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Effects of blood pressure on brain microstructure and cognition in healthy older adults

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Dissertation

Abstract

Hypertension represents one of the major modifiable health concerns in the U.S., with over one-third of adults classified as hypertensive, and another one-third meeting the classification for pre-hypertensive. Older adults are at the highest risk for hypertension. Although results have been mixed, a majority of the literature suggests that hypertension is associated with increased cognitive decline in older adults, particularly in frontally-mediated cognition such as executive functioning, processing speed, and attention. White matter hyperintensities (WMHs) and altered white matter microstructure are two consequences of hypertension that are thought to mediate the relationship between hypertension and cognitive aging. The goals of this study were to examine the impact of hypertension on two major white matter tracts that connect posterior regions of the brain with the frontal lobe and WMHs, to identify whether baseline blood pressure, baseline white matter tract integrity and baseline WMH volume contribute to frontally-mediated cognitive performance at a baseline visit, and to examine the longitudinal changes in white matter integrity and cognition in individuals who were hypertensive at baseline compared to baseline normotensives. Sixty older adults with both baseline and 3-year follow-up cognitive and imaging data were analyzed. Results indicated no significant relationships between blood pressure and white matter integrity or cognition at baseline or longitudinally. However, results suggested significant relationships between lower white matter integrity and worse cognitive performance on tests of executive functioning and processing speed. Although blood pressure did not significantly contribute to brain aging in this sample of healthy older adults, future work might identify other possible factors that could influence the relationship between aging and cognitive decline.

Effects of blood pressure on brain microstructure and cognition in healthy older adults

High blood pressure, or hypertension, is a widely prevalent health concern among older Americans. A 2013 report by the Centers for Disease Control (CDC) indicates an estimated 31%, or 78 million, of all U.S. adults aged 18 years and older are hypertensive. Another 30% of all U.S. adults are considered to be pre-hypertensive, with a blood pressure that is on the high end of the normal range. Prevalence of hypertension was highest among those individuals aged 65 years or older, where rates were estimated to be almost 70%. The lifetime risk for developing this disorder is almost 90% (Vasan et al, 2002). Hypertension, defined as a systolic blood pressure greater than or equal to 140 mm Hg *or* a diastolic blood pressure greater than or equal to 90 mm Hg, has been associated with an increased risk for the development of multiple other medical conditions. The most significant among these are the increased risks of cardiovascular disease (Vasan et al., 2001) and cerebrovascular disease, particularly risk of stroke (MacMahon et al., 1990). A 2013 report by the American Heart Association and American Stroke Association estimates that hypertension is present in 75-77% of people who have congestive heart failure or a first stroke (Go et al., 2013).

Hypertension and Cognitive Aging. Research has supported a role for blood pressure in cognitive aging. Specifically, hypertension has been associated with cognitive decline in older adults. Impaired performance on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), a brief screening measure of cognitive status, has repeatedly been associated with hypertension in older adults (Cacciatore et al., 1997; Kilander, Nyman, Boberg, Hansson, & Lithell, 1998; Kuusisto et

al., 1993; Swan et al., 1998; Tzourio, Dufouil, Ducimetière, Alpérovitch, & the EVA Study Group, 1999; van Swieten et al., 1991). Poor performance on a more comprehensive analysis of global cognition, formed by summing composite scores across multiple tests and domains, was associated with higher systolic blood pressure in middle-aged and older adults (Knecht et al., 2008). Knecht et al. (2008) also reported impaired global cognition was associated with higher systolic blood pressure in the normotensive range, indicating that even high-normal (or pre-hypertensive) blood pressure can be detrimental to cognitive status. Results are more variable when examining specific cognitive domains, with no significant relationships between performance and hypertension in some studies (Di Carlo et al., 2000; Farmer et al., 1987; van Boxtel et al., 1997) and significant relationships reported in other studies. When present, hypertension has been correlated with worse performance on tests of visual memory (van Swieten et al., 1991), verbal fluency (Swan et al., 1998), psychomotor speed (Kuo et al., 2004; Waldstein, Giggey, Thayer, & Zonderman, 2005), naming (Waldstein, Giggey, Thayer & Zonderman, 2005), immediate and delayed word recognition (Harrington, Saxby, McKeith, Wesnes & Ford, 2000; Pase et al., 2013), delayed recall (Vicario, Martinez, Baretto, Diaz - Casale & Nicolosi, 2005), and spatial memory (Harrington et al., 2000) in older adults.

The most consistent relationships between hypertension and cognition have been observed in studies examining frontally-mediated cognitive domains such as executive function (Bucur & Madden, 2010; Kilander et al., 1998; Kuo et al., 2004; Pase et al., 2013; Raz, Rodrigue & Acker, 2003; Waldstein et al. 2005). Lower performance on tests of executive functioning has also been associated with both older age, and

interactions between high blood pressure and age (Bucur & Madden, 2010; Waldstein et al., 2005), supporting the role of hypertension as one possible contributing factor to cognitive aging. Previous research also reveals a relationship between hypertension and poor processing speed in cross sectional studies (Harrington et al., 2000; Saxby, Harrington, McKeith, Wesnes & Ford, 2003; Swan et al., 1998) and reductions in processing speed over time in prospective studies (Köhler et al., 2013). Increased blood pressure and supine hypertension have also been significantly associated with decreased performance on tests of attention (Brown, Sollers, Thayer, Zonderman, & Waldstein, 2009; Frewen, Finucane, Sawa, Boyle, & Kenny, 2014; Wharton et al., 2014).

The mechanism underlying the potential contribution of hypertension to cognitive aging is not yet clear, though vascular abnormalities linked to hypertension represents a likely candidate. Both aging and hypertension have negative effects on the vascular system. Increasing age is associated with stiffening and thickening of the arterial wall and increased pulse velocity, leading to the development of hypertension (Safar, Levy, & Struijker-Boudier, 2003; Scuteri, Nilsson, Tzourio, Redon & Laurent, 2011). In turn, arterial stiffening and narrowing of the lumen of small perforating arteries and arterioles leads to general and regional reductions in cerebral blood flow (Martin, Friston, Colebatch & Frackowiak, 1991; Melamed, Lavy, Bentin, Cooper & Rinot, 1980) and decreased vasodilatory response (Bakker, de Leeuw, de Groot, Hofman, Koudstaal & Breteler, 1999), resulting in lowered blood supply, particularly to the deep white matter regions of the brain. The appearance of white matter hyperintensities (WMHs; Aribisala et al., 2014; Brickman et al., 2009*a*) and altered white matter microstructure (Chen, Rosas & Salat, 2013) are two consequences of reduced cerebral blood flow. In particular,

periventricular white matter is located at an arterial border zone ("watershed" region) that receives blood supply from small perforating arteries and arterioles. Periventricular WMHs are likely to develop as a result of reduced cerebral blood flow in these regions (Pantoni & Garcia, 1997). Additionally, previous research has demonstrated degeneration of white matter microstructure caused by tortuosity of the arterioles, identified as particularly severe in white matter (Brown, Moody, Challa, Thore & Anstrom, 2002). Accordingly, hypertension has been heavily associated with both WMHs and abnormalities in white matter microstructure.

Hypertension and WMH. Historically, WMHs have been the primary focus of research examining the relationship between hypertension and white matter in older adults. It has been theorized that WMHs primarily develop in response to consequences of arteriolosclerosis and reductions in blood flow, including ischemic tissue damage and loss of fibers (Fazekas et al., 1993). High blood pressure has been significantly associated with increased burden and volume of WMHs in the brain (Breteler et al., 1994; Brickman et al., 2010; Dufouil et al., 2001; Fazekas et al., 1988; Jeerakathil et al., 2004; Raz, Rodrigue & Acker, 2003; Raz, Rodrigue, Kennedy & Acker, 2007; Schmidt et al., 1993). This increased presence of WMHs is identified primarily in the frontal lobe (Raz et al., 2003; Raz et al., 2007), indicating a particular vulnerability of frontal regions to the negative effects of vascular risk factors associated with age. However, other research has suggested a vulnerability of posterior regions of the brain in hypertension. Hypertension has been associated with WMH burden in the occipital lobe (Artero et al., 2004), and elevated systolic blood pressure is associated with increased volume of posterior WMHs over a 5-year follow-up period (Raz et al., 2007). As posterior WMHs are relatively rare

in healthy older adults without hypertension, it is likely that increased cardiovascular risk factors, such as hypertension, contribute to their development in addition to other non-cardiovascular risk factors, such as apolipoprotein ε4 genotype status (Zhu et al., 2012). Although not all studies link higher mean blood pressure to increased volume of WMHs (Gunstad et al., 2005), the majority of the literature provides support for this association.

Research suggests that WMHs significantly and negatively impact brain function. Previous studies demonstrate a relationship between the vulnerability of frontal white matter to WMHs and frontally-mediated cognition, including processing speed and executive functioning (deCarli et al., 1995; Raz et al., 2003; Schmidt et al., 1993). For example, a study by Raz et al. (2003) established that individuals with hypertension had decreased prefrontal cortex volume, increased frontal WMHs, and increased perseverative errors on a test of executive functioning. Other studies have identified poorer performance on tests of executive functioning and processing speed in older adults with WMHs compared to those without WMHs (Schmidt et al., 1993). Decreased global cognitive functioning and subjective reports of mental decline have also been significantly associated with WMHs (Breteler et al., 1994; Brickman et al., 2009*b*; de Groot et al., 2000; Gunning-Dixon & Raz, 2000). The literature supports a role for increased burden and localization of WMHs in the brain in impacting cognitive function in older adults.

Diffusion Tensor Imaging Studies of Hypertension. The relationship between hypertension and white matter microstructure has been less well-studied until recent years. Diffusion tensor imaging (DTI) has been utilized over the past two decades to non-invasively examine neuronal, axonal, and myelin integrity in the brain (Le Bihan et

al., 2001). DTI is a neuroimaging method that measures the rate of water diffusion along neural pathways. In healthy neurons, water diffuses in a directionally-dependent manner. In damaged neurons, the reduced integrity of neuron fibers allow for random and non-directional diffusion of water molecules. Studies utilizing DTI have primarily examined white matter, measuring the diffusion of water along myelinated axonal fibers. Primary indices of DTI utilized as markers of brain integrity include fractional anisotropy (FA) and mean diffusivity (MD). FA refers to a scalar, ratio measure of the directional dependency of water diffusion. A value of zero signifies complete isotropy, indicating an equal diffusion rate in all directions. MD is the average rate of diffusion of water molecules within a voxel, independent of direction-specific restrictions such as membranes and tissues. FA and MD are generally recognized as measures of overall neuronal density and integrity. Low MD values and high FA values are generally associated with increased microstructural integrity and neuronal density (Alexander, Lee, Lazar & Field, 2007; Le Bihan et al., 2001).

DTI has been utilized to examine the relationship between hypertension and regional white matter microstructural integrity in older adults. Generally, hypertension is linked to reduced white matter microstructural integrity in normal-appearing white matter. Older adults with treated arterial hypertension exhibit reduced FA in temporal and occipital white matter beyond the effects of age (Kennedy & Raz, 2009). In this study, normotensives with elevated arterial pulse pressure (difference between systolic and diastolic blood pressure) exhibited reduced FA and increased MD in prefrontal white matter. The authors theorize that vascular risk factors, including hypertension, may result in a shift from primarily anterior patterns of white matter damage in normal aging to a

pattern that conjointly includes white matter damage in posterior brain regions. Recent studies demonstrated a significant relationship between mean arterial blood pressure and decreased FA in precuneus, occipital, parietal, frontal, and temporal white matter in older adults after controlling for age and WMH, and a trending relationship for whole brain white matter (Burgmans et al., 2010; Leritz et al., 2010; Salat et al., 2012). Systolic blood pressure has been reported to be positively and significantly correlated with MD in frontal, parietal, temporal and occipital white matter (MacLullich et al., 2009). Additionally, a significant relationship between hypertension and reduced FA in normal-appearing white matter has been reported in individuals with small vessel disease (Gons et al., 2010).

Recent studies have examined the relationship between microstructural integrity of major white matter tracts in the brain and hypertension using DTI tractography. This relatively novel DTI technique allows for the visualization and measurement of diffusion metrics along entire white matter pathways connecting different regions of the brain (Basser, Pajevic, Pierpaoli, Duda & Aldroubi, 2000; Conturo et al., 1999). Historically, the corpus callosum has been a primary focus in the DTI literature given the size of the structure and relative ease of anatomical specificity. Elevated blood pressure has been significantly associated with reduced FA and increased MD in the corpus callosum (Maillard et al., 2012; MacLullich et al., 2009; Leritz et al., 2010; Salat et al., 2012). Apart from the corpus callosum, there have been few DTI studies examining and establishing a pattern of altered white matter microstructure in other major white matter tracts in hypertensive individuals. A recent study of healthy adults age 18-81 identified a significant relationship between elevated systolic blood pressure and reduced FA in the

fornix, posterior thalamic radiation, and sagittal stratum (Aine et al., 2014). These reductions in FA were also significantly related to impaired spatial working memory accuracy. In young-to-middle-aged adults, increased systolic blood pressure was significantly associated with reduced FA and increased MD in the inferior-fronto-occipital fasciculus (Maillard et al., 2012). In very old adults (mean age = 83 years), it has been reported that elevated systolic blood pressure is significantly related to reduced FA in the uncinate fasciculus and the superior longitudinal fasciculus (Rosano et al., 2014). The most comprehensive analysis of white matter tracts in the hypertensive literature was completed by Salat et al. (2012), and identified significant relationships between increased mean arterial blood pressure and reduced FA of the inferior cerebellar peduncle, fornix, anterior corona radiata, uncinate fasciculus, superior fronto-occipital fasciculus, and left external capsule. Combined with regional results listed previously, Salat et al. (2012) noted a pattern of associations between blood pressure and white matter integrity that was similar to the pattern ascribed to associations between normal aging and white matter integrity. The authors suggest that vascular health and vascular risk factors may contribute to the neural degeneration characteristically attributed to aging.

