8-17-2018

Predicting Age-Related Decline in Processing Speed and Executive Functioning: An MRI Study of White Matter Integrity

Faith Steffen-Allen
University of Connecticut, faith.steffen@uconn.edu

Predicting Age-Related Decline in Processing Speed and Executive Functioning: An MRI Study of White Matter Integrity

Faith Trost Steffen-Allen, PhD

University of Connecticut, 2018

Normal aging is associated with changes in white matter (WM) integrity including visible lesions such as white matter hyperintensities (WMH) as well as microstructural changes in normal appearing WM (NAWM) measured with diffusion tensor imaging (DTI). Research suggests that WMH and microstructural changes in NAWM may provide independent but complementary information on WM integrity. Reductions in WM integrity and advanced age are also associated with reductions in executive functioning (EF) and processing speed (PS); however, the relationship between WM change and cognition in older adults over time is not fully understood. It is also important to consider other factors that may moderate change in cognition over time, such as intellectual functioning and vascular risk factors. The current study examined how demographics and change in WM integrity predict change on measures of executive functioning and processing speed in a 4-year longitudinal study with a normal aging sample. Eighty-five adults between the ages of 75 and 89 participated in baseline neuropsychological testing. Sixty-four remained at 2 years and 37 remained at 4 years. Multilevel Modeling was conducted to examine how change in WM integrity predicted change on the cognitive measures over and above predictive utility of between-subjects effects. The present study provides support for the hypothesis that reduction in WM integrity predicts cognitive decline in typical aging. Additionally, WMH burden and microstructural indices of WM integrity in NAWM provide non-overlapping but complementary information on how change in WM integrity predicts cognitive decline. Finally, we found evidence that cognitive reserve reflects both the persistence of earlier differences in cognitive functioning in some cognitive domains and the differential rates of decline in other domains. These findings underscore the importance of longitudinal studies in evaluating the role of WM integrity and demographic factors in shaping trajectories of cognitive aging.

Predicting Age-Related Decline in Processing Speed and Executive Functioning: An MRI Study of White Matter Integrity

Faith Trost Steffen-Allen

B.A., Washington University in St. Louis, 2010

M.S., University of Connecticut, 2016

A Dissertation

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Doctor of Philosophy

at the

University of Connecticut

2018

APPROVAL PAGE

Doctor of Philosophy Dissertation

Predicting Age-Related Decline in Processing Speed and Executive Functioning:

An MRI Study of White Matter Integrity

Presented by

Faith Trost Steffen-Allen, B.A., M.S.

Major Advisor _____
Chi-Ming Chen, Ph.D.

Associate Advisor _____
Deborah Fein, Ph.D.

Associate Advisor _____
Kevin Manning, Ph.D.

University of Connecticut
2018

ACKNOWLEDGEMENTS

First and foremost, I would like to thank all of the study participants without whom this work would not be possible. I would also like to thank all of our collaborators, including Leslie Wolfson, M.D. and Dorothy Wakefield, M.S. at the University of Connecticut Health Center and Nicola Moscufo, Ph.D. and Charles R Guttmann, M.D. at Harvard Medical School, and the other collaborators who devoted their time. Thank you to committee members Kevin J. Manning, Ph.D. and Richard Kaplan, Ph.D. at the University of Connecticut, who generously gave their time and knowledge, included me in this study, and served as mentors during my time on this project.

To my advisor, Chi-Ming Chen, Ph.D., thank you for your support, guidance, and mentorship throughout my graduate career at UConn. I would not be here without you. To Deborah Fein, Ph.D., my associate advisor, thank you for serving as an additional mentor throughout my graduate training and providing a model to aspire to. A special thank you to committee member Marianne Barton, Ph.D. whose support, understanding, and grace under pressure were critical for my development as a person and a professional. I would also like to acknowledge Jeffrey Burke, Ph.D. and Grace Chan, Ph.D. for consultation on statistical analyses.

A huge thank you to my social support – my fellow lab mates, cohort members, family, and friends who believed in me and supported me. To Rachel and Kate, going through this with you made every step easier and more enjoyable. To Cody, thank you for your patience and support. I could not have come this far without you.

Table of Contents

Introduction……..1

Aging and White Matter Changes……..……2

Cognitive Aging and White Matter Integrity.……6

Impacts on Cognitive Aging: Understanding Cognitive Reserve..……8

Vascular Impact on Cognitive Aging and White Matter Integrity…….9

The Present Study...……...10

Methods……13

Participants……13

Brain Imaging.……....15

Neuropsychological Measures……...…17

Blood Pressure……...18

Statistical Analysis…….....19

Results……...21

Descriptives……..…….21

Hypothesis 1……..21

Hypothesis 2……..……...…….22

Hypothesis 3……..22

Hypothesis 4……..23

Hypothesis 5……..23

Discussion…….24

Hypothesis 1……..25

Hypothesis 2 & 3……..……...……..26

Hypothesis 4……..28

Hypothesis 5……..33

Limitations……..……35

Summary & Conclusions……...36

Tables……38

Table 1. Characteristics of the Cohort at Baseline and Over 4 Years of Observation…..38

Table 2. Time only models of change in cognitive outcome variables…….39

Table 3. Cross-sectional analysis of baseline demographic factors with cognitive outcome variables…….....40

Table 4. Baseline demographic moderation of change on the Trail Making Test…….41

Table 5. Predicting change on the Trail Making Test with change in global white matter integrity……..42

Table 6. Cross-sectional prediction of cognitive outcome variables: Age and MABP model …….43

Table 7. Cross-sectional prediction of cognitive outcome variables: MABP only model……..44

Table 8. Longitudinal prediction of change on the Trail Making Test: MABP model……..45

Figures……46

Figure 1. Sample size flow chart……..46

Figure 2. Interaction of Time and Education on performance on the Trail Making Test Part A. ……...47

References……...48

Cognitive aging is a selective process, and advanced age is associated with decrements across several cognitive domains (Horn & Cattell, 1967; Salthouse, 1994; Salthouse, 2011; West, 1996). Decades of research in aging have found declines in both basic cognitive processes (such as processing speed), as well as in higher-order cognitive processing (such as episodic memory, fluid reasoning, and executive functioning); however, crystallized knowledge (such as semantic memory) is relatively preserved (Bennett & Madden, 2014; Salthouse, 2011). Such declines in cognition occur even in the absence of overt pathology (clinically symptomatic neurodegenerative or vascular conditions) and are considered an aspect of "normal" or "typical" cognitive aging (Kennedy & Raz, 2009; Lockhart & DeCarli, 2014).

While cognitive aging is considered normal, and such declines are considered minor, they can still impact clinical outcomes in advancing age (Lockhart & DeCarli, 2014). Even in the absence of a frank neurocognitive disorder, lower cognitive performance in older adults is associated with poorer medication adherence and increased rates of hospitalization (Hayes, Larimer, Adami, & Kaye, 2009; Wilson et al., 2014). Slowed processing speed (PS) in older adults is an important predictor of driving cessation and may impact the efficiency of other higher-order cognitive processing (Canolty et al., 2006; Salthouse, 1994). Reductions in executive functioning (EF) can impact performance on complex tasks and processes required for self-care, such as insight, planning, decision making, and medical self-monitoring (Sédille-Mostafaie, Zehetmayer, Krampla, Krugluger, & Fischer, 2015). Understanding the biological basis of cognitive differences in typical aging may allow prediction and treatment of age-related cognitive decline, with the goal of enhancing quality of life and survival in later life (Lockhart & DeCarli, 2014).

Aging and White Matter Changes

While many elements of cognitive tasks are highly localized, others are dependent on coordination between both local and global neural networks and rely on cross-cortical connections (Catani & Ffytche, 2005). Thus, white matter (WM) integrity is important for the coordination of normal cognitive functioning, and loss of WM, or decline in WM integrity, likely contributes to age-related cognitive decline (Catani & Ffytche, 2005; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998). Imaging studies have revealed age-related changes in WM, even during normal aging (Bender & Raz, 2015; Gunning-Dixon & Raz, 2000; Malloy, Correia, Stebbins, & Laidlaw, 2007; O'Sullivan et al., 2001). Additionally, histopathological studies have shown that aging is associated with breakdown of myelin integrity as well as overall loss of myelin (Bartzokis et al., 2004; Marner, Nyengaard, Tang, & Pakkenberg, 2003).

Gray and white matter volume both decline with increasing age and are associated with changes in cognition; however, the pattern of decline appears to differ (Bartzokis et al., 2004; Lockhart & DeCarli, 2014). Evidence suggests that gray matter volume declines in a linear manner, but that white matter volume decline is non-linear, accelerates after age 50, and correlates with expansion of cerebral spinal fluid (Lockhart & DeCarli, 2014; Raz et al., 2005; Salat, 2014). Further, WM volume changes appear to be most pronounced in anterior brain regions, such as prefrontal (orbital and dorsolateral) and inferior partial WM (Gunning-Dixon et al., 2009; Raz et al., 2005, 1998). Pathological studies suggest that change in myelinated fiber size and expansion of perivascular spaces results from atrophy of cerebral white (Lockhart & DeCarli, 2014).

In addition to changes in WM volume, advancing age is also associated with reductions in WM integrity, observed in magnetic resonance imaging studies (Bartzokis et al., 2004; Bender, Völkle, & Raz, 2016; Bennett & Madden, 2014; Gunning-Dixon et al., 2009). Macrostructural white matter changes are frequently measured as white matter hyperintensities (WMH), which are bright foci observed on T2 weighted magnetic resonance images (MRI) in brain parenchyma (Gunning-Dixon et al., 2009). WMH reflect alterations in WM that are thought to be the result of ischemic lesions, demyelination, gliosis, axonal atrophy and breaches of the blood-brain barrier (Erten-Lyons et al., 2013). The number and volume of WMH increase with increasing age (chronological age appears to be the strongest predictor of severity) and are associated with vascular risk factors (hypertension, diabetes mellitus, and smoking) and cerebrovascular disease (Bartzokis et al., 2004; Bender, Prindle, Brandmaier, & Raz, 2016; Gunning-Dixon et al., 2009; Raz et al., 1998). WMH generally begin as punctuate regions that expand and form larger confluent regions with disease progression. WM lesions usually are most prevalent in anterior periventricuar regions, though they occur in both the anterior and posterior periventricular regions and extend outward with increasing age (Lockhart & DeCarli, 2014; Wakefield et al., 2010). Historically, WMH were thought to represent pre-disease processes, and the extent and distribution of WMH do increase in the context of mild cognitive impairment and dementia (Lockhart & DeCarli, 2014); however, more recent neuroimaging research has revealed that decreases in WM integrity can occur in older age in the absence of specific neurologic disease. Indeed, studies show that many older adults have WMH and do not have dementia (Bennett & Madden, 2014; O'Sullivan, 2008).

In contrast to measurement of macrostructural white matter changes with T2 WMH, Diffusion Tensor Imaging (DTI) provides a means of investigating microstructural properties of

the brain WM and allows examination of WM integrity in otherwise normal appearing WM (Gunning-Dixon et al., 2009; Pierpaoli & Basser, 1996). DTI measures the diffusion of water molecules in biological tissue (Basser, Mattiello, & LeBihan, 1994). Diffusion within cerebral spinal fluid (e.g. ventricles) is largely unbounded and non-directional (isotropic). Within gray matter, barriers to diffusion (cell bodies and dendrites) are non-uniform and result in relatively isotropic diffusion. In contrast, diffusion within WM is restricted by axonal cell membranes, myelin sheaths, and other cytoskeletal elements, such that diffusion runs largely parallel to the axons and is more directionally restricted (anisotropic) (Beaulieu, 2002).

DTI provides several indices that are thought to reflect WM integrity. Fractional anisotropy (FA) is a scalar value that reflects the degree of anisotropy (directional dependency) of diffusion. FA represents a ratio of the likelihood of diffusion along the principal axis of the diffusion tensor to diffusion in orthogonal directions. FA values closer to 1 indicate diffusion that is more directionally dependent, where values closer to 0 indicate diffusion that is not directionally restricted. FA is thought to reflect integrity of biological boundaries that constrain the diffusion of water molecules (Beaulieu, 2002). Mean diffusivity (MD) is a scalar measure of the rate of diffusion within a given voxel, independent of directionality. MD values closer to 0 indicate more barriers to diffusion, and are found in regions of the brain with more axonal membranes, myelin sheaths, and neurofilaments. Further, in studies of aging, FA and MD often show an inverse, but complementary, relation as decreases in FA are accompanied by MD increases within the same region (Sullivan & Pfefferbaum, 2006). Lower FA is thought to reflect axonal injury, whereas higher MD is suggested to represent changes in tract integrity due to demyelination (Santiago et al., 2015). Thus, higher FA and lower MD values are thought to indicate greater white matter integrity (Bennett & Madden, 2014).

Age-related declines in DTI measures of white matter integrity have been well documented, with reduced FA and increased MD found with increasing age in cross-sectional studies, as well as fewer longitudinal designs (Kochunov et al., 2012; Madden et al., 2012; Madden, Bennett, & Song, 2009). The most consistent finding from DTI studies in aging is that prefrontal WM is more vulnerable to declines in integrity relative to other WM and that WM integrity decline (as assessed by FA and MD) follows an anterior to posterior gradient (Gunning-Dixon et al., 2009; Kennedy & Raz, 2009; Lockhart & DeCarli, 2014). Further, reductions in DTI indices may precede and predict further WM decline, including development of WMH or WM atrophy (Hugenschmidt et al., 2008; Maillard et al., 2013).

