Blood Pressure, White Matter Disease, and Cognitive Decline in the Normal Elderly Population

Beth Ann Springate

Age-related changes in brain morphology have been linked to memory loss, declines in executive functioning, and slower reaction time. Furthermore, hypertension is a strong risk factor for cognitive decline. However, few studies have examined longitudinal relationships between blood pressure, frontal white matter integrity, hippocampal grey matter volume, and cognition within a healthy elderly population. This study utilized structural MRI and neuropsychological tests administered two years apart to examine these relationships in a sample of healthy, community-dwelling older adults aged 75-90. Results indicated that increases in frontal white matter disease and, more strongly, declines in hippocampal volume were better predictors of cognitive change than age and education. No significant associations were observed between blood pressure and cognition. These findings suggest tracking trajectories of structural change within the brains of elderly individuals over time can facilitate identification of those at risk for cognitive decline.

Blood Pressure, White Matter Disease, and Cognitive Decline

in the Normal Elderly Population

Beth Ann Springate

B.A., University of Rochester, 2005

M.A., University of Connecticut, 2008

A Dissertation

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Doctor of Philosophy

at the

University of Connecticut

2011

APPROVAL PAGE

Doctor of Philosophy Dissertation

Blood Pressure, White Matter Disease, and Cognitive Decline

in the Normal Elderly Population

Presented by
Beth Ann Springate, B.A., M.A.

Major Advisor

George J. Allen, Ph.D.

Associate Advisor

Richard F. Kaplan, Ph.D.

Associate Advisor

Deborah Fein, Ph.D.

University of Connecticut
2011

Acknowledgements

This dissertation would not have been possible were it not for the guidance and support that so many people have given me Special thanks to my advisors, Drs Richard Kaplan and George Allen, for sharing their expertise and providing me with the support I needed to pursue my goals You have been generous with your time and forever encouraging and supportive while continuing to hold me to high standards Most importantly, thank you for all you have taught me and the lessons you have yet to teach, as they extend well beyond the academic world I can only hope to offer a fraction of what you have provided me to a future student Thanks also to Dr Deborah Fein for supervising my graduate coursework in neuropsychology, and I consider myself honored to have studied with you

Special thanks also go to Dr Leslie Wolfson at the University of Connecticut Health Center for allowing me to use data from his "Brain Changes and Risk Factors Causing Impaired Mobility" study for my dissertation research This study was supported in part by Research Grant R01 AG022092 from the National Institutes of Health Dr Wolfson's research assistant, Julie Schmidt, helped in so many ways on this project, and I am grateful for her assistance Finally, many thanks to my family and friends, I never could have embarked upon or finished this journey without you

Table of Contents

List of Tables

The United States is an aging society At the present time, people over 65 equal 13% of the population Projections indicate that over 20% of the population, or more than 70 million people, will be 65 or older by 2030 (U S Census Bureau, 2008) The "baby boom" generation (individuals born from 1946-1954) represents the greatest demographic spike in the history of this nation, and beginning in 2011 the earliest baby boomers will reach 65, greatly altering the demographic composition of the United States Many researchers agree that a key challenge for the future will be to ensure that good health and quality of life are maintained during this demographic shift

Diseases such as dementia and cardiovascular disease are commonly associated with old age and have substantial fiscal impact For example, the total worldwide societal cost of dementia was estimated to be $422 billion in 2009, including $142 billion for informal care, and increasing by 34% between 2005 and 2009 (Wimo, Winblad, & Jonsson, 2010) Cardiovascular disease has been estimated to cost the European Union more than €169 billion annually, with healthcare costs alone accounting for 62% of this figure (Leal, Luengo-Fernández, Gray, Petersen, & Rayner, 2006) Considering these great costs, delaying the onset of these diseases could have great benefits, and the identification of risk and protective factors is becoming increasingly important in order to delay or slow the progression of these diseases

Aging and Changes in Brain Morphology

The relationship between aging and declining cognitive function has often been tied to the loss of grey matter, or the loss of neurons within the brain Early research focused on changes in brain volume throughout the lifespan, and the association between

age and reduced brain weight and volume has been well-established A classic paper reviewed early studies of human brain volume which, depending on the study, estimated that peak brain weight occurs between ages 14-35 with approximately 90g lost by age 80 (Brody, 1955) According to Brody, these age-associated reductions in brain weight are likely related to significant cellular death

More recent studies have continued to support this paper's finding of reduced brain volume Structural MRIs obtained from adults aged 18-97 revealed a strong linear pattern of decline in whole-brain volume beginning in early adulthood, with differences detected by age 30 (Fotenos, Snyder, Girton, Morris, & Buckner, 2005) In a longitudinal study of older adults without dementia, significant changes were found in total brain volume, even within a subgroup of very healthy elderly, with frontal and parietal regions showing greater decline than temporal and occipital regions (Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003).

Given this decline in brain volume with age, a debate began to emerge regarding whether cortical shrinkage was actually due to grey matter loss Early researchers held that that aging was associated with reductions in overall volume but accompanied by increases in neuronal density Later researchers expanded upon these papers, suggesting that changes in brain weight are explained by changes in the distribution between large and small neurons In an examination of 51 normal brains between the ages of 24 and 100, whole brain weight began to decrease at 55 years of age, but no significant changes in neuronal populations within mid-frontal, superior temporal, or inferior parietal sections were observed Large cells (those greater than 90 μm^2) decreased with age, while small neurons (40-90 μm^2) increased, primarily within the mid-frontal cortex These

observations suggest that neuronal counts do not necessarily diminish with age, but instead, estimates of volume loss are reflective of the replacement of larger neurons with an approximately equal number of smaller ones (Terry, DeTeresa, & Hansen, 1987) Considerable research within the field of aging has focused on changes in morphology within the hippocampus, as memory decline is stereotypically associated with aging

Hippocampus. The hippocampus is integral to intact declarative memory, as evidenced by repeated findings of reduced hippocampal volume in neurological conditions whose central symptom is prominent declarative memory deficits (Bottino et al , 2002, Jack et al , 1997) Given that declines in memory are closely tied to aging in the absence of neurodegenerative disorders, researchers have turned their attention to age-related changes in the hippocampus and, in turn, how these structural changes relate to declines in memory

Increasing age is generally associated with reduced learning and free recall of verbal and visual information (Drobny, Anstey, & Andrews, 2005, Jones et al , 2005, McCarty, Siegler, & Logue, 1982, Ylikoski et al , 1998) For example, Jones et al (1995) found that for every 10-year increase in age, participants recalled approximately one fewer word from a word list at delayed recall Age-related declines in memory are also observed when the same elderly subjects are followed longitudinally McCarty et al (1982) observed significant longitudinal declines on the same figural memory task after 4, 10, and 16 years for those aged 60-80 years old at initial testing

In addition to age-related declines in memory, age-related declines in hippocampal volume are well documented (Chen, Chuah, Sim, & Chee, 2010, Pruessner, Collins, Pruessner, & Evans, 2001, Ystad et al , 2009) Relationships between

hippocampal volume and memory performance have also been demonstrated For example, in a cross-sectional study of nondemented elderly aged 60-90, participants with larger hippocampal heads scored significantly higher on memory tests, most notably on delayed recall, with a 0 41 word per SD increase in the left hippocampal head and 0 33 word per SD increase in the right hippocampal head (Hackert et al , 2002) Similarly, in another cross-sectional study of middle-aged and elderly individuals, delayed recall of a list positively correlated with hippocampal volume (Ystad et al , 2009) This relationship between delayed recall and hippocampal volume was especially strong in women for the left hippocampus These findings are not restricted to studies of verbal memory, for example, right hippocampal tail volume has been shown to positively correlate with spatial memory on a maze learning task (Chen et al , 2010)

However, not all cross-sectional studies support this finding No association was seen between hippocampal volume and total recall in an elderly sample once individuals with an Alzheimer's disease diagnosis were removed (Reitz et al , 2009) Similarly, in a recent meta-analysis, the evidence for a positive relationship between hippocampal size and memory ability in older adults was surprisingly weak (Van Petten, 2004) This surprising lack of a strong relationship was attributed to the extreme variability across studies associated with statistical methods of normalizing for age and head size, arguing for the need for more methodologically rigorous studies

Most longitudinal studies, however, support a relationship between declining hippocampal volume and poorer memory An annual 1 1% rate of decline in hippocampal volume over an average of 3 4 years in a study of nondemented adults aged 58-87, the rate of loss accelerated in individuals with cognitive complaints (Mungas et

al , 2005) Furthermore, the change in hippocampal volume was significantly related to changes in memory, with greater hippocampal volume loss associated with poorer memory performance

However, the loss of grey matter cannot solely explain cognitive decline with age, in a comparison of white and gray matter volumes in prefrontal regions between young healthy elderly (mean age = 70) and older healthy elderly (mean age = 90) individuals, grey matter differences were not significant, whereas white matter volume was significantly less in the older group (Salat, Kaye, & Janowsky, 1999) Age-related changes in white matter have taken the lead in explaining cognitive changes experienced by non-demented elderly (Hinman & Abraham, 2007)

White Matter Disease. White matter represents bundles of myelinated axons connecting neurons throughout the brain Myelination of axons allows the conduction of action potentials to occur at up to 10 times the speed of unmyelinated axons Myelin volume and integrity typically reach their peak by mid-age and then begin to decline with advancing age (Bartzokis, Beckson, Nuechterlein, Edwards, & Mintz, 2001, Davatzikos & Resnick, 2002, Ge et al , 2002)

Historically, white matter abnormalities were referred to as Binswanger's disease (Babikian & Ropper, 1987) Some argue this terminology evolved from an inaccurate and over-reaching description of white matter abnormalities to describe not only the pathology relating to a vascular dementia but also including more common and benign incidents of white matter abnormalities that did not produce the cognitive changes associated with dementia (Hachinski, Potter, & Merskey, 1987) The term leukoaraiosis

was introduced to reflect a more "neutral" characterization of white matter changes without necessarily implying an underlying dementing condition

Leukoaraiosis (LA) is often reflected by regions of white matter hyperintensities (WMH) on MRI imaging These regions of hyperintensity within the cerebral white matter of T2-weighted and fluid-attenuated inversion recovery (FLAIR) techniques provide macrostructural assessment of white matter changes Diffusion tensor imaging (DTI), an extension of MRI techniques which provides information about the microstructural integrity of existing white matter by measuring the magnitude and direction of water diffusion, has also been used to examine damage to nerve fibers

Evidence suggests LA may contribute to the mild age-related cognitive declines found within the healthy older adult population For example, it has been estimated that about 10% of people aged 50-75 without cognitive complaints show regions of WMH on MRI (O'Sullivan, 2008), and longitudinal analysis of nondemented older adults in the Baltimore Longitudinal Study of Aging revealed widespread white matter changes, with an average of 3 1 cm^3 of white matter lost annually (Resnick et al , 2003)

