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Functional Interplay Between Neurocognitive Decline and Risk Factors in Older Adults: A Multivariate Latent Growth Curve Model of Risk

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ABSTRACT

Alzheimer's disease (AD) is a heterogeneous brain disease with multiple interacting risk factors, suggesting equifinality. Research indicates that the pathophysiological processes involved in AD are evident years prior to disease onset with significant variability in neurocognitive functioning being apparent during preclinical stages. Identification of individuals in preclinical stages is vital, as earlier interventions may prove more effective at ameliorating AD's devastating effects. In this respect, clarifying relationships between risk factors and neurocognitive functioning in cognitively intact older adults can improve our understanding of mechanisms involved in preclinical AD, which may allow for earlier detection and intervention.

The present study employed Latent Growth Curve modeling to longitudinally examine relevant risk factors relationship with neurocognitive functioning via neuropsychological assessment of executive attention, processing speed, episodic memory, language and working memory in 576 relatively healthy older adults over a three-year period. Results indicated on average Executive Attention/Processing Speed declined over time, while Memory and Language performance benefitted from practice effects over the three-year period. Substantial heterogeneity in initial levels of neurocognitive functioning and in linear changes in these processes were explained by individual differences in patterns of risk and resiliency variables. Specifically, differences in age, sex (men), and race (African Americans) respectively predicted worse neurocognitive functioning and Neurocardiovascular risk, while higher education and estimated intelligence predicted better neurocognitive functioning. Women were significantly higher in Depression/Endocrine risk. Neurocardiovascular and Depression/Endocrine risk factors emerged as unique predictors of worse neurocognitive functioning. Genetic risk for AD

(apolipoprotein E genotype: APOE-e4) specifically associated with worse baseline Memory functioning, supporting episodic memory's role as a neurocognitive endophenotype for AD. APOE-e4 also associated with lower estimated intelligence and Depression but not Neurocardiovascular history. In sum, the present study found distinct yet identifiable cognitive profiles of risk for neurocognitive decline. These results support conceptual models that suggest individual differences in sex, genetic risk, cognitive reserve, medical and mental health comorbidities in combination influence cognitive decline with age. These data have important treatment implications as they strongly indicate that there are modifiable risk factors that influence neurocognitive decline that can be targeted early on through behavioral and/or medical interventions.

CHAPTER 1: INTRODUCTION

Alzheimer's disease (AD) is a complex progressive brain disease that is the most common cause of dementia among older adults (National Institute on Aging, 2013). From a public health standpoint, the societal, individual, and financial costs of AD in the United States are enormous. According to the Center for Disease Control (CDC; 2014), AD is one of the top ten leading causes of death in the United States and it is believed that five million individuals in the United States aged 65 years or older have AD as of 2013. This number is expected to increase to nearly 14 million individuals by 2050 (CDC, 2014). Projected costs of AD from 2010 were estimated to fall between 159 and 215 billion dollars; this number is expected to be as high as 500 billion dollars by 2040 (CDC, 2014). Relevantly, to date, interventions for AD have not proven to be very effective at ameliorating its devastating effects. In this regard, early identification of individuals at risk for AD remains the holy grail within AD research, in that it is possible that interventions (both pharmacological and behavioral) that target systems involved in these earlier changes may slow or ideally impede propagation to other neural systems, prior to the development of likely psychological and neural compensatory changes as a result of these earlier liabilities.

A continuum model of AD pathology and neurocognitive decline that has been proposed by the National Institute on Aging (NIA) in conjunction with the Alzheimer's Association is that there is a "preclinical" stage of AD (and other dementia disorders) that precedes the diagnosis of mild cognitive impairment (MCI, which comes before transition to dementia along this continuum; Sperling et al., 2011). MCI is posited to be an earlier stage of dementia in which deficits in memory and/or thinking skills is evident yet the individual does not meet criteria for

dementia (see Petersen, 1999, 2004; Morris et al., 2001). MCI has gained acceptance among the medical field as a diagnosis, and the International Classification of Diseases, Revision 9 now has a billing code for MCI; consistent with NIA's continuum model many health professionals view MCI as early AD given the observed high rate of clinical conversion to AD in MCI individuals (see Roberts et al., 2010). According to the NIA-Alzheimer's Association (NIA-AA) guidelines, clinical diagnosis of MCI requires that there is a noticeable reported change in cognitive functioning beyond that of normal-advancing age decline (Sperling et al., 2011). There should also be evidence of worse neurocognitive performance in one or more processes as measured by tests beyond what would be expected based on the individual's age and years of education; and, if repeated measures are available than there should be a noticeable decline in their performance. When memory is the function primarily affected this is considered to be amnestic MCI (aMCI) and non-amnestic MCI refers to when cognitive abilities other than memory are affected (e.g., the ability to plan and sequence events and/or visual perception deficits). While individuals with MCI may be less efficient at instrumental activities of daily living (iADLs) these functions remain relatively well preserved. This definition of MCI and its research has informed the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) diagnosis of mild neurocognitive disorder (mNCD), which is also defined as a noticeable change in cognitive functioning in one or more cognitive domains in the absence of decline in ADLs (American Psychiatric Association, 2013).

Although clinical research has begun to intervene at the MCI stage, the NIA-AA's task force suggests that this may even be too late for optimal treatment effects (Sperling et al., 2011). For research settings, the NIA-AA has defined a preclinical phase in which brain changes may

already be in process; however, significant clinical symptoms are not yet evident (Sperling et al., 2011) Preclinical individuals display subtle signs of neurocognitive decline but do not yet meet criteria for MCI. Importantly, this preclinical period (prior to substantial beta-amyloid accumulation and clinical symptoms of AD) can last for over a decade, and may represent an opportunity for preventive measures and/or potentially more successful pharmacological and behavioral interventions within individuals who are defined as high-risk for MCI/AD (Sperling et al., 2011). Thus, a critical research direction proposed by the NIA-AA is the need to better define biomarkers and/or neurocognitive profiles that can best predict progression from the preclinical to the clinical stages of MCI and AD (Sperling et al., 2011). This continuum model of preclinical levels of neurocognitive decline provides a conceptual framework that inspired this study's design.

There is increasing evidence that many factors appear to contribute to the pathogenesis of AD and other dementia disorders. Notably, while there is a high conversion rate of individuals from MCI to AD, many individuals with MCI remain clinically stable and a subset of individuals diagnosed with MCI have been found to revert back to normal cognitive functioning (Alzheimer's Association, 2014). Thus, it is possible that certain MCI cases have been misclassified due to lack of sensitivity and/or specificity of the clinical assessment measures used (see Bondi & Smith, 2014), and it also possible that there are specific factors involved in maintaining clinical stability (or even providing resiliency) in those with MCI. Of further relevance, while research has identified several important risk factors for neurocognitive decline and subsequent development of MCI /AD, these findings have been largely mixed and there still remains a substantial amount of uncertainty regarding the causal relationships between these

predictors. Furthermore, it has become increasingly evident that none of the known risk factors to date are alone sufficient to accurately predict neurocognitive decline within older adults. Thus, the present study aimed to help to disentangle the relationships between age-related declines in specific neurocognitive processes (using objective sensitive neuropsychological test measures) and theoretically important predictors of risk over time in order to better define "normal" as compared to potentially preclinical neurocognitive variability in older adults.

Etiological model of risk for MCI/AD. A current challenge within cognitive aging research is distinguishing normal age-related changes in neurocognitive functioning from potential preclinical disease stages of MCI/AD. While memory impairments are a hallmark of AD, a growing body of research has implicated subtle deficits in executive functioning, attention, processing speed, and language processing in the earlier clinical manifestations of MCI/AD (see Bondi et al., 2008; Elias et al., 2000; Sperling et al., 2011; Weintraub et al., 2009). There is also evidence that individual differences in neural and "cognitive reserves" with age, as well as certain demographic and health related risk factors differentially influence the trajectory of neurocognitive decline within older adults with suspected AD pathology (e.g., Okonkwo et al., 2010; Sperling et al., 2011; Wilkosz et al., 2010). And, as will be discussed, there is a growing body of evidence that suggests age-related shifts in neural recruitment (e.g., increased bilateral activity in frontal and posterior parietal brain regions) might serve to help older adults compensate for declines in other neural resources with advanced age (e.g., Cabeza et al., 2004; Davis et al., 2008; Grady, 2012). Notably, these same regions posited to compensate for age-related shifts that are associated with preserved neurocognitive functioning have been implicated in early stages of neuronal degeneration in MCI/AD. Other relevant factors that have been

associated with an increased risk of developing MCI/AD and its course (i.e., the degree of impairment and rate of deterioration) include individual differences in demographic (age, race and sex), genetic (presence of APOE-e4) and health-related risk factors (e.g., depression, cardiovascular issues, diabetes, hypertension), which as will be later discussed have been shown to have additive and interactive effects with one another.

Lastly, while structural and functional changes in neurocognitive capacity can occur with normal aging, overall evidence across a broad age range of older adults (including the "oldest-old") suggests that well-educated healthy aging adults do not experience measurable declines in neuropsychological test performance over a four-year period (Hickman et al., 2000). This notion corresponds well with cognitive reserve theory, which suggests that individual differences in education, intelligence, and other psychosocial factors increase resiliency to cognitive decline through their beneficial effects on brain structure and function (Stern, 2006). According to cognitive reserve theory, underlying neurocognitive processes and/or differences in preexisting brain networks appear to allow certain individuals to more effectively cope with brain damage through these greater cognitive reserves (See Stern 2002, 2006, 2009). Indeed, higher levels of education and intelligence, as well as measures of quality of life have been shown to have a protective effect on neurocognitive functioning in the face of neural insult and are also associated with reduced dementia incidence rates (Kukull, et al., 2002; Stern, 2009).

In summary, it has become increasingly evident that there is substantial variance in the earlier clinical manifestations of AD as well as within "normal" aging. Importantly, despite increased recognition of heterogeneity within neurocognitive functioning with age, to date there has been little longitudinal research that has concurrently investigated for well-known risk

factors for MCI/AD (demographic, genetic, and health-related risk factors) in relation to specific changes in neurocognitive functioning within cognitively intact older adults. To address important gaps within the literature, the present study systematically investigated the interplay between memory, executive function, attention/processing speed, language, and working memory at baseline and over time; and, the degree to which genetic risk for AD (APOE-e4 allele), demographic factors (age, race, and sex), factors associated with cognitive reserves (levels of education and estimated intelligence), and health related risk factors explained heterogeneity in interindividual differences in neurocognitive functioning in older non-demented adults over a three-year period.

Given the complexity of the variables involved within this study and the vast literature for each respective component, it was beyond the scope of this study to provide a comprehensive literature review of each factor. Instead, some key findings and reviews were selected to provide a summary that should enable the reader to fully conceptualize this study's rationale, aims, and reasons for selected methodology. To begin, a brief description of AD pathophysiology in relation to genetic risk for AD is provided. Next, context for Aim 1's hypotheses is provided through an overview of developmental theories on the relationship between aging and cognition, and a discussion on age-related changes in brain functioning. Subsequently, anatomical findings that are relevant to the present study are presented, and are followed by a summary discussion. In the following section, relevant theories and/or research in relation to Aim 2's posited risk factors are presented. This is followed by a brief discussion on practice effects and validity concerns. Study variables are then integrated and presented within the study's aims and specific hypotheses. This is followed by a description of the study's design and method(s). To conclude,

the results and their theoretical importance for future research on studying neurocognitive change in older adults are discussed.

Prevalent theory on AD pathophysiology. This section provides a brief description of molecular events that are crucial to understanding AD pathology. While it is outside the scope of this study to address the underlying hypothesized biochemistry that occurs in the preclinical and clinical stages of AD pathology (as well as other certain neurodegenerative disorders) – for the purpose of this study and its conceptualization it is important to note that beta-amyloids (Aβ, a biomarker of AD) are believed to disrupt the architecture of neural tissue and that the apolipoprotein E (APOE) gene is posited to exert its effects through modulation of the amount of Aβ deposits during what is considered the *initiation stage* (Johnson, McCleary, Oshita, & Cotman, 1998). The initiation stage of AD disease processes is conceptualized as Aβs triggering a cascade of biological events at the molecular level, and there is a growing consensus that once the Aβs initiation of pathophysiological events occurs, these activated processes may come to act independently of the initiating amyloid. The end result being the structural and functional changes observed within the brain in relation to AD pathology (i.e., the propagation stage; Hyman, 2011; Johnson et al., 1998; Sperling et al., 2011).

In relation to genetic risk and AD pathophysiology, the APOE-e4 genotype is the strongest known genetic risk factor for late-onset AD (NIA, 2013; Sperling et al., 2011). The APOE gene provides instructions for making its namesake protein, apolipoprotein E. Apolipoprotein E is one of the proteins that combines with lipids to form lipoproteins that are responsible for packaging and transporting cholesterol through the blood stream (Uranga & Keller, 2010). There are several gene variations of the APOE in humans that significantly differ

both in their structure and function. The three major APOE allelic variations are ε2, ε3, and ε4 with the ε3 allele being the most common (alleles respective frequency: 8%, 77%, 14%; see Corder et al., 1994). The ε4 allele (APOE-e4) remains the most robust predictor of genetic risk for late-onset AD, whereas the ε2 allele (APOE-e2) is associated with decreased risk for late-onset AD (see National Institute on Aging, 2013). Furthermore, the presence of one or two APOE-e4 alleles has been specifically linked to poor performance on neuropsychological tests of learning, memory, and psychomotor speed across a wide range of ages in non-demented individuals (see Waldstein, 2000).

Although the exact role of the APOE gene in AD pathology remains uncertain, different polymorphisms in the gene appear to play a role in the efficiency in which plaques are removed from the brain as they have been differentially implicated in levels of Aβ accumulation (Sperling et al., 2011; Uranga & Keller, 2010). In studying autopsied brains, Johnson et al.'s (1998) seminal work found that: (1) the APOE-e4 allele was related to the initiation of Aβ and earlier AD onset, while (2) the APOE-e2 allele and sex were the best predictors of Aβ accumulation. These findings indicated that once initiated, the degree of Aβ accumulation was less pronounced in APOE-e2 allele carriers and that its protective effect was greater in males as compared to females. This study provided the first neuroanatomical evidence of different factors being involved in the initiation and propagation of amyloid plaques.

Of relevance, research currently is uncertain as to whether Aβ accumulation is itself a risk factor or whether Aβ accumulation is an early biomarker/detectable stage of AD (see Sperling et al., 2011). Knopman et al.'s (2013) novel cross-sectional findings suggest that brain injury biomarkers may precede or be independent of β-amyloidosis within preclinical stages of

AD. In this study, cognitively intact individuals with and without presumed preclinical AD pathology did not differ in their brain injury biomarkers (e.g., lower hippocampal volume or reduced glucose metabolism as measured by positron emission tomography), cardiovascular, or cerebrovascular characteristics. Rather, AD suspected as compared to non-Alzheimer pathway (characterized as individuals with brain injury but normal brain β-amyloidosis) groups only differed in their ratio of APOE-e4 carriers and the presence of β-amyloidosis. Results from this study suggest that brain injury might occur independent of β-amyloidosis within AD suspected pathology, and also potentially indicates that these factors interact in such a way that might accelerate pathological processes. Similarly, Jack et al.'s work (2015) strongly indicates that pathological processes other than β-amyloidosis cause declines in brain structure and memory function in middle age. Such findings are extremely relevant to the field as they suggest that preclinical stages of MCI/AD presumed pathology might have multiple etiologies that occur independent of β-amyloidosis. In this respect, linking relevant genetic, behavioral health and mental risk factors to specific neurocognitive profiles can inform research that might lead to earlier intervention entry points, which in turn may prove to have more success than current interventions in slowing and/or altering the progression of MCI/AD pathology and its debilitating effects.

CHAPTER 2: LITERATURE REVIEW

Investigating Within and Between Neurocognitive Domain Variance

It is recognized that developmental changes in neurocognitive functioning are diverse and sometimes widespread within older adults. Notably, executive functioning, attention, processing speed, episodic memory, and language abilities are the neurocognitive processes that have been proposed to be the most sensitive to age-related changes and to the early stages of AD (Weintraub et al., 2009). An important limitation within many studies to date is the lack of comprehensive neurocognitive evaluations in examining change over time in relation to relevant risk variables that have demonstrated significant interactions with one another (e.g., many have used gross screener measures of cognitive functioning, such as the Mini Mental State Exam: MMSE; Folstein et al., 2001). Relevantly, while measures such as the MMSE are useful in detecting stages of change within individuals with dementia, the MMSE has been found to lack sensitivity in detecting those with mild cognitive impairments (for review, see Mitchell, 2009). Furthermore, use of such measures can result in a lack of specificity in identifying the nature of cognitive impairments, as they are not capable of identifying which neurocognitive processes are first affected within individuals at risk for a dementia disorder.

Another issue that arises is that there is significant variation within the amount and degree of neurocognitive changes that can occur with "normal" aging. Although there are some studies to suggest that older adults demonstrate significant neurocognitive impairment on neuropsychological tests compared to younger adults, other studies suggest that older adults' neurocognitive functioning is generally well preserved; and, in some cases older adults have been shown to perform as well if not better, than younger adults on certain neuropsychological

tests (see Glisky, 2007). For instance, while language-processing deficits have been observed when older adults are faced with rapid speech rates, overall language abilities appear intact and oratory skills are frequently better within normal aging adults (for review, see Wingfield & Stine-Morrow, 2000). A review of the normative data from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) suggests that over-learned "crystallized" skills (verbal comprehension index and arithmetic tests) appear to be the least affected by advanced age, while measures of fluid intelligence and processing speed (Digit Symbol) show the greatest age effects (Wechsler, 1997; as cited in Lezak, Howieson, & Loring, 2004). Taken together, language abilities and "over-learned material" appears to be relatively preserved within normal aging older adults; whereas, as will be discussed next, executive functioning, attention, and processing speed appear to be more impacted with advanced age.

With respect to memory, the findings regarding memory and aging have been mixed. For the purpose of this study, we will specifically focus on two aspects of long-term explicit memory. There is evidence that there is an initially a steep decline in episodic memory (defined as the ability to deliberately recall contextual information for specific events and situations) that occurs with advanced age, whereas semantic memory (i.e., the ability to retain knowledge about facts and deeply learned materials and/or historical events, such as birth dates) appears to stable in non-diseased brains (Zacks, Hasher, & Li, 2002). Importantly, while both semantic and episodic processes generally recruit similar processes for encoding, there appears to be differences in their underlying neural storage systems that suggest that they are partially dissociable (see Vargha-Khadem et al., 1997). Furthermore, as will be discussed, successful memory recall with age also appears to differ as a function of individual differences in age-

related shifts recruitment and neural resources. Finally, while memory declines have been noted as part of the normal aging process, there is longitudinal research that suggests significant impairment on tests of episodic and semantic memory is rare within healthy aging older adults (aged 65 to 94 years), and thus verbal memory declines are a potential indicator of early disease pathology (Hickman et al., 2000).

Upon closer examination of respective neurocognitive processes, neuropsychological measures that are presumed to tap frontal and superior parietal lobe functioning in particular have demonstrated increased age-related decrements (see Raz, 2000; 2004). Specifically, working memory, attention, and executive functioning (e.g., tasks that require set-switching) appear to be substantially impacted with advanced age (for review, see Grady, 2012). Here, it is worth noting that working memory deficits within older adults are still poorly understood, as it appears to have significant overlap with both executive function and attentional processes (Raz, 2000). In this respect, the difficulty of the working memory task appears to play an important role in performance decrements in older adults. Accordingly, decreased attentional resources, deficits in information processing speed, and poor inhibitory control all have been posited to play a role in working memory deficits that have been observed within older adults neuropsychological test performance (Glisky, 2007). Furthermore, there is evidence to suggest that slower processing speed, poorer executive functioning and attention contribute to the age-related decrements in other neurocognitive functions (see Salthouse, 2000; Salthouse, Atkinson, & Berish, 2003; Verhaeghen & Cerella, 2000).

The relationship between processing speed, poorer executive functioning and attention with changes in other neurocognitive processes is not surprising, considering well-evidenced

information process models that have demonstrated attention and cognitive control of information selection is necessary for successful memory encoding and thus its subsequent storage and retrieval (Smith & Kosslyn, 2010). Still, to date, the majority of studies have been cross-sectional, so the degree to which these relationships actually reflect changes in neurocognitive functioning over time remains uncertain and there also is considerable heterogeneity within older adults' neuropsychological test performance. In this regard, better understanding between neurocognitive-domain covariance (particularly between executive functioning and attention with language and memory functioning) within older adults in relation to factors that predict longitudinal changes within these processes remains an important area of study.

Interplay between neurocognitive domains. Executive function, which appears to be compromised in elderly who exhibit early signs of MCI, has an inhibitory influence on attention and working memory processes (Grady et al., 2003; Heun et al., 2007; Morris et al., 2001). Of relevance, the relationship between executive function and other neurocognitive systems, particularly attention, appears to be bidirectional, in that intact executive functioning not only involves frontal lobe recruitment but also requires recruitment of non-frontal lobe regions (for review, see Alvarez & Eugene, 2006). For instance, a gold standard test of executive function (i.e., the Wisconsin Card Sorting Task: WCST) has been shown to activate numerous regions to include: the inferior parietal cortex, temporal-parietal association cortex, and occipito-temporal, temporal pole, and occipital cortices (see Alvarez & Eugene, 2006). Similarly, brain imaging studies have found that the Stroop, a test widely used to assess for frontal lobe dysfunction, has been associated with activation not only in its expected frontal lobe networks, but also activated

the middle frontal gyrus, parietal lobe regions, motor areas, and temporal lobe regions (see Alvarez & Eugene, 2006). Moreover, brain-imaging studies have found that phonemic tests of verbal fluency activate the parietal lobes, thalamus and temporal lobes, in addition to their hypothesized frontal lobe networks (see Alvarez & Eugene, 2006). Overall, these and other results indicate that executive function and attention processes have significant overlap in their underlying neural substrates, and that respective neurocognitive processes are reliant on one another for optimal functioning. All considered, taking a more fine-grained approach to understanding the interplay between specific neurocognitive processes in older adults may be fruitful in identifying which factors best predict risk for early neurocognitive decline in preclinical MCI/AD individuals.

Relevantly, age-related variability in neurocognitive functioning may be explained by shifts in neural resources and individual differences in potential compensatory mechanisms (e.g., Cabeza et al., 2001, 2002, 2004; Grady et al., 2003). The next section(s) will build on these findings and provide evidence to support the hypothesis that a substantial amount of the variance found in higher-level cognitive processes within cognitively intact older adults may be explained by differences in compensatory mechanisms that are related to executive function and attention capacity (and posited underlying differences in neural and cognitive reserves).

Individual differences in neurocognitive functioning with advanced age. There is a growing consensus that variability in normal age-related neurocognitive changes may be explained by shifts in neural resources and individual differences in potential compensatory mechanisms (e.g., Cabeza et al., 2001, 2002, 2004; Grady et al., 2003). Importantly, these neural changes are considered to be adaptive processes when they are connected to better

neurocognitive performance. For instance, a review of fMRI language studies suggests that, in healthy aging brains, older adults selectively recruit non-traditional language areas to compensate for age-related changes in the brain in order to maintain language stability (Wingfield & Grossman, 2006). Specifically, interconnected regions that are associated with attention and executive control (left dorsal inferior frontal and right temporal-parietal regions) appear to be upregulated in conjunction with reduced language center activation (left temporal-parietal activation) in older adults who maintain good intact language comprehension performance as compared to younger adults (Wingfield & Grossman, 2006). These findings are in line with those who have argued that age-related decrements in language processing are a function of changes in working memory, attentional control and/or processing speed (see Wingfield & Stine-Morrow, 2000). Taken together, maintenance of language abilities appears to be reliant on the plasticity of neural networks, and the integrity of systems involved in attention and executive control. Thus, it may be that the rate of decline in attention or executive functioning processes would predict later declines in language abilities.

Similar to language functioning, memory functioning also appears to be highly reliant on the plasticity of neural systems. Older adults who demonstrate better neurocognitive performance on cognitively demanding memory source tests appear to display increased bilaterality within the PFC, as compared to older adults with poorer memory functioning who recruited similar regions as young adults (right lateralized PFC activation as measured by PET scans; Cabeza, Anderson, Locantore, & McIntosh, 2002). These authors suggest that this decreased lateralization in higher performing older adults is adaptive in that it serves to compensate for age-related neurocognitive decline. These findings are consistent with other studies that have found evidence of age-related

differences in bilateral compensation in prefrontal activation during memory recall tasks. For instance, while younger and older adults both demonstrate activation in left parietal and temporal regions during verbal memory tasks, during episodic memory retrieval and working memory tasks older adults show greater bilateral prefrontal activity as compared to younger adults who display lateralized prefrontal activity during the task (for review, see Grady & Craik, 2000). Additionally, evidence for differences in activations to working memory, visual attention and episodic retrieval tasks in younger versus older adults via fMRI has also been found (Cabeza et al., 2004). Across all three tasks the older adults showed weaker occipital activity along with stronger prefrontal and parietal activity than the younger adults. Behaviorally, older adults as compared to younger adults were as accurate but slower on the majority of neuropsychological tasks. Of further interest, although not anticipated, greater activation within parietal regions and decreased activation within the hippocampal formation was also found in older as compared younger adults within all three of the tasks. Of relevance, the reduction in occipital activity (which may be an indicator of sensory decline) and the increased parietal activity in tandem appears to suggest a compensatory age-related shift from ventral stream to dorsal stream processing (Cabeza et al., 2004). Overall, this research suggests that the dorsal stream pathway and frontoparietal network become increasingly important with age, as they may serve to compensate for declines in other neurocognitive processes that occur with advanced age.

In sum, there is evidence to suggest that changes in executive functioning and attention could give rise to episodic memory and language dysfunctions, as memory retrieval and semantic knowledge requires intact frontal lobe function. Dementia in AD is cognitively characterized by vast dysfunctions in memory that are accompanied by deficits in language and semantic

knowledge, executive functions, attention, and constructional and visuospatial abilities (see Bondi et al., 2008). It is plausible that lowered executive function, attention, and processing speed abilities heralds difficulties in memory and language functioning in a subset of older adults with suspected dementia or AD pathology, whereas, in those without underlying vulnerabilities within the brain regions associated with these functions are able to successfully compensate for normal age-related shifts in neural resources.

