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Selected Health Factors (Pulse Pressure, Type 2 Diabetes) and Genetic Polymorphisms (*ApoE*, *IDE* rs6583817) Play Independent and Interactive Roles in Patterns of Cognitive Performance and Change in Older Adults

by

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Dedication

Good work is done in the presence of passion and commitment.

Great work is done in the presence of love and support.

We did this together

Richard James

Katie Marie

Patrick Joseph Sean

Abstract

Objective: This gene x environment (health) dissertation focused on concurrent and longitudinal change in performance on executive function (EF) and declarative memory (DM) latent variables by normal aging adults. Specifically, we report three studies that tested the independent and interactive effects of (a) *Insulin degrading enzyme* (*IDE*) and type 2 diabetes (T2D) across 2 waves of EF data, (b) *IDE* and pulse pressure (PP) across 3 waves of EF data, and (c) *Apolipoprotein E* (*ApoE*) and PP across 3 waves of DM data for older adults from the Victoria Longitudinal Study. **Method**: We assembled a sample of non-demented older adults (n = 683, M age = 71, Age range = 53-95) from which we drew a slightly different group for each study. We used latent growth modeling to test a series of similar research goals within each study. **Results**: First, for Study 1, we confirmed a single factor EF model and reported independent but unrelated (non-interactive) effects of T2D and *IDE* on EF performance. Second, for Study 2, we confirmed a single factor EF model and reported independent and interactive effects of PP and *IDE* on EF performance. Regarding the interactive effect of PP x *IDE*, higher PP differentially affected EF performance in older adults with the *IDE* G allele. Third, for Study 3, we confirmed a DM model made up of a single factor episodic memory (EM) model and a single factor semantic memory (SM) model that we ran in parallel. We reported independent effects of PP on the baseline level of EM but not SM but no independent effects of *ApoE* on EM or SM performance patterns. Regarding the interactive effect of PP x *ApoE*, EM performance and change was differentially affected by higher PP for adults

with an *ApoE* ε3 or ε4 allele as compared with carriers of the potentially protective ε2 allele. **Discussion**: Genetic x health interaction analyses as performed on both concurrent and longitudinal data can reveal differential and magnifying effects of biological risk factors on cognitive aging. In the present case both *IDE* x PP and *ApoE* x PP affect concurrent and changing cognitive health in aging.

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List of Abbreviations

-2LL – -2 log likelihood

Aβ – amyloid beta

AD – Alzheimer's disease

AIC – Akaike information criterion.

ApoE – Apolipoprotein E

BIC – Bayesian information criterion

BDNF – brain-derived-neurotrophic factor

COMT – catechol-O-methyl transferase

CFI – comparative fit index

Con – configural

D – deviance statistic

DM – declarative memory

EF – executive function

EM – episodic memory

IDE – Insulin Degrading Enzyme

Met – metric

MMSE – Mini-Mental Status Exam

PScal – partial scalar

PP – pulse pressure

REY – Rey auditory verbal learning

RG – Research Goals

RMSEA – root mean square error of approximation

Scal – scalar

SM – semantic memory

SNP – Single nucleotide polymorphism

SRMR – standardized root mean square residual

T2D – type 2 diabetes

VLS – Victoria Longitudinal Study

W – Wave

Chapter One

Framework and Literature Overview

This dissertation consists of a series of three longitudinal studies, each of which focusses on one cognitive process and the extent to which this cognitive process is affected by vascular health and genetic factors, both independently and interactively. Among the cognitive domains most extensively studied in older adult populations are executive function (EF) and declarative memory (DM). Although there is evidence of general decline in most markers of these domains, some cognitive aging literature reports varying patterns of differences and changes (see Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006; Fotuhi, Hachinski, & Whitehouse, 2009; Hertzog, 2008). Regarding EF, cross-sectional comparisons show that older adults exhibit executive function deficits when compared to younger adults for both cognitive task and in neuroimaging studies (Daniels, Toth, & Jacoby, 2006). Longitudinal and epidemiological studies indicate that EF declines with advancing age and that some EF tasks may predict the onset of mild cognitive impairment and Alzheimer's disease (Adrover-Roig, Sesé, Barceló, & Palmer, 2012; de Frias, Dixon, & Strauss, 2006, 2009; Grober et al., 2008; Luszcz, 2011; Nathan, Wilkinson, Stammers, & Low, 2001; Rapp & Reischies, 2005; Turner & Spreng, 2012). Regarding DM, two proposed memory domains are identified, episodic memory and semantic memory (Nyberg et al., 2003; Tulving, 1987). Generally, episodic memory declines with advancing age, although longitudinal studies suggest that these declines start later in life (Dixon, Small, MacDonald, & McArdle, 2012) than earlier cross-sectional results would

suggest (Bäckman, Small, Wahlin, & Larsson, 2000). Semantic memory on the other hand shows a somewhat different pattern. The advantage for younger adults is no longer evident and semantic memory appears to be spared the steeper declines associated with episodic memory (Old & Naveh-Benjamin, 2008). In addition, there is a growing literature concerning the need to examine individual trajectory differences that cannot be captured by mean comparisons (Hofer & Sliwinski, 2006; Josefsson, de Luna, Pudas, Nilsson, & Nyberg, 2012; McArdle, 2009) and that both genetic and environmental factors have a role to play in producing these differences (Anstey, 2012; Finkel, Reynolds, McArdle, & Pedersen, 2005; MacDonald, DeCarlo, & Dixon, 2011). While some of these factors are stable (i.e., genetic), scientists suspect that several factors are modifiable. Specifically, changes to health and lifestyle may alter cognitive outcomes. Specific genetic alleles may be more responsive to either positive or negative environmental factors making gene-environment interactions particularly interesting to cognitive aging researchers (Belsky et al., 2009; Harris & Deary, 2011).

The overarching goal of the current research is to investigate how several modifiable and non-modifiable factors affect cognitive functioning and change in older adulthood. These include factors associated with health risk (i.e., type 2 diabetes and pulse pressure) and genetic risk (i.e., *Apolipoprotein E [ApoE] and Insulin degrading enzyme [IDE]*). The primary aims of this dissertation are to examine (a) the independent effects and (b) the interactive effects of health conditions (i.e., elevated pulse pressure, type 2 diabetes) and genetic

polymorphisms (i.e., *ApoE, IDE*) on the executive function and declarative memory performance and change in older adults (aged 53-95 years). Answers to these general aims produce a picture that will help adults make health and lifestyle choices or changes that could translate to better cognitive outcomes and continued quality of life into old age.

This dissertation is comprised of three studies in the form of separate full reports that follow a progressive line of research. The basic framework of the dissertation is presented in Chapter 1, which offers a general overview of the current literature associated with the factors explored in the three studies. This is followed by Chapter 2, which gives a basic overview of the methodology used in the three studies. Next are the chapters, each with one of three research studies. Chapter 3 shows that the *IDE* (rs6583817) polymorphism and type 2 diabetes differentially modify executive function in older adults (McFall et al., 2013)[1]. Chapter 4 shows that the *IDE* (rs6583817) polymorphism and pulse pressure are independently and interactively associated with level and change in executive function in older adults (McFall et al., in press)[2]. Chapter 5 shows that level and changes in semantic memory and episodic memory are uniquely influenced by pulse pressure and *ApoE* interactions in older adults. Finally, Chapter 6 is a general discussion of the three studies and the genetic-environment implications as they pertain to older adult executive function and declarative memory performance and change. This chapter also considers the study strengths and

[1] The present version of Chapter 3 has been published. McFall, G. P., Wiebe, S. A., Vergote, D., Westaway, D., Jhamandas, J., & Dixon, R. A. (2013). *Neurobiology of Aging, 34,* 2208-2216.
[2] A present version of Chapter 4 has been accepted for publication. McFall, G. P., Wiebe, S. A., Vergote, D., Jhamandas, J., Westaway, D., & Dixon, R. A. (in press). *Psychology and Aging.*

limitations, as well as directions of future research. Chapters 3 through 5 are "standalone" documents and contain detailed methodologies, references, tables, and figures pertinent to each study. At the end of the dissertation, there is a general reference list containing literature used in the dissertation Chapters 1, 2, and 6.

Literature Overview

The literature review in the remainder of this chapter describes (a) the cognitive domains of executive function and declarative memory, (b) the health factors type 2 diabetes and pulse pressure, and (c) the genetic polymorphisms *ApoE* and *IDE.* A more specific and detailed review relative to the research goals being explored is included in each of the three research reports (Chapters 3-5) that make up this dissertation. First executive function and declarative memory will be briefly summarized.