Numerous studies have tied the presence of WMH to cognitive decline A recent meta-analysis (Gunning-Dixon & Raz, 2000) found that increased WMH were associated with reductions in performances on tasks of processing speed, memory, executive functions, and indices of global functioning within an elderly population without cognitive complaints No relationship was found between WMH and measures of intelligence or fine motor skills Across multiple studies, the strongest relationships between WMH and cognition are typically found on tasks requiring speed and executive functions Executive functions are defined as higher-level cognitive skills such as

planning, problem solving, inhibition, working memory, and set-shifting These skills are typically localized to the frontal lobe, supported by studies of patients who have sustained injuries to this region and experience decline in these aspects of cognition (Badre, Hoffman, Cooney, & D'Esposito, 2009, Muller & Knight, 2006, Picton et al , 2007)

Within the healthy elderly population, patterns of executive dysfunction begin to emerge with increased age A population-based epidemiological study among individuals over the age of 60 found that 1 in 3 people had at least mild impairments in executive functions, while 1 in 6 had moderate to severe deficits, with greater impairment associated with advancing age (Grigsby et al , 2002) Declines in executive functions were also found in a longitudinal study of WWII veteran twins over a 13-year follow-up period (Lessov-Schlaggar, Swan, Reed, Wolf, & Carmelli, 2007)

These reductions in executive functions with advancing age have led some to propose a frontal lobe hypothesis of aging This theory speculates that cognitive functions subsumed by the frontal cortex will be the first to decline with age, and the hallmark of this decline is the failure of these higher level skills This decline in executive functioning is often tied to changes in white matter integrity Age-related increases in WMH generally appear more robust in frontal regions compared to other areas (Brickman et al , 2006, Pfefferbaum, Adalsteinsson, & Sullivan, 2005, Salat et al , 2009) It has been proposed that age-related vulnerability in frontal areas may reflect the pattern of white matter development and follow the rule of "last in, first out" (Raz, 2000) In other words, the white matter tracts that are the last to myelinate are in turn the most vulnerable to age-related decline

The relationship between WMH and decreased cognitive function exists across the lifespan. In a sample of adults aged 34-88 years without a history of stroke or dementia, individuals with WMH volumes more than 1.5 standard deviations above the age-predicted mean performed worse on tasks of visuospatial memory and organization and visual scanning and motor speed (Au et al., 2006). Furthermore, studies restricted to the elderly population have demonstrated the relationship between increased WMH volumes and poorer performances on executive skills such as cognitive set-shifting, problem solving, inhibition, and phonemic fluency (Geerlings, Appelman, Vincken, Mali, & van der Graaf, 2009; Jokinen et al., 2005; Kramer, Reed, Mungas, Weiner, & Chui, 2002; Prins et al., 2005; Verdelho et al., 2007; Wright et al., 2008).

DTI studies have also added additional information about white matter integrity within both WMH and normal-appearing white matter. Microstructural alterations in white matter were correlated with declines in executive function, working memory, and speed in a study of healthy adults aged 50-90 (Charlton et al., 2006). Microstructural WM deterioration was associated with reduced performances on a composite index which included measures of working memory, inhibition, and phonemic fluency in adults over 61 years of age without dementia or serious heart disease (Ziegler et al., 2010). In a population-based study of individuals over the age of 60 without dementia, higher diffusivities within both WMH and normal-appearing white matter were related to worse performances on tasks of information processing speed and global cognition. In addition, diffusivity within WMH on MRI related to memory function, while in normal-appearing white matter it also related to executive functions. These relationships held regardless of the extent of white matter atrophy and white matter lesion volume, further lending

support to the importance of examining microstructural changes within "normal" white matter (Vernooij et al , 2009)

Cognitive Impairment and Cerebrovascular Disease

"Dementia" is a generic term characterizing declines in brain function resulting in impairments in completing activities of daily living and potentially accompanied by changes in personality and mood Although dementia is not a natural consequence of aging, its incidence and prevalence increase dramatically with age For example, the prevalence of dementia is 1-2% among those aged 65-74 but rises to over 30% for those 85 or older (Chapman, Williams, Strine, Anda, & Moore, 2006) Several different subtypes of dementia have been established based upon clinical presentation and neuropathology, and after Alzheimer's disease, vascular dementia is the next most common form of dementia in the United States (Onyike, 2006)

In the 1970s the term multi-infarct dementia was introduced (Hachinski, Lassen, & Marshall, 1974) and reflected the idea that the cumulative effect of multiple strokes was key to the development of dementia Within the last 20 years, the term multi-infarct dementia has been replaced by vascular dementia (VD) in order to account for cases with etiology due to a single stroke or progressive microcerebrovascular changes

VD is the most common form of dementia after Alzheimer's disease, accounting for approximately 18% of dementia cases (Plassman et al , 2007) VD is a heterogeneous condition, clinical presentation is determined by the precise location of infarcts Current DSM-IV criteria indicate that VD is diagnosed in the context of cognitive and functional decline in close temporal association with a stroke or series of strokes However,

approximately 40% of patients with VD do not have specific evidence of a stroke (Bowler, 2002) Researchers have argued argued that patients with VD can be separated into two groups one group with "typical" VD with an acute onset characterized by multi-infarct or intracranial hemorrhagic presentation, and a second group with VD caused by subcortical small-vessel disease with an insidious onset linked to gradually progressive microvascular changes (Meyer, Xu, Thornby, Chowdhury, & Quach, 2002)

Increasingly, researchers and clinicians have recognized that vascular disease can be associated with more insidious and milder forms of cognitive impairment than that required for a diagnosis of dementia, and the term vascular cognitive impairment (VCI) was developed in order to provide a diagnostic label for patients with these milder impairments Similarly to the conceptualization of mild cognitive impairment (MCI) as a potential precursor to Alzheimer's disease, mild VCI is thought to represent the earliest stages of cognitive decline and may represent a potential window of intervention prior to the onset of vascular dementia However, there are currently no universally accepted formal criteria for this disorder and criteria for VCI are quite broad In general, although the cognitive changes associated with VCI have been less well studied, they are generally conceptualized as similar to but less severe than those associated with VD VCI is typically associated with declines in executive functions, visuospatial skills, and information processing speed (Garrett et al , 2004, Sachdev et al , 2004)

Both VD and VCI can be viewed as the end-result of cerebrovascular and cardiovascular disease (CVD) CVD is quite prevalent among the U S population, with over 80 million American adults (1 in 3) having one or more types of CVD Of these, over 38 million are estimated to be over 60 years of age (Rosamond et al , 2008) Age is

one of the most significant predictors of CVD, so significant increases in the prevalence of CVD are expected given the United States' aging population Physiological changes that occur with increasing age, such as decreased elasticity of blood vessel walls, make older individuals more susceptible to CVD and lead to higher prevalence rates among the geriatric population For example, more than half of those aged 60-69 and three-quarters of those over 70 years of age have hypertension (Kearney et al , 2005) Other risk factors for CVD include physical inactivity, diabetes, and smoking In addition, some forms of CVD (e g , hypertension, hypercholesterolemia, and coronary artery disease) are themselves risk factors for more serious cardiovascular and cerebrovascular events such as myocardial infarction and stroke

Unfortunately, most research has focused on cognitive deficits that emerge following stroke, and it is only recently that researchers have begun to examine the effects of vascular disease risk factors on cognitive functions in the absence of stroke (Roman, 2005) Numerous vascular disease risk factors have been linked to cognitive impairment, including hypertension, diabetes mellitus, atrial fibrillation, atherosclerosis, hypercholesterolemia, alcohol use, and smoking

Several studies have shown hypertension is a strong risk factor for cognitive decline (Birns & Kalra, 2009, Kilander, Nyman, Boberg, Hansson, & Lithell, 1998, Knecht et al , 2008) The risk for hypertension increases with increasing age, and despite pharmacological treatments, blood pressure control in older adults remains less than ideal With only 50% of elderly patients with hypertension being treated (Ong, Cheung, Man, Lau, & Lam, 2007), hypertension may represent a key point of intervention Hypertension is associated with decreases over time in cerebral blood flow

in prefrontal, anterior cingulate, and occipital areas (Beason-Held, Moghekar, Zonderman, Kraut, & Resnick, 2007) Furthermore, hypotension and resultant hypoperfusion states in later life may also be risks for cognitive decline (Zuccalà et al , 2001)

Mechanisms for Effects of CVD on Cognition

Several methods have been proposed to explain why vascular risk factors may impair cognitive performance in the absence of a stroke It has been hypothesized that these risk factors lead to subclincal vascular disease, and even individuals in relatively good health are believed to experience vascular changes in the brain before development of clinical cerebrovascular disease (Elias et al , 2004)

Conditions such plaque build-up lead to blood vessel narrowing or closure, and these occlusions can lead to subsequent infarction of surrounding cerebral tissue Chronic hypertension also leads to the thickening of blood vessel walls and reduced vessel diameter, potentially leading to the same outcomes In addition, heart failure and atrial fibrillation are more prevalent in hypertensive patients, and the resultant thrombotic material can become unstable, break down into circulating microemboli, and lodge in and occlude cerebral arteries, also leading to infarction

The aging of the vasculature and subsequent changes in mechanical and structural properties of cell walls is thought to contribute to cerebrovascular changes and subsequent cerebral damage The loss of arterial elasticity and reduced arterial compliance is likely to lead to a decline in the autoregulatory abilities of arteries which typically maintain cerebral perfusion at a constant level despite changes in blood pressure

(Jani & Rajkumar, 2006) The loss of this ability may make the brain more vulnerable to ischemic insults when blood pressure dips below some critical threshold, leading to hypoperfusion Evidence suggests that hypoperfusion leads to the activation of amyloidogenesis as well as neuronal dysfunction and death, which may ultimately lead to the presentation of diseases such as Alzheimer's disease (Onyike, 2006)

A common pathway for several vascular risk factors has been described as their impact upon the presence of white matter disease, grey matter is relatively unaffected by the presence of hypertension The integrity of white matter tracts depends on intact vasculature to provide a continuous supply of oxygen and nutrients to myelinated fibers throughout the brain The vessels feeding the white matter are typically very small, measuring between 20 and 50 mm in length with an average diameter of 100 to 200 μm (Moody, Bell, & Challa, 1990) The association between white matter lesions and vascular risk factors may be mediated through several different pathways, but other than age, hypertension is consistently reported as one of the central risk factors for the development of white matter lesions (de Leeuw et al , 2002) Hypertension places additional strain on the already vulnerable aging vascular system, increasing the risk of hemorrhage In addition, hypertension may also lead to alterations in the blood-brain barrier which may cause white matter lesions via cerebral edema, activation of astrocytes, or destructive enzymes and other matter which pass through damaged vessel walls (Girouard & Iadecola, 2006) WML may additionally be caused by mechanisms such as arteriosclerosis directly occluding small arteries nourishing the white matter as well as subclinical ischemia in the form of repeated transient events characterized by moderate drops in blood flow (Pantoni & Garcia, 1997)