Neural regions affected in MCI/AD. Although memory impairments and temporal atrophy particularly within the hippocampus and the entorhinal cortex are considered a hallmark of AD pathology (Raz, 2000), there is increasing evidence that executive function and attention in addition to memory are disrupted early on in MCI/AD. A novel view is that the earlier stages of AD may be better predicted through examination of parietal lobe functioning and changes in its connectivity (for review, see Jacobs, Van Boxtel, Jolles, Verhey, & Uylings, 2012). As discussed, theories regarding AD suggest that beta-amyloids trigger a cascade of biological events and that amyloid accumulation is the predominating view of the biochemistry of AD. There is research to suggest that the posterior association cortices are the first to be affected by amyloid plaques in AD, and that observed hypometabolism within the medial parietal areas appears to be effective at discriminating AD patients from control participants (Jacobs et al., 2012).

Damage to the parietal lobe (particularly posterior regions) affects a wide range of functions to include attentional, memory retrieval, movement perception and visuospatial relationship judgment processes (Pinel, 2013). Grey matter loss in the posterior parietal cortex is found in patients with MCI (Jacobs et al., 2012). Atrophy of the posteromedial (precuneus) and

inferior parietal lobule have been consistently found within longitudinal studies that have investigated conversion rates to AD, and evidence for posterior parietal lobe involvement has been found in studies that have investigated individuals with neurocognitive decline without a diagnosis of MCI or AD (Jacobs et al., 2012). Loss of white matter integrity within tracts that innervate this region have also been found in patients with MCI, and although not consistently found there is also evidence for reductions in parietal white matter in MCI when compared to healthy controls (Jacobs et al., 2012). Parietal white matter hyperintensities are also pronounced in MCI patients (Jacobs et al., 2012). Notably, the composition of myelin within the parietal areas may be more vulnerable to toxicity and disease processes (for reviews, see Bartzokis 2011; Jacobs et al., 2012). It is also worth noting that APOE-e4 carriers have been shown to have lower myelin repair and maintenance capacities in the areas most affected by AD pathology, and lower white matter and gray matter volume within these regions (precuneus, posterior/middle cingulate, lateral temporal, and medial occipitotemporal regions) is evident as early as two months year old in infant carriers (for review, see Bartzokis 2011; Dean et al., 2014; Jacobs et al., 2012). In sum, there is evidence that factors other than temporal atrophy contribute to the early pathogenesis of MCI/AD.

Behaviorally, dysfunction in frontoparietal functioning has been linked to worse executive attention performance on the Attention Network Test in individuals with MCI (Van Dam et al., 2013). In comparing relatively healthy aging adults to individuals with MCI, there is longitudinal research that suggests that identification of wide spread neurocognitive impairments on tests of executive function, processing speed, language, visuospatial, and attention is a better indicator of underlying neurodegenerative decline than memory alone (Johnson et al., 2012).

Similarly, another longitudinal study found that in addition to verbal memory, semantic/language processing (category fluency) and visuospatial construction tests were the best early behavioral markers of MCI in preclinical older adults over the age of 80 (Howieson et al., 2008); however, the sample mean age for this study was relatively restricted (Mean age at study entry = 83). Furthermore, a systematic review of preclinical AD provides evidence of subtle deficits in learning and memory, executive functioning, processing speed, attention, and semantic knowledge that are apparent on neuropsychological tests prior to disease states; relevantly, this study also indicated that specific impairments in episodic memory are a sensitive predictor in identifying those at higher risk for AD (Bondi et al., 2008). From interpretation of these and other findings (e.g., Albert, Moss, Tanzi, & Jones, 2001; Grober et al., 2008; Rapp & Reischies, 2005), it would follow that executive function and attention processes, which have been shown to rely on frontal and frontoparietal network functioning (Koenigs, Barbey, Postle, & Grafman, 2009), would be significantly affected in those with MCI, and dysfunction within this region may be evident prior to MCI diagnosis and visible impairments in other functions.

All considered, as neurocognitive processes appear to somewhat rely on one another, observed deficits seen in typically spared processes within older adults may to some extent reflect difficulty in neural recruitment or connectivity within attention network and frontal lobe systems. Taken together, individuals with preexisting vulnerabilities within these neural regions would be expected to have a steeper age-related decline on neuropsychological tests that serve as proxies of functioning within these regions, and that over time more wide spread neurocognitive impairments in memory and language processing becomes evident as function of increased neurocognitive demands within the preclinical stages of MCI.

Cognitive Aging Theories: Compensation versus dedifferentiation of neurocognitive functioning. A challenge within the field is differentiating normal age-related changes from presumed disease related changes in neurocognitive functioning (e.g., determining the extent to which greater activations, particularly within left prefrontal cortex regions, represent successful compensatory mechanisms as compared to undifferentiated-diffuse activity). Important changes in neuroanatomical structures that occur with advanced age include decreases in white and gray matter[1], loss of functional connectivity, irregularity in blood flow in various regions of the brain, changes in plasticity and neurogenesis as well as alterations in neurochemistry (see Raz, 2000; Cabeza, 2001, 2002). One theory is that vast age-related changes in non-diseased brains are indicative of neural/brain compensations (as evidenced by greater activations in regions other than would be expected by the task or greater bilateral activation) that occur throughout different regions of the brain in dynamic and complex ways that can serve to decrease age-related declines in neurocognitive functioning (Cabeza, 2001, 2002). However, there is some question as to whether or not neural compensations represent "successful" compensation or aberrant dedifferentiation of neural functioning in older adults (e.g., Li, Lindenberger, Frensch, 2000). In order to unravel this question, more longitudinal research on neural functioning and behavioral changes in neurocognitive functioning is needed across a broad range of cognitively intact older adults.

[1] Decreased gray matter volume is believed to be more a function of neuronal shrinkage than neuronal loss within non-diseased aging brains.

Importantly, changes in neural recruitment and functional connectivity are seen as both part of the normal aging process and can also be related to disease pathology (e.g., aberrant plasticity; see Albers et al., 2014). The dedifferentiation hypothesis posits that heightened correlations observed between different neurocognitive domains with advanced age are evidence of a loss of specialization of functioning, rather than evidence of compensatory mechanisms (often referred to as "dedifferentiation" when the greater activation is paired with worse neurocognitive performance; see Grady & Craik, 2000). Notably, there is research to suggest that dedifferentiation and compensation theories are not mutually exclusive. As discussed, the maintenance of neurocognitive performance observed in Cabeza's and others work may potentially reflect greater neural plasticity as indicated by the greater bilateral activation within the prefrontal and parietal regions within the relatively higher functioning older adults. Or alternatively, and not incompatible with the former, lower functioning older adults may have less cognitive reserves and/or greater neural vulnerability due to changes in their neurochemistry that affects functioning in the regions which may serve to compensate for normal age-related changes in brain functioning. Indeed, loss of efficiency in dopaminergic functioning and its associated pathways is tied to mild cognitive impairments with advanced age; and, as neural efficiency decreases neurocognitive impairment becomes more evident (Li, Duncan, Mcauley, Harmer, & Smolkowski, 2000; Li, Lindenberger, & Sikstrom, 2001). Thus, in preclinical stages of diseased brains, greater activations may be an indication of greater burden upon these processes. The later example is consistent with evidence that the early preclinical stage of MCI/AD is different from normal brain aging.

Scaffolding theory is somewhat integrative of these two theories in that it posits observed increased functional activity in older adults is due to the process of *compensatory scaffolding,* that is throughout the lifespan there is dedicated neural circuitry that helps individuals to acquire and learn new skills; once, skill acquisition occurs there are shifts in neural recruitment to the same cognitive task suggesting that the neural regions involved in the guiding learning are no longer recruited/required once cognitive demands are decreased (Park & Reuter-Lorenz, 2009; Petersen, Mier, Fiez, & Raichle, 1998). According to the scaffolding theory of aging and cognition (STAC), compensatory neural recruitment (particularly the PFC) occurs in response to increased cognitive demands in order to restore homeostatic cognitive functions within aging brains (Park & Reuter-Lorenz, 2009). Relevantly, scaffolding occurs in response to increased cognitive demands that are a function of age-related as well as pathology related declines in neural structures and their function. An important component to STAC, which is in accord with cognitive reserve models, is that it helps to account for the significant variability seen with advanced age in that the efficiency of scaffolding appears to be moderated by factors such as intelligence and education. STAC is also harmonious with the notion that overlearned skills, such as language processing, should not be as affected by normal age related changes in neurocognitive functioning.

In relation to presumed MCI/AD pathology, there is evidence to suggest that greater activations may initially serve to help individuals compensate for neurological decline. For instance, increased activation in task positive regions and reduced deactivations in task negative regions are associated with better visual memory encoding within non-demented older adults with Aβ accumulation (Elman et al., 2014). These results (and others) support the notion that

increased activations, at least initially, serve as compensatory mechanisms in the face of pathological processes. However, as disease burden along with normal age-related decrements within parietal and frontal networks increase, wider spread neurocognitive deficits become more evident. This suggestion is also in relative accord with Bookheimer et al.'s (2002) finding that greater magnitudes of left hemisphere base-line brain activation predicted the degree of subsequent memory decline two-years later.

As Park & Reuter-Lorenz (2009) discussed, in order to determine whether increases in neural activation and regions recruited are adaptive, one needs to assess the function for which these neural changes are compensating. In comparing neurocognitive profiles of patients with mild AD to cognitively intact older adults, who are in turn compared to younger adults – there are notable differences and similarities within the older adult groups (Sperling et al., 2003). Within AD patients, less bilateral activation in the hippocampal formation during encoding of complex visually presented stimuli (NvF condition) and less right hemisphere activation in the hippocampal formation during encoding of novel as compared to familiar (NvR condition) visual stimuli when the complexity was held constant was noted. However, bilateral activation in the medial parietal cortex (precuneus), the right posterior cingulate, and the superior frontal cortex regions during memory encoding of face-name associations when compared to cognitively intact older adults was also observed in patients with mild AD as compared to the cognitively intact older adults. Interestingly, in comparing these same relatively healthy older adults to younger adults, no differences in hippocampal activation during the NvF task were noted. Older adults also demonstrated greater activation in parietal regions, and less right but not left hippocampal activation as compared to younger adults during the NvR task. Furthermore, the non-AD older

adults demonstrated significantly less activation in both superior and inferior prefrontal cortices during memory encoding in the NvF when compared to the younger adults.

Somewhat similar effects have been found in cognitively intact APOE-e4 allele carriers, in which APOE-e4 allele carriers as compared to APOE-e3 allele carriers demonstrate significantly greater activation within the left prefrontal and bilateral orbitofrontal, superior temporal, and inferior and superior parietal regions in response to memory recall tasks; these effects were not found during the resting or active-learning state (Bookheimer et al., 2000). Notably, this baseline measurement of increased left hemisphere activity (as measured by blood oxygen level-dependent: BOLD signal intensity) associated with subsequent memory decline at the two-year follow-up. Individuals with the APOE-e4 allele as compared to those with the APOE-e3 allele also displayed significantly worse delayed memory performance [as measured by Wechsler Memory Scale (WMS) Logical Memory Delayed Recall]. These authors concluded that this greater and less focal activation within the ROIs is an indication of greater cognitive load within the APOE-e4 allele carriers during the memory task; and, that this increased neural activity may be a result of neural compensatory mechanisms attempts to restore memory performance to normal levels.

Relevantly, decreased activation in response to memory tasks in APOE-e4 carriers has also been found. In cognitively intact individuals with a family history of AD (at least one biological parent), decreased activity in the hippocampus and MTL in response to memory tasks was detected in APOE-e4 carriers as compared to non-carriers (Trivedi et al., 2006). Notably, within this study, greater left anterior MTL activation positively associated better encoding performance in the non-carriers but not in the APOE-e4 carriers. However, despite these

differences in activations the APOE-e4 carriers as compared to non-carriers did not differ in their neuropsychological task performance. Consequently, it could be argued that the greater activation could be interpreted as being an indicator of greater cognitive load within the non-carriers – however, this explanation would not be harmonious with the finding of greater left MTL activation positively associating with better encoding performance within the non-carrier group. Thus, the authors concluded that the observed lower activity in APOE-e4 carriers is an indication of early biological changes within the MTL (e.g., disruption of the relationship between MTL and learning) that precede observable declines in neuropsychological test performance.

Right-left asymmetrical differences (particularly within medial temporal lobe regions) have been reported in patients with AD, and a review of the imaging literature provides some support for APOE-e4 allele playing a role in asymmetrical damage to the left medial temporal lobe regions within AD patients that is also evident in cognitively intact APOE-e4 carriers (for review, see Lehtovirta, Laakso, Frisoni, & Soininen, 2000). In cognitively intact older adults and in patients with AD, the APOE-4 allele also appears to play a role in hemispheric asymmetry in a region of the medial temporal lobe that is believed to be first affected in AD (entorhinal cortex thickness right > left; Donix et al., 2013). Notably, the opposite effect has also been found, as there is evidence of a dose dependent effect of APOE-e4 on hippocampal volume asymmetry in patients with AD; such that, a reverse effect of greater left than right hippocampal volumes are found in homozygous APOE-e4 carriers, while in those with only one APOE-e4 allele asymmetry appears abolished and within non-carriers greater right than left asymmetry within the hippocampus appears disturbed (Geroldi et al., 2000). All considered, individual differences

in early asymmetrical hemisphere damage may at least to some extent explain both the greater activations within left hemisphere processes and reduced right hemisphere activations in mild AD and APOE-e4 carriers.

Overall, these finding emphasize the need for more research on specific neurocognitive changes over time across a broad range of older adults with and without signs of neurocognitive impairment, before any solid conclusions on age-related changes in neural recruitment may be made. Problematically, differences found in regards to neural activations across studies could be related to a host of potential moderating factors (e.g., differences in genetic predispositions, health or demographic differences), different methodologies used and brain regions examined, and/or could potentially be reflective of individuals farther along on the continuum to MCI/AD pathology (see Grady, 2012). Thus, it is difficult to determine what differences in activations across studies means with any certainty. Notably, as deficits in any neurocognitive process can lead to impairments in functioning with widely different manifestations across individuals, research that longitudinally investigates within and between neurocognitive domain variance in relation to relevant risk factors in older non-demented adults is clearly needed.

Relevant Predictors of Neurocognitive Functioning within Older Adults

Although there are mixed findings in regards to the APOE-e4 allele, there is clearly a link between neurocognitive functioning and APOE-e4 carrier status. There is research to suggest that APOE-e4 carrier status differentially associates with neurocognitive functioning in individuals with mild AD as well in relatively healthy older adults. Specifically, a cross-sectional study found a pattern of greater medial temporal lobe (MTL) atrophy was coupled to greater reported impairments in memory functioning within APOE-e4 carriers, whereas greater

frontoparietal atrophy was coupled to greater impairment on tests related to working memory, attention, executive control, and verbal fluency in non-carriers (Wolk et al., 2010). In non-clinical older adults, longitudinal research on the effects of APOE-e4 suggests that it exerts its effects on memory early on, as APOE-e4 carriers' memory functioning significantly diverges from non-carriers prior to the of age 60 (Casselli et al., 2009). Interestingly, within this study, worse visuospatial perception (as measured by Judgment of Line Orientation) also displayed a trend relationship with APOE-e4 carrier status, thereby indicating that right hemisphere dysfunction is evident early on. These results provide initial evidence that the underlying mechanism and the extent of memory and/or executive attention related deficits within mild AD might differ as a function of genetic risk, and suggest that there may be early identifiable subtypes of MCI/AD (with different trajectories of neurocognitive decline with corresponding neural networks). In this regard, research that increases our understanding of the interplay between memory, language, executive function, attention, processing speed, and working memory functioning over time in cognitively intact older adults may lead to better identification of individuals who are displaying early signs of cognitive decline prior to MCI/AD conversion.

Genetic risk and its interaction with other risk factors for AD/MCI. Despite the APOE-e4 allele being the strongest known genetic risk factor for AD there is substantial variability within the findings that may be better understood through investigation in individual differences in demographic, cognitive reserve, and health related risk factors. To begin, while greater age remains a robust independent predictor of MCI/AD, the overall risk for AD appears to decrease after the age of 90 (Lautenschlager et al., 1997) and neither the APOE-e4 nor the APOE-e2 alleles are associated with incidence rates for dementia or AD in individuals aged 90

and older (Corrada, Paganini-Hill, Berlau, & Kawas, 2013). Additionally, as already discussed, there is evidence to suggest that the APOE-e4 allele exerts its effects early on prior to MCI or AD being present. Consistent with this notion, the odd risk of AD among APOE-e4 allele carriers appears to have a curvilinear relationship with age (Farrer et al., 1997). Furthermore, within this same large meta-analysis ($k = 40$) that assessed several demographics factors that might contribute to the considerable amount of mixed findings regarding APOE carrier status within the AD literature found that age, sex and race differentially influenced the relationship AD and APOE genotype (Farrer et al., 1997). Notably, the effect of sex (being female) was related to an increased risk of AD across genotypes as well as there being a significant interaction effect between APOE-e4 and sex (i.e., females with an e4 allele carried a 1.5 times greater risk) even after controlling for age. Race differences were also noted within this study, across a series of racially diverse studies representing African Americans, Caucasians, Hispanics, and Japanese, a significant relationship between APOE-e4 allele carriers and AD was found; however, this effect appeared to be somewhat weaker within African Americans as compared to Caucasian carriers and strongest within Japanese carriers (Farrer et al., 1997). The finding that genetic risk was somewhat weaker within African Americans as compared to Caucasian carriers is of particular interest considering the prevalence rate of AD/dementia disorders is approximately two times higher in African American as compared to Caucasian individuals (Alzheimer's Association, 2014).

Remarkably, women on average carry an inherently higher risk of AD than men (almost two-thirds of Americans with AD are women; see Alzheimer's Association, 2014). Several studies indicate that females' greater longevity when compared to males may be responsible for

the higher prevalence of AD in women (Alzheimer's Association, 2014). However, there is research to suggest that females' relatively longer life span cannot entirely explain the higher prevalence rate (Lautenschlager et al., 1995). Notably, within the oldest old, the APOE-e4 allele is significantly associated with increased prevalence of dementia and AD in females but not males, such that the odds ratio of female APOE-e4 allele carriers having dementia or AD was twice that of APOE-e3/ε3 carriers (Corrada et al, 2013). Altmann, Tian, Henderson, and Greicius (2014) also recently found that while the conversion risk from healthy to MCI and from MCI to AD was significantly greater in APOE e4carriers, overall the conferred genetic risk was substantially greater within women as compared to men.

It is important to note that the relationship between sex and APOE-e4 carrier status on AD outcomes has been mixed. Some studies have failed to find a interaction between sex and carrier status (Combarros et al., 1998; Corder et al., 1995), while other studies have found that male as compared to female APOE-e4 allele carriers had twice the relative risk of AD (Qiu et al., 2003) and, once age is adjusted, a greater relative risk of AD associated mortality (Dal Forno et al., 2002). It is also worth noting that Corrada et al. (2013) study found sex differences in regards to the protective effects of the APOE-e2 allele, in favor of women (i.e., male APOE-e2 carriers had an increased odds risk of dementia and AD, whereas female APOE-e2 carriers had decreased odds risk). In all these studies emphasize the need for a more comprehensive investigation of sex differences in relation to genetic risk and neurocognitive decline in older adults.

On average the prevalence of AD is significantly higher in African Americans and Latino/as as compared to Caucasians (Alzheimer's Association, 2014). While there is much debate regarding the factors underlying this heightened degree of risk in minority populations,

there is evidence that health-related risk factors (e.g., cardiovascular risk) and/or psychosocial factors (levels of education) contribute to this heightened risk for AD (see Chin, Negash, & Hamilton, 2011). Indeed, there is a considerable amount of research that indicates cardiovascular disease and diabetes is linked to a heightened AD risk (Alzheimer's Association, 2014). Such findings are also consistent with research that has found that both health-related risk factors and levels of education are associated with an increased risk for MCI. A large population based study that followed older adults over a three-year period found that increased age, presence of genetic risk (APOE-e4 allele), and medicated hypertension all substantially increased risk for MCI; whereas, higher education was linked to a significantly lower risk of cognitive decline suggesting that it may exert a protective effect against age-related decline (Tervo et al., 2004). Furthermore, the combination of the APOE-e4 allele and cardiovascular disease had an additive non-interacting effect such that odd ratio for conversion to MCI was 3.92 higher in those with both risk factors as compared to those without either of these risk factors. Similarly, another large longitudinal study that respectively examined predictors of MCI noted that the presence of the APOE-e4 allele, race differences (African American individuals having a higher rate of MCI than Caucasians), lower educational level, presence of health related risk factors (hypertension, diabetes mellitus, and depression) were unique predictors of MCI risk (Lopez et al., 2003). Additionally, poor neurocognitive test performance (MMSE and digit coding tests) and positive MRI findings (degree of atrophy, ventricular volume, white matter lesions, and infarcts) positively associated with MCI.

Notably, the relationship between APOE-e4 carrier status and specific neurocognitive functions within the literature has been equivocal as indicated by a large meta-analysis ($k = 38$;

Small, Rosnick, Fratiglioni and Backman, 2004). While this cross-sectional meta-analysis found evidence of worse global cognitive functioning, episodic memory, and executive functioning in APOE-e4 carriers, the overall magnitude of APOE-e4 effects on neurocognition were small. Notably, potential moderators of sex, race, health, and education were not assessed within this meta-analysis. Here, it is worth noting that past research has found that the beneficial effects of education on age-related changes in neurocognition has been found to interact with APOE-e4 allele, such that there is a steeper rate of decline in memory functioning in older adults (aged 70–79) with an APOE-e4 allele whose educational obtainment is equivalent to or greater than ninth grade (Seeman et al., 2005). Furthermore, there is cross-sectional research that suggests that the effects of the APOE genotype on memory functioning and cognition in general disappear in non-demented older adults - once the effects of age, sex and education are adjusted for (Welsh-Bohmer et al., 2009). In sum, while there is research to suggest that APOE-e4 plays a specific role in neurocognitive decline within both mild AD and non-clinical older adult populations, studies that systematically assess longitudinal changes in neuropsychological test performance in relation to relevant predictors for MCI/AD are strongly needed in order to elucidate whether, the degree to which, and in whom, lower initial memory and/or executive function predicts subsequent declines in other neurocognitive processes.

To review, there are substantial mixed findings in regards to the APOE-e4 allele; however, it clearly appears to be an important variable whose role in neurocognitive functioning needs to better defined. As discussed, the effects of the APOE-e4 and APOE-e2 allele appear to change with age, and the degree of risk for MCI or AD conferred from the APOE-e4 genotype might vary with race, age and sex. There is also evidence to suggest that older adults without a

significant history of health problems experience relatively little cognitive decline (Hickman et al., 2000), while cardio- and/or cerebrovasular events are strongly associated with impairments in executive function, attention and processing speed and higher rates of decline in language and memory functioning (e.g., Okonkwo et al., 2010; Weinstein et al., 2013). Furthermore, depression has been linked to a greater risk of MCI and there is research to suggest that depression precede memory decline rather than the converse (Zahodne, Stern, & Manly, 2014). Lastly, it is important to highlight that demographic, cognitive reserve, and health related risk factors appear to make unique contributions to MCI/AD pathology, as well as there being significant interactions amongst these factors with APOE-e4 carrier status.

In summary, individual differences in demographic factors, cognitive reserve (higher levels of education and/or intelligence), as well as other health related biomarkers (e.g., high cholesterol) and neurocardiovascular risk (e.g., hypertension or history of stroke) appear to respectively account for individual differences in neurocognitive functioning. In this regard, investigating individual differences in risk variables and their potential interactions may help clarify "normal" age-related as compared to disease related decrements in neurocognitive functioning. Furthermore, comprehensive investigation of these factors may help explain the mixed findings within the literature on APOE genotype and functional outcomes, as these variables may act as moderating or potentially suppressor variable(s). All considered, increased understanding of the interplay between individual differences in risk factors and neurocognitive functioning may lead to improved assessment sensitivity that will allow for earlier detection and serve to inform preclinical models of MCI/AD, through providing indicators for potential treatment intervention points.

Validity Issues in Longitudinal Research

Before proceeding to the study's hypotheses, it is important to discuss validity issues that were anticipated to be present within this study. First, past research has found that certain neurocognitive tests are particularly susceptible to practice effects. Specifically, memory tests and/or tests that have a strong psychomotor component to them have been found to have substantial practice effects (for review, see Calamia, Markon, & Tranel, 2012; McCaffrey & Westervelt, 1995; Mitrushina & Satz, 1991). Consistent with this research, our group has previously reported practice effects in measures of memory and attention/processing speed in individuals without cognitive decline; of interest, in this same study a subset of participants defined as "cognitive decliners" did not benefit from previous exposures to testing and instead exhibited a performance decrement in these measures (MacAulay et al., 2014). Thus, while practice effects are a relevant concern, our work and others (e.g., Duff et al., 2007) also indicate that the failure to benefit from previous test exposure on tests that are susceptible to practice effects might serve as an indicator of a decline in that cognitive process. In considering these methodological limitations/concerns, the present study anticipated that there would be significant practice effects, particularly on tests of memory, and thus it was specifically hypothesized that those with lower initial memory functioning would demonstrate less benefit from previous test exposures.

Instrumentation effects must be also considered. When the posited properties of a measurement changes with age (i.e., demonstrates factorial variance over time), the conclusions made regarding observed changes in such measures might lack validity (Little, 2013). Relatedly, another potential issue that can arise in longitudinal research involves the law of initial values –

that is, the higher or lower the initial level of functioning, the smaller the degree of change that can be produced (e.g., those with higher initial scores may demonstrate less gains over time due to their higher start point; Mosby's online dictionary, n.d.). It is also possible that certain effects may be missed in those who are higher or lower functioning due to lack of measurement of sensitivity (e.g., pronounced ceiling or floor effects). To address these validity concerns, it is important to briefly mention measurement selection. The present study utilized a well-validated neuropsychological test battery established by the National Alzheimer's Coordinating Center (NACC), which is frequently used within longitudinal research with older adults, that has proven to be sensitive measure of neurocognitive change. Previous confirmatory factor analyses (CFA) conducted on the factor structure of the NACC's Uniform Data Set (UDS) neuropsychological test battery has demonstrated a good model fit for the proposed factor structure that is consistent with there being strict factorial invariance across a wide range of older adults with varying levels of cognitive functioning (e.g., Hayden et al., 2011; Weintraub et al., 2009).

