Spring 4-22-2014

Intraindividual Variability as a Correlate of White Matter Decline

Jonathan David Jackson
Washington University in St. Louis

WASHINGTON UNIVERSITY IN ST. LOUIS

Department of Psychology

Dissertation Examination Committee:
Denise Head, Chair
Beau Ances
David Balota
Tammie Benzinger
Julie Bugg
Janet Duchek

Intraindividual Variability as a Correlate of White Matter Decline

by

Jonathan David Jackson

A dissertation presented to the
Graduate School of Arts and Sciences
of Washington University in
partial fulfillment of the
requirements for the degree
of Doctor of Philosophy

May 2014

Saint Louis, Missouri

Table of Contents

List of Figures

List of Tables

Acknowledgements

I thank the Clinical Core of the Knight Alzheimer's Disease Research Center at Washington University for the clinical assessments and the Imaging Core for the structural MRI data, and Denise Head, David Balota, and Janet Duchek for helpful comments. This work was supported by NIH grants P50 AG05861, P01 AG 03991, PO1 AGO26276, and by National Institute of General Medical Sciences grant T32-GM81739-02.

ABSTRACT OF THE DISSERTATION

Intraindividual Variability as a Correlate of White Matter Decline

by

Jonathan David Jackson

Doctor of Philosophy in Psychology

Washington University in St. Louis, 2014

Associate Professor Denise Head, Chair

Aging and early-stage Alzheimer disease (AD) have been associated with increased reaction time intraindividual variability (IIV). In previous studies this age-related increase in IIV has been associated with white matter volumes and microstructure. However, the association between IIV and white matter has not been contextualized with other aspects of cognitive performance and neuroanatomical structure, in particular with median reaction time and estimates of gray matter. Using cognitive composites derived from three attentional tasks (Stroop, Simon, and CVOE switching), in conjunction with estimates of regional gray matter thickness and white matter volume, the present dissertation examined two aims on a group of cognitively normal and early-stage AD participants. Based on previous literature, the first aim examined evidence for a double dissociation between aspects of cognitive performance and neuroanatomical structure, such that the coefficient of variation (CoV, a measure of IIV) would uniquely be associated with white matter while median RT associated with gray matter thickness. The second aim examined evidence for a mediational role of CoV, such that this variable accounted for the association observed between regional white matter and performance on working memory and episodic memory tasks. Furthermore, Aim 2 examined whether CoV mediated the relationship between

two genetic factors (Apolipoprotein and catechol-*O*-methyltransferase) and memory performance as well. No support was found for either aim. Discussion focuses on possible explanations for the lack of reliable associations. Based on observations from post-hoc analyses it is suggested that group differences (e.g., cognitively normal vs. early-stage AD) in the sensitivity of IIV to cognitive performance and white matter may be a factor in the association of IIV with neurocognitive measures.

Introduction

Despite many investigations focused on human aging using structural and functional neuroimaging over the past quarter-century, questions abound regarding the complex consequences of healthy and pathological aging on neurological structure and cognition (Raz & Lindenberger, 2011; Salthouse, 2011). Recent advances in neuroanatomical and cognitive measurement have not been fully explored in concert, and a neurocognitive approach may shed additional light on the structure-function relationship of the human brain as it ages. For example, the reduced structural integrity or volume of the brain appears to be particularly related to reaction time intraindividual variability (IIV), over and above an association with mean or median reaction time (Burton et al., 2006; Jackson, Balota, Duchek, & Head, 2012). The present dissertation focuses on the relationship between the brain's structural integrity and estimates of central tendency and IIV in reaction time in tasks of cognitive performance for cognitively normal older adults and individuals with early-stage Alzheimer disease (AD). Specifically, given that the extant literature has yoked reaction time variability with white matter integrity (Anstey et al., 2007; Bunce et al., 2007; Fjell, Westlye, Amlien, & Walhovd, 2011; MacDonald, Li, & Bäckman, 2009; Moy et al., 2011; Ullén, Forsman, Blom, Karabanov, & Madison, 2008; Walhovd & Fjell, 2007), two aims directly examined whether increased reaction time intraindividual variability in cognitive tasks is associated with white matter. The first aim explored whether increased intraindividual variability better reflected compromised white matter relative to median performance estimates in older adults. The converse of this association, that gray matter may more strongly associate with estimates of central tendency (i.e., median reaction time) likewise was tested in order to demonstrate a possible double dissociation between estimates of cognitive performance and neuroanatomical integrity. Given this proposed dissociation, the second aim explored whether intraindividual variability mediated the

relationship between white matter integrity and working memory and episodic memory performance, as well as the relationship between genetic factors and memory performance.

Defining Intraindividual Variability

Broadly, the study of reaction time (RT) variability in cognitive tasks is a relatively recent development in experimental psychology (Luce, 1977, 1986), and has only lately been applied to cognitive aging (Hultsch, Strauss, Hunter, & MacDonald, 2008; MacDonald, Hultsch, & Dixon, 2003). Typically, examinations of cognitive functioning tend to rely on mean RTs, a measure of central tendency that assumes stability within individuals or groups. Exclusive focus on the mean, however, necessarily relegates RT instability to random noise, ignoring potentially systematic variations that may inform cognitive and neurobiological processes. Furthermore, qualitative differences in cognitive performance can be obscured when focusing on mean performance alone (Balota, Yap, Cortese, & Watson, 2008). Work by Jensen (1992) suggested that while there is shared variance among estimates of reaction time central tendency and dispersion, independent contributions of each emerge. Jensen revealed that median RTs and RT standard deviations were independently correlated with psychometric *g* as well as age, gender, and racial group differences, and he also reported unique sources of variance for each component of reaction time performance using principal components analyses. Therefore, the consideration of intraindividual variability—whether in concert with mean performance or in place of it—is critical to augment our understanding of neurocognitive changes associated with aging and dementia. Indeed, recent work by Garrett (Garrett, Kovacevic, McIntosh, & Grady, 2011, 2013a, 2013b) has demonstrated that even the standard deviation of blood-oxygen-level-dependent (BOLD) signal in functional magnetic resonance imaging (fMRI) reflects meaningful development across the lifespan, and is related to task engagement and performance.

Reaction time variability comprises several types of cognitive performance, including *interindividual differences* (variability across individuals within a given task on a single measurement occasion), *intraindividual differences* (variability within an individual across tasks on a single measurement occasion), and *intraindividual variability* (variability within an individual within a given task across multiple measurement occasions). The present dissertation focuses on this latter measure, intraindividual variability (IIV) of reaction time, specifically in cognitive tasks. Studies of IIV typically find that its magnitude is fully half that of interindividual variability (Hultsch, Strauss, Hunter, & MacDonald, 2008; Nesselroade & Salthouse, 2004), suggesting that IIV is an important, informative source of variance.

IIV itself can be multiply defined, largely with respect to the timescale over which a particular type of variability is investigated. Special consideration is given to *inconsistency*, a type of intraindividual variability indicating fluctuations in performance over very short intervals. Typically, inconsistency deals with variability on a trial-to-trial level in RT tasks, and in their review Hultsch and colleagues (2008) suggested that inconsistency in particular is ideally suited for investigation of neurobiological and endogenous sources of variability. Although an individual's standard deviation (SD) is frequently employed as an index of inconsistency, SDs tend to show high positive correlations with mean RT (Faust, Balota, Spieler, & Ferraro, 1999; Myerson, Hale, Chen, & Lawrence, 1997; Wagenmakers & Brown, 2007; Wagenmakers, Grasman, & Molenaar, 2005), thus obscuring potentially useful distinctions within individuals and across groups over and above mean-level effects. IIV researchers have therefore turned to the coefficient of variation (CoV; SD/mean) and the intraindividual standard deviation (ISD; residual *T* scores partialed for age, gender, trial position, and their interactions), which are emerging as standard measures of inconsistency, due to low bias from mean RTs and high

association with other measures of inconsistency (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000). Critically, mean-corrected measures of IIV like CoV and ISD have been shown to be sensitive measures of cognitive change, revealing key differences between younger and older adults, and between healthy and pathological aging (Dixon et al., 2007; Duchek et al., 2009; Hultsch et al., 2008). The dissertation first considers the utility of investigating IIV in aging and early-stage AD, discusses white matter declines associated with healthy and pathological aging, and then combines these to hypothesize potential neuroanatomical correlates of IIV in older adults.

Intraindividual Variability and Aging

Previous research into the effects of aging on IIV has been remarkably consistent. Older individuals tend to become more variable across a wide range of behaviors, most notably in terms of their performance on cognitive tasks (Bunce, MacDonald, & Hultsch, 2004; Duchek et al., 2009; Myerson, Robertson, & Hale, 2007). Hultsch et al. (2008) reported a number of studies that observed a positive relationship between age and reaction time IIV in cognitive tasks, both in cross-sectional studies (Anstey, Dear, Christensen, & Jorm, 2005; Anstey, 1999; Bunce et al., 2004; Dixon et al., 2007; Duchek et al., 2009; Hultsch, MacDonald, & Dixon, 2002; Nesselroade & Salthouse, 2004; Strauss, Bielak, Bunce, Hunter, & Hultsch, 2007) as well as longitudinal studies (Deary & Der, 2005; Lövdén, Li, Shing, & Lindenberger, 2007; MacDonald et al., 2003).

Myerson et al. (2007), however, argued that age-related differences in IIV might be accommodated using a general slowing account, which suggests that variability has little to contribute to our understanding of aging processes over other measures of reaction time performance. On the other hand, it has been shown that tasks that fail to yield an independent IIV-age relationship tend to be relatively low in cognitive demand (West, Murphy, Armilio, Craik, & Stuss, 2002), and Hultsch et al. (2008) clarified that effects of age on IIV tend to

increase disproportionately for older adults as task complexity increases (Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010a; Lövdén, Li, Shing, & Lindenberger, 2007; MacDonald et al., 2003).

Others have suggested that, task complexity aside, aging is not associated with increased IIV (Salthouse & Nesselroade, 2010; Salthouse, Nesselroade, & Berish, 2006). These studies, however, tend to rely on the standard deviation, which as discussed previously is a confounded estimate of IIV. Further, IIV in the Salthouse and Nesselroade longitudinal studies spanned multiple measurement occasions, rather than variability within a single measurement occasion. Finally, both Salthouse and Nesselroade (2010) and Salthouse et al. (2006) focused on variability in accuracy rather than in reaction time, and investigations examining intraindividual variability in accuracy typically fail to find age effects (Hultsch et al., 2008). Given that accuracy is a single point-estimate of task-set maintenance, it may be a less-dynamic measure than IIV in RTs, which relies on multiple observations within a measurement occasion. Thus, it appears that RT IIV reliably increases with age, although the magnitude of this effect is dependent on task complexity.

Recent work has associated increased IIV with failures of attentional control (Duchek et al., 2009). Bellgrove, Hester, and Garavan (2004) drew a link between RT IIV and inhibitory failures, which the authors likened to attentional lapses in their Go/No-Go paradigm. Bellgrove et al. reported a negative correlation between successful inhibition and the CoV on Go trials, suggesting that IIV may index attentional control. Similar associations between IIV and attentional control in older adults have been reported using various measures of trial-to-trial variability, indicating a certain robustness in the relationship between IIV and attentional lapses

in older adults (Bunce et al., 2004; Duchek et al., 2009; Hultsch et al., 2000; MacDonald et al., 2003; Weissman, Roberts, Visscher, & Woldorff, 2006; West et al., 2002).

Research has also demonstrated that increases in IIV can predict declines in cognitive performance in older adults (Bielak, Hultsch, Strauss, Macdonald, & Hunter, 2010b; Lövdén et al., 2007). Lövdén et al. (2007), in an impressive five-occasion, 13-year longitudinal study of over 400 older adults, reported that increased CoV and ISD in a perceptual speed task reliably preceded declines in verbal digit-symbol substitution and category fluency tasks. Bielak and colleagues (2010b) observed that increased ISD successfully predicted converters to cognitive impairment five years in advance. Furthermore, increased ISD also predicted those likely to drop out of the study by the five-year follow-up. In addition to longitudinal observations, differences in IIV distinguished cognitively impaired individuals from cognitively normal older adults, even when mean cognitive performance was taken into account (Dixon et al., 2007; Duchek et al., 2009; Strauss et al., 2007; although see Christensen et al., 2005). Duchek et al. (2009) demonstrated reliable differences in IIV for early-stage AD relative to cognitively normal older adults. Indeed, Duchek et al. reported greater CoV in cognitively normal older adults at increased genetic risk for AD (i.e., carriers of the Apolipoprotein ε4 allele) relative to cognitively normal older adults not at risk. This finding suggests impairments in attentional control processes in these groups prior to an AD diagnosis, given the strong relationship between increased IIV and breakdowns in attentional control. Increased IIV may also be associated with the Val allele variant of the catechol-*O*-methyltransferase (COMT) gene, another potential risk factor for AD, particularly when it is present in conjunction with Apolipoprotein ε4 (APOE4+; Martínez et al., 2009; Wang et al., 2005). There is some evidence that carriers of the Val polymorphism of the COMT gene, like young-adult APOE4+ carriers, also experience increased IIV (MacDonald,

Cervenka, Farde, Nyberg, & Bäckman, 2009; MacDonald, Li, & Bäckman, 2009; MacDonald, Nyberg, & Bäckman, 2006).

White Matter Structural Changes in Aging and AD

Structural changes in the brain are a natural consequence of aging. In gray matter, there appears to be disproportionate vulnerability of the prefrontal cortex, somewhat more modest declines in some temporal and parietal regions, and relative sparing of primary visual cortex (Hedden & Gabrieli, 2004; Raz et al., 1997; Raz & Rodrigue, 2006).Volumetric declines in cortical gray matter may tend to accelerate with age (Walhovd et al., 2005). Reduced gray matter volume is associated with poorer cognitive performance (Raz, 2000; Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998; Raz & Rodrigue, 2006; although see Van Petten et al., 2004), particularly at the level of accuracy in cognitive domains. In his seminal review, Raz (2000) noted that age-related changes in dorsolateral prefrontal cortex and parietal regions are associated with declines in selective and divided attention. Age-related differences in gray matter thickness often corroborate that of gray matter volume (Fjell, Westlye et al., 2009), although differences between effects on gray thickness and volume have been observed as well (Fjell, Westlye et al., 2009; Salat et al., 2004).

White matter also undergoes changes with advancing age. White matter may be measured in a variety of ways. White matter volume may be derived from the same automated processes as gray matter volume and thickness (Fischl et al., 2002; Fischl et al., 2004a), and white matter integrity may also be quantified by measurement of white matter hyperintensities, which are areas of increased contrast on T2-weighted MRI images. Analysis of white matter microstructure includes several ways of measuring the directional diffusivity of water molecules along white matter tracts. Generally speaking, white matter integrity has been shown to be compromised in both cognitively normal aging and early-stage AD (Gunning-Dixon, Brickman, Cheng, &

Alexopoulos, 2009; Johnson et al., 2010), and there is emerging evidence that white matter changes occur independently of gray matter alterations (see Bai et al., 2009, for a review). The increased presence of white matter hyperintensities may reflect a number of changes associated with healthy and pathological aging, including changes in white matter integrity, compromised vasculature, changes in perivascular spaces, and even atrophy of the neuropil, a region typically associated with gray matter (Gunning-Dixon & Raz, 2000; Yoshita et al., 2006). In cognitively normal aging, there are typically greater anterior declines in white matter volume that may accelerate with time (e.g., Bartzokis et al., 2003; Gunning-Dixon et al., 2009; Head et al., 2004; Salat et al., 2009). Furthermore, white matter integrity in aging may be tied to altered regulation of functional activity in frontal regions more strongly than gray matter integrity (Grady, 2008). The importance of white matter integrity is revealed in its association with reduced connectivity in functional networks of the brain in aging. For example, Andrews-Hanna et al. (2007) reported a positive association between reduced functional network connectivity and reduced white matter integrity, even after controlling for the influence of age. Critically, associations between white matter integrity and cognitive performance have also been reported in cognitively normal older adults (Gunning-Dixon et al., 2009; Raz et al., 2008; Raz, Rodrigue, Kennedy, & Acker, 2007). Hedden et al. (2011) found that white matter hyperintensities fully mediated the relationship between functional network activation and performance on a global-local processing task, suggesting that white matter integrity may play a significant role in cognitive function.

More recently, white matter has been shown to reliably distinguish between healthy and pathological aging processes. Early-stage AD is marked by a differential vulnerability in more posterior regions in AD (Head et al., 2004; Kavcic, Ni, Zhu, Zhong, & Duffy, 2008; Salat et al., 2009). This is also supported in recent work by Salat and colleagues (2010), who demonstrated

that early-stage AD was associated with reduced fractional anisotropy over and above changes attributable to gray matter. Further evidence demonstrates strong links between hippocampal atrophy, an early region of decline in AD, and atrophy of critical white matter regions (Villain et al., 2010; but see Bai et al., 2009). Furthermore, frontal, temporal, corpus callosal, and parietal white matter integrity have been associated with AD-related impairments in memory and executive function (Amar, Bucks, Lewis, Scott, & Wilcock, 1996; Anstey et al., 2007; Huang & Auchus, 2007; Kavcic et al., 2008).

Evidence suggests that the sensitivity of white matter to cognitive aging may occur at least somewhat independently of gray matter contributions. Indeed, Bartzokis (2011) suggested that myelin integrity might uniquely index age-related changes in the brain as well as AD-related pathology. Based on white matter structural changes noted in his previous work (Bartzokis et al., 2003, 2004), Bartzokis (2011) proposed a myelin model of healthy and pathological aging, in which breakdowns in myelin must precede other markers of brain atrophy associated with aging and AD. Oligodendrocytes that differentiate late in their own life cycle create thinner, more vulnerable myelin sheaths in temporoparietal regions of the brain, and to a lesser extent in frontal regions (Bartzokis et al., 2007; Bartzokis, 2011; Wood & Bunger, 1984). The reduced efficiency of myelin repair may trigger upregulation of BACE1 and γ-secretase to compensate (Michailov et al., 2004; Taveggia et al., 2008). Both of these enzymes upregulate amyloid precursor protein processing, which in turn results in greater deposition of β-amyloid (Bartzokis, 2011). Increased β-amyloid deposition is aggravated in individuals with an APOE4 allele, and is currently thought to be a major component in the increased AD risk for APOE4+ individuals (Bartzokis et al., 2003). Ultimately, Bartzokis (2011) suggested that compromised white matter integrity may

underlie a host of changes in the aging brain, and may serve as an ideal early marker of structural and functional decline.

In sum, the study of white matter in conjunction with gray matter estimates may provide additional insight into patterns of the aging brain and the role of neuroanatomy in cognitive decline. Previous research has made clear that using gray and white matter indices reveals a complex pattern of age-related change that could not be discerned examining just one of these measures (Abe et al., 2008; Good et al., 2002; Moy et al., 2011; Salat et al., 2010; Villain et al., 2010; Ziegler et al., 2010); therefore, it is critical that investigations of neuroanatomical correlates of cognitive performance make use of both gray and white matter measures.

Thus far, this dissertation has focused on the unique, albeit separate, association of IIV and white matter integrity with age-related declines in cognitive performance. There is emerging evidence that IIV and white matter are associated with one another, however. Attention therefore now turns toward surveying the evidence in support of an association between IIV and white matter.

Intraindividual Variability as a Correlate of Neuroanatomical Decline

Evidence has accumulated in recent years demonstrating that IIV is a correlate of age-related neuroanatomical decline. MacDonald, Nyberg, and Bäckman (2006) noted that white matter volume and IIV show a similar timescale of development and decline across the lifespan. Specifically, both tend to yield inverted U-shaped functions. Bunce et al. (2007) reported a link between white matter hyperintensities and mean-corrected IIV in 60 – 64 year olds. Recent investigations have demonstrated a negative relationship between IIV and white matter integrity in older adults in wide number of regions across the brain (Anstey et al., 2007; Fjell, Westlye, Amlien, & Walhovd, 2011; Jackson, Balota, Duchek, & Head, 2012; Walhovd & Fjell, 2007). For example, Jackson, Balota, Duchek, and Head (2012) examined three tasks of cognitive

attention (Stroop, Simon, and a switching task) in conjunction with cerebral and regional white matter volume in 133 cognitively normal and 33 early-stage AD individuals. They reported that larger volumes in frontal and temporoparietal regions were associated with lower CoV and less slowing in the tail of the RT distribution, and larger total cerebral and inferior parietal white matter volumes were associated with faster modal reaction time. These results are consistent with previous research investigating prefrontal, temporal, and parietal volumes (Ullén et. al, 2008), the corpus callosum (Anstey et al., 2007), whole-brain volumes (Walhovd & Fjell, 2007), and white matter microstructure (Moy et al., 2011) and macrostructure (Bunce et al., 2007; Ota, Nemoto, Sato, Yamashita, & Asada, 2009). The cross-sectional association between white matter integrity and IIV, then, appears to be relatively robust, although the relationship between IIV and gray matter is less clear.

Intraindividual variability and gray matter

Given that increased variability may reflect breakdowns in neural fidelity (Rabbitt, Osman, Moore, & Stollery, 2001), increased IIV may be associated with gray matter integrity as well as white matter. There is, however, little research demonstrating a unique association of gray matter with IIV, perhaps partly because few studies have directly examined the relationship between gray matter and IIV. Many studies that are often invoked in support of gray matter associations with variability tend to examine variability across cognitive tasks rather than within-task IIV (Sowell et al., 2003), involve lesion studies (Stuss, Murphy, Binns, & Alexander, 2003) or disease states (Murtha, Cismaru, Waechter, & Chertkow, 2002) that do not selectively target gray matter.

Few studies have simultaneously investigated independent associations between white and gray matter integrity and IIV. Recently, Ziegler and colleagues (2010) reported that

attentional control (which is linked to IIV; Duchek et al., 2009, 2013) and episodic memory were more associated with white matter microstructure than gray matter thickness. Additionally, Walhovd and Fjell (2007) demonstrated a potential double dissociation in the influence of white and gray matter on cognitive performance. The authors collected volumetric estimates of total gray and white matter on 71 adults as well as cognitive performance via a visual oddball task. Significant correlations were reported between white matter and sdRT normalized, a CoV-like estimate of the reaction time standard deviation divided by the individual participant mean RT. These correlations persisted even after taking age and gender into consideration, but critically no correlation was observed between sdRT normalized and total gray matter estimates, nor did white matter correlate with mean RT. Gray matter correlated negatively with mean RT, although this became a nonsignificant trend after controlling for age. Subsequent path analyses further validated these independent relationships, with the constructed double-dissociation model, using age as an exogenous variable, providing an excellent fit to data. Walhovd and Fjell reiterated arguments by Jensen (1982, 1992), namely that IIV and modal performance in RT arise from fundamentally different processes. They suggested that IIV was particularly associated with white matter integrity because well-myelinated neural pathways allow for more stable signaling from one neuron to another. The association between gray matter volume and modal RT is less clear, but was informed by previous work by Haier and colleagues (2005). In Haier et al., using an exploratory voxel-based morphometric approach, gray matter but not white matter regions were correlated with mean RT in a study of healthy aging. Fjell, Walhovd, Fischl and Reinvang (2007) also found that P3 latency, associated with age-related changes in mean RT, was associated with gray matter volume, suggesting that modal RT may be particularly associated with gray matter integrity, although this study did not examine modal RT associations with white

matter. Another study found that white matter microstructure, but not gray matter density, was associated with ISD (Moy et al., 2011), and highlights a possible neurological basis for the distinction between modal RT and IIV estimates (Jensen, 1992). Thus, gray matter may underlie aspects of modal performance while white matter may influence the stability of a maintained task set. It is possible that white matter integrity may be more sensitive than gray matter integrity to the subtle neurobiological changes underlying performance instability (Bartzokis, 2011; Bartzokis et al., 2004); thus, white matter may be more likely to associate with IIV. Gray matter, on the other hand, may serve as a proxy for the overall efficiency of brain structure (Haier et al., 2005), and may associate with modal estimates of RT.

