Cardiovascular Disease Risk Factors, Tract-Based Structural Connectomics,

and Cognition in Older Adults

BY

ELIZABETH A. BOOTS,
B.S., University of Wisconsin – Madison, 2014

THESIS

Submitted as partial fulfillment of the requirements
for the degree of Master of Arts in Psychology
in the Graduate College of the
University of Illinois at Chicago, 2018

Chicago, Illinois

Defense Committee:

Stewart A. Shankman, Chair
Melissa Lamar, Advisor, Rush University Medical Center
Olusola Ajilore, Psychiatry

This thesis is dedicated to my parents, Emilie and Bill Boots, and to my fiancé, Tim Pairitz,

without whom this work simply would never have been accomplished.

ACKNOWLEDGMENTS

TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AC-PC	Anterior Commissure – Posterior Commissure
AD	Alzheimer's Disease
AIP	Attention and Information Processing Speed
ANTs	Advanced Normalization Tools
BAI	Beck Anxiety Inventory
BCT	Brain Connectivity Toolbox
BDI	Beck Depression Inventory
BET	Brain Extraction Tool
BRAVO	Brain Volume
CVD-RFs	Cardiovascular Disease Risk Factors
CVLT-II	California Verbal Learning Test-II
DM	Type 2 Diabetes Mellitus
DTI	Diffusion Tensor Imaging
EPI	Echo-Planar Imaging
FA	Fractional Anisotrophy
FAS	Letter Fluency
FOV	Field of View
FSRP	Framingham 10-Year Stroke Risk Profile
HAM-D	Hamilton Depression Rating Scale
ICV	Intracranial Volume
IRB	Institutional Review Board
LH	Left Hemisphere

LIST OF ABBREVIATIONS (continued)

MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
PCA	Principal Component Analysis
PVIQ	Predicted Verbal Intelligence Quotient
RH	Right Hemisphere
ROIs	Regions of Interest
SCID	Structured Clinical Interview for DSM-IV-TR
SMI	Subjective Memory Impairment
TE	Echo Time
TMT	Trail Making Test
TR	Repetition Time
UIC	University of Illinois at Chicago
WTAR	Wechsler Test of Adult Reading

SUMMARY

Cardiovascular disease risk factors (CVD-RFs) are associated with decreased gray and white matter integrity and cognitive impairment in older adults. Less is known regarding the interplay between CVD-RFs, structural integrity *between* gray and white matter regions, and cognition. Using data from non-demented/non-depressed older adults, we examined whether CVD-RFs were associated with measures of tract-based structural connectivity; if alterations in connectivity mediated the association between CVD-RFs and cognition; and whether educational quality was protective against connectivity alterations.

Ninety-six participants (age=67.9 years; 53.1% female; 46.9% Black) underwent CVD-RF assessment, MRI, and cognitive evaluation. Framingham 10-year stroke risk (FSRP) quantified CVD-RFs. Graph theory analysis integrated T1-derived gray matter regions of interest (ROIs) and DTI-derived white matter tractography into connectivity matrices, which were analyzed for local efficiency and centrality. PCA of cognitive variables resulted in three rotated factor scores: memory (CVLT-II Trial 1-5 Total, Delayed Free Recall, Recognition Discriminability); executive function (FAS, Trail Making Test (TMT) B-A, Letter-Number Sequencing, Matrix Reasoning); attention/information processing (AIP; TMT-A, TMT-M, Digit Symbol).

Linear regressions adjusting for word reading and intracranial volume revealed associations between FSRP and centrality in six ROIs, efficiency in seven ROIs, and AIP. Analyses revealed mediation of right hippocampal centrality on FSRP and AIP and left caudal middle frontal gyrus efficiency on FSRP and AIP. No protective effects of educational quality were noted. In sum, stroke risk plays deleterious roles in connectivity that negatively impact cognition, suggesting the importance of multi-modal neuroimaging biomarkers in understanding brain-behavior pathways in preclinical aging.

I. **INTRODUCTION**

A.   **Background**

Dementia, and more specifically Alzheimer's disease (AD), has quickly become a health epidemic in the United States, with approximately 5.5 million adults affected to date, and 8.3 million additional cases expected by the year 2050 (Alzheimer's Association, 2018). Further, of the 244 drugs tested in clinical trials for AD from 2002 through 2012, only one drug received Food and Drug Administration approval, and no trials have resulted in curative therapies for AD (Alzheimer's Association, 2018). With no curative therapies currently available, attention has shifted to identifying modifiable risk factors that could delay or even prevent the onset of dementia. One such modifiable risk factor is cardiovascular health, including factors such as hypertension and Type 2 diabetes mellitus (DM; Barnes & Yaffe, 2011).

A well-established literature of over 3,000 publications has demonstrated that cardiovascular disease risk factors (CVD-RFs) are associated with brain structure and cognition, as well as risk for and development of dementia both cross-sectionally and longitudinally. For example, in gray matter, hypertension has been associated with less whole brain volume in older adults (Firbank et al., 2007; Wiseman et al., 2004). More specifically, hypertension was linked with decreases in frontal, parietal, and hippocampal volumes in a recent meta-analysis (Beauchet et al., 2013). DM has also been associated with decreased whole brain as well as hippocampal volume in older adults (Roberts et al., 2014). Additionally, several comprehensive empirical studies examining a variety of CVD-RFs including hypertension, diabetes, smoking, and obesity across the lifespan found relationships between increased cardiovascular disease risk and decreased whole brain and hippocampal volumes, and alterations in frontal as well as more posterior regions of the brain (Debette et al., 2011; Gonzales et al., 2017; Leritz et al., 2011). It

should be noted that a recent review outlined that in individuals without a history of overt cardiovascular disease, the presence of CVD-RFs including hypertension, DM, obesity, hyperlipidemia, and smoking were not only associated with structural brain changes, but also functional changes including alterations in cerebral blood flow (Friedman et al., 2014).

CVD-RFs are also widely known to affect the white matter of the brain. Hypertension and DM are associated with increased white matter hyperintensities, i.e., change of pallor in white matter as seen on T2-FLAIR scans (Debette et al., 2011; Iadecola et al., 2016; Meusel et al., 2014), as well as diffusion-tensor imaging (DTI) measures of white matter microstructural integrity (Gonzales et al., 2017; Hoogenboom et al., 2014; Jacobs et al., 2013). In a large empirical study of older adults, severe hypertension, current smoking, and DM were all associated with worse white matter integrity in several white matter tracts including association and commissural tracts (de Groot et al., 2015). Further, research done in a cross-sectional study of late-middle-aged men found that individuals with more years of hypertension showed lower DTI-derived measures of fractional anisotropy and higher mean diffusivity in white matter tracts including the uncinate fasciculus, inferior and superior lateral fasciculi, and anterior thalamic radiation (McEvoy et al., 2015). Similar findings have been noted in more racially/ethnically diverse samples both cross-sectionally (Gonzales et al., 2017; Kennedy & Raz, 2009) and longitudinally (Wang et al., 2015). Additional research has shown that in older adults, higher mean systolic blood pressure is associated with reduced white matter integrity bilaterally in the uncinate and superior lateral fasciculi, and that these white matter findings moderated the relationship between systolic blood pressure and a cognitive test of processing speed (Rosano et al., 2015). Likewise, glucose dysfunction associated with DM has been related to alterations in inferior and superior longitudinal fasciculi in middle-aged adults (Gonzales et al., 2017).

Not surprisingly given the role CVD-RFs play in brain alterations, there is a large literature outlining the effect of these same risk factors on cognitive function (Iadecola et al., 2016; Lamar et al., 2015), particularly in domains of executive function (Elias et al., 2004), processing speed (Llewellyn et al., 2008) and to a lesser extent, memory (Gifford et al., 2013). In a meta-analysis of nineteen composite CVD-RF studies in older adults (DeRight, Jorgensen, & Cabral, 2015), higher CVD-RF burden was associated with lower global cognition as well as lower performance in cognitive domains of executive function, attention, memory, and visuospatial processing. Similar findings have been noted in comprehensive reviews by Harrison and colleagues (2014) and Kerola and colleagues (2011). Longitudinally, greater CVD-RFs at baseline have been linked with lower global cognition, as well as memory and executive function at a four-year follow-up of adults aged 50 years and older (Dregan, Stewart, & Gulliford, 2013). Further, empirical research studying 25 years of cumulative exposure to CVD-RFs (i.e., systolic blood pressure, diastolic blood pressure, and fasting glucose) throughout early (mean age = 25 years) to midlife (mean age = 50 years) showed that greater exposure to CVD-RFs during this time period was associated with worse performance on cognitive tests of attention, executive function, and verbal memory, indicating that CVD-RFs could be playing an injurious role earlier in life than previously expected (Yaffe et al., 2014).

While great strides have been made in understanding the impact of CVD-RFs in gray and white matter as they relate to cognition, a more thorough understanding of the connectivity *between* gray and white matter regions is warranted (Iadecola, 2013). Initial work in this area has focused on the relationship between CVD-RFs and functional connectivity. For example, a functional connectivity analysis revealed that compared with controls, hypertensive older adults had reduced frontal-parietal activity, which mediated the relationship between white matter

integrity in the superior longitudinal fasciculi and executive function (Li et al., 2015). Additionally, a recent review demonstrated that reduced functional connectivity and disruption of fronto-subcortical white matter tracts associated with decreased processing speed in individuals with cerebral vessel disease, a condition associated with CVD-RFs (Dey, Stamenova, Turner, Black, & Levine, 2016). Thus far, however, there has been little work examining the structural connectivity of white matter and gray matter as it relates to CVD-RFs.

Advances in image analytics through the application of graph theory have made possible the ability to examine the structural connectivity of gray *and* white matter as it relates to indices of interest (Rubinov & Sporns, 2010). These advanced neuroimaging methods allow analysis of brain structure in a more integrated form, including but not limited to measures of the efficiency of local networks, determined by the path length (a proxy for white matter tracts) across nodes (or gray matter regions) within a region, and the centrality of networks, which measures the influence of a node based on the number of paths associated with it through combination of gray matter volumes and DTI measures of white matter integrity. Gaining a better understanding of the effect CVD-RFs have on connectivity between white matter and gray matter regions through use of these techniques is critical as it could help target areas vulnerable to cardiovascular dysfunction and signify biomarkers that could be targeted in prevention studies against cognitive decline.

B.   **Purpose of the Study**

This project investigated the associations between CVD-RFs, tract-based structural brain connectivity, and cognition. It is important to note that the associations between CVD-RFs, brain health, and cognition may be heterogeneous across racially and/or ethnically diverse populations (Schneider et al., 2015). Thus, this project focused on a cross-sectional, community sample of non-demented/non-depressed older adults who were racially and ethnically diverse. We specifically

examined (1) whether CVD-RFs are associated with structural connectivity in key brain regions associated with cardiovascular health and AD and (2) if this connectivity mediates the well-established link between CVD-RFs and cognition. We hypothesize that higher CVD-RFs will be associated with lower local efficiency, e.g., path length across nodes within a region, and lower centrality, e.g., node influence based on the number of paths associated with it. We further hypothesize that efficiency and centrality metrics will mediate the relationship between cumulative CVD-RF burden and *a priori* chosen cognitive domains of executive function, attention and information processing speed (AIP), and memory. Additionally, given that our sample population represents a racially and ethnically diverse group of urban dwelling adults, we will also explore whether educational quality – a better metric of education than number of years for minority populations (Manly, Jacobs, Touradji, Small, & Stern, 2002) – serves as a moderator of connectivity and cognitive function in stratified analyses by race. We hypothesize that better educational quality will reduce the association between connectivity and cognition associated with CVD-RFs.

II. **METHODS**

A.   **<u>Participants</u>**

Participant data for this study came from a larger study of healthy aging and CVD-RFs at the University of Illinois at Chicago (UIC) Department of Psychiatry. Adults aged 60 years and older were recruited via community outreach, including flyers, newspaper advertisements, word of mouth, as well as through recruitment from research registries. The study was approved by the UIC Institutional Review Board (IRB) and conducted in accordance with the Declaration of Helsinki with written informed consent obtained from all participants. This study has also been approved by the Rush University Medical Center IRB with all requisite data use agreements in place prior to data analysis.

Interested individuals underwent a brief telephone screening to determine initial study eligibility. At this screen, exclusion criteria consisted of self-reported current or past history of neurological conditions including AD or any other form of dementia or mild cognitive impairment, Parkinson's disease or any other movement disorder, stroke, or seizure disorder, current or past history of Axis I or II disorders (e.g., depression or bipolar disorder), a history of head injury or loss of consciousness, a present or past history of substance abuse or dependence, psychotropic medication use, or contraindications for magnetic resonance imaging (MRI) including metallic implants. A self-reported history of stable (e.g., diabetes) or remitted medical illness (e.g., cancer) was not an exclusionary factor. Individuals were not eligible for this study if they had received cognitive testing within the past year, or if they reported current involvement in a study with cognitive testing. Additionally, the presence of CVD-RFs was not considered exclusionary for this study but were examined as part of a cardiovascular risk assessment outlined below.

Individuals who passed this initial screen were then scheduled for a more intensive evaluation of inclusion and exclusion criteria. This evaluation consisted of affective and cognitive screens including the Structured Clinical Interview for DSM-IV-TR (SCID; First, Spitzer, Gibbon, & Williams, 2002) and the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975). These screening measures were administered by a trained research assistant, and were followed by a blinded evaluation by a psychiatrist, who completed the 17-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960). Participants were also asked about subjective memory impairment (SMI) during this time.

Final inclusion criteria consisted of an absence of psychiatric symptoms based on the SCID, a score ≤8 on the HAM-D, an MMSE score ≥24, as well as an absence of SMI. All study participants completed the Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996) as well as the Beck Anxiety Inventory (BAI; Beck & Steer, 1990) for a subjective measure of depressive and anxiety symptomatology, respectively. In total, 121 individuals met final inclusion criteria for the overall study. Ten participants received their evaluations in Spanish and were excluded given that not all aspects of the assessment outlined below were English/Spanish compatible. This left 111 potential participants for the current study.