Study Summary with Aims and Hypotheses

Of note, there are relatively few longitudinal studies that have concurrently examined relevant risk factors for MCI/AD in relation to neurocognitive functioning over time in relatively cognitively intact older adults. Using longitudinal data collected at three distinct time points spaced approximately a year apart in older adults, the purpose of this study was to help to disentangle the relationships between age-related declines in specific neurocognitive processes (using objective valid neuropsychological test measures) and theoretically important predictors of risk over time in order to better define "normal" as compared to potentially preclinical neurocognitive variability. By furthering our understanding of the interplay between these

processes, clinical models based on neurocognitive endophenotypes may be built in order to determine specific trajectories that increase risk so that individuals at risk for MCI/AD may be detected earlier on. Defining the functional relationships between changes in specific neurocognitive domains over time also has future research and treatment implications. For instance, specifying neurocognitive domains that are affected early on may indicate which neurotransmitter pathways are first impacted, which can help to inform future pharmacological treatment research (e.g., executive function/attention performance is modulated by dopamine functioning and dopamine dysfunction is believed to affect synaptic plasticity which can lead to structural changes within the brain). Hypothetically through preventing aberrant plasticity, interventions (both pharmacological and behavioral) that target systems involved in these earlier changes may slow or ideally impede propagation to other neural systems. Additionally, through better understanding the neurocognitive domains that are first affected novel behavioral and cognitive remediation techniques may be designed to target deficits within those showing early signs of dysfunction (e.g., cognitive remediation strategies to enhance attention allocation). In this regard, improved understanding of the interaction between risk factors and neurocognitive decline may lead to more effective interventions that can target pathological processes prior to AD conversion.

This study took a comprehensive approach to examining neurocognitive functioning over a three-year period in conjunction with theoretically important predictors of age-related decline (demographic, genetic, cognitive reserve, and health related risk factors). Specific aims and hypotheses for the study are presented next.

Aim 1: Investigating within and between neurocognitive domain variance

Aim 1 sought to better understand the interrelationships between the specific neurocognitive processes of memory, executive function, attention, processing speed, language and working memory in older adults. Multivariate latent growth curve modeling methods were used to examine Memory, Executive Attention/Processing Speed, Language and Working Memory functioning over time (Year 1 to Year 3) and to assess whether changes in the respective growth trajectories differed as a function of within or between neurocognitive domain functioning. Specific goals and hypotheses for these analyses are as follows.

Within-neurocognitive domain covariance. It was expected that Executive Attention/Processing Speed scores would on average demonstrate a decline from Year 1 to Year 3 (as measured by a negative value for M_{slope}) within the non-demented older adults. Whereas, based on evidence that memory tests in particular are subject to significant practice effects, it was hypothesized that on average there would be an increase in memory scores from Year 1 to Year 3 as measured by the latent variable, Memory M_{slope}. Additionally, individuals with initially lower Executive Attention/Processing Speed scores would demonstrate a steeper rate of decrement than individuals who started with higher Executive Attention/Processing Speed scores at baseline (as measured by the within-domain covariance). Similarly, participants' whose Memory performance was lowest as compared to those who were highest at baseline would demonstrate a slower rate of growth in memory over time (i.e., will benefit less from practice effects as evidenced by a significant within-domain covariance between Memory M_{slope} and $M_{intercept}$). Furthermore, based on prior research that has examined the preclinical profiles of those that have converted from preclinical to MCI stages (Howieson et al., 2008), it was also

expected that individuals with initially lower language performance would display a steeper rate of decrements in these functions over time (as evidenced by a significant within-domain covariance between Language M_{slope} and $M_{intercept}$). Given the previously discussed mixed findings with working memory, no specific hypotheses were made regarding this latent variable other than higher initial Working Memory scores were expected to positively associate with the other neurocognitive processes at baseline.

Between-neurocognitive domains covariance at baseline. This set of analyses assessed the amount of interplay between neurocognitive domains at baseline. It was hypothesized that individuals with higher scores in one neurocognitive domain would on average also be higher in the other neurocognitive domains at baseline (and vice versa, those with lower neurocognitive functioning in one neurocognitive domain would generally have worse neurocognitive performance on all measures at baseline). Specifically, it was expected that individuals with initially lower Executive Attention/Processing Speed would concomitantly demonstrate poorer Memory and/or Language test scores than individuals with higher initial scores at baseline.

Between-neurocognitive domains intercept and slope covariances. This set of analyses was specifically interested in the degree to which changes in Memory and Executive Attention/Processing Speed associates with changes in other neurocognitive processes over time. It was hypothesized that initially lower Executive Attention/Processing Speed scores would be shown to precede changes in other neurocognitive processes (as measured by the relationship between mean levels of Executive Attention/Processing Speed's $M_{intercept}$ with the other neurocognitive domains' Mslopes). Exploratory analysis examined whether initial low memory functioning predicted steeper annual rate of declines in other neurocognitive processes.

Between-neurocognitive domains slope covariances. It was expected that on average as Executive Attention/Processing Speed demonstrated steeper decreases over time, so would memory and language scores (as measured by covariances between domains' M_{slope}). Additionally, on average as Memory scores increase from Year 1 to Year 3, Executive Attention/Processing Speed and Language scores would increase in accord. Exploratory analysis investigated the remaining relationships between changes in neurocognitive domains in relation to one another from Year 1 to Year 3.

Heterogeneity in neurocognitive functioning. It was expected that variance estimates (slope, intercept, and random measurement errors) for each of the neurocognitive domains would be statistically significant. Such findings would indicate that there were robust between individual differences in initial neurocognitive score values and rates of change from Year 1 through Year 3, and thus provide support for the next set of analyses outlined in Aim 2.

Competing models utilizing a global neurocognitive latent variable. In the interest of parsimony, prior to conducting Aim 2's analyses, competing models (factor-of-curves and curve-of-factor latent growth models; see Duncan, Duncan, & Strycker, 2006) utilized a global neurocognitive latent variable to determine whether a high order global neurocognitive latent factor could better explain the data. These models' factor structures were contrary to the study's posited four-factor model, in that they assume that the first-order factors (i.e., each respective neurocognitive domain) would be better explained by a higher order global neurocognitive latent variable's intercept and slope.

Aim 2: Relevant predictors of neurocognitive functioning

Given mixed findings within the literature in respect to demographic factors (age, race and sex), cognitive reserve (higher levels of education and estimated intelligence), health related risk factors (e.g., history of heart disease), and genetic risk for AD in relation to neurocognitive decline, Aim 2's analyses were interested in whether, and to what degree, individual differences in these risk characteristics might explain heterogeneity within the present study's posited model of neurocognitive functioning. This set of analyses was also interested in the amount of interplay between these variables and testing an etiological model of MCI. Thus, both specific (direct) and indirect effects of these factors were tested. Specific effects of these factors were modeled first in order to account for their respective influence on each of the growth parameters, as well as to assess for potential moderating or suppressor effects with their inclusion. Specific goals and hypotheses for these analyses are as follows.

Demographic factors. Given strong evidence for their interrelationships within the literature, a goal of Aim 2 was to assess the degree to which age predicts neurocognitive functioning when sex and race are adjusted for in the model. It was posited that age would be a statistically significant predictor of initial neurocognitive scores at baseline and associate with a greater rate of memory and executive attention/processing speed decline from Year 1 to Year 3 (even when age and sex were adjusted for in the model). Although no specific hypotheses were made in regards to race and sex, it was expected that these predictor variables would have a moderating influence on neurocognitive functioning.

Cognitive reserve. While adjusting for the relevant demographic factors of age, race and sex, it was posited that the time invariant cognitive reserve variables (greater levels of education

and intelligence) would associate with higher neurocognitive functioning at baseline. Exploratory analyses also investigated these variables influence on rates of neurocognitive change over time.

APOE-e4 carrier status. Based on previous research that has found that the APOE-e4 allele preferentially associates with memory decline in MCI and mild AD patients, analyses investigated the influence of APOE genotype on specific neurocognitive domains. It was posited that while adjusting for relevant demographic factors (age, sex, and education), APOE-e4 carriers as compared to non-carriers would demonstrate greater Memory impairment at baseline and a steeper rate of Memory decrement from Year 1 to Year 3. APOE-e4 carriers as compared to non-carriers were also expected to demonstrate a steeper rate of decline in Executive Attention/Processing Speed and Language scores over time. Exploratory analysis investigated APOE-e4's relationship with the remaining neurocognitive domains mean levels at baseline and their incremental rates of change over the three-year period.

Given mixed findings within the literature regarding the role of APOE-e4 genotype in respect to individual differences in age, race, education, sex, these factors relationship with neurocognitive functioning were systematically investigated in conjunction with APOE-e4 carrier status. Once the relevant risk variables of age, sex, education and race were included within the model, it was expected that the effect of APOE-e4 on neurocognitive functioning would be attenuated. Sex was specifically expected to have a moderating effect on the relationship between APOE-e4 carrier status and neurocognition. No specific hypotheses were made in regards to race.

Health-related risk factors. There is substantial evidence that health related risk factors contribute to neurocognitive decline in older adults. The direct effect of Cardiovascular, Cerebrovascular, and Depression/Endocrine risk factors on Memory, Language, Executive Attention/Processing Speed, and Working Memory functioning was assessed while adjusting for potential moderating variables. It was expected that cardiovascular risk in particular would emerge as a strong predictor of neurocognitive functioning and would also associate with APOE-e4 carrier status. It was also hypothesized that individual differences in demographic factors would contribute to the degree of health related risk factors. It was expected that: (1) advanced age would associate with a higher amount of health related risk factors, (2) sex and race differences would be found in the pattern of health related risk factors, and (3) cardiovascular risk in particular would be a strong predictor of neurocognitive functioning and would also associate with APOE-e4 carrier status. Exploratory analyses investigated the role of the cognitive reserve variables in this model.

Etiological model of risk of cognitive decline. Based on Ritchie's (2004) hypothetical model etiological model of MCI, the last set of analyses' goal was to provide an etiological model of risk for cognitive decline in healthy older adults through testing the indirect effects of age, race, sex, and genetic risk on neurocognition through their impact on health related risk factors. According to Ritchie's model, age-related brain changes predict overall vascular pathology/infarctions and MCI. Sex has direct effects on genetic predispositions and lipid metabolism, while genetic predispositions have both direct and indirect effects on development of MCI through its influence on lipid metabolism, as well as environmental and psychological factors (e.g., history of depression or trauma). Environmental and psychological factors, which

are influenced by educational and treatment intervention factors (e.g., antidepressants), are posited to have direct effects on MCI outcomes. Lipid metabolism is posited to predict cardiovascular risk factors (e.g., midlife hypertension) and overall vascular pathology/infarctions, which in turn are posited to predict MCI.

Neurocardiovascular and depression health risk factors. As depression and neurocardiovascular factors have been shown to make independent contributions to MCI risk (Lopez et al., 2003), the present study was specifically interested in testing two paths of risk for neurocognitive decline. The first path of risk represented Neurocardiovascular pathology, while the second pathway represented a Depression/Endocrine pattern of neurocognitive risk. In accord with this hypothetical etiological model of MCI, within the present study:

1. Sex, age, race, and genetic risk were presumed to be relevant individual difference factors that influence health related risk factors, which in turn a greater degree of health related risk factors would directly impact neurocognitive functioning.
2. Furthermore, within this model, education and intelligence are posited to provide cognitive resiliency. Accordingly, the variables of education and intelligence served as cognitive reserve variables with specific effects on neurocognitive functioning that were adjusted for in the model, while examining the above described effects in Point 1.

CHAPTER 3: RESEARCH METHOD AND DESIGN

Participants

This study utilized data collected between 2009-2013 from an on-going longitudinal study that investigates the effects of aging upon neurocognitive processes and daily living functioning in relatively healthy older adults, the Louisiana Aging Brain Study (LABrainS, PI: J.N. Keller). LABrainS is an open enrollment longitudinal study that has been following participants since 2009 (overall retention rate of 87%). Participants are recruited throughout Louisiana using traditional media sources (e.g., newspaper ads and television and newspaper press) as well regular community outreach efforts. Telephone screening procedures are used for initial enrollment. Age of enrollment is generally equivalent or greater than 60 years old; however, there are some participants who have been classified as higher-risk due to their familial status that have been admitted prior to their sixtieth birthday. Eligibility criteria for LABrainS requires that participants be willing to undergo annual neurocognitive assessment and have no existing diagnosis of dementia or neurocognitive impairment at the time of baseline screening. Participants are relatively healthy and cognitively intact (Mini-Mental Status Exam scores: MMSE > 25; Folstein et al., 2001) at time of enrollment. Initial (first visit) exclusion criteria for LABrainS includes: a Geriatric Depression Scale score ≥ 6 (15 item version; Sheikh & Yesavage, 1986), a recent history of cardiovascular, cerebrovascular or neurological (e.g., cerebrovascular disease and/or a traumatic brain injury within the past two years) or untreated health conditions (e.g., hypertension) that might cause neurocognitive impairment. Participants with a history of significant substance abuse or Parkinson's disease are also excluded. All included participants have normal or corrected vision.

LABrainS is primarily conducted at the Pennington Biomedical Research Center's Institute for Dementia Research and Prevention (IDRP) in Baton Rouge, LA. Study procedures are conducted by well trained, certified research assistants. Each year participants undergo informed consent followed by neuropsychological testing in a private testing suite. Participants had their blood drawn for APOE genotyping at the end of their visit after all other procedures had been completed. Oral and written informed consent were obtained from participants at each clinic visit. Pennington Biomedical Center's Institutional Review Board and Ethics Committee approved of the longitudinal study and its data collected for use in research (Appendix B provides a copy of the most recent informed consent form).

The present study limited participants to age 60 and above. 59 participants under the age of 60 (Median = 56.00; range = 40-59; Skew Index = 3.95) were excluded from this study. Participants seen at satellite sites (e.g., nursing homes or doctor's offices) were also excluded. As analyses were interested in predictors of cognitive decline, participants who were from families considered to be at a relatively higher risk for AD were included if they met all other study requirements. Due to a LABrainS protocol change in 2013, only new enrollees were administered the full UDS battery that year. In all, there were a total of 694 participants at Visit One, with a total N of 556 participants who had complete data on the primary variables of interest (with the exception of APOE genotype). Of these 556 individuals, 403 had participated in the APOE genotyping. Data analyses examined for potential attrition biases in those with incomplete datasets (i.e., study dropouts) and maximum likelihood estimates were compared to listwise deletion methods in handling the missing data (for further details on sample characteristics and missing data see the Results section).

Measures

Neuropsychological test battery. The Uniform Data Set (UDS), a neuropsychological test battery established by the National Alzheimer's Coordinating Center (NACC), was utilized for this study. The UDS test battery consists of brief measures of attention, processing speed, executive function, episodic memory, and language that were selected due to their sensitivity to detect neurocognitive change in the elderly (see Weintraub et al., 2009). The UDS specific tests include: a screener measure of global cognitive functioning (MMSE), Wechsler's Memory Scale-Revised (WMS-R) Logical Memory Story-A Immediate and Delayed Recall, WMS-R Digit Span Forward and Backward tests, Category Fluency (Animals and Vegetables), Trails Making Test (TMT): Parts A and B, Wechsler's Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol, and the Boston Naming Test (BNT). In addition to the UDS neuropsychological test battery, the Clock Drawing Test (CDT) 18-point version was administered (see Babins, Slater, Whitehead, & Cherkow, 2008).

Specific test descriptions follow:

1. The MMSE is a widely used brief-screening measure for gross cognitive impairment that tests orientation, immediate and short-term memory recall, attention/concentration, language, and spatial construction. MMSE scores below 25 are believed to be suggestive of a dementia disorder. Given the lack of sensitivity of the MMSE in cognitively intact individuals, this measure only served as an exclusionary measure for participant selection (i.e., MMSE scores > 25 were required for participation).
2. The WMS-R Logical Memory test assesses immediate and delayed episodic memory (Wechsler, 1987). The UDS version of the WMS-R Logical Memory consists of one

short vignette ("Story A") that is read once to participants. Participants are then asked to recall the story twice: immediately after it is read, and following a twenty-minute delay with a brief story prompt.

3. WMS-R Digit Span tests are widely used as measure of working memory and are also believed to involve attention processes (Wechsler, 1987). The Digit Span Forward test requires that participants repeat back a string of numbers in increasing length, while the Digit Span Backward test requires one to mentally manipulate the numbers' order through having participants repeat the string of numbers read to them in backwards order. Participants receive one point for each string of numbers correctly repeated on these tests. Digit span tests are discontinued if the participant makes two consecutive errors at the same digit string length.
4. Category Fluency tests are widely used measures of language fluency and semantic memory, however they also require intact retrieval ability and executive function (Goodglass & Kaplan, 1983). For the Category Fluency test, participants are given one minute to name as many words as they can for the two respectively given categories of "animals" and "vegetables". They receive one point for each newly named item for each category test.
5. The TMT (Trails A and B) is a complex visual scanning timed-task that assesses aspects of attention, processing speed and executive function (Reitan & Wolfson, 1993). The TMT is highly sensitive to cognitive decline and elderly persons who perform poorly on the TMT tend to also demonstrate significant deficits in their daily living skills (Lezak et al., 2004). A three (Trail A) and five (Trail B) minute time limit is imposed during the

TMT. A practice trial is always administered prior to each trail. For Trail A, participant are presented with a scattered array of 25 sequential numbers that appear inside small circles and are instructed to connect the numbers in ascending numerical sequence (e.g., 1, 2, 3, etc.). For Trail B, participants are shown a form with an array of numbers and letters in circles and are instructed to connect the number to letters in a progressive order (e.g., 1-A-2-B-3-C, etc.). While Trail B is technically similar to Trail A, it involves greater cognitive control as the task requires the ability to shift response sets.

6. In relatively healthy adults, the WAIS-R Digit Symbol (Weschler, 1981) test is largely a test of psychomotor speed that also requires sustained attention, processing speed, and visuomotor coordination (Lezak et al., 2004). Notably, it has proven to be one of the most sensitive (albeit non-specific) measures for brain damage; and has proven to be a good predictor of dementia progression (Lezak et al., 2004). The UDS version of the WAIS-R Digit Symbol test has slightly enlarged symbols meant for older adult population as compared to the standard WAIS-R test. For this task, participants are shown a form that has many rows with randomized numbers inside the boxes ("numbered boxes"), below these numbered box rows there are rows with blank boxes. At the very top of the page, there is a row with numbered boxes in sequential order (1-9) with a row of distinct meaningless symbols in boxes below each of the numbers. For the Digit Symbol test, participants are informed that each number at the top of the page has its own unique mark below it. They are then shown a line of boxes with marks with empty boxes below it and are instructed to put marks that correspond to the number above in the empty boxes during a practice trial. Following practice, they are instructed to notice the empty rows of

boxes with the numbers above them and that they are to put marks that correspond to the number above in the empty boxes. They are given 90 seconds to fill in as many boxes as they can without skipping any of the boxes.

7. The BNT is a confrontational naming task that serves as a measure of language disturbance and word-retrieval deficits (Kaplan, Goodglass, & Weintraub, 1983). The BNT requires participants to verbally name line-drawn objects (e.g., a bed or giraffe). The UDS version is reduced to 30 odd-numbered items from the BNT.
8. The CDT is an untimed test of visuospatial constructional ability that also involves intact auditory comprehension (responding to commands) and components of spatial planning and working memory (see Price et al., 2011). For this task, participants are required to draw a clock according to the following provided verbal instructions, "I want you to draw a face of a clock showing all the numbers. I want you to set the clocks hands to ten after eleven."

Demographic and cognitive reserve predictor variables. Baseline information collected regarding participants' demographic (age, sex, race and education level) and estimated intelligence served as time invariant predictor variables. Demographic information was collected via clinical interview and the North American Adult Reading Test (NAART; Blair & Spreen, 1989) was administered as an estimate of intelligence. The NAART is a widely accepted measure for estimating premorbid intelligence levels of English-speaking that has demonstrated acceptable convergence with other gold-star measures of intelligence (WAIS-Fourth Edition) and has been used to estimate intellectual functioning within patients with dementia (Uttl, 2002). It comprises 61 words assembled in four columns in order of increasing difficulty that participants

were requested to read aloud. NAART words are intentionally relatively short in order to avoid over complexity, and are "irregular" in their pronunciation rules to minimize phonemic decoding effects (Nelson & Wilson, 1991). Each incorrectly read word counts as an error. Estimated Full Scale IQ (FS-IQ) standardized scores are based on the number of correctly read words and adjusted age and education norms.

Health-related risk predictor variables. The UDS Health History clinician administered interview form was used to collect information on the participants' cardiovascular disease (CVD), cerebrovascular disease (CBD), neurological (e.g., seizures and/or traumatic brain injury), biological indicators of health (hypertension, hypercholesterolemia, diabetes, thyroid disease, B12 deficiency), and psychological history at baseline. Baseline information regarding participants' UDS health history formed the time invariant health-related risk predictor variables. Health history variables on this measure are categorized as absent, active (defined as within the last two years), or remote/inactive (defined as greater than two years). Participants with untreated health conditions are excluded from the study. Remote and active health variables were collapsed given no significant between-group differences on these outcome variables. Factor analyses were used for data reduction purposes before proceeding to the primary analyses. Three health-related risk factors emerged from the UDS Health History data: (1) CVD factor (history of CVD loaded with biological indicators of hypertension, hypercholesterolemia, and diabetes), (2) Cerebrovascular factor (history of CBD loaded with seizures and/or traumatic brain injury), and (3) Depression/Endocrine factor (history of a psychiatric disorder loaded with thyroid disease and B12 deficiency).

Deoxyribonucleic acid (DNA) extraction and genotyping procedure. The dichotomized variable of APOE-E4 carrier status served as a predictor within the Multivariate LGC model(s). Genomic deoxyribonucleic acid (DNA) was extracted from blood samples by a phlebotomist at Pennington Biomedical Research Center. APOE genotyping was performed by polymerase chain reaction (PCR) methodology (using recommended procedures described in Mufson et al., 2000). As expected, there were insufficient cases to examine homozygous APOE-e4 genotypes. Consistent with the relative frequencies of the APOE genotypes within the general population, the frequencies of homozygous APOE-e4 (n = 4) and APOE-e2 (n = 4) genotypes were rare (respective frequencies within sample equal 0.7%). Thus, as proposed, participants were dichotomized into two genotype groups: APOE-e4 carriers (defined as individuals with at least one copy of the APOE-E4 allele: e4/e4; e4/e3; e4/e2; N = 96) or non-carriers (individuals without an APOE-e4 allele (e2/e2, e2/e3, e3/e3; N = 302).

Analyses

Data analyses were conducted over a multitude of steps. Prior to conducting the study's primary analyses via LGC modeling, preliminary analyses examined variable distributions and sample characteristics. Next, potential confounds regarding attrition bias, demographic factors, and APOE-e4 carrier status were each systematically assessed. Subsequently, the relationship between baseline neurocognitive functioning and rates of change of change in Memory, Executive Attention/Processing Speed, Language and Working Memory factors were examined. Finally, the degree to which the individual differences in risk factors explained heterogeneity in neurocognitive function within the present sample was assessed. Specific descriptions for analyses undertaken are as follows.

Preliminary analyses. Preliminary analyses examined variable distributions and sample characteristics. Recommended guidelines for large samples (N > 200; Field, 2009 and Kline, 2011) were followed in testing whether assumptions of normality were met for each neurocognitive variable. Data distributions for continuous variables were visually inspected, and index values for skewness and kurtosis were assessed (kurtosis defined as > 10 and skew defined as > 3). To allow for ease of comparison, reaction time (RT) scores on the TMT were reflected using the formula [(X – Maximum Test Score +1) * -1] so that higher RT scores reflect lower values. Neuropsychological test scores were then converted into z-scores in order to assess for outliers within the dataset. Outlier neuropsychological test scores were defined based as per Field (2009; i.e., absolute value *z*s ± 3.29). As removal of outliers may remove true variance that introduces bias and retaining extreme outliers can introduce Heywood cases (Kline, 2011), Winsorized means (a more robust estimator of the population mean) were used for exceptionally extreme z-score values (i.e., extreme values of $z \pm 3.29$ were replaced with the next closest observed value in the dataset). Once extreme z-scores were replaced, consistent with previous LGC modeling research methods (Johnson et al., 2012), neuropsychological test scores were converted to *t*-scores using the mean and standard deviation from the initial visit [*t*-score = 10 (Raw Test Score$_{individual}$ – Mean$_{Time\ 1}$/Standard Deviation$_{Time\ 1}$) + 50)]. This conversion allows for comparison of the parameters of interest and retains any longitudinal change over time. As this study was interested in the degree to which demographic factors contribute to the variance within the LGC model, neurocognitive test scores were standardized relative to the mean of the entire sample, rather than adjusting for age, education, etc.; thereby, allowing these demographic factors to be assessed as independent predictors within the LGC model(s).

Potential confounds regarding attrition bias, demographic factors, and genotype were assessed via One-Way ANOVAs or chi-square tests prior to the SEM analyses. When Levene's statistic indicated that assumptions of homogeneity were not met, Welch's *F* test was used to adjust degrees of freedom. Chi-square tests of independence examined for differences in the categorical variables (sex, race and health factors). Two-tailed tests were used for all *p*-values. Given evidence of non-random attrition biases that could potentially affect the study outcomes, analyses were performed to investigate for differences in enrollees and dropouts on primary variables of interest and overall differences in model fit (further details are presented within the Result's section).

Latent growth curve (LGC) modeling. LGC modeling offers a dynamic and valid way of capturing linear changes in cognition over time (see Duncan et al., 2013; Li et al., 2000; McArdle & Anderson, 1990). LGC models are typically analyzed in two steps (Kline, 2011). The first level attempts to explain the covariances and variances of the repeated measure variables (in this case, the latent neurocognitive variables). This first level provides two latent growth parameters: intercept and slope (Byrne, 2011). For each respective neurocognitive domain within this study, the intercept parameter represents an individual's level at baseline, while the slope parameter represents the rate of change over the three-year period (from visit one through visit three) within this domain. LGC model methodology also allows for the examination of variables (e.g., APOE genotype) that might explain heterogeneity within these individual growth trajectories. The prediction model(s) is also considered a multiple indicators and multiple causes (MIMIC) model because the latent factors have both effect and cause indicators (Kline, 2011). Another important advantage to LGC is that maximum likelihood methods allow missing data,

which is assumed to be missing completely at random (MCAR) or missing at random (MAR; i.e., missing data does not depend on the measured variables of interest), to be modeled based on available information to estimate values for the exogenous variables, rather than relying on more biased methods for handling missing data (e.g., pairwise deletion or mean imputation procedures; Allison, 2003; Arbuckle, 2013). A critical assumption in conducting SEM is that multivariate data are normally distributed (Byrne, 2010). Data that are multivariate kurtotic are particularly problematic to SEM analysis. Thus, prior to any analysis descriptive statistics were computed for all variables to determine that assumptions of normality were met. Multivariate normality was measured through the use of Mardia's normalized estimate (Byrne, 2010). Mardia's coefficient was used to assess whether assumptions of multivariate normality were met.