Previous studies examining the relationship between hypertension and white matter integrity suggest that hypertension represents a contributing factor to the established anterior patterns of white matter abnormalities ascribed to normal aging. Specifically, frontal white matter and frontally-mediated executive functioning, processing speed, and attention are significantly impacted by hypertension. Additionally, literature supports a role for hypertension in extending this pattern of reduced white

matter integrity to posterior regions of the brain. However, there is a lack of research that examines integrity of major white matter tracts that connect frontal and posterior brain regions in older adults with hypertension. To fully understand the complex interactions between the effects of blood pressure and aging on cognition, it is important to identify the patterns of reduced white matter integrity at the level of tracts connecting frontal and posterior regions of the brain in hypertensive older adults and to examine the evolution of these changes over time.

The superior longitudinal fasciculus (SLF) and inferior fronto-occipital fasciculus (IFOF) are two major white matter tracts that span from regions of the frontal lobe to the occipital lobe. Both white matter tracts have been previously associated with reduced integrity in normal aging, as evidenced by reductions in FA among healthy older adults (Teipel et al., 2010). Reduced FA in the SLF has previously been associated with poor executive functioning in children and adolescents (Urger et al., 2014) and in adults (Sasson, Doniger, Pasternak, Tarrasch & Assaf, 2013). Aspects of executive functioning, particularly set-shifting (switching between two or more tasks), have also been significantly associated with IFOF integrity (Perry et al., 2009). Further, reduced FA in the SLF and IFOF is significantly associated with decreased performance on tests of processing speed (Santiago et al., 2014; Turken et al., 2008), and reduced FA of the SLF has been significantly correlated with decreased performance on tasks of sustained attention (Frye et al., 2010; Klarborg et al., 2012). Collectively, these results indicate that the integrity of the SLF and IFOF are affected by normal aging and play a role in executive functioning, processing speed and attention. These cognitive domains are also affected by hypertension.

Exploration of the effect of hypertension on the SLF, IFOF, volume of WMHs and the degree that these impact frontally-mediated cognitive function both at baseline and longitudinally, represents an important area of research on the relationship between hypertension, the brain and cognition in older adults. As previously mentioned, the SLF and IFOF connect regions of the brain impacted by aging (anterior regions) and hypertension (globally). It is necessary to identify differences in the patterns between normotensive and hypertensive older adults in order to determine the impact of interactions between hypertension and aging on white matter integrity beyond those of aging alone. Additionally, the recent research examining the relationships between blood pressure, white matter tract microstructure and cognition has almost exclusively been cross-sectional, and has not yet fully identified the contribution of elevated blood pressure and altered white matter tract microstructure in older adults to performance on tests of executive functioning, processing speed, and attention. Currently, no known studies have included both white matter tract and WMHs outcomes in a longitudinally study. Determining the impact of blood pressure, tract microstructure, and WMHs volume on cognitive performance will help fully establish the relationship between hypertension and cognitive aging, and whether increased blood pressure in older adults accelerates cognitive decline associated with normal aging.

Summary

Hypertension represents one of the major modifiable health concerns in the U.S., with over one-third of adults classified as hypertensive, and another one-third meeting the classification for pre-hypertensive. Individuals with hypertension are at higher risk for other conditions, including cerebrovascular disease, cardiovascular disease and vascular

dementia. Older adults are at the highest risk for hypertension. Although results have been mixed, a majority of the literature suggests that hypertension is associated with increased cognitive decline in older adults, particularly in frontally-mediated cognition such as executive functioning, processing speed, and attention. WMHs and altered white matter microstructure are two consequences of hypertension that are thought to mediate the relationship between hypertension and cognitive aging. While studies have identified associations between hypertension, WMHs and cognition, the relationships between hypertension, white matter microstructure and cognition remains less clear.

The goals of this study are to examine the impact of hypertension on two major white matter tracts that connect posterior regions of the brain with the frontal lobe (SLF and IFOF, occipital-to-frontal) and WMHs, to identify whether baseline blood pressure, baseline white matter tract integrity and baseline WMH volume contribute to frontally-mediated cognitive performance at a baseline visit, and to examine the longitudinal changes in selected white matter integrity, and cognition in individuals who were hypertensive at baseline compared to baseline normotensives. The following hypotheses will be tested:

1) Older adults with hypertension at baseline will have altered baseline white matter tract microstructure and increased WMH volume.

2) Higher systolic, diastolic and pulse (systolic – diastolic pressures) blood pressures, and reduced white matter integrity will significantly relate to lower cognitive performance.

3) Older adults with hypertension at baseline will have significantly greater reductions in white matter integrity and decreases in cognitive performance between

baseline and 36 month follow-up compared to older adults who are normotensive at baseline.

4) At baseline, older adults with pre-hypertension will demonstrate significantly reduced white matter integrity compared to normotensives, and hypertensives will demonstrate significantly reduced white matter integrity compared to pre-hypertensives. Additionally, those in the highest quartile of pulse pressure, systolic and diastolic blood pressures will demonstrate significantly reduced white matter integrity and lower cognitive performance compared to those in lower quartiles.

Design Considerations

Several important methodological and approach considerations related to the proposed study have been considered. Below, four potential concerns and the rationale for each corresponding methodological decision are discussed.

The first methodological consideration is the grouping of the participants. Previous research has utilized both a categorical grouping of normotensives versus hypertensives (Dufouil et al., 2001; Hannesdottir et al., 2009; Harrington et al. 2000; Raz et al., 2003) and blood pressure (total, systolic or diastolic) along a continuum (Knecht et al., 2008; Kuo et al., 2004; MacLullich et al., 2009; Rosano et al., 2014) to examine the relationships between blood pressure, white matter microstructure, and cognition. In this study, the first aim is to examine the difference between normotensive and hypertensive individuals in white matter tract microstructure and WMHs volume to indicate whether a clinical definition of high blood pressure is associated with structural integrity of the brain. The decision was made that a categorical grouping of individuals into normotensive and hypertensive groups would best answer this specific question.

However, to examine the more complex question of how blood pressure, white matter tract microstructure, WMHs and cognition are related, the decision was made to use systolic and diastolic variables as continuous variables. This decision was based both on the type of analysis proposed (hierarchical linear regression) and previous literature supporting differential effects of systolic and diastolic blood pressure on cognition even in individuals with high-normal blood pressure (Knecht et al., 2008). Due to the literature support for possible differential effects, correlations examining the individual relationships between systolic blood pressure, diastolic blood pressure, pulse pressure (calculated as systolic – diastolic blood pressure) and dependent variables with significant group differences in hypothesis 1 will also be included.

In addition to grouping individuals as normotensive or hypertensive, the possibility of classifying individuals as "pre-hypertensive" (systolic = 120 – 139 mm Hg *or* diastolic = 80 – 89 mm Hg) was considered. Prior research has described differences in brain integrity between normotensives and pre-hypertensives (Maillard et al., 2012), suggesting that within the traditional normotensive group, individuals with high-normal blood pressure may have altered white matter microstructure and poorer cognition than those with lower blood pressure. Although the categorization of hypertensive individuals appears to be clinically important, the available sample size is not sufficient to identify significant differences between three groups. Consequently, the decision was made to include the examination of group differences in white matter integrity between normotensives, pre-hypertensives and hypertensives as a secondary analysis. Similarly, the sample size was not sufficient to include hypotensive (<90mm Hg systolic or <60mm) Hg diastolic individuals. Only one individual demonstrated a recorded blood

pressure categorized as hypotensive, and this person was excluded from the current analyses.

A second consideration is the inclusion of individuals on antihypertensive medications. Although there are conflicting results on the effects of antihypertensive medications, a majority of prior research supports the inclusion of individuals on antihypertensive medications in studies examining relationships among blood pressure, WMHs, white matter microstructure and cognition. The method of defining individuals on antihypertensive medications as hypertensive, regardless of average blood pressure at time of testing, has been previously supported in the literature (Dufouil et al., 2001; Tzourio et al., 1999). Therefore, the decision was made to include individuals on antihypertensive medications in the hypertensive group regardless of measured blood pressure results on the day of neuropsychological assessment. This approach is consistent with previous studies (Raz et al., 2003; Salat et al., 2012; Shmidt et al., 1991).

A final consideration of the proposed study is the selection of white matter tracts. As previously stated, the frontal lobe, and the prefrontal cortex in particular, appear to be most vulnerable to the effects of hypertension and aging (Gunning-Dixon et al., 2009; Raz et al., 2003). Additionally, posterior regions of the brain have also been found to be particularly vulnerable to vascular risk factors, including hypertension (Kennedy & Raz, 2009). The SLF and IFOF are two major white matter tracts that connect frontal regions of the brain with posterior regions, suggesting that the integrity of these tracts may be compromised in older adults with hypertension. Additionally, both tracts have been previously associated with aspects of executive functioning, processing speed, and attention (Frye et al., 2010; Perry et al., 2009; Santiago et al., 2014; Sasson et al., 2013;

Turken et al., 2008). The decision to not include other major white matter tracts in the proposed study was based both on selecting tracts that connect frontal lobe to posterior regions of the brain, and tracts that have not frequently been a focus of study in this population in relation to the proposed dependent variables. A methodological advantage of this focus includes the reduced number of dependent variables and potential for type 1 error.

Methods

Participants

Data for the proposed study were extracted from an existing database containing healthy older adults (NIH R01-NS052470). A total of 60 participants between the ages of 51 and 81 years were identified as having both imaging and neuropsychological data that meet the proposed criteria for inclusion. All participants provided informed consent as part of the parent study procedure.

Inclusion/Exclusion Criteria

Inclusion criteria included fluent English-speaking adults over the age of 50, with ≥12 years of education. Exclusion criteria included neurological conditions (e.g., current diagnosis of dementia, stroke, or Parkinson's disease; score of <24 on the Mini-Mental State Exam), diabetes requiring medication (i.e., not diet-controlled), head injury with loss of consciousness > 30 min, past or current substance abuse, a major psychiatric condition (e.g., schizophrenia, untreated anxiety or depression, bipolar disorder) or other medical conditions that could affect cognition including thyroid disease, HIV, epilepsy, multiple sclerosis, or cancer.

Blood Pressure Measurement

All blood pressure measurements were taken using a digital blood pressure monitor with an oscillometric measurement system (Samsung Healthy Living Model BA-508AC). Systolic and diastolic blood pressures were measured at three set time-points during the baseline neuropsychological testing session. Measurements from all three time-points were averaged for a final mean systolic over diastolic value. Pulse pressure was calculated as the difference in average systolic and diastolic blood pressures. All blood pressure measurements were taken while participants were seated.

Neuropsychological Tests

Neuropsychological tests were chosen from the domains of executive function, processing speed and attention. These domains represent the key cognitive domains examined in previous studies focused on hypertension (Kilander et al., 1998; Kuo et al., 2004; Raz et al., 2003; Swan et al., 1998; Wharton et al., 2014). All neuropsychological tests were completed at baseline and 36 month follow-up as part of a larger neuropsychological test battery following demographic and health questionnaires. Cognition will be assessed using Trails A and B from the Trail Making Test (TMT; Army Individual Test Battery, 1944), Letter Number Sequencing (LNS) from the Wechsler Adult Intelligence Scale – III (WAIS-III; Wechsler, 1997), and Trials 1, 3 and 4 of the Color-Word Interference Test (CWIT) from the Delis – Kaplan Executive Function System (D-KEFS; Delis, 2001), Digit Span from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, Tierney, Mohr, & Chase, 1998), and Coding from the RBANS. These tests are described in greater detail below.

The Trails A test of the TMT requires participants to draw lines connecting the numbers 1 through 25 in numerical order as quickly as possible. The Trails B test of the

TMT requires participants to draw lines connecting alternating letters and numbers, in numerical and alphabetical order (e.g. 1-A-2-B-3-C...). Time to completion was used as the outcome measure for both tests. The Trails A test is considered a test of processing speed, while Trails B represents executive functioning.

During the LNS test, participants are read a string of numbers and letters by the examiner. Participants are instructed to repeat the string of numbers and letters back to the examiner, beginning with numbers in order from lowest to highest and ending with the letters in alphabetical order. For example, if the participant was read the sequence "9-C-3", the participant should respond with "3-9-C." After each correct answer, the string of letters and numbers increases in length. The number of correct answers was used as the outcome measure for the LNS test, which represents a test of working memory (executive function).

Trial 1 of the D-KEFS CWIT requires participants to name squares of ink color as quickly as possible. Trial 3 of the D-KEFS CWIT is a measure of response inhibition. In this task, the names of colors (green, red, and blue) are printed in ink of a different color than the color the word represents (i.e. the word "green" is printed in red ink). The participant is asked to name the color of ink the words are printed in, rather than reading the word itself. In Trial 4, the set-up is similar with the exception that a number of color words are printed within a box. Participants are instructed to name the color of ink the word is printed in if the word is not in a box, or read the printed word if it is within a box. This task requires both response inhibition and task switching. Time to completion was used as the outcome measure for both Trials 3 and 4 of the CWIT. Trial 1 is considered a test of processing speed, while Trials 3 and 4 represent executive functioning.

Digit Span requires the participant to repeat a list of numbers from 2 to 9 digits in the exact order as they were read aloud by the examiner. After each correct answer, the length of the string is increased. Total number of strings correctly recalled was used as the outcome variable. The Digit Span test represents attention. The Coding task presents participants with rows of boxes, where the top half contains a shape and the bottom half is empty, and a coding key, where numbers correspond to specific shapes. Participants are asked to fill in the rows of empty boxes with numbers that correspond to the shapes in the top halves of the boxes as quickly as possible based on the coding key. Number of correctly filled in numbers within 90 seconds represents the outcome measure for this task. This test is considered a test of attention, processing speed and executive function.

Diffusion Tensor Imaging.

All neuroimaging and processing of neuroimaging data were previously completed as part of the parent longitudinal study. MRI scans were obtained using a head-only Magnetom Allegra 3T MRI scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany) at Washington University in Saint Louis. Head movement was restrained using foam pads and RF coil. Whole brain structural MRI data were obtained utilizing T1-weighted magnetization-prepared rapid-acquisition gradient echo (MP-RAGE) sequence (176 slices on the sagittal plane, TR=2,100 ms, TE = 3.93 ms, TI = 1,000 ms [non-selective inversion], flip angle = 7°, voxel size = 1.05 x 1.05 x 1.05 mm^3), T2-weighted turbo spin echo (TSE), and T2-weighted fluid-attenuated inversion recovery (FLAIR; 43 slices in the transverse plane, TR = 8,040 ms, TE_1 = 18 ms, TE_2 = 105 ms, voxel size = 1.0 x 1.0 x 3.0 mm^3). An initial pilot sample from the same parent study was used to establish slice coverage and field of view parameters.