Executive Function

Executive function (EF) is a set of cognitive processes that organize behavior. They involve planning, problem solving, reasoning, and goal-directed endeavors (West, 1996). EF is among the cognitive domains most sensitive to age-related cognitive decline and is thought to be linked to the neurodegeneration of the prefrontal cortex (Luszcz, 2011; Turner & Spreng, 2012). With a focus on aging, several researchers have reported the connection between EF performance and structural and functional markers of the prefrontal cortex (Duncan, 2005; Gunning-Dixon & Raz, 2003; Head, Rodrigue, Kennedy, & Raz, 2008; Luszcz & Lane, 2008; Raz, 2000; Schretlen et al., 2000). With older adults, smaller

prefrontal cortex volumes and increased frontal white-matter hyperintensities are associated with EF changes and are, in turn, influenced by aging-related biomarkers such as hypertension and the *ApoE* ε4 allele (Bender & Raz, 2012b; Raz, Rodrigue, & Acker, 2003). Overall, aging-related compromises to the prefrontal cortex may lead to EF deficits. In addition, lower EF performance is predictive of future development of mild cognitive impairment (Nathan et al., 2001) and Alzheimer's disease (AD; Grober et al., 2008; Rapp & Reischies, 2005). With aging, EF performance appears to be affected in terms of both level and structure. Whereas for younger adults EF is comprised of three subdomains (i.e., inhibition, switching and updating), the dedifferentiation into one factor may also reflect brain changes in typically aging older adults (de Frias et al., 2006; Luszcz, 2011; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000; Wiebe, Espy, & Charak, 2008; Wiebe et al., 2011), although not necessarily in older adults who display characteristics of healthy brain and cognitive aging (de Frias et al., 2009). Notably, young children exhibit a single factor EF model (Wiebe et al., 2008), which gradually differentiates into the three factor model observed for performance by mature brains (Miyake et al., 2000). As noted, research indicates that EFs are modified by a host of risk (or protection) factors making it necessary to examine the aging of EF in the context of genetic factors, health risk, and environmental or lifestyle factors (Lindenberger et al., 2008; Nagel et al., 2008). Significant age-related EF deficits were observed in older adults and adults with health conditions such as T2D or high PP exhibited greater group-level deficits in numerous related studies (Dahle, Jacobs, & Raz, 2009; McFall, Geall, Fischer,

Dolcos, & Dixon, 2010; Yeung, Fischer, & Dixon, 2009; but see Waldstein et al., 2008).

Declarative Memory (Episodic and Semantic Memory)

Declarative memory is made up of two types or systems of memory (Tulving, 1987) that exhibit different patterns of age effects and aging-related change – semantic memory and episodic memory (Nyberg et al., 2003). Semantic memory (SM) is the accumulation of cultural knowledge, such as recalling political facts or definitions of vocabulary, and is thought to be preserved into very old age (Nyberg, Bäckman, Erngrund, Olofsson, & Nilsson, 1996; Old & Naveh-Benjamin, 2008). Episodic memory (EM) is associated with events that have been personally experienced, such as remembering names of people you have just met or a mental shopping list. EM is thought to be the first type of memory to decline but the long-term change patterns are generally modest and gradual (Dixon et al., 2012; Nilsson et al., 1997; Schaie, 2013). This suggests that declarative memory models may include substantially different patterns for EM and SM. Individual differences in EM or SM deficits and declines may be more substantial—and theoretically important—than group mean differences or changes (Dixon et al., 2012). Moreover, researchers suspect that these dynamic individual differences in cognitive performance and change may be due to factors that influence performance both independently and interactively (e.g., functional, genetic, health, lifestyle; Anstey, 2012; Anstey & Christensen, 2000; Dahle et al., 2009; Harris & Deary, 2011; Nilsson et al., 2006; Nyberg et al., 2003; Rönnlund, Nyberg, Bäckman, & Nilsson, 2005; Small, Dixon, & McArdle, 2011; Waldstein

et al., 2008). For example changes in structure and activation patterns of the hippocampus have been linked to memory performance (Persson et al., 2012) and hypertension has been associated with accelerated shrinkage of the hippocampus and memory performance deficits (Raz et al., 2005).

Vascular Health

Various indicators of vascular health have been linked to neurocognitive deficits. Decreased vascular health is associated with age-related vascular stiffening. This may lead to brain lesions and stroke that in turn are thought to cause decrements in neurocognitive abilities (Schiffrin, 2004). Several indicators of vascular health have been identified and used in the aging literature. First, systolic blood pressure is the highest arterial pressure exerted during the cardiac cycle, the end of the heart's contraction cycle or when the blood is being pushed from the heart into the body. Second, diastolic blood pressure, in contrast, is the lowest arterial pressure exerted and occurs when the heart is not contracting or when the heart is filling with blood. According to the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, normal or healthy systolic blood pressure is less than 120 mmHg and normal or healthy diastolic blood pressure at less than 80mm Hg (JNC VII; U. S. Department of Health and Human Services, 2003). Typical age-related changes include an increase for systolic blood pressure and a decrease for diastolic blood pressure (Franklin et al., 1997; Franklin, Jacobs, Wong, L'Italien, & Lapuerta, 2001). This results in a proliferation of isolated systolic hypertension among older adults and makes systolic blood pressure a greater risk for cardiovascular disease

than diastolic blood pressure. Hypertension, a measure of elevated blood pressure, is a measure of poor vascular health and is defined as greater than 140 mmHg systolic blood pressure and 90 mmHg diastolic blood pressure. The VLS measures blood pressure for each wave of data as an average of seated blood pressure collected over four occasions with two measurements at each occasion (8 total assessments).Third, mean arterial pressure is the average arterial pressure exerted during a full cardiac cycle. Mean arterial pressure can be ascertained with the use of analog electrical circuitry but is usually estimated by the following equation: Mean arterial pressure = diastolic blood pressure + 1/3 (systolic blood pressure – diastolic blood pressure). Usually mean arterial pressure gradually increases until around 65 years of age and then remains at a consistent level into older age (Franklin et al., 1997).

The fourth indicator of vascular health is pulse pressure (PP), which is conceptually linked to arterial stiffening. PP is the focus of the current research. Arterial stiffening increases with age and is associated with increases in systolic blood pressure and decreases in diastolic blood pressure (Franklin et al., 1997; Mattace-Raso et al., 2006; Raz, Dahle, Rodrigue, Kennedy, & Land, 2011). Arterial stiffness is measured directly by pulse wave velocity (for a detailed description see Vaitkevicius et al., 1993), but PP is considered a proxy for pulse wave velocity. PP is calculated as systolic blood pressure - diastolic blood pressure. Typically, PP shows a steep age-related increase in older adults and is considered a better predictor of declining vascular health than mean arterial pressure or systolic blood pressure (Raz et al., 2011). Research indicates that PP

has an independent effect on cardiovascular disease (Dart & Kingwell, 2001; Mitchell et al., 2007; Schiffrin, 2004) and cognitive performance in older non-demented adults (Dahle et al., 2009; Waldstein et al., 2008). Several researchers have reported PP associations with EF and DM deficits (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003; Raz et al., 2011; Saxby, Harrington, McKeith, Wesnes, & Ford, 2003; Waldstein et al., 2008).

In a systematic review of vascular risk factors, cognitive decrements were observed in association with elevated blood pressure for both executive function and memory (van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009). Executive function decrements have been associated with systolic blood pressure, diastolic blood pressure, mean arterial pressure, and PP. Increases in systolic blood pressure or PP, related to declining vascular health, have been associated with reduced brain tissue volume, especially prefrontal structures and, not surprisingly, decreases in EF performance (Raz, Rodrigue, & Acker, 2003; Waldstein et al., 2008). Poor vascular health has resulted in lower levels of EF performance (Elias, Elias, Robbins, & Budge, 2004; Elias et al., 2003; Raz et al., 2003; Saxby et al., 2003). However, some mixed results have been reported: Other researchers observed no effect of vascular health on EF (Dahle et al., 2009; Smith, Blumenthal, Babyak, Hinderliter, & Sherwood, 2011) and that when genetic (e.g., *angiotensin converting enzyme*, *catechol-O-methyl transferase* [*COMT*]) and age factors were included in analyses, PP exhibited no additional effect on EF (Elias et al., 2004; Raz et al., 2011).