Three fit indices were used to evaluate the goodness of a model's fit to the data: Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI), and Akaike's Information Criterion (AIC). Each of these indices describes the model fit from a different perspective, and they are amongst the most widely reported within the SEM literature (Kline, 2011). The CFI index is an incremental measure that represents the improvement in fit between the assumed model and the baseline model of uncorrelatedness (i.e., not varying together) between the observed variables, the RMSEA is an absolute measure of fit, and the AIC is a comparative measure of model fit. Recommended cut-off values for model fit vary from .90 to above (with close to .95 or above being more optimal) for CFI, while RMSEA values close to .06 or less serve as indicators that the model(s) adequately fitted the data (Hu & Bentler, 1999). AIC was used for comparing fit of competing models, with lower AIC values indicating a better model fit (Duncan et al., 2006). Chi-square is reported but not used as measure of fitness, given

its over sensitivity to large sample sizes (Kline, 2011). Data analyses investigated for differences in parameter and goodness-of-fit estimates using non-corrected data as compared to bootstrap analyses. Parameter estimates and fit indices remained consistent across these different procedures.

Aim 1 analyses. In order to test Aim 1's hypotheses, a multivariate[2] LGC model was used to fit the growth curve to the respective neurocognitive domain factor scores (also referred to as "curve-of-factors" latent growth model; see Duncan et al., 2006). To allow us to interpret the latent variables initial status values, parameters from each respective neurocognitive latent variable's intercept to its observed indicator values were held constant (set to unity). Parameters from each respective neurocognitive latent variable's slope were connected to their observed indicator measures and fixed at values reflecting each Time Point (Year 1 = 0, Year 2 = 1, Year 3 = 2). The latent factors' covariances were allowed to covary over time. Residuals of each indicator were freely estimated at each time point, and correlations amongst the corresponding residuals' indicators were estimated. A scaling reference variable set to unity was used for each of the first common order factors, and consistent with strict temporal invariance the remaining common factor loadings for the non-referenced indicator measures to the respective latent constructs were constrained to be equal across time points. Model specification was theory driven. Specification searches were used to improve model when the original hypothesized model did not adequately fit the data, as indicated by fit indices. Once the measurement model was fit to the data, the structural model analyzed the associations among the neurocognitive variables.

[2] Analyses used are also considered a parallel growth process as each neurocognitive process growth estimate is being measured separately

Two models were used to test whether a high order global neurocognitive latent factor could better explain the data. In the interest of parsimony, a factor-of-curves LGM was used to determine whether a higher order global neurocognitive latent factor could better explain the data (See Duncan et al., 2006). This model assumed that the factor covariances amongst the first-order factors (i.e., each respective neurocognitive domain) are better explained by a higher order factor's intercept and slope. Model procedures required that the covariances amongst the first-order factors (Memory, Executive Attention/Processing Speed, Language and Working Memory) be restricted to be equal over time for each neurocognitive domain (through utilization of a reference variable and constraining remaining factor loadings for each respective factor between the first- and second order factors to be equal over time). The second model compared the posited four latent factor curve-of-factors model fit to a single neurocognitive latent factor curve-of-factors model fit. To judge the different models' fit, each model's fit indicators (parameter estimates, CFI, and RMSEA) were inspected and their AIC values were compared.

Aim 2 analyses. To test Aim 2's hypotheses, separate analyses were conducted to examine the respective influence of relevant predictor variables on each of the neurocognitive domains. Predictor variables (demographic, cognitive reserve, health related risk factors, and genotype) were separately entered into the model in phases in order to detect the degree to which these variables respectively influenced neurocognitive functioning. Predictors were initially specified to have direct effects on both latent growth factors (i.e., the respective intercepts and slopes) for each neurocognitive domain. Within the predictor model(s), latent factor residuals ("disturbances") serve as proxies for the Intercept and Slope factors each of the latent neurocognitive variables as these factors now represent endogenous factors; covariance between

these disturbances are used to reflect the assumption that the latent growth factors share common causes other than the respective predictors variables (Kline, 2011).

Once provided with a well-fitted model of predictors of heterogeneity in neurocognitive functioning, two final models tested the proposed etiological model of MCI. Two separate sets of analyses were necessary to investigate the effect of race and genetics in relation to the other etiological factors for MCI. The first model examined race in conjunction with sex, age, and the cognitive reserve variables, while the second model examined APOE-e4 carrier status in conjunction with sex, age, and the cognitive reserve variables. In these respective models of race and genetic risk, sex, age, race and genetic risk were specified to have direct effects on the health-related risk factors, while Neurocardiovascular and Depression/Endocrine risk factors were specified to have direct effects on both latent growth factors (i.e., the respective intercepts and slopes) for each neurocognitive domain; the cognitive reserve variables of education and intelligence remained independent predictors of neurocognitive functioning within this model.

Power analyses. In order to conduct a LGC model, data must be obtained from each individual on three or more occasions. The present study utilized three-years of consecutively obtained data. Second, in order to have sufficient power for LGC models, it is recommended that there is a minimum sample size of not less than 200 persons at each time point (Byrne, 2010; Kline, 2011), as anticipated this study far exceeded this minimal expectation. Third, an additional guideline for obtaining sufficient power in SEM is that that there be a minimum ratio of cases (*N = 10 minimum with N = 20* being ideal) to the number of model parameters per each estimated parameter (i.e., the *N:q* ratio; Kline, 2011). For the present study, the degrees of freedom for all distinct parameters to be estimated, reached a highly desirable ratio that resulted

in all models having positive degrees of freedom to allow for respective rejection of each model (i.e., each specified model met the criteria of over identification). Details regarding the degrees of freedom for the estimated model(s) are provided within the results.

Preliminary analyses for LGC models. AMOS (Version 22) was used to investigate the study's aims via several LGC model(s). Neuropsychological test data scores collected from participants at Years 1, 2, and 3 were used to form the respective latent neurocognitive variables. Research suggests that age adjustment for neuropsychological test performance removes the variance that is associated with age-related changes in brain structure as evidenced by weaker relationships of neuropsychological test scores with MRI measured brain volumes; and, findings have been mixed regarding the influence of education-adjusted means on brain-test behavior relationships (Mungas, Reed, Farias, & DeCarli 2009). Thus, the present study chose to respectively assess demographic factors influence on neurocognition, rather than using norm based approaches to "control" for these factors. Binary variables were created for the predictor variables of sex (Male = 1 and Female = 2), APOE-E4 Carrier status (Non-carrier = 1 and Carrier = 2), and race (Caucasian/Latino = 1; African American = 2). Age was centered at its grand mean to aid in its interpretation. Prior to conducting Aim 2's analyses, descriptive statistics were generated for the relevant study variables. When applicable to model(s), one-way ANOVAs or chi-square tests followed up on group differences in the predictor variables and are reported within the results.

Mardia's coefficient indicated that assumptions of multivariate normality were violated, $p < .001$. Given that transformations alone are not very effective at normalizing multivariate distributions and that deleting outliers until the multivariate kurtosis index reaches an acceptable

level can be an effective method of handling multivariate non-normality (Gao, Mokhtarian, & Johnston, 2008), Mahalanobis Distance[3] (D^2) investigated for cases that significantly contributed to the multivariate non-normality. Three participants who were identified as extreme outliers (i.e., D^2 distances were greater than three Standard Deviations from centroid) were removed from the primary analyses. Subsequent examination of Mardia's coefficient indicated that removal of these participants substantially reduced but did not entirely eliminate multivariate non-normality. Therefore, bootstrap analyses were used to assess bias corrected confidence intervals. Bootstrap analyses were successfully performed on data and 500 usable bootstrap samples were obtained (0 bootstrap samples were unused because of a singular covariance matrix or because a solution was not found). Parameter estimates for these analyses remained significant.

Structural model. Building on prior research, four latent neurocognitive variables of Memory, Executive Attention/Processing Speed, Working Memory and Language were formed for each respective time point. The Memory factor was comprised of WMS-R's Logical Memory immediate and the delayed subtest scores. The Executive Attention/Processing Speed factor was formed from the Digit Symbol Subtest and the Trails Making Test: Parts A and B, this measure was posited to reflect aspects of executive function, attention and processing speed. The Working Memory factor was compromised of the Digit Span Forward and Backward tests. Lastly, the Language factor was formed from the BNT and Category Fluency (Animals and Vegetables) test scores. All indicator variables with the exception of CDT demonstrated acceptable to excellent factor loadings (respective factor loadings ranged between .32 and .82 in standardized units) on each of the respective neurocognitive variables. Notably, a truncated score

[3] D^2; reflects in standardized units the squared distance from the centroid

range for CDT for each year suggested the presence of a ceiling effect for this measure. When allowed to load on the Working Memory factor, examination of the squared multiple correlation for the CDT (range: .15-.17) suggested that this measure had unacceptable reliability in its ability to measure this latent variable; similar poor reliability (range: .05-.18) was found in its ability to measure each of the other latent neurocognitive variables, and thus the CDT was discarded from any further analyses.

CHAPTER 4: RESULTS

Attrition Analyses and Sample Characteristics

To determine whether there were potential predictors of attrition in those that dropped out of the study, One-Way ANOVAs and chi-square tests of independence examined for group differences in demographic factors (e.g., education and age), health related risk factors, estimated intelligence and neurocognitive test performance in those with 3-years of follow-up visits as compared to study dropouts. Results revealed significant between group differences in the predictor variables and in the neurocognitive test scores of study dropouts as compared to those with three consecutive visits from Year 1 to Year 3.

Missing Data. Analyses first examined patterns of missing values within the database in regards to participant attrition in relation to the neurocognitive test scores. There was a total of 118 participants who either formally or informally dropped out (through non-response) from the study at Year 2 (n = 64) and Year 3 (n = 54). 694[4] individuals invited to enroll between 2009 (n = 331) and 2010 (n = 363) were eligible for the present study. Of these 694 individuals enrolled at the IDRP, 72 formally withdrew from the study for a variety of reasons (e.g., transportation, not willing to participate, moving, caregiver status, etc.), 36 participants inactivity is not accounted for due to either inability to respond or refusal to respond, 20 participants were not administered the full UDS battery (i.e., only Digit Symbol Coding was administered), 7 died, and 3 converted to presumed AD. Three participants with physical impairments were missing data on neuropsychological tests that required intact visual or motor functioning (i.e., the TMT-A and B, CDT, DC). Two visually impaired participants (mentioned previously) were also missing BNT

[4] LABrainS has an initial inclusion rate of 82.9%

scores. Listwise deletion was used to remove these three participants from the primary set of LGC analyses. This decision was based on research that suggests that visual and/or motor impairments may precede decline in other cognitive processes (Albers et al., 2015), thus data could not be presumed to be missing at random as these dependent variables are dependent on intact vision and motor processes. This resulted in 553 participants with complete non-missing values in the dataset for Years 1 through 3. Of these 553 participants, 398 participants had completed APOE genotype analyses.

Sex was not related to the likelihood of dropping out from the study [X^2 (1, N = 694) = .979, $p > .10$] and enrolled participants ("enrollees") and "dropouts" did not significantly differ in age, $F(2, 693) = 0.618$, $p = .539$. There was a greater likelihood of attrition in African Americans ($n = 14$; expected count = 7) than Caucasians ($n = 120$; expected count = 127), X^2 (2, N = 134) = 9.98, $p = .019$. Enrollees on average obtained 16.18 years of education as compared to dropouts who had on average 14.86 years of education, $F(2, 693) = 15.01$, $p < .001$. Enrollees ($M = 1.15$, $SD = 1.02$) and dropouts ($M = 1.53$, $SD = 1.32$) also significantly differed in the number of cardiovascular risk factors that were present, Welch's $F(1, 147.13) = 8.78$, $p = .04$; no other significant differences in health related factors were found, all ps > .10.

Analyses next examined for potential differences in the neuropsychological characteristics in study dropouts as compared to those consecutively enrolled for three years. Enrollees had significantly higher estimated intelligence and baseline neurocognitive test scores than dropouts (See Table 1). These effects remained largely the same in those who completed two- but not three years of visits. In sum, the findings indicated that the attrition group was

significantly different than the enrolled participants on several of the predictor and dependent variables.

Table 1.
Neuropsychological Test Scores for Years 1 and 2 by Enrollment Status at Year 3

Year 1 Test Scores M (SD)	**Dropouts** (*n* = 118)	**Enrollees** (*n* = 576)	***F* =**
National Adult Reading Test †	105.08 (9.06)	109.17 (7.64)	186.70**
Mini Mental State Exam †	28.42 (1.52)	29.01 (1.19)	16.05**
Logical Memory-I†	12.36 (4.00)	13.04 (3.25)	2.98*
Logical Memory-II†	10.97 (4.11)	11.89 (3.47)	5.12*
Digit Span Forward Total	8.42 (1.84)	9.17 (1.90)	15.00**
Digit Span Backward Total	6.15 (2.15)	7.11 (2.11)	20.16**
Category Fluency - Animals	18.65 (5.28)	21.29 (5.53)	22.59**
Category Fluency Vegetables	13.96 (4.24)	15.40 (4.25)	11.37**
Trails Making Test – Trail A	38.34 (14.04)	34.07 (11.98)	11.60**
Trails Making Test – Trail B†	107.75 (61.70)	83.99 (37.38)	16.14**
Digit symbol	43.23 (9.96)	48.13 (10.60)	21.06**
Boston Naming Test†	26.54 (3.25)	27.57 (2.45)	10.52**
Clock Drawing Test†	16.11 (2.01)	16.57 (1.57)	5.12**
Year 2 Test Scores M (SD)	**Dropouts** (*n* = 54)	**Enrollees** (*n* = 576)	***F* =**
Mini Mental State Exam †	28.63 (1.67)	28.93 (1.60)	1.64
Logical Memory-I	12.81 (4.09)	14.03 (3.32)	4.48*
Logical Memory-II	11.69 (4.45)	13.21 (3.53)	8.79**
Digit Span Forward Total	8.57 (1.99)	9.13 (1.84)	4.41*
Digit Span Backward Total	6.52 (2.16)	6.96 (2.21)	1.99
Category Fluency - Animals	19.87 (6.14)	21.26 (5.48)	3.09†
Category Fluency Vegetables	14.09 (4.54)	15.56 (4.52)	5.19*
Trails Making Test – Trail A†	38.63 (14.15)	33.60 (12.38)	6.35*
Trails Making Test – Trail B†	101.46 (57.62)	85.13 (40.92)	4.14*
Digit symbol†	43.44 (9.02)	48.51 (10.89)	15.00**
Boston Naming Test†	26.87 (3.27)	27.87 (2.38)	1.23
Clock Drawing Test	16.60 (1.63)	16.84 (1.45)	8.79**

Notes: Mean (*M*); Standard Deviation (*SD*); † denotes that Welch's F test was used due to violations in assumptions of homogeneity between groups. † $p < .10$; * $p < .05$; ** $p < .01$.

Non-normality within the sample distribution was not amenable to transformations in the data set containing missing values for the study dropouts. Importantly, multiple imputations for missing values are not recommended when data is non-normally distributed and replacing missing values via MLE is problematic when the probability of attrition is related to later values on the dependent variables (Allison, 2003). Thus, listwise deletions methods were utilized for cases missing consecutive visits for Years 2 and/or 3. The decision to utilize listwise deletion methods for the primary analyses was based on the significant differences between the enrollees and dropouts on the dependent variables and the significant non-normality within the data set that contained the missing values.

Notwithstanding the aforementioned limitations, for the interested reader, tables with supplementary analyses using MLE estimations for missing values are provided within Appendix C and D. Comparison of parameter estimates between complete and incomplete data sets and their respective fit indices were relatively close to one another. Thereby, further increasing our confidence in the identified latent neurocognitive constructs and their relationships with one another. Regarding the predictor model, MLE estimates were largely similar for the findings regarding age and sex; however, attempts to adjust for estimated intelligence in the model resulted in a non-positive covariance matrix and MLE estimated values regarding the relationship between race differences and neurocognitive functioning were substantially lower within the supplementary analyses. Given multivariate non-normality and group differences on these factors, it was outside the scope of this paper to provide further analyses that might allow for interpretation of the nature of these differences. Future studies intend to investigate the nature of these differences.

Descriptive Statistics for the Study Variables

Sample characteristics. The mean age of the final sample population was 68.62 (*SD* = 6.45) with a total of 553 participants. There were a higher proportion of female participants (67.5% female vs. 32.5% male). The sample was primarily Caucasian participants (94.8%, 4% African American, and 1.2% Latino/a origins). Given the small number of Latino/a participants and no evidence of group differences on any of the variables of interest with Caucasians (all *p*s > .10), Latino/as were collapsed into the Caucasian group. Table 2 presents the descriptive statistics for the raw neurocognitive test scores for the participants who had complete datasets for three consecutive visits by year.

Table 2.
Neuropsychological Test Scores for the Primary Dataset by Year

Neuropsychological Test: *M (SD)*	**Year 1**	**Year 2**	**Year 3**
Mini Mental State Exam †	29.03 (1.17)	28.99 (1.25)	29.10 (1.26)
Logical Memory-I	13.03 (3.27)	14.00 (3.33)	14.09 (3.63)
Logical Memory-II	11.88 (3.48)	13.22 (3.57)	13.48 (3.85)
Digit Span Forward – Total Correct	9.17 (1.89)	9.13 (1.82)	9.10 (1.86)
Digit Span Backward – Total Correct	7.12 (2.10)	6.95 (2.21)	6.89 (2.23)
Category Fluency - Animals	21.22 (5.42)	21.28 (5.51)	21.31 (5.69)
Category Fluency - Vegetables	15.36 (4.24)	15.51 (4.53)	15.71 (4.43)
Trails Making Test – Trail A	34.01 (11.94)	33.69 (12.41)	32.86 (11.61)
Trails Making Test – Trail B	84.00 (37.59)	84.90 (40.24)	83.48 (40.53)
Digit Symbol Coding†	48.10 (10.58)	48.53 (10.92)	49.03 (11.16)
Boston Naming Test†	27.58 (2.42)	27.85 (2.40)	28.07 (2.34)
Clock Drawing Test	16.57 (1.57)	16.84 (1.46)	16.80 (1.62)

Notes: Data presented are raw untransformed scores (values contain significant skew and kurtosis). Mean (*M*); Standard Deviation (*SD*); Lower scores on the TMT Trails A and B indicates better performance.

Sex. On average male participants (M = 69.85, SD = 6.85) were significantly older than females participants (M = 67.99, SD = 6.15), Welch's $F(1, 552) = 10.50$, $p = .001$. Males on average obtained a higher level of education (M = 17.02, SD = 2.35) than females (M = 15.74, SD = 6.15), Welch's $F(1, 552) = 10.50$, $p = .001$. Females as compared to males did not significantly differ in estimated intelligence but generally had higher neurocognitive test scores on measures of Memory, Language and attention/processing speed at each year with the exception of TMT-B, BNT, and Category Fluency "animal" test, all ps < .001.

Race. No significant difference in age by race group was found, $F(1, 552) = .021$, $p = .885$. African American (n = 22) as compared to Caucasian/Latino[5] participants (n = 531) had significantly higher levels of education (M = 17.32, SD = 2.34 vs. M = 16.13, SD = 2.44), $F(1, 552) = 5.02$, $p = .025$. African Americans as compared to Caucasian participants had lower NAART scores (M = 100.36, SD = 6.74 vs. M = 109.52, SD = 7.50) and neurocognitive test scores on all measures at each year with the exception of CDT and Category Fluency tests, all ps < .001. Although African American participants significantly differed on neurocognitive test measures, similar to Caucasian participants all t-scores with the exception of the TMT fell within the average range, ps < .001.

Cognitive Reserve. As noted prior, participants were generally well educated (M = 16.18 years, SD = 2.45) and were of average estimated intelligence (FS-IQ: M = 109.16, SD = 7.68). As expected, education and estimated intelligence were highly correlated with one another even when sex and race were adjusted for in the model, $r = .521$, $p < .001$.

[5] Given the small ratio of Latino/a participants within this group, this group will heretofore be referred to as the Caucasian group for simplicity.

APOE Genotype. This study excluded cases that were missing genetic material from the primary APOE-e4 analyses, as use of MLE estimates for missing genotype values could have potentially resulted in inflated relationships between the APOE-e4 allele with the other study variables. Of the 553 participants, 398 participants had completed APOE genotype analyses (Carriers = 96 and Non-Carriers = 302). Those who were genotyped were significantly younger [M = 68.69, SD = 7.37 vs. M = 69.99, SD = 7.11, Welch's $F(1, 247.33) = 8.56$, $p = .004$] and more likely to be African American than Caucasian [X^2 (1) = 5.48, $p = .019$] than those without genotyping. They also were lower in cardiovascular risk [M = 1.06, SD = 1.02 vs. M = 1.46, SD = 1.00, Welch's $F(1, 285.60) = 13.28$, $p < .001$] and cerebrovascular risk [M = .12, SD = .36 vs. M = .24, SD = .54, Welch's $F(1, 210.16) = 6.11$, $p = .014$] factors.

The likelihood of being an APOE-e4 carrier did not differ between males and females, X^2 (1) = 0.72, $p = .396$. Male APOE-e4 carriers had lower estimated intelligence scores (M = 106.62, SD = 7.37) than non-carriers (M = 110.65, SD = 7.36), $F(1, 130) = 6.95$, $p = .009$; whereas, female APOE-e4 carriers did not differ from non-carriers in estimated intelligence, p = .848. The likelihood of being an APOE-e4 carrier was significantly greater within African American (54.5%) as compared to Caucasian (23.3%) participants, Fisher's Exact Test[6], p = .027; however, the gross number of African American participants with APOE-e4 genotyping (n = 11) as compared to Caucasian participants (n = 387) prohibited examination of race effects in regards to APOE-e4 due to the significant skew and kurtosis of the race variable (SI = 5.76 and KI = 31.21, ps < .001). Thus, separate analyses were conducted to respectively investigate race and APOE-e4 carrier status in relationship to the other predictor variables.

[6] Fisher's exact test was used as it is more accurate than the chi-square statistic when the expected numbers are small.

Aim 1 Results: Investigating within and between neurocognitive domain variance

The following set of analyses aimed to elucidate the interplay between Memory, Executive Attention/Processing Speed, Language and Working Memory functioning in older adults over a three-year period through multivariate parallel process LGC modeling. A series of analyses systematically investigated: (1) individual differences in initial score values at baseline and the rate of change of each respective neurocognitive domain, (2) whether changes in the specific neurocognitive domains vary across participant as a consequence/function of different Memory and/or Executive Attention/Processing Speed intercepts and slopes, and (3) the interplay between neurocognitive process at baseline and rate of changes in the neurocognitive domains in relation to one another from Year 1 to Year 3.

Model fit. Consistent with previous research on the UDS neuropsychological battery, the posited four-factor solution of Memory, Executive Attention/Processing Speed, Language and Working Memory provided an excellent fit for the data. However, contrary to expectations, the CDT was an unreliable predictor of working memory as well as other variables (see Preliminary Analyses for details). Fitting of the curve-of-factor model resulted in an excellent fit of the data once CDT was discarded, (Chi-square (df = 373) = 674.32, $p < .001$; CFI = .978; RMSEA = .037, 90% Confidence Interval = .032-.042). Provided with a well-fitting model, the structural model analyzed the associations among the latent neurocognitive domains.

Within-neurocognitive domain covariance. As expected, older adults demonstrated substantial heterogeneity in their neurocognitive functioning both at baseline and in their annual rate of change. Significant mean levels existed for all intercept parameters (M_{INT}) and almost all slope parameters (M_{Slope} reflects the on average year-to-year linear change). Table 3 presents the

results for the estimated values for each respective neurocognitive domain's intercept and slope. The average score at baseline for Executive Attention/ Processing Speed was higher relative to all other neurocognitive domains. Memory, Language, and Working Memory performance had negligible differences from each other at baseline. As hypothesized, Memory scores on average significantly increased over time, while Executive Attention/Processing Speed performance demonstrated a decrease from Year 1 to Year 3. Interestingly, on average Language functioning demonstrated incremental improvements over time. Estimates for Working Memory M_{Slope} failed to reach significance suggesting that on average there was limited change over time in working memory functioning.

Table 3.
Parameter Estimates for Intercept and Slope Means for Neurocognitive Domains

Variable	Estimate	Standard Error	Critical Ratio	*p*-values
Memory Intercept	50.164	0.419	119.858	< .001
Memory Slope	1.601	0.197	8.147	< .001
EA/PS Intercept	53.406	2.687	19.876	< .001
EA/PS Slope	-.866	0.190	-4.545	< .001
Language Intercept	50.044	0.411	121.803	< .001
Language Slope	1.065	0.147	7.229	< .001
WM Intercept	49.972	0.397	125.937	< .001
WM Slope	-0.161	0.185	-.873	0.261

Notes: Executive Attention/Processing Speed (EA/PS); Working Memory (WM).

Next, the degree to which lower (or higher) initial neurocognitive functioning predicts change over time in each of the respective neurocognitive domains was examined. Table 4 presents the descriptive statistics for each of the respective within-neurocognitive domain covariance estimates. As expected, the estimated within-domain covariance between Memory's

intercept and slope was significant; however, contrary to assumptions, the negative value indicates that participants' whose Memory scores were highest as compared to those with lower scores at baseline demonstrated a slower linear growth rate in Memory over time. Furthermore, the hypothesis that individuals with initially lower Executive Attention/Processing Speed scores as compared to higher scores would display greater decrements in Executive Attention/Processing Speed functioning over time was not supported. Similarly, the hypothesis that individuals with initially lower Language as compared to higher Language scores would display greater decrements in Language functions over time was not supported. Lastly, exploratory analysis found that the estimated within-domain covariance between Working Memory's intercept and slope factor means was also non-significant. These results indicate that those who started with lower as compared to higher scores on each of these respective factors, with the exception of Memory, did not differ in their annual rate of change over time.