Each individual's DWIs were initially preprocessed using Function MRI of the Brain (FMRIB) software library (FSL) 5.0 (Jenkinson et al., 2012). To correct for subject motion, all volumes were registered to the first I0 image using FMRIB's linear image registration tool (FLIRT) with the mutual information metric (Jenkinson et al., 2002). The b-vectors were rotated to account for the rotation induced by the registration (Leemans & Jones, 2009). Brain tissue was extracted automatically using the FSL Brain Extraction Tool (Smith 2002). Diffusion tensors were fit to the DWIs using linear least squares, and eigen-decomposition was used to compute scalar diffusion metrics, which included fractional anisotropy (FA) and mean diffusivity (MD). Deterministic streamline tractography (Zhang, Demiralp & Laidlaw, 2003) was performed to reconstruct canonical fiber bundles using an atlas-based multiple region-of-interest approach (Wakana et al., 2004). DTI toolkit (DTI-TK) was used for tensor-based deformable image registration with explicit orientation optimization (Zhang et al., 2006) and diffusion tensor atlas construction (Zhang et al., 2007). Whole brain diffusion MR tractography was performed in the atlas, and the bundles-of-interest were manually selected based on anatomical references (Mori, Oishi & Faria, 2009). For each bundle, three volumetric bundle masks were manually drawn in atlas-space, with one at each end of the bundles, and one "whole bundle" mask covering the entire extent. The volumetric masks were resampled to each subject's native space using the deformable registrations and nearest neighbor interpolation. Diffusion MR tractography was then performed for each subject, and fibers were included in the bundle if at least 80% of their arc-length was inside the whole bundle mask and only if they passed through both bundle endpoint masks. Quantitative metrics were computed from the resulting fiber bundles and retained for

statistical analysis; these included mean FA and mean MD (Correia et al., 2008). Tractography was performed using a custom toolkit for smooth streamline integration of the principal tensor eigenvector field with tricubic interpolation of the diffusion-weighted signal. The following tractography parameters were used: 4 randomly placed seeds per voxel, a maximum turning angle of 35°, a step size of 1mm, a minimum FA threshold of 0.15, and a minimum-length threshold of 10 mm.

Quantification of WMHs.

To derive WMH volumes, fluid attenuated inverse recovery (FLAIR) images were skull-stripped and divided into left and right hemispheres along the sagittal plane. Gaussian curves were fitted to each hemisphere's voxel intensity values, and the mean and standard deviation (SD) intensity values were derived for each cerebral hemisphere. Voxels falling at or above 2.5 SD above the mean were labeled as white matter hyperintensity seeds. Seeds from the left and right hemispheres were combined and passed into a mean intensity based region-growing algorithm. This algorithm uses the seed voxel intensity as the starting mean, and searches for and labels voxels falling within 5% of the seed mean by applying a 10-point connectivity scheme (x-y plane, and 1 up in z and 1 down in z-plane). Neighboring voxels falling within 5% of the seed mean are added to the image, and a new mean is created. This process is repeated until all seeds have been included into the WMH image. The total WMH volume was calculated from the summation of the number of voxels labeled as WMH multiplied by voxel dimensions. An anatomical atlas (Admiraal-Behloul et al., 2004) was spatially normalized to each image to derive WMH volumes in the major anatomical lobes, basal ganglia, insula and the cerebellum. All WMH volumes are in cm^3.

Proposed Statistical Analyses

Preliminary Analyses. Participants with an average systolic blood pressure greater than or equal to 140 mm Hg *or* diastolic blood pressure greater than or equal to 90 mm Hg were classified as hypertensive. Participants with an average systolic blood pressure less than 140 mm Hg and less than 90 mm Hg were classified as normotensive. For the secondary analysis, the normotensive group was further divided into pre-hypertensive individuals (systolic pressure = 120 – 139 mm Hg *or* diastolic pressure = 80 – 89 mm Hg) and normotensive individuals (systolic pressure < 120 mm Hg *and* diastolic pressure < 80 mm Hg). Independent samples *t*-tests and chi-square analyses were used to examine possible group differences in demographic factors, including age, sex and education. These variables were also analyzed for any significant associations with diastolic and systolic blood pressure, pulse pressure, white matter tracts, WMH volume and cognitive test scores using Pearson's correlation coefficients. Any variables demonstrating significant group differences ($p < .05$) and associations with the dependent variables ($r > .8$) were included as covariates in subsequent analyses. Distributions of all neuropsychological, imaging, and blood pressure variables were examined for normality and transformed if necessary.

Hypothesis 1: To examine group differences in white matter tract microstructure and WMHs between normotensive and hypertensive groups, independent *t*-tests (or ANCOVAs, if covariates are included) were conducted. The first set of *t*-tests included group (normotensive and hypertensive) as the independent variable and FA of the SLF or IFOF as the dependent variables. The second set of *t*-tests included group (normotensive and hypertensive) as the independent variable and MD of the SLF or IFOF

as the dependent variable. Finally, the last *t*-test included group (normotensive and hypertensive) as the independent variable and total WMHs volume as the dependent variable. For any significant group differences, partial correlations were conducted examining the individual relationships between systolic and diastolic blood pressures with the dependent variable, controlling for any covariates. It was predicted that individuals in the hypertensive group would have significantly reduced FA, increased MD, and increased WMHs volume compared to individuals in the normotensive group. It was also predicted that higher systolic, diastolic and pulse pressures would be significantly correlated with reduced FA, higher MD, and larger volume of WMHs.

Hypothesis 2: To examine the relationships between baseline systolic and diastolic blood pressure, pulse pressure, white matter tract microstructure, volume of WMHs, and baseline performance on tests of executive function, processing speed, and attention, a series of hierarchical linear regressions were conducted. For each regression, any covariates were entered as the first step and the specific independent variable(s) entered as the second step of the model. For the first set of regression models, systolic, diastolic, or pulse pressure were added as the independent variables in the second step. Raw cognitive scores were included as the dependent variables. The second set of regression models included volume of WMHs, FA or MD of the SLF and IFOF as independent variables, and raw cognitive scores as the dependent variables. If the regression analyses including volume of WMHs as the independent variable and tract FA or MD as the independent variables were both significant, a final hierarchical regression was conducted with WMH volume as the first step (or second, if any covariates are identified) and tract FA or MD as the second (or third) step. It was predicted that higher

systolic and diastolic blood pressure, and higher pulse pressure were significantly related to lower performance on tests of executive functioning, processing speed, and attention. It was also predicted that lower FA, higher MD and higher volume of WMHs were significantly associated with lower cognitive performance, with lower FA and higher MD retaining a significant relationship with decreased cognitive performance when total volume of WMHs was included in the model.

Hypothesis 3: To examine the differences between normotensives and hypertensives in changes in white matter tract FA and MD, WMH volume, and cognition between baseline testing and 36 month follow-up, a series of general linear model - repeated measures analyses was conducted. The baseline blood pressure group (normotensive, hypertensive) was included as the between-subjects factor. Tract FA and MD, WMH volume, and raw cognitive scores from both baseline testing and 36-month follow-up were included as the within-subjects factors. Any variables defined as covariates in the preliminary analysis were included as covariates. It was predicted that, at 36-month follow-up, results would indicate reduced tract FA and increased tract MD, increased WMH volume, and decreased performance on tests of executive functioning, processing speed, and attention compared to baseline testing. It was also predicted that there would be a significant interaction between group and time, with the hypertensive group exhibiting greater reductions in tract FA, increases in MD, increases in WMH volume and reductions in cognitive performance over time compared to the normotensive group.

Secondary Analyses/Hypothesis 4: Two hypotheses were tested in secondary analyses due to small group sizes: 1) Group differences between normotensive, pre-

hypertensive and hypertensive individuals, and 2) differences between individuals in the highest and lowest quartiles of pulse, systolic and diastolic blood pressure. To examine differences in white matter tract microstructure, volume of WMHs, and cognition between normotensive, pre-hypertensive, and hypertensive individuals, four MANOVAs (or MANCOVAs, if covariates are included) were conducted. The first two MANOVAs included group (normotensive, pre-hypertensive, and hypertensive) as the independent variable, and FA (first MANOVA) or MD (second MANCOVA) of the SLF and IFOF as the dependent variables. The third MANOVA included group (normotensive, pre-hypertensive, and hypertensive) as the independent variable and volume of WMHs as the dependent variable. A final MANOVA included group (normotensive, pre-hypertensive, and hypertensive) as the independent variable, and raw cognitive scores from baseline testing as the dependent variables. A Tukey's post-hoc analysis was conducted to analyze which groups were significantly different. It was predicted that the hypertensive group would demonstrate reduced FA, higher MD, larger volume of WMHs, and decreased performance on tests of executive functioning, processing speed, and attention compared to both the normotensive and pre-hypertensive groups. Additionally, it is predicted that the pre-hypertensive individuals would demonstrate reduced FA of the SLF and IFOF, increased MD of the SLF and IFOF, increased WMHs, and decreased cognitive performance when compared to normotensive individuals.

To examine differences in white matter microstructure, volume of WMHs, and cognitive performance between those in the highest quartile of blood pressure compared to those in the lowest quartile, a series of MANOVAs (or MANCOVAS, if covariates are included) were performed. First, three SPSS frequency analysis were conducted to divide

participants into quartiles based on pulse pressure, systolic pressure and diastolic pressure. MANOVAs then compared participants in the 4th (highest) quartile to those in the 1st (lowest) quartile, with FA of the SLF and IFOF as the dependent variables of the first analyses, MD of the SLF and IFOF the dependent variables of the second analyses, volume of WMHs the dependent variable of the third analyses, and raw cognitive scores as the dependent variables of the fourth analyses. It was predicted that individuals in the highest quartile of pulse pressure, systolic blood pressure and diastolic blood pressure would demonstrate significantly reduced white matter integrity and cognitive performance compared to those in the lowest quartile.

Results

Preliminary and Demographic Analyses

The final sample was comprised of 60 participants (18 males (30%), 42 females (70%)) with blood pressure, DTI, WMH and cognitive data. The majority of participants in this sample were Caucasian (77%), followed by African-American (16%), Hispanic (5%) and Asian (2%). The average age of participants was 62.7 years (SD = 8.0; range = 51-78) and the average education level was 15.7 years (SD = 2.4). Comparisons by blood pressure group indicated that normotensive individuals (n = 36) did not significantly differ from hypertensive individuals (n = 24) on age (t (58) = 2.0, p = .06), years of education (t (58) = -.38, p = .71), BMI (t (58) = 1.4, p = .17), gender (χ^2 (1, n = 60) = 1.07, p = .30), or ethnicity (χ^2 (3, n = 60) = 1.6, p = .67). When participants were divided into three blood pressure classifications (hypertensive (n = 24), pre-hypertensive (n = 25), and normotensive (n = 11)), all comparisons remained non-significant with the exception of BMI, where normotensive individuals demonstrated significantly lower BMI

compared to both pre-hypertensive and hypertensive individuals ($F(2,57) = 3.36$, $p = .04$). Sample characteristics are listed in Table 1.

Data were screened for normality using Q-Q plots. Results of these analyses concluded that most data did not violate assumptions of normality. However, neither baseline nor 36M total WMH data demonstrated a normal distribution and therefore these data were log-transformed. Outliers in dependent variables were identified using standardized z-scores, with a cutoff of $z \geq +/- 3$, and removed from analyses in a pairwise fashion.

Hypothesis 1

Preliminary analyses did not reveal any significant differences in demographic and health variables between groups. Accordingly, no covariates were utilized in the group analyses. Independent *t*-tests demonstrated that normotensive and hypertensive individuals differed significantly on FA ($t(58) = -2.03$, $p = .047$, Cohen's $d = 0.54$) and MD ($t(58) = 2.23$, $p = .03$, $d = 0.61$) in the IFOF. Neither FA ($t(58) = -1.10$, $p = .27$, $d = 0.29$) nor MD in the SLF ($t(58) = 1.61$, $p = .11$, $d = 0.42$) demonstrated a significant difference by group. However, no results remained significant after FDR correction. Additionally, no significant group differences were identified in total volume of WMHs at baseline ($t(57) = .72$, $p = .46$, $d = .19$).

Correlational analyses to determine the relationship of the dependent variables to systolic pressure, diastolic pressure and pulse pressure at baseline were also conducted. Analyses revealed a significant relationship between systolic blood pressure and FA of the SLF ($r = -.28$, $p = .03$). However, this result did not remain significant after FDR correction. Results from the independent *t*-tests and correlations are displayed in Table 2.

Hypothesis 2

Preliminary analyses indicated that even after FDR correction, age was significantly associated with MD of the SLF and IFOF, FA of the IFOF, DKEFS Trial 1, and coding. As such, if any regression analysis including these as dependent variables demonstrated significance, a secondary hierarchical regression with age as a first step was conducted to examine the individual impact of the independent variable after the effects of age. No other demographic or health variables were significantly associated with any dependent variables.

Regressions examining the relationship between cognitive performance and systolic, diastolic and pulse pressures identified no significant relationships (p's > .05). Baseline performance on DKEFS trial 1 demonstrated significant relationships with pulse pressure ($F(1,58) = 6.82$, $p = .01$, $\beta = 0.33$, $R^2 = 0.11$, Cohen's $f^2 = 0.12$) and systolic blood pressure ($F(1,58) = 4.12$, $p = .045$, $\beta = .26$, $R^2 = .07$, $f^2 = 0.08$). Additionally, DKEFS trial 4 also demonstrated initial significant positive associations with both pulse pressure ($F(1,58) = 9.02$, $p = .004$, $\beta = .38$, $R^2 = .14$, $f^2 = 0.16$) and systolic blood pressure ($F(1,58) = 8.94$, $p = .004$, $\beta = .37$, $R^2 = .14$, $f^2 = 0.16$). However, no relationships remained after FDR correction. Regression results are presented in Table 3.

Regressions examining the relationship between cognitive performance and tract FA, tract MD, and total volume of WMHs initially identified several significant relationships. Higher total volume of WMHs was significantly associated with slower performance on Trails B ($F(1,55) = 5.42$, $p = .02$, $\beta = .30$, $R^2 = .09$, $f^2 = 0.10$).