Utility of Examining Vascular Risk Factors

The early identification of cognitive impairment may have several important benefits First, by identifying patients at risk for VCI or in the early stages of this disease, primary prevention efforts, such as better medical management of vascular risk factors, may be started As conditions such as hypertension, diabetes, and hypercholesterolemia are treatable, it may be possible to postpone or even prevent more severe cognitive decline in the future In addition, existing pharmacological treatments for cognitive impairment, such as cholinesterase inhibitors which have been shown to effectively treat VCI (Erkinjuntti, Roman, & Gauthier, 2004, Erkinjuntti, Roman, Gauthier, Feldman, & Rockwood, 2004), as well as non-pharmacological interventions (e g , cognitive remediation) can be started in order to maximize the length of time patients have relatively good cognitive function

Limitations of Previous Studies

Many studies attempting to examine relationships between vascular risk factors and cognitive decline have utilized cross-sectional rather than longitudinal designs While useful for examining correlations between these variables, causal links between vascular risk factors and cognitive performance cannot be drawn In addition, several studies are limited by their failure to control for potentially confounding factors such as education in their analyses Furthermore, few connections have been made between the medical literature, which focuses on biological factors potentially related to cognitive aging, and the psychological literature which has examined the role of psychosocial and behavioral factors These factors do not exist in isolation but instead interact in a

complex manner, emphasizing the need for studies which comprehensively examine their impact on cognitive functioning

Finally, a substantial number of investigations have not utilized comprehensive measures of cognitive functioning, instead often relying on screening tests that are limited in their ability to detect fine changes in specific cognitive functions and lack the sensitivity and specificity of a comprehensive neuropsychological evaluation Even in studies utilizing more comprehensive measures, many fail to thoroughly investigate cognitive functions sensitive to the presence of vascular disease such as processing speed and executive functions

Purpose

This study aims to explore longitudinal relationships between frontal white matter integrity, hippocampal grey matter volume, blood pressure and cognition within a healthy elderly population Since this is a largely healthy group without neurological disease but with cardiovascular risk factors, it was hypothesized there would be a small yet detectable deterioration in specific cognitive functions over a two-year period Tests of executive functioning were predicted to decline while memory skills would remain largely intact

Based on prior research suggesting a relationship between the integrity of frontal lobe anatomy and executive functions, it was hypothesized that there would be a relationship between increases in frontal WMH and declines in executive functions, with no relationship between frontal WMH and memory Conversely, declines in

hippocampal volume were hypothesized to predict declines in memory functions but not changes in executive functions.

Finally, the role of changes in blood pressure on cognition was examined. Blood pressure was hypothesized to predict changes in cognitive functioning, with WMH changes mediating this relationship. Blood pressure was not expected to impact hippocampal volume as grey matter is much less dependent upon cerebrovascular integrity.

METHODS

Participants

Healthy older adult participants were part of the "Brain Changes and Risk Factors Causing Impaired Mobility" study, a longitudinal cohort study of community-dwelling older adults residing in the Farmington, CT area This parent study was designed to examine links between vascular risk factors, white matter signal abnormalities, mobility impairments, and cognitive sequelae of normal aging The parent study was approved by the University of Connecticut Health Center Institutional Review Board, and the present investigation was approved by the Institutional Review Boards of the University of Connecticut Health Center and Storrs Campus

To be eligible for enrollment in the parent study, volunteers could not meet any of the following exclusion criteria (a) history of systemic conditions or neurological diseases comprising mobility (e g , arthritis, peripheral vascular disease, Parkinson's disease), (b) sensory deficit (e g , vestibular impairment and corrected distance vision greater than 20/70), (c) medication impairing motor function, (d) unstable cardiovascular disease (e g , myocardial infarct within six months or unstable angina), (e) pulmonary disease requiring oxygen, (f) inability to walk 10 meters independently in 50 seconds or less, (g) lower extremity amputation, (h) weight greater than 250 pounds, (i) excessive alcohol intake, (j) expected lifespan of less than four years

The current study focused on data collected at the initial visit and two-year follow-up time points Of the 107 participants originally recruited in the protocol, 81 had valid MRI images and a full complement of cognitive data at both time points and were included in this sample Sample characteristics are reported in Table 1 Overall, the 81

participants were well-educated, non-Hispanic Caucasians They ranged in age from 75-89 (M = 81 71, SD = 4 00) and included 50 women (a significant difference in proportions X^2 (1) = 4 46, p = 05) However, there were no differences between men and women in age, education level, or verbal IQ

Procedures

Screening Measures and Physical Exam

After consent was obtained, participants were screened for dementia with the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) A score of at least 24 out of 30 at the initial visit was required for continued study participation Presence of depression was determined using the Center for Epidemiologic Studies Depression Scale (Radloff, 1977), all volunteers were enrolled regardless of depression status

A neurologist conducted a physical examination and medical history review at the University of Connecticut Health Center Clinical Trials Unit A primary goal of this visit was to collect information regarding participants' history of vascular risk factors, including hypertension, arrhythmia, hypercholesterolemia, congestive heart failure, coronary artery disease, transient ischemic attacks, stroke, and diabetes mellitus To qualify as having a history of these risk factors, participants must have been previously diagnosed by a physician In addition, various physiological measures were obtained to confirm diagnoses Participants were asked about their current and past alcohol use, smoking history, and current medications Participants also received a 24-hour blood

pressure monitor at this visit Average systolic blood pressure over 24-hours was used as the measure of participants' blood pressure for this study

Neuropsychological Evaluation

All participants underwent a brief semi-structured clinical interview and a one-hour neuropsychological test battery which occurred within one week of the physical examination The neuropsychological evaluation included the following measures Wechsler Test of Adult Reading (Psychological Corporation, 2001), Repeatable Battery for the Assessment of Neuropsychological Status (Randolph, 1998, Randolph, Tierney, Mohr, & Chase, 1998), Trail Making Test A & B (Lezak, Howieson, Loring, Hannay, & Fischer, 2004), Stroop Color and Word Test (Golden & Freshwater, 2002), and California Computerized Assessment Package (Miller, 2001)

The Wechsler Test of Adult Reading (WTAR, Psychological Corporation, 2001) was used as an estimate of participants' verbal IQ This test involves asking examinees to pronounce a list of 50 words with atypical grapheme to phoneme translations, which helps assess previous knowledge of the words rather than measuring their current ability to apply standard pronunciation rules

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Randolph, 1998) is a commonly used neuropsychological screening instrument This test is comprised of twelve subtests that are combined to form five Index Scores as well as a Total Scale Score In order to minimize practice effects while allowing retesting to examine changes over time, Form A was administered at the initial visit and Form B was administered at the two-year follow-up appointment A description

of the subtests utilized in the present investigation follows The RBANS list learning task involves the oral presentation of a list of 10 semantically unrelated words four times in succession (maximum score = 40) The list recall subtest involves the delayed free recall of this list (maximum score = 10) The story recall subtest requires the free recall of a previously heard story with 12 elements for a maximum score of 12

The Trail Making Test (TMT) involves two components Part A requires examinees to draw lines connecting consecutively numbered circles and is often considered to be a measure of visuomotor processing speed Part B requires examinees to alternate between numbers and letters in sequential order (e g , 1-A-2-B-3-C, etc) In addition to involving processing speed, Part B also adds executive function demands as participants must both switch between cognitive sets (numbers and letters) and hold information on-line in working memory The score for this measure is the completion time in seconds

The Stroop Color and Word Test (Golden & Freshwater, 2002) consists of three pages, each consisting of 100 items presented in five columns On the Word reading page, the words "RED," "GREEN," and "BLUE" are printed in black ink and distributed randomly, and participants are asked to read aloud down the columns as quickly as they can The Color page consists of 100 groups of "XXXX" printed in red, green, or blue ink, and examinees are asked to name the colors aloud as rapidly as they can On the Color-Word page, the words from the Word page are printed in the colors from the color page In all cases, the words and ink colors do not match (i e , there is no case in which the word "BLUE" is printed in blue ink) Examinees are asked to name the color of the ink words are printed in (e g , saying "blue" when they see the word "RED" printed in

blue ink) as quickly as they can. The raw score for each of the three parts of the Stroop Test is the number of correct responses provided in 45 seconds.

The California Computerized Assessment Package (CalCAP; Miller, 2001) is a computerized program that assesses reaction time. The Simple Reaction Time (SRT Base) subtest requires examinees to press a key as soon as they seen any number appear on the screen, providing a basal measure of reaction time. The Choice Reaction Time (CRT base) subtest involves pressing a key as soon as the examinees see a specific number, adding a simple element of memory to the task. For the Sequential Reaction Time One (Seq RT) subtest, examinees are asked to press a key only when they see two of the same number in sequence (e.g., if the number "4" is followed by a second "4"). This final task adds a more complex element of memory since participants must keep in mind the last number that was seen.

All neuropsychological testing was conducted at the Clinical Trials Unit or the Balance and Gait Enhancement Laboratory at the University of Connecticut Health Center, and tests were administered by graduate students enrolled in a clinical psychology doctoral program. Standard administration procedures were followed, and tests were scored according to the procedures outlined in their respective manuals.