Other neuroanatomical correlates of intraindividual variability

In spite of the number of studies that associate IIV with white matter integrity, few frameworks have been developed that specifically and uniquely associate IIV with white matter integrity or volume. It is likely that the distinction of white matter versus gray matter associations with IIV does not capture the totality of the brain's relationship with RT variability. Across several reviews on neuroanatomical correlates of IIV (Hultsch et al., 2008; MacDonald et al., 2006, 2009), researchers contended that differences in IIV are multiply determined, ranging from fluctuations in neurotransmitter function to white matter demyelination to cortical lesions. Increases in IIV may occur for both adaptive as well as maladaptive purposes, suggesting that a constellation of neurobiological alterations may result in altered IIV. Hultsch et al. (2008, see Table 10.2) reported on a rich history of associations between variability and traumatic brain injury, lesions, dementia, and mild cognitive impairment, indicating that increased IIV may be associated with impairment anywhere from a molecular level up to the brain's functional networks.

Rabbitt, Osman, Moore, and Stollery (2001) suggested that the common link between IIV and attentional lapses may occur via increasingly inefficient neural and network activation, and this possibility is supported by neurocomputational models (Li, von Oertzen, & Lindenberger, 2006). Models by Li and colleagues (Li, Brehmer, Shing, Werkle-Bergner, & Lindenberger, 2006; Li, von Oertzen, et al., 2006) have demonstrated that increasingly inefficient neurons and neural networks result in increased IIV in cognitive and sensorimotor tasks. In particular, neural models indicate that reductions in the gain parameter on a neuronal level reduces the responsiveness in each node, increasing the random activation fluctuation in the network (Li, Lindenberger, & Sikström, 2001). This change accounted for a host of age-related declines, including deficits in associative binding and memory in addition to increased intraindividual variability in reaction time performance. Interestingly, the reduction in the gain parameter is thought to reflect changes in dopaminergic modulation in the brain (Li et al., 2001), both within and across functional networks (MacDonald, Li, & Bäckman, 2009). Experimental evidence further supports this relationship. For example, a recent positron emission tomography study (MacDonald et al., 2009) found that dopamine uptake in D2 receptors was associated with ISD in middle-aged adults (age range 41 – 65 years).

The link between dopamine binding and IIV is strengthened by recent genetic work involving COMT, an enzyme which degrades dopamine in frontal regions (Goldberg & Weinberger, 2004; Weinshilboum & Otterness, 1999). Individuals, depending on genotype, will carry homozygous or heterozygous combinations of Val and Met alleles. There are reductions in dopamine levels in the synaptic cleft in Val carriers because these individuals have higher COMT activity than Met carriers, which is in turn associated with poorer performance in executive tasks (Egan et al., 2001; Goldberg & Weinberger, 2004; Parasuraman & Jiang, 2011).

Val carriers also exhibit increased IIV relative to Met carriers, which may be related to poorer dopamine binding to D2 receptors (Li et al., 2001; MacDonald et al., 2006). Therefore, if dopamine dysregulation underlies cognitive declines due to COMT, IIV may serve as an important mediator of this relationship.

Most frequently, however, increased IIV is thought to be a consequence of a brain that becomes increasingly disconnected and inefficient with age and disease. Hultsch et al. (2008) hypothesized that this disconnection occurs via a slowdown of transmission speed between neurons, due to a combination of compromised white matter myelination and inefficient binding of dopamine to D2 receptors (MacDonald, Cervenka, Farde, Nyberg, & Bäckman, 2009). Ultimately, poor neuromodulation and reduced signal fidelity may result in an asynchrony of otherwise orchestrated brain regions. This asynchrony may not always be enough to cause overt failures in the execution of a given task set, but stochastic processes in the brain may occasionally exacerbate this inefficiency, making execution of some trials more difficult than others. Similar mechanisms are invoked in the cortical disconnection theory of cognitive aging advanced by O'Sullivan et al. (2001). It is worth noting that in the model proposed by O'Sullivan et al., changes in gray matter integrity are largely presumed to be independent of changes in the orchestration of brain regions, suggesting that IIV ought to be more associated with compromised white matter integrity. Alternate models of IIV, however, hypothesize an increasingly noisy brain, but remain agnostic with regard to whether gray or white matter is responsible for the change (Li & Lindenberger, 1999; Li, Lindenberger, & Sikström, 2001). Here, IIV could be associated with measures of either white or gray matter integrity, both measures, or possibly neither in favor of some other aspect of neurobiological function. In sum, much work remains to be done on neuroanatomical correlates of IIV, and while a host of factors

at multiple levels of organization may be associated with IIV, white matter integrity may be more likely to be correlated with variability than gray matter (Bartzokis, 2009). There is a need, however, to replicate the white matter observations of Walhovd & Fjell (2007) in a larger sample, using regional volume estimates, given that IIV typically is linked to frontal regions (MacDonald, Li, et al., 2009; MacDonald et al., 2006; although see Anstey et al., 2007; Jackson et al., 2012; Ullén et al., 2008; Ziegler et al., 2010).

Functional neuroimaging and intraindividual variability

Although the current dissertation focuses exclusively on the brain's structural integrity, brief consideration will be given to functional neuroimaging research involving IIV. Functional magnetic resonance imaging (fMRI) studies may shed light on potential regions of interest in a structural investigation (Damoiseaux, Prater, Miller, & Greicius, 2012), and indeed have informed some recent research on associations between IIV and white matter (Jackson et al., 2012). Several fMRI investigations of IIV have demonstrated an association between frontal activation and variability (Bellgrove, Hester, & Garavan, 2004; Duchek et al., 2013; Kelly, Uddin, Biswal, Castellanos, & Milham, 2008; MacDonald, Nyberg, Sandblom, Fischer, & Bäckman, 2008; Yarkoni et al., 2009), which corroborates structural findings (Jackson et al., 2012; Ullén et al., 2008). Bellgrove, Hester, and Garavan (2004) reported what is regarded as the earliest study of IIV using functional neuroimaging (Hultsch et al., 2008). CoV on a Go/No-Go task was positively correlated with activation in middle frontal, right inferior frontal, right inferior parietal, and thalamic regions. Moreover, mean RT was not correlated with any of these regions or with CoV, highlighting an independent association with within-subject variability (Jensen, 1992). Bellgrove et al. hypothesized that the functional ROIs comprise part of a network of regions involved in attentional control. Positive correlations between this network and IIV

reflect poorer efficiency of executive control. MacDonald et al. (2008) demonstrated a conceptual replication of Bellgrove et al. (2004) using response latencies in visual word recognition, and linked lower ISDs with bilateral activation of the supramarginal gyrus. Yarkoni et al. (2009) examined RT variations on a trial-by-trial level, and found strong bilateral activation in medial frontal and temporoparietal regions. Curiously, this latter group also reported BOLD signals associated with RT fluctuations in white matter, suggesting that it may be possible to detect functional changes in deep white matter, and that once again IIV may serve as a useful, sensitive measure to do so.

Consistent with these trends, Kelly et al. (2008) reported that IIV was associated with the connectivity between functional networks. Connectivity in the default network, a group of frontal and parietal brain regions that become active and spontaneously correlate in the absence of an explicit task (Buckner, Andrews-Hanna, & Schacter, 2008; Gusnard & Raichle, 2001; Raichle et al., 2001; Shulman et al., 1997), has been central in a number of recent studies of neurological decline in aging and early stage AD. Indeed, both aging and AD are associated with alterations of the default network (Andrews-Hanna et al., 2007; Bai et al., 2008; Buckner et al., 2009; Damoiseaux et al., 2008, 2012; Greicius, Srivastava, Reiss, & Menon, 2004). Typically, the default network is anticorrelated (that is, exhibits a strong antiphase relationship) with task-positive attentional and executive networks; one network is suppressed while the other is active. Kelly et al. (2008) reported that an attenuated anticorrelation is associated with increased IIV. As might be expected given the structural and functional data previously reported, the strength of the anticorrelation was not associated with mean RT. The authors suggested that network dysregulation may underlie breakdowns in attentional control, particularly in clinical diseases

and disorders, and that IIV may serve as a useful diagnostic criterion in advance of these declines.

In summary, while the neuroanatomical and functional correlates of IIV have been well studied in some respects, many questions remain, particularly the differences that may occur as a function of age. Increased IIV has been linked to changes in D2 receptor binding, head injury, presence of genetic risk factors for AD, and reduced structural volumes in the brain. Despite a paucity of research exploring the relationship between IIV and gray matter, there is a rich body of work that particularly links IIV with measures of white matter integrity, and it is on this premise that the following rationale for the dissertation is outlined.

Rationale for the Dissertation

Evidence demonstrates that a number of changes in the brain with age – ranging from neurotransmitters to functional networks – appear to particularly associate with reaction time intraindividual variability. IIV appears to be associated with brain structure and function, over and above associations with estimates of RT central tendency. Thus, IIV may be a sensitive correlate of neuroanatomy in both cognitively normal aging and early-stage AD. Although Jackson et al. (2012) demonstrated a reliable relationship between IIV and white matter in aging and AD, questions remain regarding differential associations of IIV with white and gray matter. Furthermore, it is unclear whether IIV can serve as a mediator of brain-behavior associations. The dissertation aims to extend the findings of Jackson et al. (2012) to address these issues; namely to clarify the relationship of IIV with neurological, genetic, and cognitive performance in old age. To my knowledge, no work has clearly established the differential association of IIV with white and gray matter (Specific Aim 1), particularly in targeted regions of interest. Furthermore, it is important to determine whether IIV mediates the relationship between

estimates of regional white matter integrity, and genetic risk factors with cognitive outcomes (Specific Aim 2).

As previously mentioned, investigation of both white and gray matter estimates may strike the best balance of sensitivity and expedience. Gray and white matter may be differentially associated with certain aspects of cognitive performance; namely, gray matter may be associated with central tendency while white matter may be associated with cognitive variability (Jensen, 1992; Walhovd & Fjell, 2007). Reliance on previous research has revealed several gaps in understanding the relationship between structural integrity and reaction time measures. Although there have been some trends toward a double dissociation between gray and white matter in their association with modal RT and IIV, this has yet to be replicated beyond the initial study, which made use of a relatively young, small sample (Walhovd & Fjell, 2007). Furthermore, these associations have not been adequately explored with respect to cognitively normal and pathological aging. The investigation of both gray and white matter as variables of interest represents a significant difference relative to the methods of Jackson et al. (2012). Because the dissertation attempts to fill the gaps in the understanding of the association between gray/white matter and IIV in older adults, path models were employed rather than hierarchical linear regressions used by Jackson et al. There are several advantages to using path analysis in this manner, namely that path analysis is the appropriate approach for examining mediation rather than the regression method used in Jackson et al. The methodological change allows for the simultaneous study of white and gray matter contributions to modal and IIV variance in RT. Path analyses thus provides an advantage over linear regression in determining the independent contribution of gray and white matter in the current study.

Given the constellation of neurological markers that are associated with IIV (MacDonald, Li et al., 2009) and the cascade of changes preceding cognitive decline in healthy and pathological aging, a pressing question regards the role of IIV in the broader scope of cognitive decline in older adulthood. It would be ideal to directly measure synaptic dopamine levels *in vivo*, along with structural, functional, and functional connectivity estimates to provide a rich, multimodal tapestry of upstream and downstream changes associated with IIV; however, this presents prohibitive challenges in time, data, and cost. The selection of a few useful correlates of these changes, such as COMT status as an index of dopamine regulation (MacDonald, Cervenka, et al., 2009) and APOE status as a genetic risk factor for cognitive decline and conversion to early-stage AD (Filippini et al., 2009), in concert with estimates of white matter volume, may allow the construction of a multilevel model of factors associated with IIV. Specifically, IIV may mediate the association of COMT (Bruder et al., 2005; Goldberg et al., 2003), APOE (Reinvang, Winjevoll, Rootwelt, & Espeseth, 2010; Rosen, Bergeson, Putnam, Harwell, & Sunderland, 2002), and white matter (Charlton et al., 2006) with cognitive performance in particular domains, such as working memory and episodic memory. Thus, the APOE and COMT polymorphisms are included in the current study to better understand whether these may affect cognitive performance using increased IIV as one potential mechanism. In this way, the results of Jackson et al. (2012) may be contextualized with respect to additional genetic risk factors for cognitive decline.

In addition to the use of path analyses, other methodological changes have been introduced relative to Jackson et al. (2012). These differences have been made in order to leverage more powerful and robust statistical methods. Notably, where Jackson et al. partialed covariates only from other predictor variables, here I have chosen to partial covariates from all

variables included in the path models. This was done in order to ensure that any relationship between the cognitive and neuroanatomical variables is not attributable to covariates acting on either predictor or outcome variables. Additionally, the current dissertation makes use of a larger sample size, which provides greater statistical power to detect reliable associations.

Aims of the Dissertation

The aims below follow a primary theme, namely that RT IIV may serve as a mediational hub in the cognitive neuroscience of aging, connecting neuroanatomy and genetic risk factors with cognitive differences in healthy and pathological aging. White matter in particular should be associated with increased IIV, although independent gray matter associations with variability have rarely been investigated. Both aims are concerned with understanding the relationship of white and gray matter to estimates of median RT and IIV, and Aim 2 investigates how these are affected by APOE and COMT status, and inform cognitive changes as a consequence of healthy aging and AD. Aim 1 tests the hypothesized double dissociation, with IIV linked to white matter but not gray matter, and median RT linked to gray matter but not white matter. Aim 2 determines whether IIV mediates the relationship between white matter and working memory / episodic memory, as well as between APOE/COMT and the memory measures.

This dissertation extends the findings of Jackson, Balota, Duchek, and Head (2012) to investigate whether white and gray matter are differentially sensitive to measures of RT in cognitively normal and early-stage AD older adults. These questions are investigated using the coefficient of variation and median RT from tasks of cognitive performance. Although CoV is typically contrasted with mean RT, given that means and standard deviations are correlated in reaction time (e.g., Duchek et al., 2009; Faust et al., 1999), this dissertation will use median RT to minimize multicollinearity between the CoV measure, which contains the variance from mean RT, and modal RT more generally. The present dissertation explores associations in targeted

prefrontal and parietal white and gray matter regions. Similarities between healthy and pathological aging have also been considered.

Specific Aim 1 tested the relative associations of gray and white matter estimates with median RT and CoV from attentional control tasks in cognitively normal older adults and early-stage AD. Aim 1 consisted of two hypotheses: a) A double dissociation will be observed in frontal and default-network ROIs, such that gray matter volumes uniquely predict median RT but not IIV, and white matter estimates predict IIV but not median RT; and b) this double dissociation is observed in both cognitively normal and early-stage AD groups.

Specific Aim 2 employed mediational analyses to examine causal relationships among COMT/APOE, IIV, regional white matter volume, and cognitive performance. Aim 2 hypothesized that path analyses demonstrate that a) IIV mediates the relationship between frontal and default-network white matter integrity and performance on memory tasks, b) IIV also mediates the relationship between APOE/COMT status and memory, c) carriers of APOE4 and COMT Val polymorphisms demonstrate increased IIV relative to those who are not carriers, and d) that cognitively normal older adults demonstrate a similar structure but weaker loadings than early-stage AD participants.

Method

Participants. All participants were screened for non-AD neurological, psychiatric, or medical disorders with the potential to cause dementia. The inclusion and exclusion criteria for the diagnosis of AD conformed to those outlined in the criteria of the National Institute of Neurological and Communications Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984). Dementia severity for each individual was staged in accordance with the Washington University Clinical Dementia Rating (CDR) scale (Hughes,

Berg, Danziger, Coben, & Martin, 1982; Morris, 1993). The CDR staging and diagnostic evaluation is based on interviews with the participant and an informed collateral source. According to this scale, a CDR of 0 indicates no cognitive impairment, a CDR of 0.5 indicates very mild dementia, a CDR of 1 indicates mild dementia, a CDR of 2 indicates moderate dementia, and a CDR of 3 indicates severe dementia. At the Knight Alzheimer's Disease Research Center (ADRC), a CDR of 0.5 has been found to accurately indicate the earliest stages of AD (Morris, McKeel, & Storandt, 1991). Both the reliability of the CDR and the validation of the diagnosis (based upon autopsy) by the research team have been excellent (93% diagnostic accuracy) and well-documented (e.g., Berg et al., 1998; Morris, Storandt, McKeel, et al., 1996; Morris, Storandt, Miller, et al., 2001; Storandt, Grant, Miller, & Morris, 2006). Based on these criteria, 271 cognitively normal (CDR 0) and 49 individuals with early-stage AD (CDR 0.5) were recruited from the Knight ADRC at Washington University.

Participant inclusion was restricted to those individuals with cognitive testing performed within two years of their MRI scan. Exclusion criteria included lifetime history of neurological illness or injury (e.g., Parkinson's disease, stroke, seizure, or head trauma resulting in loss of consciousness). Eight cognitively normal and 4 early-stage AD participants reported history of stroke. Six cognitively normal and 2 early-stage AD participants reported history of seizure. Twenty-six cognitively normal and 7 early-stage AD participants reported history of trauma resulting in loss of consciousness. Two early-stage AD participants reported Parkinson's disease. Because some participants endorsed multiple criteria, the final sample included 229 cognitively normal (151 females), aged 45-86 (M = 67.3; SD = 8.9) and 33 early-stage AD (13 females) participants, aged 50 – 88 (M = 73.3; SD = 8.3). Demographics are summarized in Table 1. The

Human Research Protection Office at Washington University approved this study, and all participants provided their informed consent at the beginning of the study.

Cognitive testing. Cognitive performance comprised of an arithmetically averaged composite of three attentional tasks. The coefficient of variation (standard deviation RT / mean RT) from incongruent trials in the Stroop and Simon tasks, and switch trials in the Consonant-Vowel Odd-Even task served as the primary index of IIV. Because mean RT appears in the denominator of the CoV term, median RT was selected as the estimate of central tendency. Brief methods for each of the cognitive tasks follow. Because some participants completed slightly different protocols than others, only 149 participants completed the memory measures. Aim 2 therefore focuses on this subset of participants, and demographics for this subsample are also summarized in Table 1.

Stroop task. This task involves the presentation of four color names (red, blue, green, and yellow) and four neutral words (bad, poor, deep, and legal). The task consisted of 36 congruent trials, during which each word appeared in its corresponding color; 36 incongruent trials, during which each word appeared in a nonmatching color; and 32 neutral trials, in which each of the four neutral words appeared in one of the four colors. Participants were instructed to read aloud each word's color.

Simon task. Participants were presented with an arrow pointing either left or right. The arrow appeared on the left half, right half, or center of the screen. Participants were told to ignore the arrow location on the screen and respond according to its direction by pressing a key on either the left (*q* key) or right side (*p* key) of the keyboard when the arrow was pointing left or right, respectively. The task consisted of 40 congruent trials, 40 incongruent trials, and 40 neutral trials, during which the arrow appeared at the center of the screen.

Consonant-Vowel Odd-Even (CVOE) switching task. Participants engaged in two different tasks across trials. On each trial, a letter–number pair (e.g., *A 3*) appeared at the center of the screen with a cue appearing at the top of the screen indicating if it is a letter or number trial (adapted from Minear & Shah, 2008). On a letter trial, participants were told to decide whether the letter was a consonant or vowel (CV). On a number trial, they were told to decide whether the number was odd or even (OE). Participants completed a block of 60 switch/nonswitch trials in an alternate runs sequence, CV, CV, OE, OE, CV, CV, and so forth, with 30 switch trials (e.g., CV trial followed by OE trial) and 30 nonswitch trials (e.g., CV trial followed by CV trial).

Working memory. Participants completed four tasks of working memory, as defined via factor analysis in Johnson et al. (2008, 2009): 1) Digit Forward was taken from the Weschler Memory Scale – Revised (WMS-R; Weschler, 1987). In this task, participants recited, in numerical order, digits read aloud in a random order by an experimenter. The number of digits increased every two trials until a participant failed to correctly recite two sets of an equal number of digits. Scoring was calculated as a function of the digit length of the final set of correct trials. 2) Digit Backward was also taken from the WMS-R. In this task, participants recited, in reverse numerical order, digits read aloud in a random order by an experimenter. The number of digits increased every two trials until a participant failed to correctly recite two sets of an equal number of digits. Scoring was calculated as a function of the digit length of the final set of correct trials. 3) WMS-R Mental Control, which is comprised of three subtasks, a) counting backward from 20 to 1, b) reciting the alphabet, and c) counting serially by 3s. Each subtask is scored on a scale from 0 to 3, and the three scores are summed. 4) Word Fluency – Letters S and P. Participants are asked to name as many words that start with S as possible in 60 seconds, then are asked to

repeat the task with the letter P. Both fluency tests are scored on an open-ended range starting with 0, and increasing for each nonrepeated, non-conjugated word that starts with the appropriate letter. Performance for each letter is summed to provide an overall score. Scores from the four working memory tasks were standardized and then averaged into a composite score.

Episodic memory. Participants completed three tasks of episodic memory, also defined by Johnson et al. (2008, 2009): 1) Immediate recall scores were taken from WMS-R Logical Memory. In this task, participants recalled details from a verbally-presented story (Story A). Scoring comprised of the number of relevant details recalled immediately following the story's presentation on a scale from 0 to 25. 2) Associate Learning was taken from the original WMS measure (Weschler & Stone, 1945). In this task, participants attended to a list of word pairs read aloud by an experimenter. Some word pairs were easy, with high lexical frequency and association, or hard, where pairs were comprised of infrequent, rarely-associated words. Participants then performed a recall test on pairs of words that were intact, recombined, or novel. Scoring was determined by the number of word-pairs correctly recalled. Recall of easy pairs received a scored of 1 point, while hard pairs received a score of 2 points. The total score was divided by 2 to yield a maximum of 21 across three blocks of recall. 3) Free recall performance from the Selective Reminding test, in which participants first identified exemplars of particular categories presented on a card. After identifying all exemplars on a given card, they performed immediate recall of the items, and moved on to the next card after 20 seconds of interference (i.e., counting backwards by 3s from 97). Participants later completed a free recall task, with the experimenter prompting additional recall via verbal presentation of categories. Scoring was comprised of the sum of recalled items across 3 trial blocks.