Table 4.
Parameter Estimates for Neurocognitive Functioning at Baseline in Relation to Within-Neurocognitive Change Over Time

Within-Domain Covariance	Estimate	Standard Error	Critical Ratio	*p*-values
Memory Intercept <--> Memory Slope	-8.253	1.527	-5.405	< .001
EA/PS Intercept <--> EA/PS Slope	-0.138	0.642	-0.215	0.830
Language Intercept <--> Language Slope	-0.837	0.680	-1.231	0.218
WM Intercept <--> WM Slope	2.031	1.444	1.407	0.160

Notes: Executive Attention/Processing Speed (EA/PS); Working Memory (WM).

Neurocognitive domains at baseline. Examination of the between-neurocognitive domains associations at baseline supported the hypothesis that older adults who are initially higher functioning in one neurocognitive domain are also on average higher in the other neurocognitive domains, while those who are lower functioning in one neurocognitive domain generally have worse overall neurocognitive performance at baseline. Prior to examining the between-neurocognitive domain covariances, the three non-statistically significant within-domain covariances for Executive Attention/Processing Speed, Language, and Working Memory were deleted from the model. Improvement to fit indices upon deletion of these factors was inappreciable (Change from AIC = 901.35 to AIC = 898.82). The between-domain covariance estimates for each of the respective neurocognitive domains intercepts in relation to one another were significant as predicted (See Table 5). Specifically, individuals with lower Memory, Language, Executive Attention/Processing Speed, and Working Memory test scores concomitantly had lower scores on each of the other neurocognitive latent variables.

Table 5.
Parameter Estimates for Between-Neurocognitive Domains Functioning at Baseline

Variables	Estimate	Standard Error	Critical Ratio	*p*-values
Memory Intercept <--> Language Intercept	27.287	3.161	8.632	< .001
Memory Intercept <--> EA/PS Intercept	28.576	3.627	7.878	< .001
Memory Intercept <--> WM Intercept	14.155	3.238	4.371	< .001
EA/PS Intercept <--> Language Intercept	28.418	3.135	9.066	< .001
EA/PS Intercept <--> WM Intercept	23.809	3.220	7.395	< .001
WM Intercept <--> Language Intercept	14.625	2.454	5.959	< .001

Notes: Executive Attention/Processing Speed (EA/PS); Working Memory (WM).

Between-neurocognitive domains intercept and slope covariances. Analyses next investigated the degree to which baseline Memory and Executive Attention/Processing Speed functioning respectively predicted changes in the other neurocognitive processes (Table 6 presents the descriptive statistics). Consistent with the study's hypothesis that initial Executive Attention/Processing Speed scores would predict rates of changes in other neurocognitive processes over time, those with lower initial as compared to higher Executive Attention/Processing Speed scores demonstrated slower rates of increase in Memory scores from Year 1 to Year 3 (as indicated by the significant covariance between Executive Attention/Processing Speed M_{INT} and Memory M_{Slope}). Similarly, although to a lesser degree, those with lower as compared to higher Memory Scores at baseline demonstrated a slower rate of increase in Language scores over time (Memory M_{INT} and Language M_{Slope}). Notably, no other significant relationships between baseline estimates of Executive Attention/Processing Speed or Memory with rates of linear change in the other neurocognitive processes were found.

Table 6.
Parameter Estimates for Neurocognitive Change in Relation to Memory and Executive Attention/Processing Speed Functioning at Baseline

Variables	Estimate	Standard Error	Critical Ratio	*p*-values
Memory Intercept <--> Language Slope	1.520	0.776	1.960	0.050
Memory Intercept <--> EA/PS Slope	0.837	0.695	1.203	0.229
Memory Intercept <--> WM Slope	0.381	1.190	0.320	0.749
EA/PS Intercept <--> Memory Slope	2.882	1.173	2.456	0.014
EA/PS Intercept <--> Language Slope	0.517	0.646	0.799	0.424
EA/PS Intercept <--> WM Slope	-0.264	1.004	-0.263	0.793

Notes: Executive Attention/Processing Speed (EA/PS); Working Memory (WM).

Between-neurocognitive domains slope covariances. This set of analyses was specifically interested in the degree to which changes in Memory and Executive Attention/Processing Speed associated with changes in other neurocognitive processes over time. Here (see Table 7), we see that on average as Memory scores increased over time, Executive Attention/Processing Speed and Language scores increased in accord. Similarly, the annual rate of change in Executive Attention/Processing Speed positively associated with the rate of change in Language scores. Next, exploratory analysis investigated the remaining relationships between changes in neurocognitive domains in relation to one another from Year 1 to Year 3. The annual rate of change in Working Memory was positively related to rates of change in Language, but not Memory or Executive Attention/Processing Speed changes from Year 1 to Year 3.

Table 7.
Parameter Estimates for Between-Neurocognitive Domains Slope Covariances

Variables	Estimate	Standard Error	Critical Ratio	*P*-values
Memory Slope <--> EA/PS Slope	0.894	0.339	2.637	0.008
Memory Slope <--> Language Slope	1.622	0.361	4.486	< .001
Memory Slope <--> WM Slope	0.656	0.540	1.213	0.225
EA/PS Slope <--> Language Slope	0.451	0.174	2.594	0.009
EA/PS Slope <--> WM Slope	0.296	0.271	1.095	0.274
WM Slope <--> Language Slope	0.801	0.285	2.806	0.005

Notes: Executive Attention/Processing Speed (EA/PS); Working Memory (WM).

Heterogeneity in neurocognitive functioning. Lastly, in examining the variance estimates associated with the intercept and slopes for each neurocognitive domain, all variance estimates were significant (all *p*s < .05). These findings provide strong evidence for interindividual differences, and thus support investigation of factors that might account for this

substantial variability within neurocognitive functioning. See Appendix E for the standardized coefficients and variance estimates for the neuropsychological domains.

Competing models using a global neurocognitive latent variable. While the posited curve-of-factors LGM had an excellent fit, in the interest of parsimony, a factors-of-curves LGM and curve-of-factors LGM utilizing a global neurocognitive latent factor was used to compare the fit of the posited model to these competing models. Fit indices for the competing factors-of-curves (CFI = .833; RMSEA = .099) and the curve-of-factors LGM (CFI = .810; RMSEA = .107) models proved to be inadequate. Moreover, the substantially lower AIC value for the posited model (AIC = 898.83) as compared to the global neurocognitive latent variable's factors-of-curves (AIC = 2747.32) and curve-of-factors (AIC = 3053.25) values suggested that the present study's hypothesized model was superior to both of these competing models. Thus, given confidence in our model fit and provided with evidence of significant interindividual differences, the next set of analyses investigated time-invariant predictors of neurocognitive functioning within the older adult sample.

Aim 2 Results: Relevant predictors of neurocognitive functioning

Based on previous research and theoretical speculation, multiple indicator parallel growth process LGC model(s) relating older adults neurocognitive performance to relevant predictors was conducted to answer the degree to which of Memory, Executive Attention/Processing Speed, Language and Working Memory differ as a function of these factors at baseline and individual differences in growth trajectories over time (Year 1 to Year 3). Demographic factors (sex, race, and age), APOE genotype (APOE-e4 carriers vs. non-carriers), indicators of cognitive reserve (education and FS-IQ scores) and health-related risk factors were respectively entered into the

model in different stages in order to account for their influence on neurocognitive functioning. First, the relationships between demographic factors and each neurocognitive growth trajectory (i.e., the respective M_{int} and M_{slope}) were examined. Next, cognitive reserve predictors followed by APOE genotype, and then health related risk factors were examined with relevant demographic predictors. The last set of analyses examined relevant predictors of heterogeneity in the intercepts and slopes of Memory, Executive Attention/Processing Speed, Language and Working Memory in a comprehensive etiological model. Significant parameter estimates of the respective predictors were retained at each stage of analysis, while non-significant parameters were discarded from subsequent analyses.

Demographic factors as predictor variables. This set of analyses assesses the degree to which age predicts neurocognitive functioning when sex and race are adjusted for in the model. Given strong evidence for their interrelationships within the literature that were also evident in the present sample, the time invariant variables of years of age (centered at its mean), sex, and race were simultaneously investigated within the first predictor model. Table 8 provides the parameter estimates with tests of significance for the demographic predictor model of neurocognitive functioning. Given significant between group differences, sex and age were allowed to covary within the model. This model provided an excellent fit for the data (Chi-square (df = 449) = 949.97, $p < .001$; CFI = .963; RMSEA = .045, 90% Confidence Interval = .041-.049).

Age and sex shared variance (estimate = -.42, SE = 0.13; CR = -3.18, $p < .001$) indicating that women on average were younger than men. When sex and race were adjusted for, greater age at baseline predicted worse initial functioning in each of the respective neurocognitive

domains, as well as older age associated with slower growth rates in Memory and Executive Attention/Processing Speed from Year 1 to Year 3, all *p*s < .10. As anticipated, differential effects for sex and race on neurocognitive functioning were found. In regards to race, Memory, Executive Attention/Processing Speed, Language, and Working Memory functioning on average appeared to be initially lower in African American as compared to Caucasian participants. Race did not predict annual rates of neurocognitive change in the model. Women generally had higher initial scores on Memory and Executive Attention/Processing Speed, while men on average demonstrated better Working Memory functioning at baseline. A trend relationship between better baseline Language and significantly greater incremental growth in Language functioning was found in women as compared to men. Lastly, a trend level sex difference in the average rate of linear increase in Memory scores over time was found. The effect sizes of age, race, and sex on neurocognitive functioning ranged from small to moderate (see Appendix E for standardized estimates).

Table 8.
Demographic Predictors of Neurocognitive Functioning at Baseline and Over Time

Variable Estimates	Age	Race	Sex
Memory Intercept	-0.45**	-6.98**	3.78**
Memory Slope	-0.07**	0.42	.577†
EA/PS Intercept	-0.63**	-8.39**	1.38*
EA/PS Slope	-0.04**	-0.51	-0.24
Language Intercept	-0.37**	-3.037*	1.73†
Language Slope	-0.02	-0.14	1.93*
WM Intercept	-0.25**	-5.32**	-1.90*
WM Slope	0.02	0.32	0.31

Notes: Race (1 = Caucasian, 2 = African American); Sex (1 = Men, 2 = Women); Executive Attention/Processing Speed (EA/PS); Working Memory (WM); † $p < .10$; * $p < .05$; ** $p < .01$.

Cognitive reserve as a predictor variable. A formative indicator approach attempted to form a latent Cognitive Reserve variable. Formative indicators differ in that the measurement variables are posited to "cause" the latent construct, rather than the factors "reflecting" the latent variable. In the case of the continuous variables of education (measured in years) and estimated intelligence (NAART standardized FS-IQ scores), this assumption is tenable, as research has suggested that greater levels of education and intelligence contribute to cognitive reserve. In this respect, cognitive resources may be created or enhanced by the degree of one's education and intelligence. In doing so, the parameter estimates for the posited latent cognitive reserve variable failed to be identified. Similarly, a reflective Cognitive Reserve latent construct (with education and estimated intelligence as indicators) solution proved to be unacceptable even when the error variance for education was constrained to unity (X^2(df = 3) = 4987.614, $p < .001$; NFI = 35.31; CFI = .000; RMSEA = 1.74). Thus, education and estimated intelligence were both entered as unique predictor variables into the model.

Demographic predictor model with cognitive reserve variables on neurocognitive functioning. The analyses next turn towards investigating the effect of education and estimated intelligence on neurocognitive functioning. The significant predictors of age, sex and race were also included in this model. Given evidence of between group differences in education and estimated intelligences, education was set to covary with race and sex, while FS-IQ scores were set to covary with race. Inclusion of the cognitive reserve variables into the previous LGC model resulted in a well-fit model (Chi-square (df = 496) = 1053.489, $p < .001$; CFI = .960 RMSEA = .045, 90% Confidence Interval = .041-.049). As expected, the covariances between predictor variables were all statistically significant, all *p*s < .001. The significant covariances found reflect:

(1) the higher education levels found in African American participants and men when respectively compared to Caucasian participants and women, and (2) the lower estimated FS-IQ scores found in African American as compared to Caucasian participants.

Results from this model indicated that once the predictor variables of education and estimated intelligence were taken into account, the effect of age on neurocognitive functioning remained stable (as indicated by only marginal changes in its estimated M_{int} and M_{slope} values); whereas, changes to some of the previous statistically significant relationships with sex and race on neurocognitive functioning were noted (See Table 9). Specifically, the previously reported effects of race on initial Working Memory and Language functioning were both no longer significant; conversely, the effect of sex on Memory, Executive Attention/Processing Speed, Language, and Working Memory function appeared to be strengthened by their inclusion in the model. As hypothesized, higher levels of estimated intelligence predicted higher initial neurocognitive functioning within each domain at baseline, while greater years of education predicted both higher initial Memory and Language functioning. Education levels were not predictive of initial differences in Executive Attention/Processing Speed or Working Memory performance. Speculative analysis found that higher levels of estimated intelligence predicted modestly steeper rates of increase in Memory and Executive Attention/Processing Speed scores from Year 1 to Year 3. Obtained education was not related to rates of change in neurocognitive functioning over time.

Table 9.
Effects of Demographic and Cognitive Reserve Predictors on Estimates for Neurocognitive Functioning at Baseline and Over Time

Variable Estimates	Age	Race	Sex	Ed	FS-IQ
Memory Intercept	-0.41**	-4.95**	4.48**	0.40*	0.28**
Memory Slope	-0.07**	0.94	.480	-0.11	0.04†
EA/PS Intercept	-0.60**	-6.44**	1.67**	0.14	0.24**
EA/PS Slope	-0.03*	-0.30	-.24	-0.01	0.02†
Language Intercept	-0.35**	-0.91	1.41**	0.31*	0.32**
Language Slope	-0.02	-0.27	0.44*	0.03	-0.01
WM Intercept	-0.20**	-1.57	-1.60*	0.06	0.42**
WM Slope	0.02	0.26	0.36	0.04	0.00

Notes: Education (Ed); Race (1 = Caucasian, 2 = African American); Sex (1 = Men, 2 = Women); Executive Attention/Processing Speed (EA/PS); Working Memory (WM); † $p < .10$; * $p < .05$; ** $p < .01$.

APOE-e4 carrier status as a predictor variable. Analyses next investigated the effect of APOE-e4 allele on neurocognitive functioning. Prior to presenting the results for differences in APOE-e4 carriers as compared to non-carriers, it is important to emphasize that these findings are not directly comparable with the prior analyses as this analysis was conducted on a subset of the sample population. It is possible that those who were genotyped may represent a different sample population and there was also a decrease in power to detect effects due to the reduced sample size. Furthermore, as noted previously, race effects in conjunction with APOE-e4 carrier status was not conducted due to the low number of African American participants within the present sample.

Effects of APOE-e4 on neurocognitive function adjusting for demographic factors and cognitive reserve. Given significant interactions between sex, age, and education with APOE-e4 carrier status within the literature, the next model investigated the degree to which

APOE-e4 predicts neurocognitive functioning when these variables are adjusted for in the model. APOE genotype was initially allowed to covary with age, sex and education; however, given non-significance these paths were removed. Sex was allowed to covary with age and education. Testing of this model resulted in a good fit (X^2 (481, N = 398) = 918.55, $p < .001$; CFI = .953; RMSEA = .048, 90% Confidence Interval = .043-.053). As hypothesized, APOE-e4 carriers' initial Memory functioning was significantly lower than non-carriers at baseline, even when the direct effects of sex, age, and education were included within the model. The hypothesis that sex would have a moderating effect on the relationship between APOE-e4 status and neurocognitive functioning was not supported. Results indicated that APOE-e4 carrier status did not covary with sex, education or age, all *p*s > .10. Overall, the predictors of age, sex, and education relationships with neurocognitive functioning remained largely unchanged from the prior set analyses (see Table 10 for descriptive statistics).

Table 10.
Effects of Genotype with Demographic and Cognitive Reserve Predictors on Neurocognitive Functioning at Baseline and Over Time

Variable Estimates	Age	Sex	Ed	APOE Genotype
Memory Intercept	-0.48**	4.65**	0.46*	-1.98*
Memory Slope	-0.04	0.59	-0.11	-0.06
EA/PS Intercept	-0.65**	1.09	0.14	-0.62
EA/PS Slope	-0.03*	-0.18	-0.01	-0.35
Language Intercept	-0.38**	1.17*	0.47*	-0.50
Language Slope	-0.02	0.36†	0.03	-0.28
WM Intercept	-0.20**	-1.76*	0.06	-1.44
WM Slope	0.02	0.14	0.04	-0.12

Notes: Education (Ed); APOE Genotype (1 = non-carrier 2 = e4 carrier); Sex (1 = Men, 2 = Women); Executive Attention/Processing Speed (EA/PS); Working Memory (WM); † $p < .10$; * $p < .05$; ** $p < .01$.

Lastly, exploratory analyses examined the influence of estimated intelligence within the model, in which its inclusion revealed a trend relationship between FS-IQ and APOE-e4 carriers status (Estimate: -.254, SE = .14, CR = -1.78, p = .075), as well as its inclusion attenuated the significant effect between Memory and APOE-e4 (Estimate: -1.53, SE = .93, CR = -1.64, p = .10). No other notable changes in the model's parameters were noted.

Zygosity. Next, as the APOE-e2 allele has been posited to have protective effects, follow-up analysis excluded e2 allele carriers, to test whether e3/e3 as compared to e3/e4 allele carriers differed in neurocognitive functioning (N = 337). Here, again baseline Memory was on average lower in carriers (Estimate: -1.84, SE = .914, CR = -2.01, p = .044) and a strong trend relationship between steeper growth rates in Executive Attention/Processing Speed in non-carriers as compared to APOE-e4 carriers was revealed (Estimate: -.473, SE = .996, CR = -1.95, p = .052). No other exploratory relationships with APOE-e4 carrier status and neurocognitive functioning were found, all ps > .10. These results potentially indicate the APOE-e2 exerts a protective effect on in Executive Attention/Processing Speed; however, further study is required.

Post-hoc MLE for missing APOE-e4 values. Men and women did not differ in their likelihood of being genotyped; however, those who consented to genotyping were significantly younger than non-genotyped participants (Mean difference in years = 1.90; Cohen's d = .30). Thus, follow-up analysis used MLE methods for replacing missing APOE-e4[7] values to test whether the found effects remained similar in the larger study sample. Consistent with the previous analysis, even when age, sex, and education were adjusted for, significantly worse initial Memory functioning (Estimate: -1.63 SE = .81, CR = -2.02, p = .044) was noted in APOE-

[7] This study excluded subjects who were missing genetic material from the APOE-e4 analyses to avoid potential inflation errors in the phenotypic expressions (Xu & Vogl, 2000).

e4 carriers as compared to non-carriers - thereby, increasing our confidence in these findings. A trend relationship with slower annual growth in Executive Attention/Processing Speed was also found (Estimate: -.395, SE = .22 CR = -1.80, p = .072). The effect of age on the linear rate of change in Memory, Executive Attention/Processing Speed and Language remained statistically significant (all ps <. 10). Similar to the prior analysis, sex differences in initial Working Memory functioning were no longer significant when APOE-e4 carrier status was included in the model, p = .22. Overall, the post-hoc analysis supports the relationship between memory and APOE-e4 carrier status, and potentially indicates that Executive Attention/Processing Speed and Working Memory functioning are also influenced by APOE-e4.

Health related risk factors as predictor variables. The present set of analyses was specifically interested in testing the specific effects of Cardiovascular, Cerebrovascular and Depression/Endocrine risk on Memory, Language, Executive Attention/Processing Speed, and Working Memory functioning once individual differences in race, sex, genetics were adjusted for. Direct effects of each predictor variable were simultaneously modeled in order to account for their respective influence on each of the growth parameters, as well as to account for their potential moderating or suppressor effects on the relationship between health and neurocognitive functioning.

Direct effects of health related risk on neurocognitive functioning. Adjusting for the previously found effects of age, sex, and race on neurocognitive variables, each health related risk factor was to set to directly predict the respective neurocognitive domain's intercept and slope factors. Covariances between the predictor variables were based on previous analyses and all statistically significant parameters remained the same within this model with the exception of

cognitive reserve variables that were entered in a second step. Additionally, age, sex and race were allowed to covary with the health related risk factors. Testing of this model had little change on the model's fit, which remained good (CFI = .962; RMSEA = .042, 90% CI= .038-.046). Table 11 presents the results between the covariance estimates and predictor variables: (1) greater age associated with a higher amount of Cardiovascular and Cerebrovascular risk factors. (2) men were higher in Cardiovascular and Cerebrovascular risk factors than women, (3) women were more likely to have a history of Depression/Endocrine factors, and (4) African American as compared to Caucasian participants had a higher amount of Cardiovascular risk factors.

Table 11.
Covariance Estimates Between the Predictor Variables

Variables (N = 553)	Estimate	S.E.	C.R.	$p \leq$
Cardiovascular <--> Age	0.94	0.28	3.34	0.001
Cardiovascular <--> Race	0.02	0.01	3.05	0.002
Cardiovascular <--> Sex	-0.10	0.02	-5.06	0.001
Cerebrovascular <--> Age	0.23	0.11	2.04	0.041
Cerebrovascular <--> Sex	0.00	0.00	-0.99	0.323
Cerebrovascular <--> Race	-0.03	0.01	-3.54	0.001
Depression/Endocrine <--> Age	-0.06	0.17	-0.33	0.741
Depression/Endocrine <--> Sex	-0.01	0.01	-1.57	0.117
Depression/Endocrine <--> Race	0.08	0.01	6.53	0.001

Notes: Race (Caucasian = 1, African American = 2); Sex (1 = Men, 2 = Women).

In relation to neurocognitive functioning, Cardiovascular and Depression/Endocrine risk factors were both significant predictors of worse Executive Attention/Processing Speed and Language functioning at baseline, and there was trend relationship between greater Cerebrovascular risk factors predicting slower annual growth rates in Working Memory functioning from Year 1 to Year 3 (See Table 12).

Table 12.
Direct Effects of Health Related Risk on Neurocognitive Functioning Adjusting for Age, Sex, and Race

Variables	Cardiovascular	Cerebrovascular	Depression/Endocrine
Memory Intercept	-0.23	0.68	-0.59
Memory Slope	-0.04	-0.47	0.13
EA/PS Intercept	-0.68*	-0.94	-1.35**
EA/PS Slope	0.02	-0.03	-0.09
Language Intercept	-0.45†	-0.56	-1.22**
Language Slope	-0.07	-0.28	0.06
WM Intercept	-0.25	0.43	-0.67
WM Slope	-0.23	-0.64†	-0.08

Notes: Executive Attention/Processing Speed (EA/PS); Working Memory (WM).
† $p < .10$; * $p < .05$; ** $p < .01$.

Lastly, the significant paths for the respective cognitive reserve variables were entered into the model. Notably, the inclusion of education and estimated intelligence significantly attenuated Cardiovascular risk's effect on Language functioning (estimate = -.19, SE = 0.25; CR = -0.76, $p = .448$) at baseline. The relationship between Depression/Endocrine risk factors with worse initial Executive Attention/Processing Speed and Language functioning remained significant, and there were no notable changes in the relationship between Working Memory and Cerebrovascular risk with inclusion of the cognitive reserve variables.

Direct effects of health related risk on neurocognitive functioning while adjusting for age, sex, and APOE-e4 carrier status. The next set of analyses examined health-related risk factors effect on neurocognition in conjunction with genetic risk. All parameters for the model remained the same as described previously with the exception of race as a predictor being removed and APOE-e4 carrier status as a predictor of health related risk factors was added to the model. Given that race was a significant predictor within the previous models, groups were

stratified into a Caucasian and collapsed race groups in order to examine whether there were differences in the parameter estimates for these two groups. Results indicated that these two models' fit and parameters estimates obtained were largely similar (AIC Change was negligible = 1268.78 vs. 1240.89) and both were considerably better than the Independence Model (AIC = 9780.53). Thus, the reported analyses used the collapsed race group. Testing of this model had resulted in little change to the model's fit, which remained good (CFI = .958; RMSEA = .043, 90% Confidence Interval = .039-.048).

Within this model (see Table 13), APOE-e4 carrier status associated with Depression/Endocrine risk, but not as hypothesized Cardiovascular or Cerebrovascular risk. The independent covariance estimates between age with Cardiovascular and Cerebrovascular risk were not significant within this set of analyses; however, this may potentially reflect individual differences in the characteristics of those genotyped from those not genotyped. Similar to previous analyses, sex remained a significant predictor of Cardiovascular and Depression/Endocrine risk factors within this model; such that, men had a greater amount of Cardiovascular risk factors, while women on average had a greater amount of Depression/Endocrine health risk factors. Cardiovascular risk significantly associated with worse baseline Executive Attention/Processing speed. Depression/Endocrine risk significantly associated with worse language functioning and had a trend relationship worse baseline Executive Attention/Processing speed (See Appendix F for the statistically significant parameter estimates).

Table 13.
Covariance Estimates Between the Predictor Variables with APOE-e4

Variables ($N = 398$)	Estimate	S.E.	C.R.	$p \leq$
Cardiovascular <--> APOE-e4	0.02	0.02	1.11	0.269
Cardiovascular <--> Age	0.46	0.31	1.47	0.142
Cardiovascular <--> Sex	-0.10	0.02	-4.16	0.001
Cerebrovascular <--> APOE-e4	-0.01	0.01	-1.02	0.307
Cerebrovascular <--> Age	0.13	0.11	1.20	0.231
Cerebrovascular <--> Sex	-0.01	0.01	-1.12	0.265
Depression/Endocrine <--> APOE-e4	0.03	0.01	2.03	0.042
Depression/Endocrine <--> Age	0.03	0.19	0.15	0.883
Depression/Endocrine <--> Sex	0.09	0.02	6.26	0.001
Age <--> Sex	-0.37	0.14	-2.53	0.012

Notes: APOE-e4 (1 = Non-carrier, 2 = carrier); Sex (1 = Men, 2 = Women); Executive Attention/Processing Speed (EA/PS); Working Memory (WM).