B. **Study Protocol**

1. **Cardiovascular Disease Risk Factor Assessment**

Participants underwent a cardiovascular disease risk assessment with a registered nurse in the Center for Clinical and Translational Science's Clinical Research Center at UIC. This evaluation consisted of a medical history and physical examination, in addition to two seated blood pressure readings separated by five minutes and an electrocardiogram. A 12-hour fasting blood

draw for quantification of glucose, hemoglobin A1c, lipid profiles, and other blood-based biomarkers was also performed.

Given our interest in the impact of CVD-RF burden on tract-based structural connectivity and cognition, we chose to use a comprehensive measure of risk, namely the Framingham Stroke Risk Profile (FSRP). This measure incorporates age, sex, systolic blood pressure, anti-hypertensive therapy, diabetes, smoking, cardiovascular disease, and atrial fibrillation in calculating an overall 10-year risk profile of stroke (Dufouil et al., 2017). The FSRP is a widely-used measure of cardiovascular risk as it includes a range of measures implicated in cardiovascular health, and has recently been revised from its original version (Wolf, D'Agostino, Belanger, & Kannel, 1991) to more accurately predict stroke risk in diverse populations; for details on calculation of the FSRP, see Dufouil and colleagues (2017).

2. **Neuroimaging**

    a. **Data Acquisition**

Participants underwent neuroimaging at the Center for Magnetic Resonance (total scan time ~45 minutes). Whole brain images were acquired on a GE MR 750 Discovery 3T scanner (General Electric Health Care, Waukesha, WI) using an 8-channel head coil. Participants were positioned supine on the scanner table, with earplugs to improve patient comfort and foam pads to minimize head movement. Participants were instructed to remain still throughout the scan. Sequences relevant for the current analyses included a high resolution three-dimensional T1-weighted image and DTI. The T1-weighted images were acquired using a Brain Volume (BRAVO) imaging sequence (field of view: FOV = 22mm; voxel size = $0.42 \times 0.42 \times 1.5 mm^3$; 120 contiguous axial slices; TR/TE = 1200ms/5.3ms; flip angle = 13°) for quantification of gray matter volumes. DTI images were acquired using 2-D spin-echo EPI sequence (FOV=20mm; voxel

size=$0.78 \times 0.78 \times 3.0$mm^3; TR/TE=5,525/93.5ms; flip angle=90º) for measures of white matter integrity. Forty contiguous axial slices aligned to the AC-PC line were collected in 32 gradient directions with b=1400s/mm^2 and 6 b_0 images.

b. **Image Processing**

Structural connectivity networks were created using a pipeline that integrates a series of image processing and analysis techniques. First, T1-weighted images were used to generate label maps for volumetric segmentation using FreeSurfer 6.0 software (https://surfer.nmr.mgh.harvard.edu/). Each label map was composed of 82 different gray matter regions of interest (ROI) using the Destrieux atlas (Desikan et al., 2006; Destrieux, Fischl, Dale, & Halgren, 2010; Fischl et al., 2004). Intracranial volume (ICV) was also derived from FreeSurfer. Next, for computation of probabilistic tractography (see Zhan et al., 2015 for a more comprehensive description), FSL DTI images were corrected for eddy current distortions and head motion using the FSL eddy-correct tool and aligned to their corresponding b_0 images (https://fsl.fmrib.ox.ac.uk/fsl/). The FSL Brain Extraction Tool (BET) removed non-brain tissue; the gradient table was also corrected. Diffusion tensor models at each voxel were then fit using the FSL DTIFit tool for calculation of three principal eigenvectors, and three eigenvalues, as well as fractional anisotrophy (FA). Then, images were linearly aligned and elastically registered to T1-weighted scans using an inverse consistent registration algorithm with a mutual information cost function via Advanced Normalization Tools (ANTs; http://stnava.github.io/ANTs/), see Leow et al. (2007) and Zhan et al. (2015). In preparation for probabilistic tractography, we applied the FSL Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques for modeling crossing fibers (Bedpostx). This process uses Markov Chain Monte Carlo sampling to "build up

distributions on diffusion parameters at each voxel" (https://fsl.fmrib.ox.ac.uk/fsl/); we modeled up to three fibers per voxel.

For construction of connectivity matrices, FSL Probtrackx was run on individual seed voxels – we chose voxels with FA $\geq$ 0.2 as seeds. Probtrackx repeatedly samples from the distributions of voxel-wise principal diffusion directions calculated from Bedpostx, each time computing probabilistic streamlines. Based on the provided data, this builds a distribution on the likely tract location and path in the matrix. One thousand iterations were run to ensure convergence of the Markov chains. Finally, the matrix was formed by detecting the number of fibers connecting ROI pairs determined from Probtrackx. The matrix is symmetric and has no self-connections (Zhan et al., 2013). Matrices were normalized by adjusting for the volume of individual ROIs. See Zhan and colleagues (Zhan et al., 2015) for additional information. Resulting weighted and undirected matrices were then analyzed in Brain Connectivity Toolbox (BCT; Rubinov & Sporns, 2010) as outlined below.

c.   **Connectivity Matrix Analyses**

In graph theory, a network is a set of 'nodes' or brain regions with 'edges' or connections between them, i.e., white matter tracts. For this study, we were particularly interested in measures of local efficiency – a measure of the average inverse path length across nodes for a given region – and centrality – a measure of the influence of a node based on the sum of neighboring path weights associated with it (Rubinov & Sporns, 2010). Each of these measures were extracted for analysis using BCT. We targeted specific ROIs (see Figure 1, Appendix B) known to be affected by both CVD-RF burden as well as AD, including the superior frontal gyrus, inferior frontal gyrus (pars opercularis, pars triangularis, pars orbitalis), rostral and caudal middle frontal gyrus, caudal and rostral anterior, posterior, and isthmus cingulate cortex, entorhinal cortex,

supramarginal gyrus, middle and inferior temporal gyrus, hippocampus, amygdala, superior and inferior parietal cortex, the basal ganglia (caudate, putamen, pallidum, and accumbens), and precuneus (Beauchet et al., 2013; Boots et al., 2015; Cardenas et al., 2012; Dickerson et al., 2009; Glodzik et al., 2012; Lamar, Charlton, Zhang, & Kumar, 2012; Moulton, Costafreda, Horton, Ismail, & Fu, 2015; Pini et al., 2016). Measures of the right and left hemisphere were analyzed separately.

3. **Cognition**

Participants underwent a comprehensive neuropsychological evaluation administered by trained research assistants supervised by a licensed clinical neuropsychologist. For this project, we focused on cognitive tests specifically associated with cognitive domains implicated in cardiovascular disease risk (DeRight et al., 2015). These cognitive domains, and their relevant tests, are listed below.

a. **Attention and Information Processing Speed**

1) **Trail Making Test A**

Trail Making Test A is a test where participants are required to connect numbers that are shown inside of circles in ascending order as quickly as possible (Army Individual Test Battery, 1944). Numbers are distributed randomly across the sheet of paper. This is a test of processing speed, and the variable of interest is time to completion of connecting the numbers.

2) **Trail Making Test Motor**

Trail Making Test Motor examines how quickly participants can trace a line that connects numbers (Army Individual Test Battery, 1944). This assessment is

another measure of processing speed, and the variable of interest is the time to completion of tracing the line.

3) Digit Symbol Coding

Digit Symbol Coding requires individuals to correctly fill in symbols associated with particular digits as fast as possible (Wechsler, 1997). The symbol and digit associations are shown in a key at the top of the page. Digit Symbol Coding additionally measures processing speed, and the outcome of interest is the raw number of correct responses within a time limit of two minutes.

b. Executive Function

1) Trail Making Test B

Trail Making Test B is a test where participants are asked to connect a series of numbers and letters that are presented in circles randomly throughout the page in alternate, ascending order (e.g., 1-A-2-B-3) as quickly as possible (Army Individual Test Battery, 1944). We chose to specifically use the variable of interest of time to completion of number-letter connections subtracted from Trail Making Test A time to completion (i.e., $B - A$), as this measure rules out processing speed and is considered a clearer measure of executive function.

2) Letter Fluency

Letter Fluency asks individuals to say as many words as possible that begin with a particular letter in a 60 second time interval (Benton & Hamsher, 1976). Three letters total are administered in this cognitive test. This is a measure of executive function, and the outcome of interest is the total number of correct words given across the three letter trials.

3) Letter Number Sequencing

Letter Number Sequencing requires individuals to listen to a string of numbers and letters, and then state back the numbers in numerical order and then the letters in alphabetical order (Wechsler, 1997). This is another measure of executive function, and the variable of interest is the total number of correctly stated letter number sequences.

4) **Matrix Reasoning**

Matrix Reasoning is a test where participants are asked to choose the correct shape to complete a pattern in a matrix that is presented before them (Wechsler, 1997). This is a measure of executive function and visuospatial processing, and the variable of interest is the total number of correct choices made for matrix completion.

c. **Memory**

1) **California Verbal Learning Test – II**

California Verbal Learning Test – II (CVLT-II) is a measure of learning and memory (Delis, Kramer, Kaplan, & Ober, 2000). In the initial portion of this test, participants are asked to repeat back as many words they can from a 16-word list read by the administrator. The list is read five times, and the total number of words recalled over the five trials is one of the variables of interest from this test. In the memory portion of this test, participants are asked to freely recall any of the 16 words they can remember approximately 20 minutes after they were read for the last time. The memory variable of interest is the number of correctly recalled words from the list. Finally, recognition is assessed by asking participants to respond "yes" or "no" to whether or not a particular word was on the 16-word list. The outcome of interest is recognition discriminability, a measure of hit rate relative to false-positive rate.

4. **Education and Educational Quality**

Lastly, self-reported years of education was obtained from all participants, as well as their highest degree earned. The Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) was administered as a measure of educational quality, as this is considered a more accurate means of assessing educational attainment rather than years of education in racially/ethnically diverse samples of older adults (Manly et al., 2002). The WTAR requires participants to accurately pronounce words from a 50-item list of increasingly advanced words. Total number of words pronounced correctly provides a raw score which is used to estimate predicted verbal IQ (pVIQ) normed for age, sex, and race.

C. **Statistical Analyses**

All analyses were conducted in SPSS Version 24, with $p \leq .05$ for significance. Participant characteristics including demographic variables were averaged for the entire sample. Cronbach's alpha, initially utilized to assess whether our chosen cognitive tests accurately mapped onto the domains listed above, did not meet a standard threshold of 0.7 for one of the cognitive domains (Memory $\alpha = 0.81$; AIP $\alpha = 0.71$; Executive Function $\alpha = 0.36$). Given these findings, Principle Component Analysis (PCA) with Varimax Rotation was utilized to statistically group the cognitive tests, with factor loadings >0.6 per rotated component included in resulting factor composite scores. In order to compute each composite score, relevant test scores were recoded such that "better" scores were positive (i.e., multiplied reversed variables by -1), and z-scores were computed for each cognitive variable. Finally, z-scores for the tests within each cognitive domain were averaged for all participants for a final composite measure of each of the cognitive domains of interest.

1. **Aim 1: Association between Cardiovascular Disease Risk Factors and Structural Connectivity**

Multivariate linear regression was used to evaluate the associations between FSRP and connectivity measures of local efficiency and centrality in key ROIs as listed above. Covariates in this model included ICV and educational quality, as measured by pVIQ from the WTAR. Of note, age and sex were not included as covariates as they are adjusted for within the FSRP calculation. Given we were testing pre-specified hypotheses, we did not correct for multiple comparisons as doing so may have decreased our power to detect true associations and increased the false negative rate (Rothman, 1990). Further, all efficiency variables were multiplied by a factor of 1,000 for ease of interpretation of beta values.

2. **Aim 2: Mediation of Structural Connectivity on Cardiovascular Risk and Cognition**

Mediation analysis examined whether brain connectivity mediated the relationship between FSRP and cognition. Using the Baron and Kenny method (1986), we assessed using a series of regression analyses (1) whether FSRP is associated with connectivity (i.e., analyses above), (2) whether FSRP is associated with any of the cognitive domains of interest, and (3) whether FSRP and/or connectivity are associated with cognition when included in the same regression model. All models included intracranial volume and educational quality as covariates.

3. **Aim 3: Exploratory Analyses**

Educational quality can be further tested as a moderator of these relationships for better understanding of cognitive resilience in relation to cardiovascular health in the form of interaction analyses and moderated mediation. Therefore, we tested the interaction between pVIQ and connectivity metrics on cognition while including covariates of intracranial volume and stratified by race (i.e., non-Latinx White and Black). We also conducted a moderated mediation,

which included the same covariates, FSRP, and the pVIQ and connectivity metric interaction, and

was stratified by race.

III. **RESULTS**

A.   **Participant Characteristics**

Of the 111 eligible participants, 7 did not complete neuroimaging, 5 did not pass our MRI quality assurance procedures, and 3 had incidental findings on T1-weighted scans; thus, our sample size for the current analyses was reduced to 96. These participants were, on average, 68 years of age at the time of study participation, with approximately 15 years of education. Women comprised just over half of the sample, and nearly half of participants identified as Black, with less than 10% identifying as Latinx. MMSE, HAM-D, and other screening measures of cognition and affect were all in the normal range, demonstrating the non-demented, non-depressed nature of this sample. For more participant demographic information, see Table I, Appendix A.

For most CVD-RFs included in the FSRP (i.e., smoking, cardiovascular disease, atrial fibrillation) the vast majority of participants did *not* endorse presence of these factors (see Table II, Appendix A for details). Despite this, approximately 44% of individuals were taking medication for hypertension, and average systolic blood pressure was approximately 138 mmHg. Calculation of the FSRP showed that the probability of stroke in the next 10 years for women in this sample was 6%, and for men was 7%, consistent with average 10-year stroke risk probability found by Dufouil and colleagues (2017).

B.   **Cognitive Factors**

PCA with Varimax Rotation revealed the following cognitive domains and constituent tests: *Memory* – CVLT-II Trial 1-5 Total Recall, Long Delay Free Recall, and Recognition Discriminability; *Executive Function* – Letter Fluency (FAS), Trail Making Test B minus A, Matrix Reasoning, and Letter-Number Sequencing; and *Attention and Information Processing Speed* – Trail Making Test A, Trail Making Test Motor, and Digit Symbol; see Table III, Appendix

A for rotated factor loadings. As described above, these constituent tests were z-scored and averaged to create composite factor scores for each cognitive domain and used in subsequent analyses.