WMH and change in DTI indices are related processes. Studies have found lower FA and higher MD in WMH than in normal appearing white matter (NAWM; WM without WMH) (Maniega et al., 2015). The level of deterioration of NAWM has been shown to be associated with the severity of WMH (Maniega et al., 2015). Additionally, studies suggest that WMH are surrounded by penumbra of subtly injured tissue and that WMH may represent merely the focal peaks of more wide-spread and subtle white matter injury, as evidenced by findings that FA decreases and MD increases as a function of spatial proximity to WMH (Maillard et al., 2013). Thus, WMH studies may have failed to capture the true degree and extent of age-associated WM change. DTI, meanwhile, may be better suited for modeling WM decline as a continuous process and has been shown to be sensitive to subtle WM changes that occur with advancing age. It is important to note, however, that there is a large body of WMH literature and that using DTI scans to make inferences about WM injury requires more sophistication than WMH studies (Maillard et al., 2013). Finally, the DTI studies variably include total WM or NAWM for analysis and studies utilizing DTI and WMH in conjunction are limited (Bennett & Madden,

2014). This is important to explicate because DTI studies in NAWM and total WM do not reveal the same outcomes (Maillard et al., 2013; Vernooij et al., 2008).

Cognitive Aging and White Matter Integrity

Cross-sectional imaging studies in healthy adults consistently suggest a relationship between decline in white matter integrity and decline in cognition, with the greatest effect sizes observed on measures of executive functioning and processing speed. These results have been demonstrated in WMH studies (Gunning-Dixon & Raz, 2003; Rabbitt et al., 2007; Raz et al., 2012), as well as DTI studies (Bennett & Madden, 2014; Gunning-Dixon et al., 2009; MacPherson et al., 2017; Madden, Bennett, et al., 2009). Furthermore, these effects persist, though to a lesser extent, after controlling for age (Bennett & Madden, 2014). However, the scarcity of longitudinal studies remains a major obstacle to understanding the impact of age-related changes in WM on cognition (Bender & Raz, 2015).

Several longitudinal studies have found that change in overall WMH volume is associated with change in executive functioning (including working memory) and processing speed (Carmichael et al., 2012; Kramer et al., 2007; Lockhart & DeCarli, 2014; Longstreth et al., 1996; Vannorsdall, Waldstein, Kraut, Pearlson, & Schretlen, 2009). The few longitudinal DTI studies have used a variety of techniques and obtained mixed results. Some studies have shown no association between change in DTI indices and executive functioning (Bender, Prindle, et al., 2016; Lövdén et al., 2014) or processing speed (Bender, Prindle, et al., 2016; Charlton, Schiavone, Barrick, Morris, & Markus, 2010; Ritchie et al., 2015), while others have shown that reductions in WM integrity are associated with reductions in executive functioning (Charlton et al., 2010; Faget-Agius et al., 2013; Fjell, Sneve, Grydeland, Storsve, & Walhovd, 2016) and processing speed (Lövdén et al., 2014). Another limitation of the field is that few studies have

utilized both WMH and DTI indices, so the relative contribution of microstructural versus macrostructural variation in WM integrity to age-related differences in cognition has not been resolved (Bennett & Madden, 2014). Some studies have suggested that DTI is a more sensitive measure of WM change (Burgmans et al., 2010; Hugenschmidt et al., 2008), but a large scale study found that WMH explained more of the age-related differences in cognition (Vernooij et al., 2008). Another study found that only overall FA predicted age-related differences in processing speed but in no other cognitive domains (Burgmans et al., 2010).

Another limitation in this area is that across DTI studies, there has been minimal overlap in the region-specificity of WM tract integrity and cognition, with the exception that the relationships are stronger in anterior brain regions (Madden, Spaniol, et al., 2009; Perry et al., 2009). One possible reason for the discrepancies found in the body of literature around microstructural WM integrity and cognition is the large variety of methodologies used. Methods include whole brain voxel-wise analyses, measures in very large regions of interest (ROI), or localized and specific regional measures. Further, studies variably exclude WMH from DTI analysis. The selection of cognitive measures varies widely across studies, and often includes global indices amalgamating multiple cognitive domains. There is also a large variety in sample composition across studies, with some samples containing only one gender, some with mixed handedness, and variable age ranges (Kennedy & Raz, 2009). Finally, it is unclear if age-related declines in DTI indices represent effects associated with individual tracts, or instead are global effects occurring across the whole brain. Some studies have indicated that global changes in WM may be more prominent and predictive (particularly when studying the relationship between WM integrity and processing speed) than tract-specific effects , while other studies have demonstrated the opposite (Bennett & Madden, 2014; Jolly et al., 2017). Even in the absence of a general

effect, the data for individual tracts is likely to be correlated, particularly in tracts that are spatially contiguous. Therefore, by analyzing each tract individually, the contribution from the shared variance across tracts is not taken into account, though it is unclear if different regions may contribute unequally to global WM indices (Bennett & Madden, 2014; Wakefield et al., 2010). Given the lack of clarity in this area, it may be important for studies to first examine the global impact of DTI measures on WM integrity before trying to examine tract-specific effects.

Impacts on Cognitive Aging: Understanding Cognitive Reserve

Reductions in WM integrity may disrupt cortical-cortical connections that integrate global neural networks that are essential for cognitive tasks. Thus, age-related reductions in (WM) integrity may reduce the efficiency of cortical networks and consequently increase the reliance on compensatory processes (Brickman et al., 2011; Catani & Ffytche, 2005; Jolly et al., 2017). Cognitive reserve may be important to consider when engaging in studies of age-related cognitive decline. The cognitive reserve hypothesis states that individuals with higher reserve (greater experiential resources, such as education or knowledge) are able to better cope with brain pathology through compensatory strategies than individuals with lower reserve (Brickman et al., 2011; Mitchell, Shaughnessy, Shirk, Yang, & Atri, 2012). From a developmental perspective, reserve is the accumulation of experiences and exposures that moderates the relationship between brain pathology and its clinical expression. Brickman and colleagues (2011) have suggested that cognitive reserve does not protect the brain against the development of brain pathology, but rather moderates the association between pathology and the expression of that pathology through compensation.

Cognitive reserve is generally associated with higher educational and occupational attainment, and more involvement in physical, social, and leisure activities in normal aging and

dementia populations (Stern et al., 1994; Wilson, Scherr, Schneider, Tang, & Bennett, 2007). The cognitive reserve hypothesis has been supported by studies that found that high levels of reserve (as indexed by variables such as education, occupation, and premorbid IQ) was associated with lower risks for incident dementia (Valenzuela & Sachdev, 2006). However, it is unclear if cognitive reserve results in a slower rate of age-related cognitive decline, or rather acts as protective merely due to higher starting cognitive functioning (i.e. further to fall) (Brickman et al., 2011; Mitchell et al., 2012). Thus, longitudinal studies of age-related cognitive decline should also consider the impact of cognitive reserve factors (such as level of education) that may contribute to findings.

Vascular Impact on Cognitive Aging and White Matter Integrity

Vascular risk factors (hypertension, diabetes mellitus, and smoking) and cerebrovascular disease are thought to contribute to and possibly confound the study of typical brain aging (Lockhart & DeCarli, 2014). Community based studies suggest that clinically silent hypertension and cerebrovascular disease is common even among cognitively typical older adults (Lockhart & DeCarli, 2014; Yang, Bender, & Raz, 2015). Hypertension and other vascular factors have been found to be associated with cognitive performance, with the most frequent effects including declines in attention and working memory, processing speed, and executive functioning (Debette & Markus, 2010; Scott et al., 2016).

In addition to the association between vascular factors and cognition, vascular factors have also been linked to declines in WM integrity. The number and volume of WMH have been shown to be associated with vascular risk factors (hypertension, diabetes mellitus, and smoking) and cerebrovascular disease (Bartzokis et al., 2004; Bender, Prindle, et al., 2016; Gunning-Dixon et al., 2009; Raz et al., 1998). Several studies have found that hypertension accounts for much of

the variability of WMH volume, independent of age (Gunning-Dixon et al., 2009). Additionally, midlife hypertension and increasing systolic blood pressure may predict the rate of increase in WMH in older age (Allan et al., 2015; Debette et al., 2011; Debette & Markus, 2010; Mechelli et al., 2007). These findings are even observed among individuals with medication controlled hypertension (Scott et al., 2016). Similar patterns have been observed in DTI studies, where increased vascular risk (such as mean arterial blood pressure) predicted worse WM integrity after controlling for age and WMH load (Salat et al., 2012; Yang et al., 2015). Thus, any study that examines the impact of WM integrity on cognition should also consider the impact of vascular risk factors.

The Present Study

The extant literature suggests that WMH and NAWM undergo continuous changes over time, even during typical aging. As such, these changes may be subject to potential intervention. WMH and reduced DTI indices are consistently found to be associated with lower performance on cognitive tasks, particularly in processing speed and executive functioning. Longitudinal studies demonstrate some evidence that changes in WM integrity are associated with vascular risk factors and may predict decline in executive functioning and processing speed. Clinically, cognitive aging has important impacts on the outcomes for older adults, and decline in processing speed and executive functioning in particular may have impacts on independence (driving, planning, medication management, etc.) (Kerchner et al., 2012; Lockhart & DeCarli, 2014). Understanding the biological basis of cognitive changes in typical aging may allow prediction and treatment of age-related cognitive decline, with the goal of improving outcomes in later life. Understanding the relevant factors in typical aging may provide clues to understanding and preventing the progression of disease processes. Studies that examine WM integrity,

cognitive aging, and vascular risk may help to identify new outcome measures for clinical trials that seek to control vascular risk factors and improve cognitive outcomes. In particular, measures of WM integrity may serve as bio-markers for early intervention trials aimed at improving cognitive health.

The current study aimed to address gaps in the extant literature on the impact of white matter integrity on cognitive aging. First, in response to the paucity of longitudinal studies, this study allows for examining the predictors of age-related change on cognitive measures, reducing the possibility that the findings are confounded by age effects. Second, this study addresses another limitation in the field: the scarcity of studies utilizing both WMH and DTI indices. By including both methods this study examined the relative contribution of WM integrity in NAWM and WMH accumulation to cognitive aging. Third, given the lack of agreement in the extant DTI literature on tract-specific WM integrity effects on cognitive decline, this study examined whole brain measures of WMH and DTI in order to contribute to the understanding of the global impact of WM integrity on cognitive aging. Studies such as this can serve as a base for future studies that examine tract-specific effects. Finally, this study included other factors that may impact WM integrity and/or age-related cognitive decline: cognitive reserve and blood pressure (as a proxy for relative hypertensive effects). The cognitive measures for analysis were selected in the following way: A previously published analysis of this cohort (Papp et al., 2014) found that total WMH volume predicted performance on several measures of executive functioning and processing speed (after controlling for age), at the 2-year time point. We wanted to expand this analysis to see if WMH volume predicted change on measures of PS and EF, and if WMH and DTI differentially predicted change. We included Trails B and Stroop CW as these measures

were administered to individuals at all three time points. We also included Trails A as a measure of PS without an EF component. This study has five broad hypotheses:

H1: Declines in performance will be observed on all cognitive measures across the study time frame. This is consistent with previous literature demonstrating age-related cognitive decline in EF and PS; we expected to see decline on all tasks across the study time-frame.

H2: Demographic variables will predict baseline scores on cognitive measures. We expected that age would predict raw score performance on all tasks, consistent with extant literature. We expected that education, an indication of cognitive reserve, would predict performance on EF tasks, given the findings that cognitive reserve is associated with higher levels of executive functioning (Lezak, Howieson, Bigler, & Tranel, 2012; Siedlecki et al., 2009). Finally, we expected to see a slight effect of gender (women performing more slowly than men) on the TMT B, but no gender differences on TMT A or Stroop CW (Lezak et al., 2012).

H3: Baseline education, but not age will moderate change in cognition over time. We evaluated whether the rate of change on measures of EF and PS was predicted by baseline age (to evaluate whether age-related cognitive decline was non-linear) or education (to evaluate whether cognitive reserve is associated with slower age-related cognitive decline). We hypothesized that higher levels of education would predict slower decline on cognitive measures, particularly EF measures. We did not expect age to predict rate of decline given the literature base suggesting monotonic declines in many domains of cognitive functioning (Salthouse, 2014).

H4: Indicators of macrostructural WM integrity (WMH) and microstructural WM integrity in NAWM (DTI) will independently predict change in cognitive measures across the study. This is consistent with the literature suggesting that change in WM integrity is

associated with change in EF and PS, as well as the findings that WMH and integrity in NAWM provide independent but complementary information on WM integrity and both are predictive of cognitive performance. We expected that these relationships would exist even after controlling for demographic factors.

H5: Higher MABP will predict worse cognitive performance cross-sectionally and longitudinally. We included mean arterial blood pressure (MABP) as a proxy for relative hypertensive effects. MABP is a metric commonly used in clinical settings to obtain a measure of overall BP, as it contains both systolic and diastolic measurements in its formula. Prior studies have utilized MABP, particularly when examining blood pressure in the context of cognition or brain structure in older adults (Allan et al., 2015; Jacobs et al., 2013). We predicted that higher MABP would be associated with worse performance on cognitive measures. Additionally, we expected that worsening MABP would predict decline on cognitive measures across the study, consistent with findings that MABP is related to decline in EF and PS and that greater MABP is associated with increased WMH volume (Allan et al., 2015; Salat et al., 2012; Tsao et al., 2016).

