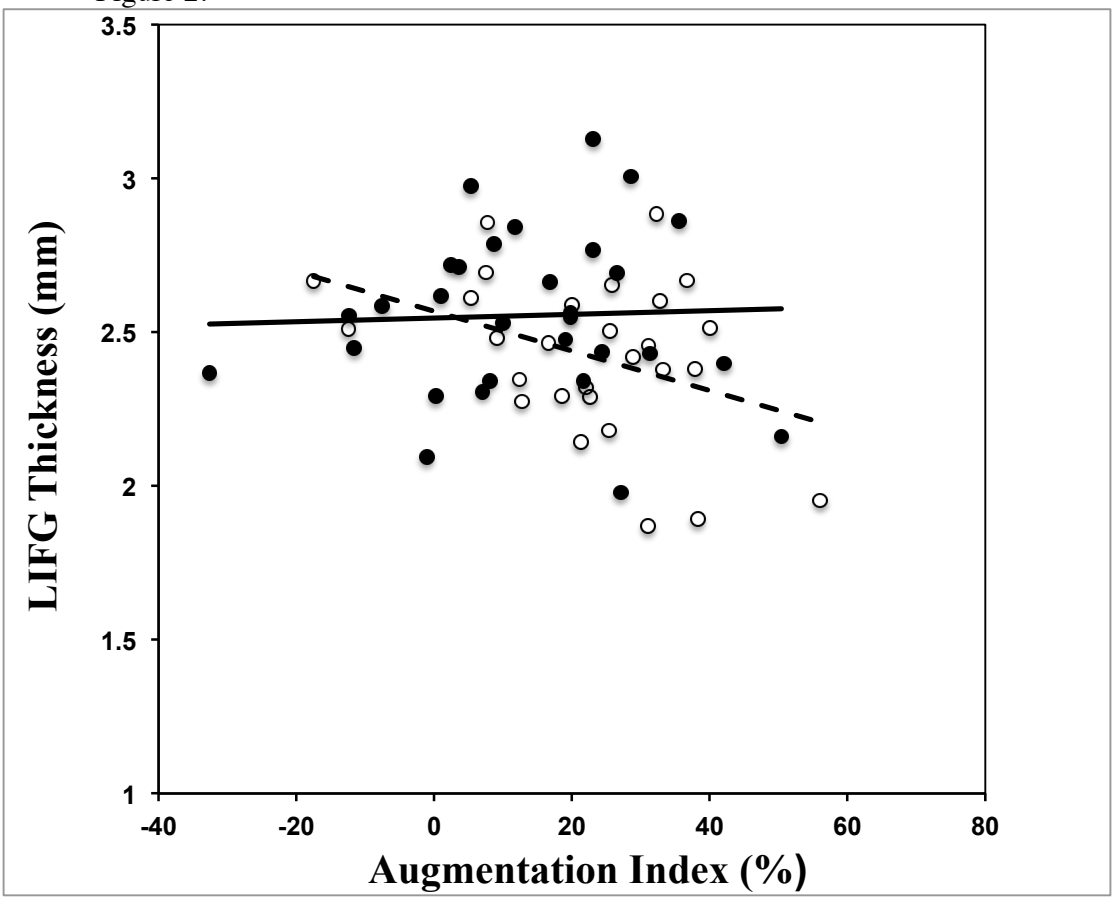
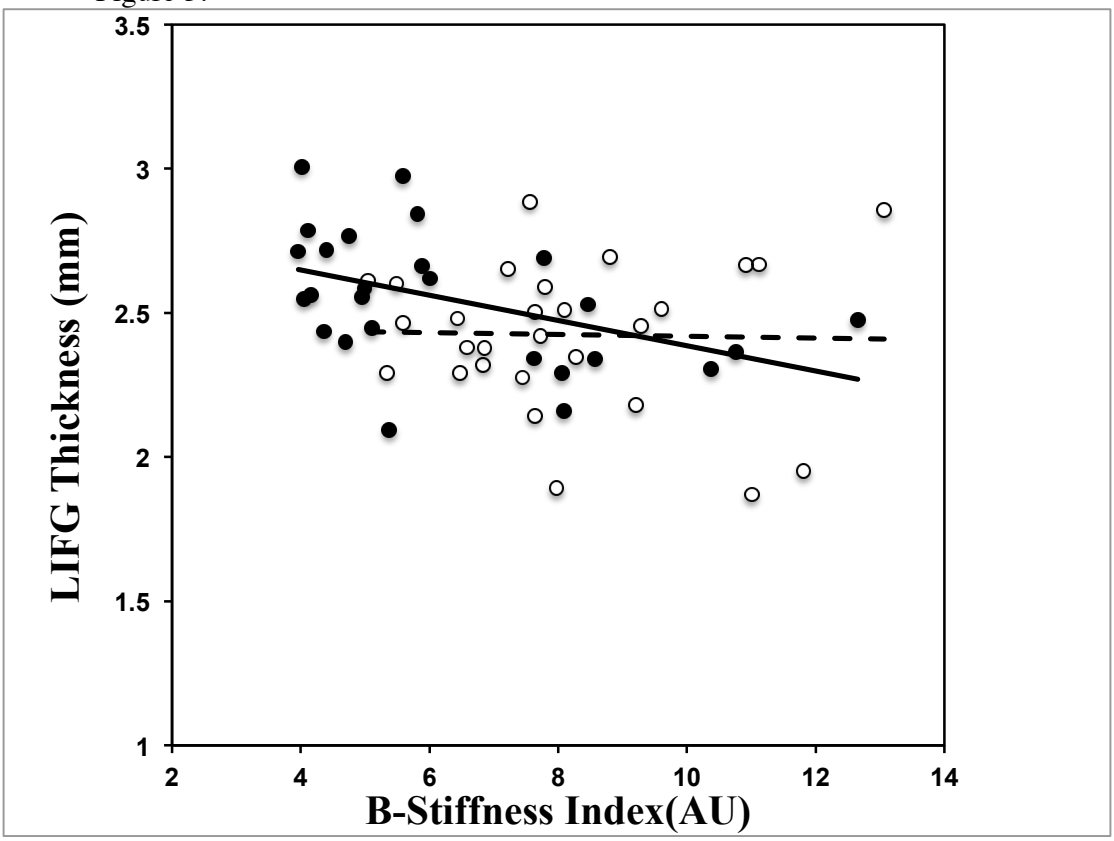