Poor vascular health has been associated with EM deficits (Dahle et al., 2009; Elias et al., 2003; Saxby et al., 2003), although when age, sex, and genetic variants were taken into account PP and memory correlations were no longer significant (Raz et al., 2011). Raz and colleagues found a vascular health (i.e., measured by hypertension) x genetic (*brain-derived neurotrophic factor*, [*BDNF*]) interaction which lead to decreased EM performance for *BDNF* MET carriers with an increased effect in the presence of hypertension (Raz, Rodrigue, Kennedy, & Land, 2009). Persons with high PP exhibited accelerated EM decline in comparison to their counterparts with lower PP (Waldstein et al., 2008). In contrast, other researchers observed no vascular health group differences, as measured by hypertensive and normotensive adults, on EM tasks (Bender & Raz, 2012a; Dahle et al., 2009; Waldstein & Katzel, 2006). In contrast to EM research, there is a limited research linking direct indicators of vascular health to SM performance and change among older adults. One study reported no effect of vascular health on SM task performance (Elias et al., 2004). In contrast, other researchers have observed independent effects of cholesterol level (Sternäng et al., 2009) and metabolic syndrome symptoms (Gatto et al., 2008) on SM performance. Notably, some aspects of vascular health may be modifiable and indeed maintenance of good vascular health in older adulthood may be correspondingly protective of cognitive functioning as evidenced by preserved brain tissue (Colcombe et al., 2003) and the possible postponement of dementia onset (Qiu, Winblad, & Fratiglioni, 2005; Staessen, Richart, & Birkenhäger, 2007). Understanding the relationship between vascular and cognitive health can

encourage lifestyle choices and interventions that could lead to maintenance of cognitive health in older adults.

There are several mechanisms that may be associated with the influence of vascular health on cognition. First, high blood pressure has been linked to cerebrovascular disease which is known to affect the brain through white matter lesions and silent cerebral infarctions. This damage to the white matter causes an information slowing or interruption between information transmitting areas of the brain (grey matter) which leads to cognitive impairment. Second, hypertension increases the risk of atherosclerosis which, like hypotension, may cause cerebral hypoperfusion. This lack of blood supply to the brain results in destabilization of neurons and synapses and may result in neurodegenerative processes. Third, genetics may play an independent role through risk allele association with increased hypertension, increased vasoconstriction, and the suspected interaction of these (Raz et al., 2011).

Type 2 Diabetes

Diabetes is generally defined by high blood glucose levels and the inability to control glucose levels. Type 2 diabetes (T2D) is age-related, non-insulin dependent diabetes and usually develops after the age of 40. People with T2D are able to produce insulin but have slower glucose absorption. This can result in hyperinsulinemia, which is the body's attempt to maintain normal glucose levels (insulin resistance) by increasing insulin production. When hyperinsulinemia can no longer be sustained (i.e., insulin sensitivity and secretion of insulin become impaired), glucose levels rise and hyperglycemia develops. This leads to a relative

decrease in insulin secretion (insulin deficiency). This loss of glycemic control leads to a clinical diagnosis of T2D and may be due to either insulin resistance or insulin deficiency. T2D is initially treated by incorporation of lifestyle changes, especially improved diet and increased exercise. If this is not effective due to inability of the person with T2D to adhere to the dietary and exercise requirements, medication for hyperglycemia is the next step. If hyperglycemia medication is not able to maintain normal blood glucose, the final treatment is daily insulin injections.

T2D has been linked to increased risk of AD (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004; Profenno, Porsteinsson, & Faraone, 2010; Qiu & Folstein, 2006) and changes in the non-AD brain (e.g., exacerbated insulin dysregulation, disrupted amyloid beta [Aβ] clearance) that are associated with decrements in neurocognitive performance (Awad, Gagnon, & Messier, 2004; Cholerton, Baker, & Craft, 2011; Nilsson, 2006; Okereke et al., 2009; Seaquist, Lattemann, & Dixon, 2012; Strachan, Reynolds, Marioni, & Price, 2011). For example, older adults with T2D have exhibited lower performance on EF, learning, and memory tasks in both cross sectional and short-term longitudinal studies (Biessels, Deary, & Ryan, 2008; Fischer, de Frias, Yeung, & Dixon, 2009; Yeung et al., 2009).

Studies related to the effect of T2D on EF have produced mixed results (Awad et al., 2004; Dahle et al., 2009; Fischer et al., 2009; van den Berg et al., 2009; Yeung et al., 2009). Whereas some studies have reported that controls perform better than persons with T2D on EF tasks (Fischer et al., 2009; van den

Berg et al., 2009; Yeung et al., 2009), others have reported mixed (Arvanitakis et al., 2004; Awad et al., 2004) or no EF differences associated with T2D status (Dahle et al., 2009).

The relationship T2D has to EM may be more consistent, with EM deficits often reported for adults with T2D (e.g., Arvanitakis et al., 2004; Awad et al., 2004; Dahle et al., 2009; Okereke et al., 2009; van den Berg et al., 2009; Wahlin, Nilsson, & Fastbom, 2002). However, some researchers have reported no significant group-level mean differences between controls and adults with T2D for EM (Fischer et al., 2009; Yeung et al., 2009). SM research is less common in the T2D literature with some researchers reporting SM decrements associated with T2D (Awad et al., 2004; Wahlin et al., 2002) and others reporting no significant differences between adults with T2D and controls (e.g., Yeung et al., 2009).

Cognitive decrements associated with T2D have been linked to mediators from functional, vascular, genetic, and other biological domains (McFall et al., 2010; Strachan et al., 2011). Several mechanisms have been associated with the effects of T2D on cognition and these will be outlined next. First, high glucose levels associated with T2D may have an adverse effect on brain neurons due to osmotic insult and oxidative stress (Umegaki, 2012). Second, insulin is important in the brain for the control of food intake and for cognitive function. When these levels are compromised cognition may also show decrements. Third, insulin resistance (hyperinsulinemia) reduces the effectiveness with which insulin degrading enzyme degrades Aβ oligomers in the brain, a link to the

neuropathogenesis of AD. When regulated in normal aging, cerebral insulin performs multiple cognitive-supportive functions, such as increasing neurotransmitter levels, enhancing glucose utilization, and promoting lipid metabolism. However, when the aging brain experiences chronic dysregulation (or reduced levels) of insulin uptake, cognitive deficits may be exacerbated to levels that are consistent with those of clinical impaired patients (Cholerton et al., 2011). Insulin receptors are distributed in brain regions such as the hippocampus and frontal lobe, opening the possibility that both EM and EF may be a target cognitive phenotype for research integrating T2D, *insulin degrading enzyme* (*IDE*) polymorphisms, and human brain and cognitive aging.

Overall, risk factors associated with vascular health (i.e., T2D, high PP) have been associated with the cognitive domains of EF, EM, and (to a lesser extent) SM. As neurodegenerative processes may start far earlier than the subsequent cognitive decline, it is imperative to identify possible risk factors as early as possible. Identification of potential non-modifiable risk factors such as chronological age, gender, and genetic status (of particular polymorphisms) could lead to better understanding of modifiable risk factors such as lifestyle and health risk management that may delay the onset of cognitive decline and improved quality of life for older adults. Research examining the potential influence of specific genetic polymorphisms on cognitive performance is important to the maintenance of older adult cognitive health.

Interestingly, the interactive and integrated contributions of sources conveniently aligned with nature (genetic) and nurture (environment) in the

development of psychological characteristics has been an ongoing theme in lifespan approaches to the study of aging (Anstey, 2012; Dixon, 2011; McClearn, 2006). Until recently, much research looking at genetic influences on various phenotypes has been focused on quantitative methodologies (i.e., related to twin studies). Due to breakthroughs in (a) human genome research (including genome-wide association studies), (b) the advent of epigenetic technologies and research, and (c) the development of more sophisticated statistical methodologies, researchers from neuroscientific and psychological backgrounds have approached these issues by incorporating molecular genetic concepts and methods (Harris & Deary, 2011; Kremen & Lyons, 2011; Plomin & Crabbe, 2000). The most common way to approach molecular genetic studies of development and aging is to investigate the associations between a particular DNA sequence and a particular phenotype (e.g., Deary, Wright, Harris, Whalley, & Starr, 2004). Single nucleotide polymorphisms (SNPs) are genes that differ by one nucleotide across individuals. To be considered a SNP, the variant must be present in at least one percent of the population. If a SNP is associated with a particular trait, there is a supposition that it may, at least in part, reflect underlying biological mechanisms.