C.   **Aim 1: Association between Cardiovascular Risk and Structural Connectivity**

Linear regressions adjusted for educational quality and ICV revealed significant associations between FSRP 10-year stroke risk and measures of local efficiency in seven ROIs, including the left caudal anterior cingulate, right isthmus cingulate, left and right caudal middle frontal gyrus, left pars triangularis, and left and right supramarginal gyrus (all p's ≤ .05). In all associations, greater stroke risk was associated with higher local efficiency of these regions (see Table IV, Appendix A). Additionally, regressions investigating the association between FSRP 10-year stroke risk and local centrality while adjusting for educational quality and ICV indicated associations for six ROIs, including the left and right rostral middle frontal gyrus, right and left hippocampus, left caudate, and left accumbens (all p's ≤ .05). With the exception of the caudate, all associations indicated that greater stroke risk was associated with worse centrality in these regions (see Table IV, Appendix A).

D.   **Aim 2: Mediation of Structural Connectivity on Cardiovascular Risk and Cognition**

Linear regressions adjusting for educational quality and ICV revealed significant associations between FSRP 10-year stroke risk and AIP (p = .021), but not the cognitive domains of Memory or Executive Function (all p's ≥ .342; see Table V, Appendix A and Figure 2, Appendix B). Then, following standard steps for mediation established by Baron and Kenny (1986), simple linear regressions adjusting for educational quality and ICV revealed (1) significant associations between FSRP and AIP (see above); (2) FSRP and centrality in six ROIs, and efficiency in seven ROIs (see Aim 1 analyses); and (3) significant mediation of right hippocampal centrality on FSRP-

10 and AIP (p=.04; see Figures 3 and 5, Appendix B) and left caudal middle frontal gyrus on FSRP-10 and AIP (p=.01; see Figures 4 and 5, Appendix B).

E. **Aim 3: Moderation of Educational Quality**

We investigated whether greater educational quality would be protective of cognitive function despite poorer connectivity and greater 10-year stroke risk in analyses stratified by race. First, to test whether educational quality was protective for cognition against worse centrality, we fit a linear regression with a pVIQ*centrality interaction, while including ICV as a covariate; AIP was the dependent variable for all analyses. This regression was run for each of the six ROIs significantly associated with FSRP from the Aim 1 analyses. No significant interactions were found for either non-Latinx Whites or Blacks (data not shown). Similar linear regressions were run for the seven efficiency ROIs significantly related with FSRP from the Aim 1 analyses, where a pVIQ*efficiency interaction term was included while adjusting for ICV. Again, no significant interactions were found for either racial group (data not shown). Finally, to assure there was no moderated mediation of pVIQ for the two significant mediations indicated above, two final models were fit that included FSRP, a pVIQ*hippocampal centrality interaction, and ICV (Model 1), and FSRP, a pVIQ*caudal middle frontal efficiency interaction, and ICV (Model 2). No significant results were indicated for either non-Latinx Whites or Blacks (data not shown).

IV. **DISCUSSION**

A.   **<u>Summary of Findings</u>**

Although the relationship between CVD-RFs and gray *or* white matter is well-documented, to our knowledge, this is one of the first studies to address the relationship between CVD-RFs, cognition, and structural connectivity *between* gray and white matter. Our results indicate that CVD-RFs impact both the efficiency and centrality of structural brain networks in AD-associated regions of interest. Specifically, 10-year stroke risk was associated with poorer centrality in the bilateral rostral middle frontal gyri and hippocampi, as well as the left accumbens and caudate. We also found that, contrary to our initial hypothesis, greater 10-year stroke risk was associated with *increased* efficiency in the bilateral caudal middle frontal and supramarginal gyrus, pars triangularis, and isthmus and caudal anterior cingulate. Additionally, centrality of the right hippocampus mediated the association between FSRP and AIP while efficiency of the left caudal middle frontal gyrus mediated the association between FSRP and this same cognitive domain. Educational quality did not moderate either of these mediations. Together, these findings suggest that CVD-RFs are associated with tract-based structural connectivity metrics in AD-related brain regions, and that these relationships relate to alterations in specific cognitive functions in non-demented/non-depressed older adults independent of educational quality.

B.   **<u>Cardiovascular Risk, Centrality, and Efficiency</u>**

By applying advances in image analytics through the application of graph theory, our study revealed that CVD-RF burden is associated with the structural connectivity of gray *and* white matter, providing a more integrated form of analysis as it pertains to vascular brain aging. For all brain regions identified in this study to have relationships between higher CVD-RF burden and poorer centrality or greater efficiency measures, prior work has shown that presence of CVD-RFs

results in cortical gray matter thinning (Beauchet et al., 2013; Friedman et al., 2014; Leritz et al., 2011). Interestingly, increases in local efficiency have been shown to occur in aging and possibly ensue due to compensation for other altered brain regions (Barulli & Stern, 2013; Deslauriers, Ansado, Marrelec, Provost, & Joanette, 2017). Thus, it is possible that structural connectivity of the bilateral caudal middle frontal and supramarginal gyrus, left pars triangularis, right isthmus and left caudal anterior cingulate may increase in efficiency with other nearby structures to compensate for damage elsewhere. When combined with the fact that *lower* centrality of neighboring but not overlapping regions within the frontal and parietal lobes was associated with higher CVD-RF burden, a possible explanation for our findings is that regions with greater efficiency are providing compensation for regions with lower centrality. Because lower centrality reflects decreased strength or density in the weight of connections to identified brain regions (Rubinov & Sporns, 2010), some potential underlying mechanisms for the associations between CVD-RF burden, efficiency, and centrality may be that white matter tracts permeating these identified regions are damaged, which results in a breakdown in information transfer to associated gray matter regions. A possible explanation for this white matter breakdown is poor vasculature. In particular, brain regions in frontal and temporal areas are thought to be subjected to worse vascular circulation due to reliance on supply from distal blood flow, which may couple with CVD-RF burden to result in poor oxygenation to white and gray matter in these regions (Leritz et al., 2011). In contrast, deeper sub-cortical structures implicated in this study may have structural connectivity alterations associated with CVD-RF burden due to blood flow abnormalities as well as insulin receptor expression and inflammation related to diabetic symptomatology (Moulton et al., 2015). Ultimately, the mechanisms for our findings are unknown, and future work is needed

to more fully elucidate the interplay of higher efficiency and lower centrality as it relates to CVD-RF burden in older adults.

C.   **Mediations of Centrality and Efficiency on Cardiovascular Risk and Attention and Information Processing Speed**

Results from this study support the mediation of centrality and efficiency metrics on the relationship between CVD-RF burden and cognition. Our finding that CVD-RF burden is associated with poorer performance on AIP corroborates with prior work regarding CVD-RFs and cognition (DeRight et al., 2015; Iadecola et al., 2016; Llewellyn et al., 2008) and extends them by showing this association in a non-demented and racially/ethnically-diverse cohort, indicating that early detection of cognitive differences in 'preclinical' stages is possible. Furthermore, our results indicated a mediation of this known effect, where greater stroke risk was associated with poorer hippocampal centrality, which in turn was associated with worse AIP. The findings suggest that CVD-RF burden is negatively associated with the ability of the right hippocampus to serve as a 'hub' for white matter connectivity, which subsequently affects the cognitive domain of attention. Our study combines several prior studies in older adults reporting one-to-one relationships between hippocampal volume and CVD-RFs (Beauchet et al., 2013), hippocampal volume and centrality (Zhu et al., 2012), and hippocampal volume and attention (Aly & Turk-Browne, 2017) and information processing speed (O'Shea, Cohen, Porges, Nissim, & Woods, 2016; Papp et al., 2014) by demonstrating that hippocampal centrality mediates the effect of CVD-RFs on AIP. Disruption of the centrality of the hippocampus may be caused by CVD-RFs' injurious effects on white matter near this region, which then slows down communication throughout structural networks associated with AIP (Aly & Turk-Browne, 2017). Prior DTI results suggest that white matter integrity deterioration in temporal regions mediates the age-related association with slower

processing speed (Burgmans et al., 2011); however, longitudinal work incorporating tract-based structural connectomics is required to test this assertion.

Additionally, efficiency in the left caudal middle frontal gyrus also mediated the relationship between 10-year stroke risk and AIP, such that greater stroke risk was associated to greater efficiency, which in turn was associated with poorer AIP. This suggests that CVD-RFs are linked to increases in short path length connections to this region which then result in poorer cognitive outcomes, suggesting structural compensation for 'failure' in nearby or associated brain regions. This finding integrates prior work showing isolated relationships between greater CVD-RFs and less volume in the middle frontal gyrus bilaterally (Leritz et al., 2011), *right* caudal middle frontal gyrus function in the ventral attentional network, which becomes disconnected in early AD (Corbetta, Patel, & Shulman, 2008; Neufang et al., 2011), and greater *left* caudal middle frontal gyrus connectivity in relation to attentional network compensation in older age (Deslauriers et al., 2017). Therefore, a possible mechanism for this mediation is that CVD-RFs disrupt structural connections in attentional networks leading to compensation by the left caudal middle frontal gyrus, which could ultimately lead to poorer AIP because compensation is not a permanent solution to deterioration in other brain areas (Barulli & Stern, 2013). Future work is necessary to determine the biological underpinnings for how CVD-RFs effect the centrality and efficiency of the right hippocampus and left caudal middle frontal gyrus, respectively, and their subsequent impacts on cognition.

D.   **Conceptualization on Null Findings**

Although we did find that greater 10-year stroke risk was associated with poorer performance on AIP, we did not see similar relationships with the FSRP and memory or executive function. Indeed, relationships between CVD-RFs and memory are not seen quite as robustly as

associations with processing speed and executive function in the literature; this is particularly true in regard to hypertension (Iadecola et al., 2016), which is an FSRP variable that many individuals in our cohort endorsed. It is possible that memory impairments emerge later in the disease course as they relate to CVD-RFs, and that within this sample of overall unimpaired individuals, CVD-RFs initially take toll on the processing speed domain of cognition. Our lack of findings in an association between FSRP and executive function is in contrast to current literature (Elias et al., 2004). It is important to note, however, that although the PCA analysis grouped the cognitive variables of Trails B minus A, Letter Number Sequencing, Matrix Reasoning, and Letter Fluency into one component, when Cronbach's alpha was tested for these four variables, $\alpha = 0.36$. Thus, it is possible that our executive function measure was not assessing this domain in the most comprehensive manner, or may have been additionally assessing other domains such as visuospatial function, resulting in null findings.

This study did not find that educational quality was protective against cognitive dysfunction given CVD-RFs and connectivity alterations. While prior research suggests that educational *attainment* (i.e., years of education) can be protective of global cognition against white matter injury (Pinter, Enzinger, & Fazekas, 2015), educational *quality* represents not the number of years in school but the level of academic achievement that resulted from those school years. In fact, adjusting for educational quality nullified previously noted differences in memory performance between non-Latinx Whites and African Americans (Fyffe et al., 2011). We only tested these educational quality relationships with our significant result in AIP; it is possible that educational quality provides protection against alterations in some, but not all, cognitive domains. Furthermore, our cohort was highly educated with many reporting post-baccalaureate degrees, potentially negating the role of educational quality in this sample.

E.   **Strengths and Limitations**

Strengths of this study include the use of tract-based structural connectomics, a novel neuroimaging method, to better understand the integration between gray and white matter in key brain regions as it relates to CVD-RF burden and AD. We utilized probabilistic tractography to allow for better delineation of crossing fibers in the brain, and ultimately a more accurate depiction of white matter tracts in regions with dense fiber connections (Zhan et al., 2015). Additionally, this study utilized the most recent version of the FSRP (Dufouil et al., 2017), allowing for a more nuanced understanding of increased levels of CVD-RFs and their influence on structural connectivity and cognition. Further, this work involved a racially and ethnically diverse cohort of non-demented, non-depressed older adults, which not only may facilitate the generalizability of our findings but additionally appears to suggest that brain-behavior relationships related to CVD-RFs are detectable prior to onset of gross cognitive impairment.

Our study must be interpreted within the context of its limitations. Due to the cross-sectional nature of this study, we are unable to determine the direction of the relationships reported, particularly in respect to our mediation analyses. Nevertheless, our findings provide new insight into potential brain-mediated pathways by which CVD-RFs affect cognition, which future longitudinal work would be well poised to address. While the effect of *mid-life* CVD-RFs on late-life cognition and brain structure is well documented (Yaffe et al., 2014), our study included older adults. Thus, it is possible that results were not as strong in our current sample as they may have been in a younger sample. Additionally, our sample size of 96 individuals may not have been well-powered enough to detect certain relationships, particularly regarding educational quality as a moderator. Despite this, we did find significant relationships in our older cohort; relationships that

are noteworthy given that CVD-RF burden and 10-year stroke risk were quite low and suggestive of the cohort's overall cognitive health.

F.   **Conclusion**

Our work highlights the usefulness of novel neuroimaging tools such as tract-based structural connectomics, which may provide initial insight into mechanisms for how CVD-RFs relate to brain-behavior relationships. Additionally, this work shows that in non-demented/non-depressed older adults, there are detectable alterations in brain connectivity that associate with subtle alterations in cognitive function in the presence of CVD-RFs. If replicated, such early, i.e., preclinical detection of altered brain-behavior relationships in the context of CVD-RFs could point toward biomarkers that may be useful targets in prevention studies against cognitive decline and AD. At a minimum, our results may allow for more work to appreciate how CVD-RFs interact with brain and cognitive health at earlier, preclinical time points, where intervention may still be possible against pathological aging and dementia including AD.

REFERENCES

Aly, M., & Turk-Browne, N. B. (2017). How Hippocampal Memory Shapes, and Is Shaped by,
Attention. In D. E. Hannula & M. C. Duff (Eds.), *The Hippocampus from Cells to
Systems: Structure, Connectivity, and Functional Contributions to Memory and Flexible
Cognition* (pp. 369-403). Cham: Springer International Publishing.