MR acquisition and processing. Imaging was performed using either a Siemens Trio 3T or Siemens Vision 1.5T scanner (Erlangen, Germany). For all scans, cushions reduced head movement during scanning and a scout image was acquired first in order to center the field of view on the brain. For the Vision 1.5T scans, 2 to 4 T1-weighted sagittal MP-RAGE scans (TR= 9.7 ms, TE= 4 ms, flip angle = 10º, TI = 20 ms, TD = 200 ms, 1 mm × 1 mm × 1.25 mm resolution) were acquired for each subject. For the Trio 3T scans, up to two T1-weighted sagittal MP-RAGE scans (TR = 2400 ms, TE = 3.16 ms, flip angle = 8º, TI = 1000 ms, TD = 200 ms, 1 × 1 × 1 mm resolution) were acquired in each participant. Cortical reconstruction and volumetric segmentation was performed with the Freesurfer 4.0 image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000; Fischl et al., 2001; Fischl et al., 2002; Fischl et al., 1999a; Fischl et al., 1999b; Fischl et al., 2004). Briefly, this processing includes motion correction and averaging of multiple volumetric T1 weighted images, removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures intensity normalization, tessellation of the gray matter white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class. Once the cortical models are complete, the cerebral cortex is parcellated into units based on gyral and sulcal structure (Desikan et al., 2006; Fischl et al., 2004). Neuroanatomical labels are applied to each voxel based on a probabilistic atlas derived from a manually labeled training set that included older adults

(Desikan, et al. 2006). The cortical gray matter parcellations are then used to label the associated underlying white matter (Fischl, et al. 2004). Regions-of-interest (ROIs) included white matter volume for 5 regions: superior frontal gyrus (SFG), ventral/dorsal-lateral prefrontal cortex (VLDLPFC, combined middle and inferior frontal gyri), posterior cingulate, precuneus, and inferior parietal lobule (IPL), combined across the left and right hemispheres.

Cortical thickness measures were calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). This method uses both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness. The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. A neuroanatomical label is applied to each vertex, and average cortical thickness estimates were obtained for 5 ROIS: SFG, VLDLFPC, posterior cingulate, precuneus, and IPL. Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas et al., 2002) and manual measurements (Kuperberg et al., 2003; Salat et al., 2004).

The average interval between the MRI scan and the cognitive assessment was computed as an integer in days; that is, the interval between scan and assessment could assume negative values if the cognitive assessment preceded the structural MRI scan. It is possible that directional information about the scan and assessment may contain value that would be lost if the scan-assessment interval were construed as an absolute value, as in Jackson et al. (2012). Thus, the average scan-assessment interval was +15 days (SD = 294 days). For purposes of comparison with Jackson et al., the average interval using absolute values was 216 days (SD = 199 days). Of the 262 participants, 36 were assessed using the Vision scanner, and 226 were assessed using the

Trio scanner. Pearson chi-square tests of independence were conducted to determine whether there were differences in the proportion of CDR participants or gender between scanner types. Both tests were nonsignificant, both $\chi^2 < 1$. Gray matter thickness and white matter volume were also compared between scanner types. Gray matter thickness measures from the Trio scanner were larger compared with the Vision scanner, $t = 2.26$, $p = .03$, but there were no scanner differences as a function of white matter volume, $t = 1.32$, $p = .18$. Therefore, scanner type was included as a covariate in all measures.

Regions of interest. Volumes were normalized with respect to body size differences using estimated total intracranial volume (ICV; Buckner et al., 2004) in an analysis of covariance. Here, adjusted volume = raw volume – (b × (ICV – mean ICV)), where b represents individual subjects' regression slopes of the ROI volume on ICV. This approach has been used in a number of previous studies investigating regional volumes (e.g., Buckner et al., 2004; Head, Rodrigue, Kennedy, & Raz, 2008; Jackson, Balota, & Head, 2011; Jackson et al., 2012; Salat et al., 2009).

Because predictions did not differ across regions of interest, and in order to reduce the number of analyses conducted on the dataset, composites were constructed for the neuroanatomical white and gray matter structures. For Aim 1, arithmetic sums of the five white matter volume measures and averages of the five gray matter thickness measures were computed to create composite white matter volume and gray matter thickness measures, respectively. For Aim 2, frontal and parietal white matter were expected to differ in their associations with the memory measures, so separate composites were created for these structures. This was done primarily because working memory measures tend to associate with frontal regions (e.g., Kimberg & Farah, 1993; Owen et al., 1990, 1996) while episodic memory tends to associate with more posterior regions, including those in the parietal lobe (e.g., Cabeza et al., 2008; Wagner et

al., 2005). SFG and VLDLPFC measures were summed to form a frontal composite for white matter volume. Posterior cingulate, precuneus, and IPL were also averaged to form a separate default-network composite for white matter volume.

Analytic approach

Outliers. Univariate and multivariate outliers were identified. Multivariate outliers were calculated using Mahalanobis D^2 distance (Lattin, Carroll, & Green, 2003). Eight individuals (3 early-stage AD) had a significant chi-square statistic ($p < .001$), constituting multivariate outliers, and were declared missing. Univariate outliers, defined as a datapoint greater than three standard deviations from the group mean, were also examined. Twenty-eight datapoints were identified as univariate outliers, and were also declared missing.

Missing data. The multivariate outliers constituted 136 datapoints (8 subjects multiplied by 17 measures), together with the 28 univariate outlier datapoints yielded a total of 164 datapoints (representing 164/4490 or 3.7% of the total dataset) that were declared missing at random, and imputed using measures outlined in Schafer & Graham (2002). Missing values were multiply imputed ($m = 20$) using the Expectation-Maximization algorithm, which replaces the missing data point based on the values of all other variables (i.e., all attention and regional brain volume data). The imputations were averaged to provide final values for each missing datapoint.

Covariates. Covariates were regressed onto each of the predictors and outcomes in the dataset, and the standardized residuals were obtained. Age, education, gender, depression, diabetes diagnosis, cardiovascular health (i.e., history of heart problems and hypertension), scanner type, and interval between structural MRI scan and the cognitive assessment (in days) were all significantly correlated with at least one of the cognitive or brain variables, and were therefore regressed on each of the variables of interest. Standardized residuals were then used in

the path model and to test for mediation. These covariates were also correlated with one another to determine shared variance among these variables of non-interest. A correlation matrix was computed among the ordinal- and ratio-scale covariates of interest (i.e., age, years of education, depression scale, and scan-assessment interval). Age and years of education were negatively associated, $r(262) = -.159$, $p = .010$, with a nonsignificant negative association observed between depression and years of education, $r(262) = -.118$, $p = .056$. No other correlations were reliable, all rs < .07, ps > .29.

The four covariates were also examined as a function of binary group status for the gender, diabetes diagnosis, cardiovascular health, and scanner type covariates. Females were younger, $t(260) = 3.20$, $p = .002$, and had fewer years of education, $t(260) = 2.94$, $p = .004$, relative to males. Individuals with a positive diabetes diagnosis were higher on the depression scale relative to those without a diabetes diagnosis, $t(36.721) = 2.36$, $p = .024$, after correcting for unequal variances. Individuals with a history of cardiovascular complaint were older than those without reported cardiovascular trouble, $t(260) = 3.62$, $p < .001$. Finally, individuals using the Vision MRI scanner had a longer interval between the MRI scan and cognitive assessment relative to those using the Trio scanner, $t(260) = 2.73$, $p = .007$. No other group comparisons were significant, all ts < 1.27, ps > .20.

Statistical analyses – Aim 1. To verify the double dissociation between white and gray matter, and between median RT and IIV, a path model was constructed in Mplus 7 (Los Angeles, CA) to determine whether eliminating the paths between gray matter thickness and IIV, and between white matter volume and median RT would result in a significantly worse fit to data than an unconstrained model (Figure 1). Fit statistics of interest included the chi-square test of model fit, which compares estimated values from the model to observed data. Nonsignificant

chi-squares indicate model fit. The comparative fit index (CFI) and the Tucker-Lewis index (TLI) also measure model fit but are more robust with regard to sample size and distributional assumptions. Here, values above .95 indicate excellent fit, although values above .90 are acceptable provided satisfactory values in other fit statistics. The root mean square error of approximation (RMSEA), a fit index that examines model parsimony and is less susceptible to sample size, was also examined, using a criterion of .08 or lower as indicating good model fit. Finally, the standardized root mean square residual (SRMR), another measure of model parsimony, was assessed, with a criterion of .05 or lower. No single fit statistic can definitively prove adequate model fit; so all statistics were taken into consideration to evaluate the hypothesized models.

Statistical analyses – Aim 2. A classic path analysis approach was employed to confirm whether IIV serves as a mediator between white matter integrity and cognitive performance (Figure 2). The goal of successful mediation as described in Baron and Kenny (1986) is to determine a) whether white matter integrity (predictor variable) is associated with working memory/episodic memory performance (outcome variable); b) whether white matter integrity is associated with CoV (mediator); c) whether CoV is associated with working memory/episodic memory performance and d) whether the white matter-working memory and the white matter-episodic memory associations are substantially reduced with the addition of IIV in the model. Similarly, IIV may mediate the relationship between APOE/COMT status and working memory/episodic memory performance. Using Mplus, hierarchically nested models were constructed with increasing data constraints to determine the most parsimonious model that successfully accounts for the observed data. Within the models, the first tier included APOE and COMT statuses, as well as normalized, standardized white matter ROI volume; the second tier

consisted of the standardized, composite measure of CoV; the third tier consisted of the working memory or episodic memory composites, which served as the outcome variables. No reciprocal causation was assumed in the model; thus, only unidirectional effects were included.

Results

Aim 1 – A priori analyses

The double-dissociation model was created by restricting two paths on the baseline (saturated) model. Specifically, the path between median RT and white matter volume as well as the one between CoV and gray matter thickness was set to zero. This model provided a poor fit to the data, $\chi^2 = 8.582$, $df = 2$, $p = .014$; CFI = .791; TLI = .476; SRMR = .048; RMSEA = .112. Follow-up analyses, summarized in Table 2, revealed that residualized CoV was uncorrelated with the white and gray matter variables ($r(262) = -.109$, and $r(262) = -.053$ respectively; Figure 3), while residualized median RT was significantly correlated with the gray and white matter variables ($r(262) = -.133$, and $r(262) = -.138$, respectively; Figure 4).

Aim 1 – Post-hoc analyses

Given that the a priori hypotheses were unsupported in Aim 1, post-hoc analyses focused on possible relationships among the variables of interest within specific subgroups, in addition to somewhat broader investigation of the attentional measures. Post-hoc correlations for the total sample were explored among the individual variables comprising each of the composite measures. The composite measures were explored separately for several subgroups within the sample that may differ in the strength of the relationship among the variables. For example, although Jackson et al. (2012) failed to find reliable differences between cognitively normal older adults and individuals with early-stage AD in the relationship between neuroanatomical structures and cognition, there is a precedent for differences in structure-function relationships between cognitive groups (e.g., Anstey et al., 2007). In addition to cognitive status, correlations

were examined as a function of age, APOE status, COMT status, and high versus low years of education within the cognitively normal group. Finally, Ex-Gaussian parameters of the reaction time distribution were included to facilitate comparison with Jackson et al. (2012).

Post-hoc analyses – total sample

Correlations among individual measures. Table 3 summarizes the correlation matrix of the individual measures for the Aim 1 sample. Simon CoV was significantly negatively correlated with SFG gray matter thickness and CVOE CoV was significantly negatively correlated with posterior cingulate white matter volume, but no other CoV measures correlated with regions of interest in white or gray matter. Stroop median RT was significantly negatively correlated with precuneus and IPL white matter volume, while Simon median RT was significantly negatively correlated with SFG, precuneus, and IPL gray matter thicknesses. CVOE median RT was uncorrelated with the structural measures.

Distributional analyses – composite measures. Following Jackson et al. (2012), response time distributional analyses were employed to further examine the relationship between cognitive performance and possible neuroanatomical correlates. The Ex-Gaussian model of reaction time distribution uses three parameters, the mean (μ) and standard deviation (σ) of a Gaussian distribution, along with a single parameter (τ) capturing the exponential distribution. Jackson et al. reported a trend whereby τ associated more strongly with white matter volume than CoV, although the two measures were highly correlated. Table 4 summarizes the correlation matrix for the μ and τ distributional parameters with respect to the composite measures. The modal portion of the RT distribution, μ, was significantly negatively correlated with white matter volume. No other correlations among the composite measures were observed.

Distributional analyses – individual measures. Table 5 summarizes the correlation matrix

for the distributional parameters with respect to the individual measures. Simon μ was significantly negatively correlated with precuneus and IPL gray matter thickness, and CVOE μ was significantly negatively correlated with posterior cingulate gray matter thickness. No other correlations among the individual measures were observed.

Post-hoc analyses – examination of subgroups

Cognitive status. Tables 6 and 7 summarize the correlation matrices of composite measures for the cognitively normal group (n = 229) and the early-stage AD group (n = 33), respectively. Within the cognitively normal group, a significant negative correlation between median RT and white matter volume was observed. A significant negative correlation was observed between median RT and gray matter thickness as well. Within the early-stage AD group, CoV was significantly negatively correlated with white matter volume. No other significant correlations were observed in either group.

Age. It is possible that age may modulate the observed relationship between the neuroanatomical measures and the cognitive measures. Tables 8 and 9 summarize the correlation matrices of composite measures for the younger (n = 121) and older (n = 108) halves of the cognitively normal sample, based on a median split. In the younger subsample, white matter volume was negatively associated with CoV. In the older subsample, however, median RT was significantly negatively associated with both white matter volume and gray matter thickness. No other significant correlations were observed in either group.

APOE status. APOE status may affect the relationship between the neuroanatomical measures and the cognitive measures in the cognitively normal sample. Given APOE's effects on white matter integrity (Bartzokis, 2011), it is possible that white matter volume may become more strongly correlated with attentional or memory performance in the APOE4+ group. Tables

10 and 11 summarize the correlation matrices of the composite measures as a function of APOE status for the cognitively normal group. Within the APOE4- group (n = 151; Table 10) median RT and gray matter thickness were significantly negatively correlated. No significant correlations were observed for the APOE4+ group (n = 76; Table 11). No correlations with white matter were observed in either group.

COMT status. Given the effects of COMT status on IIV it is possible that genetic group membership may influence the relationship between white matter volume and IIV. Tables 12 and 13 summarize the correlation matrices of the composite measures as a function of COMT status for the cognitively normal group. No significant correlations were observed in the Val- group (n = 50; Table 12), but median RT was significantly negatively correlated with white matter volume in the Val+ group (n = 130; Table 13). No other significant correlations were observed in the Val+ group.

Education. It is possible that differences in estimates of cognitive reserve such as years of education may moderate the relationship between neuroanatomical structures and cognitive function (Stern, 2003, 2009). Correlations among the variables of interest were examined separately as a function of lower and higher education within the cognitively normal group. Given that education was a covariate on which the variables of interest were originally residualized, the dataset was re-residualized to exclude education. Instead, a median split was performed on years of education within the cognitively normal group. Sixteen years of education and above were categorized as the high-education group, while 15 years of education or fewer were categorized as low education.

Table 14 summarizes the correlation matrix for the low education group (n = 92). There was a significant negative correlation between median RT and gray matter thickness. No other

significant correlations were observed. Table 15 summarizes the correlation matrix for the high education group (n = 137). None of the composite measures significantly correlated with any other in this group.

Post-hoc analyses – comparison with Jackson, Balota, Duchek, and Head (2012)

Jackson, Balota, Duchek, and Head (2012) reported several strong associations between white matter volume and CoV, using the same covariates on the same pool of participants from Knight ADRC. The fact that the current results did not conceptually replicate Jackson et al. may raise serious concerns about the robustness of the relationship between IIV and white matter volume. In order to examine this further, a direct replication of the Jackson et al. design was conducted on the current sample in order to compare results between the two studies. That is, a regression model was constructed with standardized, but unpartialed measures with overall, not incongruent, CoV as the dependent variable. In the first step, gender, depression scores, history of cardiovascular disease, years of education, scanner type, and the interval between scan and cognitive assessment were entered, representing the covariates from Jackson et al. In the next step, standardized age was entered, followed by CDR in the third step, the individual white matter region in the fourth step, the region-by-CDR interaction in the fifth step, and all other two-way interactions in the sixth step. Thus, it is possible to compare the relative contribution of white matter volume to CoV in both studies to determine whether there is consistency in the robustness of the association between white matter volume and CoV. Zero-order correlations were calculated for both studies, examining the association between CoV and the five common white matter ROIs. Table 16 summarizes the comparison between the two studies, which shows somewhat larger correlations in Jackson et al. (2012) relative to the present analyses. Five linear regression models were constructed for each of the five white matter volume ROIs. SFG (ΔR^2 =

.02, $F(1, 251) = 4.81$, $p = .029$), VLDLPFC ($\Delta R^2 = .02$, $F(1, 251) = 6.26$, $p = .013$), and posterior cingulate ($\Delta R^2 = .02$, $F(1, 251) = 5.29$, $p = .022$) contributed significant variance to CoV. IPL and precuneus white matter volume (both *p*s > .12) did not contribute significant variance to CoV, largely replicating Jackson et al. (2012). The size of the association between CoV and white matter volume was similar across studies, but approximately 1% smaller in the current study. By way of contrast, none of the five gray matter thickness measures from the current study contributed significant variance to CoV in the regression models (all *p*s > .075), with the exception of IPL ($\Delta R^2 = .02$, $F(1, 251) = 6.62$, $p = .011$), which was negatively associated with CoV.

Post-hoc comparisons with Jackson et al. (2012) were also conducted with respect to τ, the skewing parameter of Ex-Gaussian distributional analysis. Zero-order correlation comparisons between the current study and Jackson et al. are again summarized in Table 14. As in Jackson et al. (2012), τ was significantly negatively correlated with white matter volume in all overlapping regions of interest, though the correlations were attenuated in the current study. VLDLPFC ($\Delta R^2 = .01$, $F(1, 251) = 3.80$, $p = .052$) and precuneus ($\Delta R^2 = .01$, $F(1, 251) = 3.46$, $p = .064$) contributed nonsignificant trends towards association with τ. SFG, posterior cingulate, and IPL did not contribute significant variance to τ in the regression models (all *p*s > .12). Using gray matter thickness as a predictor, both precuneus ($\Delta R^2 = .02$, $F(1, 251) = 5.49$, $p = .020$) and IPL ($\Delta R^2 = .02$, $F(1, 251) = 4.50$, $p = .035$) were associated with τ. IPL interacted with CDR ($\Delta R^2 = .02$, $F(1, 250) = 4.52$, $p = .034$), such that thickness modulated τ in the CDR 0 group, but not in the CDR 0.5 group. No other regions contributed significant variance, *p*s > .38.

Aim 2 – A priori analyses

Working memory. Prior to examining mediation, tests of requisite associations among the

variables of interest were conducted. In particular, correlations were computed to determine whether there were significant associations between frontal white matter volume and CoV, default white matter volume and CoV, frontal white matter volume and working memory, default white matter volume and working memory, and between CoV and working memory. An abbreviated correlation matrix is summarized in Table 17. Frontal white matter was significantly negatively correlated with CoV ($r(149) = -.187$, $p = .023$, Figure 5a), but default white matter was not significantly correlated with CoV ($r = -.12$, Figure 5b). Neither frontal nor default white matter volume was correlated with working memory (both rs < .05, Figure 6). CoV was significantly negatively correlated with working memory ($r(149) = -.235$, $p = .004$, Figure 7a). Independent-samples t tests were also conducted to test for differences in CoV and working memory as a function of COMT status or APOE status. Neither CoV nor working memory differed as a function of APOE status (both ts < 1.3). Neither CoV nor working memory differed as a function of COMT status (both ts < 1). Because COMT, APOE, and white matter volumes were uncorrelated with working memory and CoV, mediation was not possible (Baron & Kenny, 1986).

Episodic memory. Once again, prior to examining mediation, tests of requisite associations among the variables of interest were conducted. In particular, correlations were computed to determine the correlations between frontal white matter volume and CoV, default white matter volume and CoV, frontal white matter volume and episodic memory, default white matter volume and episodic memory, and between CoV and episodic memory. These correlations are summarized in Table 17. As before, frontal white matter was significantly negatively correlated with CoV ($r(149) = -.187$, $p = .023$, Figure 5a), but default white matter was not significantly correlated with CoV ($r = -.12$, Figure 5b). Neither frontal nor default white

matter volume was correlated with episodic memory (both *r*s < .07, Figure 8). CoV was significantly negatively correlated with episodic memory ($r(149) = -.308$, $p < .001$, Figure 7b). Independent-samples *t* tests were also conducted to test for differences in CoV and episodic memory as a function of COMT status or APOE status. CoV did not differ as a function of APOE status ($t < 1$), but episodic memory performance was higher in the APOE4- group, $t = 2.35$, $p = .020$. Neither CoV nor episodic memory differed as a function of COMT status (both *t*s < 1). Because COMT, APOE, and white matter volumes were largely uncorrelated with episodic memory and CoV, mediation was not possible (Baron & Kenny, 1986).

Aim 2 – Post-hoc analyses

As in Aim 1, exploratory correlations of individual measures were examined in the full sample. Additionally, post-hoc testing focused on possible differences between groups in the sample to determine whether conditions for mediation might be met in a subsample of the collected data. Specifically, correlations among the composites for CoV, median RT, white matter volume, and gray matter thickness were explored separately for cognitively normal and early-stage AD groups. Correlations were also examined as a function of APOE status, COMT status, and high versus low years of education within the cognitively normal group. Estimates of the Ex-Gaussian skewing parameter, τ, were again included to facilitate comparison with Jackson et al. (2012).

Post-hoc analyses – total sample

Individual correlations. Table 18 summarizes the correlation matrix of the individual measures for the Aim 2 sample. Of the working memory measures, Digit Backward and Mental Control were both significantly negatively correlated with CVOE CoV. Word Fluency was significantly negatively correlated with Simon CoV, and was significantly positively correlated with posterior cingulate white matter volume. There was no correlation pattern consistent with

the mediation hypothesis.

Of the episodic memory measures, Associate Memory was significantly negatively correlated with CVOE CoV. Selective Reminding performance was significantly negatively correlated with Stroop CoV, Simon CoV, and CVOE CoV. Again, there was no correlation pattern consistent with the mediation hypothesis.

Distributional analyses – composite measures. Table 17 summarizes the correlations of the RT distributional skewing parameter, τ, with episodic and working memory. Neither episodic nor working memory was significantly correlated with τ.

Distributional analyses – individual measures. Table 18 summarizes the correlations of τ in each of the attentional tasks with individual measures of working and episodic memory. Of the working memory measures, Word Fluency was significantly negatively correlated with Stroop τ.

Of the episodic memory measures, Associate Memory was significantly positively correlated with CVOE τ. Selective Reminding performance was significantly negatively correlated with Stroop τ. Again, there was no correlation pattern consistent with the mediation hypothesis for the τ measures.

Covariate control. In order to examine the possible contribution of removing variance associated with covariates, correlations among the unstandardized variables of interest were investigated for Aim 2. Using these measures, CoV was significantly associated with frontal white matter volume ($r(153) = -.232$, $p = .004$), and trended toward an association with default white matter volume ($r(153) = -.158$, $p = .051$). CoV was also associated with episodic memory ($r(153) = -.451$, $p < .001$) and working memory ($r(153) = -.271$, $p = .001$). However, the white matter regions remained uncorrelated with the memory measures, all rs < .11.

Post-hoc analyses – examination of subgroups

Cognitive status. Tables 19 and 20 summarize the correlation matrices of composite measures for the cognitively normal group (n = 126) and the early-stage AD group (n = 23), respectively. Within the cognitively normal group, both working memory and episodic memory were significantly negatively correlated with CoV. No other correlations reached significance for this group, however. No significant correlations were observed for the early-stage AD group.