Although genotype remains constant across the lifespan, there is evidence that particular genes may remain dormant during some developmental stages and become ‘switched on’ during others (Vogler, 2006), a fact that results in differential heritability related to age. Specifically, the percentage of heritability (i.e., proportion of genetic factors to non-genetic [or environmental] factors in determining the variability of a trait) increases across the lifespan until

approximately 80 years of age when it starts to decline (e.g., 40% for children, up to 80% in adulthood, and 60% after the age of 80 years; Reynolds, 2008). Heritability studies, which are based on twin research, produce information about population differences, but offer little information about individual characteristics. However, these studies do provide important information to molecular genetic researchers when making decisions about which gene affects which trait. In addition, these differences in heritability make studying genetic influences very important for cognitive aging researchers (e.g., Deary et al., 2004). For example, there is quantitative evidence of moderate to high (ranging from 30 to 70%) genetic influences on older adult cognition in a wide range of cognitive domains (Reynolds, 2008). Most association studies in cognitive aging have explored the relationship *Apolipoprotein E* (*ApoE)* has to the development of late onset AD. However, researchers are beginning to explore the relationship of other specific genes to cognitive aging (Kremen & Lyons, 2011; Laukka et al., 2013). The genes most commonly studied in regard to cognitive aging are: *ApoE*, *COMT*, and *BDNF*. In the next subsection we will explore *ApoE* and the little-explored *IDE* gene that has been recently linked to increased risk of T2D, dementia, and AD.

Apolipoprotein E (ApoE)

ApoE is a gene that is located on chromosome 19 and produces apolipoprotein E which is involved in lipid transport and cell maintenance and repair; *ApoE* modulates the efficiency of neuronal repair and plasticity (Lind & Nyberg, 2010; Mahley, 1988). A combination of two SNPs, *ApoE* consists of three isoforms *ApoE*2, *ApoE*3, and *ApoE*4, and the corresponding ε2, ε3, and ε4

alleles. The ε4 variant is associated with low density lipoprotein and the ε3 variant with high density lipoprotein (Mahley & Huang, 1999). *ApoE* has been studied most extensively in regard to risk of developing AD and increased risk of cardiovascular disease but has more recently been linked to the development of mild cognitive impairment and differences in cognitive performance (Boyle, Buchman, Wilson, Kelly, & Bennett, 2010; Brainerd, Reyna, Petersen, Smith, & Taub, 2011; Corder et al., 1993; Raz et al., 2009; Small, Rosnick, Fratiglioni, & Bäckman, 2004; Smith, 2002; Wisdom, Callahan, & Hawkins, 2011). The most common allele ε3 is considered the 'normal' form. The ε2 allele has been associated with lower levels of cholesterol, heart disease, risk of dementia or AD (Corder et al., 1993; Mahley & Rall, 2000), and better cognitive performance in non-demented populations (Small et al., 2004). The ε2 allele is considered by some to be a gene that promotes optimal aging (Smith, 2002). In contrast, the ε4 variant is the largest known risk factor for sporadic AD (Brainerd et al., 2011; Corder et al., 1993) and is associated with poorer cognitive outcomes in aging populations (Small et al., 2004). In the domains of EM and EF the ε4 allele was associated with the most pronounced performance deficits whereas ε2 allele carriers exhibited better performance than either ε3ε3, ε3ε4, or ε4ε4 carriers (Small et al., 2004). There is a paucity of research examining the effects of ε2 on EF but those available report ε2 carriers show no cognitive change or less cognitive change than ε4 carriers (Anstey & Christensen, 2000; Deary et al., 2004; Hyman et al., 1996; Lindahl-Jacobsen et al., 2012; Small et al., 2004; Wilson, Bienias, Berry-Kravis, Evans, & Bennett, 2002; Wisdom et al., 2011).

Research examining the relationship between EF and *ApoE* has indicated a negative effect associated with the ε4 allele and a positive (or protective) effect with the ε2 allele. More EF decrements have been associated with ε4 carriers than with non- ε4 carriers (Haan, Shemanski, Jagust, Manolio, & Kuller, 1999; Lee et al., 2008; Small et al., 2004; Swan, Lessov-Schlaggar, Carmelli, Schellenberg, & La Rue, 2005; Wisdom et al., 2011). There have been exceptions to these findings with researchers reporting no decrements in EF associated with ε4 (Deary et al., 2004). Of special interest to the current study is that EF decrements have been identified but only when considered in interaction with factors such as age (Raz et al., 2009).

The relationship between memory and *ApoE* has also been associated with negative effects for ε4 allele and positive (or protective) effects for ε2 allele (Anstey & Christensen, 2000; Lee et al., 2008; Swan et al., 2005). The ε2 allele has been associated with maintained or better EM performance over controls (Deary et al., 2004; Wisdom et al., 2011) and the ε4 allele with EM decrements (Anstey & Christensen, 2000; Deary et al., 2004; Nilsson et al., 2006; Small et al., 2004; Wisdom et al., 2011). One group of researchers found no EM deficits associated with ε4 allele (Raz et al., 2009). There is limited research reporting the effect of *ApoE* on SM. However, Nilsson and colleagues (2006) reported a negative ε4 x wave effect on SM performance. It is interesting to note the increased EM deficits observed when interactions such as ε4 x hypertension (or gender or age) were considered (Deary et al., 2004; Nilsson et al., 2006; Swan et al., 2005).

The mechanisms associated with *ApoE* and cognitive aging deficits may have to do with decreases in Aβ metabolism, increased loss of cholinergic neurons, or the impairments to neuronal integrity and repair associated with the ε4 allele (Fotuhi et al., 2009; Smith, 2002). ApoE has been associated with Aβ binding and aggregation. Higher levels of Aβ binding occur in presence of the ε2, followed by ε3, and finally by ε4, but it is unclear if this process has negative or positive consequences to human cognition. Smith (2002) points out that ApoE binding could lead to additional Aβ deposition or it could stimulate Aβ clearance. In regard to neuronal survival or repair, research shows that ε3 promotes more neurite extension and neuronal repair that the ε4 allele (Fotuhi et al., 2009; Smith, 2002). In addition, a protection against oxidative cytotoxicity has been observed with more protection associated with the three alleles in the following order, ε2 > ε3 > ε4. As *ApoE* is associated with cardiovascular outcomes, AD, and cognitive decline there is a supposition that cardiovascular mechanisms underlie the effects of *ApoE* on cognitive decline. Bender and Raz (2012b) reported *ApoE* ε4 carriers were more vulnerable to the effects of small differences in systolic blood pressure on prefrontal brain volumes. Altered cerebral blood flow, hippocampal volume differences, and differences in frontal brain activity have been associated with both ε4 and ε2 carriers, with ε4 carriers associated with cognitive deficits and ε2 with neuroprotective effects (Alexopoulos et al., 2011; Ferencz et al., 2013; Fotuhi et al., 2009; Lind, Larsson, et al., 2006; Lind, Persson, et al., 2006; Nilsson et al., 2006; Smith, 2002).

Insulin Degrading Enzyme (IDE)

IDE is a gene for which several variants have been linked to increased risk of Type 2 diabetes (T2D) and/or AD (Bartl et al., 2011). *IDE* is responsible for transcription of IDE, an enzyme that functions in the degradation of hormones and bioactive peptides. IDE was first recognized as the most important proteolytic enzyme for insulin and later identified in the processing of other glycemia regulating peptides (i.e., amylin, glucagon; Bennett, Duckworth, & Hamel, 2000; Shen, Joachimiak, Rosner, & Tang, 2006) and of a 4 kDa neuropeptide product of the human precursor protein, Aβ (Kurochkin & Goto, 1994).

The *IDE* locus has demonstrated a linkage peak on chromosome 10q which is a chromosomic region consistently linked to late onset Alzheimer's disease (Bartl et al., 2011; Carrasquillo et al., 2010; Farris et al., 2003; Lendon & Craddock, 2001). The mechanism through which this may work is thought to be associated with the degradation of insulin in the follow manner. Although *IDE* has also been associated with an increased risk of T2D, specific polymorphisms have not as yet been clearly identified and may in fact involve several SNPs located in *IDE* area (Bartl et al., 2011; Duggirala et al., 1999; Karamohamed et al., 2003; Rudovich et al., 2009; Vionnet et al., 2000; Zeggini et al., 2009). *IDE* risk alleles associated with T2D may result in lower capacity to degrade insulin leading to insulin resistance (Bartl et al., 2011) that in turn leads to the compensating hyperinsulinema associated with T2D and associated cognitive deficits (Awad et al., 2004; Umegaki, 2012). A different *IDE* haplotype has been associated with decreased risk of T2D, suggesting an increase in insulin degradation (Kwak et al.,

2008). The diversion of the limited supply of IDE to the degradation of insulin may be linked to increased Aβ levels (Qiu & Folstein, 2006), which is a hallmark of AD (Blomqvist et al., 2005; Kurochkin & Goto, 1994).