Lower FA of the SLF was significantly related to slower performance on Trails A ($F(1,58) = 6.53$, $p = .01$, $\beta = -.33$, $R^2 = .11$, $f^2 = 0.12$) and worse performance on the RBANS coding test ($F(1,58) = 6.56$, $p = .01$, $\beta = .32$, $R^2 = .11$, $f^2 = 0.11$). Lower FA of

the IFOF significantly related to slower performance on Trails A ($F(1,58) = 4.39$, $p = .04$, $\beta = -.27$, $R^2 = .07$, $f^2 = 0.08$) and Trails B ($F(1,58) = 5.29$, $p = .03$, $\beta = -.30$, $R^2 = .09$, $f^2 = 0.10$), worse performance on LNS ($F(1,58) = 5.58$, $p = .02$, $\beta = .30$, $R^2 = .09$, $f^2 = 0.09$), and worse performance on the RBANS coding test ($F(1,58) = 5.59$, $p = .02$, $\beta = .30$, $R^2 = .09$, $f^2 = 0.10$).

Higher MD of the SLF demonstrated a significant relationship with slower performance on Trails A ($F(1,58) = 8.77$, $p = .004$, $\beta = .37$, $R^2 = .13$, $f^2 = 0.15$) and Trails B ($F(1,58) = 5.13$, $p = .03$, $\beta = .29$, $R^2 = .08$, $f^2 = 0.09$), and worse performance on the RBANS coding test ($F(1,58) = 13.57$, $p = .001$, $\beta = -.44$, $R^2 = .19$, $f^2 = 0.24$). Higher MD of the IFOF also significantly related to worse performance on the RBANS coding ($F(1,58) = 9.55$, $p = .003$, $\beta = -.38$, $R^2 = .14$, $f^2 = 0.17$). All regression results are reported in Table 4.

Of these results, only the relationship between MD of the SLF and RBANS coding remained significant after FDR correction. A hierarchical regression analysis demonstrated that this significant relationship also remained after correcting for age ($F(2, 57) = 13.08$, $p < .001$, $\beta = -.28$, $R^2 = .32$, R^2 change attributed to SLF MD = .064; see Table 5).

As no significant WMH and tract results remained after FDR correction, the hierarchical regression analyses intended to investigate the contribution of tract data in predicting cognitive performance beyond total volume of WMHs were not completed.

Hypothesis 3

A series of repeated measures general linear models were conducted to analyze changes in tract FA and MD, total volume of WMHs, and cognitive performance between

normotensive and hypertensive individuals over a three year period. No significant group differences in demographic or health variables were identified in the preliminary analysis.

Results revealed that across all participants, IFOF MD significantly increased over time ($F(1,52) = 12.27$, $p = .001$). However, the group x time interaction was not significant ($F(1,52) = .66$, $p = .42$). Additionally, total volume of WMHs significantly increased over time ($F(1,53) = 17.02$, $p < .001$) but did not demonstrate a group x time interaction ($F(1,53) = 1.2$, $p = .28$). Time to complete Trails A significantly increased over time ($F(1,53) = 4.28$, $p = .04$) with no group x time interaction ($F(1,53) = .03$, $p = .96$). Time to complete the DKEFS Trial 4 significantly declined across time for all participants ($F(1,53) = 8.55$, $p = .005$) with no group x time interaction ($F(1,53) = .54$, $p = .43$).

All significant results except change in Trails A over time remained significant after FDR correction. No other dependent variables demonstrated significant changes between baseline and follow-up testing or group x time interactions. Results for all participants over time and for the group x time interactions are reported in Table 6.

Secondary Analyses/Hypothesis 4

The secondary analysis first examined group differences similar to Aim 1, with participants divided into three groups (hypertensive, pre-hypertensive, and normotensive). As preliminary analyses identified significant group differences in BMI, this variable was added as a covariate to the series of MANCOVAs performed to examine group differences in tract FA and MD, total volume of WMHs, and cognitive performance.

The first MANCOVA investigating group differences in FA of the SLF and IFOF was non-significant (Wilks' Lambda = .92; F (4, 108) = 1.15, p = .34, ηp^2 = .04). Additionally, the second MANCOVA examining group differences in MD of the SLF and IFOF was also non-significant (Wilks' Lambda = .93; F(4, 108) = 1.01, p = .41, ηp^2 = .04). Total volume of WMHs also did not significantly differ between the three groups (F(2, 57) = .81, p = .45, ηp^2 = .03). The MANCOVA investigating group differences in cognitive performance demonstrated a trend-level effect (Wilks' Lambda = .58; F (16, 88) = 1.70, p = .06, ηp^2 = .24). Univariate analyses revealed significant group differences on DKEFS Trial 4 (F(2,51) = 3.31, p = .045, ηp^2 = .12) and RBANS coding (F(2,51) = 5.33, p = .008, ηp^2 = .18). On DKEFS Trial 4, hypertensive individuals performed significantly worse than both pre-hypertensive and normotensive individuals but there were no differences between pre-hypertensive and normotensive individuals. Pre-hypertensive individuals also performed significantly better on RBANS coding than both normotensive and hypertensive individuals. However, no significant differences remained after correcting for multiple comparisons.

Additionally, participants were divided into groups based on quartile of pulse pressure (upper bound for 1st quartile = 41.8; lower bound for 4th quartile = 58.25), systolic blood pressure (upper bound for 1st quartile = 119.3; lower bound for 4th quartile = 138.1), and diastolic blood pressure (upper bound for 1st quartile = 73.2; lower bound for 4th quartile = 85.0). MANOVAs did not identify any significant differences between groups on cognitive performance or any white matter integrity variables (p's > .05). The ranges of blood pressure measurements assigned to each quartile and p-values of the MANOVAs are listed in Table 7.

Discussion

The primary goal of this research was to determine if healthy older adults with high blood pressure demonstrate reduced white matter integrity and poorer cognitive performance compared to those with normal blood pressure levels, both at a baseline visit and at a three year follow-up. The results of the present study indicate that individuals classified as hypertensive do not have reduced white matter integrity, both at the tract-specific level and with total volume of WMHs. Additionally, higher systolic, diastolic and pulse pressures were not significantly related to white matter integrity or cognitive performance. There was some evidence to suggest that integrity of the SLF and IFOF were significantly associated with diminished cognitive performance in this sample. Longitudinally, results revealed significant changes in white matter integrity and cognitive performance, but no significant blood pressure group x time interactions were observed. Secondary analyses results suggested worse cognitive performance in hypertensive individuals than pre-hypertensive and normotensive individuals on some tests of attention, processing speed and executive functioning, although these did not remain significant after FDR correction. Additional secondary analyses suggested no significant differences in cognitive performance or white matter integrity between individuals in the highest and lowest quartiles of pulse pressure and systolic blood pressure.

White Matter Integrity

Results from the present study did not support the prediction of a significant reduction in white matter integrity among individuals with higher blood pressures at baseline testing. There was no significant difference identified between the normotensive

and hypertensive groups in total volume of WMHs. These results are not consistent with those previously identified in the literature that demonstrate significantly increased WMHs in hypertensive individuals compared to those without hypertension (Raz et al., 2003). Additional analyses were conducted to examine the individual association of systolic blood pressure, diastolic blood pressure, and pulse pressure to the total volume of WMHs. Previous research has identified increased systolic blood pressure as a particular risk factor for increased volume of WMHs (Raz et al., 2007), along with higher pulse pressure. However, results from the present study did not reveal any significant associations between systolic, diastolic or pulse pressures and total volume of WMHs. Secondary analyses also did not reveal significant relationships between those in the highest and lowest quartiles of pulse pressure, systolic blood pressure or diastolic blood pressure and volume of WMHs.

One possible reason for the disparity in the results is the overall low level of WMH burden in the sample. The majority (78%) of participants demonstrated a volume of WMHs <1 cm^3 providing little variation in volume of WMHs and few participants with significant burden. Other studies identifying a significant relationship between blood pressure variables and WMHs demonstrated higher total volumes of WMHs, with averages of 2.6 cm^2 - 6.4 cm^3 across participants (Raz et al., 2003, Raz et al., 2007, Schmidt et al., 1993). It is possible that this association is not evident until WMHs become more severe. Additionally, several studies have identified blood pressure variability or 24 hour ambulatory blood pressure as stronger predictors of WMH burden, rather than average systolic and diastolic blood pressures (Gunstad et al., 2005, Mancia et

al., 2007; Sierra 2011), suggesting that significant associations may have been identified using other measures of blood pressure.

In addition to the global measurement of volume of WMHs, the first aim examined group differences in white matter integrity at a network-specific level. Similar to the development of WMHs, white matter tracts may be impacted by the stiffening and tortuosity of deep-penetrating arterioles leading to reduced blood supply to these white matter tracts and damage to white matter fibers. Specifically, differences in FA and MD of the SLF and IFOF, two tracts that connect the frontal lobe with posterior regions of the brain, were analyzed between normotensive and hypertensive individuals. As white matter damage related to hypertension has been suggested to demonstrate a more widespread pattern throughout the brain, including posterior regions often spared in normal aging (Raz et al., 2003), reduced integrity of these tracts may further reveal the spread of hypertension-related white matter damage beyond the effects of age.

Results of these analyses do not provide support for the first aim. No significant group differences were identified in FA or MD of either tract at the baseline testing. Additionally, the individual relationships of systolic, diastolic and pulse pressures were examined in relation to tract integrity variables. No significant associations were identified to suggest that higher systolic, diastolic or pulse pressure is related to reduced integrity of the SLF or IFOF. Secondary analyses also did not suggest that those in the highest quartile group of pulse, systolic or diastolic pressures significantly differed on white matter tract integrity from individuals in the lowest quartile. Previous studies examining this relationship in tracts other than the corpus callosum are few in number. However, results of the current study are inconsistent with what would be expected based

on results of these previous studies. Higher systolic blood pressure or increased mean arterial blood pressure has been significantly associated with reduced FA and increased MD of white matter tracts throughout the brain (Aine et al., 2014; Maillard et al., 2012; Rosano et al., 2014; Salat et al., 2012), indicating reduced microstructural integrity of these tracts. No previous studies examining this relationship in tracts other than the corpus callosum have included the classification of participants into hypertensive and normotensive groups to investigate the clinical relevance of these groupings in relation to white matter tract integrity. As participants included in the present study were otherwise medically and cognitively healthy, it is possible that the severity or duration of hypertension in the current sample was not sufficient to produce significant and detectable white matter damage. Even within the hypertensive group, average systolic (M = 140.0, SD = 17.5), diastolic (M = 85.2, SD = 6.8) and pulse pressures (M = 53.9, SD = 13.5) were relatively low. Future studies are needed to examine this relationship at the network-based level in older adults with more severe levels of hypertension, with well-documented histories of duration of high blood pressure.

Secondary analyses divided participants into three blood pressure classifications to determine the significance of a pre-hypertension classification on white matter integrity. MANCOVAs controlling for the effect of BMI, which demonstrated a significant difference across group, identified no significant group differences in total volume of WMHs or FA and MD of the SLF and IFOF. These results suggest that the classification of "pre-hypertensive" does not indicate higher risk for reduced white matter integrity compared to normotensive individuals in this sample. It should be noted that group sizes in the present study were small. A larger sample with more equivalent group

sizes is needed to fully examine these relationships between group classification and white matter integrity. Overall, these results suggest that blood pressure variables including classification as hypertensive, systolic blood pressure, diastolic blood pressure and pulse pressure, are not significantly associated with white matter integrity in the current sample.

Cognitive Performance

Results of the present study partially support the second aim of the study predicting poorer cognitive performance on tests of attention, processing speed and executive functioning associated with increasing systolic, diastolic and pulse pressures, and reduced white matter integrity. Preliminary analyses identified significant relationships between age and white matter integrity variables, suggesting that increased age was related to reduced integrity of both white matter tracts. Additionally increased age was significantly related to poorer performance on two tests of attention and executive functioning. Analyses examining the relationship between blood pressure variables and cognitive performance revealed four significant relationships. Lower performance on the DKEFS Trial 1 and Trial 4, represented by longer time to completion, were associated with higher systolic blood pressure and higher pulse pressure. However, these results did not remain significant after the FDR correction and may represent spurious findings. Secondary analyses that examined cognitive performance by quartile of pulse pressure, systolic pressure and diastolic pressure did not reveal any significant relationships between the highest and lowest quartiles on cognitive performance.

Analyses examining the differences in cognitive performance between hypertensive, pre-hypertensive and normotensive individuals were conducted to identify

the significance of the classification of "pre-hypertension" in relation to diminished cognitive functioning. Although the MANCOVA identified a trend-level relationship between group classification and cognition, this result was not significant and any significant univariate results did not survive FDR correction. These results suggest that pre-hypertension is not related to significantly worse cognitive performance compared to hypertensive individuals in this sample.

There are several possible contributing factors to the non-significant relationship between blood pressure and cognition identified in the current study. As previously stated, hypertension in these participants may not be sufficiently severe to affect cognition beyond age itself. Specifically, age correlated with most white matter variables and several cognitive tests while systolic, diastolic and pulse pressures did not significantly correlate with any cognitive variables. Literature also suggests that microstructural white matter changes precede cognitive changes (Brickman et al., 2006; Medina et al., 2006). No group differences or significant associations with blood pressure variables were identified in the white matter analyses, suggesting that it is unlikely that cognition would be impacted in the absence of any significant reduction in white matter integrity. Additionally, the current study included participants from a longitudinal study of markers of healthy aging where significant cognitive impairment is not expected. The inclusion or lack of inclusion of select covariates may also play a role. For example, the duration of high blood pressure or duration of antihypertensive medication likely moderate the impact on cognitive dysfunction. Previous work has identified mid-life hypertension, rather than hypertension at time of study, as a significant predictor of decline in cognitive performance and white matter integrity in older adults

(Knecht et al., 2008; Swan et al., 1998). However, this information was unavailable for the current study. It is possible that in a larger sample of hypertensive individuals, with greater variability in systolic blood pressure, pulse pressure and cognitive functioning, the results of the current study would demonstrate consistency with the previous literature.

The second component of the second aim was to examine the relationship between white matter integrity variables and cognitive performance on tests of executive functioning, attention and processing speed. Regression analyses initially identified several significant relationships. Larger total volume of WMHs was significantly related to slower performance on Trails B, a test of executive functioning. Lower FA and higher MD of the SLF and IFOF significantly related to worse performance on Trails A, Trails B, DKEFS trial 1, LNS and RBANS coding. After FDR correction, only the relationship between higher MD of the SLF and poorer performance on the RBANS coding remained significant. This relationship also remained significant after controlling for the effect of age. These results suggest that reduced microstructural integrity of the SLF is associated with worse performance on a test of executive functioning and processing speed beyond the negative effect of older age.