Brain MR Imaging

Imaging was performed on a Siemens 3T Allegra Scanner located at the Olin Neuropsychiatry Research Center at the Institute of Living, Hartford, CT. Three brain MR series were acquired for this analysis: the T1-weighted magnetization prepared rapid gradient echo (MPRAGE), T2-weighted 3D fast spin echo (FSE), and T2-weighted fluid

attenuated inversion recovery (FLAIR) The main acquisition parameters are as follows MPRAGE 176 contiguous 1-mm-thick axial slices, TR/TE = 2500/2 74-3 19 ms, matrix size = 258x208, voxel size = 1x1x1 mm, FOV = 25 6x20 8 cm T2 176 contiguous 1 mm-thick sagittal slices, TR/TE = 2500/353-355 ms, matrix size = 256x220, voxel size = 1x1x1 mm, FOV = 25 6x22 cm FLAIR 128 contiguous 1 3 mm-thick sagittal slices, TR/TE = 6000-6800/353 ms, TI = 2200 ms, matrix size = 256x208, voxel size = 1x1x1 3 mm, FOV = 25 6x20 8 The variations in some parameters were due to the scanner system's update by the manufacturer The digital image data were transferred to the Brigham and Women's Hospital for further processing

T1-weighted Probabilistic Brain Atlas (ICBM)

A reference brain atlas (International Consortium on Brain Mapping, ICBM) was obtained from the Laboratory of NeuroImaging (LONI, UCLA) The ICBM provided probabilistic maps of brain white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) which were used for calibrating the segmentation method (as described below)

Brain Tissue Segmentation

Semi-automated segmentation of MPRAGE and FLAIR images from individual subjects classified the brain into WM, GM, CSF and T2 white matter hyperintensities (WMH) Two applications, 3D-Slicer (Pohl, Bouix, Kikinis, & Grimson, 2004) and Freesurfer (Fischl et al , 2002, Fischl, Sereno, & Dale, 1999), were used to automatically segment the images WMH volumes were normalized by the volume of the intracranial

cavity (ICC) and expressed as fractions in order to correct for differences in head size ICC maps were obtained by using in-house software that identified non-brain tissues (skull, skin) from the T2 image set of each subject

Regional WMH Burden

For regional analysis the ICBM DTI-81 WM parcellation atlas (WMPA) was used (Mori et al , 2008) WMPA combines DTI-based white matter and anatomical information to provide a functional map of approximately 32% of total brain WM WMPA was first co-aligned to the WMH segmentation map of each subject and then was used as a mask to measure WMH burden within selected regions of interest (ROIs) WMH burdens were calculated by dividing the regional WMH volume by the volume of the region, and expressed as fractions Frontal regions were manually outlined on the ICBM atlas brain to include frontal WM anterior to the precentral gyrus comprising association areas as well as parts of premotor areas and did not include the anterior cingulate cortex These maps were subsequently warped to align them to each individual brain and used as mask to determine the frontal regional WMH volumes These volumes were normalized and expressed as fraction of the subject ICC

Statistical Analyses

The overall plan of data analysis involved five steps, carried out first for memory indices and then repeated for measures of executive functioning The first step involved examining relationships between age and the memory measures collected two years apart The second step involved assessing relationships cross-sectionally among demographic

factors (i e , age and education), blood pressure, imaging variables, and performance on selected neuropsychological assessments by correlational and regression analyses This assessment was conducted for separate sets of data collected at the initial assessment and follow-up, respectively The third step involved longitudinal assessment of mean changes over time via paired *t*-test comparisons of data collected between the two time periods The fourth step involved a two stage assessment of the rate of change across the two assessment periods This analysis involved computation of standardized residual change scores for outcome data and then predicting these performance indices from predictor residual change scores This analysis addresses the possibility that the rate of change in various predictors (e g , white matter lesions) would predict the rate of decline in outcome variables The fifth and final step involved evaluating the extent to which imaging variables mediated relationships between blood pressure and changes in cognitive function These mediation analyses used standardized residual change scores

RESULTS

Table 2 shows baseline and follow-up data for neuropsychological testing and neuroimaging variables Scores on individual neuropsychological measures were highly correlated at both time points (r = 58 - 77, all p's < 001) Age correlated significantly and negatively with tests of memory and executive functioning, indicating that performance was lower as age increased Cognition in these participants remained relatively stable over 2 years, with a significant decline in performance occurring only on Trails B performance In contrast to their largely stable cognition, participants experienced a significant increase in frontal white matter hyperintensities as well as a significant decrease in the volume of their hippocampal grey matter

MEMORY

Cross-Sectional Relationships Among Memory, Blood Pressure, Neuroimaging Variables

A hierarchial multiple regression analysis was used to examine the utility of demographic, blood pressure, and MRI measures in predicting memory function at each time point (see Tables 3 and 4) In these analyses, age and education were always entered in the first block as these have repeatedly been shown to be strong predictors of cognitive function

When age and education alone were regressed on list learning, 17% of the variance was accounted for at baseline and 9% of the variance was accounted for at follow-up The inclusion of SBP did not reliably improve the proportion of explained variance at either time point However, addition of frontal WMH volume and

hippocampal GM volume significantly increased the proportion of explained variance to 23% and 31% at baseline and follow-up, respectively. At baseline, only age was a significant predictor, although there was a trend for hippocampal GM volume (p = .08) to serve as significant predictors. At follow-up, however, only hippocampal GM volume significantly predicted list learning and a trend for age and frontal WMH was observed (p = .09 and .08, respectively).

For delayed list recall, age and education accounted for 12% and 14% of the variance at baseline and follow-up, respectively. The addition of SBP in the next step did not reliably improve the proportion of explained variance at either time point. However, the addition of frontal WMH volume and hippocampal GM volume in the final step significantly improved prediction of list recall with 17% of the variance accounted for at baseline and 26% of the variance accounted for at follow-up. At baseline, only age was a significant predictor of list recall, but there was a trend for hippocampal GM volume to add significantly to the model (p = .06). At follow-up, both age and hippocampal GM volume were significant predictors of list recall.

For delayed story recall, age and education accounted for 12% and 19% of the variance at baseline and follow-up, respectively. The addition of SBP in the next step did not reliably improve the prediction of story recall. The addition of frontal WMH volume and hippocampal GM volume did not significantly improve model fit at baseline but did improve model fit at follow-up. Overall, the final model accounted for 15% and 29% of the variance at baseline and follow-up, respectively. At baseline, only age was a significant predictor of story recall, while at follow-up, education and hippocampal GM volume were significant predictors of story recall. Taken together, for all three measures

of memory, age was the most frequent predictor of memory function at baseline while hippocampal volume was the most frequent predictor at follow-up

Longitudinal Changes over Two Years

Mean changes over time for the group on memory measures was assessed via paired *t*-test comparisons of data collected between the two time periods None of these comparisons were significant, suggesting that as a group, these participants did not experience significant changes in mean memory scores over two years

While the comparison of raw test scores at the two time points provides some information regarding changes in cognition within the normal older adult population, of interest is how the rate of change in brain structures impacts the rate of change in cognition, and also how blood pressure plays a role as a risk factor for change To explore these relationships, the influence of baseline scores on follow-up scores was first examined utilizing regression analyses, with baseline scores used as predictors and scores at follow-up used as criterion variables As expected, significant correlations were found between measures at both time points, with higher scores at baseline associated with higher scores at follow-up

These regression analyses yielded difference scores for each participant that subtracted the predicted score from the actual outcome score These residual differences were normalized to adjust for differences in the scalar values of the various neuropsychological and MRI outcome measures Resultant residual difference scores could be either positive or negative in value A positive score indicated that a participant's follow-up score was better than what would be expected given that person's

baseline score (relatively less decline compared to the group was experienced), whereas a negative score indicated their performance at follow-up was poorer than would have been predicted (relatively greater decline compared to the group was experienced)

Relationships Among Rates of Brain Deterioration and Cognitive Impairment

A regression analysis was then used to examine the utility of relative rate of change in frontal WMH and hippocampal GM volumes in predicting relative rate of change in memory functions (Table 7) In these analyses, age at initial visit and education were always entered in the first step as these have repeatedly been shown to be strong predictors of cognitive function For list learning, when age and education alone were entered in the model, only 2% of the variance in rate of change in list learning was explained The addition of the rate of change in frontal WMH and hippocampal volumes in the second step significantly increased the proportion of explained variance to 17% However, the only significant predictor was rate of change in hippocampal volume, with individuals experiencing a relatively faster rate of hippocampal volume loss experiencing a relatively greater rate of decline in list learning

For list recall, when age and education alone entered the model, only 6% of the variance in rate of change in list recall was explained The addition of the rate of change in frontal WMH and hippocampal GM volumes in the second step did not significantly increase the proportion of explained variance, although there was a trend for the model to significantly explain the rate of change in list recall ($p = 09$) There was a trend for rate of change in hippocampal GM volume to serve as a significant predictor of rate of change in list recall performance ($p = 06$), with individuals experiencing a relatively faster rate

of hippocampal volume loss experiencing a relatively greater rate of decline in list recall performance

For story recall, age and education alone predicted 4% of the variance in rate of change in story recall performance The addition of rate of change in frontal WMH and hippocampal GM volume in the second step significantly improved the model, with 16% of the variance in rate of change in story recall performance explained The rate of change in hippocampal GM volume was the only significant predictor of rate of change in story recall, although there was a trend toward significance for education (p = 07), individuals with slower rates of hippocampal GM volume loss and greater education experienced a relatively slower rate of decline in story recall performance

Finally, these standardized residuals were utilized in a meditational procedure to examine how changes in frontal WMH and hippocampal GM volume mediate the relationship between blood pressure and change in cognitive function However, as expected, the relationship between change in BP and change in hippocampal volume was found to be non-significant, so only frontal white matter disease was tested as a potential mediator For all memory measures no mediation was present between BP, frontal WMH, and cognition

EXECUTIVE FUNCTIONS

Cross-Sectional Relationships Among Executive Function, Blood Pressure, and Neuroimaging Variables

Similarly to the procedure utilized for memory tests, a hierarchial multiple regression analysis was used to examine the utility of demographic, blood pressure, and

MRI measures in predicting memory function at each time point (see Tables 5 and 6) For Trails B, age and education accounted for 9% and 17% of the variance at baseline and follow-up, respectively The addition of SBP in the next step did not reliably improve the proportion of explained variance at either time point However, the addition of frontal WMH volume and hippocampal GM volume in the final step significantly improved the prediction of Trails B performance with 16% of the variance accounted for at baseline and 28% of the variance accounted for at follow-up Although none of the predictors were individually significant at baseline, age, education, frontal WMH volume, and hippocampal GM volume all emerged as significant predictors at follow-up

For SeqRT, age and education accounted for only 1% and 4% of the variance in performance at baseline and follow-up, respectively The addition of SBP in the next step did not reliably improve prediction of SeqRT at either time point Frontal WMH volume and hippocampal GM volume significantly improved the model when added to the final step, increasing explained variance to 10% and 15% at baseline and follow-up, respectively At baseline, only frontal WMH volume and age were significant predictors of SeqRT performance, while at follow-up only frontal WMH volume was significant

For Stroop CW, age and education alone accounted for 23% and 28% of the variance in performance at baseline and follow-up, respectively The addition of SBP in the second step did not reliably improve model fit at either time point When added to the final step, frontal WMH volume and hippocampal GM volume significantly improved model fit at both time points Overall, the final model explained 37% and 40% of the variance in Stroop CW performance at baseline and follow-up, respectively At baseline, age, education, and hippocampal GM volume were all significant predictors At follow-

up, age, frontal WMH volume, and hippocampal GM volume were significant predictors of Stroop CW performance.

Longitudinal Changes over Two Years

Mean changes over time for the group on tests of executive functioning were assessed via paired *t*-test comparisons of data collected between the two time periods. Trails B showed a significant decline over time [$t(79) = -2.428$, $p < .05$]; neither Stroop CW nor SeqRT comparisons were significant.