Final Etiological Model of Risk of Cognitive Decline

Provided with a well-fitted model of predictors of heterogeneity in neurocognitive functioning, a modified version of Ritchie's (2004) hypothesized etiological model of MCI was conducted. In this model, demographic factors and genetic risk are presumed to be relevant factors that influence health related risk factors, which in turn impact neurocognitive functioning. Furthermore, within this model, education and intelligence are posited to have direct effects upon neurocognitive functioning. As depression and vascular risk factors have been shown to make independent contributions to MCI, the present study was specifically interested in testing two paths of risk for cognitive decline: Neurocardiovascular (combined cardio- and cerebrovascular risk factors) and Depression/Endocrine risk.

Two separate sets of analyses were necessary in order to investigate the effect of race and genetics in relation to the other etiological factors for MCI. Model 1 examined race in conjunction with sex, age, and the cognitive reserve variables, while Model 2 examined APOE-e4 carrier status in conjunction with sex, age, and the cognitive reserve variables. Results were largely similar for the two models and the respective models' fit remained good (Model 1: CFI = .957; RMSEA = .042, 90% Confidence Interval = .039-.046 and Model 2: CFI = .954; RMSEA = .043, 90% Confidence Interval = .038-.047). Given the corresponding patterns between the race and APOE-e4 models, their results are jointly discussed.

The addition of the latent health variables to the model elucidated the interplay between the respective predictor variables on neurocognitive functioning. As hypothesized, the Neurocardiovascular and Depression/Endocrine latent variables associated with worse neurocognitive functioning in those with a greater number of risk factors and vice versa (see Table 14). The creation of the Neurocardiovascular latent variable representing cardio- and cerebrovascular risk factors significantly strengthened the relationship between neurocognitive functioning and vascular risk. Specifically, Neurocardiovascular risk when predicted by age, sex and race differences significantly associated with worse neurocognitive performance within each domain at baseline, as well as those with a higher amount of Neurocardiovascular risk factors generally demonstrated slower growth rates in neurocognitive performance from Year 1 to Year 3 (i.e., less practice effects/learning). In assessing the specific effects of sex and APOE-e4 as predictors of Depression/Endocrine risk, Depression/Endocrine risk predicted worse baseline Executive Attention/Processing Speed and Language functioning.

Table 14.
Etiological Model of Neurocardiovascular and Depression/Endocrine Risk Factors Effect on Neurocognitive Functioning at Baseline and Over Time

Variables	Neurocardiovascular	Depression/Endocrine
Model 1: Predicted by Age, Sex, and Race with Cognitive Reserve (N = 553)		
Memory Intercept	-14.31**	-.13
Memory Slope	-2.02**	<.01
EA/PS Intercept	-17.14**	-1.74**
EA/PS Slope	-.64†	-.12
Language Intercept	-10.44**	-1.40**
Language Slope	-.85*	-.07
WM Intercept	-3.69*	-.78
WM Slope	.20	-.09
Model 2: Predicted by Age, Sex, and APOE-e4 with Cognitive Reserve (N = 398)		
Memory Intercept	-22.21**	.23
Memory Slope	-1.50	.28
EA/PS Intercept	-25.42**	-1.37*
EA/PS Slope	-.44	-.12
Language Intercept	-15.45**	-1.01*
Language Slope	-.10	.16
WM Intercept	-5.21†	-.60
WM Slope	2.28*	.08

Notes: Executive Attention/Processing Speed (EA/PS); Working Memory (WM).
† $p < .10$; * $p < .05$; ** $p < .01$.

As expected there was considerable interplay between the predictor variables (as indicated by the significant covariances between these variables). Appendix G and H presents the final models' parameters with standardized estimates. Evidence for both direct and indirect effects on neurocognition indicated that these factors at the very least play a moderating role in the relationship between health-related risk factors and neurocognitive decline. These results bolster the argument that APOE genotype, age, sex, race, and health-related risk factors act as independent predictors but also share common variance in their effect on neurocognitive functioning. Figure 1 provides a combined schematic of the final etiological model(s).

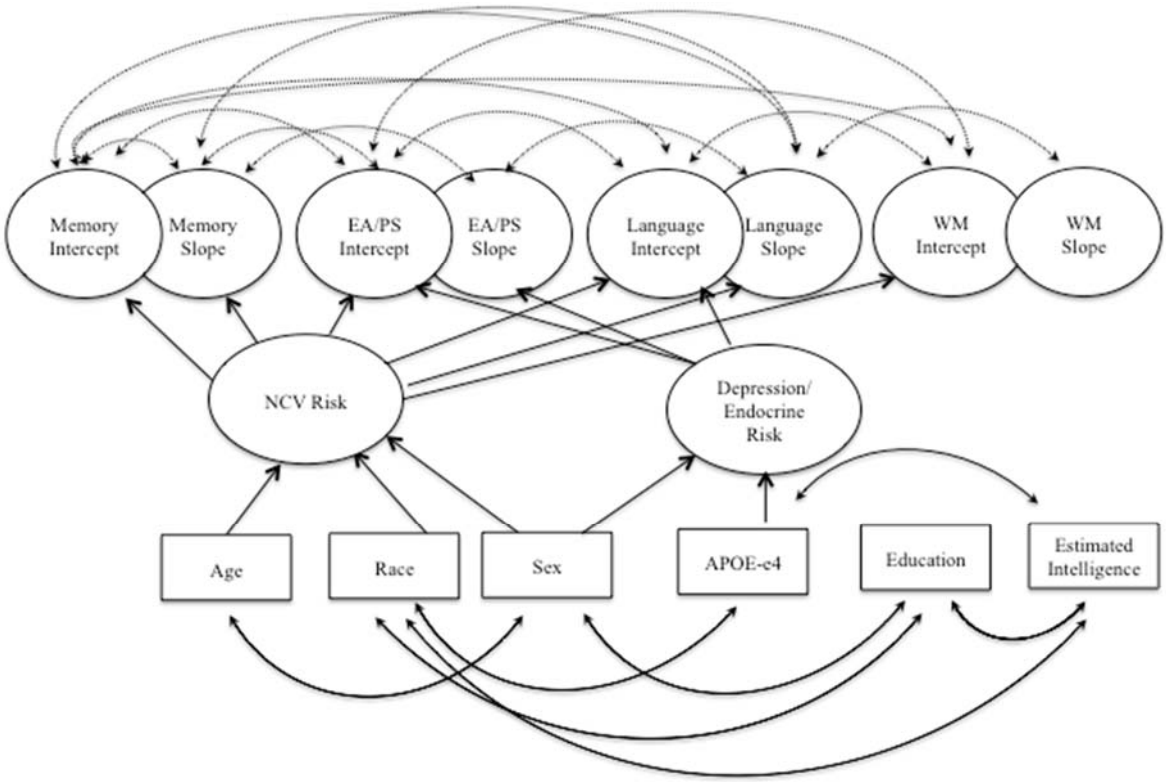

Figure 1. Schematic of Neurocardiovascular (NCV) and Depression/Endocrine Risk Effect on Neurocognitive Functioning. Dashed lines indicate significant path coefficients. Bold lines indicate significant covariance between the predictor variables. The direct effects of education and estimated intelligence on neurocognition are not depicted in the figure for simplicity.

CHAPTER 5: DISCUSSION

The results of this longitudinal study provide insight into the interplay between Memory, Language, Executive Attention/Processing Speed, and Working Memory functioning in older adults. The current study adds to the literature as it provides a detailed description of the relationship between neurocognitive changes in relation to baseline functioning within non-demented older adults and relevant risk factors that have been associated with MCI/AD. Consistent with past evidence, significant decrements over time in neuropsychological test measures of executive function and attention/processing speed were found in cognitively intact older adults. Whereas, episodic memory and language performance on average improved over time within the present sample – thus, suggesting that these functions are relatively stable in healthy aging adults and that practice effects are also occurring in the majority of participants. All considered, these results are consistent with research that suggests intact frontal lobe functioning (as evidenced by performance on tests of executive function and attention/processing speed) is important to maintaining language and memory functioning with advanced age.

Within the present study, several factors appeared to have moderating (and potentially mediating) effects on neurocognitive functioning. As hypothesized, age, race, sex, education, estimated intelligence, health and genetic risk were all significant predictors of neurocognitive functioning; such that, on average older participants, African Americans, men, less education and lower estimated intelligence, APOE-e4 carriers, and the presence of health risk factors associated with worse baseline neuropsychological test performance and differences in the estimated growth trajectories. Furthermore, there was a significant amount of interplay between the individual difference variables and evidence of different patterns of cognitive profiles in relation

to individual differences in the predictor variables. Overall, results indicate that there was substantial heterogeneity within neurocognitive functioning that might be explained by individual differences in the degree of risk variables.

The sections that follow provide a discussion on the present study's findings with their potential implications integrated into each section. To begin, the interplay between neurocognitive functions as measured by the latent variables of Memory, Executive Attention/Processing Speed, Language and Working Memory are discussed within the context of Aim 1's hypotheses and goals. Following the presentation of the structural model's results, the effects of the respective predictor variables on these neurocognitive functions in older adults are discussed and integrated into an etiological model of risk for cognitive decline. Subsequently, potential implications of study attrition and differences between demographic groups in relation to neurocognitive functioning are considered and study limitations are presented. A brief summary of the main findings with future research directions concludes the discussion section.

Within and Between Neurocognitive Domain Variance in Older Adults

Aim 1 sought to elucidate the interplay between Memory, Executive Attention/Processing Speed, Language and Working Memory functioning in older adults through systematically investigating relationships between baseline neuropsychological performance and linear changes in these processes over a three-year period via multivariate LGC modeling. Consistent with previous research on the UDS neuropsychological battery, the posited four-factor solution provided an excellent fit for the data. Analyses were designed to avoid over-parameterization of the model and to ensure that a more parsimonious model of global cognition did not better explain the data. The covariances placed between the neurocognitive domain

intercepts was soundly based on the well-accepted notion that Memory, Executive Attention/Processing Speed, Language, and Working Memory all, to some degree, share cognitive resources yet have specialized functions. Relatedly, although it was posited that there would be shared variance between these factors, it was not expected that a global second-order neurocognitive factor would better explain the data. Indeed, it was the case that the four-factor model of neurocognition had an excellent fit as compared to the competing global common process models. Furthermore, the expectation of shared variance was supported, as each covariance between the different neurocognitive domains intercept means were significant at baseline.

Provided with an excellent fitting model, Aim 1's analyses assessed baseline neurocognitive functioning and the degree to which specific neurocognitive processes changed over time in relatively healthy older adults. In accord with past research and the present study's hypotheses, individuals with initially lower Memory, Language, Executive Attention/Processing Speed, and Working Memory performance concomitantly had lower scores on each of the other neurocognitive latent variables at baseline. There was also evidence of practice effects as indicated by the linear growth rate in Memory scores from Year 1 to Year 3, and although not hypothesized performance enhancement was noted on the Language factor over time. There were no notable changes in the Working Memory factor over time suggesting that verbal working memory/auditory attention is relatively stable within normal aging. As hypothesized Executive Attention/Processing Speed performance declined over the three-year period. This finding is consistent with Raz et al.'s (2000, 2004) suggestion that neuropsychological test measures

presumed to tap frontal and superior parietal lobe functioning show a significant decrement over time even in cognitively intact older adults.

Contrary to the study's posited directionality, but consistent with the law of initial values, initially higher Memory functioning associated with a slower annual growth rate in memory. The hypothesis that lower baseline Executive Attention/Processing Speed would predict steeper annual rates of decline in Executive Attention/Processing Speed was not supported. Exploratory analyses indicated that initial differences in baseline Language and Working Memory functioning did not respectively predict within-neurocognitive domain incremental annual changes in these processes.

As expected, there was considerable interplay between the neurocognitive processes in relation to linear changes over the three-year period. Consistent with the study's hypotheses,, older adults who demonstrated higher initial Executive Attention/Processing Speed functioning at baseline demonstrated greater incremental increases in Memory performance over time. In turn, higher initial Memory functioning predicted greater incremental increases in Language performance over time. Although the relationship between baseline episodic memory and incremental language change was not anticipated, these findings are of interest, considering verbal fluency in conjunction with memory functioning has been posited to be the best predictor of MCI/AD (Howieson et al., 2008). The hypothesis that incremental changes in Language functioning would be predicted by baseline Executive Attention/Processing Speed performance was not supported.

In analyzing the degree to which annual rates of neurocognitive change associated with one another, results indicated that on average as Memory, Language, and Executive Attention/Processing Speed scores increased over time, there were respective increases in each of the other processes with the exception of Working Memory. Notably, incremental increases in Language functioning from Year 1 to Year 3 was the only neurocognitive process to associate with gradual increases in Working Memory functioning. Lastly, as expected, there was consistently large variability in these processes across individuals.

Aim 1 summary and future directions. In all, these results indicate that there is substantial heterogeneity in older adults in their initial levels of cognitive functioning and in linear changes in these processes over time. Subtle declines in executive function and attention processes over the three-year period were found, while on average memory and language performance improved with repeated testing within the cognitively intact older adults. As expected, lower executive function and attention performance at baseline predicted less incremental growth rates in memory. In turn, higher initial memory functioning associated with incremental improvements in language from Year 1 to Year 3. Improvement in language functioning did not associate with measures of executive function and attention/processing speed at baseline; this may partially due to the different nature of the language tasks (verbal fluency vs. confrontation naming).

Mechanistically efficient semantic knowledge retrieval (particularly verbal fluency) is believed to involve frontal lobe processes as well as language systems, while deficits in confrontational naming tasks (BNT) in older adults has been linked to damage in memory regions (left hippocampal damage, see Lezak et al., 2004). There is also research that suggests

that the posterior parietal cortex plays an intermediary role in extending long-term memory processes through its interconnections with both the frontal lobe and the medial temporal lobe (see Shannon & Buckner, 2004). Thus, in light of these findings, it may be that language tasks (which are believed to involve frontal and parietal cortices in addition to language systems) recruit similar compensatory processes as episodic memory to preserve cognitive functioning with advanced age. This suggestion, although highly speculative, seems consistent with the evidence that has thus been presented.

The above conceptualization is consistent with previous research that indicates that decrements in executive function and attention (accompanied by slower processing speed) are common within "normally" aging older adults. Relevantly, brain imaging studies indicate that the regions of the brain (e.g., frontal and frontoparietal areas) that are primarily responsible for these neurocognitive processes serve to compensate for age-related decline in more posterior regions of the brain that support memory and language functioning (e.g., the hippocampus and medial temporal lobe). Furthermore, as evidenced by activations during older adults' successful memory recall, there appears to be an age-related shift in neural recruitment that indicates that frontal and the posterior parietal regions become increasingly involved in memory functioning within older adults. Putting it all together, older adults who have preexisting vulnerabilities within any one of these regions (as evidenced by neurocognitive test performance and/or imaging studies) are at greater risk of moving closer to MCI/AD disease threshold as a function of age-related shifts in neural resources. Importantly, more longitudinal research integrating brain imaging with neuropsychological assessment is needed to reconcile that the brain regions (frontal and superior parietal areas) posited to compensate for declines in other neural processes

are also believed to be amongst the first to decline with age (Raz, 2000). Further research is also needed to shed light on the relationship between episodic memory and changes in language processes in cognitively intact older adults.

Practice Effects

The nature of the present study design was that participants had equal exposure to tests, and thus, theoretically could equally benefit from previous test exposures. It was posited that failure to benefit from practice effects would be linked to neurocognitive decline. Indeed, the present study found several notable relationships that were suggestive of individual differences in practice effects that may serve as useful indicators of cognitive decline.

First, as noted previously, memory functioning improved over time with additional exposures, providing support for the hypothesis that there would be practice effects on the memory measures. However, inconsistent with expectations, those with higher initial Memory functioning did not demonstrate a steeper increase in these scores over time. Rather, those with lower initial Memory functioning demonstrated greater gains in these abilities from Year 1 to Year 3. These results could be interpreted as those with higher initial Memory functioning demonstrated a slower rate of improvement due to their initial higher values (i.e., less to gain) or conversely higher functioning individuals did not experience practice effects (suggesting cognitive decline within these individuals). Relevantly, as discussed, a problem that can arise with interpretation of longitudinal research involves the law of initial values, which suggests that the degree of change produced is dependent on initial values. In considering these alternative explanations as to why participants did not equally benefit from previous test exposures, it is important to note that while there did not appear to be evidence of ceiling effects on the episodic

memory tests (as indicated by significant skew or a truncated range at any time point), test sensitivity alone does not rule out the law of initial values. Thus, it is important to consider the overall pattern of results, that is, those with higher memory functioning at baseline concomitantly demonstrated higher performance across each of the other neurocognitive domains. Furthermore, higher initial Memory functioning was predictive of subsequent annual gains on the language measure. Taken together, these findings argue against those with higher baseline as compared to lower baseline memory performance demonstrating memory decline.

Secondly, these results may indicate that in order to optimally benefit from previous test exposures executive function and attention processes need to be intact, as those who started with higher executive function and attention/processing speed functioning at baseline demonstrated a steeper rate of growth in memory functioning over time. This suggestion is somewhat consistent with scaffolding theories that suggest that the neural networks believed to underlie executive function and attention processes play a vital role in learning processes that increase overall neurocognitive efficiency. As Petersen et al.'s (1998) seminal work on the functional anatomy of skill acquisition cogently argued, the systems involved in practice effects are not entirely task-specific, as novel verbal generation tasks require effort and thus employ top-down cognitive control to effectively cope with cognitive demands. However, once learning processes have occurred (as suggested by greater proficiency at task), the task becomes more automatic and no longer requires higher cognitive control. While this evidence on the anatomical basis of practice effects was cross-sectional in its nature, others have noted that practice effects appear to be enduring and are evident across neuropsychological domains.

Determining the true nature of potential practice effect differences within this study is difficult in that there was a significant interplay between the neurocognitive domains and there was also consistently large variability in these processes across individuals. Furthermore, in regards to memory performance, the amount of material recalled at any given time point may be limited by factors other than memory functioning (e.g., initial test anxiety could lower baseline memory scores). Indeed, as will be discussed, the rate of change in memory over time was influenced by other factors (e.g., age and estimated intelligence). Thus, these findings will be further discussed in the context of the predictor variables.

Relevant Predictors of Neurocognitive Functioning in Older Adults

While subtle changes in neurocognitive functioning occur as part of the normal aging process, there is considerable variability in the degree to which older adults experience cognitive impairments. Based on previous research and theoretical speculation, multiple indicator parallel growth process LGC model(s) relating older adults neurocognitive performance to relevant predictors were conducted to answer the degree to which of Memory, Executive Attention/Processing Speed, Language and Working Memory at baseline and changes over time (Year 1 to Year 3) differ as a function of these factors.

Age. The first set of analyses was specifically interested in the degree to which age impacts neurocognitive functioning when sex and race are adjusted for in the model. As hypothesized, greater age at baseline predicted worse initial functioning in each of the respective neurocognitive domains. Consistent with past research (see Calamia et al., 2012), older age associated with slower growth rates in Memory, Executive Attention/Processing Speed, and Language functioning from Year 1 to Year 3. The finding that older adults benefited less from

previous test exposures (as evidenced by older adults' slower annual growth rate) may indicate an age-related vulnerability in the cognitive processes involved in procedural test learning (i.e., failure to benefit from practice effects).

Race. Consistent with previous research, differential effects for race on neurocognitive functioning and the degree of risk factors for cognitive decline were found. African American as compared to Caucasian participants had a higher rate of cardiovascular risk factors and the likelihood of being an APOE-e4 carrier was also significantly greater within African American (54.5%) as compared to Caucasian/Latino (23.3%) participants. On average Memory, Executive Attention/Processing Speed, Language, and Working Memory functioning appeared to be initially lower in African American as compared to Caucasian participants; however, race was not related to the annual rate of growth or decline in neurocognitive functioning. For cognitive reserve factors, African American participants on average obtained higher levels in education but were lower in estimated intelligence than Caucasian participants. The addition of the cognitive reserve variables attenuated the relationship between race with Language and Working Memory functioning – however, significant effects remained between race with Memory and Executive Attention/Processing Speed even when these factors were adjusted for in the model.

In discussing the findings in regards to race it is important to note that the NAART word reading test might be a biased indicator of intellectual functioning within African Americans. Research indicates that educational quality and/or ethnic differences in pronunciation can contribute to race/ethnic performance differences on word reading tests (See Lezak et al., 2004). Of interest, a study that conceptualized the original version of the NAART (i.e., the National Adult Reading Test that has not been modified for North American pronunciations) as a measure

of educational quality found that word reading scores was the only the factor to explain race differences in episodic memory functioning within older adults (Fyffe et al., 2011). Similar to the present study, African American participants were higher in education than Caucasian participants; however, this study did not investigate relevant genetic risk in relationship to race differences in episodic memory. Relevantly, the present study (and others) have found associations between APOE-e4 with episodic memory. In addition, the present study found NAART scores associated with APOE-e4 and predicted both baseline and incremental growth in episodic memory functioning (indicative of learning/practice effects). Considering the higher ratio of APOE-e4 carriers in African Americans along with the pattern of findings within the present study, it is possible that lower cognitive reserve as a function of genetic risk may potentially explain the relationship between NAART and episodic memory. Collectively, these results suggest that improving education quality, particularly in reading abilities may lend cognitive resilience in older adults. In this respect, albeit a controversial measure of estimated intelligence, the NAART overall appears to be a useful predictor of cognitive reserve.

Finally, it worth noting this study is a Deep South cohort. From a biopsychosocial perspective it is important to acknowledge the potential contribution of racial disparities and prejudice that may increase daily life stress – which, both psychologically and biologically (e.g., chronic psychosocial stress activation of the hypothalamic-pituitary-adrenal axis) would be expected to impact neurocognitive functioning and overall cardiovascular health. It is also conceivable that the higher proportion of APOE-e4 allele carriers and lower neurocognitive functioning within the African American participants within the present sample could be indicative of a selection bias, that is African Americans on average participated in the study due

to having greater concerns regarding their cognitive functioning. Overall, these findings emphasize the need for more ethnically and racially diverse sample populations, before any conclusions on racial differences be made (see study limitations for further discussion).

Sex. Despite women having higher rates of AD, research suggests that within the oldest-old women overall outperform men on cognitive tests despite their lower education levels (Van Exel et al., 2001). Similarly, normative research on the NACC's UDS neuropsychological test battery found that older adult women as compared to men perform significantly better on all its measures with the exception of digit span and category fluency (animal) tests (Weintraub et al., 2009). Consistent with previous research, within the present study on average women had higher initial scores on Memory, Executive Attention/Processing Speed, and Language measures than men, while men generally demonstrated better Working Memory functioning than women at baseline. Women when compared to men also demonstrated overall greater gains in their language scores over time. In addition to sex differences in neurocognitive performance, women with the present sample were on average younger than men, had less cardiovascular risk factors but greater depression/endocrine risk factors, and were lower in years of education. These results provide further evidence that on average women demonstrate greater resilience to age-related cognitive decline than men (McCarrey et al., 2016), which may potentially be explained by differences in health risk factors.

Cognitive reserve. In the present study, while levels of education and estimated intelligence were correlated with one another, attempts to form a common latent variable from these factors failed. Thus, indicating that they may make unique contributions to neurocognitive functioning. Consistent with this notion, estimated intelligence as compared to education levels

demonstrated both common and unique relationships with neurocognitive functioning. Specifically, while both higher levels of education and estimated intelligence predicted higher initial Memory and Language functioning, only estimated intelligence associated with better Executive Attention/Processing Speed and Working Memory performance at baseline. Additionally, higher levels of estimated intelligence predicted modest annual increases in Memory and Executive Attention/Processing Speed latent factor scores; whereas, education level was not related to linear changes in neurocognitive functioning over time. Of further interest, after adjusting for the influence of education and intelligence within the model, the previously reported effects of race on initial working memory and language functioning were both no longer significant. Conversely, sex differences were strengthened by inclusion of the cognitive reserve variables. Notably, significant sex differences predicted Memory, Executive Attention/Processing Speed, Language, and Working Memory functioning. Considering women on average obtained lower education levels as compared to men, yet demonstrated better overall neurocognitive performance (with the exception of working memory), these enhanced effects were not surprising. In sum, these factors appeared to have a moderating effect on observed race and sex differences in neurocognitive performance.

Genetic risk. Given significant interactions between sex, age, and education with APOE-e4 carrier status within the literature, the degree to which the presence of APOE-e4 predicted neurocognitive functioning when these variables are adjusted for in the model was investigated. Those who were genotyped were more likely to be younger, African American, with less cardiovascular and cerebrovascular risk factors. The shared covariance between race and APOE-e4 carrier status indicated that African American participants had a higher ratio of APOE-e4

carriers than Caucasians. However, due to the limited African American participants with genotyping within the present sample, examination of race differences would not have been statistically valid given the skewed sample distribution. Importantly, the hypothesized sex difference in APOE-e4 carrier status was not found. Furthermore, results within the present sample indicated that APOE-e4 carrier status did not covary with sex, education or age. Consistent with previous research, memory functioning was significantly lower in APOE-e4 carriers as compared to non-carriers – this effect remained even when sex, age, and education were adjusted for in the model.

Next, exploratory analyses examined the influence of estimated intelligence within the model. Notably, inclusion of estimated intelligence revealed a trend relationship between lower intelligence in APOE-e4 carriers, and attenuated the significant effect of APOE-e4 on baseline memory functioning. Although not part of the original hypotheses, the relationship between APOE-e4 and estimated intelligence is compatible with evidence that the APOE-e4 exert its effects on neurocognition earlier on prior to the onset of significant disease pathology. Or alternatively, lower estimated intelligence scores within APOE-e4 carriers may be an indication of cognitive deterioration as evidenced by its significant relationship with lower neurocognitive functioning; however, this suggestion is less consistent with research that has demonstrated that the NAART is a relatively robust measure of estimated intelligence in cognitively intact adults. NAART scores have demonstrated strong intraindividual correlations across the life span (age eleven to seventy-seven, r = .77) and word reading tests have been found to be fairly resistant to brain insult within healthy aging adults (See Strauss, Sherman, Spreen, 2006). Furthermore,

word reading deterioration is usually not evident until the later stages of dementia and overall word reading scores tend to improve with age (Strauss et al., 2006).