Previous studies have identified significant relationships between reduced white matter integrity and poorer cognitive performance (Breteler et al., 1994; Brickman et al., 2009*b*; deCarli et al., 1995; Gunning-Dixon & Raz, 2000; Raz et al., 2003; Schmidt et al., 1993). Higher systolic blood pressure significantly related to reduced FA of the fornix, sagittal stratum and posterior thalamic radiation in a sample of healthy adults, and these reductions in FA were significantly associated with poorer executive functioning (Aine et

al., 2014). However, several other studies have demonstrated no significant relationship between white matter integrity and cognition. For example, previous studies have identified no significant relationship between WMHs and cognitive performance both cross-sectionally (Söderlund et al., 2003) and longitudinally (Schmidt et al., 1999), or between whole brain FA and cognitive performance (Leritz et al., 2010). The reasons for these contradictory results in the literature is unknown. However, one possible explanation includes the extent of white matter damage not reaching a threshold of clinical significance in a large enough proportion of participants. Previous literature identified significantly worse performance on tests of frontally-mediated cognitive functioning in individuals with total area of WMHs >10cm^2, compared to three other groups with no observable WMHs, area of WMHs <1cm^2, and >1 to ≤10cm^2 (Boone et al., 1992). Additionally, location of WMHs in the brain is an important factor in cognitive performance and may contribute to differences observed between studies.

Longitudinal Changes in White Matter and Cognition

The results of the longitudinal analyses partially support the third aim predicting changes in white matter integrity and cognition over a three-year span, with participants classified as hypertensive at baseline exhibiting a faster decline compared to normotensive individuals. The repeated measures analyses revealed three important results. First, total volume of WMHs and MD of the IFOF significantly increased over time for all participants, indicating reduced white matter integrity three years after baseline testing. Second, participants performed unexpectedly better on DKEFS Trial 4 at follow-up testing compared to baseline, signaling an increase in performance on a test of executive functioning. This result may be due to practice effects, with repeated

administration of tests resulting in better performance. Both significant results remained statistically significant after FDR correction. Third, no group x time interactions were identified, suggesting that classification as hypertension does not relate to white matter integrity or cognitive performance three years later. It is likely that these changes in white matter integrity and cognition are instead the result of normal changes associated with aging (Pfefferbaum, Adalsteinsson, & Sullivan, 2005; Salat et al., 2005; Salthouse, 2009; Ziegler et al., 2010).

Although no studies have examined the SLF, IFOF, WMHs and cognition together over time in relation to hypertension, the results from the present study are partially consistent with what is expected based on prior research. Reduced white matter integrity has been demonstrated longitudinally in healthy older adults (Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Pfefferbaum et al., 2005; Sachdev et al., 2007; Salthouse, 2009). However, the literature suggests that these reductions over time are more robust in individuals with higher blood pressure and hypertension (Dufoil et al., 2001; Köhler et al., 2013; Raz et al., 2007). Additionally, decline in cognitive performance over time has been associated with both aging and high blood pressure (Salthouse 2009; Swan et al., 1998). It is possible that a longer time period is needed to identify significant changes in white matter and cognition due to hypertension. Other studies that have identified significant changes in cognition or white matter integrity due to higher baseline blood pressure have used periods of four years (Dufoil et al., 2001), five years (Raz et al., 2007), ten years (Rosano et al., 2014; Swan et al., 1998) and twenty years (Kilander et al., 1998). One study that did incorporate a three-year follow-up was identified a progression in WMHs over this time period, but no significant relationship

between change in WMHs and change in cognitive performance. These results indicate that a longer time period is necessary to observe this association (Schmidt et al., 1999).

Other Moderating Factors

It is possible that individual differences in inflammatory markers associated with vascular disease masked differences between groups in the present study. The role of inflammation and inflammatory markers in hypertension and cognitive dysfunction has been extensively investigated. Inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) have been repeatedly associated with presence of hypertension, although the exact temporal relationship is unclear. For example, a cross-sectional study examining the relationships between high blood pressure and inflammatory markers demonstrated that high levels of IL-6 and TNF-α were associated with higher prevalence of hypertension (Bautista, Vera, Arenas, & Gamarra, 2005). Other studies have identified significant associations between high levels of CRP and increased rate of hypertension (Bautista, Atwood, O'Malley, & Taylor, 2004; Sung et al., 2003). Another study identified a significant association between elevated levels of systolic and diastolic blood pressures, pulse pressure, and mean arterial pressure with increased levels of IL-6 and intercellular adhesion molecule-1 (sICAM-1; Chae, Lee, Rifai & Riker, 2001). Literature suggests that increased levels of inflammatory markers, such as TNF-α, may result in decreased bioavailability of nitric oxide (NO), a substance released by the endothelial cells that promotes relaxation of underlying vascular smooth muscle (Yoshimi, Perrella, Burnett, & Lee, 1993). This decline in NO has been associated with endothelial dysfunction, vasoconstriction and increases in blood pressure (Bautista, 2003). Higher levels of

inflammatory markers have also been associated with poor cognitive performance (Gimeno, Marmot, Singh-Manoux, 2008; Wright et al., 2006). Additionally, individuals with both metabolic syndrome, a term that includes hypertension and encompasses several common disorders that represent cardiovascular and metabolic risk factors, and high levels of inflammatory markers demonstrated significant decline in global cognitive performance at three- and five-year follow-ups (Yaffe et al., 2004). Conversely, those with metabolic syndrome and low levels of inflammatory markers, or without metabolic syndrome, had a lower likelihood of cognitive decline. These results suggest that levels of inflammatory markers and endothelial dysfunction may moderate the relationship between blood pressure and cognitive decline.

Another mechanism that may have introduced variance in the study relates to amyloid β (Aβ) in the brain. The accumulation of Aβ plaques has been well-established as a significant risk factor for the development of AD (Jack et al., 2010). Additionally, there is evidence suggesting that at least 20% of healthy, non-demented older adults have a significant level of Aβ in the brain (Rodrigue, Kennedy & Park, 2009). Hypertension and increased pulse pressure has been associated with greater Aβ levels (Rodrigue et al., 2013) in conjunction with the presence of at least one apolipoprotein ε4 (ApoE) allele, a genetic factor that has been associated with increased Aβ accumulation (Castellano et al., 2011; Deane et al., 2008; Nelson et al., 2013). Reduced cerebral blood flow, a possible consequence of increased blood pressure resulting in arterial stiffening and narrowing, has also been associated with impaired Aβ clearance and increased Aβ accumulation (Mattsson et al., 2014). In regards to cognition, research suggests that accumulations of Aβ may demonstrate a significant relationship with decreased cognitive performance in

older adults (Rodrigue et al., 2009). As neither Aβ levels nor APOE e4 allele status were analyzed in the current study, it is unknown as to whether Aβ accumulation, or lack thereof, may have contributed to the results. Future longitudinal studies are needed that examine these relationships between hypertension, Aβ, ApoE4, and brain aging in older adults.

Limitations and Future Directions

There are several important limitations to the current study that highlight the need for future research. One primarily limitation is an absence of hypertension history. Although information was recorded on antihypertensive medications, these were listed if the participant was currently taking them at the time of testing. Additionally, questionnaires did not inquire about past history of high blood pressure. As research suggests that high blood pressure as early as mid-life may lead to significant reductions in white matter integrity and cognitive impairment in old age (Swan et al., 1998), controlling for duration of hypertension may be necessary in examining these relationships in those with and without chronic hypertension. Additionally, other factors affecting blood pressure that were not controlled may have impacted the results. For example, blood pressure can vary widely over the course of the day, particularly in older adults. A blood pressure result is influenced by a variety of conditions, including time of day, whether the individual has recently eaten or exercised, and stress. While testing in the present study primarily occurred in morning and early afternoon, the time of day was not controlled across all participants or over time. Additionally, previous research suggests that a 24-hour average blood pressure may be more strongly related to volume

of WMHs and cognitive performance than blood pressure measurements taken at one time-point or over a short time period during the day (White et al., 2011).

Finally, participants included in the present study were healthy older adults with predominantly normal cognitive functioning. In the hypertensive group, high blood pressure was mostly mild, with few exceptions. To fully understand these relationships between blood pressure, cognitive performance, and white matter integrity, future studies should include a wider range of cognitive ability and blood pressure. The inclusion of a hypotensive group would be ideal, as previous research suggests an inverted-U pattern of blood pressure and brain integrity (Lie et al., 2013; Qiu et al., 2005). Future studies may also benefit from a more comprehensive inclusion of brain integrity markers and additional measures of blood pressure such as pulse wave velocity. Pulse wave velocity has emerged as a sensitive marker of arterial stiffness, and may significantly predict cognitive performance (Elias et al., 2009; Fujiwara et al., 2005; Waldstein et al., 2008; Zhang et al., 2014) and white matter integrity (Henskens et al., 2008; King et al., 2013).

Conclusions

Results from the present study suggest that in this sample of healthy older adults, hypertension and increased blood pressure are not significantly related to integrity of two tracts that connect the frontal lobe to posterior regions of the brain, volume of WMHs, or performance on tests of executive functioning, attention and processing speed. However, age significantly contributed to reduced white matter integrity and cognitive performance over a period of three years and integrity of the SLF was related to cognitive performance. Future work is needed to identify possible modifiers of the association between hypertension and cognitive decline, including inflammatory markers and Aβ

accumulation. Other measures of blood pressure that are sensitive to arterial stiffness may also be beneficial. Overall, results suggest that hypertension did not significantly contribute to brain aging in otherwise healthy older adults.

References

Aine, C., Sanfratello, L., Adair, J., Knoefel, J., Qualls, C., & Lundy, S., … Stephen, J. (2014). Characterization of a normal control group: Are they healthy? *Neuroimage*, *84*, 796-809. doi:10.1016/j.neuroimage.2013.09.025

Alexander, A., Lee, J., Lazar, M., & Field, A. (2007). Diffusion tensor imaging of the brain. *Neurotherapeutics*, *4*(3), 316-329. doi:10.1016/j.nurt.2007.05.011

Alvarez, J., & Emory, E. (2006). Executive Function and the Frontal Lobes: A Meta-Analytic Review. *Neuropsychol Rev*, *16*(1), 17-42. doi:10.1007/s11065-006-9002-x

Aribisala, B., Morris, Z., Eadie, E., Thomas, A., Gow, A., Valdes Hernandez, M., … Wardlaw, J.M. (2014). Blood Pressure, Internal Carotid Artery Flow Parameters, and Age-Related White Matter Hyperintensities. *Hypertension*, *63*(5), 1011-1018. doi:10.1161/hypertensionaha.113.02735

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

Artero, S., Tiemeier, H., Prins, N., Sabatier, R., Breteler, M., & Ritchie, K. (2004). Neuroanatomical localisation and clinical correlates of white matter lesions in the elderly. *Journal Of Neurology, Neurosurgery & Psychiatry*, *75*(9), 1304-1308. doi:10.1136/jnnp.2003.023713

Bakker, S., de Leeuw, F., de Groot, J., Hofman, A., Koudstaal, P., & Breteler, M. (1999).

Cerebral vasomotor reactivity and cerebral white matter lesions in the elderly. *Neurology*, *52*(3), 578-578. doi:10.1212/wnl.52.3.578

Basser, P., Pajevic, S., Pierpaoli, C., Duda, J., & Aldroubi, A. (2000). In vivo fiber tractography using DT-MRI data. *Magn. Reson. Med.*, *44*(4), 625-632.

Bautista, L.E. (2003). Inflammation, endothelial dysfunction, and the risk of high blood pressure: Epidemiologic and biological evidence. *Journal of Human Hypertension, 17*(4), 223-230.

Bautista, L.E., Atwood, J.E., O'Malley, P.G., & Taylor, A.J. (2004). Association between C-reactive protein and hypertension in healthy middle-aged men and women. *Coronary artery disease, 15*(6), 331-336.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of The Royal Statistical Society*, *57*(1), 289-300.

Bonelli, R., & Cummings, J. (2007). Frontal-subcortical circuitry and behavior. *Dialogues in Clinical Neuroscience*, *9*(2), 141-151.

Boone, K.B., Miller, B.L., Lesser, I.M., Mehringer, C.M., Hill-Gutierrez, E., Goldberg, M.A., & Berman, N.G. (1992). Neuropsychological correlates of white-matter lesions in healthy elderly subjects: A threshold effect. *JAMA Neurology, 49*(5), 549-554.

Breteler, M., van Swieten, J., Bots, M., Grobbee, D., Claus, J., van den Hout, J., … Hofman, A. (1994). Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: The Rotterdam Study. *Neurology*, *44*(7), 1246-1246. doi:10.1212/wnl.44.7.1246

Brickman, A., Reitz, C., Luchsinger, J., Manly, J., Schupf, N., Muraskin, J., … Mayeux, R. (2010). Long-term Blood Pressure Fluctuation and Cerebrovascular Disease in an Elderly Cohort. *Archives Of Neurology*, *67*(5). doi:10.1001/archneurol.2010.70

Brickman, A., Siedlecki, K., Muraskin, J., Manly, J., Luchsinger, J., Yeung, L., … Stern,

Y. (2009). White matter hyperintensities and cognition: Testing the reserve hypothesis. *Neurobiology Of Aging*, *32*(9), 1588-1598. doi:10.1016/j.neurobiolaging.2009.10.013

Brickman, A., Zahra, A., Muraskin, J., Steffener, J., Holland, C., Habeck, C., … Stern, Y. (2009). Reduction in cerebral blood flow in areas appearing as white matter hyperintensities on magnetic resonance imaging. *Psychiatry Research: Neuroimaging*, *172*(2), 117-120. doi:10.1016/j.pscychresns.2008.11.006

Brickman, A.M., Zimmerman, M.E., Paul, R.H., Grieve, S.M., Tate, D.F., Cohen, R.A., … Gordon, E. (2006). Regional white matter and neuropsychological functioning across the adult lifespan. *Biological Psychiatry, 60*, 444-453.