Methods

Participants

The protocol for the current study was approved by the University of Connecticut Health Center Institutional Review Board. Participants (aged 75-89) were recruited for a longitudinal follow up study from the greater Hartford, CT region from senior centers, senior living facilities, physician referrals, and newspaper advertisements to take part in a study on mobility, white matter integrity and cognition. Three hundred twelve potential participants were screened via telephone. One hundred sixty-four individuals were eligible, and 117 gave written, informed consent and underwent neurological examination. Exclusion criteria included neurologic disease

compromising mobility (e.g., Parkinson's disease, stroke, ataxia), sensory deficit (e.g., vestibular impairment, corrected distance vision more than 20 over 70), medications impairing motor function, cognitive impairment (Mini-Mental State Examination score <24), unstable cardiovascular disease, pulmonary disease requiring oxygen, inability to walk 10 meters independently in 50 seconds or less, weight greater than 250 pounds, excessive alcohol intake, pacemaker or other metallic device/implant which prohibits MRI, and expected lifespan less than 4 years. Seventeen individuals were excluded at baseline due to arthritis, Parkinson's disease, and claustrophobia and one due to tentorial meningioma. Participants were given a detailed description of the study, after which they provided informed consent.

The sample was originally recruited for a study investigating the association between mobility and white matter integrity in older adults. Thus the original recruitment methods included a balanced enrollment of gender, age, and mobility performance. Subjects were entered into a balanced 3 × 3 matrix which stratified age (75–79, 80–84, and ≥ 85), gender (60% female), and mobility performance using Short Physical Performance Battery (SPPB) scores (11–12, 9–10, and <9). At baseline, 2- and 4-years subjects underwent physical, neurological, mobility, and cognitive assessment, followed by brain MRI. At each time point, clinic blood pressure (BP), mobility, depression, and cognition were all assessed on the same day. The MRI was completed within 3 weeks. Participants and assessors were blinded to clinical and imaging outcomes.

Ninety-nine subjects were enrolled for baseline evaluation (39 males, 60 females). Subjects were well-educated non-Hispanic white individuals with only 7 non-high school graduates, despite efforts to recruit more diverse participants. Of the 99 subjects at baseline, 14 did not have complete data for the current analysis, including cognitive measures and MRI. At time 2 an additional 16 participants were lost to follow-up and one did not have complete data.

At time three, a further seven were lost to follow-up and 26 did not have complete data. Reasons for attrition include death, disability, refusal of MRI, unable to be located, moved from the area, no longer interested, and health reasons. For baseline, 2 years, and 4 years, valid and complete data was present for 85, 64, and 37 participants, respectively. See Figure 1 for final sample size flow chart.

Brain Imaging

Image analysis. High-resolution MR images of the brain were acquired at the Institute of Living (Hartford, Connecticut) using three MR sequences on a 3-Tesla Siemens Allegra scanner (Erlangen, Germany): T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) (176 contiguous 1-mm thick axial slices, TR/TE = 2500/2.74 ms, TI=900 ms, matrix size = 256×208, in-plane pixel spacing = 1mm×1 mm); 3D-Fast Spin Echo (T2) (176 contiguous 1mm thick sagittal slices, TR/TE = 2500/353 ms, matrix size = 256×220, in-plane pixel spacing = 1mm×1 mm), and Fluid Attenuated Inversion Recovery (FLAIR) (128 contiguous 1.3mm thick sagittal slices, TR/TE = 6000/353 ms, TI = 2200 ms, matrix size = 256×208, in-plane pixel spacing = 1mm×1 mm). Pre-processing included correction of magnetic field-related signal in homogeneities (Sled, Zijdenbos, & Evans, 1998) and linear affine registration of FLAIR and T2 series to the MPRAGE series (Jenkinson & Smith, 2001).

Intracranial cavity determination. The intracranial cavity (ICC) was obtained from the T2 series via semi-automated skull stripping using custom-made software implemented in Matlab (Mathworks Inc., Natick, Massachusetts). ICC included cortical cerebrospinal fluid and was used to exclude non-brain voxels from the subsequent tissue class segmentation.

Probabilistic brain atlas (ICBM) creation. During segmentation, ICBM brain atlas (International Consortium on Brain Mapping, UCLA) was warped to each subject's brain

through linear affine registration (Jenkinson & Smith, 2001), followed by non-rigid registration as implemented in 3D-Slicer to provide a probabilistic template for gray matter (GM) and WM classification (Pohl, Bouix, Kikinis, & Grimson, 2004). The ICBM was also used for stereotaxic analysis as standard space to which the brain of each subject was normalized.

Brain segmentation. MPRAGE and FLAIR images were used for semi-automated segmentation into WM, WMH, and cerebrospinal fluid. To account for head size variability, individual tissue class volumes were also normalized and expressed as fraction of ICC (WMF, WMHF). WMH were defined as WM areas that were hyper-intense in FLAIR images. To obtain the optimal segmentation we combined the outputs of three separate pipelines: single-channel and double-channel using 3D-Slicer (Pohl et al., 2004) and the segmentation module of Free Surfer (Fischl et al., 2002). True WMH had to be classified in at least two of the three segmentation outputs (>10% spatial overlap). WMH three pixels or less in size were excluded.

Global Diffusion Indices. DTI was performed using a standard twice-refocused EPI sequence with TR/TE = 5800/87 ms, FOV = 20 cm, acquisition and reconstruction matrices = 128 × 96 and 128 × 128, diffusion sensitizing orientations in 12 directions with one B0, and 8 averages for each direction at b = 1000 s/mm^2. Forty-five contiguous axial slices with 3 mm section thickness were acquired. DTI data were checked for excessive background noise, motion and other artifacts; significant artifacts resulted in subject exclusion. FSL software (MMRIB software library; www.fmrib.ox.ac.uk/fsl) was used for standard analysis including motion and eddy current corrections. All DTI images were co-registered to the B0 image, with gradient directions corrected for the applied rotation. To enhance reproducibility and ensure overlap of narrow WM structures between subjects, Tract Based Spatial Statistics (TBSS) (Smith et al., 2006) were utilized. This approach defines a WM skeleton from the DTI data (one for the

whole study population, using all data) by finding continuous tracts of local FA maxima. Each subject's FA and MD maps were then propagated to this skeleton to ensure that narrow WM tracts, which may not precisely overlap after whole brain co-registration, are projected to the same WM skeleton. For each subject, the NAWM and WMH parcellation maps were consolidated to a single map with NAWM and WMH labeled differently. This map was used in subsequent steps to determine pixels for diffusion indices determination. NAWM was defined as the cerebral white matter pixels not classified as WMH by the above stated method. Diffusion indices were expressed as mean values (sum of pixel values divided by the number of pixels) and their relative units represent either arbitrary units (FA) or μm^2/second (MD).

Neuropsychological Measures

The study neuropsychological test battery included the following measures: Trail Making Test, Parts A (TMT A) and B (TMT B) (Reitan, 1958); Stroop Color and Word Test (Golden, 1978); California Computerized Assessment Package, a continuous performance test (CalCAP); the Grooved Pegboard Test, a measure of eye hand coordination and fine motor speed and control (GPT; Lafayette Instrument Company; Model 32025); and the Controlled Oral Word Association Test (COWAT), a measure of semantic and phonemic verbal fluency. The Wechsler Test of Adult Reading Test (WTAR) was also included to provide an IQ estimate. All tests were administered by trained examiners using standardized procedures.

This report focuses on the TMT A and B and the Stroop Color and Word Test Color-Word trial (Stroop CW). The TMT is a test of scanning, visuomotor tracking, divided attention, and cognitive flexibility. The test is given in two parts, A and B. In part A, the participant is first asked to draw lines to rapidly connect consecutively numbered circles on one sheet. Part A involves visual scanning, psychomotor processing speed, and attention (Lezak et al., 2012;

Reitan, 1958). On part B, the participant is asked to rapidly connect consecutively numbered and lettered circles on another sheet by alternating between the two sequences. Part B involves the same cognitive components as part A, as well as an executive functioning component (i.e. divided attention, cognitive flexibility, and working memory) (Lezak et al., 2012; Reitan, 1958). While a ratio of the Trail Making Test (B/A) is often used to isolate the executive component of the task without a processing speed component, it is not clear that how ratios of B/A may increase over time (Salthouse et al., 2000). Thus, raw time scores (rather than ratio scores) on the Trail Making Test were used in the current longitudinal study maximize the changes of picking up on ag-related decline on the test. The Stroop Color and Word Test is a measure of processing speed, selective processing, and response inhibition. On the word reading trial, participants are asked to rapidly read words printed in black ink. On the color naming trial, participants are asked to rapidly name color patches presented on a page. On the color-word trial, participants are asked to rapidly name the color of the ink of words in which incongruent color names are printed (e.g., the word "green" printed in red ink) (Golden, 1978; Lezak et al., 2012). Mean and standard deviations of participants' performance on these tasks at each time point are summarized in Table 1.

Blood Pressure

Systolic and diastolic blood pressure were measured at each clinic visit. Mean arterial blood pressure (MABP) was calculated from the systolic and diastolic arterial pressure using the formula: $MABP = ([2 \times P_{diastolic}]+P_{systolic})/3$. This allowed one value of blood pressure to be included in models. Mean and standard deviations of participants' MABP at each time point are summarized in Table 1. MABP is a metric commonly used in clinical settings to

obtain a metric of overall BP, as it contains both systolic and diastolic measurements in its formula. It is believed to indicate perfusion pressure, particularly in body organs. Prior studies have utilized MABP, particularly when examining blood pressure in the context of cognition or brain structure in older adults (Allan et al., 2015; Jacobs et al., 2013)

Statistical Analysis

Hierarchical Linear Modeling (HLM) was used to address the research questions as it allows for analysis of longitudinal data with attrition over time and uses all available data for estimating the model parameters. It allows for estimation of individual growth trajectories for each participant on each cognitive variable of interest. Thus, HLM allows for the examination of prediction individuals' change in cognition over time (within-subjects effects) as well as the examination of what predicts differences between individuals in cognitive scores (between-subjects effects). HLM version 7.00 (Scientific Software International, Inc., Lincolnwood, IL) and SPSS version 24.0 (SPSS Inc., Chicago, IL) were used for analysis.

To address H1 of the study—is there significant change on the cognitive measures over time—models predicting each of the cognitive variables were estimated to model change in them over time. Each model consisted of the intercept and a time variable centered at baseline (coded 0, 1, and 2). Coding the time variable in this manner allowed for interpreting the intercept as participants' baseline score on the variable, and the time slope as the change in the baseline score over each time point.

To address H2 of the study— do demographic variables predict baseline scores on cognitive measures—models predicting baseline performance on each cognitive variable were run with age, education, and gender as between-subjects variables.

To address H3—do baseline demographic factors moderate change in cognition over time—for each cognitive measure that demonstrated significant change trajectories in H1 analyses models were run. At the between-subjects level (level 2), age and education were used as predictors of the time slope for each cognitive measure.

To address H4 of the study—white matter integrity variables as predictors of change trajectories in the cognitive measures—models predicting each cognitive variable that demonstrated significant change trajectories in aim 1 were run with age, education, and gender as between-subjects variables (level 2) and percent WMH, FA, and MD as within-subjects variables (level 1). For cognitive measures that did not demonstrate significant change trajectories in H1 analyses, models were run with level 2 predictors only (age, education, and gender).

To explore H5—does blood pressure predict performance on cognitive measures—HLM was used to examine the predictive validity of mean arterial blood pressure on cognition. Models were run for each task with age, education, gender, and MABP as between-subjects variables. Models were run without age to examine whether age may confound MABP effects. Models were also run for TMT A & B tasks with age, education, and gender as between-subjects control variables and MABP as a within-subjects variable.

In all HLM models, estimated, level 1 predictors were person-mean centered and level 2 predictors (except gender) were grand mean centered, to better tease apart within-person effects. Time was included in all of the within-subjects analysis, to control for the effects of time, and to more confidently attribute the change in the cognitive variables to the change in the predictors.

Results

Descriptives

Individuals who remained at four years did not differ significantly from those who dropped out before four years in gender ($\chi^2(1, N = 85) = 0.041$, $p = 0.84$), education ($t(83) = 0.94$, $p = 0.35$), or estimated IQ (WTAR: $t(83) = 1.67$, $p = 0.10$). The two groups differed significantly on age ($t(83) = -2.21$, $p = 0.03$), such that individuals who remained at four years ($M = 81.89$, $SD = 4.29$) were younger than those who did not ($M = 83.76$, $SD = 3.55$). See Table 1 for descriptives of variables for the final sample across the study span.

H1: Declines in performance will be observed on all cognitive measures across the study time frame.