Alzheimer's Association. (2018). 2018 Alzheimer's disease facts and figures. *Alzheimer's &
Dementia: The Journal of the Alzheimer's Association, 14*(3), 367-429.
doi:10.1016/j.jalz.2018.02.001

Army Individual Test Battery. (1944). *Manual of Directions and Scoring*. Washington, D.C.:
War Department, Adjutant General's Office.

Barnes, D. E., & Yaffe, K. (2011). The projected effect of risk factor reduction on Alzheimer's
disease prevalence. *Lancet Neurol, 10*(9), 819-828. doi:10.1016/S1474-4422(11)70072-2

Baron, R. M., & Kenny, D. A. (1986). The moderator–mediator variable distinction in social
psychological research: Conceptual, strategic, and statistical considerations. *Journal of
Personality and Social Psychology, 51*(6), 1173-1182. doi:10.1037/0022-3514.51.6.1173

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity:
emerging concepts in cognitive reserve. *Trends Cogn Sci, 17*(10), 502-509.
doi:10.1016/j.tics.2013.08.012

Beauchet, O., Celle, S., Roche, F., Bartha, R., Montero-Odasso, M., Allali, G., & Annweiler, C.
(2013). Blood pressure levels and brain volume reduction: a systematic review and meta-
analysis. *J Hypertens, 31*(8), 1502-1516. doi:10.1097/HJH.0b013e32836184b5

Beck, A. T., & Steer, R. A. (1990). *Beck Anxiety Inventory Manual*. San Antonio, TX:
Psychological Corporation.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation.

Benton, A. L., & Hamsher, K. d. S. (1976). *Multilingual Aphasia Examination*. Iowa City: University of Iowa.

Boots, E. A., Schultz, S. A., Oh, J. M., Larson, J., Edwards, D., Cook, D., . . . Okonkwo, O. C. (2015). Cardiorespiratory fitness is associated with brain structure, cognition, and mood in a middle-aged cohort at risk for Alzheimer's disease. *Brain Imaging Behav, 9*(3), 639-649. doi:10.1007/s11682-014-9325-9

Burgmans, S., Gronenschild, E. H., Fandakova, Y., Shing, Y. L., van Boxtel, M. P., Vuurman, E. F., . . . Raz, N. (2011). Age differences in speed of processing are partially mediated by differences in axonal integrity. *Neuroimage, 55*(3), 1287-1297. doi:10.1016/j.neuroimage.2011.01.002

Cardenas, V. A., Reed, B., Chao, L. L., Chui, H., Sanossian, N., DeCarli, C. C., . . . Weiner, M. W. (2012). Associations among vascular risk factors, carotid atherosclerosis, and cortical volume and thickness in older adults. *Stroke, 43*(11), 2865-2870. doi:10.1161/STROKEAHA.112.659722

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The reorienting system of the human brain: from environment to theory of mind. *Neuron, 58*(3), 306-324. doi:10.1016/j.neuron.2008.04.017

de Groot, M., Ikram, M. A., Akoudad, S., Krestin, G. P., Hofman, A., van der Lugt, A., . . . Vernooij, M. W. (2015). Tract-specific white matter degeneration in aging: the Rotterdam Study. *Alzheimers Dement, 11*(3), 321-330. doi:10.1016/j.jalz.2014.06.011

Debette, S., Seshadri, S., Beiser, A., Au, R., Himali, J. J., Palumbo, C., . . . DeCarli, C. (2011).

    Midlife vascular risk factor exposure accelerates structural brain aging and cognitive

    decline. *Neurology, 77*(5), 461-468. doi:10.1212/WNL.0b013e318227b227

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (2000). *California Verbal Learning Test -*

    Second Edition. Adult Version. Manual. San Antonio, TX: Psychological Corporation.

DeRight, J., Jorgensen, R. S., & Cabral, M. J. (2015). Composite cardiovascular risk scores and

    neuropsychological functioning: a meta-analytic review. *Ann Behav Med, 49*(3), 344-357.

    doi:10.1007/s12160-014-9681-0

Desikan, R. S., Segonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., . . . Killiany,

    R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on

    MRI scans into gyral based regions of interest. *Neuroimage, 31*(3), 968-980.

    doi:10.1016/j.neuroimage.2006.01.021

Deslauriers, J., Ansado, J., Marrelec, G., Provost, J. S., & Joanette, Y. (2017). Increase of

    posterior connectivity in aging within the Ventral Attention Network: A functional

    connectivity analysis using independent component analysis. *Brain Res, 1657*, 288-296.

    doi:10.1016/j.brainres.2016.12.017

Destrieux, C., Fischl, B., Dale, A., & Halgren, E. (2010). Automatic parcellation of human

    cortical gyri and sulci using standard anatomical nomenclature. *Neuroimage, 53*(1), 1-15.

    doi:10.1016/j.neuroimage.2010.06.010

Dey, A. K., Stamenova, V., Turner, G., Black, S. E., & Levine, B. (2016). Pathoconnectomics of

    cognitive impairment in small vessel disease: A systematic review. *Alzheimers Dement,*

    12(7), 831-845. doi:10.1016/j.jalz.2016.01.007

Dickerson, B. C., Bakkour, A., Salat, D. H., Feczko, E., Pacheco, J., Greve, D. N., . . . Buckner, R. L. (2009). The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb Cortex, 19*(3), 497-510. doi:10.1093/cercor/bhn113

Dregan, A., Stewart, R., & Gulliford, M. C. (2013). Cardiovascular risk factors and cognitive decline in adults aged 50 and over: a population-based cohort study. *Age Ageing, 42*(3), 338-345. doi:10.1093/ageing/afs166

Dufouil, C., Beiser, A., McLure, L. A., Wolf, P. A., Tzourio, C., Howard, V. J., . . . Seshadri, S. (2017). Revised Framingham Stroke Risk Profile to Reflect Temporal Trends. *Circulation, 135*(12), 1145-1159. doi:10.1161/CIRCULATIONAHA.115.021275

Elias, M. F., Sullivan, L. M., D'Agostino, R. B., Elias, P. K., Beiser, A., Au, R., . . . Wolf, P. A. (2004). Framingham stroke risk profile and lowered cognitive performance. *Stroke, 35*(2), 404-409. doi:10.1161/01.STR.0000103141.82869.77

Firbank, M. J., Wiseman, R. M., Burton, E. J., Saxby, B. K., O'Brien, J. T., & Ford, G. A. (2007). Brain atrophy and white matter hyperintensity change in older adults and relationship to blood pressure. Brain atrophy, WMH change and blood pressure. *J Neurol, 254*(6), 713-721. doi:10.1007/s00415-006-0238-4

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition With Psychotic Screen (SCID-I/P W/ PSY SCREEN)*. New York: Biometrics Research, New York State Psychiatric Institute.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D. H., . . . Dale, A. M. (2004). Automatically parcellating the human cerebral cortex. *Cereb Cortex, 14*(1), 11-22.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res, 12*(3), 189-198.

Friedman, J. I., Tang, C. Y., de Haas, H. J., Changchien, L., Goliasch, G., Dabas, P., . . . Narula, J. (2014). Brain imaging changes associated with risk factors for cardiovascular and cerebrovascular disease in asymptomatic patients. *JACC Cardiovasc Imaging, 7*(10), 1039-1053. doi:10.1016/j.jcmg.2014.06.014

Fyffe, D. C., Mukherjee, S., Barnes, L. L., Manly, J. J., Bennett, D. A., & Crane, P. K. (2011). Explaining differences in episodic memory performance among older African Americans and Whites: the roles of factors related to cognitive reserve and test bias. *J Int Neuropsychol Soc, 17*(4), 625-638. doi:10.1017/S1355617711000476

Gifford, K. A., Badaracco, M., Liu, D., Tripodis, Y., Gentile, A., Lu, Z., . . . Jefferson, A. L. (2013). Blood pressure and cognition among older adults: a meta-analysis. *Arch Clin Neuropsychol, 28*(7), 649-664. doi:10.1093/arclin/act046

Glodzik, L., Mosconi, L., Tsui, W., de Santi, S., Zinkowski, R., Pirraglia, E., . . . de Leon, M. J. (2012). Alzheimer's disease markers, hypertension, and gray matter damage in normal elderly. *Neurobiol Aging, 33*(7), 1215-1227. doi:10.1016/j.neurobiolaging.2011.02.012

Gonzales, M. M., Ajilore, O., Charlton, R. C., Cohen, J., Yang, S., Sieg, E., . . . Lamar, M. (2017). Divergent Influences of Cardiovascular Disease Risk Factor Domains on

Cognition and Gray and White Matter Morphology. *Psychosom Med, 79*(5), 541-548. doi:10.1097/PSY.0000000000000448

Hamilton, M. (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry, 23*, 56-62.

Harrison, S. L., Ding, J., Tang, E. Y., Siervo, M., Robinson, L., Jagger, C., & Stephan, B. C. (2014). Cardiovascular disease risk models and longitudinal changes in cognition: a systematic review. *PLoS One, 9*(12), e114431. doi:10.1371/journal.pone.0114431

Hoogenboom, W. S., Marder, T. J., Flores, V. L., Huisman, S., Eaton, H. P., Schneiderman, J. S., . . . Musen, G. (2014). Cerebral white matter integrity and resting-state functional connectivity in middle-aged patients with type 2 diabetes. *Diabetes, 63*(2), 728-738. doi:10.2337/db13-1219

Iadecola, C. (2013). The pathobiology of vascular dementia. *Neuron, 80*(4), 844-866. doi:10.1016/j.neuron.2013.10.008

Iadecola, C., Yaffe, K., Biller, J., Bratzke, L. C., Faraci, F. M., Gorelick, P. B., . . . Stroke, C. (2016). Impact of Hypertension on Cognitive Function: A Scientific Statement From the American Heart Association. *Hypertension, 68*(6), e67-e94. doi:10.1161/HYP.0000000000000053

Jacobs, H. I., Leritz, E. C., Williams, V. J., Van Boxtel, M. P., van der Elst, W., Jolles, J., . . . Salat, D. H. (2013). Association between white matter microstructure, executive functions, and processing speed in older adults: the impact of vascular health. *Hum Brain Mapp, 34*(1), 77-95. doi:10.1002/hbm.21412

Kennedy, K. M., & Raz, N. (2009). Pattern of normal age-related regional differences in white matter microstructure is modified by vascular risk. *Brain Res, 1297*, 41-56. doi:10.1016/j.brainres.2009.08.058

Kerola, T., Kettunen, R., & Nieminen, T. (2011). The complex interplay of cardiovascular system and cognition: how to predict dementia in the elderly? *Int J Cardiol, 150*(2), 123-129. doi:10.1016/j.ijcard.2010.10.018

Lamar, M., Charlton, R., Zhang, A., & Kumar, A. (2012). Differential associations between types of verbal memory and prefrontal brain structure in healthy aging and late life depression. *Neuropsychologia, 50*(8), 1823-1829. doi:10.1016/j.neuropsychologia.2012.04.007

Lamar, M., Rubin, L. H., Ajilore, O., Charlton, R., Zhang, A., Yang, S., . . . Kumar, A. (2015). What Metabolic Syndrome Contributes to Brain Outcomes in African American & Caucasian Cohorts. *Curr Alzheimer Res, 12*(7), 640-647.

Leow, A. D., Yanovsky, I., Chiang, M. C., Lee, A. D., Klunder, A. D., Lu, A., . . . Thompson, P. M. (2007). Statistical properties of Jacobian maps and the realization of unbiased large-deformation nonlinear image registration. *IEEE Trans Med Imaging, 26*(6), 822-832. doi:10.1109/TMI.2007.892646

Leritz, E. C., Salat, D. H., Williams, V. J., Schnyer, D. M., Rudolph, J. L., Lipsitz, L., . . . Milberg, W. P. (2011). Thickness of the human cerebral cortex is associated with metrics of cerebrovascular health in a normative sample of community dwelling older adults. *Neuroimage, 54*(4), 2659-2671. doi:10.1016/j.neuroimage.2010.10.050

Li, X., Liang, Y., Chen, Y., Zhang, J., Wei, D., Chen, K., . . . Zhang, Z. (2015). Disrupted Frontoparietal Network Mediates White Matter Structure Dysfunction Associated with Cognitive Decline in Hypertension Patients. *J Neurosci, 35*(27), 10015-10024. doi:10.1523/JNEUROSCI.5113-14.2015

Llewellyn, D. J., Lang, I. A., Xie, J., Huppert, F. A., Melzer, D., & Langa, K. M. (2008).

    Framingham Stroke Risk Profile and poor cognitive function: a population-based study.

    BMC Neurol, 8, 12. doi:10.1186/1471-2377-8-12

Manly, J. J., Jacobs, D. M., Touradji, P., Small, S. A., & Stern, Y. (2002). Reading level

    attenuates differences in neuropsychological test performance between African American

    and White elders. *J Int Neuropsychol Soc, 8*(3), 341-348.

McEvoy, L. K., Fennema-Notestine, C., Eyler, L. T., Franz, C. E., Hagler, D. J., Jr., Lyons, M.

    J., . . . Kremen, W. S. (2015). Hypertension-related alterations in white matter

    microstructure detectable in middle age. *Hypertension, 66*(2), 317-323.

    doi:10.1161/HYPERTENSIONAHA.115.05336

Meusel, L. A., Kansal, N., Tchistiakova, E., Yuen, W., MacIntosh, B. J., Greenwood, C. E., &

    Anderson, N. D. (2014). A systematic review of type 2 diabetes mellitus and

    hypertension in imaging studies of cognitive aging: time to establish new norms. *Front

    Aging Neurosci, 6*, 148. doi:10.3389/fnagi.2014.00148

Moulton, C. D., Costafreda, S. G., Horton, P., Ismail, K., & Fu, C. H. (2015). Meta-analyses of

    structural regional cerebral effects in type 1 and type 2 diabetes. *Brain Imaging Behav,

    9*(4), 651-662. doi:10.1007/s11682-014-9348-2

Neufang, S., Akhrif, A., Riedl, V., Forstl, H., Kurz, A., Zimmer, C., . . . Wohlschlager, A. M.