Brown, J., Sollers, J., Thayer, J., Zonderman, A., & Waldstein, S. (2009). Blood pressure reactivity and cognitive function in the Baltimore Longitudinal Study of Aging. *Health Psychology*, *28*(5), 641-646. doi:10.1037/a0015215

Brown, W., Moody, D., Challa, V., Thore, C., & Anstrom, J. (2002). Venous collagenosis and arteriolar tortuosity in leukoaraiosis. *Journal Of The Neurological Sciences*, *203-204*, 159-163. doi:10.1016/s0022-510x(02)00283-6

Bucur, B., & Madden, D. (2010). Effects of Adult Age and Blood Pressure on Executive Function and Speed of Processing. *Experimental Aging Research*, *36*(2), 153-168. doi:10.1080/03610731003613482

Burgmans, S., van Boxtel, M., Gronenschild, E., Vuurman, E., Hofman, P., Uylings, H., … Raz, N. (2010). Multiple indicators of age-related differences in cerebral white matter and the modifying effects of hypertension. *Neuroimage*, *49*(3), 2083-2093. doi:10.1016/j.neuroimage.2009.10.035

Cacciatore, F., Abete, P., Ferrara, N., Paolisso, G., Amato, L., Canonico, S., … Rengo, F. (1997). The role of blood pressure in cognitive impairment in an elderly population. *Journal of Hypertension*, *15*(2), 135-142. doi:10.1097/00004872-199715020-00003

Castellano, J.M., Kim, J., Stewart, F.R., Jiang, H., DeMattos, R.B., Patterson, B.W., …

Holtzman, D.M. (2011). Human apoE isoforms differentially regulate brain amyloid-beta peptide clearance. *Science Translational Medicine, 3*(89), 89ra57.

Chae, C.U., Lee, R.T., Rifai, N., Ridker, P.M. (2001). Blood pressure and inflammation in apparently healthy men. *Hypertension, 38*(3), 399-403.

Chen, J., Rosas, H., & Salat, D. (2013). The Relationship between Cortical Blood Flow and Sub-Cortical White-Matter Health across the Adult Age Span. *Plos ONE*, *8*(2), e56733. doi:10.1371/journal.pone.0056733

Conturo, T., Lori, N., Cull, T., Akbudak, E., Snyder, A., Shimony, J., … Raichle, M.E. (1999). Tracking neuronal fiber pathways in the living human brain. *Proceedings of the National Academy of Sciences*, *96*(18), 10422-10427. doi:10.1073/pnas.96.18.10422

Correia, S., Lee, S. Y., Voorn, T., Tate, D. F., Paul, R. H., Zhang, S., ... & Laidlaw, D. H. (2008). Quantitative tractography metrics of white matter integrity in diffusion-tensor MRI. *Neuroimage, 42*(2), 568-581.

Deane, R., Sagare, A., Hamm, K., Parisi, M., Lane, S., Finn, M.B., … Zlokovic, B.V. (2008). apoE isoform-specific disruption of amyloid beta peptide clearance from mouse brain. *Journal of Clinical Investigation, 118*(12), 4002-4013.

de Groot, J., de Leeuw, F., Oudkerk, M., Hofman, A., Jolles, J., Breteler, M. (2000). Cerebral white matter lesions and subjective cognitive dysfunction: The Rotterdam Scan Study. *Neurology*, *56*(11), 1539-1545. doi:10.1212/wnl.56.11.1539

de la Sierra, A., Segura, J., Banegas, J.R., Gorostidi, M., de la Cruz, J.J., Armario, P., … Ruilope, L.M. (2011). Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. *Hypertension, 57*(5), 898-902.

DeCarli, C., Murphy, D., Tranh, M., Grady, C., Haxby, J., Gillette, J., … Schapiro, M.B. (1995). The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults.

Neurology, *45*(11), 2077-2084. doi:10.1212/wnl.45.11.2077

Delis, D. C. (2001). *Delis-Kaplan Executive Function System: D-KEFS*. Orlando, FL: Psychological Corporation.

Di Carlo, A., Baldereschi, M., Amaducci, L., Maggi, S., Grigoletto, F., Scarlato, G., Inzitari, D., for the Italian Longitudinal Study on Aging Working Group (2000). Cognitive impairment without dementia in older people: Prevalence, vascular risk factors, impact on disability. The Italian Longitudinal Study on Aging. *Journal of the American Geriatrics Society, 48*(7), 775-782.

Dufouil, C., de Kersaint-Gilly, A., Besancon, V., Levy, C., Auffray, E., Brunnereau, L., … Tzourio, C. (2001). Longitudinal study of blood pressure and white matter hyperintensities: The EVA MRI Cohort. *Neurology*, *56*(7), 921-926. doi:10.1212/wnl.56.7.921

Elias, M.F., Robbins, M.A., Budge, M.M., Abhayaratna, W.P., Dore, G.A. & Elias, P.K. (2009). Arterial pulse wave velocity and cognition with advancing age. *Hypertension, 53*(4), 668-673.

Farmer, M., White, L., Abbott, R., Kittner, S., Kaplan, E., Wolz, M., … Wolf, P. (1987). Blood pressure and cognitive performance. The Framingham Study. *American Journal of Epidemiology*, *126*(6), 1103 - 1114.

Fazekas, F., Kleinert, R., Offenbacher, H., Schmidt, R., Kleinert, G., Payer, F., … Lechner, H. (1993). Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology*, *43*(9), 1683-1683. doi:10.1212/wnl.43.9.1683

Fazekas, F., Niederkorn, K., Schmidt, R., Offenbacher, H., Horner, S., Bertha, G., & Lechner, H. (1988). White matter signal abnormalities in normal individuals: correlation with carotid ultrasonography, cerebral blood flow measurements, and cerebrovascular risk factors. *Stroke*, *19*(10), 1285-1288. doi:10.1161/01.str.19.10.1285

Folstein, M., Folstein, S., & McHugh, P. (1975). "Mini-mental state". A practical method

for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189-198. doi:10.1016/0022-3956(75)90026-6

Frewen, J., Finucane, C., Savva, G., Boyle, G., & Kenny, R. (2014). Orthostatic Hypotension Is Associated With Lower Cognitive Performance in Adults Aged 50 Plus With Supine Hypertension. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *69*(7), 878-885. doi:10.1093/gerona/glt171

Frye, R., Hasan, K., Malmberg, B., Desouza, L., Swank, P., Smith, K., & Landry, S. (2010). Superior longitudinal fasciculus and cognitive dysfunction in adolescents born preterm and at term. *Developmental Medicine & Child Neurology*, *52*(8), 760-766. doi:10.1111/j.1469-8749.2010.03633.x

Fujiwara, Y., Chaves, P.H.M., Takahashi, R., Amano, H., Yoshido, H., Kumagai, S., … Shinkai, S. (2005). Arterial pulse wave velocity as a marker of poor cognitive function in an elderly community-dwelling population. *The Journals of Gerontology Series A: Biological Sciences & Medical Sciences, 60*(5), 607-612.

Gimeno, D., Marmot, M.G., & Singh-Manoux, A. (2008). Inflammatory markers and cognitive function in middle-aged adults: The Whitehall II Study. *Psychoneuroendocrinology, 33*(10), 1322-1334.

Go, A., Mozaffarian, D., Roger, V., Benjamin, E., Berry, J., Borden, W., … Turner, M.B. (2012). Heart Disease and Stroke Statistics--2013 Update: A Report from the American Heart Association. *Circulation*, *127*(1), e6-e245. doi:10.1161/cir.0b013e31828124ad

Goldstein, F., Levey, A., & Steenland, N. (2013). High blood pressure and cognitive decline in mild cognitive impairment. *Journal of The American Geriatrics Society*, *61*(1), 67-73. doi:10.1111/jgs.12067

Gons, R., de Laat, K., van Norden, A., van Oudheusden, L., van Uden, I., Norris, D., … de Leeuw, F. (2010). Hypertension and cerebral diffusion tensor imaging in small vessel disease. *Stroke*, *41*(12), 2801-2806. doi:10.1161/strokeaha.110.597237

Gunning-Dixon, F., & Raz, N. (2000). The cognitive correlates of white matter abnormalities in normal aging: A quantitative review. *Neuropsychology*, *14*(2), 224-232. doi:10.1037/0894-4105.14.2.224

Gunning-Dixon, F.M., Brickman, A.M., Cheng, J.C., & Alexopoulos, G.S. (2009). Aging of cerebral white matter: A review of MRI findings. *International Journal of Geriatric Psychiatry, 24*(2), 109-117.

Gunstad, J., Cohen, R.A., Tate, D.F., Paul, R.H., Poppas, A., Hoth, K., … Jefferson, A.L. (2005). Blood pressure variability and white matter hyperintensities in older adults with cardiovascular disease. *Blood Pressure, 14*(6), 353-358.

Hannesdottir, K., Nitkunan, A., Charlton, R., Barrick, T., MacGregor, G., & Markus, H. (2009). Cognitive impairment and white matter damage in hypertension: a pilot study. *Acta Neurologica Scandinavica*, *119*(4), 261-268. doi:10.1111/j.1600-0404.2008.01098.x

Harrington, F., Saxby, B., McKeith, I., Wesnes, K., & Ford, G. (2000). Cognitive performance in hypertensive and normotensive older subjects. *Hypertension*, *36*(6), 1079-1082. doi:10.1161/01.hyp.36.6.1079

Henskens, L.H.G., Kroon, A.A., van Oostenbrugge, R.J., Gronenschild, E. H.B.M., Fuss-Lejeune, M.M.J.J., Hofman, P.A.M.,… de Leeuw, P.W. (2008). Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. *Hypertension, 52*, 1120-1126.

Izquierdo-Porrera, A.M., & Waldstein, S.R. (2002). Cardiovascular risk factors and cognitive function in African Americans. *Journal of Gerontology, Series B: Psychological Sciences and Social Sciences, 57*(4), P377-P380.

Jack Jr., C.R., Knopman, D.S., Jaqust, W.J., Shaw, L.M., Aisen, P.S., Weiner, M.W., …Trojanowski, J.Q. (2010). Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurology, 9*(1), 119-128.

Jeerakathil, T., Wolf, P., Beiser, A., Massaro, J., Seshadri, S., D'Agostino, R., & DeCarli,

C. (2004). Stroke risk profile predicts white matter hyperintensity volume: The Framingham Study. *Stroke*, *35*(8), 1857-1861. doi:10.1161/01.str.0000135226.53499.85

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*, *17*(2), 825–841.

Jenkinson, M., Beckmann, C.F., Behrens, T.E.J., Woolrich, M.W., & Smith, S.M. (2012). FSL. *NeuroImage, 62*(2), 782-790.

Kane, M., & Engle, R. (2002). The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: An individual-differences perspective. *Psychonomic Bulletin & Review*, *9*(4), 637-671. doi:10.3758/bf03196323

Kennedy, K., & Raz, N. (2009). Aging white matter and cognition: Differential effects of regional variations in diffusion properties on memory, executive functions, and speed. *Neuropsychologia*, *47*(3), 916-927. doi:10.1016/j.neuropsychologia.2009.01.001

Kilander, L., Nyman, H., Boberg, M., Hansson, L., & Lithell, H. (1998). Hypertension is related to cognitive impairment: A 20-Year follow-up of 999 men. *Hypertension*, *31*(3), 780-786. doi:10.1161/01.hyp.31.3.780

King, K.S., Chen, K.X., Hulsey, K.M., McColl, R.W., Weiner, M.F., Nakonezny, P.A., & Peschock, R.M. (2013). White matter hyperintensities: Use of aortic arch pulse wave velocity to predict volume independent of other cardiovascular risk factors. *Radiology, 267*(3), 709-717.

Klarborg, B., Skak Madsen, K., Vestergaard, M., Skimminge, A., Jernigan, T., & Baaré, W. (2012). Sustained attention is associated with right superior longitudinal fasciculus and superior parietal white matter microstructure in children. *Human Brain Mapping*, *34*(12), 3216-3232. doi:10.1002/hbm.22139

Knecht, S., Wersching, H., Lohmann, H., Bruchmann, M., Duning, T., Dziewas, R., … Ringelstein, E.B. (2008). High-normal blood pressure is associated with poor cognitive performance. *Hypertension*, *51*(3), 663-668. doi:10.1161/hypertensionaha.107.105577

Kohler, S., Baars, M., Spauwen, P., Schievink, S., Verhey, F., & van Boxtel, M. (2013). Temporal evolution of cognitive changes in incident hypertension: Prospective cohort study across the adult age span. *Hypertension*, *63*(2), 245-251. doi:10.1161/hypertensionaha.113.02096

Kuo, H., Sorond, F., Iloputaife, I., Gagnon, M., Milberg, W., & Lipsitz, L. (2004). Effect of blood pressure on cognitive functions in elderly persons. *The Journals of Gerontology Series A: Biological Sciences And Medical Sciences*, *59*(11), 1191-1194. doi:10.1093/gerona/59.11.1191

Kuusisto, J., Koivisto, K., Mykkanen, L., Helkala, E., Vanhanen, M., Hanninen, T., … Laakso, M. (1993). Essential hypertension and cognitive function. The role of hyperinsulinemia. *Hypertension*, *22*(5), 771-779. doi:10.1161/01.hyp.22.5.771

Launer, L.J., Masaki, K., Petrovitch, H., Foley, D., & Havlik, R.J. (1995). The association between midlife blood pressure levels and late-life cognitive function: The Honolulu-Asia aging study. *JAMA, 274*(23), 1846-1851.

Le Bihan, D., Mangin, J., Poupon, C., Clark, C., Pappata, S., Molko, N., & Chabriat, H. (2001). Diffusion tensor imaging: Concepts and applications. *Journal of Magnetic Resonance Imaging*, *13*(4), 534-546. doi:10.1002/jmri.1076

Leemans, A., & Jones, D. K. (2009). The B-matrix must be rotated when correcting for subject motion in DTI data. *Magnetic Resonance in Medicine*, *61*(6), 1336-1349.