HLM models predicting each of the cognitive variables were estimated to model change in them over time (Table 2). Each model consisted of the intercept and a time variable centered at baseline (coded 0, 1, and 2). Coding the time variable in this manner allowed for interpreting the intercept as participants' baseline score on the variable, and the time slope as the change in the baseline score over each time point. Results showed a statistically significant growth curve in both TMT A and TMT B, such that individuals showed slowing on these tasks over the four years of the study. On TMT A, participants completed the task in 44.40 seconds on average and slowed by 5.17 seconds every two years ($p < 0.001$). On TMT B, participants completed the task in 120.36 seconds on average and slowed by 12.35 seconds every two years ($p = 0.002$). However, results indicated that participants' performance on the Stroop CW task did not change significantly over time, and no further longitudinal analyses were run on the task.

H2: Demographic variables will predict baseline scores on cognitive measures.

To understand the inter-individual predictive utility of the demographic variables on cognition task performance, models were run for each cognitive outcome measure with age, education, and gender as between-subjects variables (Table 3). For the TMT A task, there was a significant between-subjects effect of age, where older age was associated with longer time to complete the task: each additional year of age was associated with slower performance on TMT A by 0.84 seconds. Education and gender did not significantly predict TMT A performance.

For the TMT B task, there were significant between-subjects effects of age and education, where older age and fewer years of education were associated with longer time to complete the task: each additional year of age was associated with slower performance on TMT B by 4.08 seconds, and each additional year of education was associated with faster performance on TMT B by 5.83 seconds. Gender did not significantly predict TMT B performance.

On the Stroop CW task, results showed significant between-subjects effects of age and education, where older age and fewer years of education were associated fewer words correctly read on the task: each additional year of age was associated with 0.65 fewer words read correctly, and each additional year of education was associated with 0.68 more words read correctly. Gender did not significantly predict Stroop CW performance.

H3: Baseline education, but not age will moderate change in cognition over time.

Age and education were entered as predictors of the time slope for models predicting TMT A & B (Table 4). Results showed that education was a significant predictor of the time slope for the TMT A task, such that a higher level of education was associated with less slowing over time (Figure 2): each additional year of education reduced the rate of slowing on the TMT A task by 0.47 seconds/2 years. The model including age and education as moderators of the

time slope predicted significantly more variance in TMT A than the model with the between-subjects factors alone (χ^2 (3) = 22.32, $p < 0.001$). Age did not significantly predict the time slope for TMT A. On the TMT B task, neither age nor education significantly predicted the time slope.

H4: Indicators of macrostructural WM integrity (WMH) and microstructural WM integrity in NAWM (DTI) will independently predict change in cognitive measures across the study.

HLM was used to examine the predictive utility of change in WM integrity on change in TMT A & B (Table 5). Models were run for each task with baseline demographic variables as between-subjects controls and percent WMH, FA, and MD as within-subjects variables. Models including longitudinal WM integrity variables predicted significantly more variance in TMT A and TMT B than models with between-subjects control variables alone (TMT A: χ^2 (3) = 30.8, $p < 0.001$; TMT B: χ^2 (4) = 29.37, $p < 0.001$).

For the TMT A task, there was a significant within-subjects effect of MD, where increases in MD predicted slowing on TMT A. Change in WMH and FA did not significantly predict change on the task. For the TMT B task, there was a significant within-subjects effect of WMH, where increases in WMH predicted slowing on TMT B. Change in FA and MD did not significantly predict change on the task ($p > 0.05$). It is worth noting that as the within-subjects variables were group-centered and as time was included in the model, many typical confounds of the effect (e.g., individual differences) have been accounted for, and these effects provide evidence of the longitudinal impact of WM integrity on cognition.

H5: Higher MABP will predict lower cognitive performance cross-sectionally and longitudinally.

HLM was used to examine the predictive validity of mean arterial blood pressure (MABP) on cognition. Models were run for each task with age, education, gender, and MABP as between-subjects variables (Table 6). MABP did not significantly predict inter-individual performance on any task. Further, models including MABP did not significantly predict more variance in tasks than models without MABP (TMT A: χ^2 (1) = 3.55, $p > 0.05$; TMT B: χ^2 (1) = 3.23, $p > 0.05$; Stroop CW: χ^2 (1) = 0.57, $p > 0.05$). However, when age was excluded from the models, MABP significantly predicted performance on TMT A&B, with increased MABP associated with slower performance on those tasks (Table 7).

Models were also run for TMT A & B tasks with age, education, and gender as between-subjects control variables and MABP as a within-subjects variable (Table 8). Change in MABP did not significantly predict change on either task. Thus, no further models including MABP and WM integrity measures were run.

Discussion

The present study used a longitudinal design to examine whether change in white matter integrity predicts change in executive functioning and processing speed. Specifically, we examined 1) if subjects demonstrated cognitive decline on tasks over the course of the study, 2) if baseline demographic variables (age, education, and gender) predicted cognitive performance cross-sectionally, 3) if baseline demographic factors moderated change in cognition over time, 4) if change in WM integrity predicted change on cognitive tasks after controlling for demographic variables, and 5) if blood pressure predicted cognitive performance longitudinally or cross-sectionally. The study aimed to address several gaps in the literature. First, this study adds to the paucity of longitudinal studies in this area. Second, this study included both macro and microstructural indicators of WM integrity. Third, this study examined whole-brain measures of

WMH and DTI in NAWM to contribute to the understanding of the global impact of WM integrity on cognitive aging. Including both also allowed us to examine whether including DTI indices in NAWM differentially predicted cognitive decline from WMH accumulation. Finally, this study included other factors that may impact WM integrity and/or age-related cognitive decline: cognitive reserve and blood pressure (as a proxy for relative hypertensive effects).

H1: Declines in performance will be observed on all cognitive measures across the study time frame.

Consistent with our expectation, we found slowing on the Trail Making Test (parts A & B) over time. This finding is consistent with cross-sectional and longitudinal studies of cognitive aging (Bennett & Madden, 2014; Kennedy & Raz, 2009). Contrary to our expectation, on the Stroop Color-Word Task, we did not see a significant effect of time. This is in contrast to cross-sectional studies that indicate worse performance with increasing age (Lezak et al., 2012; Spieler, Balota, & Faust, 1996; Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006). Similarly, longitudinal studies suggest decline on this task that is observable within two years (Adólfsdóttir, Wollschlaeger, Wehling, & Lundervold, 2017; Van Gerven, Van Boxtel, Ausems, Bekers, & Jolles, 2012). One possible reason for not replicating these findings is the small sample size in this study, which may reduce the ability to detect change effects. Additionally, there is some evidence that age related decline is less pronounced in individuals with high levels of education, consistent with cognitive reserve (Van der Elst et al., 2006). Given the high education level of this sample, it may be that the sample is too small and the time frame too short to detect change effects on this task. Finally, maintenance of cognitive performance across time is a common finding in longitudinal studies and has been attributed to retest effects (Salthouse,

2014). Given lack of a time effect on the Stroop CW task in this study, it was not included in further longitudinal analyses.

H2 & H3: Demographic variables will predict baseline scores on cognitive measures & Baseline education, but not age will moderate change in cognition over time.

We tested the relationship between demographic variables and baseline cognitive scores to examine H2. We also examined how baseline age and education moderated change on TMT over the course of the study to examine H3 and to better understand the factors related to reduced performance on the TMT. We discuss both aims in the following section.

The cross-sectional analysis in H2 allowed us to compare our sample to the extant cross-sectional literature on cognitive aging and to situate our longitudinal analyses within this literature base. As expected, age was a significant predictor of performance on all three tasks, such that higher age was associated with slower completion times on TMT A & B and with fewer words read on Stroop CW. This is consistent with the preponderance of cross-sectional literature in cognitive aging and allows us to interpret the findings of our longitudinal analyses more confidently (Lezak et al., 2012; Salthouse, 2011; West, 1996). Gender did not significantly predict performance on any task, in contrast to our expectation that women would perform more slowly on TMT B than men. However, this size of this effect has been shown to be small and thus may not be observed in a sample of the size used for this study (Lezak et al., 2012; Mura et al., 2016).

Finally, we found that higher levels of education predicted better performance on the EF tasks examined (TMT B and Stroop CW), consistent with our expectations and the current literature (Lezak et al., 2012; Siedlecki et al., 2009). However, we did not see an effect of education on TMT A (a test of processing speed). While there is some evidence to suggest that

education predicts performance on TMT A cross-sectionally, the size of this effect has been shown to be smaller than on TMT B, and it may be that a larger sample size than is included in this study may be required to detect this effect (Lezak et al., 2012; Mura et al., 2016). However, when we examined how education moderated the change on TMT over the course of the study (H3), we found that individuals with higher levels of education had slower rates of decline on TMT A, but not on TMT B. Thus, in the current study education cross-sectionally predicted performance on tasks with an EF functioning component but did not predict the rate of decline on such tasks, while on a task of PS, education did not predict the baseline score but did predict the rate of decline. These findings provide support to the cognitive reserve hypothesis which states that individuals with greater experiential resources, such as education, are better able to cope with age-related cortical changes as well as cortical pathology (Brickman et al., 2011; Mitchell et al., 2012). It is interesting to note that these results were present even within a highly-educated sample (with 90% having at least a high school diploma). It is unclear how these results would generalize within a wider range of educational attainments.

In summary, in the current sample, increased age was associated with reduced performance on measures of PS and EF, while higher educational attainment was associated with higher performance on measures of EF but not measures of PS alone. Higher educational attainment predicted slower decline on a task of PS but not on a task of EF. Gender did not predict cognitive performance. These findings relate directly to the debate around whether cognitive reserve results in a slower rate of age-related cognitive decline, or rather acts as protective merely due to higher starting cognitive functioning (Brickman et al., 2011; Mitchell et al., 2012). The results of the current study suggest that cognitive reserve may reflect the persistence of earlier differences in cognitive functioning in some domains (executive

functioning), as well as impact the differential rates of decline in other domains (processing speed). These results also indicate that cross-sectional and longitudinal analyses of the impact of education on cognition may provide non-overlapping and complementary information. The possible impact of educational attainment on cognition in older age is important clinically. If such developmental factors protect against functional impairment and have substantial implications for everyday functioning in later life, society-level investment in increasing access to education may help to prevent monetary and societal costs associated with cognitive aging.

H4: Indicators of macrostructural WM integrity (WMH) and microstructural WM integrity in NAWM (DTI) will independently predict change in cognitive measures across the study.

We examined whether change on global NAWM DTI indices (FA and MD) and global WMH predicted decline on the Trail Making Test and we found that reductions in global white matter integrity predicted slowing on the TMT. This is consistent with what has been suggested from the findings of cross-sectional studies of cognition and WM integrity (Bennett & Madden, 2014; Gunning-Dixon & Raz, 2003; MacPherson et al., 2017). Furthermore, we found that WM integrity indicators predicted significantly more variability within the sample than demographic factors alone, suggesting the usefulness of longitudinal designs. Unexpectedly, we found that WMHs and NAWM DTI indices differentially predicted parts A & B of the TMT. Declines in integrity in NAWM, as measured by increases in MD, predicted slowing on the TMT A, while changes in FA and percentage of WMH did not predict change on the task. Conversely, increases in percentage of WMH predicted slowing on TMT B, while changes in DTI indices in NAWM did not predict performance on the task.

The finding that increases in WMH burden predicted slowing on TMT B is consistent with longitudinal studies that found similar associations between WMH burden and tasks of EF more generally (Bennett & Madden, 2014; Carmichael et al., 2012; Lockhart & DeCarli, 2014), as well as studies that examined TMT B performance specifically (MacPherson et al., 2017; Zheng et al., 2012). One explanation for this finding is related to frontal lobe involvement. Poor performance on the TMT B has been consistently associated with dysfunction in the prefrontal cortex or disruption of the connections between frontal cortex and other cortical regions: individuals with dorsolateral prefrontal cortex and anterior cingulate lesions tend to perform poorly on this task and reduced prefrontal WM volume has been associated with worse performance (Bennett & Madden, 2014; Lezak et al., 2012; Lockhart & DeCarli, 2014). Similarly, WMH tend to develop along an anterior to posterior gradient and may reflect decreased connections to the frontal lobes (Lockhart & DeCarli, 2014; Wakefield et al., 2010). It has been previously demonstrated that frontal, but not posterior WMH burden, may drive the relationship between WMH burden and EF performance (Papp et al., 2014). Thus, it may be that frontal WMH burden may explain the predictive utility of change in WMH on slowing on TMT B. A detailed analysis of spatial WMH burden was beyond the scope of this work. However, future studies may benefit from considering global as well as regional WMH burden.

Contrary to our expectations, we found that change in FA and MD in NAWM did not predict change on the TMT B. There are several possible explanations for this finding. First, there is not an established consensus in the extant longitudinal literature with some studies finding change in DTI indices in NAWM predicting change in EF tasks (Charlton et al., 2010; Faget-Agius et al., 2013; Fjell et al., 2016) and others showing no association (Bender, Prindle, et al., 2016; Lövdén et al., 2014). Therefore, our findings highlight the importance of continued

studies to develop a greater base of literature in this area. Second, as we did not account for the spatial locations of WMH, the anatomical locations of the NAWM included in the analysis is unclear. Thus, given that WMH are generally more pronounced in anterior regions, it may be that the frontal WM integrity decline is more strongly accounted for in the WMH change variable (Gunning-Dixon et al., 2009; Raz et al., 2005, 1998). Finally, many of the studies examining DTI indices and performance on the TMT B longitudinally have utilized tract-specific analyses (Bennett & Madden, 2014; MacPherson et al., 2017; Perry et al., 2009). It may be that whole brain analyses of DTI indices wash out the effects of specific tracks that are involved in EF (Bennett & Madden, 2014). Conversely, there is some evidence to suggest that global DTI indices are more useful for predicting performance on tasks of processing speed than other cognitive domains (Bennett & Madden, 2014; Jolly et al., 2017).