Similarly to the procedure utilized with memory measures, a regression analysis was conducted with cognitive scores at baseline used to predict cognitive scores at follow-up. These analyses yielded difference scores for each participant that subtracted the predicted score from the actual outcome score, and these differences were then normalized yielding a measure of relative rate of change. A positive score indicated a participant's performance at follow-up was better than what would be expected given their baseline performance (relatively less decline compared to the group was experienced) while a negative score indicated the reverse pattern.

Relationships among Rates of Brain Deterioration and Cognitive Impairment

A regression analysis was then used to examine the utility of relative rate of change in frontal WMH and hippocampal GM volumes in predicting relative rate of change in executive functions (Table 8). In these analyses, age at the initial visit and education were always entered in the first step as these have repeatedly been shown to be strong predictors of cognitive function. For Trails B, when age and education alone

entered the model, only 3% of the variance in rate of change in performance was explained. The addition of rate of change in frontal WMH volume and hippocampal GM volume in the second step significantly increased the proportion of variance explained to 12% , and there was a trend for the overall model to be significant (p = .06). Only the rate of change in hippocampal GM volume was a significant predictor of the rate of change in Trails B performance, with individuals experiencing a relatively greater rate of hippocampal volume loss experiencing a relatively greater rate of decline in Trails B performance.

For SeqRT, age and education alone explained only 3% of the variance in rate of change in performance on this measure. Although there was a trend for the addition of rate of change in frontal WMH and hippocampal GM volume in the second step to add significantly to the model, the overall model was not significant. No predictors were individually significant, although a trend toward significance for change in frontal WMH volume was observed, with individuals experiencing a relatively greater rate of frontal WMH increase experiencing a relatively greater rate of decline in SeqRT performance.

For Stroop CW, when age and education were entered into the first step of the model, 13% of the variance in the rate of change in performance on this measure was explained. There was a trend for the addition of rate of change in frontal WMH and hippocampal GM volume to add significantly to the model. Only age was a significant predictor of the rate of change in Stroop CW performance, although there was a trend toward significance observed for rate of change in hippocampal GM volume; older individuals and those with relatively greater hippocampal GM volume loss experienced a relatively greater rate of decline in Stroop CW performance.

Finally, these standardized residuals were utilized in a meditational procedure to examine how changes in frontal WMH and hippocampal GM volume mediate the relationship between blood pressure change and change in cognitive function However, as expected, the relationship between change in BP and change in hippocampal volume was found to be non-significant, so only frontal white matter disease was tested as a potential mediator. For all measures of executive functioning, no mediation was present between BP, frontal WMH, and cognition

DISCUSSION

This study focused on the relationships between frontal white matter integrity, hippocampal grey matter volume, blood pressure and cognition within a healthy elderly population The major findings are as follows (1) within this group of healthy elderly individuals, age and education were significant cross-sectional predictors of cognition, (2) a detectable group deterioration in specific cognitive functions over a two-year period was not observed, with the exception of declining performance on one measure of executive functioning, despite declines in hippocampal volume and increases in frontal white matter disease, (3) systolic blood pressure did not significantly predict cognitive status nor did it serve as a mediator between structural and cognitive change over two years, and (4) greater relative rates of physiologic deterioration (i e , increased frontal white matter disease and decreased hippocampal grey matter volume) were associated with greater relative rates of cognitive decline

The observed negative correlations between age and cognition are in line with what has been reported by many other researchers Increasing age is correlated with reduced learning and free recall of both verbal and visual information in many studies (Drobny et al , 2005, Jones et al , 2005, Ylikoski et al , 1998), and studies have also observed relationships between increased age and declining executive functions (Grigsby et al , 2002, Lessov-Schlaggar et al , 2007) Interestingly, cross-sectional analyses revealed that the proportion of variance in cognitive performance accounted for by age and education alone increased from baseline to follow-up As education remains constant

at both time points, this finding suggests the influence of age upon cognitive performance accelerates as people grow older

In line with expectations, memory was found to remain stable over two years while slight deteriorations in executive functions (i e , Trails B performance) were observed in this sample of healthy older adults This finding is in line with the frontal lobe hypothesis of aging which posits that cognitive functions subsumed by the frontal cortex will be the first to decline with age Raz (2000) proposed that age-related vulnerability in frontal areas may reflect the pattern of white matter development, with the white matter tracts that are the last to myelinate also the tracts that are the most vulnerable to age-related decline However, white matter disease was not found to be an especially strong predictor of cognitive change, suggesting that within this particular sample of older adults another physiological mechanism may also be playing a role

In this study's cross-sectional analyses, hippocampal volume was repeatedly associated with memory performance Given the well documented role of the hippocampus in supporting memory function (Bottino et al , 2002, Jack et al , 1997, Mungas et al , 2005), this finding is not surprising In addition, results from this study indicated hippocampal volume was also associated with some measures of executive function A growing literature points to the role of the hippocampus in modulating activity within the prefrontal cortex (Rieckmann et al , 2011, Takahashi et al , 2007, 2008) In a sample of healthy male young adults, dopamine D2 receptor binding in the hippocampus, but not the prefrontal cortex, was positively correlated with both memory and frontal lobe functions, suggesting dopaminergic modulation of connections between the hippocampus and prefrontal cortex (Takashi et al , 2007) Systemic administration of

dopamine D2 receptor agonists have been reported to improve some functions subserved by frontal regions (McDowell, Whyte, & D'Esposito, 1998), and administration of antagonists have impaired these functions (Mehta, Sahakian, McKenna, & Robbins, 1999), although the exact mechanisms of these effects remain unclear and warrant further exploration

A novel feature of this study was its analysis of rate of change In this sample of healthy older adults, greater relative rates of deterioration in frontal white matter and hippocampal grey matter volumes were strong predictors of relatively greater decline in memory and executive functioning above and beyond the effects of age and education In particular, cognitive function appears to be more affected by hippocampal volume loss than by increased frontal white matter disease in this sample This suggests that even within this population of individuals with greater cognitive reserve (represented by higher educational attainment), reserve cannot completely spare individuals from increased rates of cognitive decline if physiological deterioration is occurring at a more rapid pace Future studies should include a group of individuals with lower levels of cognitive reserve (i e , lower educational levels) to see whether this results in greater rates of cognitive decline with equivalent rates of physiological decline

The failure of this study to find an association between blood pressure and performance on neuropsychological tests was somewhat surprising given a number of previously published reports supporting this relationship For example, a study of 999 men in a Swedish population-based cohort study found elevated blood pressure was associated with cognitive impairment 20 years later, even after excluding men with a history of stroke (Kilander et al , 1998) The deleterious and cumulative effects of

hypertension occur over many years, but the present study simply used a single measurement of blood pressure A lifetime history of hypertension, rather than hypertension at the present time, may be a more useful variable to examine in the future

However, an alternative explanation for the observed lack of relationship between blood pressure and cognitive change should also be considered The participants in this study may have the pathology caused by elevated blood pressure, but that pathology may not yet have reached the level necessary for clinical expression of cognitive decline associated with vascular risk factors These threshold models suggest that functional deficits emerge only when brain reserve capacity is depleted past a critical level (Satz, 1993, Stern, 2009) Higher levels of intelligence, socioeconomic status, and years of education are thought to be good predictors of which individuals may be able to sustain greater levels of brain damage before demonstrating cognitive declines Therefore, the study's affluent, high average intelligence, and well-educated participants may have the cognitive reserve capacity to compensate for vascular disease pathology without showing declines on measures of cognition

Limitations

The neuropsychological measures used in this study may have limited the ability to detect a decline in cognitive function over time as certain cognitive functions (e g , visual memory, attention, visuospatial skills, and language were not examined) A more comprehensive battery may have been better able to detect the subtle changes that are likely to occur in a healthy sample of highly-functioning older adults, although the

selected measures improve upon past research in that they are more thorough and sensitive to the changes thought to be associated with aging and vascular disease.

In addition, participants in this study were racially homogeneous, well-educated, and affluent. Participants scored within the high average range on a measure of verbal IQ and were also highly educated; participants had an average of at three years of post-secondary education, suggesting that these individuals may not be representative of the elderly population as a whole. High IQ and high levels of education are associated with increased cognitive reserve that may serve to mask early signs of cognitive dysfunction (Scarmeas & Stern, 2003). In addition, higher levels of education and socioeconomic status play a role in the awareness of illness, treatment-seeking behavior, ability to pay for medications, and likelihood of engaging in preventative healthcare programs, and these factors likely combine to produce a healthier cohort of individuals than the larger community. Furthermore, older adults who volunteer for research projects and attend wellness programs in an academic medical center may represent a group of "super-normal" elderly.

Finally, this sample was racially homogeneous, with all subjects identifying as Caucasian. There are well-documented disparities in cardiovascular health among different racial and ethnic groups (Mensah, Mokdad, Ford, Greenlund, & Croft, 2005), suggesting that studying an all Caucasian sample considerably limits the generalizability of findings especially with respect to the null findings related to blood pressure. Overall, these limitations suggest the findings of this study may not generalize to other elderly populations with more diverse demographic characteristics. Yet despite the sample's homogeneity, especially with regard to health, relationships were found between

neuroimaging and cognitive variables, and with a more heterogeneous sample, even stronger relationships among the rate of change measures, as well as stronger moderating influences, are likely to be found

Despite these limitations, this study adds to a growing literature exploring factors associated with cognitive decline in the elderly Results of this study suggest that within the healthy elderly population, declines in hippocampal grey matter volume, and to a lesser extent increases in frontal white matter disease, are associated with greater relative rates of cognitive decline Furthermore, findings also suggest tracking the trajectories of structural change within the brains of elderly individuals over time can facilitate identification of those at risk for cognitive decline, which will become increasingly important as treatments to slow, or even prevent, cognitive deterioration are developed in the coming years Future research should aim not only to examine whether these relationships continue to hold over a longer follow-up period, but should also expand to examine the predictive utility of structural changes in other regions of the brain

Table 1: Sample demographic information by sex and total sample

	Men (n = 31)		Women (n = 50)		Total (n = 81)	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age (years)	81.71	(4.23)	81.71	(3.89)	81.71	(4.00)
Education (years)	15.55	(2.92)	14.72	(2.63)	15.04	(2.76)
Verbal IQ	111.71	(12.53)	112.58	(12.08)	112.25	(12.19)

Table 2 Baseline and Follow-up Clinical and Neuroimaging Data

	Baseline		Follow-up	
	Mean	*SD*	*Mean*	*SD*
Memory				
List Learning	23 65	5 27	23 84	5 47
List Recall	4 48	2 54	4 40	2 76
Story Recall	7 86	2 65	8 14	2 59
Executive Functions				
Stroop CW	27 07	9 14	26 24	9 37
Trails B (sec)	113 43	65 61	130 05	75 62*
Seq RT (msec)	605 75	97 82	602 58	118 43
Frontal WMH^{+}	0 20	0 24	0 32	0 33***
Hippocampal GM^{+}	0 44	0 10	0 34	0 07***
Systolic BP	129 44	11 85	129 85	13 13