Age. Tables 21 and 22 summarize the correlation matrices of the composite measures in the younger (n = 66) and older (n = 65) half of the cognitively normal sample. In the younger group, both episodic and working memory was negatively correlated with CoV. No other significant correlations were observed for this group. In the older group, episodic memory was strongly negatively correlated with CoV, while a more modest negative association was observed between working memory and CoV. No additional significant correlations were observed for this group.

APOE status. Tables 23 and 24 summarize the correlation matrices of the composite measures as a function of APOE status for the cognitively normal group. Within the APOE4- group (n = 83; Table 23), episodic memory was significantly negatively correlated with CoV. No other significant correlations were observed for this group. In the APOE4+ group (n = 42; Table 24), working memory was significantly negatively correlated with CoV, and was significantly positively correlated with default white matter volume. No correlations involving episodic memory were significant for the APOE4+ group.

COMT status. Tables 25 and 26 summarize the correlation matrices of the composite measures as a function of COMT status for the cognitively normal group. Within the Val- group (n = 30; Table 25), no significant correlations were observed. In the Val+ group (n = 70; Table 26), both working memory and episodic memory were significantly negatively correlated with

CoV. No other correlations reached significance for Val+ group.

Education. Tables 27 and 28 summarize the correlation matrices of the composite measures within the cognitively normal group as a function of low or high years of education, respectively. As before, 16+ years of education was considered high education, and <16 years of education was considered low education. Within the low education group (n = 57), working memory was significantly negatively correlated with CoV. No other significant correlations were observed for this group. In the high education group (n = 69), episodic memory was significantly negatively correlated with CoV. No other correlations reached significance for the high education group, however. As in the overall sample, there were no patterns of correlation consistent with possible mediation observed in any of the examined subgroups.

Discussion

Recent literature has focused on white matter integrity in frontal and temporoparietal areas as a possible neuroanatomical correlate of reaction time intraindividual variability, and a focus of this literature has been on older adults (Anstey et al., 2007; Jackson et al., 2012; MacDonald, Li, & Bäckman, 2009; Walhovd & Fjell, 2007; Ziegler et al., 2010). The primary aims of this study were to examine whether 1) intraindividual variability uniquely associated with white matter volume, and 2) IIV may serve as a mediator between neurobiological factors and episodic and working memory in older adults. Neither of these aims was supported by the results. Although this was unexpected given the depth of prior work, post-hoc analyses yielded some insights on the relationship between IIV and the brain in healthy and pathological aging. Discussion focuses on each aim separately.

Aim 1 – Double dissociation

The first aim hypothesized that IIV, measured by the coefficient of variation, would be uniquely associated with white matter volume and a measure of central tendency, median RT,

would uniquely associate with gray matter thickness. Results revealed that CoV was not correlated with either white or gray matter while median RT was negatively correlated with both white and gray matter. The present data therefore revealed a single dissociation – that median RT was associated with gray and white matter, while CoV was not associated with either neuroanatomical measure. The lack of association between CoV and white matter contradicts several other reports of a robust correlation between these measures (Anstey et al., 2007; Fjell et al., 2011; Jackson et al., 2012; MacDonald, Li, & Bäckman, 2009; Ullén et al., 2008; Walhovd & Fjell, 2007; Ziegler et al., 2010). It is not clear why the data do not replicate prior work, although differences in methodology between previous experiments and the current study merit consideration.

Previous studies have tended to adopt less conservative approaches with regard to covariates than those employed here. Typically, studies of white matter structure-function relationships will control for age and gender and little else (Anstey et al., 2007; Breteler et al., 1994a,b; Bunce et al., 2007, 2010; Charlton et al., 2006; Duan et al., 2006; Fjell et al., 2011; Stuss et al., 2003; Vernooij et al., 2009; Walhovd & Fjell, 2007; Ziegler et al., 2010). Exceptions to this trend, such as Bunce et al. (2007, 2010), have also controlled for cardiovascular health, diabetes, and depression, but these variables' impact on results were examined singly rather than in concert. In addition, few studies have controlled for years of education. Therefore, the adoption of relatively conservative treatment of covariates may partially account for the discrepant findings observed here. Although some of the covariates were associated with one another, these associations were modest, and the contributed variance from each covariate was largely independent. Post-hoc analyses using unstandardized data revealed that covariate control may account for the weak associations among the variables of interest.

In order to further examine possible moderating effects of the selected covariates, zero-order correlations were investigated in the total sample. White matter volume ($r(262) = -.21$, $p = .001$) and gray matter thickness ($r(262) = -.18$, $p = .003$) were significantly correlated with CoV. White matter volume ($r(262) = -.29$, $p < .001$) and gray matter thickness ($r(262) = -.29$, $p < .001$) were also significantly correlated with median RT. The Aim 1 double-dissociation model was examined using the unpartialed variables, but this model still provided a poor fit to the data, $\chi 2 = 35.906$, df = 2, p < .001; CFI = .587; TLI = .000; SRMR = .099; RMSEA = .254. Therefore, it appears that although zero-order correlations among the variables of interest were larger than partial correlations with covariates controlled, these associations were still weak and the proposed double-dissociation did not fit the data.

Covariate influence on the data was also examined in a manner more consistent with previous literature (e.g., Bunce et al., 2007, 2010). That is, rather than examining covariate influence in concert, each covariate, along with age, was singly controlled for in both aims. All Aim 1 models, controlling for age along with education, gender, depression, diabetes diagnosis, cardiovascular health, scanner type, and scan-assessment interval, respectively, provided poor fits to data, all $\chi 2 > 10.04$, df = 2, all *p*s < .007; all CFIs < .723; all TLIs < .308; all SRMRs > .050; all RMSEAs > .124. Aim 2 covariates, along with age, were also individually partialed from the predictor variables. The partialed predictor variables for each covariate were correlated with one another to determine whether Baron and Kenny's (1986) requirements for mediation were met. As in the Aim 2 a priori hypotheses, COMT, APOE, and white matter volumes were largely uncorrelated with episodic memory and CoV. Thus, mediation was again not possible. Ultimately, the selected covariates may have slightly influenced the variables of interest, but the proposed models were not a good fit for the data.

Even with the aforementioned caveats, Jackson et al. (2012) was performed using the same measures of IIV and white matter, participants were sampled from the same pool, and the authors used the same covariates as those reported here. Post-hoc results demonstrated that although the association between CoV and white matter volume was smaller in the present analyses, similar relationships to Jackson et al. (2012) were observed. Indeed, when analyses were conducted in the same manner as Jackson et al. (2012), white matter volume contributed significant variance to CoV in the same regions as the prior study, with the exception of the precuneus. Furthermore, gray matter thickness in the same regions was largely unassociated with CoV. The IPL provided an exception to this trend, given that it did not contribute significant variance using white matter measures in the previous study or in Jackson et al. (2012). For τ, the replication was less clear, with only two white matter volumes, VLDLPFC and precuneus, contributing significant variance to this parameter. Gray matter thickness in precuneus contributed significant variance to τ as well, and IPL gray matter thickness was associated with τ in the CDR 0 group, but not the CDR 0.5 group.

A difference in the handling of covariates may account for the discrepant findings between the linear regressions of Jackson et al. (2012) and the current study. In Jackson et al. (2012), the authors made use of a hierarchical linear regression to analyze the data, and covariates were addressed by entering them in the first step of the model. This allowed variance associated with those covariates to be partialed from subsequently-entered predictors, which included measures of white matter volume, but not from the dependent variable, CoV. In the present study, covariates were partialed from the dependent and predictor variables before correlations were examined, an approach that may have mitigated previously observed associations. Given the similarity between the two studies when using the same analyses, it

appears as though the handling of covariates as well as the general analytic approach may play a vital role in understanding structure-function relationships in the brain. Even where the same covariates are measured, differences in partialing procedures may influence research findings.

Trends using RT distributional parameters were difficult to discern, however. It is unusual that CoV and τ, which tend to highly correlate, associated somewhat differently with white and gray matter in the present study. Given the strong correlation between τ and CoV reported in Jackson et al. ($r(166) = .702$, $p < .001$) as well as within the current study ($r(262) = .504$, $p < .001$), it is not apparent why τ did not associate with white matter volume in the post-hoc analyses of the current report, but associated with white and gray matter measures in the Jackson et al. (2012) replication analyses. It is possible that the sensitivity of τ was limited in the present study because only incongruent or switch trials were used to compute the distributional parameters, where Jackson et al. used congruent and nonswitch conditions as well. The greater diversity of trial types for τ, though apparently not CoV, may yield stronger associations to white matter volume as observed in Jackson et al (2012). While studies that simultaneously examine τ and CoV are relatively rare, Balota et al. (2010) found reliable relationships using the τ measure, but not with the CoV measure (Balota, personal communication), although it is important to note that Balota et al. used all trials from the attentional tasks, rather than the incongruent trials alone.

Differences between the present study and other research may not only involve cognitive measures, however. The type of white matter measurement may also serve as an important factor in understanding brain-behavior associations. Measures of white matter macrostructure typically include volumetric estimates of white matter regions or white matter hyperintensities, areas of increased signal intensity observed in structural magnetic resonance imaging. White matter microstructure is typically examined using diffusion tensor imaging estimates of mean

diffusivity, which examines the rate of water diffusivity, and also fractional anisotropy, which is a measure of the strength of the directionality of water molecule movement. Healthy white matter tracts tend to constrain water so that it moves primarily along the tract in a parallel direction to the cellular boundaries, whereas damaged tracts allow more increased perpendicular and off-parallel movement (Basser & Pierpaoli, 1996). Recent research suggests that white matter microstructure and macrostructure are complementary, but not necessarily isomorphic, measures of white matter (Abe et al., 2008; Fjell, Westlye, Greve, Fischl, & Benner, 2008; Gunning-Dixon et al., 2009). In particular, alterations in white matter microstructure may precede age-related changes in white matter macrostructure (Fjell et al., 2008; Gunning-Dixon et al., 2009). Given that the current literature often studies either microstructure or macrostructure in isolation (Bunce et al., 2007; Fjell et al., 2011; Jackson et al., 2012; Moy et al., 2011; Ullén et al., 2008; Walhovd & Fjell, 2007), investigation of white matter microstructure and macrostructure may reveal different associations with cognitive and behavioral performance. Because of its sensitivity to homeostatic disturbances (Bartzokis, 2011), white matter microstructure may be more strongly associated with CoV, and perhaps less with median RT (Haier et al., 2005; Jensen 1992; Walhovd & Fjell, 2007). Although there may be convergence between the two measures, it is important to carefully differentiate the contributions from each broad measure of white matter to better understand the neuroanatomical correlates of IIV (Vernooij et al., 2009). This dissertation focused on white matter macrostructure, particularly white matter volume; however, further study of white matter microstructure may reveal the associations that were not found here.

In general, post-hoc analyses for Aim 1 did not result in any correlational patterns consistent with the hypothesized double dissociation. No consistent differences in associations

between cognitive and brain variables were observed as a function of genetic status or years of education. The examination of Aim 1 correlations within cognitive subgroups, however, may shed further light on possible group differences in the association of IIV to brain regions. The cognitively normal group had modest negative correlations between median RT and both gray matter thickness and white matter volume. In the early-stage AD group, on the other hand, CoV was correlated negatively with white matter volume. However, the post-hoc analyses examining younger and older subsamples revealed trends suggesting a different pattern. The younger subsample yielded an association between white matter and CoV, but median RT was associated with white and gray matter in the older group. That CoV was associated with white matter in younger groups while median RT was associated with white and gray matter in older groups is contrary to the trends observed in the other subgroups, although this pattern has been observed in other laboratories (e.g., Anstey et al., 2007). It is possible that in cognitively normal aging, estimates of central tendency and variability in attentional tasks are modestly contingent on overall brain integrity in frontal and parietal areas, although associations with variability were observed in the younger, but not older, sample in the cognitively normal group in the current study. In healthy aging, both white matter and gray matter may be important for overall task execution, as measured by median RT rather than CoV. As individuals convert to the earliest stages of AD, however, white matter integrity may play an increasingly important role as synchrony between orchestrated networks becomes compromised (O'Sullivan et al., 2001), making consistent execution of cognitive tasks difficult.

Other studies that have found trends toward a double dissociation (e.g., Walhovd & Fjell, 2007) may therefore have conflated healthy aging with the earliest stages of pathological aging. It is possible that white matter microstructure, rather than white matter volume, is more strongly

associated with IIV as individuals progress to later stages of dementia. Jackson et al. (2012), with its smaller sample, failed to find a difference in the association between IIV and white matter macrostructure in CDR 0.5 and CDR 1 individuals relative to CDR 0, but did find trends toward an interaction between the white matter volume ROI and CDR status in superior frontal gyrus ($\Delta R^2 = .012$, $p = .086$), the precuneus ($\Delta R^2 = .010$, $p = .118$), and ventral/dorsolateral prefrontal cortex ($\Delta R^2 = .008$, $p = .151$). An investigation of white matter microstructure in comparable regions may show differences in sensitivity to CoV as a function of cognitive status.

Aim 2 – Mediation by IIV

The second aim examined whether the relationship between neurobiological factors and episodic and working memory might be mediated by IIV. Unfortunately of the predictor variables of interest (i.e., COMT, APOE, frontal and default white matter), none were significantly associated with either of the memory measures in the full sample, which rendered moot any possibility of mediation. Removing covariates from consideration strengthened the associations among the measures, but did not yield significant associations between white matter and episodic or working memory. Although some treatment of the lack of expected associations was discussed in the previous section, attention will be given to each of the predicted relationships in the mediational model.

White matter and memory performance. The core of Aim 2's mediational model was the association between white matter volume in frontal and default-network regions with episodic and working memory measures. In Aim 2, volumetric composites of white matter were divided into frontal regions (i.e., superior frontal gyral and ventral/dorsol.ateral prefrontal cortical volumes) and regions implicated in the default network (i.e, posterior cingulate, precuneus, and inferior parietal lobule volumes). This division was proposed because it was hypothesized that

the frontal composite would be more likely to associate with working memory measures (e.g., Raz & Rodrigue, 2006), while default-network regions would associate with episodic memory (e.g., Andrews-Hanna et al., 2010). No correlations supporting this association were found, however, which indicated that any mediation by IIV measures would not be possible. The relationship between white matter and working memory may not be as clear as was assumed in the Introduction, however. Although several studies have found associations between white matter and working or episodic memory in older adults (Bucur et al., 2008; Burton et al., 2004; Brickman et al., 2006; Charlton, Barrick, Lawes, Markus, & Morris, 2010; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Gunning-Dixon & Raz, 2000; Kennedy & Raz, 2009; Madden, Bennett, & Song, 2009; Nordahl et al., 2006), the majority of these investigations focus on cognitive associations with white matter microstructure rather than white matter volume. As noted earlier, white matter microstructure and macrostructure are not necessarily isomorphic (Abe et al., 2008; Fjell, Westlye, Greve, Fischl, & Benner, 2008; Gunning-Dixon et al., 2009). This possibility suggests that white matter volume in these regions of interest may be less likely to be associated with memory measures than estimates of white matter microstructure or tractography obtained via diffusion tensor imaging. Brickman et al. (2006), however, reported an association between frontal and temporal white matter volume and episodic memory performance, raising the possibility that white matter macrostructure may indeed be related to memory measures. The significance of this observation may be tempered somewhat given Brickman et al. controlled only for age, which may not be adequate covariate control (see Jackson et al., 2012).

As a manipulation check to determine whether covariate control may have played a substantive role in the present set of analyses, 3 medial temporal gray matter volumes, often

implicated in episodic memory (e.g., Squire & Zola-Morgan, 1991; Zola-Morgan & Squire, 1986) were correlated with the residualized episodic and working memory measures. Residualized measures of hippocampal gray matter, as well as parahippocampal gray matter volume and thickness, were obtained for the Aim 2 subsample. None of the measures were correlated with either episodic or working memory, all *r*s < .095. By way of comparison, there were modest zero-order correlations of episodic memory with hippocampal ($r(149) = .304$, $p < .001$) and parahippocampal gray matter volume ($r(149) = .313$, $p < .001$). No other associations were reliable and all *r*s were less than .12. These results suggest that covariate control may mask even commonly-reported associations, and so may have prevented predicted associations from being observed. Another possibility, of course, is that these associations are spurious because the variables are modulated by age or CDR status.

Genetic factors and memory performance. APOE has been a key factor in recent explorations of genetic influences on cognition in healthy and pathological aging. A priori analyses showed only an episodic memory advantage for the APOE4- group. The negative influence of the APOE4 polymorphism on working memory is fairly well-defined (Greenwood, Lambert, Sunderland, & Parasuraman, 2005; Reinvang, Winjevoll, Rootwell, & Espeseth, 2010; Rosen, Bergeson, Putnam, Harwell, & Sunderland, 2002), as is the negative role of APOE4 in episodic memory (see Wisdom, Callahan, & Hawkins, 2011, and Small, Rosnick, Fratiglioni, & Bäckman, 2004, for meta-analyses regarding APOE and episodic memory). As in Jackson et al. (2012) and other studies drawing from similar samples as the current study (Balota et al., 2010; Duchek et al., 2009; Tse et al., 2010), it is possible that the participants were particularly high-functioning, limiting performance variability in the working and episodic memory tasks that comprised the composite measures. To test for evidence of skewness in performance, a

Kolmogorov-Smirnov test was conducted on the overall sample for both memory measures. There was no evidence of skewing for either episodic memory or working memory, however (K-S zs < 1, ps > .57), so it does not appear that the sample was subject to ceiling effects in performance. Another possibility for the lack of association between memory performance and genetic factors is that the working memory composite used in the current study included simple span tasks which may be less sensitive than complex working memory tasks to the kinds of differences explored here (e.g., Reinvang et al., 2010). Therefore, the obtained working memory measures were not able to distinguish between APOE groups. It is possible that with more complex working memory tasks, APOE effects may emerge.

COMT, like APOE, has been associated with risk for AD, particularly in conjunction with APOE (Martínez et al., 2009; Wang et al., 2005), but any link with working and episodic memory is not well-understood (de Frias et al., 2004; Egan et al., 2001; MacDonald et al., 2009). A priori analyses revealed that neither working memory nor episodic memory differed with respect to COMT group status; however, the Val+ group performed numerically worse on both memory measures relative to the Val- group. Although presence of the Val allele has been associated with increased IIV in cognitively normal populations (MacDonald, Cervenka et al., 2009), evidence supporting direct links between COMT status and working and episodic memory are much more difficult to pinpoint. Presence of the Val allele on the COMT gene is inconsistently associated with working memory, which is sometimes conflated with executive function more generally (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006; Bruder et al., 2005; Egan et al., 2001; Goldberg et al., 2003; Goldberg & Weinberger, 2004; Parasuraman & Jiang, 2011). Although group differences in COMT have emerged in episodic memory performance (de Frias et al., 2004; Gibbs, Naudts, Azevedo, & David, 2010), COMT's

association with episodic memory may be somewhat indirect. Examinations of the association between COMT and memory have typically made use of larger samples (*n*s > 250) than the COMT sample available for Aim 2 (*n* = 100), which may suggest a lack of power to detect associations involving COMT in the present study. This association may also be perhaps mediated by extracellular dopamine in frontal regions (de Frias et al., 2004; Gibbs et al., 2010; Savitz, Solms, & Ramesar, 2006; Wimber et al., 2011), rather than the temporal regions typically associated with binding in episodic memory. Thus, COMT's effect in frontal regions of the brain may influence executive function, which in turn may influence episodic memory. Ultimately, however, it is not entirely clear why genetic-memory observations consistent with the extant literature were not observed.

White matter and CoV. Consideration of the lack of association between white matter and CoV was discussed in Aim 1, but the use of frontal and default-network composites in Aim 2 warrants additional discussion. Studies investigating the relationship between white matter and IIV typically have focused on frontal regions, given that damage to these areas historically has been associated with increased IIV (Bellgrove et al., 2004; Bunce et al., 2013; Goldstein, 1942; Head, 1926; MacDonald et al., 2006, 2009; Murtha et al., 2002; Stuss et al., 2003; Ullén et al., 2008). Given the variety of methods employed in examination of the association of frontal damage with IIV, particularly those involving white matter (Bunce et al., 2010; Jackson et al., 2012; Moy et al., 2011; Ullén et al., 2008), it is surprising that the frontal white matter composite in the present study was not more strongly associated with CoV. Although the correlation (*r* = -.187) was significant, it was somewhat weaker than anticipated. As noted above, it is possible that the method of covariate control employed in the current study prevented the observation of a

stronger association between CoV and white matter (zero-order r = -.239). As noted above, the use of white matter microstructure may also yield stronger associations with CoV.

Another plausible explanation, supported by the single dissociation observed in Aim 1, is that in some regions, IIV may indeed be associated with gray matter rather than white matter. Indeed, the Jackson et al. (2012) replication analyses in Aim 1 suggested an association with the precuneus and IPL, particularly using the τ measure. Although gray matter was not tested in Aim 2, the moderate correlations observed in Aim 1 between gray matter and the CoV and median RT measures highlights the importance of considering multiple candidates for neural correlates of IIV. Although many studies have investigated the relationship between white matter and IIV, no studies to date, including the present study, have examined this association independently over and above an IIV-gray matter correlation. Indeed, even the simultaneous examination of gray and white matter measures in relation to IIV has only rarely been explored (Walhovd & Fjell, 2007). To justify an exclusive focus on white matter, previous studies have suggested that better-myelinated connections between neurons yields tighter cognitive control and better task execution, thus reducing IIV (e.g., Walhovd & Fjell, 2007), or that white matter lesions are associated with cognitive impairment (e.g., Bunce et al., 2010). This focus may stem from computational models of IIV that implicate noisy information processing as a potential cause or correlate (Li et al., 2001), or the similar trajectory noted between white matter and IIV in development and decline across the lifespan (MacDonald et al., 2006). Indeed, while there is strong theoretical basis for the association of white matter with IIV (MacDonald et al., 2006, 2009), there have been no attempts to theoretically distinguish independent contributions of white and gray matter on IIV. This, coupled with a tendency to consider white matter hyperintensities, volume, microstructure, and functional connectivity as an isomorphic white

matter construct, may have resulted in a prevailing view that IIV is primarily associated with white matter, with some potential association with prefrontal gray matter as well (MacDonald et al., 2006). Of course, a more plausible conceptualization is that IIV is associated with multiple aspects of neuronal structure, and may be also associated with gray matter than white matter. Yet despite a single study demonstrating a double dissociation similar to the one hypothesized in Aim 1 (Walhovd & Fjell, 2007), whether IIV may be associated with both gray and white matter remains an open question.

Genetic factors and CoV. IIV has been associated with both APOE (Duchek et al., 2009) as well as COMT (Egan et al., 2001; Li et al., 2001; MacDonald et al., 2009), but CoV was not sensitive to group differences for either genotype in the present study. CoV's lack of genetic sensitivity in the present study is unclear, as noted above; however, an assocation between CoV and APOE was observed in a study that drew from the same sample as the present investigation (Duchek et al., 2009). Post-hoc explorations of the relationship between genetic factors and CoV, discussed below, may shed some light on why group differences were not observed for APOE and COMT genotypes.