Many studies have found increases in WMH burden to be associated with reductions in performance on tasks of processing speed (Carmichael et al., 2012; Lockhart & DeCarli, 2014a; Longstreth et al., 1996; Vannorsdall, Waldstein, Kraut, Pearlson, & Schretlen, 2009) and cross-sectional studies have generally found an association (Rabbitt et al., 2007; Raz et al., 2012). Indeed, a greater WMH burden was correlated with slower performances on this sample at the two year mark, though analysis did not include TMT A (Papp et al., 2014). However, the current study did not replicate the expected effect as change in WMH did not predict slowing on TMT A. While this finding was unexpected and inconsistent with many previous studies in this area, it may be that a frontal WMH pattern may not account for relevant global WM integrity factors that are important for processing speed tasks (as stated above). As such, it may be that the change in processing speed is better accounted for by the global NAWM DTI indices (Bennett &

Madden, 2014; Jolly et al., 2017). This may be particularly salient on a task such as the TMT A with a strong visual scanning component (Lezak et al., 2012).

The current study found that increases in MD, but not reductions in FA, in NAWM predicted slowing on the TMT A. This is partially consistent with the extant literature base. Longitudinal studies of microstructural WM integrity have generally found that change in FA and MD predict change in PS, with the most consistent effects found in FA (Kerchner et al., 2012; Lövdén et al., 2014; O'Sullivan et al., 2001). Similarly, cross-sectional studies have found that increased MD and reduced FA is associated with slower performance (Bettcher et al., 2016; Borghesani et al., 2013; Charlton et al., 2010; Jacobs et al., 2013; Kennedy & Raz, 2009; Santiago et al., 2015). However, few of these studies utilized the same methodology as the current study, with many using measures of reaction time as indicators of PS, none using change in TMT A as an outcome variable, others using tract based analyses, and more not including longitudinal analyses.

The current finding that change in MD and FA are non-redundant in predicting performance on TMT A is not surprising. While FA and MD are generally inversely related and are derived from the same raw water molecular diffusion data, they are widely perceived to provide different information about the underlying microstructure of white matter (Bennett & Madden, 2014). Lower FA is thought to reflect loss or degeneration of axons, whereas higher MD is suggested to represent changes in WM tract integrity due to demyelination or injury to other extracellular structures (MacPherson et al., 2017; Borghesani, 2013; Santiago et al., 2015). The results of the current study are consistent with these hypotheses and suggest that that FA and MD capture different WM changes of in aging (Lövdén et al., 2014). There is also some evidence to suggest that MD may be an earlier marker of decline in NAWM throughout the brain

and thus, may be a good indicator of global NAWM integrity (Maniega et al., 2015). Given these factors, it may be that the change in TMT A (a visual scanning task) is better accounted for by the global NAWM MD (Bennett & Madden, 2014; Jolly et al., 2017). Finally, it may be that whole brain analyses of FA washes out the effects of specific tracks that are involved in performance of TMT A (Bennett & Madden, 2014).

The Trail Making Test is one of the most commonly used tests of executive functioning in clinical neuropsychological assessment. Older adults who have poor performance on TMT B are likely to have difficulties with complex activities of daily living and worse clinical outcomes. TMT B has been shown to be sensitive to the progressive cognitive decline in dementia and to predict risk for falls (Lezak et al., 2012; Zheng et al., 2012). Performance on TMT A can also differentiate individuals with dementia from typically aging adults (Lezak et al., 2012). Decline in processing speed and executive functioning have generally been shown to impact independence in typical aging, such as driving continuance and medication management, as well as rates of hospitalization (Kerchner et al., 2012; Lockhart & DeCarli, 2014). Understanding the biological basis of cognitive changes in typical aging may allow prediction and treatment of age-related cognitive decline, with the goal of enhancing quality and survival in later life. The current study supports the hypothesis that reduction in WM integrity predicts cognitive decline in typical aging. Additionally, the study suggests that WMH burden and microstructural indices of WM integrity in NAWM provide non-overlapping but complementary information on how change in WM integrity predicts cognitive decline. While DTI indices and WMH are measuring similar processes (breakdowns in WM integrity), evidence suggest that DTI is a more sensitive measure of white matter integrity (Burgmans et al., 2010; Hugenschmidt et al., 2008). DTI also allows for the examination of WM integrity in NAWM, and the current study suggests that doing so will

add important information to aid in understanding the impact of WM decline on cognition in normal aging. Changes in WM integrity (as measured by WMH and DTI indices), are now considered an expected component of normal aging rather than specific markers for neurocognitive disorders and disease; however, the current study (consistent with extant literature) suggests that WM integrity decline has measurable impacts on cognitive decline even in cognitively 'healthy' adults. Thus, understanding and preventing WM integrity decline may have important clinical implications for maximizing and maintaining cognitive abilities and promoting positive outcomes in older adults. Finally, studies will benefit from including DTI indices of WM integrity in NAWM, given the sensitivity of DTI to subtle changes and the evidence form the current study that NAWM DTI is non-redundant with WMH.

H5: MABP will predict cognitive performance cross-sectionally and longitudinally.

To better understand the possible vascular impact on cognitive aging, we examined whether mean arterial blood pressure (MABP) predicted cognitive performance cross-sectionally or longitudinally. MABP did not significantly predict performance on the Stroop CW, cross-sectionally. On the TMT, higher MABP at baseline predicted slower performance on both parts A & B, but only after age had been removed from the model. Vascular risk factors, such as blood pressure, increase with age and have been shown to contribute to cross-sectional age-related differences in DTI indices and WMH burden (Bender & Raz, 2015; Gunning-Dixon et al., 2009; Lockhart & DeCarli, 2014). The finding of predictive overlap of MABP and age on TMT performance indicates that vascular factors may indeed confound the study of cognitive aging, as has been suggested (Bennett & Madden, 2014; Lockhart et al., 2012). However, this pattern was not observed on the Stroop CW task, suggesting that blood pressure does not account for all of the aging impact observed on cognitive tasks and that other factors should also be considered.

Thus, this study provides partial support for the findings that hypertension and other vascular factors have been found to be associated with cognitive performance, with the most frequent effects including declines in attention and working memory, processing speed, and executive functioning (Debette & Markus, 2010; Scott et al., 2016). However, it is likely that MABP alone does not account for the vascular load and that vascular composite (including hypertension, diabetes mellitus, smoking, and weight status) would show better cross-sectional prediction across tasks.

In line with this, change in MABP did not predict change in performance on the TMT, indicating that blood pressure alone does not account for the predictive power of WM integrity indicators on cognitive change. Indeed, studies have found decline in WM integrity even among individuals with medication controlled hypertension (Salat et al., 2012; Scott et al., 2016). As stated above, it may be that the longitudinal prediction of cognition improves with inclusion of other vascular components; however, such analysis was beyond the scope of this study. Some relevant factors that were not accounted for include the impact of medications and the duration of treatment of hypertension. Additionally, it may be that the duration of untreated hypertension may be an important baseline factor to control for (Bender & Raz, 2015). Blood pressure is not a static number and may fluctuate over the course of the day or week, and thus this may account for the lack of longitudinal prediction in the current study. Finally, there is an accumulating body of literature which indicates that vascular risk factors predict declines in WM integrity (Allan et al., 2015; Salat et al., 2012; Scott et al., 2016; Tsao et al., 2016). While outside the scope of this study, future research should further explore the relationships between WM integrity, vascular risk, and cognition in more depth, as this may help to more fully elucidate the factors that contribute to cognitive aging.

Limitations

The present study has several notable limitations. Certain characteristics of our sample may reduce the extent to which these findings can be generalized to a broader aging population. First, our sample was exclusively Caucasian as attempts to recruit minority participants were unsuccessful. The sample was also highly educated with 90% having graduated high school, and 70% having gone beyond high school. The age range of the sample was relatively narrow, 75–90 at baseline, compared to other studies. Further, the sample was relatively healthy with 28 of 85 having Stage 1 hypertension (SBP > 140), and only 7 with Stage 2 hypertension (SBP > 160) on clinical blood pressure assessments at baseline. Finally, individuals with MMSE less than 24 were excluded, thus skewing our sample toward those who were cognitively intact, and possibly limiting our ability to demonstrate cognitive deterioration over the ensuing 4 years (on the Stroop CW task, for example). These sample characteristics may limit the generalizability of the findings as the cohort was not entirely representative of the elderly population at large. Future studies should attempt to include a more representative sample. In addition, while HLM allows for maximal inclusion of data, we did have significant attrition across the task, resulting in loss of power to detect longitudinal effects and more subtle cross-sectional effects may have been missed. Finally, we performed a large number of comparisons, so the possibility of Type I error exists.

This study aimed to address gaps in the extant literature on the impact of white matter integrity on cognitive aging. Given the limited number of studies which have examined the longitudinal relationships between WMH and microstructural WM integrity in NAWM and cognitive decline, this study was designed to answer questions using whole brain analyses. While this is a strength of this study, it also means that more detailed questions cannot be answered. For

example, we did not account for the spatial location or individual differences in the distribution of WMH lesions. Thus, we do not know the anatomical location of the WMH or NAWM utilized for analyses. Further, we did not account for WM volume loss across the study. Thus, this study cannot speak to the impact of regional or tract-specific factors that may drive the findings. Additionally, it may be that whole brain analyses of indices wash out the effects of WM integrity in specific tracts or regions on cognitive tasks, and therefore we did not pick up on important effects (Bennett & Madden, 2014). Further, though fractional anisotropy (FA) and mean diffusivity (MD) are two of the most frequently used properties of DTI measures of WM integrity, other DTI indices (radial and axial diffusivity) have also demonstrated complementary relevance to studies of WM integrity and cognitive aging (Bennett & Madden, 2014; Faith M Gunning-Dixon et al., 2009). Continued research that elucidates the most relevant DTI indices for understanding WM integrity will promote parsimonious research.

Finally, to reduce the number of multiple comparisons, the number of variables included in analyses were limited. For example, three cognitive tasks and one measure of vascular risk were included. Focusing on specific cognitive tasks, rather than creating composites of cognitive domains, allows for increased reproducibility of findings. However, it also limits our ability to generalize our findings to understand the impact of WM integrity on broader cognitive domains (such as processing speed and executive functioning). Similarly, using one indicator of blood pressure, does not allow us to speak more broadly to the impact of vascular risk factors collectively on cognition.

Summary & Conclusions

Despite its limitations, the present study makes a significant contribution to the literature, as it is one of only a small number of studies examining the impact of WMH and microstructural

NAWM integrity on cognitive performance using a longitudinal design. The present study provides support for the hypothesis that reduction in WM integrity predicts cognitive decline in typical aging. Measures of WM integrity may serve as bio-markers for early intervention trials aimed at improving cognitive health, and understanding these factors in typical aging and may have important clinical implications. While decline in WM is now considered typical in normal aging, the current study suggests that WM integrity decline has measurable impacts on cognitive decline in the absence of frank disease. Thus, preventing WM integrity decline may promote positive outcomes in older adults by maintaining cognitive abilities and related independence. Additionally, the study suggests that WMH burden and microstructural indices of WM integrity in NAWM provide non-overlapping but complementary information on how changes in WM integrity predict cognitive decline. DTI, by allowing for the examination of WM integrity in NAWM, adds important information to aid in understanding the impact of WM decline on cognition in normal aging.

The present study also examined other factors that may play a role in cognitive aging. We found evidence that cognitive reserve may reflect the persistence of earlier differences in cognitive functioning in some domains while it may impact the differential rates of decline in other domains. Finally, we found evidence that blood pressure alone does not account for the predictive power of WM integrity indicators on cognitive change in older age. Further research on cognitive aging is warranted as it has implications for clinical outcomes in later life. Future research should further tease apart the different aspects of neurological and cognitive aging, specifying the relationships between relevant variables in this process. Studies such as this one can serve as a base for those future studies.

Tables

Table 1
Characteristics of the Cohort at Baseline and Over 4 Years of Observation

Parameter	**Baseline Mean (SD)**	**Two Year Mean (SD)**	**Four Year Mean (SD)**
	n = 85	n = 64	n = 37
Baseline Age (years)	82.9 (4.0)	82.4 (3.9)	81.9 (4.3)
Years Education	15.2 (2.9)	15.3 (2.7)	15.5 (3.0)
Baseline WTAR	112.8 (12.1)	114.2 (10.9)	115.2 (12.3)
Gender			
Male	38 (44.7%)	32 (50%)	17 (45.9%)
Female	47 (55.3%)	32 (50%)	20 (54.1%)
TMTA (seconds)	43.9 (18.4)	49.5 (16.8)	50.5 (18.3)
TMTB (seconds)	119.5 (58.6)	127.7 (65.5)	126.1 (73.7)
Stroop Words (words)	90.0 (13.5)	85.0 (14.3)	84.4 (18.8)
Stroop Color (words)	57.4 (11.4)	56.5 (10.6)	55.8 (11.1)
Stroop Color-Word (words)	26.7 (8.7)	26.1 (8.9)	27.0 (8.4)
WMH/Total Brain Volume (%)	0.96 (0.89)	1.39 (1.14)	1.76 (1.28)
FA NAWM	0.41 (0.02)	0.40 (0.02)	0.36 (0.03)
MD NAWM (μm^2/second)	0.817 (0.030)	0.822 (0.031)	0.821 (0.034)
MABP (S/D) (mmHg)	93.4 (10.5)	90.1 (9.4)	91.9 (10.4)

Notes: SD = standard deviation; WMH = white matter hyperintensity lesions; WTAR = Wechsler Test of Adult Reading; TMTA = Trail Making Test A; TMTB = Trail Making Test B; FA = Fractional Anisotropy; MD = Mean Diffusivity; NAWM = Normal Appearing White Matter; MABP = mean arterial blood pressure.