Note: WMH = white matter hyperintensities, GM = grey matter, BP = blood pressure

$^{+}$percentage of intracranial cavity

*$p < 05$, **$p < 01$, ***$p < 001$

Table 3 Sequential Regression of Memory, Blood Pressure, and Neuroimaging Variables at Baseline

	(Step) Predictor	Beta[a]	R^2	R^2 change	F change	F model
List Learning	(1) Age	- 276*	17	17	$F(2,67) = 6\ 87^{**}$	$F(2,67) = 6\ 81^{**}$
	(1) Education	193				
	(2) SBP	- 092	18	01	$F(1,66) = 56$	$F(3,66) = 4\ 69^{**}$
	(3) Frontal WMH[+]	- 102	23	05	$F(2,64) = 2\ 23$	$F(5,64) = 3\ 82^{**}$
	(3) HGM[+]	204				
List Recall	(1) Age	- 251*	12	12	$F(2,67) = 4\ 33^{*}$	$F(2,67) = 4\ 33^{*}$
	(1) Education	092				
	(2) SBP	- 019	12	00	$F(1,66) = 02$	$F(3,66) = 2\ 85^{*}$
	(3) Frontal WMH	- 094	17	06	$F(2,64) = 2\ 30$	$F(5,64) = 2\ 70^{*}$
	(3) HGM	222				
Story Recall	(1) Age	- 270*	12	12	$F(2,67) = 4\ 58^{*}$	$F(2,67) = 4\ 58^{*}$
	(1) Education	118				
	(2) SBP	- 123	13	01	$F(1,66) = 1\ 05$	$F(3,66) = 3\ 41^{*}$
	(3) Frontal WMH	- 001	15	02	$F(2,64) = 70$	$F(5,64) = 2\ 30$
	(3) HGM	140				

Note: SBP = systolic blood pressure, WMH = white matter hyperintensities, HGM = hippocampal grey matter

[a] refers to beta weight at final step in each analysis

[+] expressed as a percentage of intracranial cavity

$^{*}p < 05$, $^{**}p < 01$, $^{***}p < 001$

Table 4 Sequential Regression of Memory, Blood Pressure, and Neuroimaging Variables at Follow-Up

	(Step) Predictor	Beta[a]	R^2	R^2 change	F change	F model
List Learning	(1) Age	- 186	09	09	$F(2,70) = 3\ 46$*	$F(2,70) = 3\ 46$*
	(1) Education	043				
	(2) SBP	- 111	09	00	$F\ (1,69) =$ 11	$F(3,69) = 2\ 31$
	(3) Frontal WMH[+]	- 192	31	22	$F\ (2,67) = 10\ 66$***	$F(5,67) = 6\ 04$***
	(3) HGM[+]	429***				
List Recall	(1) Age	- 281*	14	14	$F\ (2,70) = 5\ 67$**	$F(2,70) = 5\ 67$**
	(1) Education	024				
	(2) SBP	003	14	00	$F(1,69) =$ 17	$F(3,69) = 3\ 79$*
	(3) Frontal WMH[+]	- 128	26	12	$F(2,67) = 5\ 33$***	$F(5,67) = 4\ 70$***
	(3) HGM[+]	321**				
Story Recall	(1) Age	- 161	19	19	$F(2,70) = 8\ 18$***	$F(2,70) = 8\ 18$***
	(1) Education	315**				
	(2) SBP	- 101	20	01	$F(1,69) =$ 71	$F(3,69) = 5\ 67$**
	(3) Frontal WMH[+]	058	29	10	$F(2,67) = 4\ 40$*	$F(5,67) = 5\ 50$***
	(3) HGM[+]	321**				

Note: SBP = systolic blood pressure, WMH = white matter hyperintensities, HGM = hippocampal grey matter

[a] refers to beta weight at final step in each analysis

[+] expressed as a percentage of intracranial cavity

*$p <$ 05, **$p <$ 01, ***$p <$ 001

Table 5 Sequential Regression of Executive Function, Blood Pressure, and Neuroimaging Variables at Baseline

	(Step) Predictor	Beta[a]	R^2	R^2 change	F change	F model
Trails B	(1) Age	164	09	09	$F(2,67) = 3\ 46$*	$F(2,67) = 3\ 46$*
	(1) Education	- 158				
	(2) SBP	- 062	010	00	$F(1,66) = 58$	$F(3,66) = 2\ 39$
	(3) Frontal WMH[+]	173	16	07	$F(2,64) = 2\ 52$	$F(5,64) = 2\ 51$*
	(3) HGM[+]	- 178				
Seq RT	(1) Age	255	04	04	$F(2,60) = 1\ 22$	$F(2,60) = 1\ 22$
	(1) Education	101				
	(2) SBP	- 200	08	04	$F(1,59) = 2\ 65$	$F(3,59) = 1\ 72$
	(3) Frontal WMH[+]	307	10	09	$F(2,57) = 3\ 15$*	$F(5,57) = 2\ 37$*
	(3) HGM[+]	047				
Stroop CW	(1) Age	- 244*	23	23	$F(2,67) = 9\ 76$***	$F(2,67) = 9\ 76$***
	(1) Education	295**				
	(2) SBP	- 172	25	03	$F(1,66) = 2\ 25$	$F(3,66) = 7\ 38$***
	(3) Frontal WMH[+]	- 113	37	12	$F(2,64) = 6\ 14$**	$F(5,64) = 7\ 58$***
	(3) HGM[+]	326**				

Note: Seq RT = sequential reaction time, WMH = white matter hyperintensities, HGM = hippocampal grey matter

[a] refers to beta weight at final step in each analysis

[+] expressed as a percentage of intracranial cavity

*$p < 05$, **$p < 01$, ***$p < 001$

Table 6 Sequential Regression of Executive Function, Blood Pressure, and Neuroimaging Variables at Follow-Up

	(Step) Predictor	Beta[a]	R^2	R^2 change	F change	F model
Trails B	(1) Age	216*	17	17	$F(2,69) = 6\ 92^{**}$	$F(2,69) = 6\ 92^{**}$
	(1) Education	- 216*				
	(2) SBP	000	18	01	$F(1,68) = 88$	$F(3,68) = 4\ 89^{**}$
	(3) Frontal WMH[+]	325**	28	15	$F(2,66) = 7\ 43^{***}$	$F(5,66) = 6\ 47^{***}$
	(3) HGM[+]	- 216*				
Seq RT	(1) Age	071	01	01	$F(2,66) = 36$	$F(2,66) = 36$
	(1) Education	054				
	(2) SBP	- 103	01	00	$F(1,65) = 04$	$F(3,65) = 25$
	(3) Frontal WMH[+]	366**	15	14	$F(2,63) = 5\ 03^{**}$	$F(5,63) = 2\ 19$
	(3) HGM[+]	- 110				
Stroop CW	(1) Age	- 423***	28	28	$F(2,70) = 13\ 50^{***}$	$F(2,70) = 13\ 50^{***}$
	(1) Education	074				
	(2) SBP	- 030	29	01	$F(1,69) = 10$	$F(3,69) = 9\ 33^{***}$
	(3) Frontal WMH[+]	- 214*	40	11	$F(2,67) = 5\ 86^{**}$	$F(5,67) = 8\ 73^{***}$
	(3) HGM[+]	246*				

Note: Seq RT = sequential reaction time, WMH = white matter hyperintensities, HGM = hippocampal grey matter

[a] refers to beta weight at final step in each analysis

[+] expressed as a percentage of intracranial cavity

*$p < 05$, **$p < 01$, ***$p < 001$

Table 7 Sequential Regression of Standardized Memory and Neuroimaging Residual Difference Scores

	(Step) Predictor	Beta[a]	R^2	R^2 change	F change	F model
List Learning	(1) Age	- 085	02	02	$F(2,72) = 0\ 85$	$F(2,72) = 0\ 85$
	(1) Education	046				
	(2) Frontal WMH[+]	- 170	17	15	$F(2,70) = 6\ 28$**	$F(4,70) = 3\ 63$**
	(2) HGM[+]	429***				
List Recall	(1) Age	- 178	06	06	$F(2,72) = 2\ 08$	$F(2,72) = 2\ 08$
	(1) Education	068				
	(2) Frontal WMH[+]	- 058	11	05	$F(2,70) = 2\ 01$	$F(4,70) = 2\ 07$
	(2) HGM[+]	221				
Story Recall	(1) Age	- 010	04	04	$F(2,72) = 1\ 68$	$F(2,72) = 1\ 68$
	(1) Education	207				
	(2) Frontal WMH[+]	124	16	11	$F(2,70) = 4\ 59$*	$F(4,70) = 3\ 22$*
	(2) HGM[+]	317**				

Note: WMH = white matter hyperintensities, HGM = hippocampal grey matter

[a] refers to beta weight at final step in each analysis

[+] expressed as a percentage of intracranial cavity

*$p < 05$, **$p < 01$, ***$p < 001$

Table 8 Sequential Regression of Standardized Executive Function and Neuroimaging Residual Difference Scores

	(Step) Predictor	Beta[a]	R^2	R^2 change	F change	F model
Trails B	(1) Age	132	03	03	$F(2,71) = 1\ 01$	$F(2,71) = 1\ 01$
	(1) Education	007				
	(2) Frontal WMH[+]	141	12	10	$F(2,69) = 3\ 76^*$	$F(4,69) = 2\ 43$
	(2) HGM[+]	- 273*				
Seq RT	(1) Age	- 098	03	03	$F(2,61) = 1\ 03$	$F(2,61) = 1\ 03$
	(1) Education	167				
	(2) Frontal WMH[+]	205	10	07	$F(2,59) = 2\ 26$	$F(4,59) = 1\ 66$
	(2) HGM[+]	- 168				
Stroop CW	(1) Age	- 326**	13	13	$F(2,72) = 5\ 42^{**}$	$F(2,72) = 5\ 42^{**}$
	(1) Education	- 151				
	(2) Frontal WMH[+]	- 124	18	05	$F(2,70) = 2\ 30$	$F(4,70) = 3\ 95^{**}$
	(2) HGM[+]	195				

Note· Seq RT = sequential reaction time, WMH = white matter hyperintensities, HGM = hippocampal grey matter

[a] refers to beta weight at final step in each analysis

[+] expressed as a percentage of intracranial cavity

$^*p < 05$, $^{**}p < 01$, $^{***}p < 001$

REFERENCES

Au, R., Massaro, J. M., Wolf, P. A., Young, M. E., Beiser, A., Seshadri, S., D'Agostino, R. B., et al. (2006). Association of White Matter Hyperintensity Volume with Decreased Cognitive Functioning: The Framingham Heart Study. *Archives of Neurology, 63*(2), 246-250. doi:10.1001/archneur.63.2.246

Babikian, V., & Ropper, A. H. (1987). Binswanger's disease: a review. *Stroke, 18*, 2-12.