CoV and memory performance. Although many predicted associations in Aim 2's mediational model were not observed, the predicted negative association between CoV and memory performance was observed in the full sample of participants. These results are in line with previous literature. The negative association between working memory and a lack of RT stability has been noted in other studies (Lewis & Miall, 2006; Ullén et al., 2008), and the present results reinforce the observation that IIV is strongly associated with other indices of cognitive functioning. Indeed, although fewer studies have reported a direct association between IIV and episodic memory (Hultsch et al., 2002; MacDonald, Cervenka et al., 2009; MacDonald,

Nyberg et al., 2008), the current results were able to replicate and extend this association as well. Thus, as suggested in previous literature (MacDonald et al., 2006, 2009), IIV may indeed be a proxy for broader cognitive changes, particularly in older adults.

Post-hoc analyses

The majority of predicted findings in Aim 2 were not supported, and post-hoc analysis of individual measures in place of composites did not result in a coherent pattern of results. Post-hoc analyses of the subgroups yielded potentially interesting, though small and not expected, trends in associations among structural, genetic, aging, and cognitive variables. Somewhat similar trends were observed in the post-hoc analyses as a function of age, education, genetic polymorphisms, and cognitive status. In particular, the group at greater risk for cognitive decline (e.g., the early-stage AD group, COMT Val+ carriers, APOE4+ carriers, low education individuals), tended to demonstrate a significant correlation between CoV and working memory, though this was only an admittedly weak trend in the AD group and the older adult subsample had a much stronger association between CoV and episodic memory.

It is unclear why this pattern was observed, but one post-hoc speculation is that at-risk groups may have a robust link between IIV and dynamic task performance, or indeed, dynamic maintenance of an ongoing task set (Spieler, Balota, & Faust, 1996; Tse et al., 2010). On the other hand, the group at lower risk (e.g., the cognitively normal group, Val- carriers, APOE4- carriers, high education individuals) tended to have a stronger (though not consistently significant) association between CoV and episodic memory. The low-risk groups may instead see a connection between IIV and relatively less executive-dependent measures of cognitive performance, such as episodic memory recall. CoV, then, may prove to be a dynamically sensitive measure, indexing those tasks that are relatively more variable across persons within a

group of a given risk for dementia. Comparing the group-level standard deviations of residualized working and episodic memory across low- and high-risk groups, the high-risk groups for cognitive status, education and APOE group had slightly- to moderately-higher SDs for working memory measures relative to episodic memory measures. The low-risk groups for education and COMT group tended to have higher SDs for episodic memory measures relative to working memory.

This speculation did not appear to hold for the younger and older subsamples, however. Both memory mesures were associated with CoV in the younger and older groups; however episodic memory was very strongly associated with CoV in the older group. Additionally, both of the age subgroups tended to have larger SDs for the episodic memory measure relative to the working memory measure, however. This pattern represents, if anything, the opposite of what might be expected, assuming that the older group represents the higher risk. Consideration of other risk factors may suggest that this assumption is problematic, on the other hand. The older sample had a lower proportion of Val+ (59% vs. 82%) and APOE4+ (25% vs. 44%) individuals. It may be difficult, then, to compare risk as a function of age group, given how other risk factors are represented in each age subsample.

The speculative approach may not be a definitive examination of variability between risk groups, but it suggests the possibility that cognitive associations with CoV are flexible based on other factors. MacDonald and colleagues (2006, 2009; Hultsch et al., 2008) have argued that IIV is sensitive to cognitive impairment, particularly in older adults. The current results may indicate that IIV may be sensitive to different aspects of cognitive performance across cognitively normal, AD-risk, and AD groups. Those at higher risk of dementia may have more variable performance in tasks of working memory, because these groups may have relative difficulty in

maintaining task set consistently across repeated-measures designs relative to tasks tapping episodic memory, which are typically single point-estimates. Such a suggestion may help reconcile seemingly contradictory reports of the sensitivity of IIV to other neurocognitive measures in various cognitive and age groups (e.g., Christensen et al., 2005; Dixon et al., 2007), or even whether different types of IIV may differentiate between age and cognitive groups (Hultsch et al., 2008). On the other hand, those groups at lower risk for dementia may see more group-level variability in these single-measure designs because there is relatively less signal variability on a moment-to-moment basis, which may reduce variability in repeated-measures designs (Li et al., 2000; Tse et al., 2010). Group-level variability in low-risk groups therefore may be observed in single-measures tasks like those tapping episodic memory. Ultimately, this may indicate that groups at risk for AD may have different underlying biobehavioral associations. However, a much larger sample and clearer, a priori hypotheses are needed to examine this post-hoc speculation in more detail.

Limitations and future directions

There are several limitations to the current experiment. First, although the mean delay between the cognitive assessment and structural scan using absolute values was 216 days, some participants had a delay of up to two years between the measures. Although the design reported here statistically controlled for this interval, no delay between assessments would be ideal to better understand the association between cognitive measure and the integrity of brain regions. Second, given the impact of covariate selection and control (see Aim 1 Discussion), careful consideration is needed of whether to partial covariates from all measures or only predictor variables. Third, the cross-sectional nature of the design necessarily limits the generalizability of any associations reported here. Longitudinal follow-up is needed in order to draw firmer

conclusions regarding causal directions between cognitive and neuroanatomical correlates. Fourth, in the case of Aim 2, the selection of measures that accurately represent episodic and working memory constructs may merit further consideration. Although the current study used memory constructs defined in previous studies (Johnson et al., 2008; 2009), other studies have used different measures to represent working memory in particular (e.g., Tse et al., 2010). It is possible that these measures may highlight different aspects of working memory, and should be compared to determine how these constructs are associated. Finally, white matter is but one factor that is implicated in IIV, with a host of others ranging from neurotransmitter dysfunction to frontal lesions and brain injury (Stuss et al., 2003; MacDonald, Cervenka et al., 2009; MacDonald, Li et al., 2009; MacDonald, Nyberg et al., 2006; Murtha et al., 2002). The relative contributions of each of these factors remains unknown, so even the few significant relationships reported here require contextualization in order to understand the broader association between IIV and the brain.

Future work may incorporate longitudinal designs to investigate the predictive utility of IIV. Although there has been some work in this area (Balota et al., 2010; Bielak et al., 2010b, 2013; Lövdén, Li, Shing, & Lindenberger, 2007; MacDonald, Hultsch, & Dixon, 2003), substantial research is lacking, particularly with respect to the anticipation of future cognitive decline as well as conversion to early-stage AD. Predictive analyses, such as Cox hazard models, could conceptually replicate and extend the findings of Balota et al. (2010), MacDonald et al. (2003), and Bielak et al. (2010b) who demonstrated that changes in variability may serve as a useful marker of future cognitive decline and conversion to early-stage AD. Additionally, the examination of white matter microstructure via DTI may yield significant associations between white matter and IIV, as observed in other laboratories (MacDonald, Li, & Bäckman, 2009; Moy

et al., 2011; Walhovd & Fjell, 2007; Ziegler et al., 2010). Once established, it is possible that a mediation model involving CoV may be revisited.

In summary, although the present results replicated and extended the findings of Jackson et al. (2012) to gray matter, the present results largely failed to find evidence uniquely associating white matter volume with CoV, or evidence supporting CoV as a mediator in brain-behavior relationships. Intriguing patterns emerged, however, involving the role of cognitive status and genetic markers such as APOE and COMT. In particular, it is possible that groups at higher risk of dementia may have stronger associations between CoV and cognitive measures of attentional control than individuals not at risk for AD.

References

Abe, O., Yamasue, H., Aoki, S., Suga, M., Yamada, H., Kasai, K., ... & Ohtomo, K. (2008). Aging in the CNS: comparison of gray/white matter volume and diffusion tensor data. *Neurobiology of Aging, 29(1),* 102-116. doi:10.1016/j.neurobiolaging.2006.09.003

Amar, K., Bucks, R. S., Lewis, T., Scott, M., & Wilcock, G. K. (1996). The effect of white matter low attenuation on cognitive performance in dementia of the Alzheimer type. *Age and Ageing, 25(6)*, 443-8. doi:10.1093/ageing/25.6.443

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., & Buckner, R. L. (2010). Functional-anatomic fractionation of the brain's default network. *Neuron, 65(4)*, 550-562. http://dx.doi.org/10.1016/j.neuron.2010.02.005

Andrews-Hanna, J. R., Snyder, A. Z., Vincent, J. L., Lustig, C., Head, D., Raichle, M. E., & Buckner, R. L. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron, 56(5)*, 924-35. doi:10.1016/j.neuron.2007.10.038

Anstey, K. J. (1999). Sensorimotor variables and forced expiratory volume as correlates of speed, accuracy, and variability in reaction time performance in late adulthood. *Aging, Neuropsychology, and Cognition,* 6(2), 84-95. doi:10.1076/anec.6.2.84.786

Anstey, K. J., Dear, K., Christensen, H., & Jorm, A. (2005). Biomarkers, health, lifestyle, and demographic variables as correlates of reaction time performance in early, middle, and late adulthood. *The Quarterly Journal of Experimental Psychology: Section A, 58(1)*, 5-21. doi:10.1080/02724980443000232

Anstey, K. J., Mack, H. A., Christensen, H., Li, S. C., Reglade-Meslin, C., Maller, J., ... & Sachdev, P. (2007). Corpus callosum size, reaction time speed and variability in mild cognitive disorders and in a normative sample. *Neuropsychologia, 45(8)*, 1911-20. doi:10.1016/j.neuropsychologia.2006.11.020

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S. C., & Farde, L. (2006). The correlative triad among aging, dopamine, and cognition: current status and future prospects. *Neuroscience & Biobehavioral Reviews, 30(6)*, 791-807. http://dx.doi.org/10.1016/j.neubiorev.2006.06.005

Bai, F., Zhang, Z., Watson, D. R., Yu, H., Shi, Y., & Yuan, Y. (2009). Abnormal white matter independent of hippocampal atrophy in amnestic type mild cognitive impairment. *Neuroscience Letters, 462(2)*, 147-51. doi:10.1016/j.neulet.2009.07.009

Bai, F., Zhang, Z., Yu, H., Shi, Y., Yuan, Y., Zhu, W., ... & Qian, Y. (2008). Default-mode network activity distinguishes amnestic type mild cognitive impairment from healthy aging: A combined structural and resting-state functional MRI study. *Neuroscience Letters, 438(1)*, 111-5. doi:10.1016/j.neulet.2008.04.021

Balota, D. A., Tse, C.-S., Hutchison, K. A., Spieler, D. H., Duchek, J. M., & Morris, J. C. (2010). Predicting conversion to dementia of the Alzheimer's type in a healthy control sample: The power of errors in Stroop color naming. *Psychology and Aging, 25(1)*, 208-18. doi:10.1037/a0017474

Balota, D. A., Yap, M. J., Cortese, M. J., & Watson, J. M. (2008). Beyond mean response latency: Response time distributional analyses of semantic priming. Journal of Memory and Language, 59(4), 495-523. doi:10.1016/j.jml.2007.10.004

Baron, R. M., & Kenny, D. A. (1986). The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology, 51(6)*, 1173-82. doi:10.1037/0022-3514.51.6.1173

Bartzokis, G. (2011). Alzheimer's disease as homeostatic responses to age-related myelin breakdown. *Neurobiology of Aging, 32(8)*, 1341-71. doi:10.1016/j.neurobiolaging.2009.08.007.Alzheimer

Bartzokis, G., Cummings, J. L., Sultzer, D., Henderson, V. W., Nuechterlein, K. H., & Mintz, J. (2003). White matter structural integrity in healthy aging adults and patients with Alzheimer disease: A magnetic resonance imaging study. *Archives of Neurology, 60(3)*, 393-8. doi:10.1001/archneur.60.3.393

Bartzokis, G., Lu, P. H., Tishler, T. a, Fong, S. M., Oluwadara, B., Finn, J. P., Huang, D., et al. (2007). Myelin breakdown and iron changes in Huntington's disease: Pathogenesis and treatment implications. *Neurochemical Research, 32(10)*, 1655-64. doi:10.1007/s11064-007-9352-7

Bartzokis, G., Sultzer, D., Lu, P. H., Nuechterlein, K. H., Mintz, J., & Cummings, J. L. (2004). Heterogeneous age-related breakdown of white matter structural integrity: Implications for cortical "disconnection" in aging and Alzheimer's disease. *Neurobiology of Aging, 25(7)*, 843-51. doi:10.1016/j.neurobiolaging.2003.09.005

Basser, P. J., & Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of Magnetic Resonance, 111,* 209-219. doi:10.1016/j.jmr.2011.09.022

Bellgrove, M. A., Hester, R., & Garavan, H. (2004). The functional neuroanatomical correlates of response variability: Evidence from a response inhibition task. *Neuropsychologia, 42(14)*, 1910-6. doi:10.1016/j.neuropsychologia.2004.05.007

Berg, L., McKeel Jr, D. W., Miller, J. P., Storandt, M., Rubin, E. H., Morris, J. C., ... & Saunders, A. M. (1998). Clinicopathologic studies in cognitively healthy aging and

Alzheimer disease: Relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. *Archives of Neurology, 55(3)*, 326-35. doi:10.1001/archneur.55.3.326

Bielak, A. A. M., Hultsch, D. F., Strauss, E., MacDonald, S. W. S., & Hunter, M. A. (2010a). Intraindividual variability is related to cognitive change in older adults: Evidence for within-person coupling. *Psychology and Aging, 25(3)*, 575-86. doi:10.1037/a0019503

Bielak, A. A. M., Hultsch, D. F., Strauss, E., Macdonald, S. W. S., & Hunter, M. A. (2010b). Intraindividual variability in reaction time predicts cognitive outcomes 5 years later. *Neuropsychology, 24(6)*, 731-41. doi:10.1037/a0019802

Breteler, M. M., van Amerongen, N. M., van Swieten, J. C., Claus, J. J., Grobbee, D. E., Van Gijn, J., ... & Van Harskamp, F. (1994). Cognitive correlates of ventricular enlargement and cerebral white matter lesions on magnetic resonance imaging. The Rotterdam Study. *Stroke, 25(6)*, 1109-1115.

Breteler, M. M. B., Van Swieten, J. C., Bots, M. L., Grobbee, D. E., Claus, J. J., Van Den Hout, J. H. W., ... & Hofman, A. (1994). Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study. The Rotterdam Study. *Neurology, 44(7),* 1246-52. doi: 10.1212/WNL.44.7.1246

Brickman, A. M., Zimmerman, M. E., Paul, R. H., Grieve, S. M., Tate, D. F., Cohen, R. A., ... & Gordon, E. (2006). Regional white matter and neuropsychological functioning across the adult lifespan. *Biological Psychiatry, 60(5)*, 444-53.

Bruder, G. E., Keilp, J. G., Xu, H., Shikhman, M., Schori, E., Gorman, J. M., & Gilliam, T. C. (2005). Catechol-O-methyltransferase (COMT) genotypes and working memory:

Associations with differing cognitive operations. *Biological Psychiatry, 58(11)*, 901-7. doi:10.1016/j.biopsych.2005.05.010

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Annals Of The New York Academy Of Sciences, 1124,* 1-38. doi:10.1196/annals.1440.011

Buckner, R. L., Head, D., Parker, J., Fotenos, A. F., Marcus, D., Morris, J. C., & Snyder, A. Z. (2004). A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: Reliability and validation against manual measurement of total intracranial volume. *NeuroImage, 23(2)*, 724-38. doi:10.1016/j.neuroimage.2004.06.018

Buckner, R. L., Sepulcre, J., Talukdar, T., Krienen, F. M., Liu, H., Hedden, T., ... & Johnson, K. A. (2009). Cortical hubs revealed by intrinsic functional connectivity: Mapping, assessment of stability, and relation to Alzheimer's disease. *The Journal of Neuroscience, 29(6)*, 1860-73. doi:10.1523/JNEUROSCI.5062-08.2009

Bucur, B., Madden, D. J., Spaniol, J., Provenzale, J. M., Cabeza, R., White, L. E., & Huettel, S. A. (2008). Age-related slowing of memory retrieval: Contributions of perceptual speed and cerebral white matter integrity. *Neurobiology of Aging, 29(7)*, 1070-9. http://dx.doi.org/10.1016/j.neurobiolaging.2007.02.008

Bunce, D., Anstey, K. J., Cherbuin, N., Burns, R., Christensen, H., Wen, W., & Sachdev, P. S. (2010). Cognitive deficits are associated with frontal and temporal lobe white matter lesions in middle-aged adults living in the community. *PLoS One, 5(10)*, e13567. doi:10.1371/journal.pone.0013567

Bunce, D., Anstey, K. J., Christensen, H., Dear, K., Wen, W., & Sachdev, P. (2007). White matter hyperintensities and within-person variability in community-dwelling adults aged 60-64 years. *Neuropsychologia, 45(9)*, 2009-15. doi:10.1016/j.neuropsychologia.2007.02.006

Bunce, D., Bielak, A. A. M., Cherbuin, N., Batterham, P. J., Wen, W., Sachdev, P., & Anstey, K. J. (2013). Utility of intraindividual reaction time variability to predict white matter hyperintensities: A potential assessment tool for clinical contexts? *Journal of the International Neuropsychological Society, 19*, 971-6.

Bunce, D., MacDonald, S. W. S., & Hultsch, D. F. (2004). Inconsistency in serial choice decision and motor reaction times dissociate in younger and older adults. *Brain and Cognition, 56(3)*, 320-7. doi:10.1016/j.bandc.2004.08.006

Burton, C. L., Strauss, E., Hultsch, D. F., Moll, A., & Hunter, M. A. (2006). Intraindividual variability as a marker of neurological dysfunction: A comparison of Alzheimer's disease and Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology, 28(1)*, 67-83. doi:10.1080/13803390490918318

Burton, E. J., Kenny, R. A., O'Brien, J., Stephens, S., Bradbury, M., Rowan, E., ... & Ballard, C. (2004). White matter hyperintensities are associated with impairment of memory, attention, and global cognitive performance in older stroke patients. *Stroke, 35(6)*, 1270-5. doi:10.1161/01.STR.0000126041.99024.86

Cabeza, R., Ciaramelli, E., Olson, I. R., & Moscovitch, M. (2008). The parietal cortex and episodic memory: An attentional account. *Nature Reviews Neuroscience, 9(8)*, 613-25. doi:10.1038/nrn2459

Charlton, R. A., Barrick, T. R., Lawes, I. N. C., Markus, H. S., & Morris, R. G. (2010). White matter pathways associated with working memory in normal aging. *Cortex, 46(4)*, 474-89. http://dx.doi.org/10.1016/j.cortex.2009.07.005

Charlton, R. A., Barrick, T. R., McIntyre, D. J., Shen, Y., O'Sullivan, M., Howe, F. A., ... & Markus, H. S. (2006). White matter damage on diffusion tensor imaging correlates with age-related cognitive decline. *Neurology, 66(2)*, 217-22. doi:10.1212/01.wnl.0000194256.15247.83

Christensen, H., Dear, K. B. G., Anstey, K. J., Parslow, R. A., Sachdev, P., & Jorm, A. F. (2005). Within-occasion intraindividual variability and preclinical diagnostic status: Is intraindividual variability an indicator of mild cognitive impairment? *Neuropsychology, 19(3)*, 309-17. doi:10.1037/0894-4105.19.3.309

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis: I. Segmentation and surface reconstruction. *NeuroImage, 9(2)*, 179-94. http://dx.doi.org/10.1006/nimg.1998.0395

Dale, A. M., & Sereno, M. I. (1993). Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: A linear approach. *Journal of Cognitive Neuroscience, 5(2)*, 162-176. doi:10.1162/jocn.1993.5.2.162

Damoiseaux, J. S., Beckmann, C. F., Arigita, E. S., Barkhof, F., Scheltens, P., Stam, C. J., ... & Rombouts, S. A. R. B. (2008). Reduced resting-state brain activity in the "default network" in normal aging. *Cerebral Cortex, 18(8)*, 1856-64. doi:10.1093/cercor/bhm207

Damoiseaux, J. S., Prater, K. E., Miller, B. L., & Greicius, M. D. (2012). Functional connectivity tracks clinical deterioration in Alzheimer's disease. *Neurobiology of Aging, 33(4)*, 828.e19-30. doi:10.1016/j.neurobiolaging.2011.06.024

de Frias, C. M., Annerbrink, K., Westberg, L., Eriksson, E., Adolfsson, R., & Nilsson, L. G. (2004). COMT gene polymorphism is associated with declarative memory in adulthood and old age. *Behavior Genetics, 34(5)*, 533-9. doi:10.1023/B:BEGE.0000038491.06972.8c

Deary, I., & Der, G. (2005). Reaction time, age, and cognitive ability: Longitudinal findings from age 16 to 63 years in representative population samples. *Aging, Neuropsychology, and Cognition, 12(2), 187-215*. doi:10.1080/13825580590969235

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., ... & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage, 31(3)*, 968-80. doi:10.1016/j.neuroimage.2006.01.021

Dixon, R. A., Garrett, D. D., Lentz, T. L., MacDonald, S. W. S., Strauss, E., & Hultsch, D. F. (2007). Neurocognitive markers of cognitive impairment: Exploring the roles of speed and inconsistency. *Neuropsychology, 21(3)*, 381-99. doi:10.1037/0894-4105.21.3.381

Duan, J. H., Wang, H. Q., Xu, J., Lin, X., Chen, S. Q., Kang, Z., & Yao, Z. B. (2006). White matter damage of patients with Alzheimer's disease correlated with the decreased cognitive function. *Surgical and Radiologic Anatomy, 28(2)*, 150-6. doi:10.1007/s00276-006-0111-2

Duchek, J. M., Balota, D. A., Tse, C.-S., Holtzman, D. M., Fagan, A. M., & Goate, A. M. (2009). The utility of intraindividual variability in selective attention tasks as an early marker for Alzheimer's disease. *Neuropsychology, 23(6)*, 746-58. doi:10.1037/a0016583

Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Straub, R. E., ... & Weinberger, D. R. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe

function and risk for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America, 98(12)*, 6917-22. doi:10.1073/pnas.111134598

Faust, M. E., Balota, D. A., Spieler, D. H., & Ferraro, F. R. (1999). Individual differences in information-processing rate and amount: implications for group differences in response latency. *Psychological Bulletin, 125(6)*, 777. doi:10.1037/0033-2909.125.6.777

Filippini, N., MacIntosh, B. J., Hough, M. G., Goodwin, G. M., Frisoni, G. B., Smith, S. M., ... & Mackay, C. E. (2009). Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. *Proceedings of the National Academy of Sciences of the United States of America, 106(17)*, 7209-14. doi:10.1073/pnas.0811879106

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences, 97(20)*, 11050-11055. doi: 10.1073/pnas.200033797

Fischl, B., Liu, A., & Dale, A. M. (2001). Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. *Medical Imaging, IEEE Transactions on, 20(1)*, 70-80. doi:10.1109/42.906426

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. http://dx.doi.org/10.1016/S0896-6273(02)00569-X

Fischl, B., Sereno, M. I., & Dale, A. M. (1999a). Cortical surface-based analysis: II: Inflation, flattening, and a surface-based coordinate system. *NeuroImage, 9(2)*, 195-207. http://dx.doi.org/10.1006/nimg.1998.0396

Fischl, B., Sereno, M. I., Tootell, R. B., & Dale, A. M. (1999b). High-resolution intersubject averaging and a coordinate system for the cortical surface. *Human Brain Mapping, 8(4)*, 272-284. doi: 10.1002/(SICI)1097-0193(1999)8:4<272::AID-HBM10>3.0.CO;2-4

Fischl, B., Van Der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D. H., ... & Dale, A. M. (2004). Automatically parcellating the human cerebral cortex. *Cerebral Cortex, 14(1)*, 11-22. doi:10.1093/cercor/bhg087

Fjell, A. M., Walhovd, K. B., Fischl, B., & Reinvang, I. (2007). Cognitive function, P3a/P3b brain potentials, and cortical thickness in aging. *Human Brain Mapping, 28(11)*, 1098-1116. doi: 10.1002/hbm.20335

Fjell, A. M., Westlye, L. T., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., … Walhovd, K. B. (2009). High consistency of regional cortical thinning in aging across multiple samples. *Cerebral cortex, 19(9)*, 2001–12. doi:10.1093/cercor/bhn232

Fjell, A. M., Westlye, L., Greve, D., Fischl, B., & Benner, T. (2008). The relationship between diffusion tensor imaging and volumetry as measures of white matter properties. *NeuroImage, 42(4)*, 1654-68. doi:10.1016/j.neuroimage.2008.06.005.The

Fjell, A. M., Westlye, L. T., Amlien, I. K., & Walhovd, K. B. (2011). Reduced white matter integrity is related to cognitive instability. *The Journal of Neuroscience, 31(49)*, 18060-72. doi:10.1523/JNEUROSCI.4735-11.2011

Garrett, D. D., Kovacevic, N., McIntosh, A. R., & Grady, C. L. (2011). The importance of being variable. *The Journal of Neuroscience, 31(12)*, 4496-4503. doi: 10.1523/JNEUROSCI.5641-10.2011

Garrett, D. D., Kovacevic, N., McIntosh, A. R., & Grady, C. L. (2013a). The modulation of BOLD variability between cognitive states varies by age and processing speed. *Cerebral Cortex, 23(3)*, 684-693. doi:10.1093/cercor/bhs055

Garrett, D. D., McIntosh, A. R., & Grady, C. L. (7 June 2013). Brain Signal Variability is Parametrically Modifiable. *Cerebral Cortex*. Advance online publication. doi: 10.1093/cercor/bht150

Gibbs, A. A., Naudts, K. H., Azevedo, R. T., & David, A. S. (2010). Deletion variant of α2b-adrenergic receptor gene moderates the effect of COMT val158met polymorphism on episodic memory performance. *European Neuropsychopharmacology, 20(4)*, 272-275. http://dx.doi.org/10.1016/j.euroneuro.2009.12.007

Goldberg, T. E., Egan, M. F., Gscheidle, T., Coppola, R., Weickert, T., Kolachana, B. S., ... & Weinberger, D. R. (2003). Executive subprocesses in working memory: Relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. *Archives of General Psychiatry, 60(9)*, 889-96. doi:10.1001/archpsyc.60.9.889

Goldberg, T. E., & Weinberger, D. R. (2004). Genes and the parsing of cognitive processes. *Trends in Cognitive Sciences, 8(7)*, 325-35. doi:10.1016/j.tics.2004.05.011

Goldstein, K. (1942). *After effects of brain injuries in war.* New York: Grune and Stratton.