Leritz, E., Salat, D., Milberg, W., Williams, V., Chapman, C., Grande, L., … McGlinchey, R.E. (2010). Variation in blood pressure is associated with white matter microstructure but not cognition in African Americans. *Neuropsychology*, *24*(2), 199-208. doi:10.1037/a0018108

Liu, H., Gao, S., Hall, K., Unverzagt, F., Lane, K., Callahan, C., & Hendrie, H. (2013). Optimal Blood Pressure for Cognitive Function: Findings from an Elderly African-American Cohort Study. *Journal of the American Geriatrics Society*, *61*(6), 875-881. doi:10.1111/jgs.12259

MacLullich, A., Ferguson, K., Reid, L., Deary, I., Starr, J., Seckl, J., … Wardlaw, J.M. (2009). Higher systolic blood pressure is associated with increased water diffusivity in normal-appearing white matter. *Stroke*, *40*(12), 3869-3871. doi:10.1161/strokeaha.109.547877

MacMahon, S., Peto, R., Cutler, J., Collins, R., Sorlie, P., Neaton, J., … Stamler, J. (1990). Blood pressure, stroke, and coronary heart disease, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *The Lancet*, *335*(8692), 765-774. doi:10.1016/0140-6736(90)90878-9

Maillard, P., Seshadri, S., Beiser, A., Himali, J., Au, R., Fletcher, E., … DeCarli, C. (2012). Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: a cross-sectional study. *The Lancet Neurology*, *11*(12), 1039-1047. doi:10.1016/s1474-4422(12)70241-7

Mancia, G., De Backer, G., Dominiczak, A., Cifkova, R., Fagard, R., Germano, G., …European Society of Cardiology (2007). 2007 guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Journal of Hypertension, 25*(6), 1105-1187.

Martin, A., Friston, K., Colebatch, J., & Frackowiak, R. (1991). Decreases in regional cerebral blood flow with normal aging. *Journal of Cerebral Blood Flow and Metabolism*, *11*(4), 684-689. doi:10.1038/jcbfm.1991.121

Mattsson, N., Tosun, D., Insel, P.S., Simonson, A., Jack Jr., C.R., Beckett, L.A., … Alzheimer's Disease Neuroimaging Initiative (2014). Association of brain amyloid-β with cerebral perfusion and structure in Alzheimer's disease and mild cognitive impairment. *Brain, 137*, 1550-1561.

Medina, D., deToledo-Morrell, L., Urresta, F., Gabrieli, J.D.E., Moseley, M., Fleischman, D., … Stebbins, G.T. (2006). White matter changes in mild cognitive impairment and AD: A diffusion tensor imaging study. *Neurobiology of Aging, 27,* 663-672.

Melamed, E., Lavy, S., Bentin, S., Cooper, G., & Rinot, Y. (1980). Reduction in regional cerebral blood flow during normal aging in man. *Stroke*, *11*(1), 31-35. doi:10.1161/01.str.11.1.31

Mori, S., Oishi, K., & Faria, A. V. (2009). White matter atlases based on diffusion tensor imaging. *Current opinion in neurology, 22*(4), 362.

Nelson, P.T., Pious, N.M., Jicha, G.A., Wilcock, D.M., Fardo, D.A., Estus, S., & Rebeck, G.W. (2013). APOE-ε2 and APOE-ε4 correlate with increased amyloid accumulation in cerebral vasculature. *Journal of Neuropathology & Experimental Neurology, 72*(7), 708-715.

Pantoni, L., & Garcia, J. (1997). Pathogenesis of Leukoaraiosis: A Review. *Stroke*, *28*(3), 652-659. doi:10.1161/01.str.28.3.652

Pase, M., Stough, C., Grima, N., Harris, E., Macpherson, H., Scholey, A., & Pipingas, A. (2013). Blood pressure and cognitive function: The role of central aortic and brachial pressures. *Psychological Science*, *24*(11), 2173-2181. doi:10.1177/0956797613488602

Perry, M., McDonald, C., Hagler, D., Gharapetian, L., Kuperman, J., Koyama, A., … McEvoy, L.K. (2009). White matter tracts associated with set-shifting in healthy aging. *Neuropsychologia*, *47*(13), 2835-2842. doi:10.1016/j.neuropsychologia.2009.06.008

Pfefferbaum, A., Adalsteinsson, E., & Sullivan, E.V. (2005). Frontal circuitry degradation marks healthy adult aging: Evidence from diffusion tensor imaging. *Neuroimage, 26*(3), 891-899.

Qiu, C., Winblad, B., & Fratiglioni, L. (2005). The age-dependent relation of blood pressure to cognitive function and dementia. *The Lancet Neurology*, *4*(8), 487-499.

doi:10.1016/s1474-4422(05)70141-1

Randolph, C., Tierney, M. C., Mohr, E., & Chase, T. N. (1998). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *Journal of Clinical and Experimental Neuropsychology*, *20*(3), 310-319.

Raz, N., Rodrigue, K., & Acker, J. (2003). Hypertension and the brain: Vulnerability of the pefrontal regions and executive functions. *Behavioral Neuroscience*, *117*(6), 1169-1180. doi:10.1037/0735-7044.117.6.1169

Raz, N., Rodrigue, K., Kennedy, K., & Acker, J. (2007). Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. *Neuropsychology*, *21*(2), 149-157. doi:10.1037/0894-4105.21.2.149

Rodrigue, K.M., Kennedy, K.M., & Park, D.C. (2009). Beta-amyloid deposition and the aging brain. *Neuropsychology Review, 19*, 436-450.

Rodrigue, K.M., Rieck, J.R., Kennedy, K.M., Devous, M.D., Diaz-Arrastia, R., & Park, D.C. (2013). Risk factors for amyloid deposition in healthy aging: Interactive effects of vascular and genetic risk. *JAMA Neurology, 70*(5), 600-606.

Rosano, C., Abebe, K., Aizenstein, H., Boudreau, R., Jennings, J., Venkatraman, V., … Newman, A.B. (2014). Longitudinal systolic blood pressure characteristics and integrity of white matter tracts in a cohort of very old black and white adults. *American Journal of Hypertension*. doi:10.1093/ajh/hpu134

Sachdev, P., Wen, W., Chen, X., Brodaty, H. (2007). Progression of white matter hyperintensities in elderly individuals over 3 years. *Neurology, 68*(3), 214-222.

Safar, M., Levy, B., & Struijker-Boudier, H. (2003). Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation*, *107*(22), 2864-2869. doi:10.1161/01.cir.0000069826.36125.b4

Salat, D.H., Tuch, D.S., Hevelone, N.D., Fischl, B., Corkin, S., Rosas, H.D., & Dale, A.M. (2005). Age-related changes in prefrontal white matter measured by diffusion tensor imaging. *Annals of the New York Academy of Sciences, 1064,* 37-49.

Salat, D., Williams, V., Leritz, E., Schnyer, D., Rudolph, J., Lipsitz, L., … Milberg, W.P. (2012). Inter-individual variation in blood pressure is associated with regional white matter integrity in generally healthy older adults. *Neuroimage*, *59*(1), 181-192. doi:10.1016/j.neuroimage.2011.07.033

Salthouse, T.A. (2009). When does age-related cognitive decline begin? *Neurobiology of Aging, 30*(4), 507-514.

Santiago, C., Herrmann, N., Swardfager, W., Saleem, M., Oh, P., Black, S., & Lanctôt, K. (2014). White matter microstructural integrity is associated with executive function and processing speed in older adults with coronary artery disease. *The American Journal of Geriatric Psychiatry*. doi:10.1016/j.jagp.2014.09.008

Sasson, E., Doniger, G., Pasternak, O., Tarrasch, R., & Assaf, Y. (2013). White matter correlates of cognitive domains in normal aging with diffusion tensor imaging. *Frontiers in Neuroscience*, *7*. doi:10.3389/fnins.2013.00032

Saxby, B., Harrington, F., McKeith, I., Wesnes, K., & Ford, G. (2003). Effects of hypertension on attention, memory, and executive function in older adults. *Health Psychology*, *22*(6), 587-591. doi:10.1037/0278-6133.22.6.587

Scherr, P., Hebert, L., Smith, L., & Evans, D. (1991). Relation of blood pressure to cognitive function in the elderly. *American Journal of Epidemiology*, *134*(11), 1303-1315.

Schmidt, R., Fazekas, F., Offenbacher, H., Dusek, T., Zach, E., Reinhart, B., … Lechner, H. (1993). Neuropsychologic correlates of MRI white matter hyperintensities: A study of 150 normal volunteers. *Neurology*, *43*(12), 2490-2490. doi:10.1212/wnl.43.12.2490

Schmidt, R., Fazekas, F., Kapeller, P., Schmidt, H., & Hartung, H.P. (1999). MRI white matter hyperintensities: Three-year follow-up of the Austrian Stroke Prevention Study. *Neurology, 53*(1), 132-139.

Scuteri, A., Nilsson, P., Tzourio, C., Redon, J., & Laurent, S. (2011). Microvascular brain

damage with aging and hypertension. *Journal of Hypertension*, *29*(8), 1469-1477. doi:10.1097/hjh.0b013e328347cc17

Skoog, I., Nilsson, L., Persson, G., Lernfelt, B., Landahl, S., Palmertz, B., … Svanborg, A. (1996). 15-year longitudinal study of blood pressure and dementia. *The Lancet*, *347*(9009), 1141-1145. doi:10.1016/s0140-6736(96)90608-x

Smith, S. M. (2002). Fast robust automated brain extraction. *Human brain mapping*, *17*(3), 143-155.

Söderlund, H., Nyberg, L., Adolfsson, R., Nilsson, L.G., & Launer, L.J. (2003). High prevalence of white matter hyperintensities in normal aging: Relation to blood pressure and cognition. *Cortex, 39*(4-5), 1093-1105.

Sung, K.C., Suh, J.Y., Kim, B.S., Kang, J.H., Kim, H., Lee, M.H., … Kim, S.W. (2003). High sensitivity c-reactive protein as an independent risk factor for essential hypertension. *American Journal of Hypertension, 16*(6), 429-433.

Swan, G., DeCarli, C., Miller, B., Reed, T., Wolf, P., Jack, L., & Carmelli, D. (1998). Association of midlife blood pressure to late-life cognitive decline and brain morphology. *Neurology*, *51*(4), 986-993. doi:10.1212/wnl.51.4.986

Teipel, S., Meindl, T., Wagner, M., Stieltjes, B., Reuter, S., Hauenstein, K., … Hampel, H. (2010). Longitudinal changes in fiber tract integrity in healthy aging and mild cognitive impairment: A DTI follow-up study. *Journal Of Alzheimer's Disease*, *22*(2), 507-522.

Turken, U., Whitfield-Gabrieli, S., Bammer, R., Baldo, J., Dronkers, N., & Gabrieli, J. (2008). Cognitive processing speed and the structure of white matter pathways: Convergent evidence from normal variation and lesion studies. *Neuroimage*, *42*(2), 1032-1044. doi:10.1016/j.neuroimage.2008.03.057

Tzourio, C., Dufouil, C., Ducimetiere, P., & Alperovitch, A. (1999). Cognitive decline in individuals with high blood pressure: A longitudinal study in the elderly. *Neurology*, *53*(9), 1948-1948. doi:10.1212/wnl.53.9.1948

Ueda, K., Kawano, H., Hasuo, Y., & Fujishima, M. (1992). Prevalence and etiology of dementia in a Japanese community. *Stroke*, *23*(6), 798-803. doi:10.1161/01.str.23.6.798

Urger, S., De Bellis, M., Hooper, S., Woolley, D., Chen, S., & Provenzale, J. (2014). The Superior longitudinal fasciculus in typically developing children and adolescents: Diffusion tensor imaging and neuropsychological correlates. *Journal of Child Neurology*. doi:10.1177/0883073813520503

van Boxtel, M., Gaillard, C., Houx, P., Buntinx, F., de Leeuw, P., & Jolles, J. (1997). Can the blood pressure predict cognitive task performance in a healthy population sample? *Journal of Hypertension*, *15*(10), 1069-1076. doi:10.1097/00004872-199715100-00004

van Swieten, J., Geyskes, G., Derix, M., Peeck, B., Ramos, L., van Latum, J., & van Gijn, J. (1991). Hypertension in the elderly is associated with white matter lesions and cognitive decline. *Annals of Neurology*, *30*(6), 825-830. doi:10.1002/ana.410300612

Vasan, R., Beiser, A., Seshadri, S., Larson, M., Kannel, W., D'Agostino, R., & Levy, D. (2002). Residual lifetime risk for developing hypertension in middle-aged women and men. *JAMA*, *287*(8). doi:10.1001/jama.287.8.1003

Vicario, A., Martinez, C., Baretto, D., Casale, A., & Nicolosi, L. (2005). Hypertension and cognitive decline: Impact on executive function. *The Journal of Clinical Hypertension*, *7*(10), 598-604. doi:10.1111/j.1524-6175.2005.04498.x

Wakana, S., Jiang, H., Nagae-Poetscher, L. M., Van Zijl, P. C., & Mori, S. (2004). Fiber tract–based atlas of human white matter anatomy 1. *Radiology*, *230*(1), 77-87.

Waldstein, S., Giggey, P., Thayer, J., & Zonderman, A. (2005). Nonlinear relations of blood pressure to cognitive function: The Baltimore Longitudinal Study of Aging. *Hypertension*, *45*(3), 374-379. doi:10.1161/01.hyp.0000156744.44218.74

Waldstein, S.R., Rice, S.C., Thayer, J.F., Najjar, S.S., Scuteri, A., & Zonderman, A.B. (2008). Pulse pressure and pulse wave velocity are related to cognitive decline in the

Baltimore Longitudinal Study of Aging. *Hypertension, 51*(1), 99-104.

Wechsler, D. (1997). *WAIS-III Administration and Scoring Manual*. San Antonio, TX: The Psychological Corporation.

Wharton, W., Gleason, C., Dowling, N., Carlsson, C., Brinton, E., Santoro, M., … Asthana, S. (2014). The KEEPS-Cognitive and Affective Study: Baseline associations between vascular risk factors and cognition. *Journal of Alzheimer's Disease*, *40*(2), 331-341.

White, W.B., Wolfson, L., Wakefield, D.B., Hall, C.B., Campbell, P., Moscufo, N., … Guttmann, C.R. (2011). Average daily blood pressure, not office blood pressure, is associated with progression of cerebrovascular disease and cognitive decline in older people. *Circulation, 124*(21), 2312-2319.