Badre, D., Hoffman, J., Cooney, J. W., & D'Esposito, M. (2009). Hierarchical cognitive control deficits following damage to the human frontal lobe. *Nat Neurosci, 12*(4), 515-522. doi:10.1038/nn.2277

Bartzokis, G., Beckson, M., Nuechterlein, K. H., Edwards, N., & Mintz, J. (2001). Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study. *Archives of General Psychiatry, 58*(5), 461-465.

Beason-Held, L. L., Moghekar, A., Zonderman, A. B., Kraut, M. A., & Resnick, S. M. (2007). Longitudinal Changes in Cerebral Blood Flow in the Older Hypertensive Brain. *Stroke, 38*(6), 1766-1773. doi:10.1161/STROKEAHA.106.477109

Birns, J., & Kalra, L. (2009). Cognitive function and hypertension. *Journal of Human Hypertension, 23*(2), 86-96.

Bottino, C. M. C., Castro, C. C., Gomes, R. L. E., Buchpiguel, C. A., Marchetti, R. L., & Neto, M. R. L. (2002). Volumetric MRI measurements can differentiate Alzheimer's disease, mild cognitive impairment, and normal aging. *International Psychogeriatrics, 14*(1), 59-72.

Bowler, J. (2002). The concept of vascular cognitive impairment. *Journal of the Neurological Sciences, 203*, 11-15.

Brickman, A M , Zimmerman, M E , Paul, R H , Grieve, S M , Tate, D F , Cohen, R A , Williams, L M , et al (2006) Regional white matter and neuropsychological functioning across the adult lifespan *Biological Psychiatry*, *60*(5), 444-453

Brody, H (1955) Organization of the cerebral cortex III A study of aging in the human cerebral cortex *Journal of Comparative Neurology*, *102*(2), 511-556

Chapman, D P , Marshall Williams, S , Strine, T W , Anda, R F , & Moore, M J (2006) Dementia and Its Implications for Public Health *Preventing Chronic Disease*, *3*(2), A34

Charlton, R A , Barrick, T R , McIntyre, D J , Shen, Y , O'Sullivan, M , Howe, F A , Clark, C A , et al (2006) White matter damage on diffusion tensor imaging correlates with age-related cognitive decline *Neurology*, *66*(2), 217-222 doi 10 1212/01 wnl 0000194256 15247 83

Chen, K H M , Chuah, L Y M , Sim, S K Y , & Chee, M W L (2010) Hippocampal region-specific contributions to memory performance in normal elderly *Brain and Cognition*, *72*(3), 400-407 doi 10 1016/j bandc 2009 11 007

Davatzikos, C , & Resnick, S M (2002) Degenerative Age Changes in White Matter Connectivity Visualized In Vivo using Magnetic Resonance Imaging *Cerebral Cortex*, *12*(7), 767 -771 doi 10 1093/cercor/12 7 767

Drobny, J V , Anstey, K J , & Andrews, S (2005) Visual memory testing in older adults with age-related visual decline a measure of memory performance or visual functioning? *Journal of Clinical and Experimental Neuropsychology*, *27*(4), 425-435

Elias, M F , Sullivan, L M , D'Agostino, R B , Elias, P K , Beiser, A , Au, R , Seshadri,

S , et al (2004) Framingham Stroke Risk Profile and Lowered Cognitive Performance *Stroke, 35*(2), 404-409 doi 10 1161/01 STR 0000103141 82869 77

Erkinjuntti, T , Roman, G , & Gauthier, S (2004) Treatment of vascular dementia evidence from clinical trials with cholinesterase inhibitors *Journal of the Neurological Sciences, 226*(1-2), 63-66 doi 10 1016/j jns 2004 09 018

Erkinjuntti, T , Roman, G , Gauthier, S , Feldman, H., & Rockwood, K (2004) Emerging Therapies for Vascular Dementia and Vascular Cognitive Impairment *Stroke, 35*(4), 1010-1017 doi 10 1161/01 STR 0000120731 88236 33

Fischl, B , Salat, D , Busa, E , Albert, M , Dieterich, M , Haselgrove, C , van der Kouwe, A , et al (2002) Whole brain segmentation automated labeling of neuroanatomical structure in the human brain *Neuron, 33*(3), 341-355

Fischl, B , Sereno, M , & Dale, A (1999) Cortical surface-based analysis II Inflation, flattening, and a surface-based coordinate system *Neuroimage, 9*(2), 195-207

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

Fotenos, A F , Snyder, A Z , Girton, L E , Morris, J C , & Buckner, R L (2005) Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD *Neurology, 64*(6), 1032-1039
doi 10 1212/01 WNL 0000154530 72969 11

Garrett, K D , Browndyke, J N , Whelihan, W , Paul, R H , DiCarlo, M , Moser, D J , Cohen, R A , et al (2004) The neuropsychological profile of vascular cognitive impairment--no dementia comparisons to patients at risk for cerebrovascular

disease and vascular dementia *Archives of Clinical Neuropsychology, 19*(6), 745-757 doi 16/j acn 2003 09 008

Ge, Y , Grossman, R I , Babb, J S , Rabin, M L , Mannon, L J , & Kolson, D L (2002) Age-Related Total Gray Matter and White Matter Changes in Normal Adult Brain Part I Volumetric MR Imaging Analysis *AJNR Am J Neuroradiol, 23*(8), 1327-1333

Geerlings, M I , Appelman, A P A , Vincken, K L , Mali, W P T M , & van der Graaf, Y (2009) Association of white matter lesions and lacunar infarcts with executive functioning the SMART-MR study *American Journal of Epidemiology, 170*(9), 1147-1155 doi 10 1093/aje/kwp256

Girouard, H , & Iadecola, C (2006) Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer disease *Journal of Applied Physiology, 100*(1), 328-335 doi 10 1152/japplphysiol 00966 2005

Golden, C , & Freshwater, S (2002) *The Stroop Color and Word Test: A manual for clinical and experimental uses* Wooddale, IL Stoelting

Grigsby, J , Kaye, K , Shetterly, S M , Baxter, J , Morgenstern, N E , & Hamman, R F (2002) Prevalence of Disorders of Executive Cognitive Functioning among the Elderly Findings from the San Luis Valley Health and Aging Study *Neuroepidemiology, 21*(5), 213-220 doi 10 1159/000065638

Gunning-Dixon, F M , & Raz, N (2000) The cognitive correlates of white matter abnormalities in normal aging a quantitative review *Neuropsychology, 14*(2), 224-232

Hachinski, V , Lassen, N , & Marshall, J (1974) Multi-infarct dementia a cause of

mental deterioration in the elderly *The Lancet, 304*(7874), 207-209 doi 10 1016/S0140-6736(74)91496-2

Hachinski, V , Potter, P , & Merskey, H (1987) Leuko-araiosis *Archives of Neurology, 44*(1), 21-23

Hackert, V H , den Heijer, T , Oudkerk, M , Koudstaal, P J , Hofman, A , & Breteler, M M B (2002) Hippocampal head size associated with verbal memory performance in nondemented elderly *NeuroImage, 17*(3), 1365-1372

Hinman, J D , & Abraham, C R (2007) What's Behind the Decline? The Role of White Matter in Brain Aging *Neurochemical Research, 32*(12), 2023-2031 doi 10 1007/s11064-007-9341-x

Jack, C R , Petersen, R C , Xu, Y C , Waring, S C , O'Brien, P C , Tangalos, E G , Smith, G E , et al (1997) Medial Temporal Atrophy on MRI in Normal Aging and Very Mild Alzheimer's Disease *Neurology, 49*(3), 786-794

Jani, B , & Rajkumar, C (2006) Ageing and vascular ageing *Postgraduate Medical Journal, 82*(968), 357 -362 doi 10 1136/pgmj 2005 036053

Jokinen, H , Kalska, H , Mantyla, R , Ylikoski, R , Hietanen, M , Pohjasvaara, T , Kaste, M , et al (2005) White matter hyperintensities as a predictor of neuropsychological deficits post-stroke *Journal of Neurology, Neurosurgery, and Psychiatry, 76*(9), 1229-1233 doi 10 1136/jnnp 2004 055657

Jones, R N , Rosenberg, A L , Morris, J N , Allaire, J C , McCoy, K J M , Marsiske, M , Kleinman, K P , et al (2005) A growth curve model of learning acquisition among cognitively normal older adults *Experimental Aging Research, 31*(3), 291-312 doi 10 1080/03610730590948195

Kearney, P. M., Whelton, M., Reynolds, K., Muntner, P., Whelton, P. K., & He, J. (2005). Global burden of hypertension: analysis of worldwide data. *Lancet, 365*(9455), 217-223. doi:10.1016/S0140-6736(05)17741-1

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.

Knecht, S., Wersching, H., Lohmann, H., Bruchmann, M., Duning, T., Dziewas, R., Berger, K., et al. (2008). High-Normal Blood Pressure Is Associated With Poor Cognitive Performance. *Hypertension, 51*(3), 663-668. doi:10.1161/HYPERTENSIONAHA.107.105577

Kramer, J., Reed, B., Mungas, D., Weiner, M., & Chui, H. (2002). Executive dysfunction in subcortical ischaemic vascular disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 72*(2), 217-220.

Leal, J., Luengo-Fernández, R., Gray, A., Petersen, S., & Rayner, M. (2006). Economic burden of cardiovascular diseases in the enlarged European Union. *European Heart Journal, 27*(13), 1610-1619. doi:10.1093/eurheartj/ehi733

de Leeuw, F., de Groot, J. C., Oudkerk, M., Witteman, J. C. M., Hofman, A., van Gijn, J., & Breteler, M. M. B. (2002). Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain, 125*(4), 765 -772. doi:10.1093/brain/awf077

Lessov-Schlaggar, C. N., Swan, G. E., Reed, T., Wolf, P. A., & Carmelli, D. (2007). Longitudinal genetic analysis of executive function in elderly men. *Neurobiology of Aging, 28*(11), 1759-1768. doi:10.1016/j.neurobiolaging.2006.07.018

Lezak, M. D., Howieson, D. B., Loring, D. W., Hannay, H. J., & Fischer, J. S. (2004).

Neuropsychological Assessment. New York: Oxford.

McCarty, S. M., Siegler, I. C., & Logue, P. E. (1982). Cross-sectional and longitudinal patterns of three Wechsler Memory Scale Subtests. *Journal of Gerontology*, *37*(2), 169-175.

McDowell, S., Whyte, J., & D'Esposito, M. (1998). Differential effect of a dopaminergic agonist on prefrontal function in traumatic brain injury patients. *Brain*, *121*(6), 1155-1164.