    (2011). Disconnection of frontal and parietal areas contributes to impaired attention in

    very early Alzheimer's disease. *J Alzheimers Dis, 25*(2), 309-321. doi:10.3233/JAD-

    2011-102154

O'Shea, A., Cohen, R. A., Porges, E. C., Nissim, N. R., & Woods, A. J. (2016). Cognitive Aging and the Hippocampus in Older Adults. *Front Aging Neurosci, 8*, 298. doi:10.3389/fnagi.2016.00298

Papp, K. V., Kaplan, R. F., Springate, B., Moscufo, N., Wakefield, D. B., Guttmann, C. R., & Wolfson, L. (2014). Processing speed in normal aging: effects of white matter hyperintensities and hippocampal volume loss. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 21*(2), 197-213. doi:10.1080/13825585.2013.795513

Pini, L., Pievani, M., Bocchetta, M., Altomare, D., Bosco, P., Cavedo, E., . . . Frisoni, G. B. (2016). Brain atrophy in Alzheimer's Disease and aging. *Ageing Res Rev, 30*, 25-48. doi:10.1016/j.arr.2016.01.002

Pinter, D., Enzinger, C., & Fazekas, F. (2015). Cerebral small vessel disease, cognitive reserve and cognitive dysfunction. *J Neurol, 262*(11), 2411-2419. doi:10.1007/s00415-015-7776-6

Roberts, R. O., Knopman, D. S., Przybelski, S. A., Mielke, M. M., Kantarci, K., Preboske, G. M., . . . Jack, C. R., Jr. (2014). Association of type 2 diabetes with brain atrophy and cognitive impairment. *Neurology, 82*(13), 1132-1141. doi:10.1212/WNL.0000000000000269

Rosano, C., Abebe, K. Z., Aizenstein, H. J., Boudreau, R., Jennings, J. R., Venkatraman, V., . . . Health, A. B. C. S. (2015). Longitudinal systolic blood pressure characteristics and integrity of white matter tracts in a cohort of very old black and white adults. *Am J Hypertens, 28*(3), 326-334. doi:10.1093/ajh/hpu134

Rothman, K. J. (1990). No adjustments are needed for multiple comparisons. *Epidemiology, 1*(1), 43-46.

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpretations. *Neuroimage, 52*(3), 1059-1069. doi:10.1016/j.neuroimage.2009.10.003

Schneider, B. C., Gross, A. L., Bangen, K. J., Skinner, J. C., Benitez, A., Glymour, M. M., . . . Luchsinger, J. A. (2015). Association of vascular risk factors with cognition in a multiethnic sample. *J Gerontol B Psychol Sci Soc Sci, 70*(4), 532-544. doi:10.1093/geronb/gbu040

Wang, R., Fratiglioni, L., Laukka, E. J., Lovden, M., Kalpouzos, G., Keller, L., . . . Qiu, C. (2015). Effects of vascular risk factors and APOE epsilon4 on white matter integrity and cognitive decline. *Neurology, 84*(11), 1128-1135. doi:10.1212/WNL.0000000000001379

Wechsler, D. (1997). *WAIS-III: Wechsler Adult Intelligence Scale*. San Antonio, TX: Psychological Corporation.

Wechsler, D. (2001). *Wechsler Test of Adult Reading: WTAR*. San Antonio, TX: Psychological Corporation.

Wiseman, R. M., Saxby, B. K., Burton, E. J., Barber, R., Ford, G. A., & O'Brien, J. T. (2004). Hippocampal atrophy, whole brain volume, and white matter lesions in older hypertensive subjects. *Neurology, 63*(10), 1892-1897.

Wolf, P. A., D'Agostino, R. B., Belanger, A. J., & Kannel, W. B. (1991). Probability of stroke: a risk profile from the Framingham Study. *Stroke, 22*(3), 312-318.

Yaffe, K., Vittinghoff, E., Pletcher, M. J., Hoang, T. D., Launer, L. J., Whitmer, R., . . . Sidney, S. (2014). Early adult to midlife cardiovascular risk factors and cognitive function. *Circulation, 129*(15), 1560-1567. doi:10.1161/CIRCULATIONAHA.113.004798

Zhan, L., Jahanshad, N., Jin, Y., Toga, A. W., McMahon, K. L., Zubicaray, G. I. d., . . . Thompson, P. M. (2013, 7-11 April 2013). *Brain network efficiency and topology depend*

on the fiber tracking method: 11 tractography algorithms compared in 536 subjects. Paper presented at the 2013 IEEE 10th International Symposium on Biomedical Imaging.

Zhan, L., Zhou, J., Wang, Y., Jin, Y., Jahanshad, N., Prasad, G., . . . For The Alzheimer's Disease Neuroimaging, I. (2015). Comparison of nine tractography algorithms for detecting abnormal structural brain networks in Alzheimer's disease. *Front Aging Neurosci, 7*, 48. doi:10.3389/fnagi.2015.00048

Zhu, W., Wen, W., He, Y., Xia, A., Anstey, K. J., & Sachdev, P. (2012). Changing topological patterns in normal aging using large-scale structural networks. *Neurobiol Aging, 33*(5), 899-913. doi:10.1016/j.neurobiolaging.2010.06.022

APPENDICES

APPENDIX A

TABLE I

PARTICIPANT DEMOGRAPHIC INFORMATION

Characteristic	Value
Age, years	67.99 (6.73)
Female, %	53.1
Race/Ethnicity, %	
Non-Latinx White	44.8
Black	46.9
Latinx	8.3
Right Handedness, %	90.6
Degree Years of Education	15.48 (2.68)
HAM-D Total (n=83)	1.18 (1.50)
BDI Total	2.99 (3.18)
BAI Total (n=95)	2.45 (2.91)
MMSE Total	28.73 (1.41)

Note. N=96 and values are mean (SD) unless otherwise stated. HAM-D = Hamilton Depression Rating Scale; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; MMSE = Mini Mental State Examination.

APPENDIX A (continued)

TABLE II

FRAMINGHAM STROKE RISK PROFILE COMPONENT BREAKDOWN

FSRP Discrete Variables	Present	Absent
Smoking	8.3%	91.7%
Cardiovascular disease	3.1%	91.7%
Atrial fibrillation	1.0%	99.0%
Age 65+	37.5%	62.5%
Diabetes mellitus, if age <65	0.0%	100.0%
Diabetes mellitus, if age 65+	10.4%	89.6%
Hypertension medication	42.7%	57.3%
FSRP Continuous Variables	**Men**	**Women**
Age, years	66.62 (6.29)	69.20 (6.94)
Systolic blood pressure, mmHg	136.78 (17.51)	136.91 (15.70)

Note. FSRP = Framingham Stroke Risk Profile, mmHg = millimeter of mercury

APPENDIX A (continued)

TABLE III

COGNITIVE TEST SCORE FACTOR LOADINGS USING VARIMAX ROTATION

Cognitive Test Score	Memory	Executive Function	Attention & Information Processing
CVLT-II Trial 1-5 Total Recall	**0.90**	0.24	0.03
CVLT-II Long Delay Free Recall	**0.91**	0.15	0.17
CVLT-II Recognition Discriminability	**0.85**	0.18	0.03
Letter Fluency (FAS) Total	0.30	**0.67**	0.03
Trail Making Test B – A	0.17	**0.65**	0.24
Matrix Reasoning Total	0.20	**0.61**	0.20
Letter-Number Sequencing	0.02	**0.82**	0.04
Trail Making Test A	0.24	0.10	**0.82**
Trail Making Test Motor	-0.07	0.07	**0.79**
Digit Symbol Total	0.09	0.45	**0.63**
Eigenvalue	**3.86**	**1.66**	**1.15**

Note. N=90. Bold-faced numbers indicate factor loadings greater than 0.600; these factors were used to create memory, executive function, and attention and information processing speed factor scores 'by hand' to preserve sample size. Trail Making Test A, B, and Motor scores were inversed prior to factorization such that higher scores would indicate better performance.

APPENDIX A (continued)

TABLE IV

THE RELATIONSHIP BETWEEN STROKE RISK AND LOCAL CENTRALITY OR
EFFICIENCY WHILE ADJUSTING FOR EDUCATIONAL QUALITY AND
INTRACRANIAL VOLUME IN A CROSS-SECTIONAL SAMPLE OF OLDER ADULTS

Region of Interest	β (SE)	t-value	p-value	partial η^2
Centrality				
Accumbens (LH)	-0.01 (0.01)	-2.13	.036	0.05
Caudate (LH)	0.11 (0.05)	2.05	.044	0.04
Hippocampus (LH)	-0.04 (0.02)	-2.56	.012	0.07
Hippocampus (RH)	-0.07 (0.03)	-2.60	.011	0.07
Rostral Middle Frontal Gyrus (LH)	-0.04 (0.02)	-2.20	.031	0.05
Rostral Middle Frontal Gyrus (RH)	-0.04 (0.02)	-2.63	.010	0.07
Efficiency*				
Caudal Anterior Cingulate (LH)	0.29 (0.14)	1.99	.050	0.04
Caudal Middle Frontal Gyrus (LH)	0.64 (0.31)	2.04	.044	0.04
Caudal Middle Frontal Gyrus (RH)	0.84 (0.35)	2.37	.020	0.06
Isthmus Cingulate (RH)	0.32 (0.14)	2.29	.024	0.05
Pars Triangularis (LH)	0.41 (0.20)	2.09	.039	0.05
Supramarginal Gyrus (LH)	0.25 (0.10)	2.43	.017	0.06
Supramarginal Gyrus (RH)	0.36 (0.12)	2.99	.004	0.09

Note.*Efficiency variables were multiplied by a factor of 1,000 for ease of interpretation of beta

values. LH = left hemisphere; RH = right hemisphere

APPENDIX A (continued)

TABLE V

STROKE RISK IS ASSOCIATED WITH POORER ATTENTION AND INFORMATION
PROCESSING SPEED, BUT NOT WITH MEMORY OR EXECUTIVE FUNCTION IN A
CROSS-SECTIONAL SAMPLE OF OLDER ADULTS WHILE ADJUSTING FOR
EDUCATIONAL QUALITY AND INTRACRANIAL VOLUME

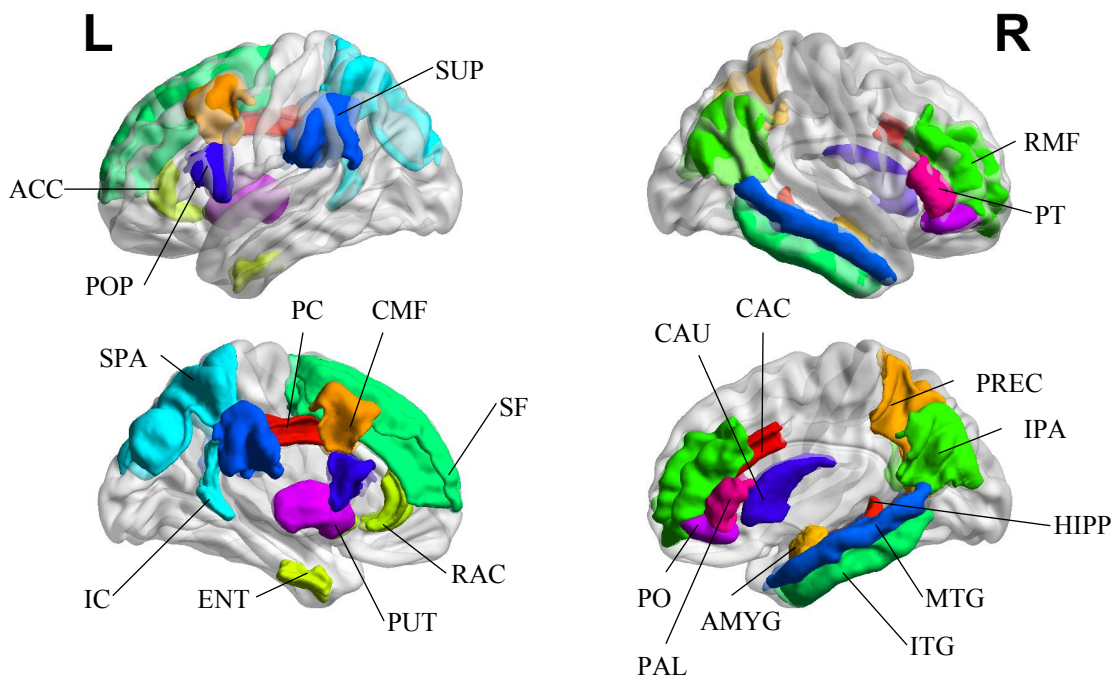| Cognitive Domain	β (SE)	t-value	p-value	partial η^2
Memory	-0.16 (0.26)	-0.62	.540	0.004
Executive Function	-0.17 (0.18)	-0.96	.342	0.01
Attention/Information Processing Speed	**-0.55 (0.23)**	**-2.35**	**.021**	**0.06**

APPENDIX B

Figure 1. Gray matter regions of interest associated with both cardiovascular risk factors and dementia. Colors do not necessarily delineate specific brain regions, as some colors were used more than once in identifying regions of interest.

Note. ACC = accumbens area; AMYG = amygdala; CAC = caudal anterior cingulate; CAU = caudate; CMF = caudal middle frontal gyrus; ENT = entorhinal cortex; HIPP = hippocampus; IC = isthmus cingulate; IPA = inferior parietal cortex; ITG = inferior temporal gyrus; MTG = middle temporal gyrus; PAL = pallidum; PC = posterior cingulate; PO = pars orbitalis; POP = pars opercularis; PREC = precuneus; PT = pars triangularis; PUT = putamen; RAC = rostral anterior cingulate; RMF = rostral middle frontal gyrus; SF = superior frontal gyrus; SPA = superior parietal cortex; SUP = supramarginal gyrus.