Table 2
Time only models of change in cognitive outcome variables

Cognitive Measure	Fixed Effect	Coefficient	Standard error	*t*-ratio	DF	*p*-value
TMT A	Intercept	44.40	1.95	22.80	84	<0.001
	Time Slope	5.17	1.18	4.37	184	**<0.001**
TMT B	Intercept	120.36	7.07	17.02	84	<0.001
	Time Slope	12.35	4.00	3.09	184	**0.002**
Stroop CW	Intercept	26.65	0.95	28.11	84	<0.001
	Time Slope	-0.64	0.47	-1.37	184	0.170

Table 3

Cross-sectional analysis of baseline demographic factors with cognitive outcome variables

Cognitive Measure	Fixed Effect	Coefficient	Standard error	*t*-ratio	DF	*p*-value
TMT A	Intercept	46.06	5.48	8.41	81	<0.001
	Age Slope	0.84	0.42	2.01	81	**0.044**
	Education Slope	-1.071098	0.588427	-1.820	81	0.068
	Gender Slope	1.150306	3.359810	0.342	81	0.732
TMT B	Intercept	131.47	19.72	6.67	81	<0.001
	Age Slope	4.08	1.50	2.71	81	**0.007**
	Education Slope	-5.83	2.11	-2.76	81	**0.006**
	Gender Slope	-1.95	12.10	-0.16	81	0.873
Stroop CW	Intercept	22.40	2.72	8.24	81	<0.001
	Age Slope	-0.65	0.21	-3.15	81	**0.002**
	Education Slope	0.68	0.29	2.32	81	**0.020**
	Gender Slope	2.44	1.67	1.46	81	0.144

Table 4
Baseline demographic moderation of change on the Trail Making Test

Cognitive Measure	Fixed Effect	Coefficient	Standard error	*t*-ratio	DF	*p*-value
TMT A	**Between-Subjects Effects**					
	Intercept	49.51	12.41	3.99	81	<0.001
	Age Slope	1.07	0.48	2.25	81	0.025
	Education Slope	-0.47	0.67	-0.71	81	0.479
	Gender Slope	1.29	3.50	0.37	81	0.712
	Interaction with Time					
	Intercept	19.76	6.24	3.17	179	0.002
	Age Slope	-0.15	0.29	-0.53	179	0.599
	Education Slope	-0.94	0.40	-2.35	179	**0.019**
TMT B	**Between-Subjects Effects**					
	Intercept	123.55	20.11	6.14	81	<0.001
	Age Slope	4.73	1.66	2.84	81	0.005
	Education Slope	-5.32	2.33	-2.29	81	0.022
	Gender Slope	-2.06	12.25	-0.17	81	0.867
	Interaction with Time					
	Intercept	12.55	4.03	3.12	179	0.002
	Age Slope	-0.43	0.99	-0.43	179	0.664
	Education Slope	-0.75	1.38	-0.54	179	0.589

Table 5
Predicting change on the Trail Making Test with change in global white matter integrity

Cognitive Measure	Fixed Effect	Coefficient	Standard error	*t*-ratio	DF	*p*-value
TMT A	**Between-Subjects Effects**					
	Intercept	44.53	5.76	7.73	81	<0.001
	Age Slope	0.90	0.43	2.09	81	0.036
	Education Slope	-1.07	0.60	-1.78	81	0.075
	Gender Slope	1.36	3.44	0.40	81	0.692
	Within-Subjects Effects					
	Intercept	1.96	2.12	0.92	178	0.356
	WMH Slope	4.12	2.96	1.39	178	0.165
	FA Slope	-56.87	80.97	-0.70	178	0.482
	MD Slope	322.73	102.07	3.16	178	**0.002**
TMT B	**Between-Subjects Effects**					
	Intercept	131.44	20.07	6.55	81	<0.001
	Age Slope	4.18	1.51	2.77	81	0.006
	Education Slope	-5.70	2.11	-2.70	81	0.007
	Gender Slope	-1.63	12.06	-0.14	81	0.893
	Within-Subjects Effects					
	Intercept	-0.04	6.69	-0.01	178	0.995
	WMH Slope	42.60	9.13	4.67	178	**<0.001**
	FA Slope	269.58	249.85	1.08	178	0.281
	MD Slope	365.07	312.28	1.17	178	0.243

Notes: WMH = percentage white matter hyperintensity burden; TMT A = Trail Making Test A; TMT B = Trail Making Test B; FA = Fractional Anisotropy; MD = Mean Diffusivity

Table 6
Cross-sectional prediction of cognitive outcome variables: Age and MABP model

Cognitive Measure	Fixed Effect	Coefficient	Standard error	*t*-ratio	DF	*p*-value
TMT A	Intercept	46.54	5.38	8.65	80	<0.001
	Age Slope	0.70	0.42	1.69	80	0.091
	Education Slope	-1.16	0.58	-2.01	80	**0.045**
	Gender Slope	0.90	3.30	0.27	80	0.786
	MABP Slope	0.30	0.16	1.90	80	0.057
TMT B	Intercept	133.22	19.40	6.87	80	<0.001
	Age Slope	3.60	1.50	2.40	80	**0.017**
	Education Slope	-6.14	2.08	-2.94	80	**0.004**
	Gender Slope	-2.94	11.91	-0.25	80	0.805
	MABP Slope	1.03	0.57	1.81	80	0.070
Stroop CW	Intercept	22.28	2.71	8.21	80	<0.001
	Age Slope	-0.63	0.21	-2.98	80	**0.003**
	Education Slope	0.69	0.29	2.38	80	**0.017**
	Gender Slope	2.51	1.67	1.51	80	0.132
	MABP Slope	-0.06	0.08	-0.75	80	0.452

Notes: MABP = mean arterial blood pressure.

Table 7
Cross-sectional prediction of cognitive outcome variables: MABP only model

Cognitive Measure	Fixed Effect	Coefficient	Standard error	*t*-ratio	DF	*p*-value
TMT A	Intercept	46.06	5.48	8.41	81	<0.001
	MABP Slope	0.35	0.16	2.20	81	**0.028**
	Education Slope	-1.07	0.59	-1.82	81	0.068
	Gender Slope	1.15	3.36	0.34	81	0.732
TMT B	Intercept	131.47	19.72	6.67	81	<0.001
	MABP Slope	1.27	0.58	2.21	81	**0.027**
	Education Slope	-5.83	2.11	-2.76	81	**0.006**
	Gender Slope	-1.95	12.10	-0.16	81	0.873
Stroop CW	Intercept	22.40	2.72	8.24	81	<0.001
	MABP Slope	-0.10	0.08	-1.23	81	0.220
	Education Slope	0.68	0.29	2.32	81	**0.020**
	Gender Slope	2.44	1.67	1.46	81	0.144

Notes: MABP = mean arterial blood pressure.

Table 8
Longitudinal prediction of change on the Trail Making Test: MABP model

Cognitive Measure	Fixed Effect	Coefficient	Standard error	*t*-ratio	DF	*p*-value
TMT A	**Between-Subjects Effects**					
	Intercept	42.43	5.70	7.45	81	<0.001
	Age Slope	0.98	0.43	2.26	81	0.024
	Education Slope	-1.08	0.61	-1.78	81	0.074
	Gender	1.26	3.47	0.37	81	0.715
	Within-Subjects Effects					
	Intercept	5.36	1.18	4.54	180	<0.001
	MABP Slope	0.15	0.16	0.96	180	0.340
TMT B	**Between-Subjects Effects**					
	Intercept	123.32	20.18	6.11	81	<0.001
	Age Slope	4.45	1.53	2.91	81	0.004
	Education Slope	-5.80	2.15	-2.70	81	0.007
	Gender	-1.98	12.30	-0.16	81	0.872
	Within-Subjects Effects					
	Intercept	12.87	3.96	3.25	180	0.002
	MABP Slope	0.34	0.47	0.71	180	0.476

Notes: MABP = mean arterial blood pressure.

Figures

Figure 1
Sample size flow chart

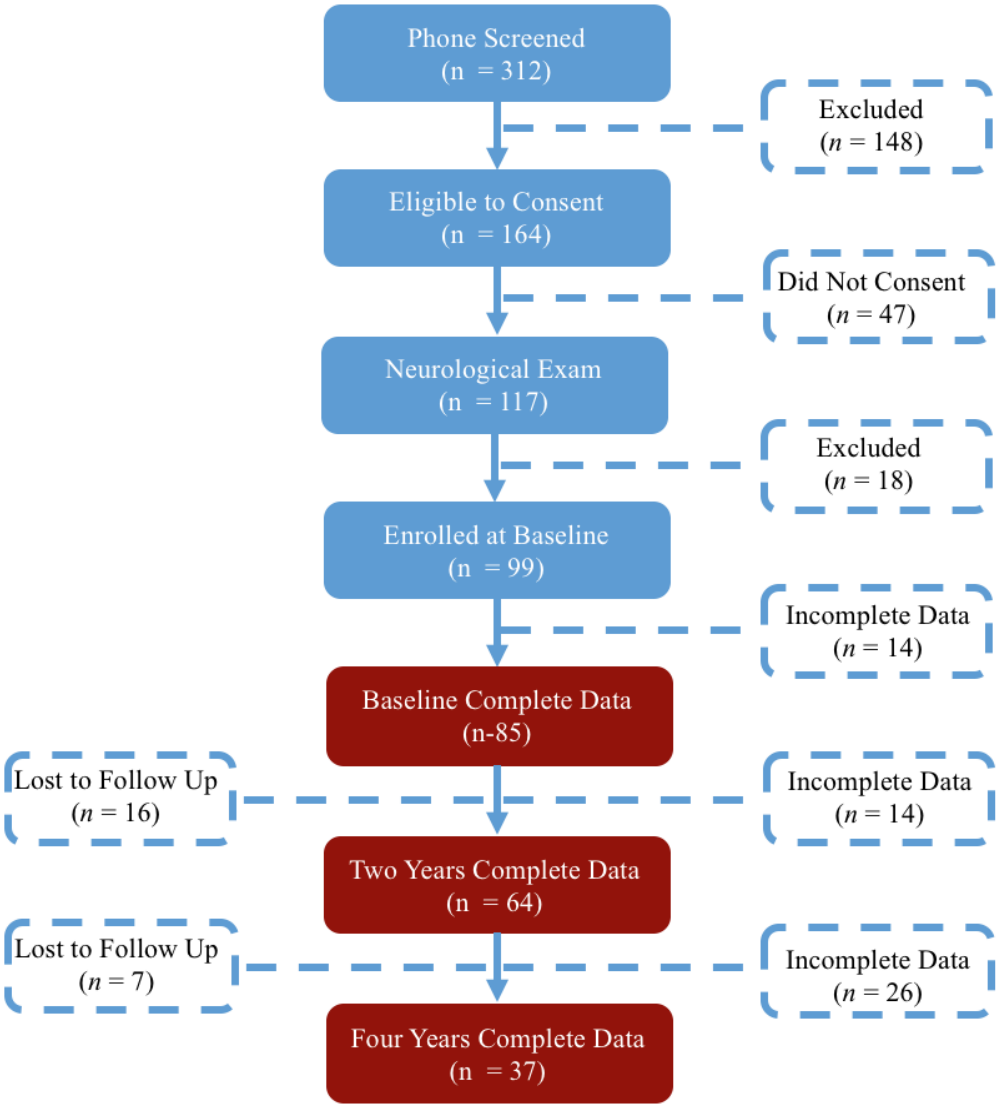
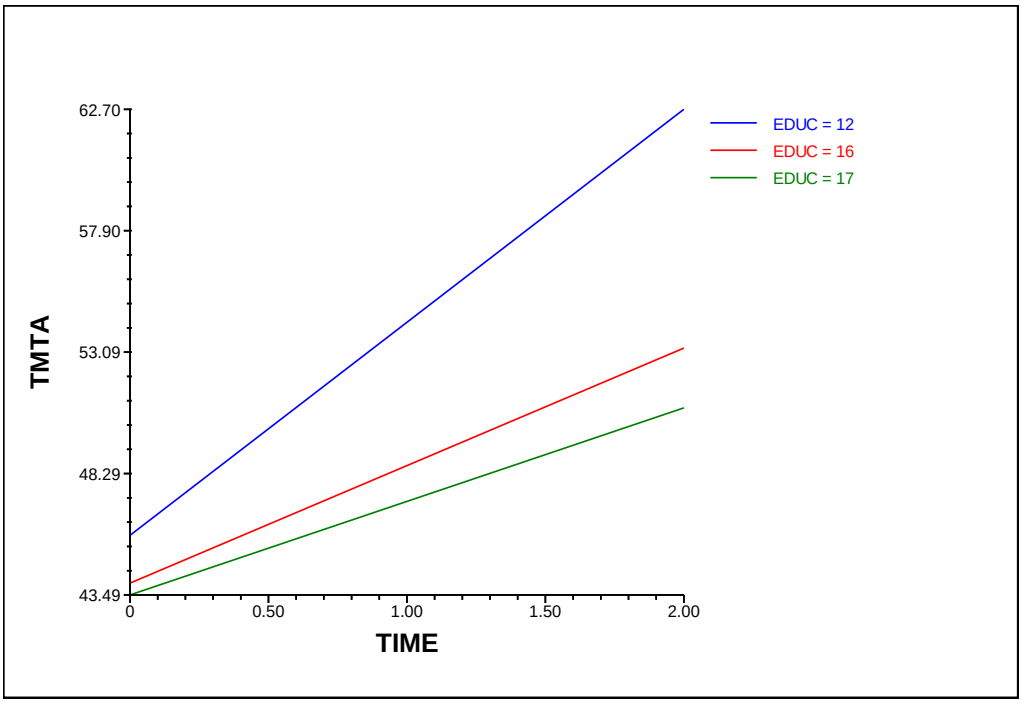


Figure 2

Interaction of Time and Education on performance on the Trail Making Test Part A. Individuals with higher levels of education demonstrated less slowing on the task across the study.