In a way compatible with the observed associations of *IDE* with Aβ degradation and its location on chromosome 10q, some *IDE* polymorphisms are risk factors for neurodegeneration in the form of AD, associations with mild cognitive impairment, or even normal cognitive decline (Bertram et al., 2000; Björk et al., 2007; Ertekin-Taner et al., 2004; Wang et al., 2012; see also Abraham et al., 2001; Boussaha et al., 2002). However, some variants of *IDE* (specifically, rs6583817, rs5786996, and rs4646953) are associated with increased levels of IDE and decreased levels of Aβ, suggesting the possibility of lowered risk for AD and perhaps associated relaxation of rates of normal cognitive decline (Bartl et al., 2011; Belbin et al., 2011). Carrasquillo and colleagues (2010) reported four *IDE* variants with significant relationships to IDE transcription. The highest association reported was for *IDE* rs6583817 and the minor allele for this variant correlated with elevated IDE expression, reduced Aβ levels, and reduced risk of AD. Whereas the relationship of *IDE* to sporadic AD status has been explored, little research has examined associations of *IDE* polymorphisms on neurocognitive performance (Okereke et al., 2009) with none for this particular *IDE* variant.

Gene x Environment Interactions

The genetic cognitive aging literature has made exploratory connections to age, gender, hypertension, and weight. For example, *ApoE* exhibits interactive

effects such that the risk allele (ε4) is associated with increased cognitive deficits (a) *ApoE* x age for EF (Raz et al., 2009), (b) *ApoE* x gender for SM (Sternäng et al., 2009), and (c) *ApoE* x hypertension, *ApoE* x PP, *ApoE* x gender, or *ApoE* x age for EM (Bender & Raz, 2012a; Deary et al., 2004; Nilsson et al., 2006; Swan et al., 2005). The connections between *ApoE, IDE,* vascular health, and T2D have not been extensively explored in cognitive aging research. It seems plausible that genes and health risk factors that affect cognition would work together to exacerbate or alleviate cognitive deficits or decrements (Corder et al., 1993; Raz et al., 2009).

In the cognitive aging literature the emphasis has been on determining patterns of cognitive performance and change; in particular, on the independent effects of specific factors thought to influence these patterns. These factors are not considered sufficient or necessary for the development of cognitive decline or dementia. For example carriers of the *ApoE* ε4 do not all develop AD and not all persons who develop AD have the ε4 allele. It is becoming more and more apparent that cognitive decline and/or dementia is the result of many factors that in combination lead to varying degrees of decline (Buckner, 2004; Fotuhi et al., 2009; Luck et al., 2013). Recently, researchers have been concentrating on the interactive effects of both genetic and environmental factors that have been associated with cognitive aging (Bender & Raz, 2012a, 2012b; Caselli et al., 2011; Deater-Deckard & Mayr, 2005; Goldberg et al., 2013; Haan et al., 1999; Josefsson et al., 2012; Lee et al., 2008; Luck et al., 2013; Raz et al., 2009; Sternäng et al., 2009; Yasuno et al., 2012). There are three important reasons for

doing this. First, the substantial interindividual difference in intraindividual change suggests a very large amount of unaccounted for variance in these models. Exploring the interactive effects helps to elucidate some of this unaccounted for variance. Second, independent effects are often so dependent on other factors that the independent effects do not manifest in the analyses but become significant in synergy with the modulating factors. This seems to be particularly evident in genetic x health factor interactions (Raz et al., 2009). Third, by examining several factors that are interactively associated with cognition we may be able to more clearly see the mechanisms that lead to poor cognitive outcomes, including exacerbated decline or even impairment. Some of the factors influencing cognitive aging (such as age, gender, or genotype) are non-modifiable, but other interactive factors (such as health status or lifestyle) are modifiable. If research can clearly identify the interactive factors that lead to poor cognitive outcomes, new programs and effective treatments can be developed that may enhance the possibility of sustained or improved cognitive performance and overall quality of life. It is important to continue to identify the factors that independently effect cognition; it is equally important to explore the interactive effects of these factors. The current research explored the independent and interactive effects of two genotypes and two health factors on cognitive aging.

Research Plan

This dissertation presents three programmatic studies addressing issues of gene x environment (health) interactions in predicting cognitive performance and up to 9-year change. Study 1 examined the independent and interactive effects of

IDE and T2D on EF across two waves of data. Study 2 expanded the dataset to include three waves of data and examined the independent and interactive effects of *IDE* and a different cardiovascular indicator, PP, on EF. Study 3 examined the independent and interactive effects of *ApoE* and PP on DM across the three waves of data.

Research goals (RG). The three studies were similar in the overall general research goals (a) determining the best fitting latent growth model, (b) testing independent effects of genetic and health factors as predictors in a conditional growth model on a cognitive measure, and (c) testing interactive effects of these predictors on a cognitive measure. The specific research goals of each study are listed next.

Study 1.* IDE *(rs6583817) polymorphism and Type 2 diabetes differentially modify executive function in older adults. We begin the series with an exploration of a gene x health interaction using *IDE* and T2D as they affect EF.

RG1. Using structural equation modeling in the context of a large sample of older adults, we estimate a latent variable model for EF using four manifest measures related to two potential EF dimensions. The purpose was to determine whether a one-factor or two-factor model would best represent EF in our population.

RG2. Using confirmatory factor analysis we test for longitudinal measurement invariance in order to determine the degree to which the latent variable was represented by the indicator variables across the two time points.

RG3. We used two-wave longitudinal data over a 40-year age band of aging (ages 53-95) to estimate latent growth mixture models examining the interindividual differences in intraindividual change in EF associated (independently) with T2D and *IDE.* We predicted that (a) adults without T2D would perform better than adults with T2D on EF tasks and (b) adults with the *IDE* major (G) allele (i.e., the allele with lower levels of IDE expression) would exhibit better EF outcomes than adults without a G allele.

RG4. We used path analyses to explore the potentially interactive effects of T2D and *IDE* on EF change. We expected that the *IDE* major (G) allele would moderate the harmful of effects of T2D on EF performance and change.

Study 2.* IDE *(rs6583817) polymorphism and pulse pressure are independently and interactively associated with level and change in executive function in older adults. The second study follows the first in that it examined the effects of *IDE* in relation to a continuous health variable related to T2D, pulse pressure. In addition, the sample was extended to a third wave of data.

RG1. To estimate an EF latent variable using four measures related to two EF domains and to test this model for longitudinal measurement invariance across three waves. We tested the model, which was accepted in the first study, across three waves of data to determine the degree to which the latent variable is represented by the indicator variables across the two time points

RG2. To determine the best fitting latent growth model for EF and for PP. This was analyzed to determine the independent change patterns for EF and PP.

We predicted that EF would show 9-year decline and that PP would show 9-year increases.

RG3. To determine how EF performance patterns of change in older adults (aged 53-95 years) were affected independently by PP and *IDE* (rs6583817). We predicted that (a) increased levels of PP would have a negative effect on EF performance and 9-year change and (b) the *IDE* major (G) allele would have a positive effect on EF performance and 9-year change.

RG4. To determine how *IDE* allele-EF relationships in older adults were modified by PP. We expected that PP level would modify the protective effect of the *IDE* G allele on EF performance and 9-year change.

Study 3. Genetic (*ApoE*) and vascular health (pulse pressure) influences on the aging of declarative memory: Selective protective effects for ε2 carriers in level and change of episodic memory. The third study supplemented the second study by examining the effects of PP and expanding to a different cognitive domain, DM (EM and SM) and a different genetic factor associated with memory, *ApoE*.

RG1. To estimate a DM variable using six measures related to two memory domains (i.e., EM, SM) and to test this model for longitudinal measurement invariance across three waves.

RG2. To determine the best fitting latent growth model for DM (EM and SM) and for PP. We predicted that (a) EM would exhibit 9-year decline, (b) SM would exhibit no 9-year change, and (c) PP would exhibit 9-year increases.

RG3. To determine how EM and SM performance patterns in older adults (aged 53-95 years) were affected independently by PP and *ApoE*. We predicted that (a) PP would have a negative effect of EM performance and change, (b) *ApoE* ε4 allele would have a negative effect on EM performance and change, (c) *ApoE* ε2 allele would have a positive effect on EM performance and change, but (d) SM would be unaffected by either PP or *ApoE* geneotype.

RG4. To determine if PP and *ApoE* interact to influence EM and SM performance and change. We expected that (a) *ApoE* ε4 would increase the detrimental effects of PP and (b) *ApoE* ε2 would modify the detrimental effects of PP.

Chapter Two

Method

The purpose of this chapter is to give a general overview of the methods, as they apply to the three included studies. Specific methodological explanations for each of the studies are included in the individual methods section respectively.