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Fristen, K. J., & Frackowiak, R. S. (2002). A voxel-based morphometric study of ageing in 465 normal adult human brains. *5th IEEE EMBS International Summer School on Biomedical Imaging*. 1-16. doi:10.1006/nimg.2001.0786

Grady, C. L. (2008). Cognitive neuroscience of aging. *Annals of the New York Academy of Sciences, 1124*, 127-44. doi:10.1196/annals.1440.009

Greenwood, P. M., Lambert, C., Sunderland, T., & Parasuraman, R. (2005). Effects of apolipoprotein E genotype on spatial attention, working memory, and their interaction in healthy, middle-aged adults: Results from the National Institute of Mental Health's BIOCARD study. *Neuropsychology, 19(2)*, 199-211. doi: 10.1037/0894-4105.19.2.199

Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI. *Proceedings of the National Academy of Sciences of the United States of America, 101(13)*, 4637-42. doi:10.1073/pnas.0308627101

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. doi: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. doi:10.1037/0894-4105.14.2.224

Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: Functional imaging and the resting human brain. *Nature Reviews Neuroscience, 2,* 685-94. doi:10.1038/35094500

Haier, R. J., Jung, R. E., Yeo, R. A., Head, K., & Alkire, M. T. (2005). Structural brain variation, age, and response time. *Cognitive, Affective, & Behavioral Neuroscience, 5(2)*, 246-51. doi: 10.3758/CABN.5.2.246

Head, D., Buckner, R. L., Shimony, J. S., Williams, L. E., Akbudak, E., Conturo, T. E., ... & Snyder, A. Z. (2004). Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: Evidence from diffusion tensor imaging. *Cerebral Cortex, 14(4)*, 410-23. doi:10.1093/cercor/bhh003

Head, D., Rodrigue, K. M., Kennedy, K. M., & Raz, N. (2008). Neuroanatomical and cognitive mediators of age-related differences in episodic memory. *Neuropsychology, 22(4)*, 491-507. doi:10.1037/0894-4105.22.4.491.Neuroanatomical

Head, H. (1926). *Aphasia and kindred disorders of speech.* Cambridge University Press.

Hedden, T., & Gabrieli, J. D. E. (2004). Insights into the ageing mind: A view from cognitive neuroscience. *Nature Reviews Neuroscience, 5(2)*, 87-96. doi:10.1038/nrn1323

Hedden, T., Van Dijk, K. R., Shire, E. H., Sperling, R. A., Johnson, K. A., & Buckner, R. L. (2012). Failure to modulate attentional control in advanced aging linked to white matter pathology. *Cerebral Cortex, 22(5),* 1038-1051. doi:10.1093/cercor/bhr172

Huang, J., & Auchus, A. P. (2007). Diffusion tensor imaging of normal appearing white matter and its correlation with cognitive functioning in mild cognitive impairment and Alzheimer's disease. *Annals of the New York Academy of Sciences, 1097,* 259-64. doi:10.1196/annals.1379.021

Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *The British Journal of Psychiatry, 140(6)*, 566-572. doi:10.1192/bjp.140.6.566

Hultsch, D. F., MacDonald, S. W. S., & Dixon, R. A. (2002). Variability in reaction time performance of younger and older adults. The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences, 57(2), P101-15. doi:10.1093/geronb/57.2.P101

Hultsch, D. F., MacDonald, S. W. S., Hunter, M. A., Levy-Bencheton, J., & Strauss, E. (2000). Intraindividual variability in cognitive performance in older adults: Comparison of

adults with mild dementia, adults with arthritis, and healthy adults. *Neuropsychology, 14(4)*, 588-598. doi:10.1037//0894-4105.14.4.588

Hultsch, D. F., Strauss, E., Hunter, M. A., & MacDonald, S. W. S. (2008). Intraindividual variability, cognition, and aging. In F. I. M. Craik & T. A. Salthouse (Eds.), *The handbook of aging and cognition, 3rd edition* (pp. 491-556). New York, NY: Psychology Press.

Jackson, J. D., Balota, D. A., Duchek, J. M., & Head, D. (2012). White matter integrity and reaction time intraindividual variability in healthy aging and early-stage Alzheimer disease. *Neuropsychologia, 50(3)*, 357-66. doi:10.1016/j.neuropsychologia.2011.11.024

Jackson, J. D., Balota, D. A., & Head, D. (2011). Exploring the relationship between personality and regional brain volume in healthy aging. *Neurobiology of Aging, 32(12)*, 2162-71. doi:10.1016/j.neurobiolaging.2009.12.009

Jensen, A. R. (1982). Reaction time and psychometric *g*. In H.J. Eysenck (Ed.), *A model for intelligence* (pp. 93-132). Berlin: Springer Berlin Heidelberg. doi: 10.1007/978-3-642-68664-1_4

Jensen, A. R. (1992). The importance of intraindividual variation in reaction time. *Personality and Individual Differences, 13(8)*, 869-881. http://dx.doi.org/10.1016/0191-8869(92)90004-9

Johnson, D. K., Barrow, W., Anderson, R., Harsha, A., Honea, R., Brooks, W. M., & Burns, J. M. (2010). Diagnostic utility of cerebral white matter integrity in early Alzheimer's disease. *The International Journal of Neuroscience, 120(8)*, 544-50. doi:10.3109/00207454.2010.494788

Johnson, D. K., Storandt, M., Morris, J. C., & Galvin, J. E. (2009). Longitudinal study of the transition from healthy aging to Alzheimer's disease. *Archives of Neurology, 66,* 1254-1259.

Johnson, D.K., Storandt, M., Morris, J. C., Langford, Z. D. & Galvin, J.E. (2008). Cognitive profiles in dementia: Alzheimer disease versus nondemented aging. *Neurology, 71*, 1783-1789.

Kavcic, V., Ni, H., Zhu, T., Zhong, J., & Duffy, C. J. (2008). White matter integrity linked to functional impairments in aging and early Alzheimer's disease. *Alzheimer's and Dementia, 4(6)*, 381–9. doi:10.1016/j.jalz.2008.07.001.White

Kelly, A. M. C., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2008). Competition between functional brain networks mediates behavioral variability. *NeuroImage, 39(1)*, 527-37. doi:10.1016/j.neuroimage.2007.08.008

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)*, 916-927. http://dx.doi.org/10.1016/j.neuropsychologia.2009.01.001

Kimberg, D. Y., & Farah, M. J. (1993). A unified account of cognitive impairments following frontal lobe damage: the role of working memory in complex, organized behavior. *Journal of Experimental Psychology: General, 122(4)*, 411-28. doi: 10.1037/0096-3445.122.4.411

Kuperberg, G. R., Broome, M. R., McGuire, P. K., David, A. S., Eddy, M., Ozawa, F., ... & Fischl, B. (2003). Regionally localized thinning of the cerebral cortex in schizophrenia. Archives of general psychiatry, 60(9), 878-88. doi:10.1001/archpsyc.60.9.878

Lattin, J. M., Carroll, J. D., Green, P. E. (2003). *Analyzing multivariate data*. Pacific Grove, CA: Brooks Cole.

Lewis, P. A., & Miall, R. C. (2006). Remembering the time: A continuous clock. *Trends in Cognitive Sciences, 10(9)*, 401-406. http://dx.doi.org/10.1016/j.tics.2006.07.006

Li, S.-C., Brehmer, Y., Shing, Y. L., Werkle-Bergner, M., & Lindenberger, U. (2006). Neuromodulation of associative and organizational plasticity across the life span: empirical evidence and neurocomputational modeling. *Neuroscience and Biobehavioral Reviews, 30(6)*, 775-90. doi:10.1016/j.neubiorev.2006.06.004

Li, S. C., & Lindenberger, U. (1999). Cross-level unification: A computational exploration of the link between deterioration of neurotransmitter systems and dedifferentiation of cognitive abilities in old age. In L.-G. Nilsson and H. J. Markowitsch (Eds.), *Cognitive neuroscience of memory*. (pp. 103-46). Ashland, Ohio: Hogrefe & Huber.

Li, S.-C., Lindenberger, U., & Frensch, P. A. (2000). Unifying cognitive aging: From neuromodulation to representation to cognition. *Neurocomputing, 32*, 879-90. http://dx.doi.org/10.1016/S0925-2312(00)00256-3

Li, S.-C., Lindenberger, U., & Sikström, S. (2001). Aging cognition: from neuromodulation to representation. *Trends in Cognitive Sciences, 5(11)*, 479-86. http://dx.doi.org/10.1016/S1364-6613(00)01769-1

Li, S.-C., von Oertzen, T., & Lindenberger, U. (2006). A neurocomputational model of stochastic resonance and aging. *Neurocomputing, 69(13-15)*, 1553-60. doi:10.1016/j.neucom.2005.06.015

Lövdén, M., Li, S.-C., Shing, Y. L., & Lindenberger, U. (2007). Within-person trial-to-trial variability precedes and predicts cognitive decline in old and very old age: longitudinal

data from the Berlin Aging Study. *Neuropsychologia, 45(12)*, 2827-38. doi:10.1016/j.neuropsychologia.2007.05.005

Luce, R. D. (1977). The choice axiom after twenty years. *Journal of Mathematical Psychology, 3,* 215–233.

Luce, R. D. (1986). *Response times: Their role in inferring elementary mental organization.* New York: Oxford University Press.

MacDonald, S. W. S., Cervenka, S., Farde, L., Nyberg, L., & Bäckman, L. (2009). Extrastriatal dopamine D2 receptor binding modulates intraindividual variability in episodic recognition and executive functioning. *Neuropsychologia, 47(11)*, 2299-304. doi:10.1016/j.neuropsychologia.2009.01.016

MacDonald, S. W. S., Hultsch, D. F., & Dixon, R. A. (2003). Performance variability is related to change in cognition: Evidence from the Victoria Longitudinal Study. *Psychology and Aging, 18(3)*, 510-23. doi:10.1037/0882-7974.18.3.510

MacDonald, S. W. S., Li, S.-C., & Bäckman, L. (2009). Neural underpinnings of within-person variability in cognitive functioning. *Psychology and Aging, 24(4)*, 792-808. doi:10.1037/a0017798

MacDonald, S. W. S., Nyberg, L., & Bäckman, L. (2006). Intra-individual variability in behavior: Links to brain structure, neurotransmission and neuronal activity. *Trends in Neurosciences, 29(8)*, 474-80. doi:10.1016/j.tins.2006.06.011

MacDonald, S. W. S., Nyberg, L., Sandblom, J., Fischer, H., & Bäckman, L. (2008). Increased response-time variability is associated with reduced inferior parietal activation during episodic recognition in aging. *Journal of Cognitive Neuroscience, 20(5)*, 779-86. doi:10.1162/jocn.2008.20502

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)*, 415-435. doi: 10.1007/s11065-009-9113-2

Martínez, M., Martín, X., Alcelay, L., Flores, J., Valiente, J., Juanbeltz, B., ... & de Pancorbo, M. (2009). The COMT Val158 Met polymorphism as an associated risk factor for Alzheimer disease and mild cognitive impairment in APOE 4 carriers. *BMC neuroscience, 10(1)*, 125. doi:10.1186/1471-2202-10-125

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology, 34(7)*, 939-44. doi: 10.1212/WNL.34.7.939

Michailov, G. V., Sereda, M. W., Brinkmann, B. G., Fischer, T. M., Haug, B., Birchmeier, C., ... & Nave, K. A. (2004). Axonal neuregulin-1 regulates myelin sheath thickness. *Science Signaling, 304(5671)*, 700-3.

Minear, M., & Shah, P. (2008). Training and transfer effects in task switching. *Memory & Cognition, 36(8)*, 1470-83. doi: 10.3758/MC.336.8.1470

Morris, J. C. (1993). The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology, 43*, 2412–2414.

Morris, J. C., McKeel, D. W., Storandt, M., Rubin, E. H., Price, J. L., Grant, E. A., ... & Berg, L. (1991). Very mild Alzheimer's disease: Informant-based clinical, psychometric, and pathologic distinction from normal aging. *Neurology, 41(4)*, 469. doi: 10.1212/WNL.41.4.469

Morris, J. C., Storandt, M., McKeel, D. W., Rubin, E. H., Price, J. L., Grant, E. A., & Berg, L. (1996). Cerebral amyloid deposition and diffuse plaques in "normal" aging: Evidence for presymptomatic and very mild Alzheimer's disease. *Neurology, 46(3)*, 707-719. doi: 10.1212/WNL.46.3.707

Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., Rubin, E. H., & Berg, L. (2001). Mild cognitive impairment represents early-stage Alzheimer disease. *Archives of Neurology, 58(3)*, 397. doi:10.1001/archneur.58.3.397

Moy, G., Millet, P., Haller, S., Baudois, S., De Bilbao, F., Weber, K., ... & Delaloye, C. (2011). Magnetic resonance imaging determinants of intraindividual variability in the elderly: combined analysis of grey and white matter. *Neuroscience, 186*, 88-93. doi:10.1016/j.neuroscience.2011.04.028

Murtha, S., Cismaru, R., Waechter, R., & Chertkow, H. (2002). Increased variability accompanies frontal lobe damage in dementia. *Journal of the International Neuropsychological Society, 8(3)*, 360-72. doi:10.1017.S1355617701020173

Myerson, J., Hale, S., Chen, J., & Lawrence, B. (1997). General lexical slowing and the semantic priming effect: The roles of age and ability. *Acta Psychologica, 96(1)*, 83-101. http://dx.doi.org/10.1016/S0001-6918(97)00002-4

Myerson, J., Robertson, S., & Hale, S. (2007). Aging and intraindividual variability in performance: Analyses of response time distributions. *Journal of the Experimental Analysis of Behavior, 88(3)*, 319-37. doi:10.1901/jeab.2007.88-319

Nesselroade, J. R., & Salthouse, T. A. (2004). Methodological and theoretical implications of intraindividual variability in perceptual-motor performance. *The Journals of*

Gerontology, Series B: Psychological Sciences and Social Sciences, 59(2), P49-55. doi: 10.1093/geronb/59.2.P49

Nordahl, C. W., Ranganath, C., Yonelinas, A. P., DeCarli, C., Fletcher, E., & Jagust, W. J. (2006). White matter changes compromise prefrontal cortex function in healthy elderly individuals. *Journal of Cognitive Neuroscience, 18(3)*, 418-29. doi:10.1162/jocn.2006.18.3.418

O'Sullivan, M. R. C. P., Jones, D. K., Summers, P. E., Morris, R. G., Williams, S. C. R., & Markus, H. S. (2001). Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology, 57(4)*, 632-8. doi: 10.1212/WNL.57.4.632

Ota, M., Nemoto, K., Sato, N., Yamashita, F., & Asada, T. (2009). Relationship between white matter changes and cognition in healthy elders. *International Journal of Geriatric Psychiatry, 24(12)*, 1463-9. doi:10.1002/gps.2289

Owen, A. M., Downes, J. J., Sahakian, B. J., Polkey, C. E., & Robbins, T. W. (1990). Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia, 28(10)*, 1021-34. doi:10.1111/j.1460-9568.1997.tb01487.x

Owen, A. M., Morris, R. G., Sahakian, B. J., Polkey, C. E., & Robbins, T. W. (1996). Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Brain, 119(5)*, 1597-1615. doi:10.1093/brain/119.5.1597

Parasuraman, R., & Jiang, Y. (2011). Individual differences in cognition, affect, and performance: Behavioral, neuroimaging, and molecular genetic approaches. *NeuroImage, 59(1)*, 70-82. doi:10.1016/j.neuroimage.2011.04.040

Rabbitt, P., Osman, P., Moore, B., & Stollery, B. (2001). There are stable individual differences in performance variability, both from moment to moment and from day to day. *The Quarterly Journal of Experimental Psychology A, 54(4)*, 981-1003. doi:10.1080/02724980042000534

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America, 98(2)*, 676-82. doi:10.1073/pnas.98.2.676

Raz, N. (2000). Aging of the brain and its impact on cognitive performance: Integration of structural and functional findings. In F. I. M. Craik & T. A. Salthouse (Eds.), *The handbook of aging and cognition, 2nd edition* (pp. 1-90). Mahwah, NJ: Lawrence Erlbaum Associates.

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(1)*, 95-114. doi:10.1037/0894-4105.12.1.95

Raz, N., Gunning, F., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., ... & Acker, J. D. (1997). Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. *Cerebral Cortex, 7(3)*, 268-82. doi:10.1093/cercor/7.3.268

Raz, N., & Lindenberger, U. (2011). Only time will tell: Cross-sectional studies offer no solution to the age-brain-cognition triangle: Comment on Salthouse (2011). *Psychological bulletin, 137(5)*, 790-5. doi:10.1037/a0024503

Raz, N., Lindenberger, U., Ghisletta, P., Rodrigue, K. M., Kennedy, K. M., & Acker, J. D. (2008). Neuroanatomical correlates of fluid intelligence in healthy adults and persons with vascular risk factors. *Cerebral cortex, 18(3)*, 718-26. doi:10.1093/cercor/bhm108

Raz, N., & Rodrigue, K. M. (2006). Differential aging of the brain: Patterns, cognitive correlates and modifiers. *Neuroscience and Biobehavioral Reviews, 30(6)*, 730-48. doi:10.1016/j.neubiorev.2006.07.001

Raz, N., Rodrigue, K. M., Kennedy, K. M., & Acker, J. D. (2007). Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. *Neuropsychology, 21(2)*, 149-57. doi:10.1037/0894-4105.21.2.149

Reinvang, I., Winjevoll, I. L., Rootwelt, H., & Espeseth, T. (2010). Working memory deficits in healthy APOE epsilon 4 carriers. *Neuropsychologia, 48(2)*, 566-73. doi:10.1016/j.neuropsychologia.2009.10.018

Rosas, H. D., Liu, A. K., Hersch, S., Glessner, M., Ferrante, R. J., Salat, D. H., ... & Fischl, B. (2002). Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology, 58(5)*, 695-701. doi:10.1212/WNL.58.5.695

Rosen, V. M., Bergeson, J. L., Putnam, K., Harwell, A., & Sunderland, T. (2002). Working memory and apolipoprotein E: What's the connection?. *Neuropsychologia, 40(13)*, 2226-33. http://dx.doi.org/10.1016/S0028-3932(02)00132-X

Salat, D. H., Buckner, R. L., Snyder, A. Z., Greve, D. N., Desikan, R. S., Busa, E., ... & Fischl, B. (2004). Thinning of the cerebral cortex in aging. *Cerebral Cortex, 14(7)*, 721-730. doi:10.1093/cercor/bhh032

Salat, D. H., Greve, D. N., Pacheco, J. L., Quinn, B. T., Helmer, K. G., Buckner, R. L., & Fischl, B. (2009). Regional white matter volume differences in nondemented aging and

Alzheimer's disease. NeuroImage, 44(4), 1247-58. Elsevier B.V. doi:10.1016/j.neuroimage.2008.10.030

Salat, D. H., Tuch, D. S., Van der Kouwe, A. J. W., Greve, D. N., Pappu, V., Lee, S. Y., ... & Rosas, H. D. (2010). White matter pathology isolates the hippocampal formation in Alzheimer's disease. *Neurobiology of Aging, 31(2)*, 244-56. doi:10.1016/j.neurobiolaging.2008.03.013.White

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

Salthouse, T. A., & Nesselroade, J. R. (2010). Dealing with short-term fluctuation in longitudinal research. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences, 65(6)*, 698-705. doi:10.1093/geronb/gbq060.

Salthouse, T. A., Nesselroade, J. R., & Berish, D. E. (2006). Short-term variability in cognitive performance and the calibration of longitudinal change. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences, 61(3)*, P144-51.