LIFG Thickness (mm)
3.5
3
2.5
2
1.5
1
-40
-20
0
20
40
60
80
Augmentation Index (%)

Figure 3.


LIFG Thickness (mm)
3.5
3
2.5
2
1.5
1
2
4
6
8
10
12
14
B-Stiffness Index(AU)

APPENDIX – C

APPROVED BY IRB ON: 08/25/2008 EXPIRES ON: 08/27/2009

IRB#2007-09-0142 *Informed Consent to Participate in Research The University of Texas at Austin*

You have been invited to participate in a research study. This form provides you with information about the study. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part. Your participation is entirely voluntary and you can refuse to participate without penalty or loss of benefits to which you are otherwise entitled. If you are a student, your decision to participate or not to participate as a test subject will NOT affect your grade in any course.

Title of Research Study: Family history of hypertension and brain function

Principal Investigator(s): Andreana P. Haley, Ph.D., Department of Psychology, (512) 232-0863
Co-Investigator(s): Hirofumi Tanaka, Ph.D., Department of Kinesiology, (512) 232-4801
Graham McDougall, Ph.D., School of Nursing, (512) 471-7936

Funding source: *N/A*

What is the purpose of this study? The purpose of this study is to understand how family history of hypertension affects brain function. If you decide to participate, you will be one of about 120 people in this study.