Victoria Longitudinal Study (VLS)

Whereas cross sectional studies allow researchers to draw inferences about cognitive difference associated with age groups, longitudinal studies provide direct evidence for cognitive changes associated with aging as they may be associated with a variety of risk or protection factors (Anstey, 2012; Arvanitakis et al., 2004; Elias et al., 2004; Okereke et al., 2009; Reynolds, 2008; Waldstein, Giggey, Thayer, & Zonderman, 2005). The VLS offers many opportunities for examination of both independent and interactive effects of health factors (i.e., T2D, PP) and genetic factors (i.e., *ApoE, IDE*) on differences and change in cognition with aging.

The VLS is a large-scale, long-term investigation of human aging that embodies the principle that human aging is multidimensional and multidirectional. The overarching goal of the VLS is to advance our understanding of how and why cognition changes with aging (Baltes & Smith, 1997; Dixon & de Frias, 2004; Dixon et al., 2012). The study investigates a wide range of factors known to change across adulthood and thought to explain interindividual differences in intraindividual change associated with aging. Included in the VLS are biological, medical or health-related, lifestyle,

environment, functional, demographic, and psychological factors that potentially influence cognitive changes with aging. Important to the study of adult cognition is the conceptual breadth and theoretical depth of the neurocognitive instruments utilized in the regular VLS data collection. The VLS follows a longitudinal sequential design that began with Sample 1 in the late 1980s. A second independent sample (Sample 2) began in the early 1990s, and a third (Sample 3) in the early 2000s. Each sample included adults initially aged 55-85 years of age that were re-tested at approximately 4-year intervals. Each testing session takes approximately 12 hours for each individual. To mitigate fatigue, these sessions are spread across four separate occasions, usually one week apart. VLS genotyping occurred in the 2009-2011 period and was limited by funding arrangement to about 700 continuing VLS participants. The studies included in this dissertation were comprised of all eligible participants with genetic data from the most recent full waves of the three VLS samples.

Overview of Participants for the Three Studies

Participants were community-dwelling adults (initially aged 55-85 years) drawn from the VLS. Using standard procedures (e.g., Dixon et al., 2012; Small et al., 2011), we assembled longitudinal data consisting of three samples and all available waves (up to three) in the 2000 - 2011 period. We use a standard nomenclature to refer to Sample (S) and Wave (W) followed by a numerical digit (details follow). The executive function tasks and several of the memory tasks required for this study were available in the VLS neuropsychological battery active during this period. Notably, the first wave included for each sample was the

first exposure to the executive function tasks. The data set assembled included (a) Sample 1 (S1) Waves 6 and 7, (b) Sample 2 (S2) Waves 4 and 5, and (c) Sample 3 (S3) Waves 1, 2, and 3. The mean intervals between the waves of data collection were 4.44 (W1-W2) and 4.46 (W2-W3) years. For terminological efficiency, the respective earliest wave of each sample became Wave 1 (W1 or baseline) for the current study, the respective second wave became Wave 2 (W2), and the respective third wave became Wave 3 (W3). It is important to note that Study 1 utilized only two waves of data (W1 and W2) whereas Study 2 and Study 3 utilized three waves of data (W1, W2, and W3).

Given the necessity for both genetic and longitudinal data in this study, these factors defined the initial opportunity in sample selection. After initial evaluations of the 700 VLS continuing and genotyped participants, the eligible source sample consisted of 683 participants. Several exclusionary criteria were applied to this sample to arrive at these numbers (a) a diagnosis of Alzheimer's disease or vascular dementia, (b) a Mini-Mental Status Exam (MMSE; Folstein, Folstein, & McHugh, 1975) score of less than 26 for Study 1 and less than 24 for Study 2 and 3, (c) a self-report of "severe" for potential comorbid conditions (i.e., epilepsy, head injury, depression), (d) a self-report of "severe" or "moderate" for potential comorbid diseases such as neurological conditions (i.e., stroke, Parkinson's disease), and (e) insufficient cognitive data. Each study consisted of a slightly different sample and the accompanying characteristics and sample size numbers are reported in the methods sections of the studies.

Cognitive Measures

The cognitive measures utilized for the three studies are outlined in detail in the methods sections associated with each study. The EF measures used in Study 1 and Study 2 included two inhibition tasks (i.e., Hayling sentence completion, Stroop) and two shifting tasks (i.e., Brixton spatial anticipation, Color trails Part 2). The DM measures used for Study 3 included two EM tasks (i.e., word recall, Rey auditory verbal learning), and two SM tasks (i.e., fact recall, vocabulary).

Health Risk Factors

Type 2 diabetes (T2D). T2D was used in Study 1 only and was coded as a dichotomous variable – either yes or no for having the condition. We applied systematic T2D inclusion and exclusionary criteria (i.e., n = 119 participants with unconfirmed T2D status were excluded). We then applied the standard VLS multi-level diagnostic regimen for classifying T2D (see McFall et al., 2010; Yeung et al., 2009). Specifically, inclusion into the T2D group required all of the following conditions: (a) W1 self-report of T2D diagnosis, (b) W1 specified method of treatment (i.e., oral medication, insulin, diet and exercise, no control), (c) W1 objective evidence of reported medication, and (d) W2 validation of T2D status (repeating the three previous steps for the second wave).

Pulse pressure (PP). PP, a reliable proxy of the arterial stiffness aspect of vascular health, is calculated as follows: PP = systolic – diastolic blood pressure. For all analyses PP was used as a continuous variable and was centered at 52 mmHg, the approximate population mean at baseline. For these analyses, we developed a sample of typically aging older adults and thus those with self-

reported higher blood pressure and blood pressure medication use were included in the analyses. PP is calculated across 8 measurements collected at each wave for each participant.

DNA Extraction and Genotyping

Saliva was collected according to standard procedures from Oragene-DNA Genotek and stored at room temperature in the Oragene® disks until DNA extraction. DNA was manually extracted from the saliva sample mix using the manufacturer's protocol quantified using a NanoDrop® ND-1000 Spectrophotometer (Wilmington, DE). Genotyping were carried out by using a PCR-RFLP strategy to analyze the allele status for *ApoE* (determined by the combination of the SNPs rs429358 and rs7412) and *IDE* (rs6583817). Briefly, SNP-containing PCR fragments were amplified from 25 ng genomic DNA using specific primers (*ApoE*: Fwd: 5'-GGCACGGCTGTCCAAGGA-3'; Rev: 5'-GCCCCGGCCTGGTACACTGCC-3'; *IDE*: Fwd: 5'-AATATATGGGCAAATATTAAGTGCAC-3'; Rev: 5'-CAGTTGTGGGAATATATT CCTGAG-3'). Reactions were setup in 96-well plates using the QIAgility robotic system (QIAgen). RFLP analysis was then performed on a high resolution DNA screening cartridge on a QIAxcel capillary electrophoresis system (QIAgen) using the protocol OL700 after digestion of the PCR amplicons with the restriction enzymes of (a) *ApoE*: HhaI (NE Biolabs) for 16 hours at 37°C and (b) *IDE*: DdeI (NE Biolabs) for 4 hours at 37°C. The analysis was confirmed on migration of the restriction fragments on 10 or 15% acrylamide gels for each SNP.

Statistical Analyses

For the most part, our statistical analyses plan applied to all three of the included studies. Variations in this plan did occur, however; these are listed briefly below and described in more detail in the individual study methods section. Analyses pertaining to our research questions included confirmatory factor analysis and latent growth modeling. Statistical model fit for all analyses was determined using standard indexes: (a) χ^2 for which a good fit would produce a non-significant test ($p > .05$) indicating that the data are not significantly different from the estimates associated with the model, (b) the comparative fit index (CFI) for which fit is judged by a value of $\geq .95$ as good and $\geq .90$ as adequate, (c) root mean square error of approximation (RMSEA) for which fit is judged by a value of $\leq .05$ as good and $\leq .08$ as adequate, and (d) standardized root mean square residual (SRMR) for which fit is judged by a value of $\leq .08$ as good (Kline, 2011).

Structure and measurement invariance of latent variables. All latent variable analyses were conducted using Mplus 6 (Muthén & Muthén, 2010). The first step in this analysis was to use confirmatory factor analysis to test the underlying structure of indicators for latent variables. Confirmatory factor analysis tests the hypothesis that data fit a measurement model based on a theoretical understanding of the shared variance for factors thought to contribute to a latent variable.