APPENDIX B (continued)
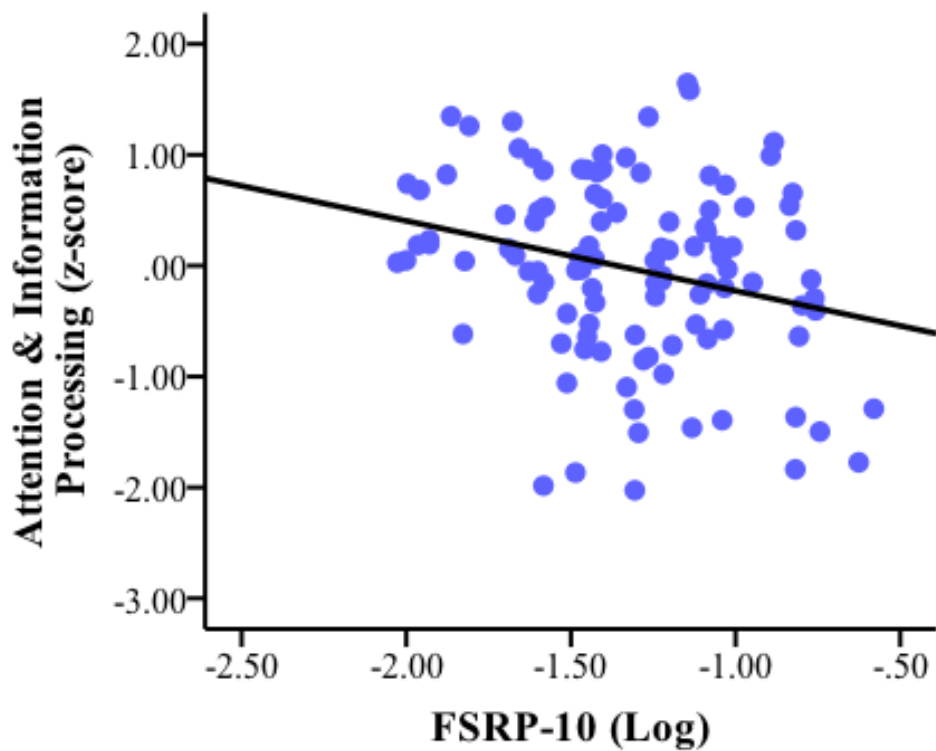
Figure 2. Higher 10-year stroke risk is associated with poorer attention and information

processing speed.

Note. FSRP-10 = Framingham 10-year stroke risk profile.
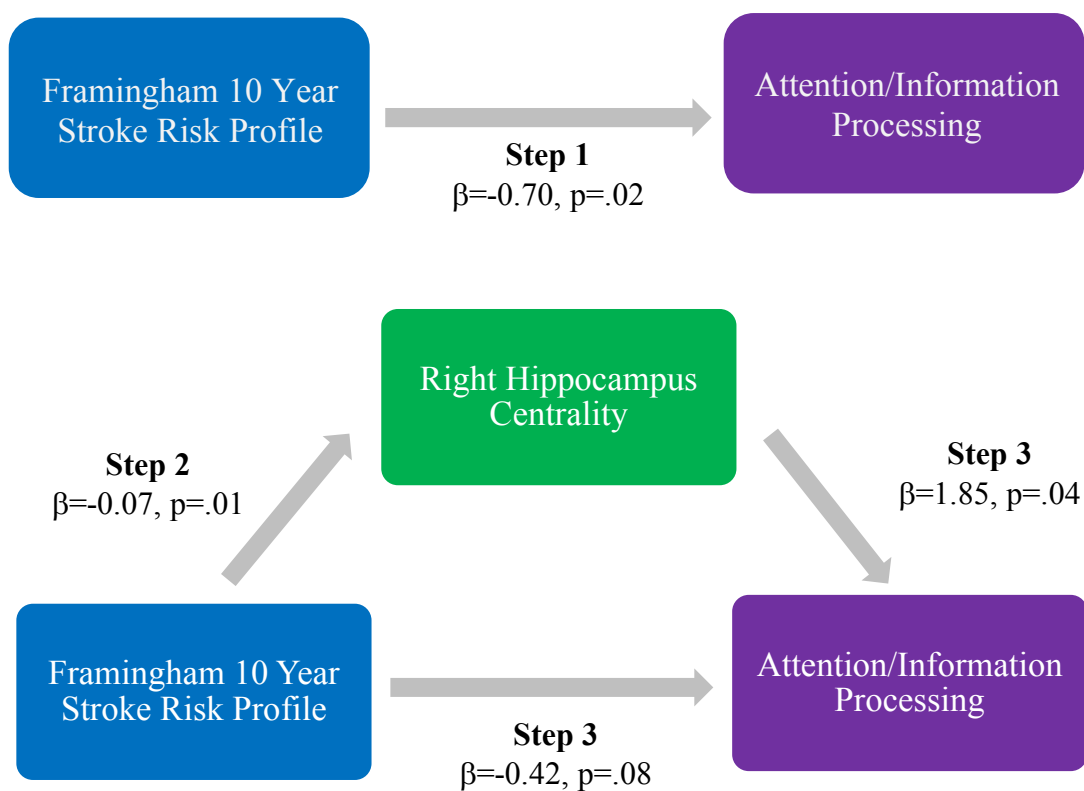
Figure 3. Mediation of right hippocampus centrality on relationship between Framingham 10-year stroke risk and attention and information processing speed.

Note. Centrality in the right hippocampus mediates the relationship between Framingham 10-year stroke risk and attention/information processing such that greater stroke risk associates with decreased centrality, which in turn is associated with poorer performance on measures of attention and information processing speed.
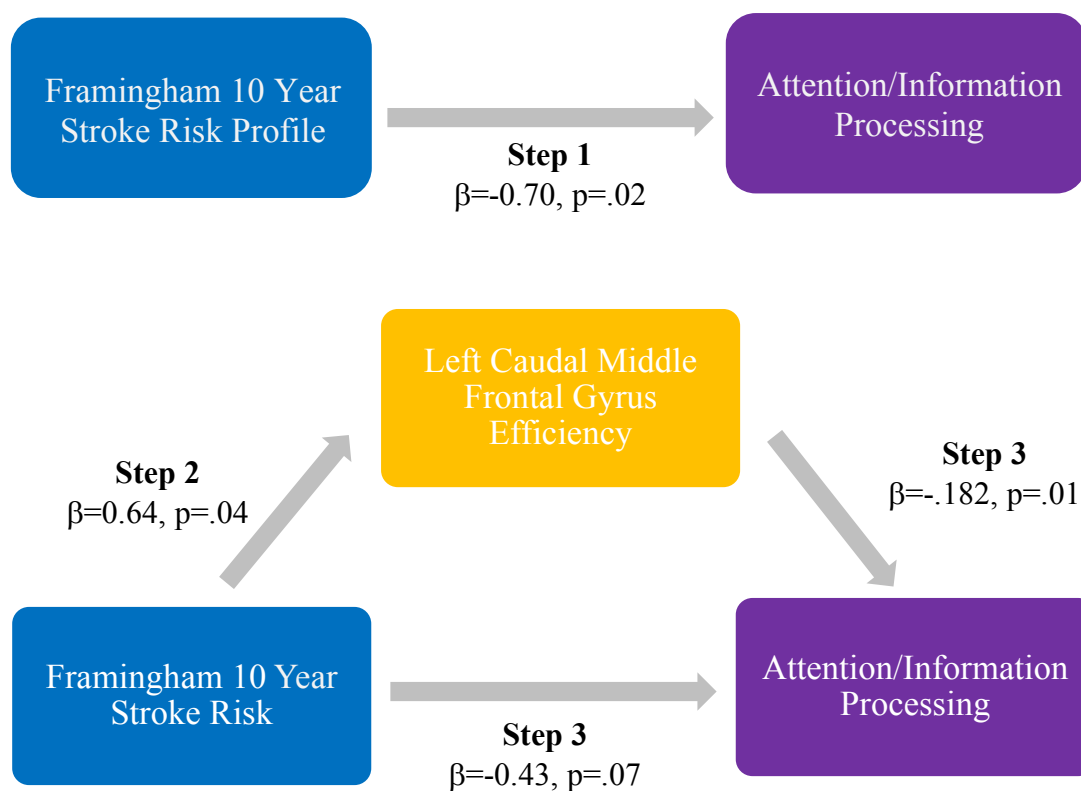
Figure 4. Mediation of left caudal middle frontal gyrus efficiency on relationship between

Framingham 10-year stroke risk and attention and information processing speed.

Note. Efficiency in the left caudal middle frontal gyrus mediates the relationship between

Framingham 10-year stroke risk and attention/information processing such that greater stroke

risk associates with increased efficiency, which in turn is associated with poorer performance on

measures of attention and information processing speed.

A.

B.
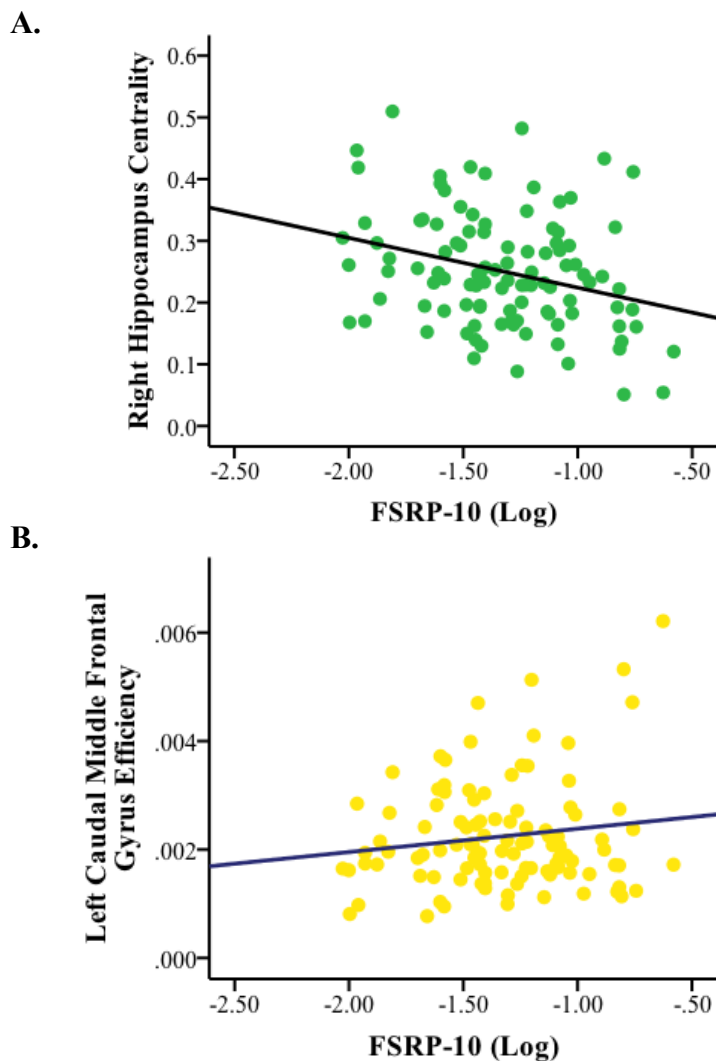
Figure 5. Associations between Framingham 10-year stroke risk and right hippocampus

centrality and left caudal middle frontal gyrus efficiency.

Note. Panels A and B depict the 'Step 2' associations of the mediation analysis, where greater

10-year stroke risk is associated with decreased centrality in the right hippocampus (A) and

increased efficiency in the left caudal middle frontal gyrus (B). Graphs depict raw data

unadjusted for covariates.

VITA

NAME

Elizabeth Anne Boots

EDUCATION

University of Illinois at Chicago, Chicago, IL	August 2016 – Present

M.A., Clinical Psychology (2018)
Ph.D., Clinical Psychology (in progress)
    Research Advisor: Melissa Lamar, PhD
    Academic Advisor: Stewart Shankman, PhD

University of Wisconsin – Madison, Madison, WI	September 2010 – May 2014

B.S., Neurobiology; Certificate in European Studies
    GPA: 3.940/4.000
    Dean's List: 8/8 semesters

RESEARCH EXPERIENCE

Rush Alzheimer's Disease Center, Chicago, IL	August 2016 - Present

Graduate Research Assistant

    Advisor: Melissa Lamar, PhD

- Recruit and screen urban community members for studies of vascular risk, cognition, and neuroimaging
- Administer and score extensive neuropsychological protocols, structured clinical interview (SCID), and psychosocial surveys to study participants
- Assist in data management
- Analyze neuroimaging and cognitive data for several projects investigating vascular risk and aging
- Supervise research assistants and other lab staff on data analysis, research projects, and other lab duties

Wisconsin Alzheimer's Disease Research Center Imaging Lab, Madison, WI

Research Specialist	August 2014 – July 2016
Research Assistant	September 2011 – August 2014

- Analyze data and prepare material for manuscript publication
- Run statistical analyses of MRI, PET, and neuropsychological datasets using software including SPSS, Analyze, AFNI, SPM and affiliated toolboxes LST and MarsBaR, MATLAB, and basic Linux commands
- Train and supervise undergraduate lab staff on data analysis, research projects, and general lab duties
- Recruit study participants and supervise participant research visits

- Administer cognitive tests and questionnaires including the CVLT-II, D-KEFS, MMSE, and Clinical Dementia Rating
- Design and update study materials for Institutional Review Board approval and internal use
- Work extensively with principal investigators, study coordinators, and fellow researchers to efficiently complete goals of studies
- Assist in grant preparation through writing and preliminary data analysis
- Oversee data entry for participant study information via Access and online databases, including the Alzheimer's Disease Neuroimaging Initiative National Study database

CLINICAL EXPERIENCE

University of Illinois Office of Applied Psychological Services, Chicago, IL

Student Clinician   January 2017 – Present

    <u>Current Supervisors:</u> Jenna Rowen, PhD, Erin Berenz, PhD, Sally Weinstein, PhD

    <u>Previous Supervisors</u>: Amanda Lorenz, PhD, S. Bibiana Adames, PhD

- Receiving training and supervision on empirically-based clinical techniques
- Providing clinical intakes and psychotherapy in a community-based training clinic
- Administering extensive psychological/neuropsychological assessments

Memory Assessment Clinic, University Station Clinic, Madison, WI

Neuropsychology Shadow   January 2015
- Observed neuropsychological testing in patients
- Interacted with physicians, social workers, and neuropsychologists

Memory Clinic, William S. Middleton Memorial Veterans Hospital, Madison, WI

Neuropsychology Extern   April 2014 – June 2014
- Observe expansive neuropsychological testing in patients
- Assist in neuropsychological test scoring
- Communicate with patients at clinic visits
- Interact with physicians, social workers, and neuropsychologists in determining patient diagnosis