Savitz, J., Solms, M., & Ramesar, R. (2006). The molecular genetics of cognition: Dopamine, COMT and BDNF. *Genes, Brain and Behavior, 5(4)*, 311-28. doi: 10.1111/j.1601-183X.2005.00163.x

Schafer, J. L., & Graham, J. W. (2002). Missing data: Our view of the state of the art. *Psychological Methods, 7(2)*, 147-77. doi:10.1037/1082-989X.7.2.147

Shulman, G. L., Fiez, J. A., Corbetta, M., Buckner, R. L., Miezin, F. M., Raichle, M. E., & Petersen, S. E. (1997). Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. *Journal of Cognitive Neuroscience, 9(5)*, 648-63. doi:10.1162/jocn.1997.9.5.648

Small, B. J., Rosnick, C. B., Fratiglioni, L., & Bäckman, L. (2004). Apolipoprotein E and cognitive performance: A meta-analysis. *Psychology and Aging, 19(4)*, 592-600. doi:10.1037/0882-7974.19.4.592

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nature Neuroscience, 6(3)*, 309-15. doi:10.1038/nn1008

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*, 461-79. doi:10.1037/0096-1523.22.2.461

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47(10)*, 2015-28. http://dx.doi.org/10.1016/j.neuropsychologia.2009.03.004

Stern, Y. (2003). The concept of cognitive reserve: A catalyst for research. *Journal of Clinical and Experimental Neuropsychology, 25(5)*, 589-93. doi: 10.1076/jcen.25.5.589.14571

Storandt, M., Grant, E. A., Miller, J. P., & Morris, J. C. (2006). Longitudinal course and neuropathologic outcomes in original vs. revised MCI and in pre-MCI. *Neurology, 67,* 467–73. doi: 10.1212/01.wnl.0000228231.26111.6e

Strauss, E., Bielak, A. A., Bunce, D., Hunter, M. A., & Hultsch, D. F. (2007). Within-person variability in response speed as an indicator of cognitive impairment in older adults. *Aging, Neuropsychology, and Cognition, 14(6)*, 608-30. doi:10.1080/13825580600932419

Stuss, D. T., Murphy, K. J., Binns, M. A., & Alexander, M. P. (2003). Staying on the job: The frontal lobes control individual performance variability. *Brain, 126(11)*, 2363-80. doi:10.1093/brain/awg237

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science, 253*(5026), 1380-1386.

Taveggia, C., Thaker, P., Petrylak, A., Caporaso, G. L., Toews, A., Falls, D. L., ... & Salzer, J. L. (2008). Type III neuregulin-1 promotes oligodendrocyte myelination. *Glia, 56(3)*, 284-93. doi:10.1002/glia.20612

Tse, C.-S., Balota, D. A., Yap, M. J., Duchek, J. M., & McCabe, D. P. (2010). Effects of healthy aging and early stage dementia of the Alzheimer's type on components of response time distributions in three attention tasks. *Neuropsychology, 24(3)*, 300-15. doi:10.1037/a0018274

Ullén, F., Forsman, L., Blom, O., Karabanov, A., & Madison, G. (2008). Intelligence and variability in a simple timing task share neural substrates in the prefrontal white matter. *The Journal of Neuroscience, 28(16)*, 4238-43. doi:10.1523/JNEUROSCI.0825-08.2008

Van Petten, C., Plante, E., Davidson, P. S. R., Kuo, T. Y., Bajuscak, L., & Glisky, E. L. (2004). Memory and executive function in older adults: Relationships with temporal and prefrontal gray matter volumes and white matter hyperintensities. *Neuropsychologia, 42(10)*, 1313-35. doi:10.1016/j.neuropsychologia.2004.02.009

Vernooij, M. W., Ikram, M. A., Vrooman, H. A., Wielopolski, P. A., Krestin, G. P., Hofman, A., ... & Breteler, M. (2009). White matter microstructural integrity and cognitive function in a general elderly population. *Archives of General Psychiatry, 66(5)*, 545-53. doi:10.1001/archgenpsychiatry.2009.5

Villain, N., Fouquet, M., Baron, J.-C., Mézenge, F., Landeau, B., de La Sayette, V., ... & Chételat, G. (2010). Sequential relationships between grey matter and white matter atrophy and brain metabolic abnormalities in early Alzheimer's disease. *Brain, 133(11)*, 3301-14. doi:10.1093/brain/awq203

Wagenmakers, E.-J., & Brown, S. (2007). On the linear relation between the mean and the standard deviation of a response time distribution. *Psychological Review, 114(3)*, 830-41. doi: 10.1037/0033-295X.114.3.830

Wagenmakers, E.-J., Grasman, R. P. P. P., & Molenaar, P. C. M. (2005). On the relation between the mean and the variance of a diffusion model response time distribution. *Journal of Mathematical Psychology, 49(3)*, 195-204. doi:10.1016/j.jmp.2005.02.003

Wagner, A. D., Shannon, B. J., Kahn, I., & Buckner, R. L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends in Cognitive Sciences, 9(9)*, 445-453. http://dx.doi.org/10.1016/j.tics.2005.07.001

Walhovd, K. B., & Fjell, A. M. (2007). White matter volume predicts reaction time instability. *Neuropsychologia, 45(10)*, 2277-84. doi:10.1016/j.neuropsychologia.2007.02.022

Walhovd, K. B., Fjell, A. M., Reinvang, I., Lundervold, A., Dale, A. M., Eilertsen, D. E., ... & Fischl, B. (2005). Effects of age on volumes of cortex, white matter and subcortical structures. *Neurobiology of Aging, 26(9)*, 1261-70. doi: 10.1016/j.neurobiolaging.2005.05.020

Wang, P. N., Liu, H. C., Liu, T. Y., Chu, A., Hong, C. J., Lin, K. N., & Chi, C. W. (2005). Estrogen-metabolizing gene COMT polymorphism synergistic APOE epsilon4 allele increases the risk of Alzheimer disease. *Dementia and Geriatric Cognitive Disorders, 19(2-3)*, 120-5. doi:10.1159/000082663

Weinshilboum, R., & Otterness, D. (1999). Methylation pharmacogenetics: Catechol O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. *Annual Review of Pharmacology and Toxicology, 39*, 19-52. doi:10.1146/annurev.pharmtox.39.1.19

Weissman, D. H., Roberts, K. C., Visscher, K. M., & Woldorff, M. G. (2006). The neural bases of momentary lapses in attention. *Nature Neuroscience, 9(7)*, 971-8. doi:10.1038/nn1727

Weschler, D. (1987). Weschler memory scale-revised. San Antonio, TX: Psychological Corp.

Weschler, D., & Stone, C. R. (1945). Instruction manual for the Weschler Memory Scale. New York: Psychological Corp.

West, R., Murphy, K. J., Armilio, M. L., Craik, F. I. M., & Stuss, D. T. (2002). Lapses of intention and performance variability reveal age-related increases in fluctuations of executive control. *Brain and Cognition, 49(3)*, 402-419. doi:10.1006/brcg.2001.1507

Wimber, M., Schott, B. H., Wendler, F., Seidenbecher, C. I., Behnisch, G., Macharadze, T., ... & Richardson-Klavehn, A. (2011). Prefrontal dopamine and the dynamic control of human long-term memory. *Translational Psychiatry, 1(7)*, e15. doi: doi:10.1038/tp.2011.15

Wisdom, N. M., Callahan, J. L., & Hawkins, K. A. (2011). The effects of apolipoprotein E on non-impaired cognitive functioning: A meta-analysis. *Neurobiology of Aging, 32(1)*, 63-74. http://dx.doi.org/10.1016/j.neurobiolaging.2009.02.003

Wood, P., & Bunger, R. P. (1984). The biology of the oligodendrocyte. In W. T. Norton (Ed.), *Oligodendroglia* (pp. 1-46). New York: Plenum Press.

Yarkoni, T., Barch, D. M., Gray, J. R., Conturo, T. E., & Braver, T. S. (2009). BOLD correlates of trial-by-trial reaction time variability in gray and white matter: a multi-study fMRI analysis. *PloS One, 4(1)*, e4257. doi:10.1371/journal.pone.0004257

Yoshita, M., Fletcher, E., Harvey, D., Ortega, M., Martinez, O., Mungas, D. M., ... & DeCarli, C. S. (2006). Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD. *Neurology, 67(12)*, 2192-8 doi:10.1212/01.wnl.0000249119.95747.1f

Ziegler, D. A., Piguet, O., Salat, D. H., Prince, K., Connally, E., & Corkin, S. (2010). Cognition in healthy aging is related to regional white matter integrity, but not cortical thickness. *Neurobiology of Aging, 31(11)*, 1912-26. doi:10.1016/j.neurobiolaging.2008.10.015

Zola-Morgan, S., Squire, L. R., & Amaral, D. G. (1986). Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *The Journal of Neuroscience, 6*(10), 2950-2967.

Tables

Table 1. Demographic characteristics of the sample.

Variable	Aim 1 Sample		Aim 2 Subsample	
	Cognitively Normal (Mean (SD))	**Early-stage AD** (Mean (SD))	**Cognitively Normal** (Mean (SD))	**Early-stage AD** (Mean (SD))
N	229	33	126	23
Age in years*	67.3 (8.9)	73.3 (8.3)	71.4 (6.7)	73.4 (7.7)
Gender (F/M)	151/78	13/20	74/52	10/13
Education in years	15.6 (2.6)	15.2 (2.3)	15.5 (2.6)	15.1 (1.9)
Apolipoprotein ε4 allele *N*			42	13
Catechol-*O*-methyltransferase Val allele *N*			70	12

* $p < .05$ for the Aim 1 sample.

Table 2. Correlation matrix of composite measures in Aim 1.

***n* = 262**	Coefficient of variation	Median reaction time
White matter volume	-.11	**-.13**
Gray matter thickness	-.05	**-.14**

Note: Correlations in **bold** reflect $p < .05$.

Table 3. Correlation matrix of individual measures in Aim 1.

***n* = 262**		Coefficient of variation			Median reaction time		
		Stroop	Simon	CVOE	Stroop	Simon	CVOE
White matter volume	SFG	-.07	-.06	-.07	-.10	-.07	.00
	VLDLPFC	-.02	-.09	-.09	-.09	-.08	-.06
	P. Cingulate	-.07	-.02	**-.15**	-.12	-.05	-.07
	Precuneus	-.05	-.02	-.05	**-.12**	-.09	-.06
	IPL	-.06	-.02	-.07	**-.14**	-.05	-.07
Gray matter thickness	SFG	-.01	**-.13**	-.02	-.05	**-.14**	-.05
	VLDLPFC	.05	-.12	.00	.07	-.10	-.06
	P. Cingulate	-.05	-.04	-.05	.02	-.09	-.04
	Precuneus	.03	-.02	.00	-.06	**-.16**	-.09
	IPL	.03	-.09	-.05	-.11	**-.20**	-.11

Note: SFG = superior frontal gyrus, VLDLPFC = ventral/dorsal-lateral prefrontal cortex, P. Cingulate = posterior cingulate, IPL = inferior parietal lobule, CVOE = Consonant-Vowel Odd-Even task.
Note: Correlations in **bold** reflect $p < .05$.

Table 4. Correlation matrix of composite reaction time distributional measures in Aim 1.

***n* = 262**	τ	μ
White matter volume	-.01	**-.15**
Gray matter thickness	-.10	-.09

Note: Correlations in **bold** reflect $p < .05$.

Table 5. Correlation matrix of individual reaction time distributional measures in Aim 1.

***n* = 262**		τ			μ		
		Stroop	Simon	CVOE	Stroop	Simon	CVOE
White matter volume	SFG	-.01	-.05	.05	-.10	-.03	-.10
	VLDLPFC	.01	-.06	.04	-.10	-.07	**-.13**
	P. Cingulate	-.05	-.01	.02	-.09	-.04	-.11
	Precuneus	.03	-.05	.05	-.11	-.08	-.10
	IPL	-.04	-.02	-.01	-.12	-.05	-.07
Gray matter thickness	SFG	-.03	-.11	-.03	-.01	-.09	-.04
	VLDLPFC	-.01	-.09	-.04	.08	-.06	-.01
	P. Cingulate	-.06	-.01	-.12	.04	-.05	.12
	Precuneus	-.05	-.03	-.02	-.06	**-.18**	-.05
	IPL	-.05	-.10	.03	-.08	**-.20**	-.09

Note: SFG = superior frontal gyrus, VLDLPFC = ventral/dorsal-lateral prefrontal cortex, P. Cingulate = posterior cingulate, IPL = inferior parietal lobule, CVOE = Consonant-Vowel Odd-Even task.
Note: Correlations in **bold** reflect $p < .05$.

Table 6. Correlation matrix of composite measures in Aim 1 for the cognitively normal group.

Cognitively normal (*n* = 229)	Coefficient of variation	Median reaction time
White matter volume	-.07	**-.16**
Gray matter thickness	-.07	**-.15**

Note: Correlations in **bold** reflect $p < .05$.

Table 7. Correlation matrix of composite measures in Aim 1 for the early-stage Alzheimer disease group.

Early-stage Alzheimer disease (*n* = 33)	Coefficient of variation	Median reaction time
White matter volume	**-.40**	.07
Gray matter thickness	.15	.01

Note: Correlations in **bold** reflect $p < .05$.

Table 8. Correlation matrix of composite measures in Aim 1 in the younger half of the sample.

Younger sample (*n* = 121)	Coefficient of variation	Median reaction time
White matter volume	**-.20**	-.16
Gray matter thickness	-.09	-.10

Note: Correlations in **bold** reflect $p < .05$.

Table 9. Correlation matrix of composite measures in Aim 1 in the older half of the sample.

Older sample (*n* = 108)	Coefficient of variation	Median reaction time
White matter volume	-.07	**-.32**
Gray matter thickness	-.16	**-.40**

Note: Correlations in **bold** reflect $p < .05$.

Table 10. Correlation matrix of composite measures in Aim 1 for the APOE4- group in the cognitively normal sample.

APOE4- (*n* = 151)	Coefficient of variation	Median reaction time
White matter volume	-.05	-.13
Gray matter thickness	-.04	**-.19**

Note: APOE4- = noncarriers of the Apolipoprotein ε4 allele.
Note: Correlations in **bold** reflect $p < .05$.

Table 11. Correlation matrix of composite measures in Aim 1 for the APOE4+ group in the cognitively normal sample.

APOE4+ (*n* = 76)	Coefficient of variation	Median reaction time
White matter volume	-.13	-.20
Gray matter thickness	-.13	-.06

Note: APOE4+ = carriers of the Apolipoprotein ε4 allele.
Note: Correlations in **bold** reflect $p < .05$.

Table 12. Correlation matrix of composite measures in Aim 1 for the Val- group in the cognitively normal sample.

Val- (*n* = 50)	Coefficient of variation	Median reaction time
White matter volume	.03	.04
Gray matter thickness	-.15	-.19

Note: Val- = noncarriers of the catchol-*O*-methyltransferase Val allele.
Note: Correlations in **bold** reflect $p < .05$.

Table 13. Correlation matrix of composite measures in Aim 1 for the Val+ group in the cognitively normal sample.

Val+ (*n* = 130)	Coefficient of variation	Median reaction time
White matter volume	-.11	**-.24**
Gray matter thickness	.00	-.07

Note: Val+ = carriers of the catchol-*O*-methyltransferase Val allele.
Note: Correlations in **bold** reflect $p < .05$.

Table 14. Correlation matrix of composite measures in Aim 1 for the low education group in the cognitively normal sample.

Low education (*n* = 92)	Coefficient of variation	Median reaction time
White matter volume	-.03	-.15
Gray matter thickness	-.14	**-.26**

Note: Correlations in **bold** reflect $p < .05$.

Table 15. Correlation matrix of composite measures in Aim 1 for the high education group in the cognitively normal sample.

High education (*n* = 137)	Coefficient of variation	Median reaction time
White matter volume	-.10	-.16
Gray matter thickness	-.02	-.07

Note: Correlations in **bold** reflect $p < .05$.

Table 16. Zero-order correlation matrices for the current study and Jackson, Balota, Duchek, and Head (2012).

	Current study (n = 262)		Jackson et al. (2012) (n = 166)	
	CoV	τ	CoV	τ
SFG	**-.26**	**-.21**	**-.36**	**-.40**
VLDLPFC	**-.28**	**-.24**	**-.39**	**-.40**
P. Cingulate	**-.26**	**-.19**	**-.31**	**-.30**
Precuneus	**-.18**	**-.18**	**-.29**	**-.36**
IPL	**-.17**	**-.16**	**-.21**	**-.30**

Note: SFG = superior frontal gyrus, VLDLPFC = ventral/dorsal-lateral prefrontal cortex, P. Cingulate = posterior cingulate, IPL = inferior parietal lobule, CoV = coefficient of variation. All regions of interest reflect white matter volumes.
Note: Correlations in **bold** reflect $p < .05$.

Table 17. Correlation matrix of composite measures in Aim 2.

***n* = 149**	Working memory	Episodic memory
Coefficient of variation	**-.31**	**-.24**
τ	-.14	-.03
Frontal white matter	.05	.05
Default white matter	.07	.04

Note: Correlations in **bold** reflect $p < .05$.

Table 18. Correlation matrix of individual measures in Aim 2.

***n* = 149**	Working memory				Episodic memory		
	Digit Forward	Digit Backward	Mental Control	Word Fluency	Logical Memory	Associate Memory	Selective Reminding - Free
Stroop CoV	.00	.00	-.05	-.12	-.08	-.03	**-.19**
Simon CoV	-.03	-.13	-.15	**-.25**	-.12	-.11	**-.27**
CVOE CoV	-.02	**-.17**	**-.18**	-.12	.01	**-.20**	**-.19**
Stroop τ	.03	-.03	-.02	**-.20**	-.10	-.02	**-.22**
Simon τ	-.12	-.12	-.09	-.16	-.01	-.04	-.13
CVOE τ	.14	.10	-.07	-.05	.03	**.17**	.14
SFG	.07	.00	.00	.12	-.05	-.08	.08
VLDLPFC	.08	.11	.05	.12	.06	-.04	.10
P. Cingulate	.03	.00	.12	**.18**	.04	.02	.12
Precuneus	-.03	-.01	.02	.15	-.14	-.02	.02
IPL	.10	.11	.05	.10	.09	-.03	.04

Note: CoV = coefficient of variation, CVOE = Consonant-Vowel Odd-Even task, SFG = superior frontal gyrus, VLDLPFC = ventral/dorsal-lateral prefrontal cortex, P. Cingulate = posterior cingulate, IPL = inferior parietal lobule. All regions of interest reflect white matter volumes.

Note: Correlations in **bold** reflect $p < .05$.

Table 19. Correlation matrix of composite measures in Aim 2 for the cognitively normal group.

Cognitively normal (*n* = 126)	Working memory	Episodic memory
Coefficient of variation	**-.24**	**-.33**
Frontal white matter	.02	.04
Default white matter	.04	.00

Note: Correlations in **bold** reflect $p < .05$.

Table 20. Correlation matrix of composite measures in Aim 2 for the early-stage Alzheimer disease group.

Early-stage Alzheimer disease (*n* = 23)	Working memory	Episodic memory
Coefficient of variation	-.18	-.02
Frontal white matter	.16	.09
Default white matter	.01	.27

Note: Correlations in **bold** reflect $p < .05$.

Table 21. Correlation matrix of composite measures in Aim 2 for the younger half of the sample.

Younger sample (*n* = 66)	Working memory	Episodic memory
Coefficient of variation	**-.29**	**-.28**
Frontal white matter	-.09	.01
Default white matter	.16	.03

Note: APOE4- = noncarriers of the Apolipoprotein ε4 allele.
Note: Correlations in **bold** reflect $p < .05$.

Table 22. Correlation matrix of composite measures in Aim 2 for the older half of the sample.

Older sample (*n* = 65)	Working memory	Episodic memory
Coefficient of variation	**-.28**	**-.54**
Frontal white matter	-.12	.21
Default white matter	-.18	.13

Note: APOE4- = noncarriers of the Apolipoprotein ε4 allele.
Note: Correlations in **bold** reflect $p < .05$.

Table 23. Correlation matrix of composite measures in Aim 2 for the APOE4- group in the cognitively normal sample.

APOE4- (*n* = 83)	Working memory	Episodic memory
Coefficient of variation	-.21	**-.36**
Frontal white matter	-.08	.01
Default white matter	-.08	-.01

Note: APOE4- = noncarriers of the Apolipoprotein ε4 allele.
Note: Correlations in **bold** reflect $p < .05$.

Table 24. Correlation matrix of composite measures in Aim 2 for the APOE4+ group in the cognitively normal sample.

APOE4+ (*n* = 42)	Working memory	Episodic memory
Coefficient of variation	**-.35**	-.25
Frontal white matter	.24	.09
Default white matter	**.32**	-.02

Note: APOE4+ = carriers of the Apolipoprotein ε4 allele.
Note: Correlations in **bold** reflect $p < .05$.

Table 25. Correlation matrix of composite measures in Aim 2 for the Val- group in the cognitively normal sample.

Val- (*n* = 30)	Working memory	Episodic memory
Coefficient of variation	-.11	-.36
Frontal white matter	-.10	.06
Default white matter	-.07	-.14

Note: Val- = noncarriers of the catechol-*O*-methyltransferase Val allele.
Note: Correlations in **bold** reflect $p < .05$.

Table 26. Correlation matrix of composite measures in Aim 2 for the Val+ group in the cognitively normal sample.

Val+ (*n* = 70)	Working memory	Episodic memory
Coefficient of variation	**-.28**	**-.38**
Frontal white matter	.07	.03
Default white matter	.01	.04

Note: Val+ = carriers of the catechol-*O*-methyltransferase Val allele.
Note: Correlations in **bold** reflect $p < .05$.

Table 27. Correlation matrix of composite measures in Aim 2 for the low education group in the cognitively normal sample.

Low education (*n* = 57)	Working memory	Episodic memory
Coefficient of variation	**-.31**	-.21
Frontal white matter	-.09	.07
Default white matter	-.11	-.04

Note: Correlations in **bold** reflect $p < .05$.

Table 28. Correlation matrix of composite measures in Aim 2 for the high education group in the cognitively normal sample.

High education (*n* = 69)	Working memory	Episodic memory
Coefficient of variation	-.18	**-.39**
Frontal white matter	.10	.02
Default white matter	.14	.03

Note: Correlations in **bold** reflect $p < .05$.

Figures

Figure 1. Hypothesized path models to establish the double dissociation in Aim 1. A) A fully unconstrained model, in which both predictor variables are permitted to correlate with each outcome measure. B) A double-dissociation model, in which white matter may only correlate with intraindividual variability, and gray matter with median reaction time.

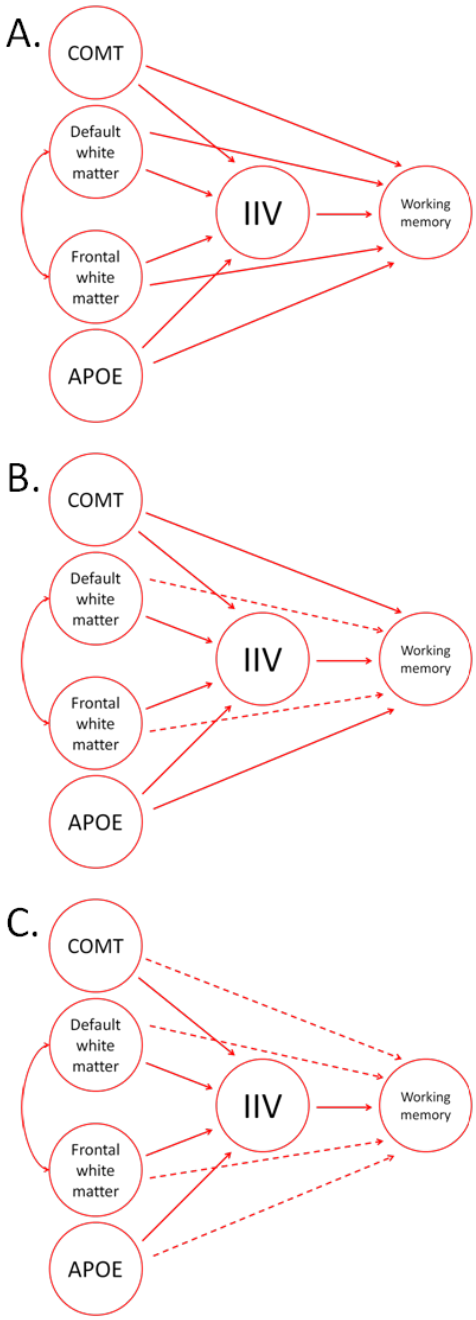

Figure 2. Hypothesized nested models to evaluate Aim 2. A) A theoretically unconstrained model, in which all variables influence working memory directly or via intraindividual variability (IIV). B) A partially constrained model, examining whether IIV mediates the relationship between white matter and working memory C) A model examining additional mediation of the relationship between APOE/COMT and working memory by IIV. Note: Models were also hypothesized testing episodic memory in the place of working memory.