What will be done if you take part in this research study? If you agree to participate in this study, you will be asked to complete a screening visit and, if eligible, two research visits scheduled within two weeks of each other. Each visit will last approximately two-to-three hours. During one of the study visits, images of your brain will be taken using a General Electric 3.0 Tesla Magnetic Resonance Imaging (MRI) scanner at the UT Imaging Research Center. The MRI scanner is a machine that enables us to acquire images of the brain non-invasively by manipulating magnetic fields. During that visit you will also be asked to complete some paper-and-pencil tests of attention, memory, and visuospatial functioning. During a separate visit, you will be asked to go to the Cardiovascular Aging Laboratory at the Department of Kinesiology at UT (Bellmont Hall) and complete some non-invasive assessments of cardiovascular functioning similar to the ones you may undergo during a visit to a Cardiologist (e.g., blood pressure assessment, echocardiogram, ultrasound assessment of the carotid artery).

Screening Visit (~2 hours)
During this visit:

Your blood pressure will be measured non-invasively by the arm cuff technique (as in your Doctor's office).

Blood samples will be taken to get information on your cholesterol, blood sugar, stress hormones, proteins related to inflammation and arterial stiffening, and gene information. Genetic research is about finding the specific location of genes on chromosomes, learning how genes work, and developing treatments and cures for diseases that are genetically based. The information will only include those genes that are closely related to the purpose of the study (genetic risk for developing hypertension) but not linked to the risk for other disease states. Your blood sample will be stored up to 10 years to give the researchers enough time to analyze the sample and then disposed of it properly according to the university guidelines. A small blood sample (4 teaspoons) will be drawn from you after a 12-hour fast. We will also test for diabetes by having you drink a sugary drink and measure your blood sugar after two hours with another blood draw (4 teaspoons).

Cardiovascular Assessment Visit (~2 hours)
During this visit:

Your blood pressure will be measured non-invasively by the arm cuff technique (as in your Doctor's office).

Your heart structure and function will be measured non-invasively by putting a gel on the chest and placing a device called a transducer of an ultrasound machine on the chest.

Hardening of your artery will be measured non-invasively by; i) placing a device called a transducer of an ultrasound machine on the skin of the carotid (neck), femoral (hip joint), and wrist arteries; and ii) placing two pencil-like devices over various arteries (carotid, femoral, brachial, wrist, and ankle arteries). An ultrasound machine is the same machine that is used to evaluate the development of a baby during pregnancy. Your blood pressure will also be measured non-invasively by placing a pencil-like device over the carotid (neck) artery.

Changes in blood pressure regulating system will be induced by a) squeezing a gripping device with a hand as hard as you can (handgrip exercise); b) placing a foot or hand in ice cold water for 2 minutes; and c) blowing air into a small tube for 15-20 seconds. Heart rate, blood pressure, and carotid (neck) artery will be measured non-invasively during these procedures.

MRI/Cognitive Testing Visit (~2 hours)
During this visit, you may be asked to do some or all of the following:

Lie on a table that will be slid into the MRI scanner (so that your head and upper

body are inside the magnet tube);

Wear earplugs and/or headphones to reduce the noise made by the MRI scanner (the magnets can make very loud noises);

Have foam pads placed around your head to help you hold your head still during the MRI scan, so that the scans will be clear;

Be fitted with a bite bar made of impression compound that will help to stabilize your head.

Have your hands resting on plastic response pads, similar to wearing gloves.

Lie still throughout your time in the MRI scanner;

View various visual stimuli and/or listen to sounds. You may be also asked to make judgments, recall certain words or pictures, or make finger, hand, or eye movements.

Complete a brief battery of paper-and-pencil measures of cognitive function such as tests of memory, attention, and visuospatial skills.

In each experimental session, anatomical images (images that show us the structures in your brain) will be obtained during the study. In addition to the anatomical images, functional images may be obtained for about 20-30 minutes. Functional images are scans that show us how the brain works by illustrating what the brain is actively doing while you view various stimuli and/or perform particular tasks. The researcher will tell you before you enter the scanner exactly how long each procedure will take, and during the exam the researcher will tell you when each procedure will occur over the intercom. We also plan to acquire images containing information about blood perfusion in your brain as well as information about chemical composition. You will not be required to do any tasks during those scans, but to relax and lie quietly in the scanner.