References

Adólfsdóttir, S., Wollschlaeger, D., Wehling, E., & Lundervold, A. J. (2017). Inhibition and Switching in Healthy Aging: A Longitudinal Study. *Journal of the International Neuropsychological Society*, *23*(1), 90–97. https://doi.org/10.1017/S1355617716000898

Allan, C. L., Zsoldos, E., Filippini, N., Sexton, C. E., Topiwala, A., Valkanova, V., … Kivimäki, M. (2015). Lifetime hypertension as a predictor of brain structure in older adults: Cohort study with a 28-year follow-up. *British Journal of Psychiatry*, *206*(4), 308–315. https://doi.org/10.1192/bjp.bp.114.153536

Bartzokis, G., Albert, M., Alonso, G., Anggard, E., Aston-Jones, G., Rogers, J., … Michikawa, M. (2004). Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. *Neurobiology of Aging*, *25*(1), 5–18. https://doi.org/10.1016/j.neurobiolaging.2003.03.001

Basser, P. J., Mattiello, J., & LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophysical Journal*, *66*(1), 259–67. https://doi.org/10.1016/S0006-3495(94)80775-1

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR in Biomedicine*, *15*(7–8), 435–55. https://doi.org/10.1002/nbm.782

Bender, A. R., Prindle, J. J., Brandmaier, A. M., & Raz, N. (2016). White matter and memory in healthy adults: Coupled changes over two years. *NeuroImage*, *131*, 193–204. https://doi.org/10.1016/j.neuroimage.2015.10.085

Bender, A. R., & Raz, N. (2015). Normal-appearing cerebral white matter in healthy adults: Mean change over 2 years and individual differences in change. *Neurobiology of Aging*, *36*(5), 1834–1848. https://doi.org/10.1016/j.neurobiolaging.2015.02.001

Bender, A. R., Völkle, M. C., & Raz, N. (2016). Differential aging of cerebral white matter in middle-aged and older adults: A seven-year follow-up. *NeuroImage, 125*, 74–83. https://doi.org/10.1016/j.neuroimage.2015.10.030

Bennett, I. J., & Madden, D. J. (2014). Disconnected aging: Cerebral white matter integrity and age-related differences in cognition. *Neuroscience, 276*, 187–205. https://doi.org/10.1016/j.neuroscience.2013.11.026

Bettcher, B. M., Mungas, D., Patel, N., Elofson, J., Dutt, S., Wynn, M., … Kramer, J. H. (2016). Neuroanatomical substrates of executive functions: Beyond prefrontal structures. *Neuropsychologia, 85*, 100–109. https://doi.org/10.1016/j.neuropsychologia.2016.03.001

Borghesani, P. R., Madhyastha, T. M., Aylward, E. H., Reiter, M. A., Swarny, B. R., Warner Schaie, K., & Willis, S. L. (2013). The association between higher order abilities, processing speed, and age are variably mediated by white matter integrity during typical aging. *Neuropsychologia, 51*(8), 1435–1444. https://doi.org/10.1016/j.neuropsychologia.2013.03.005

Brickman, A. M., Siedlecki, K. L., Muraskin, J., Manly, J. J., Luchsinger, J. A., Yeung, L. K., … Stern, Y. (2011). White matter hyperintensities and cognition: Testing the reserve hypothesis. *Neurobiology of Aging, 32*(9), 1588–1598. https://doi.org/10.1016/j.neurobiolaging.2009.10.013

Burgmans, S., van Boxtel, M. P. J., Gronenschild, E. H. B. M., Vuurman, E. F. P. M., Hofman, P., Uylings, H. B. M., … Raz, N. (2010). Multiple indicators of age-related differences in cerebral white matter and the modifying effects of hypertension. *NeuroImage, 49*(3), 2083–93. https://doi.org/10.1016/j.neuroimage.2009.10.035

Canolty, R. T., Edwards, E., Dalal, S. S., Soltani, M., Nagarajan, S. S., Kirsch, H. E., … Knight,

R. T. (2006). High gamma power is phase-locked to theta oscillations in human neocortex. *Science (New York, N.Y.), 313*(5793), 1626–8. https://doi.org/10.1126/science.1128115

Carmichael, O., Mungas, D., Beckett, L., Harvey, D., Tomaszewski, S., Reed, B., … Decarli, C. (2012). MRI predictors of cognitive change in a diverse and carefully characterized elderly population. *Neurobiology of AgingAging*, *33*(1), 83–95. https://doi.org/10.1016/j.neurobiolaging.2010.01.021.MRI

Catani, M., & Ffytche, D. H. (2005). The rises and falls of disconnection syndromes. *Brain*, *128*(10), 2224–39. https://doi.org/10.1093/brain/awh622

Charlton, R. A., Schiavone, F., Barrick, T. R., Morris, R. G., & Markus, H. S. (2010). Diffusion tensor imaging detects age related white matter change over a 2 year follow-up which is associated with working memory decline. *Journal of Neurology, Neurosurgery, and Psychiatry*, *81*(1), 13–9. https://doi.org/10.1136/jnnp.2008.167288

Debette, S., & Markus, H. S. (2010). The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ (Clinical Research Ed.), 341*(7), c3666. https://doi.org/10.1136/bmj.c3666

Debette, S., Seshadri, S., Beiser, A., Au, R., Himali, J. J., Palumbo, C., … DeCarli, C. (2011). Midlife vascular risk factor exposure accelerates structural brain aging. *Neurology*, *77*(5), 461–468. https://doi.org/https://doi.org/10.1212/WNL.0b013e318227b227

Erten-Lyons, D., Woltjer, R., Kaye, J., Mattek, N., Dodge, H. H., Green, S., … Silbert, L. C. (2013). Neuropathologic basis of white matter hyperintensity accumulation with advanced age. *Neurology*, *81*(11), 977–983. https://doi.org/10.1212/WNL.0b013e3182a43e45

Faget-Agius, C., Boyer, L., Lançon, C., Richieri, R., Fassio, E., Soulier, E., … Guye, M. (2013). Structural and functional reorganization of working memory system during the first decade

in schizophrenia. A cross-sectional study. *Schizophrenia Research*, *151*(1–3), 48–60. https://doi.org/10.1016/j.schres.2013.10.023

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., … Dale, A. M. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–55.

Fjell, A. M., Sneve, M. H., Grydeland, H., Storsve, A. B., & Walhovd, K. B. (2016). The Disconnected Brain and Executive Function Decline in Aging. *Cerebral Cortex*, 1–15. https://doi.org/10.1093/cercor/bhw082

Golden, C. (1978). *Stroop Color and Word Test: A Manual for Clinical and Experimental Uses*. Chicago, IL: Stoelting.

Gunning-Dixon, F. M., Brickman, A. M., Cheng, J. C., & Alexopoulos, G. S. (2009). Aging of cerebral white matter: a review of MRI findings. *International Journal of Geriatric Psychiatry*, *24*(2), 109–17. https://doi.org/10.1002/gps.2087

Gunning-Dixon, F. M., & Raz, N. (2000). The cognitive correlates of white matter abnormalities in normal aging: a quantitative review. *Neuropsychology*, *14*(2), 224–32. https://doi.org/10.1037//0894-4105.14.2.224

Gunning-Dixon, F. M., & Raz, N. (2003). Neuroanatomical correlates of selected executive functions in middle-aged and older adults: a prospective MRI study. *Neuropsychologia*, *41*(14), 1929–1941. https://doi.org/10.1016/S0028-3932(03)00129-5

Hayes, T. L., Larimer, N., Adami, A., & Kaye, A. J. (2009). Medication adherence in healthy elders: small cognitive changes make a big difference. *Journal of Aging Health Aging Health*, *21*(4), 567–580. https://doi.org/10.1177/0898264309332836.Medication

Horn, J. L., & Cattell, R. B. (1967). Age differences in fluid and crystallized intelligence. *Acta*

Psychologica, *26*(2), 107–29.

Hugenschmidt, C. E., Peiffer, A. M., Kraft, R. A., Casanova, R., Deibler, A. R., Burdette, J. H., … Laurienti, P. J. (2008). Relating Imaging Indices of White Matter Integrity and Volume in Healthy Older Adults. *Cerebral Cortex*, *18*(2), 433–442. https://doi.org/10.1093/cercor/bhm080

Hugenschmidt, C. E., Peiffer, A. M., Kraft, R. A., Casanova, R., Deibler, A. R., Burdette, J. H., … Laurienti, P. J. (2008). Relating imaging indices of white matter integrity and volume in healthy older adults. *Cerebral Cortex*, *18*(2), 433–42. https://doi.org/10.1093/cercor/bhm080

Jacobs, H. I. L., Leritz, E. C., Williams, V. J., Van Boxtel, M. P. J., Elst, W. Van Der, Jolles, J., … Salat, D. H. (2013). Association between white matter microstructure, executive functions, and processing speed in older adults: The impact of vascular health. *Human Brain Mapping*, *34*, 77–95. https://doi.org/10.1002/hbm.21412

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*, *5*(2), 143–56.

Jolly, T. A. D., Cooper, P. S., Rennie, J. L., Levi, C. R., Lenroot, R., Parsons, M. W., … Karayanidis, F. (2017). Age-related decline in task switching is linked to both global and tract-specific changes in white matter microstructure. *Human Brain Mapping*, *38*(3), 1588–1603. https://doi.org/10.1002/hbm.23473

Kennedy, K. M., & Raz, N. (2009). Aging white matter and cognition: differential effects of regional variations in diffusion properties on memory, executive functions, and speed. *Neuropsychologia*, *47*(3), 916–27. https://doi.org/10.1016/j.neuropsychologia.2009.01.001

Kerchner, G. A., Racine, C. A., Hale, S., Wilheim, R., Laluz, V., Miller, B. L., & Kramer, J. H.

(2012). Cognitive processing speed in older adults: relationship with white matter integrity. *PloS One*, *7*(11), e50425. https://doi.org/10.1371/journal.pone.0050425

Kochunov, P., Williamson, D. E., Lancaster, J., Fox, P., Cornell, J., Blangero, J., & Glahn, D. C. (2012). Fractional anisotropy of water diffusion in cerebral white matter across the lifespan. *Neurobiology of Aging*, *33*(1), 9–20. https://doi.org/10.1016/j.neurobiolaging.2010.01.014

Kramer, J. H., Mungas, D., Reed, B. R., Wetzel, M. E., Burnett, M. M., Miller, B. L., … Chui, H. C. (2007). Longitudinal MRI and cognitive change in healthy elderly. *Neuropsychology*, *21*(4), 412–8. https://doi.org/10.1037/0894-4105.21.4.412

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological Assessment* (5th ed.). New York: Oxford University Press.