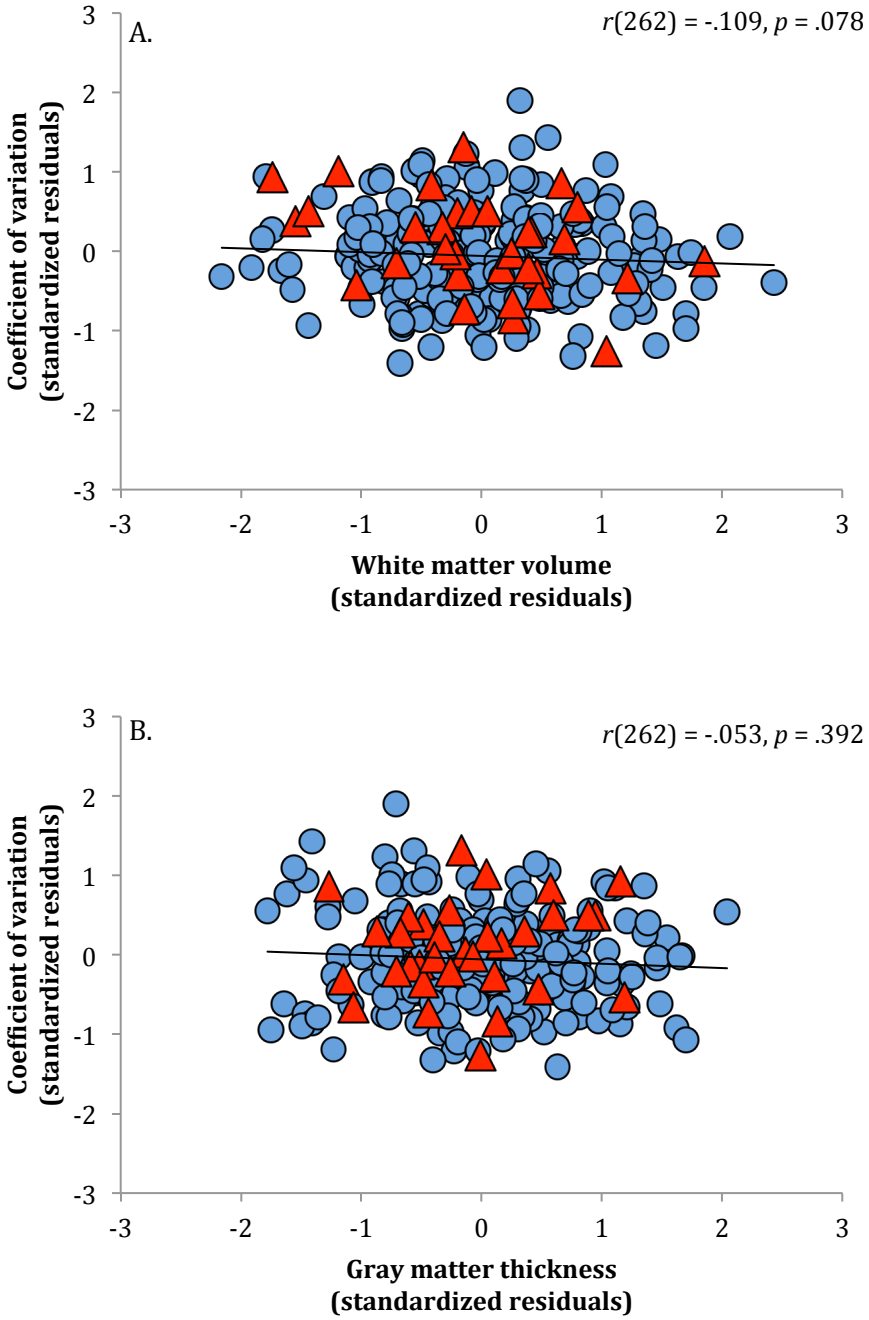

Figure 3. Aim 1 association between white matter volume and the coefficient of variation. A) White matter volume, B) gray matter thickness. Red triangles indicate participants with early-stage Alzheimer disease and blue circles indicate cognitively normal older adults. Data are standardized residuals controlling for age, education, gender, scanner type, cardiovascular health, depression, diabetes diagnosis, and the interval between the date of scan and the date of the cognitive assessment.

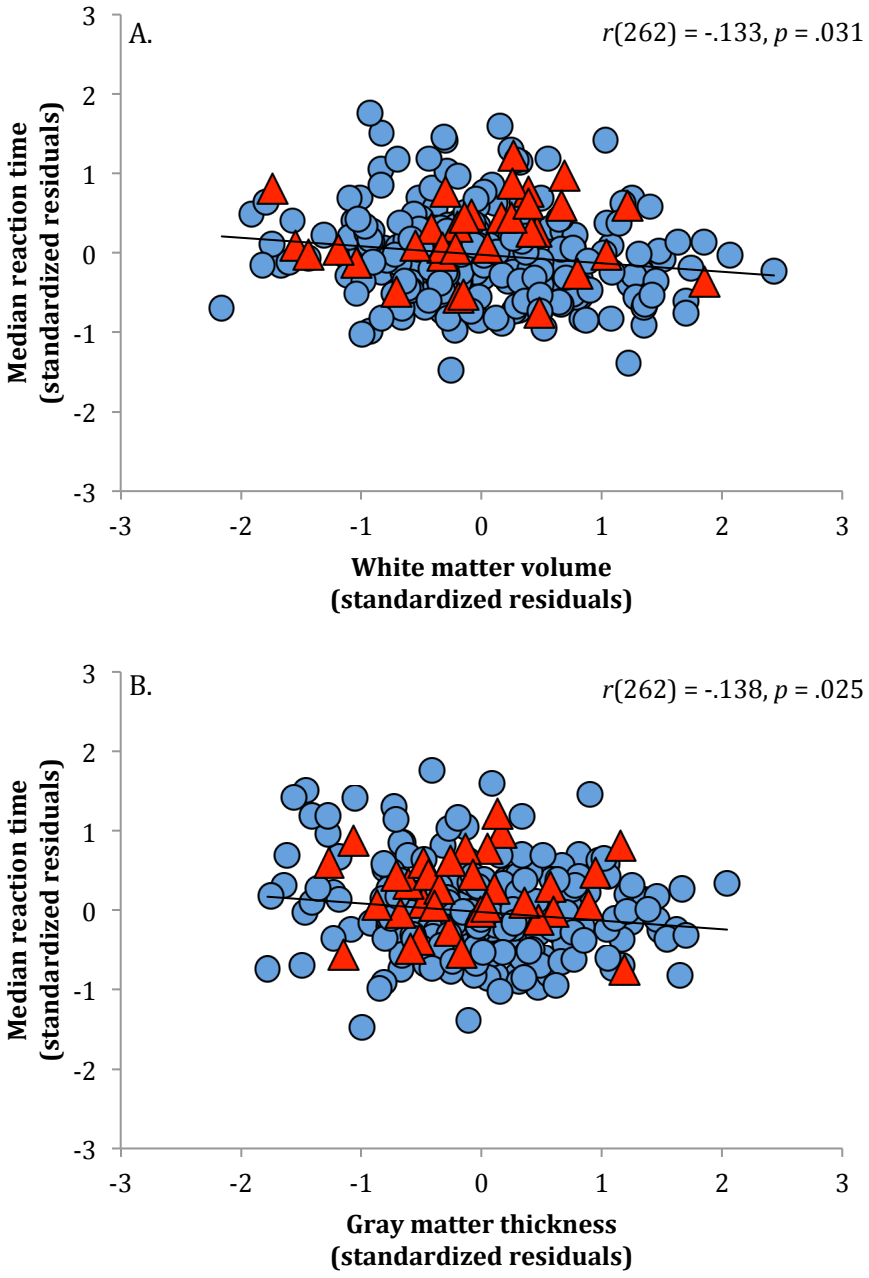

Figure 4. Aim 1 association between gray matter thickness and median reaction time. A) White matter volume, B) gray matter thickness. Red triangles indicate participants with early-stage Alzheimer disease and blue circles indicate cognitively normal older adults. Data are standardized residuals controlling for age, education, gender, scanner type, cardiovascular health, depression, diabetes diagnosis, and the interval between the date of scan and the date of the cognitive assessment.

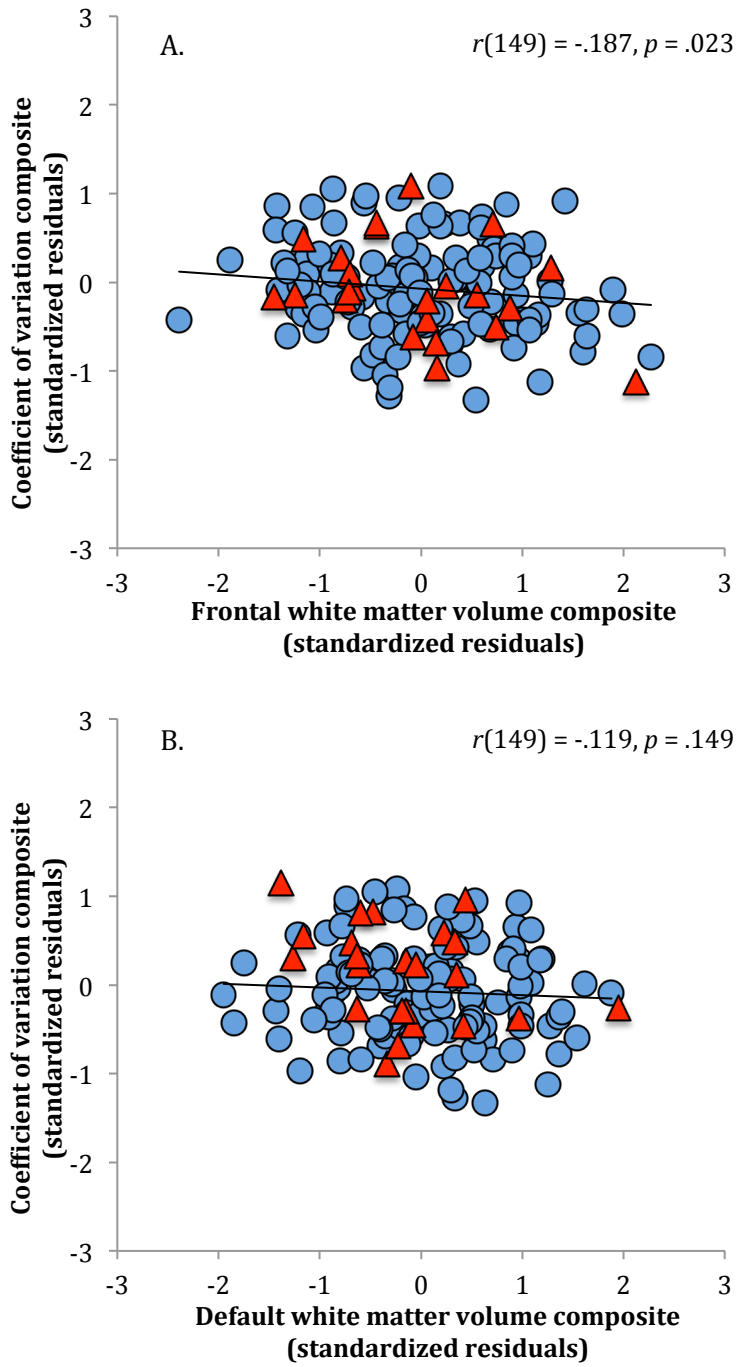

Figure 5. Aim 2 associations between regional white matter volume and the coefficient of variation. A) Frontal white matter volume, B) default white matter volume. Red triangles indicate participants with early-stage Alzheimer disease and blue circles indicate cognitively normal older adults. Data are standardized residuals controlling for age, education, gender, scanner type, cardiovascular health, depression, diabetes diagnosis, and the interval between the date of scan and the date of the cognitive assessment.

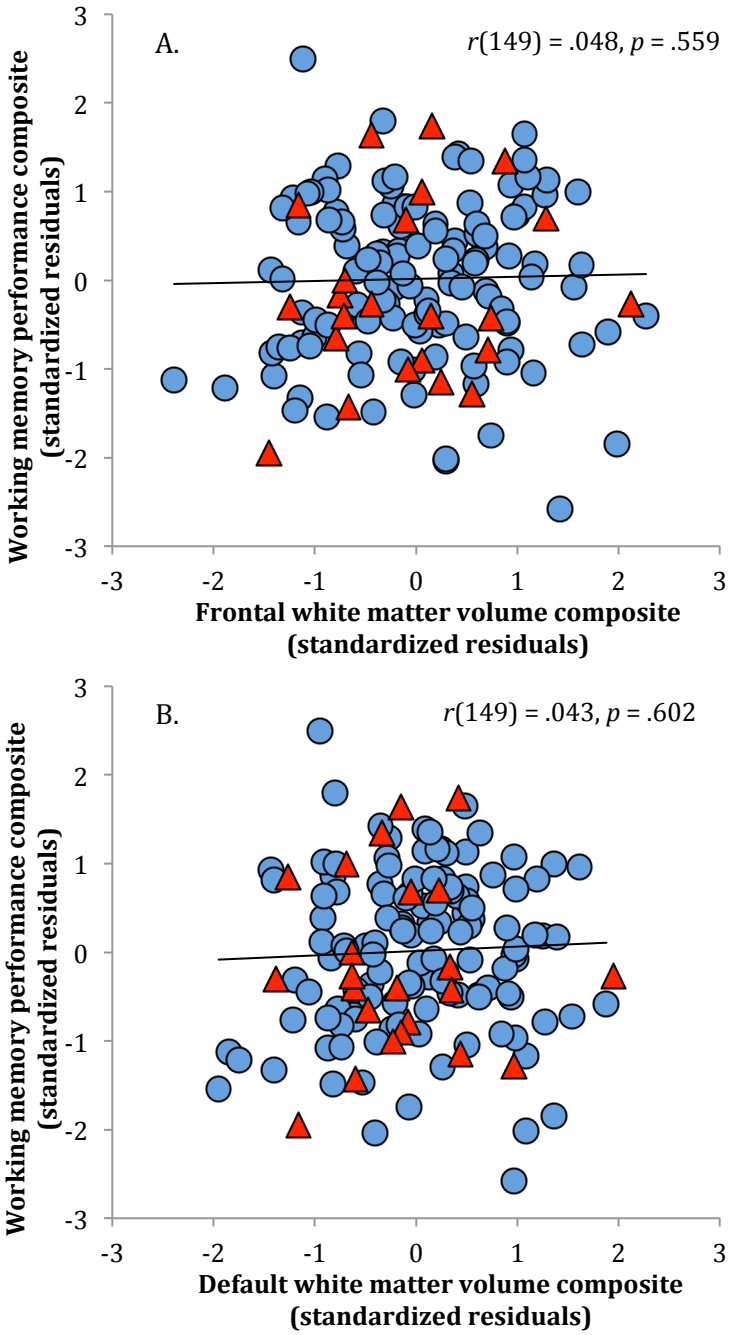

Figure 6. Aim 2 associations between regional white matter volume and working memory. A) Frontal white matter volume, B) default white matter volume. Red triangles indicate participants with early-stage Alzheimer disease and blue circles indicate cognitively normal older adults. Data are standardized residuals controlling for age, education, gender, scanner type, cardiovascular health, depression, diabetes diagnosis, and the interval between the date of scan and the date of the cognitive assessment.

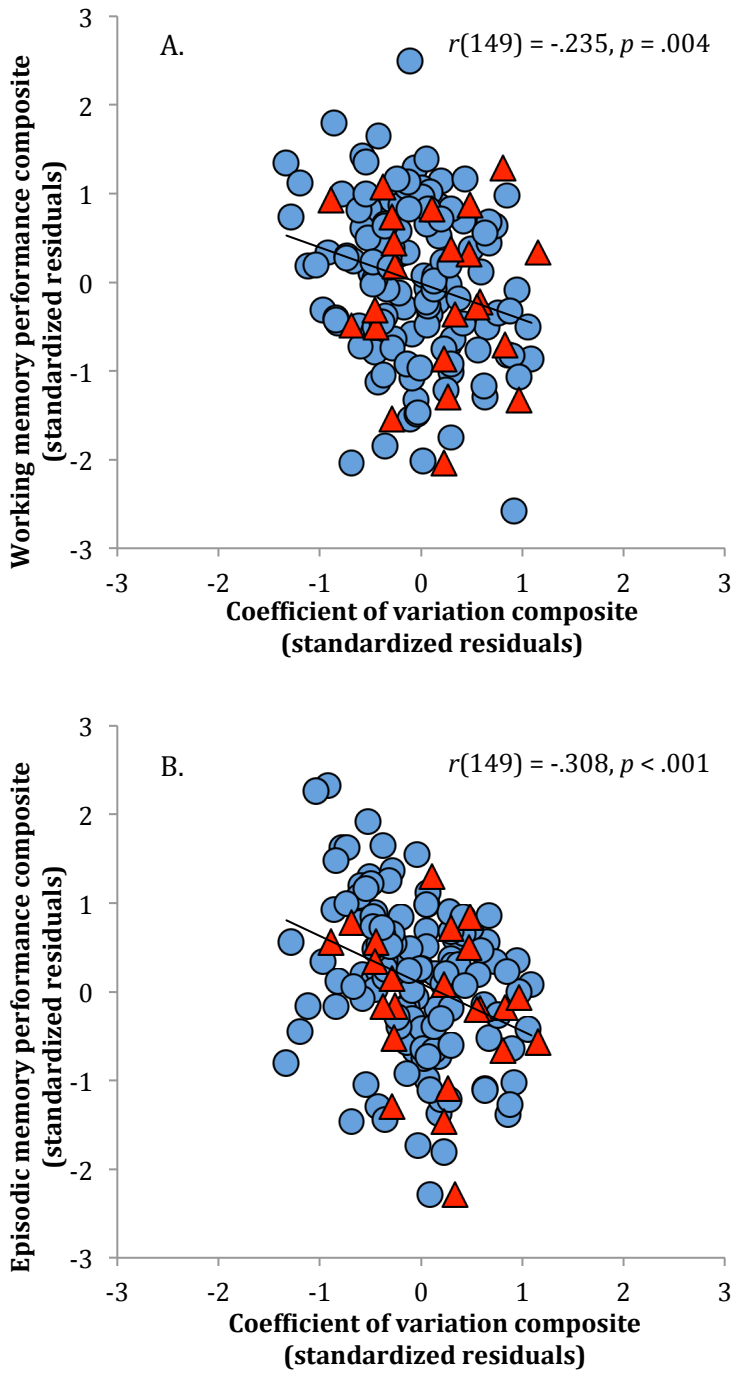

Figure 7. Aim 2 associations between the coefficient of variation and memory performance. A) Working memory, B) episodic memory. Red triangles indicate participants with early-stage Alzheimer disease and blue circles indicate cognitively normal older adults. Data are standardized residuals controlling for age, education, gender, scanner type, cardiovascular health, depression, diabetes diagnosis, and the interval between the date of scan and the date of the cognitive assessment.

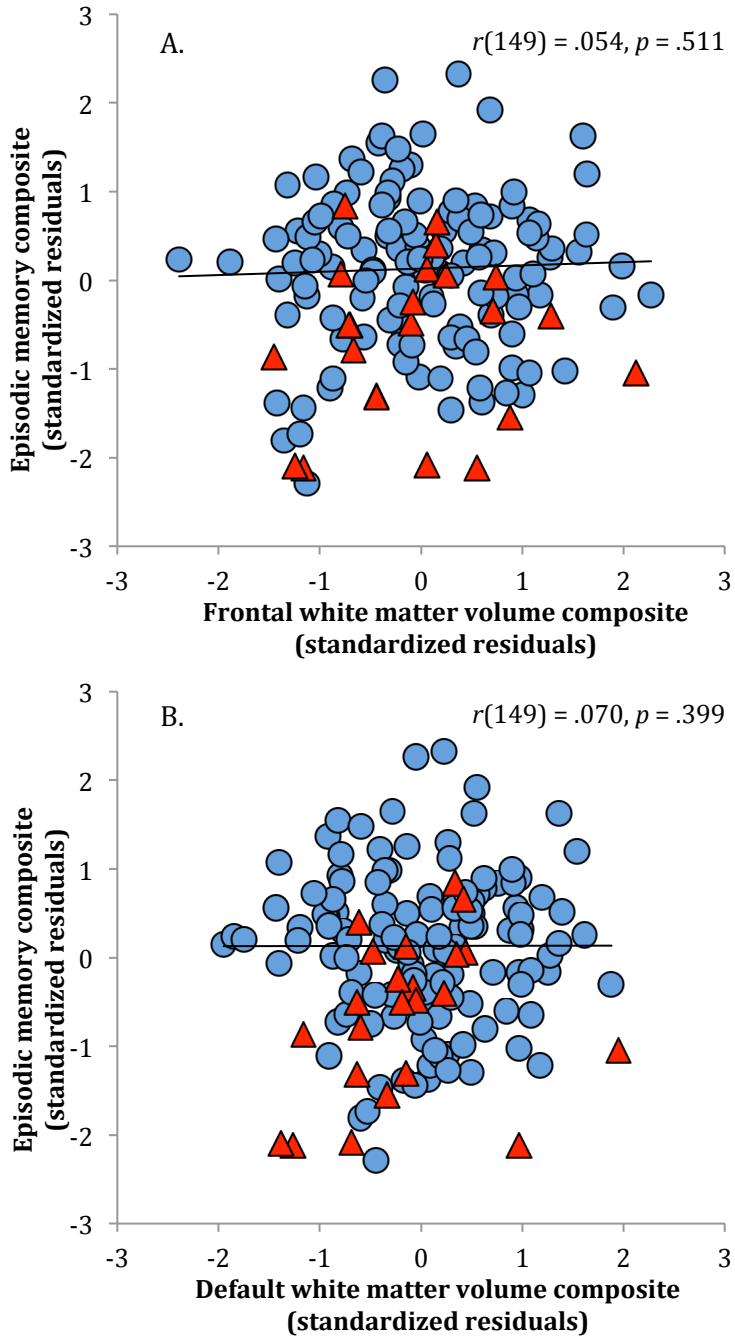

Figure 8. Aim 2 associations between regional white matter volume and episodic memory. A) Frontal white matter volume, B) default white matter volume. Red triangles indicate participants with early-stage Alzheimer disease and blue circles indicate cognitively normal older adults. Data are standardized residuals controlling for age, education, gender, scanner type, cardiovascular health, depression, diabetes diagnosis, and the interval between the date of scan and the date of the cognitive assessment.[8]