TEACHING EXPERIENCE

Introduction to Psychology Teaching Assistant   September 2016 – May 2017

    University of Illinois at Chicago
    Professors: Julie Chen, PhD, Eric Leshikar, PhD

Abnormal Psychology Teaching Assistant

University of Illinois at Chicago   September 2017 – December 2017
Professor: Julia Kim-Cohen, PhD   September 2016 – December 2016

Psychological Testing Teaching Assistant   January 2018 – May 2018

University of Illinois at Chicago
Professor: Christopher Baker, PhD

AWARDS AND HONORS

Paul D. Doolen Graduate Scholarship for the Study of Aging Recipient	October 2017
Guest lecturer for University of Illinois at Chicago Abnormal Psychology course	November 2016-17
Invited speaker for a News Briefing at the Alzheimer's Association International Conference	July 2016
Alzheimer's Association Travel Fellowship Recipient	July 2016
Invited speaker at Alzheimer's Disease Research Center Seminar Series, "Research Findings from the Wisconsin ADRC CSF Biomarker Workgroup"	October 2015
Highlight Symposium Oral Session Selection, Alzheimer's Imaging Consortium 2015	July 2015
Student Poster Competition Finalist, Alzheimer's Association International Conference 2015	July 2015
UW-Madison Academic Professional Development Grant Recipient	May 2015
Alzheimer's Association Travel Fellowship Recipient	July 2014
Winner for Best Poster (Basic/Translational), Department of Medicine Research Day, UW – Madison	May 2014
Louise Troxell Award Nominee	March 2014
Herfurth-Kubly Award for Initiative and Efficiency Nominee	February 2014
International Academic Programs Study Abroad Scholarship	April 2013
College of Agricultural and Life Sciences Scholarships	2010-2012
UW-Madison Summer Music Clinic Full Collegiate Tuition Scholarship	2010-2014

PROFESSIONAL MEMBERSHIPS

Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART), *Student Member*	July 2014 – Present
American Psychological Association, *Student Member*	October 2016 – Present

Society for Clinical Neuropsychology/Division 40, *Student Member*

Association of Neuropsychological Student Training   October 2016 – Present
 University of Illinois Chapter Member

International Neuropsychological Society*, Student Member*   October 2017 – Present

PEER-REVIEWED PUBLICATIONS

1. **Boots EA,** Schultz SA, Oh JM, Larson J, Edwards DF, Cook DB, Koscik RL, Dowling NM, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, LaRue A, Asthana S, Hermann BP, Sager MA, Johnson SC, Okonkwo OC. *Cardiorespiratory fitness is associated with brain structure, cognition, and mood in a middle-aged cohort at risk for Alzheimer's disease.* Brain Imaging Behav. 2015 Sep; 9(3): 639-649.

2. Almeida RP, Schultz SA, Austin BP, **Boots EA,** Dowling NM, Gleason CE, Bendlin BB, Sager MA, Hermann BP, Zetterberg H, Carlsson CM, Johnson SC, Asthana S, Okonkwo OC. *Effect of cognitive reserve on age-related changes in cerebrospinal fluid biomarkers of Alzheimer disease.* JAMA Neurol. 2015 Jun; 72(6): 699-706.

3. **Boots EA,** Schultz SA, Almeida RP, Oh JM, Koscik RL, Dowling NM, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, Asthana S, Sager MA, Hermann BP, Johnson SC, Okonkwo OC. *Occupational complexity and cognitive reserve in a middle-aged cohort at risk for Alzheimer's disease.* Arch Clin Neuropsychol. 2015 Nov; 30(7): 634-42.

4. Schultz SA, **Boots EA,** Almeida RP, Oh JM, Einerson JA, Korcarz CE, Edwards DF, Koscik RL, Gallagher CL, Bendlin BB, Christian BT, Zetterberg H, Blennow K, Carlsson CM, Asthana S, Hermann BP, Sager MA, Johnson SC, Stein JH, Okonkwo OC. *Cardiorespiratory fitness attenuates the influence of amyloid on cognition.* J Int Neuropsychol Soc. 2015 Nov; 21(10): 841-50.

5. Dougherty RJ, Ellingson LD, Schultz SA, **Boots EA**, Meyer JD, Lindheimer JB, Van Riper S, Stegner AJ, Edwards DF, Oh JM, Koscik RL, Dowling MN, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, Asthana S, Hermann BP, Sager MA, Johnson SC, Okonkwo OC, Cook DB. *Meeting physical activity recommendations may be protective against temporal lobe atrophy in older adults at risk for Alzheimer's disease.* Alzheimers Dement (Amst). 2016 Apr 9; 4:14-7.

6. Law LL, Schultz SA, Boots EA, Einerson JA, Dougherty RJ, Oh JM, Korcarz CE, Edwards DF, Koscik RL, Dowling NM, Gallagher CL, Bendlin BB, Carlsson CM, Asthana S, Hermann BP, Sager MA, Johnson SC, Cook DB, Stein JH, Okonkwo OC. *Chronotropic response and cognitive function in a cohort at risk for Alzheimer's disease.* J Alzheimers Dis. 2017; 56(1): 351-359

7. Dougherty RJ, Schultz SA, **Boots EA**, Ellingson LD, Meyer JD, Van Riper S, Stegner AJ, Edwards DF, Oh JM, Einerson J, Korcarz CE, Koscik RL, Dowling MN, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, Asthana S, Hermann BP, Sager MA, Stein JH, Sterling CJ, Okonkwo OC, Cook DB. *Relationships between cardiorespiratory fitness, hippocampal volume, and episodic memory in a population at risk for Alzheimer's disease.* Brain Behav. 2017 Feb 17; 7(3):e00625.

8. Schultz SA, **Boots EA,** Darst BF, Edwards DF, Zetterberg H, Blennow K, Carlsson CM, Barbara BB, Asthana S, Sager MA, Hermann BP, Johnson SC, Stein JH, Engelman CD, Cook DB, Okonkwo OC. *Cardiorespiratory fitness modifies the association between a polygenic risk score and biomarkers in preclinical Alzheimer's disease.* Neurology. 2017 Apr 25; 88(17):1650-1658.

9. **Boots EA,** Schultz SA, Clark LR, Racine AM, Darst BF, Koscik RL, Carlsson CM, Gallagher CL, Hogan KJ, Bendlin BB, Asthana S, Sager MA, Hermann BP, Christian BT, Dubal DB, Engelman CD, Johnson SC, Okonkwo OC. *BDNF Val66Met predicts cognitive decline in the Wisconsin Registry for Alzheimer's Prevention.* Neurology. 2017 May 30; 88(22):2098-2106.

10. Dougherty RJ, Schultz SA, Kirby TK, **Boots EA,** Oh JM, Edwards DF, Gallagher CL, Carlsson CM, Bendlin BB, Asthana S, Sager MA, Hermann BP, Christian BT, Johnson SC, Cook DB, Okonkwo OC. *Moderate physical activity is associated with cerebral glucose metabolism in adults at risk for AD.* J Alzheimers Dis. 2017 May 17. Epub ahead of print.

11. Dougherty RJ, **Boots EA**, Lindheimer JB, Stegner AJ, Van Riper S, Edwards DF, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, Asthana S, Hermann BP, Sagar MA, Johnson SC, Okonkwo OC, Cook DB. *Fitness, independent of physical activity, is associated with cerebral blood flow in adults at risk for Alzheimer's disease.* Under Review. 2018.

12. **Boots EA**, Dion C, Karstens AJ, Cohen J, Zhou XJ, Rajendran N, Arafanakis K, Ajilore O, Bondi MW, Libon DJ, Lamar M. *Associations of Preclinical Memory and Executive Function Phenotypes with Cognitive, Stroke Risk, and Brain Structural Integrity Metrics in Older Adults.* Under Review. 2018.

13. Vesperman CJ, Pozorski V, Yang KL, Dougherty RJ, Law LL, **Boots EA**, Oh JM, Koscik RL, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, Asthana S, Sagar MA, Hermann BP, Johnson SC, Cook DB, Okonkwo OC. *Cardiorespiratory fitness attenuates age-associated aggregation of white matter hyperintensities: Findings from the Wisconsin Registry for Alzheimer's Prevention.* Under Review. 2018.

ORAL PRESENTATIONS

1. **Boots EA**. *Aging and Neurocognitive Disorders.* Abnormal Psychology Guest Lecture. Chicago, IL. November 2016, November 2017.

2. **Boots EA,** Schultz SA, Oh JM, Racine AM, Koscik RL, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, Asthana S, Sager MA, Hermann BP, Johnson SC, Okonkwo OC. *Occupational Complexity, Cognitive Reserve, and White Matter Hyperintensities: Findings from the Wisconsin Registry for Alzheimer's Prevention.* Alzheimer's Association International Conference. Toronto, Canada. July 2016.

3. Schultz SA, **Boots EA**, Oh JM, Darst BF, Koscik RL, Gallagher CL, Carlsson CM, Rowley HA, Barbara BB, Asthana S, Sager M, Hogan KJ, Hermann BP, Engelman CD, Johnson SC, Dubal DB, Okonkwo OC. *Longevity gene KLOTHO alters APOE4-related cortical thinning: Findings from the Wisconsin Registry for Alzheimer's Prevention.* Alzheimer's Association International Conference, Toronto, Canada. July 2016.

4. Dougherty RJ, **Boots EA**, Schultz SA, Johnson SC, Okonkwo OC, Cook DB. *Influence of VO2peak criteria on Aging and Alzheimer's Research.* American College of Sports Medicine Annual Meeting. Boston, Massachusetts. May 2016.

5. **Boots EA,** Schultz SA, Darst BF, Koscik RL, Bendlin BB, Carlsson CM, Gallagher CL, Hogan KJ, Asthana S, Sager MA, Hermann BP, Johnson SC, Engelman CD, Okonkwo OC. *BDNF Val66Met polymorphism predicts cognitive decline in the Wisconsin Registry for Alzheimer's Prevention.* 44th Annual Meeting of the International Neuropsychological Society. Boston, MA. February 2016.

6. Schultz SA, **Boots EA**, Kirby T, Dougherty RJ, Edwards DF, Einerson JA, Koscik RL, Gallagher CL, Carlsson CM, Bendlin BB, Zetterberg H, Blennow K, Asthana S, Sager MA, Hermann BP, Johnson SC, Stein JH, Cook DB, Okonkwo OC. *Sedentariness and intensity of physical activity are associated with CSF biomarkers of Alzheimer's disease: Findings from the Wisconsin Registry for Alzheimer's Prevention.* 44th Annual Meeting of the International Neuropsychological Society. Boston, MA. February 2016.

7. Schultz SA, **Boots EA**, Dougherty RJ, Darst BF, Yu S, Kirby T, Edwards D, Einerson J, Korcarz CE, Zetterberg H, Blennow K, Carlsson CM, Barbara BB, Asthana S, Sager M, Hermann BP, Johnson SC, Stein JH, Engelman CD, Cook DB, Okonkwo OC. *Cardiorespiratory fitness modifies the association between a polygenic risk score and CSF biomarkers in preclinical Alzheimer's disease.* 44th Annual Meeting of the International Neuropsychological Society. Boston, MA. February 2016.

8. **Boots EA**, Schultz SA, Oh JM, Dougherty RJ, Edwards DF, Einerson JA, Korcarz CE, Rowley HA, Bendlin BB, Asthana S, Sager MA, Hermann BP, Johnson SC, Stein JH, Cook DB, Okonkwo OC. *Cardiorespiratory capacity correlates with cerebral blood flow, white matter hyperintensities, and cognition in preclinical Alzheimer's disease.* Alzheimer's Imaging Consortium, Washington, D.C. July 2015.

9. Schultz SA, Kirby T, **Boots EA**, Dougherty RJ, Yu S, Law L, Oh JM, Edwards DF, Einerson JA, Korcarz CE, Bendlin BB, Asthana S, Sager MA, Hermann BP, Christian B, Johnson SC, Stein JH, Cook DB, Okonkwo OC. *Physical activity is associated cerebral [18F] fluorodeoxyglucose-PET uptake in middle-aged adults at risk for Alzheimer's disease.* Alzheimer's Association International Conference, Washington, DC. July 2015

10. Schultz SA, **Boots EA,** Almeida RP, Yu S, Cook DB, Edwards DF, Dougherty RJ, Stein JH, Einerson JA, Korcarz CE, Carlsson CM, Bendlin BB, Asthana S, Hermann BP, Sager MA, Johnson SC, Okonkwo OC. *Cardiorespiratory capacity attenuates the influence of age and amyloid-β on cognition.* 43rd Annual Meeting of the International Neuropsychological Society Conference, Denver, CO. February 2015.

11. Almeida RP, Schultz SA, **Boots EA,** Yu S, Henrik Z, Bendlin BB, Hermann BP, Sager MA, Carlsson CM, Johnson SC, Asthana S, Okonkwo OC. *Cognitive reserve modifies age-related alterations in CSF biomarkers of Alzheimer's disease.* 43rd Annual Meeting of the International Neuropsychological Society Conference, Denver, CO. February 2015.

12. Cook DB, Okonkwo OC, Dougherty RJ, Schultz SA, **Boots EA**. *A Fit Brain is a Healthy Brain*. Alzheimer's Disease Annual Update provided by the Wisconsin Medical Society, Wisconsin Alzheimer's Institute, and University of Wisconsin School of Medicine and Public Health, Madison, WI. November 2014.

13. **Boots EA**, Oh JM, Schultz SA, Larson J, Edwards DF, Cook DB, Koscik RL, Dowling NM, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, LaRue A, Asthana S, Hermann BP, Johnson SC, Sager MA, Okonkwo OC. *Cardiorespiratory fitness is associated with brain structure, cognition, and mood in a middle-aged cohort at risk for Alzheimer's disease.* Alzheimer's Association International Conference, Copenhagen, Denmark. July 2014.

14. **Boots EA**, Oh JM, Schultz SA, Larson J, Edwards DF, Cook DB, Koscik RL, Dowling NM, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, LaRue A, Asthana S, Hermann BP, Johnson SC, Sager MA, Okonkwo OC. *Cardiorespiratory fitness is associated with brain structure, cognition, and mood in a middle-aged cohort at risk for Alzheimer's disease.* College of Agriculture and Life Sciences Research Symposium, Madison WI. April 2014.