Lockhart, S. N., & DeCarli, C. (2014). Structural Imaging Measures of Brain Aging. *Neuropsychology Review*, *24*(3), 271–289. https://doi.org/10.1007/s11065-014-9268-3

Lockhart, S. N., Mayda, A. B. V., Roach, A. E., Fletcher, E., Carmichael, O., Maillard, P., … DeCarli, C. (2012). Episodic memory function is associated with multiple measures of white matter integrity in cognitive aging. *Frontiers in Human Neuroscience*, *6*(March), 1–12. https://doi.org/10.3389/fnhum.2012.00056

Longstreth, W. T., Manolio, T. A., Arnold, A., Burke, G. L., Bryan, N., Jungreis, C. A., … Group, for the C. H. S. C. R. (1996). Clinical Correlates of White Matter Findings on Cranial Magnetic Resonance Imaging of 3301 Elderly People: The Cardiovascular Health Study. *Stroke*, *27*(8), 1274–1282. https://doi.org/10.1161/01.STR.27.8.1274

Lövdén, M., Köhncke, Y., Laukka, E. J., Kalpouzos, G., Salami, A., Li, T.-Q., … Bäckman, L. (2014). Changes in perceptual speed and white matter microstructure in the corticospinal tract are associated in very old age. *NeuroImage*, *102*(2), 520–530.

https://doi.org/10.1016/j.neuroimage.2014.08.020

MacPherson, S. E., Cox, S. R., Dickie, D. A., Karama, S., Starr, J. M., Evans, A. C., … Deary, I. J. (2017). Processing speed and the relationship between Trail Making Test-B performance, cortical thinning and white matter microstructure in older adults. *Cortex*, *95*, 92–103. https://doi.org/10.1016/j.cortex.2017.07.021

Madden, D. J., Bennett, I. J., Burzynska, A., Potter, G. G., Chen, N.-K., & Song, A. W. (2012). Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. *Biochimica et Biophysica Acta*, *1822*(3), 386–400. https://doi.org/10.1016/j.bbadis.2011.08.003

Madden, D. J., Bennett, I. J., & Song, A. W. (2009). Cerebral white matter integrity and cognitive aging: contributions from diffusion tensor imaging. *Neuropsychology Review*, *19*(4), 415–35. https://doi.org/10.1007/s11065-009-9113-2

Madden, D. J., Spaniol, J., Costello, M. C., Bucur, B., White, L. E., Cabeza, R., … Huettel, S. A. (2009). Cerebral White Matter Integrity Mediates Adult Age Differences in Cognitive Performance. *Journal of Cognitive Neuroscience*, *21*(2), 289–302. https://doi.org/10.1162/jocn.2009.21047

Maillard, P., Carmichael, O., Harvey, D., Fletcher, E., Reed, B., Mungas, D., & DeCarli, C. (2013). FLAIR and diffusion MRI signals are independent predictors of white matter hyperintensities. *American Journal of Neuroradiology*, *34*(1), 54–61. https://doi.org/10.3174/ajnr.A3146

Malloy, P., Correia, S., Stebbins, G., & Laidlaw, D. H. (2007). Neuroimaging of White Matter in Aging and Dementia. *The Clinical Neuropsychologist*, *21*(1), 73–109. https://doi.org/10.1080/13854040500263583

Maniega, S. M., Valdés Hernández, M. C., Clayden, J. D., Royle, N. A., Murray, C., Morris, Z.,

… Wardlaw, J. M. (2015). White matter hyperintensities and normal-appearing white matter integrity in the aging brain. *Neurobiology of Aging*, *36*(2), 909–918. https://doi.org/10.1016/j.neurobiolaging.2014.07.048

Marner, L., Nyengaard, J. R., Tang, Y., & Pakkenberg, B. (2003). Marked loss of myelinated nerve fibers in the human brain with age. *The Journal of Comparative Neurology*, *462*(2), 144–52. https://doi.org/10.1002/cne.10714

Mechelli, A., Allen, P., Amaro, E., Fu, C. H. Y., Williams, S. C. R., Brammer, M. J., … McGuire, P. K. (2007). Misattribution of speech and impaired connectivity in patients with auditory verbal hallucinations. *Human Brain Mapping*, *28*(11), 1213–22. https://doi.org/10.1002/hbm.20341

Mitchell, M. B., Shaughnessy, L. W., Shirk, S. D., Yang, F. M., & Atri, A. (2012). Neuropsychological test performance and cognitive reserve in healthy aging and the Alzheimer's disease spectrum: a theoretically driven factor analysis. *Journal of the International Neuropsychological Society : JINS*, *18*(6), 1071–80. https://doi.org/10.1017/S1355617712000859

Mura, T., Amieva, H., Goldberg, M., Dartigues, J. F., Ankri, J., Zins, M., & Berr, C. (2016). Effect size for the main cognitive function determinants in a large cross-sectional study. *European Journal of Neurology*, *23*(11), 1614–1626. https://doi.org/10.1111/ene.13087

O'Sullivan, M. (2008). Leukoaraiosis. *Practical Neurology*, *8*, 26–38.

O'Sullivan, M., Jones, D. K., Summers, P. E., Morris, R. G., Williams, S. C., & Markus, H. S. (2001). Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology*, *57*(4), 632–8.

Papp, K. V., Kaplan, R. F., Springate, B., Moscufo, N., Wakefield, D. B., Guttmann, C. R. G., &

Wolfson, L. (2014). Processing speed in normal aging: Effects of white matter hyperintensities and hippocampal volume loss. *Aging, Neuropsychology, and Cognition*, *21*(2), 197–213. https://doi.org/10.1080/13825585.2013.795513

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

Pierpaoli, C., & Basser, P. J. (1996). Toward a quantitative assessment of diffusion anisotropy. *Magnetic Resonance in Medicine*, *36*(6), 893–906.

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

Rabbitt, P., Scott, M., Lunn, M., Thacker, N., Lowe, C., Pendleton, N., … Jackson, A. (2007). White matter lesions account for all age-related declines in speed but not in intelligence. *Neuropsychology*, *21*(3), 363–70. https://doi.org/10.1037/0894-4105.21.3.363

Raz, N., Gunning-Dixon, F. M., Head, D., Dupuis, J. H., & Acker, J. D. (1998). Neuroanatomical correlates of cognitive aging: Evidence from structural magnetic resonance imaging. *Neuropsychology*, *12*(October 2015), 95–114. https://doi.org/10.1037/0894-4105.12.1.95

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., … Acker, J. D. (2005). Regional Brain Changes in Aging Healthy Adults: General Trends, Individual Differences and Modifiers. *Cerebral Cortex*, *15*(11), 1676–1689.

https://doi.org/10.1093/cercor/bhi044

Raz, N., Yang, Y. Q., Rodrigue, K. M., Kennedy, K. M., Lindenberger, U., & Ghisletta, P. (2012). White matter deterioration in 15 months: latent growth curve models in healthy adults. *Neurobiology of Aging*, *33*(2), 429.e1-5. https://doi.org/10.1016/j.neurobiolaging.2010.11.018

Reitan, R. M. (1958). Validity of the Trail Making Test as an Indicator of Organic Brain Damage. *Perceptual and Motor Skills*, *8*(3), 271–276.

Ritchie, S. J., Bastin, M. E., Tucker-Drob, E. M., Maniega, S. M., Engelhardt, L. E., Cox, S. R., … Deary, I. J. (2015). Coupled Changes in Brain White Matter Microstructure and Fluid Intelligence in Later Life. *Journal of Neuroscience*, *35*(22), 8672–8682. https://doi.org/10.1523/JNEUROSCI.0862-15.2015

Salat, D. H. (2014). Imaging small vessel-associated white matter changes in aging. *Neuroscience*, *276*, 174–86. https://doi.org/10.1016/j.neuroscience.2013.11.041

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

Salthouse, T. A. (1994). The Aging of Working Memory. *Neuropsychology*, *8*(4), 535–543.

Salthouse, T. A. (2011). Neuroanatomical substrates of age-related cognitive decline. *Psychological Bulletin*, *137*(5), 753–84. https://doi.org/10.1037/a0023262

Salthouse, T. A. (2014). Why Are There Different Age Relations in Cross-Sectional and Longitudinal Comparisons of Cognitive Functioning? *Current Directions in Psychological Science*, *23*(4), 252–256. https://doi.org/10.1177/0963721414535212

Salthouse, T. A., Toth, J., Daniels, K., Parks, C., Pak, R., Wolbrette, M., & Hocking, K. J. (2000). Effects of aging on efficiency of task switching in a variant of the trail making test. *Neuropsychology*, *14*(1), 102–111. https://doi.org/10.1037//0894-4105.14.1.102

Santiago, C., Herrmann, N., Swardfager, W., Saleem, M., Oh, P. I., Black, S. E., & Lanctôt, K. L. (2015). White matter microstructural integrity is associated with executive function and processing speed in older adults with coronary artery disease. *American Journal of Geriatric Psychiatry*, *23*(7), 754–763. https://doi.org/10.1016/j.jagp.2014.09.008

Scott, B. M., Maye, J., Jones, J., Thomas, K., Mangal, P. C., Trifilio, E., … Bowers, D. (2016). Post-exercise pulse pressure is a better predictor of executive function than pre-exercise pulse pressure in cognitively normal older adults. *Aging, Neuropsychology, and Cognition*, *23*(4), 464–476. https://doi.org/10.1080/13825585.2015.1118007

Sédille-Mostafaie, N., Zehetmayer, S., Krampla, W., Krugluger, W., & Fischer, P. (2015). Influence of vascular risk factors on executive function among an age-homogeneous elderly cohort. *Journal of Neural Transmission*, *122*(9), 1323–1328. https://doi.org/10.1007/s00702-015-1389-1

Siedlecki, K. L., Stern, Y., Reuben, A., Sacco, R. L., Elkind, M. S. V., & Wright, C. B. (2009). Construct validity of cognitive reserve in a multiethnic cohort: The Northern Manhattan Study. *Journal of the International Neuropsychological Society*, *15*(4), 558–69. https://doi.org/10.1017/S1355617709090857

Sled, J. G., Zijdenbos, A. P., & Evans, A. C. (1998). A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Transactions on Medical Imaging*, *17*(1), 87–97. https://doi.org/10.1109/42.668698

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., …

Behrens, T. E. J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*, *31*(4), 1487–1505. https://doi.org/10.1016/j.neuroimage.2006.02.024

Spieler, D. H., Balota, D. A., & Faust, M. E. (1996). Stroop performance in healthy younger and older adults and in individuals with dementia of the Alzheimer's type. *Journal of Experimental Psychology. Human Perception and Performance*, *22*(2), 461–79.

Stern, Y., Gurland, B., Tatemichi, T. K., Tang, M. X., Wilder, D., & Mayeux, R. (1994). Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA*, *271*(13), 1004–10.

Sullivan, E. V., & Pfefferbaum, A. (2006). Diffusion tensor imaging and aging. *Neuroscience & Biobehavioral Reviews*, *30*(6), 749–761. https://doi.org/10.1016/j.neubiorev.2006.06.002

Tsao, C. W., Himali, J. J., Beiser, A. S., Larson, M. G., Decarli, C., Vasan, R. S., … Seshadri, S. (2016). Association of arterial stiffness with progression of subclinical brain and cognitive disease. *Neurology*, *86*(7), 619–626. https://doi.org/10.1212/WNL.0000000000002368

Valenzuela, M. J., & Sachdev, P. (2006). Brain reserve and dementia: a systematic review. *Psychological Medicine*, *36*(4), 441–54. https://doi.org/10.1017/S0033291705006264

Van der Elst, W., Van Boxtel, M. P. J., Van Breukelen, G. J. P., & Jolles, J. (2006). The Stroop Color-Word Test: influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment*, *13*(1), 62–79. https://doi.org/10.1177/1073191105283427

Van Gerven, P. W. M., Van Boxtel, M. P. J., Ausems, E. E. B., Bekers, O., & Jolles, J. (2012). Do apolipoprotein e genotype and educational attainment predict the rate of cognitive decline in normal aging? A 12-year follow-up of the maastricht aging study.

Neuropsychology, *26*(4), 459–472. https://doi.org/10.1037/a0028685

Vannorsdall, T. D., Waldstein, S. R., Kraut, M., Pearlson, G. D., & Schretlen, D. J. (2009). White Matter Abnormalities and Cognition in a Community Sample. *Archives of Clinical Neuropsychology*, *24*, 209–217. https://doi.org/10.1093/arclin/acp037

Vernooij, M. W., de Groot, M., van der Lugt, A., Ikram, M. A., Krestin, G. P., Hofman, A., … Breteler, M. M. B. (2008). White matter atrophy and lesion formation explain the loss of structural integrity of white matter in aging. *NeuroImage*, *43*(3), 470–7. https://doi.org/10.1016/j.neuroimage.2008.07.052

Wakefield, D. B., Moscufo, N., Guttmann, C. R., Kuchel, G. A., Kaplan, R. F., Pearlson, G., & Wolfson, L. (2010). White matter hyperintensities predict functional decline in voiding, mobility, and cognition in older adults. *Journal of the American Geriatrics Society*, *58*(2), 275–81. https://doi.org/10.1111/j.1532-5415.2009.02699.x

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychological Bulletin*, *120*(2), 272–92.

Wilson, R. S., Rajan, K. B., Barnes, L. L., Hebert, L. E., Mendes De Leon, C. F., & Evans, D. A. (2014). Cognitive aging and rate of hospitalization in an Urban Population of Older People. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *69*(4), 447–454. https://doi.org/10.1093/gerona/glt145

Wilson, R. S., Scherr, P. A., Schneider, J. A., Tang, Y., & Bennett, D. A. (2007). Relation of cognitive activity to risk of developing Alzheimer disease. *Neurology*, *69*(20), 1911–1920. https://doi.org/10.1212/01.wnl.0000271087.67782.cb

Yang, Y., Bender, A. R., & Raz, N. (2015). Age related differences in reaction time components and diffusion properties of normal-appearing white matter in healthy adults.

Neuropsychologia, *66*, 246–58. https://doi.org/10.1016/j.neuropsychologia.2014.11.020

Zheng, J. J. J., Lord, S. R., Close, J. C. T., Sachdev, P. S., Wen, W., Brodaty, H., & Delbaere, K. (2012). Brain White Matter Hyperintensities, Executive Dysfunction, Instability, and Falls in Older People: A Prospective Cohort Study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *67*(10), 1085–1091. https://doi.org/10.1093/gerona/gls063