Wiseman, R., Saxby, B., Burton, E., Barber, R., Ford, G., & O'Brien, J. (2004). Hippocampal atrophy, whole brain volume, and white matter lesions in older hypertensive subjects. *Neurology*, *63*(10), 1892-1897. doi:10.1212/01.wnl.0000144280.59178.78

Wright, C.B., Sacco, R.L., Rundek, T.R., Delman, J.B., Rabbani, L.E. & Elkind, M.S.V. (2006). Interleukin-6 is associated with cognition function: the Northern Manhattan Study. *Journal of Stroke and Cerebrovascular Disease, 15*(1), 34-38.

Wu, C., Zhou, D., Wen, C., Zhang, L., Como, P., & Qiao, Y. (2003). Relationship between blood pressure and Alzheimer's disease in Linxian County, China. *Life Sciences*, *72*(10), 1125-1133. doi:10.1016/s0024-3205(02)02367-6

Yaffe, K., Kanaya, A., Lindquist, K., Simonsick, E.M., Harris, T., Shorr, R.I., … Newman, A.B. (2004). The metabolic syndrome, inflammation, and risk of cognitive decline. *JAMA, 292*(18), 2237-2242.

Yoshimi, M., Perrella, M.A. Burnett, J.C., Lee, M.E. (1993). Tumor necrosis factor down-regulates an endothelial nitric oxide synthase mRNA by shortening its half-life. *Ciculation Research, 73*, 205-209.

Zhang, S., Demiralp, C., & Laidlaw, D. H. (2003). Visualizing diffusion tensor MR images using streamtubes and streamsurfaces. *Visualization and Computer Graphics, IEEE Transactions on*, *9*(4), 454-462.

Zhang, H., Yushkevich, P. A., Alexander, D. C., & Gee, J. C. (2006). Deformable registration of diffusion tensor MR images with explicit orientation optimization. *Medical image analysis, 10*(5), 764-785.

Zhang, H., Avants, B. B., Yushkevich, P., Woo, J. H., Wang, S., McCluskey, L. F., ... & Gee, J. C. (2007). High-dimensional spatial normalization of diffusion tensor images improves the detection of white matter differences: an example study using amyotrophic lateral sclerosis. *Medical Imaging, IEEE Transactions on, 26*(11), 1585-1597.

Zhang, Y., Agnoletti, D., Xu, Y., Wang, J.G., Blacher, J., & Safar, M.E. (2014). Carotid-femoral pulse wave velocity in the elderly. *Journal of Hypertension, 32*(8), 1572-1576.

Zhu, Y.C., Chabriat, H., Godin, O., Dufouil, C., Rosand, J., Greenburg, S.M., … Viswanathan, A. (2012). Distribution of white matter hyperintensity in cerebral hemorrhage and healthy aging. *Journal of Neurology, 259*(3), 530-536.

Table 1. *Sample Characteristics*

		Primary Analyses		Secondary Analyses		
	Total Sample	Normotensives	Hypertensives	Normotensives	Pre-hypertensives	Hypertensives
	n= 60 *M*(*SD*)	*n*= 36 *M*(*SD*)	*n*= 24 *M*(*SD*)	*n*= 11 *M*(*SD*)	*n*= 25 *M*(*SD*)	*n*= 24 *M*(*SD*)
Age	62.7 (8.0)	61.0 (7.3)	65.1 (8.5)	58.8 (4.7)	62.0 (8.1)	65.1 (8.5)
Education (years)	15.7 (2.4)	15.8 (2.2)	15.5 (2.6)	16.9 (1.4)	15.3 (2.4)	15.5 (2.6)
BMI	25.5 (4.0)	24.9 (4.0)	26.4 (3.9)	22.9 (3.6)	25.9 (3.9)*	26.4 (3.9)*
Systolic BP	130.2 (15.4)	123.9 (9.6)	140.0 (17.6)*	112.9 (4.9)	128.7 (6.6)*	140.0 (17.6)*^
Diastolic BP	79.7 (9.8)	74.7 (7.0)	86.8 (9.1)*	71.2 (6.0)	76.3 (7.0)	86.8 (9.1)*^
Pulse Pressure	50.6 (11.4)	49.2 (9.8)	52.9 (13.3)	41.7 (5.0)	52.4 (9.6)*	52.9 (13.3)*
Gender, *n*(%)						
Male	18 (30%)	9 (25%)	9 (38%)	1 (9%)	8 (32%)	9 (38%)
Female	42 (70%)	27 (75%)	15 (63%)	10 (91%)	17 (68%)	15 (63%)
Ethnicity, *n*(%)						
Caucasian	46 (76.7%)	28 (78%)	18 (75%)	7 (64%)	21 (84%)	18 (75%)
African American	10 (16.7%)	6 (17%)	4 (17%)	2 (18%)	4 (16%)	4 (17%)
Hispanic	3 (5.0%)	1 (3%)	2 (8%)	1 (9%)	0 (0%)	2 (8%)
Asian	1 (1.7%)	1 (3%)	0 (0%)	1 (9%)	0 (0%)	0 (0%)

*Significantly different from normotensive group at p<.05

^Significantly different from pre-hypertensive group at p< .05

Table 2. *White matter variable T-tests and correlations*

	Independent T-tests			Correlations		
	Normotensive *M*(SD)	Hypertensive *M*(SD)	*p*	Systolic *r*	Diastolic *r*	Pulse pressure *r*
FA						
SLF	.45 (.03)	.44 (.03)	.27	-.28*	-.18	-.23
IFOF	.44 (.02)	.43 (.02)	.047	-.23	-.14	-.17
MD						
SLF	.61 (.03)	.62 (.03)	.11	.12	.03	.14
IFOF	.67 (.03)	.69 (.04)	.03	.19	.07	.17
WMH (cm^3)	.93 (1.1)	1.2 (1.5)	.46	-.07	.04	-.14

* Significant at $p<.05$ before FDR correction

No significant results after FDR correction

Table 3. *Regression results for cognitive test scores and blood pressure.*

	β	R^2	F	p
Systolic				
TMT-A	.20	0.04	2.27	.14
TMT-B	.18	0.03	1.85	.18
DKEFS 1	.26	.07	4.20	.045*
DKEFS 3	.04	.001	.08	.78
DKEFS 4	.37	.14	8.94	.004*
LNS	.04	.002	.09	.76
Digit Span	.08	.01	.42	.52
Coding	.15	.02	1.35	.25
Diastolic				
TMT-A	.09	.01	.47	.49
TMT-B	.02	.001	.03	.86
DKEFS 1	.03	.001	.06	.81
DKEFS 3	.11	.01	.67	.42
DKEFS 4	.15	.02	1.27	.26
LNS	.09	.01	.51	.48
Digit Span	.03	.001	.06	.81
Coding	.09	.01	.43	.52
Pulse Pressure				
TMT-A	.20	.04	2.30	.14
TMT-B	.22	.05	2.87	.10
DKEFS 1	.33	.11	6.82	.01*
DKEFS 3	.14	.02	1.22	.28
DKEFS 4	.38	.14	9.02	.004*
LNS	.03	.001	.04	.84
Digit Span	.14	.02	1.19	.28
Coding	.13	.02	.99	.32

*Significant at $p<.05$ before FDR correction

Table 4. *Regression results for cognitive test scores and white matter variables.*

	β	R^2	F	p
SLF FA				
TMT-A	.33	.11	6.53	.01*
TMT-B	.22	.05	2.70	.11
DKEFS 1	.25	.06	3.57	.06
DKEFS 3	.14	.02	1.10	.30
DKEFS 4	.05	.003	.14	.71
LNS	.09	.01	.51	.48
Digit Span	.04	.002	.10	.76
Coding	.32	.11	6.56	.01*
	β	R^2	F	p
SLF MD				
TMT-A	.37	.14	8.77	.004*
TMT-B	.29	.08	5.13	.03*
DKEFS 1	.26	.07	4.11	.047*
DKEFS 3	.06	.004	.22	.64
DKEFS 4	.01	.000	.002	.97
LNS	.21	.04	2.63	.11
Digit Span	.01	.000	.002	.96
Coding	.44	.19	13.57	.001*^
	β	R^2	F	p
IFOF FA				
TMT-A	.27	.07	4.39	.04*
TMT-B	.30	.09	5.29	.03*
DKEFS 1	.25	.06	3.77	.06
DKEFS 3	.12	.01	.82	.37
DKEFS 4	.08	.01	.39	.54
LNS	.30	.09	5.58	.02*
Digit Span	.13	.02	1.03	.31
Coding	.30	.09	5.59	.02*
	β	R^2	F	p
IFOF MD				
TMT-A	.24	.06	3.39	.07
TMT-B	.20	.04	2.36	.13
DKEFS 1	.17	.03	1.58	.21
DKEFS 3	.05	.003	.14	.71
DKEFS 4	.06	.003	.18	.67
LNS	.19	.04	2.18	.15
Digit Span	.04	.001	.07	.79
Coding	.38	.14	9.55	.003*

	β	R^2	F	p
WMH				
TMT-A	.09	.01	.48	.49
TMT-B	.30	.09	5.42	.02*
DKEFS 1	.11	.01	.65	.43
DKEFS 3	.06	.003	.17	.68
DKEFS 4	.02	.001	.03	.87
LNS	.17	.03	1.58	.21
Digit Span	.11	.01	.65	.42
Coding	.19	.04	2.16	.15

*Significant at p<.05 before FDR correction

^Significant after FDR correction

Table 5. *Hierarchical regression results for SLF MD and RBANS coding*

		β	R2	ΔR2	ΔF	Sig. ΔF
RBANS Coding	[1]Age	.50	.25	.25	19.36	<.001
	[2]SLF MD	.56	.31	.06	5.27	.03

Table 6. *Repeated measures results for time and time x group interactions.*

	All participants	All participants	Time 1 vs Time 2	Normotensive		Hypertensive		Time x Group
	M (SD)	M (SD)	p	M(SD)		M(SD)		p
	Time 1	Time 2		Time 1	Time 2	Time 1	Time 2	
White Matter								
SLF FA	.45 (.03)	.45 (.03)	.52	.45 (.03)	.45 (.03)	.44 (.03)	.45 (.03)	.19
SLF MD	.61 (.02)	.61 (.03)	.31	.60 (.02)	.60 (.03)	.60 (.03)	.60 (.03)	.12
IFOF FA	.44 (.02)	.43 (.03)	.65	.44 (.02)	.43 (.02)	.43 (.02)	.44 (.03)	.12
IFOF MD	.68 (.03)	.69 (.04)	.001*^	.67 (.03)	.68 (.03)	.70 (.04)	.70 (.05)	.42
WMH	1.1 (1.3)	1.5 (1.7)	< .001*^	.96 (1.1)	1.3 (1.3)	1.3 (1.6)	1.8 (2.2)	.28
Cognition								
TMT-A	33.1 (9.3)	30.7 (9.4)	.04*	32.5 (9.1)	30.0 (8.6)	34.1 (9.9)	31.7 (10.7)	.96
TMT-B	75.6 (30.6)	75.2 (26.6)	.82	78.4 (34.2)	72.0 (23.9)	71.6 (24.6)	79.9 (30.1)	.09
DKEFS 1	29.7 (4.6)	30.3 (5.0)	.24	29.8 (4.8)	30.2 (5.5)	29.6 (4.3)	30. 5 (4.4)	.67
DKEFS 3	57.8 (12.9)	55.3 (10.9)	.13	58.7 (14.1)	54.9 (10.3)	56.4 (11.1)	56.0 (11.9)	.22
DKEFS 4	63.1 (12.8)	58.9 (14.2)	.005*^	61.0 (9.3)	55.8 (10.8)	66.0 (16.3)	63.0 (17.1)	.43
LNS	10.7 (1.9)	10.8 (2.4)	.60	11.0 (1.9)	10.6 (2.6)	10.3 (1.9)	11.0 (2.2)	.07
Digit Span	11.3 (2.1)	11.1 (2.5)	.81	11.5 (2.4)	10.8 (2.8)	11.0 (1.5)	11.5 (2.1)	.12
Coding	48.0 (7.9)	49.5 (8.9)	.08	49.3 (8.1)	51.1 (9.0)	46.1 (7.3)	47.0 (8.3)	.57

*Significant at p<.05 before FDR correction

^Significant after FDR correction

Table 7. *MANCOVA results for secondary analysis of blood pressure groups.*

			Wilks' λ	F	p	ηp²
FA			0.92	1.15	0.34	0.04
MD			0.93	1.01	0.41	0.04
WMH			-	0.81	0.45	0.03
Cognition			0.58	1.70	.06	.24
Cognitive Tests	Normotensive *M*(SD)	Pre-hypertensive *M*(SD)	Hypertensive *M*(SD)	Univariate F	p	ηp²
TMT-A	29.7 (8.3)	31.8 (6.9)	34.7 (10.0)	1.86	.17	.07
TMT-B	63.1 (8.0)	78.1 (38.2)	74.5 (26.5)	1.01	.37	.04
DKEFS 1	28.5 (5.3)	28.5 (3.3)	30.1 (4.6)	1.02	.37	.04
DKEFS 3	57.7 (11.3)	54.6 (12.0)	56.4 (11.4)	.25	.78	.01
DKEFS 4	57.7 (8.5)	59.9 (8.1)[a]	68.4 (18.8)[ab]	3.31	.045*	.12
LNS	10.3 (1.1)	11.2 (1.6)	10.2 (2.0)[b]	2.32	.11	.09
Digit Span	12.0 (1.7)	11.1 (2.5)	10.9 (1.4)	.49	.62	.02
Coding	45.7 (7.9)	52.6 (7.4)[a]	46.0 (7.3)[b]	5.33	.008*	.18

BMI included as covariate in all analyses

*Significant at p<.05

[a] Significantly different from Normotensive group (p<.05)

[b] Significantly different from Pre-hypertensive group (p<.05)

Table 8. MANOVA *results for highest quartiles versus lowest quartiles of blood pressure.*

			Q1 vs Q4 significance level			
		Quartile Range	FA	MD	WMH	Cog
Systolic			.22	.15	.44	.13
	Q1	106.0-119.25				
	Q2	119.26-128.0				
	Q3	128.1-138				
	Q4	138.1-176.3				
Diastolic			.40	.66	.74	.89
	Q1	60.0-73.17				
	Q2	73.18-78.5				
	Q3	78.6-84.9				
	Q4	85.0-107.0				
Pulse Pressure			.23	.12	.07	.22
	Q1	25.67-41.81				
	Q2	41.82-50.0				
	Q3	50.1-58.24				
	Q4	58.25-80.0				

Q = quartile