Exploratory analyses that excluded individuals with a copy of the e2 allele, found that e3/e4 carriers as compared to e3/e3 carriers demonstrated both worse baseline memory functioning and slower growth rates in executive function and attention/processing speed from Year 1 to Year 3. This finding is worthy of future investigation, as it is possible that a copy of the e2 allele has protective effects on the underlying processes involved in executive function and attention/processing speed declines. In line with this notion, dose-related responses of reduced parietal activation within cognitively intact homozygous as compared to heterozygous APOE-e4 carriers has been found (Lind et al., 2006). Notably, these differences were found in absence of cognitive differences, thus, suggesting that changes in task-related brain responses may be evident prior to behavioral manifestations. Future studies will also need to assess zygosity effects on neurocognitive functioning in relation to relevant risk variables, as there is research to suggest that older healthy adult e3/e4 as compared to e3/e3 carriers demonstrate worse memory functioning that is linked to structural brain differences (reduced gray matter density in the right MTL, bilateral PFC, temporal cortex, and cerebellum) even in the absence of differences in demographic factors and estimated intelligence (Wishart et al., 2006). All considered, more longitudinal studies that incorporate imaging techniques in relation to APOE-e4 zygosity and risk variables are needed to further substantiate neurocognitive endophenotypes for MCI/AD.

Health related risk factors: Etiological model of neurocognitive decline. Supporting the study's etiological model(s) of neurocognitive decline, the predictor variables of sex, age, race and genetic risk had direct effects on neurocognitive functioning and were also significant

predictors of health-related risk factors. Inclusion of the direct effects of predictor variables on the latent health variables and combining the cardiovascular and cerebrovascular risk factors into a common latent variable significantly strengthened the relationship between health-related risk and neurocognitive functioning.

Review of the standardized estimates indicated that age specifically accounted for 37% of the variance in Neurocardiovascular risk, sex accounted for 18% of the variance, and race accounted for 11% in Neurocardiovascular risk. 16.3% of the variance in Depression/Endocrine risk was accounted for by sex, while APOE genotype accounted for approximately 5%. Overall, estimated intelligence was an important predictor of neurocognitive functioning, while the effects for education and APOE-e4 on neurocognitive functioning were minimal.

Within the final model(s), sex, age, and race predicted Neurocardiovascular risk, while sex and APOE-e4 carrier status were significant predictors of Depression/Endocrine risk. Greater age associated with a higher amount of Neurocardiovascular risk factors but not Depression/Endocrine risk factors. Men and African American participants were significantly more likely to have a history of Neurocardiovascular conditions, while women on average had a greater history of Depression/Endocrine risk factors. Neurocardiovascular risk was directly associated with worse neurocognitive performance across domains and accounted for the largest amount of variance in cognitive function. Consistent with previous research, Neurocardiovascular history was a significant predictor of not only lower Executive Attention/Processing Speed but also of Language and Memory functioning at baseline. Neurocardiovascular risk factors also predicted a slower growth curve in neurocognitive performance across domains from Year 1 to Year 3. Adjusting for the cognitive reserve variables

in the model significantly attenuated the relationship between Neurocardiovascular risk and Language functioning. A history of Depression/Endocrine risk predicted worse Executive Attention/Processing Speed and Language functioning at baseline; this relationship appeared to be strengthened by the inclusion of sex and APOE-e4 as predictors of Depression/Endocrine risk.

Aim 2 summary and future directions. Several important findings emerged from this study. First, despite significant relationships between the predictor variables and neurocognitive functioning, overall the effect sizes in relation to neurocognitive functioning were relatively small. Notably, there was considerable interplay between the predictor variables with health risk on neurocognitive functioning, thus suggesting that these factors at the very least play a moderating role in the relationship between health-related risk factors and neurocognitive decline. Second, there was no evidence of shared variance between sex, education or age with APOE-e4 carrier status within the present sample. Age was an important predictor of neurocognitive performance and the degree of neurocardiovasular risk. With respect to race, the findings within the present study are consistent with previous research that suggests that race differences in cognitive decline are moderated by several other factors, most notably being cardiovascular and genetic risk factors. However, given the low number of African American participants and possible selection bias, results regarding race within the present study must be interpreted with caution. Higher levels of education and estimated intelligence did indeed appear to provide cognitive resiliency, as these variables were both associated with better neurocognitive performance.

Consistent with past research, the presence of APOE-e4 was associated with worse memory functioning even when age, sex and education were adjusted for. Interestingly, lower estimated intelligence was linked to APOE-e4 and inclusion of intelligence attenuated the effect of APOE-e4 on memory functioning. Sex (women) and APOE-e4 predicted a greater history of Depression/Endocrine risk factors that, in turn, associated with worse Executive Attention/Processing Speed and Language functioning at baseline. Differences in sex (men), race (African Americans) and greater age were all significant predictors of the degree of neurocardiovascular risk. Neurocardiovascular risk in turn predicted lower neurocognitive functioning across domains.

These findings are consistent with prospective cohort studies that suggest preclinical cognitive impairments of vascular origin associate with more broad cognitive changes than preclinical AD phases (e.g., Ingles et al., 2007). Notably, research also indicates that vascular factors accelerate the pathological processes of AD (Sadowski et al., 2004); thereby, further increasing risk for cognitive decline. In sum, these findings are strongly suggestive of there being additive and interactive effects between risk factors influence on neurocognitive functioning and are consistent with past research that suggests heterogeneity in neurocognitive functioning within older adults is multifaceted. Lastly, the pattern of sex related differences in health-related risk factors and neurocognitive functioning could potentially indicate that men and women might on average differ in their risk profiles for a dementia disorder.

On a final note, the finding that genetic predisposition for AD was related to a history of depression and endocrine dysfunction is worthy of further discussion, considering the potential implications of heightened inflammatory responses (e.g., via dysregulation of the hypothalamic-

pituitary-adrenal axis) and/or catecholamine dysregulation that are common in depression. This is not the first study to link APOE-e4 to depression symptoms. In a large study conducted with 323 AD patients, 72% of depressed AD patients with depression carried at least one copy of the ε4 allele, as compared to 58% of non-depressed patients (Delano-Wood et al., 2008). Remarkably, this associated risk was four times higher within females, while APOE-e4 status did not predict depression among men. While there is evidence that depressive symptoms predict subsequent memory decline (when age, sex, education, race, ethnicity, and vascular disease are adjusted for in the model, Zahodne et al, 2014), there is also research that has demonstrated that cognitive symptoms precede depressive symptoms in older community dwelling Latina/o adults with on average lower education (Perrino, Mason, Brown, Spokane, & Szapocznik, 2008). The latter results potentially indicate that biopsychosocial factors that are associated with less education or cognitive reserve play a role in the relationship between late-life depression and neurocognitive decline. Although the directionality of the relationship between memory and depressive symptoms in late life is unclear, these results appear to suggest that depression may be an important indicator of prodromal stages of cognitive decline and/or might be an underlying etiological factor in MCI/AD pathology. Indeed, Johnson et al. (2013) have proposed a depressive endophenotype of MCI and AD. In this respect, more research is needed to investigate the underlying mechanisms between depression and cognitive changes in older adults.

Implications for Clinical Practice and Future Research

Given our increasing knowledge of the reciprocal interplay between risk factors that also are presumed to have a biological basis, it is recommended that future research uniformly assess for individual difference factors that have been shown to influence functional outcomes in older adults. In clinical practice, medical and psychological comorbidities appear to be the rule rather than the exception. In line with this, the present study demonstrated that there is significant interplay between demographic and health-related risk factors, and that their inclusion is clinically relevant in interpreting findings regarding neurocognitive functioning. Disentangling the relationship between risk factors and neurocognitive decline will require more studies that examine a broader spectrum of clinical characteristics (e.g., inclusion of individuals with depression) within cognitively intact older adults.

From a treatment perspective, currently diagnosis of MCI/AD generally remains divorced from interventions that are non-pharmacological. Given this fact, it is important that research not only continues to improve the sensitivity and specificity of measures used to detect MCI, but also that clinical recommendations be developed for suspected preclinical stages of MCI/AD. The present data indicates that there are important modifiable factors that influence neurocognitive decline. Even to the layperson, the implications are obvious – psychological and physical health impacts neurocognitive functioning. Further, the majority of individuals are aware of the ramifications of health behaviors and that they likely need to eat better, exercise more, and so on. It is also important to consider the negative effect that declines in cognitive functioning can have on psychological and physical health (e.g., decreased activities of daily living).

In light of these considerations and the enormous burden of AD, there is a present need to develop and improve upon applied behavioral interventions effectiveness so that people experiencing early symptoms of neurocognitive decline may benefit from intervention prior to substantial neurodegenerative processes are incurred. Within other neurological conditions, there is some initial support that early interventions at sensorimotor levels can improve neural functioning (e.g., neural feedback and mental simulation tasks have been shown to have rehabilitative effects) as well as changes in health-related behaviors have been shown to modify courses of diseases that are linked to cognitive decline. However, to my knowledge, research on applied cognitive behavioral interventions that target these factors in conjunction with cognitive remediation strategies within older adults has been sparse if not non-existent.

Study Attrition and Missing Data

Consistent with a previous cognitive aging study that investigated predictors of attrition over a three-year period (Van Beijsterveldt et al., 2001), individuals that dropped out obtained lower educational levels, had a greater number of cardiovascular risk factors, and demonstrated worse performance on neuropsychological tests at baseline; however, unlike Van Beijsterveldt et al. age and sex (women) were not linked to differences in attrition rates. In addition, African American participants on average had a greater attrition rate than Caucasian participants within the present sample.

In considering patterns of attrition rates on the findings within the present sample, it is important to discuss the sample characteristics. Women within our sample were younger than men, generally performed better on the neurocognitive tests, and the relative frequency of genetic risk was lower in women (i.e., a trend towards men having a greater likelihood of

carrying an APOE-e4 allele). Women were higher in factors that are associated with lower attrition rates, while African American participants tended to be higher on risk factors associated with greater attrition rates (e.g., lower neuropsychological test performance and greater cardiovascular risk factors). In assessing the cognitive reserve variables influence on study attrition outcomes, it is important to emphasize that even though the study dropouts were significantly lower in years of education and estimated intelligence, their estimated intelligence still fell well within the average range and they had obtained on average three years of college education. Furthermore, while neuropsychological test scores in dropouts as compared to enrollees were comparatively lower, the majority of dropouts' scores remained within normal ranges on the UDS standardized test measures. Finally, in addition to there being between race and sex group differences, socio-demographic factors were also highly correlated with one another suggesting that there are significant interactions between these variables. Determining the directionality and reciprocity of these relationships in relation to attrition is important in that individuals that tend to dropout of studies are also more prone to belong to groups at higher risk for a dementia disorder.

From a statistical standpoint, when attrition is associated with potentially predictable reasons (e.g., education, health, or race), and when these factors are measured, MLE methods tend to be fairly effective at recovering missing data for these cases (Little, 2013). However, given strong evidence for group differences in the dependent variables, a cautionary approach was taken in the model analyses, such that complete datasets (using listwise deletion methods) were used for the primary analyses and supplementary analyses were conducted using MLE methods to estimate missing values for Aim 1's and 2's final models. Comparison of parameter

estimates between the complete and incomplete data set models and their respective fit indices were relatively close to one another - thereby, further increasing our confidence in the identified constructs and their interrelationships.

These findings are consistent with others who have reported that attrition has little effect on longitudinal estimates of cognitive change, even in the presence of individual differences neurocognitive, demographic and educational characteristics (Beijsterveldt et al., 2001; Salthouse, 2014). Regarding the predictor model, MLE methods for the missing value dataset resulted in a non-positive covariance matrix when estimated intelligence was adjusted for in the model. It was the outside of the scope this study to further investigate the nature of theses difference, however given the strong evidence for group differences between enrollees and dropouts on many of these factors, future research intends to further investigate these patterns of missing data in those that dropped out and those with three-years of follow-up visits (e.g., testing cross-sectional factorial invariance across groups).

Finally, while it is attempting to conclude that differences in neuropsychological test performance at baseline predicted study attrition, as with all cross sectional research participant's test performance may be influenced by other extraneous variables such as stereotype threat bias, test anxiety or simply a poor night's sleep. Furthermore, it is important to consider the role of motivational factors, as it possible that group differences between enrollees and dropouts are related to environmental and/or stable individual differences in factors related to task persistence (e.g., the majority of study dropouts had attended college but had not completed their degree). In this respect, inclusion of effort measures to assess for low motivation in future cognitive aging studies is recommended.

These results and others emphasize that as we attempt to understand change in cognition with advanced age, we must also improve methods of retaining participants who may be more vulnerable to study attrition and/or cognitive decline. Notably, there was a truncated range in education levels and individuals with less education were more likely to dropout from the present study. It is possible that the lack of educational range in this study sample is related to practical issues - such as, those with higher education tend to have greater resources (e.g., available transportation and greater flexibility in their schedules) that enhance their ability to participate in research. Suggestions for broadening sample demographics in future studies include having more flexible study hours (e.g., weekend hours), and/or provision of transportation or conducting mobile assessments. Future investigation into the role of motivation on study attrition and neurocognitive decline in older adults is also warranted.

Study Limitations

As discussed above, although potentially more costly and less "convenient", there is a strong need for study protocols that implement recruitment and retention strategies to increase sample diversity in cognitive aging research. LABrainS participants are generally college educated, predominantly white, with a higher proportion of females than male, which may limit the generalizability of these findings. Lack of educational range is also relevant considering that sample populations with similar characteristics of higher in education tend to exhibit greater health related behaviors that can influence cognitive trajectories (Welsh-Bohmer et al., 2009). Unfortunately, these limitations are not specific to this study, as lack of demographic diversity is a common issue within geriatric research, if not research in general. Overall, these findings and

others clearly demonstrate the need to enhance both recruitment and retention strategies for obtaining broader demographic samples in cognitive aging research.

Other potential limitations within the present study arise from decisions regarding statistical choices and measurement selection. To begin, in order to simplify an already complicated analyses, time-invariant measures were used for all predictor variables. It is possible that different results would have emerged for age and health related risk factors had they been studied dynamically. Secondly, although accepted statistical procedures were used to handle non-normally distributed variables and in the definition of outliers, a question always remains the degree to which results were affected by such procedures. For instance, it is possible that cases removed due to multivariate non-normality are part of the population of interest. For this reason, this study specifically chose to use Winsorized means as opposed to case deletions to assist in normalizing data distributions, as we wanted to retain as many extreme cases as these participants were posited to be part of the population of interest. Of further interest, qualitative analysis of the few cases that were deleted due to significant multivariate heterogeneity that was not amenable to transformations across the neuropsychological variables (as indicated by D^2) indicated that two of the deleted cases had a significant familial history of AD in their first-degree relatives. I believe that this qualitative example serves as a reminder that it is also critical that we attempt to understand "extreme cases" – as it is easily conceivable that multivariate heterogeneity within performance is an important indicator of cognitive decline. In this regard, case studies remain an important although often overlooked contribution to the field.

A goal of this project was to provide a comprehensive investigation of the relationship between neurocognitive functioning within non-demented older adults and relevant risk factors that have been associated with MCI/AD. In doing so, many exploratory relationships were tested. Although these relationships tested were based on prior evidence within the literature and all tests were two-tailed, there is the possibility that Type I errors were increased with the use of multiple comparisons. Future research designed to replicate these results is highly encouraged.

The present study was based on archived data utilized from the NACC's UDS neuropsychological test battery, and while the UDS battery has considerable empirical support for its sensitivity in detecting cognitive change in older adults, a more comprehensive assessment of each of the neurocognitive domains, particularly in regards to executive function and memory functioning is recommended for future research. Additionally, the present study lacked an adequate measure of visuospatial functioning. The CDT was a poor indicator of visuospatial/working memory functioning within the present sample, and was thusly discarded due to its poor reliability. Despite these potential methodological limitations, the longitudinal information obtained from use of the UDS neurocognitive test battery in the present study is important in guiding future studies that utilize the NACC's database for research. For instance, as previously discussed, this study adds to the body of research that recognizes the effect of previous test exposure to future test performance. As expected, there were considerable indications of practice effects on the UDS neuropsychological test battery. In this respect, these results have important implications for the handling of cross-sectional analyses of the NACC's UDS database – in that, collapsing different annual cohorts' data for cross-sectional analyses

should be strongly discouraged given strong evidence of practice effects on many of the neuropsychological study measures.

Finally, in considering the lifespan, three years is not a very long period to observe neurocognitive change. Participants will need to be followed for a more extended duration of time to better delineate the nature and magnitude of declines in neurocognitive functioning in relation to genetic, demographic, and health risk factors.

Study Summary

Improving measures to detect preclinical AD is a vital research direction, as earlier interventions may prove more efficacious in altering the disease's trajectory. Preclinical AD patients often present with an array of neurocognitive symptoms as well as subtle impairments in visual, motor and auditory sensory systems. Research regarding which neurocognitive function(s) best predicts cognitive decline has been mixed. While some studies suggest that memory functioning is the best predictor of pre-MCI/AD disease states in older adults, other studies have indicated that wider spread neurocognitive impairments may be the best predictor for distinguishing normal aging adults from those with MCI. Endophenotype models are useful in that they help to identify individuals at high risk for MCI/AD, through linking genetic risk to cognitive functioning prior to disease states.

Within the present study, executive attention/processing speed was the only neurocognitive domain to demonstrate a significant decrement over the three-year period across a broad age range of older adults. Conversely, both memory and language performance on average improved over time, indicating that these processes benefited from practice effects within normally aging adults. As expected, lower executive function and attention/processing

speed performance at baseline predicted less incremental growth rates in memory. Furthermore, APOE-e4 specifically associated with worse baseline memory functioning supporting episodic memory's role as a neurocognitive endophenotype for AD. Of notable interest, lower initial memory functioning predicted slower language growth rates. These findings are consistent with research that suggests intact executive function and attention processes are important to preserving memory and languages functioning in older adults. Results are also compatible with indications that neuropathological changes involved in neurocognitive decline are at least to some degree associated with aging processes (Jack et al., 2015) and that cognitive inefficiency in older adults appears to some extent reflect decrements in attention network systems.

Overall, these results provide further evidence that failure to benefit from prior test exposures may serve as useful heuristic of neurocognitive decline and support the notion that deficits seen in typically spared processes on formal neuropsychological testing, such as semantic knowledge and language functioning, within older adults may reflect early diseased related pathology. As such, declines in language and/or memory functioning in older adults needs to be considered in conjunction with executive function and attention processes in order to understand the nature of the cognitive decrement.

An important limitation within many cognitive aging studies to date is the lack of comprehensive neurocognitive evaluations in examining change over time in relation to relevant risk variables that have demonstrated significant interactions with one another. It is becoming increasingly evident that there are important group differences between sex and races in relation to functional outcomes with age, which appear to be both psychosocial and biological in their

nature. Still to date, the majority of biomedical research has not acknowledged the important role that these factors can play on disease and health outcomes.

The present study provided a systematic investigation of the role of APOE-e4 in neurocognitive functioning in conjunction with the potential confounding factors of age, race, sex, and indicators of cognitive reserve and health risk. Both direct and indirect effects on neurocognitive functioning were found amongst the predictor variables, suggesting that these factors should not be studied in isolation, as there is a significant amount of interplay between them. Furthermore, unique patterns were found between education and estimated intelligence on the different neurocognitive domains growth parameters indicating that they play a role in cognitive stability with age. These results support conceptual models that suggest individual differences in sex, genetic risk, cognitive reserve, medical and mental health comorbidities in combination influence trajectories of cognitive decline. Future research intends to investigate for potential mediation and moderation between the health risk factors and demographic factors on neurocognitive functioning, as well as testing the measurement model's equivalence across sex.

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APPENDIX A
INSTITUTIONAL REVIEW BOARD APPROVAL SHEET

A copy of the approval sheet from the Institutional Review Board for the "Louisiana Aging Brain Study." This is an ongoing longitudinal study that was started in May 2009. All participants from this dissertation were recruited as part of this protocol.

PENNINGTON BIOMEDICAL RESEARCH CENTER LSU

IRB Certificate of Approval

FWA # 00006218

Date of Approval: **February 17, 2016**
Study Expiration Date: **February 16, 2017**
Submission Type: **Continuing Review**
Review Frequency: **12 months**
Number of Subjects Approved: **5000**
Review Type: Full Board
Approval Status: **Approved**

Principal Investigator: **Jeffrey Keller, Ph.D.**
IRB # **29007-PBRC LA BRAINS**
Title: **Louisiana Aging Brain Study**
Sponsor: **IDRP**

Approval Includes: Study and Investigator(s) for an additional continuing review period. This approval expires on the date noted above.

Investigators and study staff must comply with the Human Research Protection Program policies and procedures that apply to IRB members and staff, which can be found at www.pbrc.edu/HRPP

Signed Thursday, February 18, 2016 3:44:32 PM ET by Geiselman, Paula Ph.D.

6400 Perkins Road, Baton Rouge, Louisiana 70808-4124 • Phone: (225) 763-2693 • irb@pbrc.edu

APPENDIX B
INSTITUTIONAL REVIEW BOARD CONSENT FORM

PBRC29007 Full Approval by IRB Received 1-7-14

CONSENT TO PARTICIPATE IN A RESEARCH STUDY FOR AN ADULT INFORMED CONSENT - PART I

Title of Study: Louisiana Aging Brain Study (LABrainS)

What you should know about a research study

- We give you this consent form so that you may read about the purpose, risks and benefits of this research study.
- The main goal of research studies is to gain knowledge that may help future patients.
- You have the right to refuse to take part, or agree to take part now and change your mind later on.
- Please review this consent form carefully and ask any questions before you make a decision.
- Your participation is voluntary.
- By signing this consent form, you agree to participate in the study as it is described.

1- Who is doing the study?

Investigator Information:

Principal Investigator:	Jeffrey N. Keller, Ph.D. 225-763-3190
Medical Investigator:	Frank Greenway, M.D. Day Phone: 225-763-2576 24-hr. Emergency Phone Nos.: 225-763-2632 (Weekdays 7:00 a.m - 4:30 p.m.) 225-765-4644 (After 4:30 p.m. and Weekends)
Co-Investigators:	Robert M. Brouillette, M.S., Heather C. Foil, B.S., Leslie G. Jackson, B.A., Stephanie L. Fontenot, M.S.

Dr. Keller directs this study, which is under the medical supervision of Dr. Frank Greenway. We expect to enroll up to 5,000 participants. The study will take place over a period of years. Your expected time in this study will be 2 hours per year for as long as you are enrolled in the study. This is a study being done by researchers at the Pennington Biomedical Research Center in Baton Rouge, LA.

2- Where is the study being conducted?

The study takes place at the Institute for Dementia Research and Prevention (IDRP) testing suite located on the second floor of the PBRC Outpatient Clinic Building, the St. James Place Retirement Community, the Residence of the Retirement Community of the Sisters of St. Joseph, St. Paul the Apostle Catholic Church, Baton Rouge, LA, and the Diamondhead Community Church in Diamondhead, MS.

3- What is the purpose of this study?

The purpose of this research study is to establish a registry of aging individuals in Louisiana who receive annual cognitive evaluations. This allows for both the collection of "normal" data to be used for comparison in other studies and the earliest possible detection of disease onset and the factors leading up to it.

Additionally, this research allows for the investigation of the relationships between cognitive decline, mobility, activity level and fall risk.

4- Who is eligible to participate in the study? Who is ineligible?

- **Inclusion Criteria**

  You are eligible of inclusion in the study if:

  - You are a man or woman $\geq$ 60 years of age
  - You have no exclusionary health problems as outlined in the exclusion criteria below and measured by the UDS Form A5: Subject Health History and have no awareness of significant cognitive decline
  - You have a score of $\geq$ 25 on the Mini Mental Status Examination (MMSE)
  - You are not currently under treatment for any form of dementia

- **Exclusion Criteria**

  You are not eligible for inclusion in the study if:

  - You have been diagnosed, ~~or~~ have a suspected diagnosis of dementia of any kind or are taking medications for the treatment of memory loss
  - You have a history of brain injury
  - You have a history of cerebrovascular disease (Stroke or Transient Ischemic Attack)

- You have a history of Parkinson's disease
- You have a history of seizure disorder
- You have a history of B12 deficiency
- You have a history of untreated and/or severe Thyroid Disease.
- You have a history of substance abuse or alcoholism within the past 5 years.
- You have a history of significant psychiatric disorder that would interfere with the subject's ability to complete the study.
- You show symptoms of acute depression as measured by the UDS Form B6: Behavioral Assessment – Geriatric Depression Scale (GDS) (Raw $\geq$ 6)

5- What will happen to you if you take part in the study?

Your participation will consist of an annual two hour visit. At your initial visit, you will be interviewed by IDRP clinicians to collect basic information about you, your health history, and possible risk factors. You will perform screening tests of your thinking and mood. If your performance on these measures results in exclusion from the study, you will be informed at that time. If you meet the inclusion criteria you will undergo the following:

- **Cognitive Testing**
  You will undergo more extensive cognitive testing to assess your performance in the areas of memory, language, attention/concentration and reasoning.

- **Anthropometric Measures.**
  During this visit, we will measure your height and weight.

- **Questionnaires**
  You will be asked to fill out multiple questionnaires to assess your family history of dementia and cancer, your community mobility and general health history.

- **Short Physical Performance Battery**
  You will then be asked to complete a short physical performance (SPPB) test. The physical performance test has three parts:
  1. You will be asked to walk a short distance (about 13 feet)
  2. You will be asked to stand up from a chair 5 times without using your arms
  3. You will be asked to stand in 3 different positions while keeping your balance

- **GAITRite Assessment**
  You will be asked to walk across a short computerized mat which will measure your length of stride, posture and gait. You will be asked to perform this measure both normally and while completing a cognitively distracting task.

This process will be repeated annually for as long as you continue to meet criteria for inclusion/continuation.

Additionally you may choose to participate in two optional aspects of the study. Participation in the following is not necessary for enrollment in the study.

- **Optional Blood Draw**
  You will have blood drawn from an arm vein. The two samples taken will be used for the following: genetic genotyping and storage of sample for future studies related to dementia. This collection will be completed only once and is not repeated annually. The possible benefits of research from your blood and/or DNA samples include learning more about what biomarkers in the blood may be related to the onset of Alzheimer's disease and other dementias.

Genetic Genotyping
You will have blood (about one teaspoon) drawn from an arm vein for studying a gene, ApoE. Your DNA will be taken from your blood, and a test will be done to find out your ApoE status. Any sample left over after this test will be destroyed. Your sample will not be saved for future testing. These results are for research only. Since these tests are exploratory research only, they will have no clear implications about you or your family medical conditions. The results of the testing will not be returned to you.

I give permission to have my DNA collected for ApoE genotyping as explained above. Please initial next to your choice below.