The Project Duration is: Your participation will be 120-180 minutes for one-to-three sessions. The researchers will be conducting the study for approximately 36 months. However, it will take you no more than one month to complete all of your visits.

Approximate Number of Participants: 120

What are the possible discomforts and risks?

Screening Visit:

A slight risk of fainting, bruising, or infection related to the blood draw.

Cardiovascular Visit: The investigators have made every effort to keep the risks and discomforts to a minimum. You will be carefully screened at the beginning of this study to see if you could participate safely. But, the potential risks associated with this study include:

Some discomfort associated with placing a hand or a foot in cold water.

A slight risk of dizziness and/or fainting associated with rapid changes in blood pressure.

A possible risk that genetic testing might reveal information regarding a carrier or disease state that requires difficult choices regarding your current or future health, insurance coverage, career, marriage, or reproductive options. As previously stated, we intend to only pursue genes related to the development of hypertension. Due to the preliminary nature of this inquiry, all information obtained will be used for research purposes only and will not be provided to anyone including individual participants.
A possibility of accidentally exposing your health/medical information. All precautions will be taken to separate identifying information from data collected during the study.

Identifying information will be kept securely locked in a cabinet at the Department of Psychology.

MRI visit: There are no known significant risks or side effects associated with MRI scans. The magnetic fields, at the strengths used, are not harmful and the MRI scanning procedures used are within the Food and Drug Administration [FDA] guidelines for radiofrequency electromagnetic field exposure created by the MRI.
There is a risk if metal objects are near the MRI because they can be drawn into the MRI scanner and that could hurt someone in or near the machine. Metal objects might be in a body if a person has electrically, magnetically, or mechanically activated implants (such as cardiac pacemakers), or clips on blood vessels in their brain, or other metallic objects in their body such as shrapnel, bullets, buckshot, or metal fragments. To protect against this risk, you will be carefully screened for previous exposure to metallic fragments or to implanted devices. You will also be asked to place all metallic and magnetic objects in your possession (e.g. keys, jewelry, credit cards) in a locker outside the MRI room. The scanner room is also screened for such items before you are allowed to enter.
Although there are no known risks of an MRI scan to the unborn fetus, we will not let you take part in the study if you are or might be pregnant.
Some people have reported mild discomfort during MRI scans, such as:

Claustrophobia (fear of enclosed spaces). You will be asked to lie on a table that slides into a horizontal cylinder only slightly wider than your body in all directions and your head will be secured to help you stay still. If you are likely to be uncomfortable or afraid in enclosed spaces, you should let the researcher in charge of the scan know.

Reaction to noise levels. The MRI scanner makes loud knocking or beeping sounds during scans; earplugs and/or headphones will be provided to help reduce this noise.

Peripheral nerve stimulation. Because magnetic gradients are used during scans, the possibility exists for peripheral nerve stimulation. If this happens, you may feel twitching or tingling sensations, typically along your arms, torso, or back.

Dizziness and nausea, which may occur if you suddenly move your head while

you are in the MRI and it is active (not in a rest period).

You may feel some warmth from the radio frequency coils, the cables to the coils, or the response and physiological monitoring devices. The MRI scanner is set so that this heating will be no more than one degree of body temperature.

You may notify the research staff at any time if you feel uncomfortable, no matter what the reason. You will be in contact with the research staff at all times you are in the MRI scanner through an intercom system mounted in the MRI scanner. You will also be told how let the operator know if you wish to immediately stop scanning and be removed from the magnet. The MRI scan can be stopped at any time at your request. If you think that you have experienced a research-related injury, report this to the director of the

Imaging Research Center, Dr. Michael Domjan, domjan@psy.utexas.edu, (512) 471-7702.

What are the possible benefits to you or to others?
You will receive the following: 1) results of tests and physiological measures (taken by the investigators) with potential health relevance such as blood pressure readings, measurement of blood cholesterol levels and screening for diabetes. You may also experience the satisfaction of contributing to scientific knowledge that could result in the documentation of a benefit to reduce the risk of vascular cognitive impairment in men and women. Or you may receive no direct benefit at all.