15. **Boots EA**, Oh JM, Schultz SA, Larson J, Edwards DF, Cook DB, Koscik RL, Dowling NM, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, LaRue A, Asthana S, Hermann BP, Johnson SC, Sager MA, Okonkwo OC. *Cardiorespiratory fitness is associated with brain structure, cognition, and mood in a middle-aged cohort at risk for Alzheimer's disease.* Undergraduate Symposium, Madison WI. April 2014.

POSTERS

1. **Boots EA**, Zhan L, Dion C, Karstens AJ, Cohen J, Lamar M. *Tract-based structural connectomics influences on stroke risk and cognition in cognitively-normal older adults.* Alzheimer's Association International Conference. Chicago, IL. July 2018.

2. Dougherty RJ, Moon HY, **Boots EA**, Becke A, Cook DB, van Praag H, Okonkwo OC. *The effect of aerobic exercise training on serum BDNF in preclinical Alzheimer's disease.* Alzheimer's Association International Conference. Chicago, IL. July 2018.

3. Ennis GE, Dougherty RJ, **Boots EA**, Edwards DF, Koscik RL, Duezel E, Wagner M, Carlsson CM, Gallagher CL, Bendlin BB, Asthana S, Sager MA, Hermann BP, Johnson SC, Cook DB, Okonkwo OC. *Aerobic training is related to cognitive health in adults at risk for Alzheimer's disease: Results from the aerobic Exercise And Cognitive Health (REACH) pilot study.* Alzheimer's Association International Conference. Chicago, IL. July 2018.

4. **Boots EA**, Dion C, Rajendran N, Karstens AJ, Cohen J, Ajilore O, Lamar M. *Preclinical profiles of memory versus executive function weakness as related to cognition, stroke risk, and white matter integrity in older adults.* 46th Annual Meeting of the International Neuropsychological Society. Washington, D.C. February 2018.

5. Dion C, **Boots EA**, Zhan L, Karstens AJ, Cohen J, Ajilore O, Maki PM, Marquez DX, Lamar M. *Sex differences in the contribution of physical activity to verbal learning and memory in older adults.* 46th Annual Meeting of the International Neuropsychological Society. Washington, D.C. February 2018.

6. **Boots EA**, Dean DC III, Ajilore O, Zhou X, Deoni SCL, Lamar M. *Blood pressure and blood glucose are associated with myelin vulnerability in an ethnically diverse sample of older adults.* Alzheimer's Association International Conference. London, England. July 2017.

7. **Boots EA**, Dean DC III, Ajilore O, Zhou X, Deoni SCL, Lamar M. *Blood pressure and blood glucose are associated with myelin vulnerability in an ethnically diverse sample of older adults.* Alzheimer's Imaging Consortium. London, England. July 2017.

8. Dougherty RJ, **Boots EA**, Johnson SC, Edwards DF, Okonkwo OC, Cook DB. *Exercise training and cerebral blood flow in preclinical Alzheimer's disease: Results from the aerobic exercise and cognitive health (REACH) study.* Alzheimer's Imaging Consortium. London, England. July 2017.

9. Dougherty RJ, **Boots EA**, Cody KA, Schultz SA, Edwards DF, Johnson SC, Einerson J, Okonkwo OC, Cook DB. *Fitness, independent of physical activity is associated with cerebral blood flow in older adults at-risk for Alzheimer's disease.* American College of Sports Medicine Annual Meeting, Denver, Colorado. May 2017.

10. Dion C, Karstens A, Zhang L, Cohen J, **Boots EA**, Ajilore O, Leow A, Marquez D, Lamar M. *Associations of sedentary behavior as well as physical activity with learning, memory, and hippocampal volume in a diverse sample of older adults.* 45th Annual Meeting of the International Neuropsychological Society. New Orleans, LA. February 2017.

11. **Boots EA,** Schultz SA, Oh JM, Racine AM, Koscik RL, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, Asthana S, Sager MA, Hermann BP, Johnson SC, Okonkwo OC. *Occupational Complexity, Cognitive Reserve, and White Matter Hyperintensities: Findings from the Wisconsin Registry for Alzheimer's Prevention.* Alzheimer's Imaging Consortium. Toronto, Canada. July 2016.

12. **Boots EA**, Schultz SA, Oh JM, Dougherty RJ, Edwards DF, Einerson JA, Korcarz CE, Rowley HA, Bendlin BB, Asthana S, Sager MA, Hermann BP, Johnson SC, Stein JH, Cook DB, Okonkwo OC. *Cardiorespiratory capacity correlates with cerebral blood flow, white matter hyperintensities, and cognition in preclinical Alzheimer's disease.* UW-Madison Institute on Aging Colloquium, Madison, WI. September 2015.

13. Dougherty RJ, Schultz SA, **Boots EA,** Okonkwo OC, Cook DB. *Cardiorespiratory fitness is associated with temporal lobe volume in adults at risk for Alzheimer's disease.* UW-Madison Institute on Aging Colloquium, Madison, WI. September 2015.

14. **Boots EA**, Schultz SA, Oh JM, Dougherty RJ, Edwards DF, Einerson JA, Korcarz CE, Rowley HA, Bendlin BB, Asthana S, Sager MA, Hermann BP, Johnson SC, Stein JH, Cook DB, Okonkwo OC. *Cardiorespiratory capacity correlates with cerebral blood flow, white matter hyperintensities, and cognition in preclinical Alzheimer's disease.* Alzheimer's Association International Conference, Washington, D.C. July 2015.

15. Schultz SA, **Boots EA**, Darst BF, Yu S, Kirby T, Edwards DF, Einerson JA, Korcarz CE, Zetterberg H, Blennow K, Carlsson CM, Bendlin BB, Asthana S, Sager MA, Hermann BP, Johnson SC, Stein JH, Engelman CD, Cook DB, Okonkwo OC. *Cardiorespiratory capacity*

modifies the association between a polygenic risk score and CSF biomarkers in preclinical Alzheimer's disease. Alzheimer's Imaging Consortium, Washington, D.C. July 2015.

16. Schultz SA, **Boots EA**, Darst BF, Yu S, Kirby T, Edwards DF, Einerson JA, Korcarz CE, Zetterberg H, Blennow K, Carlsson CM, Bendlin BB, Asthana S, Sager MA, Hermann BP, Johnson SC, Stein JH, Engelman CD, Cook DB, Okonkwo OC. *Cardiorespiratory capacity modifies the association between a polygenic risk score and CSF biomarkers in preclinical Alzheimer's disease.* Alzheimer's Association International Conference, Washington, D.C. July 2015.

17. **Boots EA**, Schultz SA, Oh JM, Dougherty RJ, Edwards DF, Einerson JA, Korcarz CE, Rowley HA, Bendlin BB, Asthana S, Sager MA, Hermann BP, Johnson SC, Stein JH, Cook DB, Okonkwo OC. *Cardiorespiratory capacity correlates with cerebral blood flow, white matter hyperintensities, and cognition in preclinical Alzheimer's disease.* 8th Annual UW-Madison Department of Medicine Research Day, Madison, WI. May 2015.

18. Schultz SA, **Boots EA**, Darst BF, Yu S, Kirby T, Edwards DF, Einerson JA, Korcarz CE, Zetterberg H, Blennow K, Carlsson CM, Bendlin BB, Asthana S, Sager MA, Hermann BP, Johnson SC, Stein JH, Engelman CD, Cook DB, Okonkwo OC. *Cardiorespiratory fitness modifies the association between a polygenic risk score and CSF biomarkers in preclinical Alzheimer's disease.* 8th Annual UW-Madison Department of Medicine Research Day, Madison, WI. May 2015.

19. Law LL, Schultz SA**, Boots EA,** Dougherty RJ, Oh JM, Almeida RP, Oh JM, Einerson JA, Korcarz CE, Edwards DF, Koscik RL, Dowling NM, Gallagher CL, Bendlin BB, Carlsson CM, Asthana S, Hermann BP, Sager MA, Johnson SC, Stein JH, Cook DB, Okonkwo OC. *Cardiorespiratory fitness modifies age-related changes on cognition.* 8th Annual UW-Madison Department of Medicine Research Day, Madison, WI. May 2015.

20. **Boots EA,** Schultz SA, Almeida RP, Yu S, Oh JM, Koscik RL, Dowling NM, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, LaRue A, Asthana S, Hermann BP, Sager MA, Johnson SC, Okonkwo OC. *Occupational complexity and cognitive reserve in middle-aged adults at risk for Alzheimer's disease.* Alzheimer's & Parkinson's Research Day. Madison, WI. March 2015.

21. Schultz SA, **Boots EA**, Darst BF, Yu S, Kirby T, Edwards DF, Einerson JA, Korcarz CE, Zetterberg H, Blennow K, Carlsson CM, Bendlin BB, Asthana S, Sager MA, Hermann BP, Johnson SC, Stein JH, Engelman CD, Cook DB, Okonkwo OC. *Cardiorespiratory capacity modifies the association between a polygenic risk score and CSF biomarkers in preclinical Alzheimer's disease.* Alzheimer's & Parkinson's Research Day. Madison, WI. March 2015.

22. Dougherty RJ, Schultz SA, **Boots EA**, Okonkwo OC, Cook DB. *Cardiorespiratory fitness and hippocampal volume: a review of the literature.* Alzheimer's & Parkinson's Research Day. Madison, WI. March 2015.

23. **Boots EA,** Schultz SA, Almeida RP, Yu S, Oh JM, Koscik RL, Dowling NM, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, LaRue A, Asthana S, Hermann BP, Sager MA, Johnson SC, Okonkwo OC. *Occupational complexity and cognitive reserve in middle-aged adults at risk for Alzheimer's disease.* 43rd Annual Meeting of the International Neuropsychological Society Conference, Denver, CO. February 2015.

24. **Boots EA**, Oh JM, Schultz SA, Larson J, Edwards DF, Cook DB, Koscik RL, Dowling NM, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, LaRue A, Asthana S, Hermann BP, Johnson SC, Sager MA, Okonkwo OC. *Cardiorespiratory fitness is associated with brain structure, cognition, and mood in a middle-aged cohort at risk for Alzheimer's disease.* UW-Madison Institute on Aging Colloquium, Madison, WI. September 2014.

25. Almeida RP, Schultz SA, **Boots EA,** Yu S, Henrik Z, Bendlin BB, Hermann BP, Sager MA, Carlsson CM, Johnson SC, Asthana S, Okonkwo OC. *Cognitive reserve modifies age-related alterations in CSF biomarkers of Alzheimer's disease*. UW-Madison Institute on Aging Colloquium, Madison, WI. September 2014.

26. **Boots EA**, Oh JM, Schultz SA, Larson J, Edwards DF, Cook DB, Koscik RL, Dowling NM, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, LaRue A, Asthana S, Hermann BP, Johnson SC, Sager MA, Okonkwo OC. *Cardiorespiratory fitness is associated with brain structure, cognition, and mood in a middle-aged cohort at risk for Alzheimer's disease.* Alzheimer's Imaging Conference, Copenhagen, Denmark. May 2014.

27. **Boots EA**, Oh JM, Schultz SA, Larson J, Edwards DF, Cook DB, Koscik RL, Dowling NM, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, LaRue A, Asthana S, Hermann BP, Johnson SC, Sager MA, Okonkwo OC. *Cardiorespiratory fitness is associated with brain structure, cognition, and mood in a middle-aged cohort at risk for Alzheimer's disease.* 7th Annual UW-Madison Department of Medicine Research Day, Madison, WI. May 2014.

28. **Boots EA**, Oh JM, Schultz SA, Larson J, Edwards DF, Cook DB, Koscik RL, Dowling NM, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, LaRue A, Asthana S, Hermann BP, Johnson SC, Sager MA, Okonkwo OC. *Cardiorespiratory fitness is associated with brain structure, cognition, and mood in a middle-aged cohort at risk for Alzheimer's disease.* Alzheimer's Research Day, Madison, WI. March 2014.

29. **Boots EA**, Bendlin BB. *Metabolic syndrome and its effects on Alzheimer's disease*. UW-Madison Biology 152 Independent Research Poster Session, Madison WI. December 2011.

SKILLS

Neuropsychological Tests

Benton Judgment of Line Orientation Test; Boston Naming Test; California Verbal Learning Test-II; Card Sorting, Category Fluency; Color-Word Interference Test, Conner's Continuous Performance Test; Delis-Kaplan Executive Function System; Design Fluency; Digital Clock Drawing Test; Digit Span; Digit Symbol; Letter-Number Sequencing, Mini-Mental Status Examination; Montreal Cognitive Assessment; Oral and Written Language Scales-II; Rey Auditory Verbal Learning Test; Tower Test; Trail Making Test Parts A, B, & Motor; Wechsler Adult Intelligence Scale IV; Wechsler Memory Scale; Wechsler Test of Adult Reading; Woodcock Johnson Achievement IV; Woodcock Johnson IV Tests of Cognitive Abilities; Word Fluency

Clinical Scales and Questionnaires

Beck Depression Inventory; Beck Anxiety Inventory; Center for Epidemiologic Studies Depression Scale; Clinical Dementia Rating; Community Healthy Activities Model Program for Seniors Questionnaire; Conner's Adult ADHD Rating Scale Self and Observer report; Functional Assessment Questionnaire; Geriatric Depression Scale; Learning and Study Strategies Inventory 2nd Edition; Minnesota Multiphasic Personality Inventory-2RF; Multidimensional Anxiety Questionnaire; Outcome Questionnaire; Pittsburgh Sleep Quality Index, Structured Clinical Interview for the Diagnostic Statistical Manual IV, Tennessee Self-Concept Scale; Trauma Symptom Inventory-2; Wender Utah Rating Scale

Computer Software

SPSS, R, FSL, Brain Connectivity Toolbox, DTI Studio, Analyze, AFNI, MRIcron, SPM and affiliated toolboxes including LST and MarsBar, MATLAB, basic Linux commands, Titanium, Microsoft Office, Adobe Acrobat, Windows and Mac operating systems