_____Yes _____No

- **Optional Activity Monitors**
  Your participation will consist of wearing a combination of two activity monitors for a period of seven consecutive days. You will be given oral and written instructions regarding the proper wearing of the monitors and asked to return the monitors to the front desk of the PBRC Clinic Building at the end of the seven day period. You will also be asked to keep a simple log of wearing activities.

- Subjects agreeing to enrollment in this ancillary study will receive the following in addition to their annual cognitive screens:

  - **Physical Activity Monitor: 7 days -** After completion of annual cognitive assessments, you will be fitted with a combination of two activity monitors (GT3X+ accelerometer, pedometer) and will be asked to wear the activity monitors for 7 consecutive days, except while showering/bathing. The accelerometer is to be worn while sleeping and awake whereas the pedometer is to be worn only when awake. You will be asked to complete brief records of your

daily wearing time, the number of steps you take (displayed on the pedometer), and activities you engaged in during the day.

- **Activity Monitor Descriptions**

Pedometer
This monitor is small (approximately the size of a matchbox) and is worn at the waist when awake.

GT3X+
This monitor is small (approximately the size of a matchbox) and is worn at the waist on an elasticized belt while sleeping and awake.

- I agree to wear the activity monitors for a period of seven days as outlined above.

_____ Yes _____ No _____ Initials

6- What are the possible risks and discomforts?

The risks associated with a study such as this are minimal.

Cognitive Testing
The procedures used for cognitive testing are completely non-invasive and painless. Some subjects may experience mild performance anxiety associated with taking the tests or experience mental fatigue during or after completion of the evaluation.

Risk of Falling:
There is a risk of losing your balance and falling associated with the physical performance-based testing (e.g., balance tests, rising from a chair). We will minimize this risk by:

- safely escorting you to chairs
- following you at a close distance when walking
- being at your side should you need assistance

Optional Blood Draw:
There is the possibility of pain and bruising at the vein on your arm where the needle is inserted. Aseptic (sterile) technique and trained personnel minimize these risks.

Optional Genetic Testing:
Although we have made every effort to protect your identity, there is a small risk of loss of confidentiality. If the results of these studies of your genetic makeup were to be accidentally released, it might be possible that the information we will gather about you as part of this study could become available to an insurer, an employer, a relative or someone else outside the study. Even though there are discrimination protections in Louisiana state law, there is still a small chance that you could be harmed if a release occurred.

- A new federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health

plans, and most employers to discriminate against you based on your genetic information. Be aware that this new federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination if you have already been diagnosed with the genetic disease being tested.

Optional Activity Monitors:

Precautions
The devices should not be exposed to water so you should remove them when showering/bathing and secure them back onto your body after drying off. You will be asked to note the time of day when the devices are removed to shower/bathe or for any other reason.

Risks
All devices may cause some mild discomfort while initially getting used to wearing the devices.

You will be allowed to refuse or terminate any procedures that cause you distress.

7- What are the possible benefits?

We cannot promise any benefits from your being in the study. However, your participation will help researchers and health care practitioners better understand the process of normal aging and identify factors which could potentially cause the process to become accelerated (dementia). By your participation in this study you insure the earliest possible detection of a Dementia process for yourself, which is very important to maximize treatment of the illness. If, during the course of screening or evaluation, you are found to exhibit cognitive symptoms indicative of dementia, you will be encouraged to seek medical attention from you primary care physician, as soon as possible for further evaluation. Additionally, your participation in this study will afford you the collection of baseline cognitive data, which can prove vital to your physicians in diagnosis and care of future disease states. These records will be made available to personal physicians upon request.

8- If you do not want to take part in the study, are there other choices?

You have the choice at any time not to participate in this research study. If you choose not to participate, any health benefits to which you are entitled will not be affected in any way.

9- If you have any questions or problems, whom can you call?

If you have any questions about your rights as a research volunteer, you should call the Institutional Review Board Office at 225/763-2693 or the Executive Director of PBRC at 225/763-2513. If you have any questions about the research study, contact Dr. Jeffrey Keller at 225/763-3190. If you think you have a research-related injury or medical illness, you should call Dr. Frank Greenway at 225/763-2576 during regular working hours. After working hours and on weekends, you should call the answering service at 225/765-4644. The on-call physician will respond to your call.

10- What information will be kept private?

Every effort will be made to maintain the confidentiality of your study records. However, someone from the Food and Drug Administration, the National Institutes of Health, the Pennington Biomedical Research Center, and the Institute for Dementia Research and Prevention may inspect and/or copy the medical records related to the study. Results of the study may be published; however, we will keep your name and other identifying information private. Other than as set forth above, your identity will remain confidential unless disclosure is required by law.

11- Can your taking part in the study end early?

Dr. Keller can withdraw you from the study for any reason or for no reason. You may withdraw from the study at any time without penalty; however, all data Pennington Biomedical has previously collected cannot be removed from the study. Possible reasons for withdrawal include conversion from a normal aging state to one suggestive of a dementia process or development of medical conditions which are listed in the exclusion criteria.

12- What if information becomes available that might affect your decision to stay in the study?

During the course of this study there may be new findings from this or other research which may affect your willingness to continue participation. Information concerning any such new findings will be provided to you.

13- What charges will you have to pay?

None

14- What payment will you receive?

None

15- Will you be compensated for a study-related injury or medical illness?

No form of compensation for medical treatment or for other damages (i.e., lost wages, time lost from work, etc.) is available from the Pennington Biomedical Research Center. In the event of injury or medical illness resulting from the research procedures in which you participate, you will be referred to a treatment facility. Medical treatment may be provided at your expense or at the expense of your health care insurer (e.g., Medicare, Medicaid, Blue Cross-Blue Shield, Dental Insurer, etc.) which may or may not provide coverage. The Pennington Biomedical Research Center is a research facility and provides medical treatment only as part of research protocols. Should you require ongoing medical treatments, they must be provided by community physicians and hospitals.

16- HIPAA

Records that you give us permission to keep, and that identify you, will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law, you will not be identified by name, social

security number, address, telephone number, or any other direct personal identifier in records disclosed outside of Pennington Biomedical Research Center (PBRC). For records disclosed outside of PBRC, you will be assigned a unique code number.

17- Signatures

The study has been discussed with me and all my questions have been answered. I understand that additional questions regarding the study should be directed to the study investigators. I agree with the terms above and acknowledge that I have been given a copy of the signed consent form.

With my signature, I also acknowledge that I have been given either today or in the past a copy of the Notice of Privacy Practices for Protected Health Information.

_____
Printed Name of Volunteer

_____ _____
Signature of Volunteer Date

_____
Date of Birth of Volunteer

_____ _____
Signature of Person Administering Informed Consent Date

Jeffrey N. Keller, Ph.D., Principal Investigator
Frank Greenway, M.D., Medical Investigator

I give my permission to the IDRP to contact me for future studies, for which I may be qualified to participate.

_____ Yes _____ No _____ Initials

The study volunteer has indicated to me that the volunteer is unable to read. I certify that I have read this consent form to the volunteer and explained that by completing the signature line above the volunteer has agreed to participate.

_____ _____
Signature of Reader Date

18- Specimen Storage for Future Research

Storage of Blood Sample for Future Research

Biospecimens for future research:

You are being asked to allow some of your blood to be stored and used for research at a later time. These bodily materials are called biospecimens. The donation of biospecimens in this study is optional. No matter what you decide to do, it will not affect your study participation. You will still be allowed to take part in the study even if you don't want your specimens to be collected and used for future research. Some biospecimen samples will be stored and used for the study and other biospecimen samples will be stored for future studies. The collection of samples may give scientists valuable research material that can help them to develop new diagnostic tests, new treatments, and new ways to prevent diseases. If you agree to have your samples stored, you can change your mind later.

The samples will be stored indefinitely. If you agree to donate your samples, they may be given to other investigators for future research as well. The future research may take place at Pennington Biomedical and may involve Pennington Biomedical Researchers in this study. The future research may not take place at Pennington Biomedical Research Center and may not be reviewed by Pennington Biomedical Research Center's Institutional Review Board. For privacy and confidentiality, your biospecimens will be labeled with a unique series of letters and numbers. Pennington Biomedical will store your biospecimens with this unique identifier and the minimum number of personal identifiers to meet laboratory standards. The research done with your specimens may help to develop new products in the future, or may be used to establish a cell line or test that could be patented or licensed. You will not receive any financial compensation for any patents, inventions or licenses developed from this research.

Making your choice about future research:
Please read about each biospecimen below. It is your choice which samples will be collected, stored and used for future research for this study or future studies. After reading about each below, sign next to "Yes" or "No" to show your choice about the collections for this research study and for future research studies.

Blood
If you give permission, approximately 3 teaspoons (1 tablespoon) of blood will be collected and stored by this study. Your stored samples may be tested at Pennington Biomedical Research Center or other locations used in future research. Do you give permission for your blood to be collected and used in future research by this study?

Yes, I give permission _____ _____
Signature Date

No, I do not give permission _____ _____
Signature Date

APPENDIX C
MAXIMUM LIKELIHOOD ESTIMATION FOR MISSING VALUES

Maximum Likelihood Estimates of Structural Model (N = 694)

Computation of degrees of freedom (Default model)

Number of distinct sample moments:	495
Number of distinct parameters to be estimated:	116
Degrees of freedom (495 - 116):	379

Result (Default model)

Minimum was achieved
Chi-square = 718.163
Degrees of freedom = 379
Probability level = .000

Fit Indices:

CFI = .976
RMSEA = .036; 90% CI: 032-.040

Means for Neuropsychological Variables: (Group number 1 - Default model)

	Estimate	SE	C.R.	*p* =
Memory Intercept	12.972	.127	101.824	< .001
Memory Slope	.483	.062	7.780	< .001
EA/PS Intercept	68.156	2.710	25.150	< .001
EA/PS Slope	-12.703	.527	-24.107	< .001
WM Intercept	9.037	.070	129.750	< .001
WM Slope	-.026	.034	-.755	.450
Language Intercept	27.398	.097	281.739	< .001
Language Slope	.255	.036	7.155	< .001

Covariances:

			Estimate	SE	C.R.	*p* =
Memory Intercept	<-->	Memory Slope	-.891	.162	-5.508	< .001
Memory Intercept	<-->	Language Intercept	2.599	.263	9.901	< .001
Memory Intercept	<-->	EA/PS Intercept	11.534	1.220	9.454	< .001
EA/PS Intercept	<-->	Language Intercept	8.139	.806	10.092	< .001
EA/PS Intercept	<-->	WM Intercept	5.105	.597	8.550	< .001
WM Intercept	<-->	Language Intercept	.913	.120	7.605	< .001
Memory Intercept	<-->	Language Slope	.149	.067	2.236	.025
Memory Intercept	<-->	EA/PS Slope	.353	.235	1.503	.133
EA/PS Intercept	<-->	Language Slope	.263	.180	1.467	.142
Memory Slope	<-->	EA/PS Intercept	1.042	.406	2.566	.010
Memory Slope	<-->	EA/PS Slope	.273	.115	2.379	.017
EA/PS Slope	<-->	Language Slope	.135	.047	2.872	.004
WM Slope	<-->	Language Slope	.033	.013	2.525	.012
Memory Slope	<-->	Language Slope	.133	.031	4.331	< .001
Memory Intercept	<-->	WM Intercept	1.217	.192	6.332	< .001

Note(s): Values are based on raw untransformed data. Standard Error (SE); Critical Ratio (CR); Executive Attention/Processing Speed (EA/PS); Working Memory (WM).

APPENDIX D
MAXIMUM LIKELIHOOD ESTIMATION FOR MISSING VALUES WITH PREDICTOR VARIABLES

Maximum Likelihood Estimates of Predictor Model

Computation of degrees of freedom (Default model)

Number of distinct sample moments: 629
Number of distinct parameters to be estimated: 151
Degrees of freedom (629 - 151): 478

Result (Default model)

Minimum was achieved
Chi-square = 1233.592
Degrees of freedom = 478
Probability level = .000

Fit Indices:

CFI = .949
RMSEA = .048; 90% CI: 044-.051.

Regression Weights Between the Neuropsychological Variables and Predictor Variables (*N* = 694)

			Estimate	Standard Error	Critical Ratio	*p* =
Memory Intercept	<---	Age	-.148	.017	-8.814	< .001
Memory Slope	<---	Age	-.025	.008	-3.016	.003
EA/PS Intercept	<---	Age	-.666	.049	-13.695	< .001
EA/PS Slope	<---	Age	-.029	.013	-2.243	.025
Language Intercept	<---	Age	-.086	.010	-8.739	< .001
Language Slope	<---	Age	-.013	.004	-3.341	< .001
WM Intercept	<---	Age	-.041	.009	-4.566	< .001
Language Intercept	<---	Sex	.440	.126	3.491	< .001
Memory Intercept	<---	Sex	1.636	.220	7.450	< .001
EA/PS Intercept	<---	Sex	1.972	.613	3.220	.001
WM Intercept	<---	Sex	-.102	.127	-.800	.424
Language Slope	<---	Sex	.129	.053	2.442	.015
Language Intercept	<---	Race	-.013	.009	-1.375	.169
Memory Intercept	<---	Race	-.002	.018	-.089	.929
Language Slope	<---	Race	-.003	.004	-.862	.389
Memory Slope	<---	Race	-.004	.009	-.513	.608
EA/PS Intercept	<---	Race	-.081	.047	-1.732	.083
EA/PS Slope	<---	Race	.006	.014	.439	.661
WM Intercept	<---	Race	-.017	.010	-1.710	.087
WM Slope	<---	Race	-.002	.004	-.446	.656
Language Intercept	<---	Ed	.191	.025	7.587	< .001
Language Slope	<---	Ed	.008	.010	.778	.436
Memory Slope	<---	Ed	-.027	.021	-1.277	.202
Memory Intercept	<---	Ed	.327	.044	7.442	< .001
EA/PS Intercept	<---	Ed	.693	.116	5.965	< .001
WM Slope	<---	Ed	.168	.024	7.047	< .001

Note(s): Values are based on raw data. Executive Attention/Processing Speed (EA/PS); Working Memory (WM); Education level (Ed); FS-IQ was excluded as MLE estimates resulted in a non-positive covariance matrix when estimated intelligence was entered into the model.

APPENDIX E
VARIANCE ESTIMATES AND STANDARDIZED COEFFICIENTS FOR THE NEUROCOGNITIVE DOMAINS

Variances:	Estimate	S.E.	C.R.	p ≤
Memory Intercept	79.737	5.68	14.039	0.001
Memory Slope	13.039	1.055	12.359	0.001
EA/PS Intercept	57.416	5.533	10.378	0.001
EA/PS Slope	0.979	0.272	3.598	0.001
WM Intercept	58.32	4.309	13.536	0.001
WM Slope	1.545	0.747	2.068	0.039
Language Slope	0.811	0.294	2.754	0.006
Language Intercept	31.427	3.951	7.954	0.001
Correlations between Neurocognitive Domains				
WM Slope	<-->	Language Slope	0.716	
EA/PS Intercept	<-->	Language Intercept	0.660	
Memory Intercept	<-->	Language Intercept	0.544	
EA/PS Slope	<-->	Language Slope	0.507	
Memory Slope	<-->	Language Slope	0.499	
Memory	<-->	EA/PS Intercept	0.426	
EA/PS Intercept	<-->	WM Intercept	0.414	
WM Intercept	<-->	Language Intercept	0.337	
Memory Intercept	<-->	Memory Slope	-0.256	
Memory Slope	<-->	EA/PS Slope	0.250	
EA/PS Slope	<-->	WM Slope	0.241	
Memory Intercept	<-->	WM Intercept	0.206	
Memory Intercept	<-->	Language Slope	0.189	
Memory Slope	<-->	WM Slope	0.146	
Memory Slope	<-->	EA/PS Intercept	0.105	
Memory Intercept	<-->	EA/PS Slope	0.095	
EA/PS Intercept	<-->	Language Slope	0.076	
Memory Intercept	<-->	WM Slope	0.034	
EA/PS Intercept	<-->	WM Slope	-0.028	

Notes: Executive Attention/Processing Speed (EA/PS); Working Memory (WM).

APPENDIX F
STANDARDIZED ESTIMATES BETWEEN THE NEUROCOGNITIVE DOMAINS AND THE DEMOGRAPHIC PREDICTOR VARIABLES

Variable (N = 553)		Predictor	Estimate
EA/PS Intercept	<---	age	-0.533
Language Intercept	<---	age	-0.428
Memory Intercept	<---	age	-0.319
EA/PS Slope	<---	age	-0.234
EA/PS Intercept	<---	race	-0.225
Memory Intercept	<---	sex	0.225
WM Intercept	<---	age	-0.208
Language Slope	<---	age	-0.187
Language Slope	<---	sex	0.177
EA/PS Slope	<---	sex	-0.145
Memory Intercept	<---	race	-0.141
Memory Slope	<---	age	-0.135
WM Intercept	<---	race	-0.129
Language Intercept	<---	race	-0.111
WM Intercept	<---	sex	-0.105
Language Intercept	<---	sex	0.079
EA/PS Intercept	<---	sex	0.072

Notes: Executive Attention/Processing Speed (EA/PS); Working Memory (WM).

APPENDIX G
RELEVANT PREDICTOR VARIABLES OF NEUROCOGNITIVE FUNCTIONING WITH APOE GENOTYPE

Variables ($N = 398$)			Estimate	S.E.	C.R.	$p \leq$
Memory Intercept	<---	Age	-0.441	0.066	-6.694	0.001
Memory Slope	<---	Age	-0.044	0.031	-1.392	0.164
EA/PS Intercept	<---	Age	-0.583	0.06	-9.737	0.001
EA/PS Slope	<---	Age	-0.029	0.016	-1.839	0.066
Language Intercept	<---	Age	-0.349	0.045	-7.805	0.001
WM Intercept	<---	Age	-0.114	0.059	-1.921	0.055
Memory Intercept	<---	Sex	4.866	0.87	5.594	0.001
EA/PS Intercept	<---	Sex	1.309	0.736	1.778	0.075
Language Intercept	<---	Sex	1.429	0.629	2.272	0.023
Language_Slope	<---	Sex	0.269	0.231	1.163	0.245
Memory Intercept	<---	Education	0.135	0.166	0.812	0.417
Language Intercept	<---	Education	0.224	0.109	2.048	0.041
Memory Intercept	<---	FSIQ	0.323	0.054	5.975	0.001
EA/PS Intercept	<---	FSIQ	0.279	0.044	6.288	0.001
Language Intercept	<---	FSIQ	0.294	0.04	7.408	0.001
WM Intercept	<---	FSIQ	0.452	0.048	9.354	0.001
EA/PS Intercept	<---	Cardiovascular	-1.052	0.337	-3.117	0.002
EA/PS Intercept	<---	Depression/Endocrine	-0.939	0.564	-1.666	0.096
Language Intercept	<---	Depression/Endocrine	-0.894	0.446	-2.005	0.045
Memory Intercept	<---	APOE-e4	-1.251	0.684	-1.831	0.067

Notes: Executive Attention/Processing Speed (EA/PS); Working Memory (WM).

APPENDIX H
AGE, SEX, RACE AS PREDICTORS OF HEALTH RISKS EFFECT ON NEUROCOGNITIVE FUNCTIONING

Variables			Est.	S.E.	C.R.	p ≤	Std Est.
Neurocardiovascular	<---	Age	0.03	0.01	5.83	.001	0.74
EA/PS Intercept	<---	Neurocardiovascular	-17.14	3.11	-5.52	.001	-0.64
Language Intercept	<---	Neurocardiovascular	-10.44	2.06	-5.07	.001	-0.50
Memory Intercept	<---	Neurocardiovascular	-14.31	2.76	-5.19	.001	-0.45
WM Intercept	<---	FS-IQ	0.44	0.05	9.86	.001	0.45
Language Intercept	<---	FS-IQ	0.30	0.04	7.85	.001	0.40
Neurocardiovascular	<---	Sex	-0.21	0.04	-4.87	.001	-0.36
Language Slope	<---	Neurocardiovascular	-0.85	0.40	-2.10	.036	-0.29
Depression/Endocrine	<---	Sex	0.37	0.05	6.88	.001	0.28
EA/PS Intercept	<---	FS-IQ	0.27	0.04	6.88	.001	0.27
Memory Intercept	<---	FS-IQ	0.31	0.05	6.13	.001	0.27
Neurocardiovascular	<---	Race	0.32	0.08	3.87	.001	0.22
EA/PS Slope	<---	Neurocardiovascular	-0.64	0.35	-1.83	.068	-0.19
EA/PS Slope	<---	FS-IQ	0.02	0.01	2.09	.037	0.19
Memory Slope	<---	Neurocardiovascular	-2.02	0.76	-2.65	.008	-0.16
Language Intercept	<---	Depression/Endocrine	-1.40	0.41	-3.41	.001	-0.15
EA/PS Intercept	<---	Depression/Endocrine	-1.74	0.47	-3.68	.001	-0.14
Language Intercept	<---	Education	0.34	0.10	3.31	.001	0.14
WM Intercept	<---	Neurocardiovascular	-3.69	1.51	-2.45	.014	-0.14
EA/PS Slope	<---	Depression/Endocrine	-0.12	0.14	-0.85	.395	-0.08
WM Intercept	<---	Depression/Endocrine	-0.78	0.56	-1.40	.162	-0.06
Memory Intercept	<---	Education	0.20	0.15	1.35	.179	0.05
Language Slope	<---	Depression/Endocrine	0.07	0.15	0.46	.646	0.05
Language Slope	<---	FS-IQ	-0.01	0.01	-0.46	.644	-0.05
WM Slope	<---	Neurocardiovascular	0.20	0.57	0.35	.724	0.05
WM Slope	<---	Depression/Endocrine	-0.09	0.24	-0.38	.706	-0.05
Memory Slope	<---	FS-IQ	0.02	0.02	0.73	.464	0.03
WM Slope	<---	FS-IQ	0.00	0.02	0.13	.901	0.02
Memory Intercept	<---	Depression/Endocrine	-0.13	0.56	-0.23	.821	-0.01
Memory Slope	<---	Depression/Endocrine	0.00	0.28	0.01	.991	0.00

Notes: Values are sorted by Standardized Regression Weights.
Estimate (Est.); Standardized (Std Est.); Executive Attention/Processing Speed (EA/PS); Working Memory (WM).

APPENDIX I
AGE, SEX, AND GENOTYPE AS PREDICTORS OF HEALTH RISKS EFFECT ON NEUROCOGNITIVE FUNCTIONING

Variables			Est.	S.E.	C.R.	p ≤	Std Est.
EA/PS Intercept	<---	Neurocardiovascular	-25.42	7.89	-3.22	.001	-0.75
Language Intercept	<---	Neurocardiovascular	-15.45	4.95	-3.12	.002	-0.64
Neurocardiovascular	<---	Age	0.02	0.01	3.28	.001	0.64
Memory Intercept	<---	Neurocardiovascular	-22.21	7.09	-3.14	.002	-0.56
WM Intercept	<---	FS-IQ	0.47	0.05	8.83	.001	0.47
Language Intercept	<---	FS-IQ	0.31	0.04	7.21	.001	0.45
WM Slope	<---	Neurocardiovascular	2.28	1.09	2.09	.037	0.37
Depression/Endocrine	<---	Sex	0.43	0.06	6.91	.001	0.33
EA/PS Intercept	<---	FS-IQ	0.27	0.05	5.82	.001	0.28
Neurocardiovascular	<---	Sex	-0.13	0.04	-2.88	.004	-0.28
Memory Intercept	<---	FS-IQ	0.31	0.06	5.26	.001	0.27
EA/PS Slope	<---	FS-IQ	0.02	0.01	1.50	.134	0.17
WM Intercept	<---	Neurocardiovascular	-5.21	2.86	-1.82	.069	-0.15
Language Intercept	<---	Depression/Endocrine	-1.01	0.44	-2.30	.022	-0.12
Language Slope	<---	Depression/Endocrine	0.16	0.17	0.96	.336	0.12
EA/PS Intercept	<---	Depression/Endocrine	-1.37	0.57	-2.41	.016	-0.12
EA/PS Slope	<---	Neurocardiovascular	-0.44	0.55	-0.81	.420	-0.11
Language Intercept	<---	Education	0.22	0.11	2.01	.045	0.10
Depression/Endocrine	<---	APOE-e4	0.14	0.07	1.99	.047	0.09
Memory Slope	<---	Neurocardiovascular	-1.50	1.22	-1.24	.217	-0.09
EA/PS Slope	<---	Depression/Endocrine	-0.12	0.16	-0.77	.440	-0.09
Memory Slope	<---	FS-IQ	0.04	0.03	1.36	.175	0.08
WM Slope	<---	FS-IQ	-0.01	0.02	-0.56	.574	-0.07
Language Slope	<---	FS-IQ	-0.01	0.01	-0.49	.624	-0.06
Memory Slope	<---	Depression/Endocrine	0.28	0.31	0.89	.373	0.05
WM Intercept	<---	Depression/Endocrine	-0.60	0.65	-0.93	.353	-0.05
WM Slope	<---	Depression/Endocrine	0.08	0.28	0.28	.780	0.037
Language Slope	<---	Neurocardiovascular	-0.10	0.58	-0.17	.863	-0.03
Memory Intercept	<---	Depression/Endocrine	0.23	0.66	0.36	.721	0.02
Memory Intercept	<---	Education	-0.01	0.17	-0.08	.938	0.00

Notes: Values are sorted by Standardized Regression Weights.
Estimate (Est.); Standardized (Std Est.); Executive Attention/Processing Speed (EA/PS); Working Memory (WM).

VITA

Rebecca Kathryn MacAulay was born and raised in Los Angles, CA. She received her Bachelors of Arts in Psychology from the University of California at Los Angeles (UCLA), graduating magna cum laude with College Honors distinction. At UCLA, she completed her senior thesis on psychosocial moderators of the stress response in schizophrenia under the guidance of Dr. Cindy Yee-Bradbury, an expert in the area of neurocognitive and emotional functioning in schizophrenia. As a Clinical Psychology graduate student at Louisiana State University (LSU), Rebecca has continued to foster her research interest in the complex interplay between neurocognitive functioning and psychosocial risk factors in severe mental illnesses and older adult populations under the guidance of Dr. Alex Cohen. She currently is completing her predoctoral internship in Clinical Neuropsychology at the Charleston Consortium (Medical University of South Carolina and Ralph H. Johnson VA Medical Center). Upon receiving her doctoral degree in Summer 2016, she will join the University of Maine faculty as an assistant professor who specializes in aging and cognition across the adult life span.