Once the best confirmatory factor model was established a series of longitudinal invariance tests were conducted to confirm that the indicators chosen

to define the latent variable are the same across time. Two-wave invariance was tested for Study 1. Three-wave invariance was tested for Study 2 and Study 3. The invariance testing included (a) configural invariance, the same indicator variables load onto the latent variable at each time point, (b) metric invariance, factor loadings are constrained to be equal for each latent variable indicating that the latent variable is measuring the same construct, (c) scalar invariance, indicator intercepts are constrained to be equal allowing mean differences to be evident at the latent mean level, and (d) residual invariance, indicator residuals are constrained to be equal accounting for error variability and thus group differences are based on their common variability. We estimated factor scores for the cognitive measures and used these scores for all subsequent latent growth models. In addition, we used multiple imputations to estimate missing values for models that included PP (i.e., Study 2 and Study 3). By VLS convention, 50 datasets were generated and pooled before analyses were conducted.

Latent growth models. We used age as a continuous factor and computed latent growth models with individually varying ages. Using age as the basis of measurement, rather than wave, allowed an accelerated longitudinal design across the youngest and the oldest age for each participant (Dixon et al., 2012). Age was centered at 75 years of age, as this was the approximate center point of the 40-year band of data (i.e., 53-95 years) and because 75 is an observed meaningful point in cognitive aging (Dixon et al., 2012; Schaie, 2013; Small et al., 2011).

To identify the functional form of change, we determined the best-fitting unconditional growth model by testing in sequence (a) a fixed intercept model,

which assumes no inter- or intraindividual variation; (b) a random intercept model, which models interindividual variability in overall level but no intraindividual change; (c) a random intercept fixed slope model, which allows interindividual variation in level but assumes all individuals change at the same rate; and (d) a random intercept random slope model, which models interindividual variation in initial level and change (Singer & Willett, 2003).

Conditional growth models testing the independent effects of T2D, PP, *ApoE*, and *IDE*. Using the best unconditional growth model identified for EF and DM, predictors were added to the model (see Figure 2-1). For Study 1, the intercept and slope of the best fitting EF model were regressed separately on (a) *IDE* genotype and (b) T2D status. For Study 2, the intercept and slope of the best fitting EF model were regressed separately on (a) *IDE* genotype and (b) PP. For Study 3, the intercept and slope of the best fitting EM and SM model were regressed separately on (a) *ApoE* genotype and (b) PP.

Testing the interactive effects. We tested interactive effects on level and change as follows: Study 1, *IDE* x T2D; Study 2, *IDE* x PP; Study 3, *ApoE* x PP. Based on the results of the previous research goals within each study, we tested the possible moderation effects of T2D or PP on the non-modifiable genetic allele factor-cognition relationship. For Study 1, we added intercept and slope regression pathways for *IDE* genotype, T2D status, and *IDE* genotype x T2D status to test our moderation hypothesis. For Study 2 and 3, we tested the moderation effects of the genetic allele factor-cognition relationship by using PP as a predictor for genotype groups (i.e., *IDE* [G+/G-]; *ApoE* [ε2+, ε3, ε4+]).

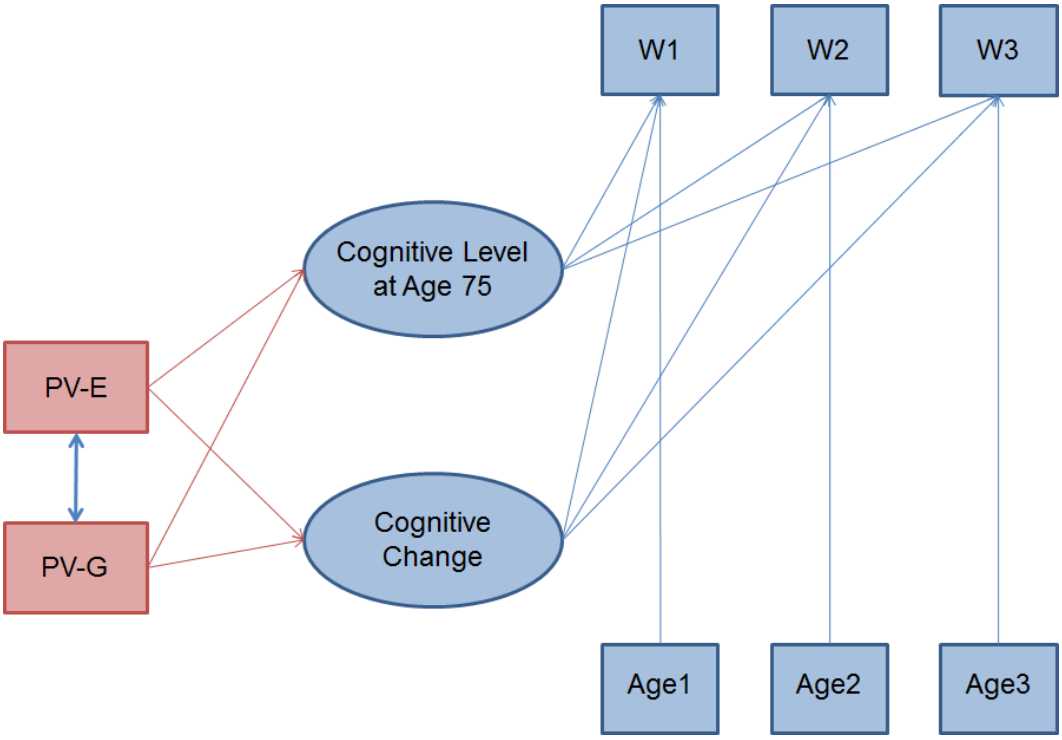

Figure 2-1. Theoretical conditional growth model with individually-varying age as time variable, and individual and interactive predictors of cognitive level (at centering age of 75 years) and cognitive change. W = wave; Age = individually-varying age at each wave; PV-E = environmental (health) predictor variable; PV-G = genetic predictor variable.

Chapter Three (Study 1)

IDE (rs6583817) Polymorphism and Type 2 Diabetes Differentially Modify Executive Function in Older Adults

Increasingly, mechanisms associated with neurocognitive phenotypes of normal aging, preclinical (impaired) aging, and neurodegenerative diseases are understood as exerting influence either independently or interactively (e.g., Lindenberger et al., 2008). These mechanisms include both risk-elevating and risk-reducing influences that range across potentially modifying domains such as neurobiological (e.g., genetic), bio-health (e.g., metabolic conditions), and environmental (e.g., lifestyle activities) (e.g., Nagel et al., 2008; Raz et al., 2008; Raz et al., 2011). We examine independent and interactive associations of two factors receiving growing attention for their influence on normal cognitive aging and Alzheimer's disease (AD). Specifically, we test associations of a recently noted *Insulin Degrading Enzym*e polymorphism (*IDE* rs6583817) and Type 2 diabetes (T2D) on both level and actual two-wave change for a latent variable of executive function in a large sample of older adults spanning 40 years of aging. Among other interesting *IDE* polymorphisms, this *IDE* variant has been identified as carrying the strongest association with AD (Carrasquillo et al., 2010) and may be particularly promising as a marker of normal or preclinical neurocognitive changes. Correspondingly, T2D has been linked with AD risk and accelerated neurocognitive deficits (e.g., EF) in normal aging, and genetic susceptibility, but further research on genetic influences on level and (especially) longitudinal change in associated cognitive decline is required (Seaquist et al., 2012). We

assembled a 2-wave longitudinal data set from the Victoria Longitudinal Study (VLS) and performed structural and latent growth curve analyses to distinguish potential patterns, influences, and interactions among the neurobiological (*IDE* variant) and metabolic-health (T2D) factors on EF level and 4-year change.

Executive functions (EF) are involved in monitoring, organizing, and regulating complex cognitive operations, especially those requiring planning, problem solving, and goal directed components (West, 1996). As linked to aging-related changes in prefrontal cortex, EF performance declines with aging (Turner and Spreng, 2012). Such decrements may (a) be observed in terms of both level and structure (dimensionality) of EFs, (b) create difficulties for cognitive performance, (c) be affected by risk (or protection) factors from biological (e.g., genetic), neurobiological (e.g., dopaminergic), health (e.g., diabetes), and environmental (e.g., lifestyle) domains, (d) predict mild cognitive impairment and sporadic AD, and (e) be exacerbated or moderated by combinations exerting increasing influence with aging (e.g., de Frias et al., 2006; Grober et al., 2008; Lindenberger et al., 2008; Luszcz, 2011; Nathan et al., 2001; Rapp and Reischies, 2005; Wishart et al., 2011; Yeung et al., 2009). In addition to gradual changes in level of performance, the structure of EF varies systematically across the lifespan. The observed pattern includes unitary (single-factor) models for children (Wiebe et al., 2008; Wiebe et al., 2010), differentiated three-factor models for prefrontal mature young adults (Miyake et al., 2000), and de-differentiated single-factor models for typical aging adults (e.g., Adrover-Roig et al., 2012; de Frias et al., 2006; but see exception reported by de Frias et al., 2009, for older adults with

sustained cognitive and brain health). Current emphases in EF and aging research call for studying longitudinal trajectories as potentially modified by neurobiological, metabolic, and health covariates (Luszcz, 2011).