Mehta, M. A., Sahakian, B. J., McKenna, P. J., & Robbins, T. W. (1999). Systemic sulpiride in young adult volunteers simulates the profile of cognitive deficits in Parkinson's disease. *Psychopharmacology*, *146*(2), 162-174. doi:10.1007/s002130051102

Mensah, G. A., Mokdad, A. H., Ford, E. S., Greenlund, K. J., & Croft, J. B. (2005). State of Disparities in Cardiovascular Health in the United States. *Circulation*, *111*(10), 1233-1241. doi:10.1161/01.CIR.0000158136.76824.04

Meyer, J. S., Xu, G., Thornby, J., Chowdhury, M. H., & Quach, M. (2002). Is Mild Cognitive Impairment Prodromal for Vascular Dementia Like Alzheimer's Disease? *Stroke*, *33*(8), 1981-1985. doi:10.1161/01.STR.0000024432.34557.10

Miller, E. (2001). *California Computerized Assessment Package*. Los Angeles, CA: Norland Software.

Moody, D., Bell, M., & Challa, V. (1990). Features of the cerebral vascular pattern that predict vulnerability to perfusion or oxygenation deficiency: an anatomic study. *American Journal of Neuroradiology*, *11*(3), 431-439.

Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K., Hua, K., et al. (2008).

Stereotaxic White Matter Atlas Based on Diffusion Tensor Imaging in an ICBM Template *NeuroImage*, *40*(2), 570-582 doi 10 1016/j neuroimage 2007 12 035

Muller, N G , & Knight, R T (2006) The functional neuroanatomy of working memory contributions of human brain lesion studies *Neuroscience*, *139*(1), 51-58

Mungas, D , Harvey, D , Reed, B R , Jagust, W J , DeCarli, C , Beckett, L , Mack, W J , et al (2005) Longitudinal volumetric MRI change and rate of cognitive decline *Neurology*, *65*(4), 565 -571 doi 10 1212/01 wnl 0000172913 88973 0d

O'Sullivan, M (2008) Leukoaraiosis *Practical Neurology*, *8*(1), 26 -38 doi 10 1136/jnnp 2007 139428

Ong, K L , Cheung, B M , Man, Y B , Lau, C P , & Lam, K S (2007) Prevalence, Awareness, Treatment, and Control of Hypertension Among United States Adults 1999-2004 *Hypertension*, *49*(1), 69-75 doi 10 1161/01 HYP 0000252676 46043 18

Onyike, C U (2006) Cerebrovascular disease and dementia *International Review of Psychiatry*, *18*(5), 423-431 doi 10 1080/09540260600935421

Pantoni, L , & Garcia, J H (1997) Pathogenesis of Leukoaraiosis A Review *Stroke*, *28*(3), 652-659

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 doi 10 1016/j neuroimage 2005 02 034

Picton, T W , Stuss, D T , Alexander, M P , Shallice, T , Binns, M A , & Gillingham, S (2007) Effects of Focal Frontal Lesions on Response Inhibition *Cerebral*

Cortex, *17*(4), 826 -838. doi:10.1093/cercor/bhk031

Plassman, B., Langa, K., Fisher, G., Heeringa, S., Weir, D., Ofstedal, M., Burke, J., et al. (2007). Prevalence of Dementia in the United States: The Aging, Demographics, and Memory Study. *Neuroepidemiology*, *29*(1-2), 125-132. doi:10.1159/000109998

Pohl, K., Bouix, S., Kikinis, R., & Grimson, W. (2004). Anatomical guided segmentation with non-stationary tissue class distributions in an expectation maximization framework (Vol. 1, pp. 81-84). Presented at the IEEE International Symposium on Biomedical Imaging: From Nano to Macro, Arlington, VA, USA.

Prins, N. D., van Dijk, E. J., den Heijer, T., Vermeer, S. E., Jolles, J., Koudstaal, P. J., Hofman, A., et al. (2005). Cerebral small-vessel disease and decline in information processing speed, executive function and memory. *Brain: A Journal of Neurology*, *128*(Pt 9), 2034-2041. doi:10.1093/brain/awh553

Pruessner, J. C., Collins, D. L., Pruessner, M., & Evans, A. C. (2001). Age and Gender Predict Volume Decline in the Anterior and Posterior Hippocampus in Early Adulthood. *Journal of Neuroscience*, *21*(1), 194-200.

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

Radloff, L. (1977). The CESD Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*, *1*, 385-401.

Randolph, C. (1998). *RBANS Manual - Repeatable Battery for the Assessment of Neuropsychological Status*. San Antonio, TX: The Psychological Corporation.

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. (2000). Aging of the brain and its impact on cognitive performance: integration of structural and functional findings. In *The Handbook of Aging and Cognition.* Mahwah, NJ: Lawrence Erlbaum Associates.

Reitz, C., Brickman, A. M., Brown, T. R., Manly, J., DeCarli, C., Small, S. A., & Mayeux, R. (2009). Linking hippocampal structure and function to memory performance in an aging population. *Archives of Neurology*, *66*(11), 1385-1392. doi:10.1001/archneurol.2009.214

Resnick, S. M., Pham, D. L., Kraut, M. A., Zonderman, A. B., & Davatzikos, C. (2003). Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *23*(8), 3295-3301.

Rieckmann, A., Karlsson, S., Karlsson, P., Brehmer, Y., Fischer, H., Farde, L., Nyberg, L., et al. (2011). Dopamine D1 Receptor Associations within and between Dopaminergic Pathways in Younger and Elderly Adults: Links to Cognitive Performance. *Cerebral Cortex*. doi:10.1093/cercor/bhq266

Roman, G. (2005). Vascular Dementia Prevention: A Risk Factor Analysis. *Cerebrovascular Diseases*, *20*(2), 91-100. doi:10.1159/000089361

Rosamond, W., Flegal, K., Furie, K., Go, A., Greenlund, K., Haase, N., Hailpern, S. M., et al. (2008). Heart Disease and Stroke Statistics--2008 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*, *117*(4), e25-146.

doi:10.1161/CIRCULATIONAHA.107.187998

Sachdev, P. S., Brodaty, H., Valenzuela, M. J., Lorentz, L., Looi, J. C., Wen, W., & Zagami, A. S. (2004). The neuropsychological profile of vascular cognitive impairment in stroke and TIA patients. *Neurology*, *62*(6), 912 -919. doi:10.1212/01.WNL.0000115108.65264.4B

Salat, D., Kaye, J., & Janowsky, J. (1999). Prefrontal Gray and White Matter Volumes in Healthy Aging and Alzheimer Disease. *Archives of Neurology*, *56*(3), 338-344. doi:10.1001/archneur.56.3.338

Salat, D., Lee, S., van der Kouwe, A., Greve, D., Fischl, B., & Rosas, H. (2009). Age-associated alterations in cortical gray and white matter signal intensity and gray to white matter contrast. *NeuroImage*, *48*(1), 21-28. doi:10.1016/j.neuroimage.2009.06.074

Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: a formulation and review of evidence for threshold theory. *Neuropsychology*, *7*, 273-295.

Stern, Y. (2009). Cognitive Reserve. *Neuropsychologia*, *47*(10), 2015-2028. doi:10.1016/j.neuropsychologia.2009.03.004

Takahashi, H., Kato, M., Hayashi, M., Okubo, Y., Takano, A., Ito, H., & Suhara, T. (2007). Memory and frontal lobe functions: possible relations with dopamine D2 receptors in the hippocampus. *NeuroImage*, *34*(4), 1643-1649.

Takahashi, H., Kato, M., Takano, H., Arakawa, R., Okumura, M., Otsuka, T., Kodaka, F., et al. (2008). Differential contributions of prefrontal and hippocampal dopamine D1 and D2 receptors in human cognitive functions. *Journal of Neuroscience*, *28*(46), 12032-12038.

Terry, R., DeTeresa, R., & Hansen, L. (1987). Neocortical cell counts in normal human adult aging. *Annals of Neurology, 21*(6), 530-539.

Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia, 42*(10), 1394-1413. doi:10.1016/j.neuropsychologia.2004.04.006

Verdelho, A., Madureira, S., Ferro, J. M., Basile, A., Chabriat, H., Erkinjuntti, T., Fazekas, F., et al. (2007). Differential impact of cerebral white matter changes, diabetes, hypertension and stroke on cognitive performance among non-disabled elderly. The LADIS study. *Journal of Neurology, Neurosurgery, and Psychiatry, 78*(12), 1325-1330. doi:10.1136/jnnp.2006.110361

Vernooij, M. W., Ikram, M. A., Vrooman, H. A., Wielopolski, P. A., Krestin, G. P., Hofman, A., Niessen, W. J., et al. (2009). White Matter Microstructural Integrity and Cognitive Function in a General Elderly Population. *Archives of General Psychiatry, 66*(5), 545-553. doi:10.1001/archgenpsychiatry.2009.5

Wimo, A., Winblad, B., & Jönsson, L. (2010). The worldwide societal costs of dementia: Estimates for 2009. *Alzheimer's and Dementia, 6*(2), 98-103. doi:10.1016/j.jalz.2010.01.010

Wright, C. B., Festa, J. R., Paik, M. C., Schmiedigen, A., Brown, T. R., Yoshita, M., DeCarli, C., et al. (2008). White Matter Hyperintensities and Subclinical Infarction: Associations With Psychomotor Speed and Cognitive Flexibility. *Stroke, 39*(3), 800-805. doi:10.1161/STROKEAHA.107.484147

Ylikoski, R., Ylikoski, A., Erkinjuntti, T., Sulkava, R., Keskivaara, P., Raininko, R., &

Tilvis, R. (1998). Differences in neuropsychological functioning associated with age, education, neurological status, and magnetic resonance imaging findings in neurologically healthy elderly individuals. *Applied Neuropsychology*, *5*(1), 1-14. doi:10.1207/s15324826an0501_1

Ystad, M. A., Lundervold, A. J., Wehling, E., Espeseth, T., Rootwelt, H., Westlye, L. T., Andersson, M., et al. (2009). Hippocampal volumes are important predictors for memory function in elderly women. *BMC Medical Imaging*, *9*, 17. doi:10.1186/1471-2342-9-17

Ziegler, D. A., Piguet, O., Salat, D. H., Prince, K., Connally, E., & Corkin, S. (2010). Cognition in healthy aging is related to regional white matter integrity, but not cortical thickness. *Neurobiology of Aging*, *31*(11), 1912-1926. doi:10.1016/j.neurobiolaging.2008.10.015

Zuccalà, G., Onder, G., Pedone, C., Carosella, L., Pahor, M., Bernabei, R., Cocchi, A., et al. (2001). Hypotension and cognitive impairment. *Neurology*, *57*(11), 1986 - 1992.