If you choose to take part in this study, will it cost you anything? There are no costs to you for participating as a test subject.

Will you receive compensation for your participation in this study? You will receive 25 dollars to complete the screening visit, 35 dollars for the first study visit, and 65 dollars for the second study visit.

What if you are injured because of the study? Many forms of research involve some risk of injury. If any complications arose, the researchers would assist you by referring you to appropriate medical practitioners, but the University has no program or plan to provide treatment for research related injury or payment in the event of a medical problem. If injuries occur as a result of study activity, eligible University students may be treated at the usual level of care with the usual cost for services at the Student Health Center, but the University has no policy to provide payment in the event of a medical problem. In the unlikely event of a research related injury, please contact the principal investigator. **If you do not want to take part in this study, what other options are available to you?** Your participation in this study is entirely voluntary. You may refuse

to participate or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. Nonparticipation or withdrawal will not affect your grades or academic standing.

How can you withdraw from this research study and whom should you call if you have questions?

If you wish to stop your participation in this research study for any reason, you should contact the principal investigator: **Andreana Haley at (512) 232-0863. You should also call the principal investigator for any questions, concerns, or complaints about the research. You are free to withdraw your consent and stop participation in this research study at any time without penalty or loss of benefits for which you may be entitled. Throughout the study, the researchers will notify you of new information that may become available and that might affect your decision to remain in the study.**

In addition, if you have questions about your rights as a research participant, or if you have complaints, concerns, or questions about the research, please contact Jody Jensen, Ph.D., Chair, The University of Texas at Austin Institutional Review Board for the Protection of Human Subjects, or the Office of Research Compliance and Support at (512) 232-2685.
How will your privacy and the confidentiality of your research records be protected?

Images generated in this study will be stored on the Department of Psychology server, with the primary reference field being the study or scan number, which is automatically generated by the MRI system. Personal information linking a participant with a scan will be maintained in a manually generated log, which will be stored in a securely locked cabinet in the Department of Psychology. This is to insure that there is an "air gap" between the images/data generated for research purposes and personal identifying information. The Department of Psychology sever is backed up on a daily basis. Access to the scans/data on the server is password protected and only available to relevant researchers.

All scans and paperwork (cognitive and cardiovascular assessment data) will be protected to the extent provided by law.

Possible Discovery of Findings Related to Medical Imaging
If you volunteer for this research study, the MRI scans that we will perform are NOT necessarily equivalent to MRI scans used to diagnose medical problems. Many

potentially serious problems may be undetectable on these scans. A negative MRI should not be used to avoid a visit to your primary physician. If you are having physical symptoms that you are concerned about, you should see your primary physician, who will determine the examinations required to arrive at a proper medical diagnosis.

If in the unlikely event it becomes necessary for the Institutional Review Board to review your research records, then the University of Texas at Austin will protect the confidentiality of those records to the extent permitted by law. Your research records will not be released without your consent unless required by law or a court order. The data resulting from your participation may be made available to other researchers in the future for research purposes not detailed within this consent form. In these cases, the data will contain no identifying information that could associate you with it, or with your participation in any study.

Will the researchers benefit from your participation in this study*?* N/A

Signatures:

As a representative of this study, I have explained the purpose, the procedures, the benefits, and the risks that are involved in this research study:

_____

Signature and printed name of person obtaining consent Date

You have been informed about this study's purpose, procedures, possible benefits and risks, and you have received a copy of this form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time. You voluntarily agree to participate in this study. By signing this form, you are not waiving any of your legal rights.

_____

Printed Name of Subject Date

_____

Signature of Subject Date

_____

Signature of Principal Investigator Date

APPROVED BY IRB ON: 08/25/2008 EXPIRES ON: 08/27/2009

Medical Release

Name and address of Personal Physician

_____

_

I hereby agree to have the Principal Investigator or the Medical Director of the Imaging Research Center report to my Personal Physician findings of potential medical significance that might be obtained as a result of my participation in this study.

_____

Signature of Subject Date

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