Accordingly, we identified two biological and health factors theoretically related to the EF cognitive phenotype. First, genetic involvement in individual differences in executive functioning is apparent and complex (Friedman et al., 2008; Kremen et al., 2009). We selected and tested the *IDE* gene because several variants of this gene have been linked to risk of developing both T2D and AD (Bartl et al., 2011). IDE has the function of degrading hormones and bioactive peptides. It was first recognized as the most important proteolytic enzyme for insulin and has since been identified in the processing of other glycemia regulating peptides (amylin and glucagon; Bennett et al., 2000; Shen et al., 2006) and of a 4 kDa neuropeptide product of the human precursor protein, Amyloid Beta (Aβ; Kurochkin and Goto, 1994). In the genetics realm, the *IDE* locus has demonstrated a linkage peak for both T2D and late onset Alzheimer's disease (Bartl et al., 2011; Carrasquillo et al., 2010; Farris et al., 2003; Grarup et al., 2007). Although *IDE* has also been associated with an increased risk of T2D, specific polymorphisms have not as yet been clearly identified and may in fact involve several SNPs located in the *IDE* area (Bartl et al., 2011; Duggirala et al., 1999; Karamohamed et al., 2003; Rudovich et al., 2009; Vionnet et al., 2000; Zeggini et al., 2008). *IDE* risk alleles are associated with lower capacity to degrade insulin possibly resulting in insulin resistance (Bartl et al., 2011), which could in turn lead to the compensating hyperinsulinema associated with T2D and

implicated cognitive deficits (Awad et al., 2004; Umegaki, 2012). A different *IDE* haplotype has been associated with decreased risk of T2D, suggesting an increase in insulin degradation (Kwak et al., 2008). In fact, the diversion of the limited supply of IDE to the degradation of insulin may be linked to increased Aβ levels (Qiu and Folstein, 2006), which is a hallmark of AD (Blomqvist et al., 2005; Kurochkin and Goto, 1994).

Arguably compatible with the observed associations of *IDE* with Aβ degradation and its location on chromosome 10q (a chromosomal region consistently linked to late-onset AD; Lendon & Craddock, 2001), some *IDE* polymorphisms are risk factors for neurodegeneration in the form of AD, associations with MCI, or even normal cognitive decline (Bertram et al., 2000; Björk et al., 2007; Ertekin-Taner et al., 2004; Wang et al., 2012; see also Abraham et al., 2001; Boussaha et al., 2002; Vardy et al., 2012). However, some variants of *IDE* (specifically, rs6583817, rs5786996, and rs4646953) are associated with increased levels of IDE and decreased levels of Aβ, suggesting the possibility of lowered risk for AD (Bartl et al., 2011; Belbin et al., 2011). Conceivably—but not previously studied—differences in risk of AD outcome status may be preceded by differences in risk of level and change in cognitive decline. Carrasquillo and colleagues (2010) reported four *IDE* variants with significant relationships to IDE transcription. The present variant, *IDE* rs6583817, had the highest association. Notably, the minor allele for this variant correlated with elevated IDE expression, reduced Aβ levels, and reduced risk of AD status. Whereas the relationship of *IDE* to sporadic AD status has been explored, little

research has examined associations of *IDE* polymorphisms on neurocognitive performance (Okereke et al., 2009; see also Vardy et al., 2012), and none for this particular and promising *IDE* variant. We selected this *IDE* polymorphism to examine whether the minor allele (A) or the major allele (G) would be associated with normal aging-related preservation of (a) performance level of the EF phenotype and (b) trajectory of 4-year change in a large sample of older adults.

For the second factor we selected T2D, which has been linked to increased risk of AD (Arvanitakis et al., 2004; Profenno et al., 2010; Qiu and Folstein, 2006) and changes in the non-AD brain (e.g., exacerbated insulin dysregulation, disrupted Aβ clearance) that are associated with decrements in neurocognitive performance (Awad et al., 2004; Cholerton et al., 2011; Nilsson, 2006; Okereke et al., 2009; Seaquist et al., 2012; Strachan et al., 2011). For example, older adults with T2D have exhibited lower performance on speed-related EF shifting and inhibition tasks in both cross sectional and short-term longitudinal studies (Biessels et al., 2008; Fischer et al., 2009; Yeung et al., 2009). These decrements have been linked to mediators from functional, vascular, genetic, and other biological domains (McFall et al., 2010; Strachan et al., 2011). Regarding AD, insulin resistance (hyperinsulinemia) reduces the effectiveness with which IDE degrades Aβ oligomers in the brain, a link to the neuropathogenesis of AD. When regulated in normal aging, cerebral insulin performs multiple cognitive-supportive functions, such as increasing neurotransmitter levels, enhancing glucose utilization, and promoting lipid metabolism. However, when the aging brain experiences chronic dysregulation (or reduced levels) of insulin uptake, cognitive

deficits may be exacerbated to levels that are consistent with those of clinically impaired patients (Cholerton et al., 2011). Insulin receptors are distributed in brain regions such as the hippocampus and frontal lobe, with the latter opening the possibility that EF may be a target cognitive phenotype for research integrating T2D, *IDE* polymorphisms, and human aging.

The aim of this study is to examine potential independent and interactive contributions of selected genetic (*IDE* rs6583817) and metabolic-health (T2D) markers to concurrent performance and longitudinal change in executive functioning among a large sample of older adults. We test the relationship with sensitive statistical techniques as implemented concurrently and across two longitudinal waves. Notably, the approach includes a unique combination of a risk factor (T2D) and a potential risk-reduction factor (*IDE*) theoretically related to executive functioning, an important cognitive phenotype of aging. We pursue four specific research goals. First, using structural equation modeling in the context of a large sample of older adults, we estimate a latent variable model for EF using four manifest measures related to two potential EF dimensions. Second, using confirmatory factor analysis we test for longitudinal measurement invariance. Third, we used two-wave longitudinal data over a 40-year age band of aging (ages 53-95) to estimate latent growth mixture models examining the interindividual differences in intraindividual change in EF associated (independently) with T2D and *IDE.* Fourth, we used path analyses to explore the potentially interactive effects of T2D and *IDE* on EF change. Based on previous reports, we

hypothesized an interaction between the two factors in which the *IDE* rs6583817 would moderate the harmful effects of T2D on EF performance and change.

Method

Participants

Data were assembled from the Victoria Longitudinal Study (VLS), a large-scale study of biomedical, genetic, health, cognitive, and neuropsychological aspects of aging (see Dixon and de Frias, 2004, for methodological details). The VLS and all present data collection procedures are in full and certified compliance with prevailing human research ethics guidelines and boards. Written informed consent was obtained from all participants. Using standard procedures (e.g., Dixon et al., 2012; Small et al., 2011), we assembled a two-wave longitudinal data set. We began with a Wave 1 (W1) data set of $N = 694$ adults (ages 53-100 years), all with genetic data. We then applied T2D inclusion and participant exclusionary criteria, targeting conditions that could modify EF performance independent of the factors modeled in this study. We excluded $n = 119$ participants with unconfirmed T2D status, MMSE scores<26, reported severe health conditions with cognitive implications (i.e., high blood pressure), moderate or severe stroke, anti-psychotic medication, and incomplete EF data. Not excluded were participants on anti-hypertension medications. An additional participant ($n = 1$) provided data only for W2. From the remainder we applied the standard VLS multi-level diagnostic regimen for classifying T2D (see McFall et al., 2010; Yeung et al., 2009). Specifically, inclusion into the T2D group required all of the following conditions: (a) W1 self-report of T2D diagnosis, (b) W1

specified method of treatment (i.e., oral medication, insulin, diet and exercise, no control), (c) W1 objective evidence of reported medication, and (d) W2 validation of T2D status (repeating the three previous steps).

The final W1 sample included *n* = 574 adults (*M* age = 70.1, *SD* = 8.54, range = 53.2 – 95.2 years, *n* = 384 [66.9%] women). The diagnostic procedure identified *n* = 46 [8.0%] adults with T2D (*M* age = 71.4, *SD* = 7.97, range = 55.4 – 90.5, *n* = 24 [52.2%] women). The remainder constituted the normal aging group of *n* = 528 (*M* age = 70.0, *SD* = 8.59, range = 53.2 – 95.2 years, *n* = 360 [68.2%] women). At W2, *n* = 474 of W1 adults were available (*M* age = 74.3, *SD* = 8.46, range = 57.3 – 94.5 years, *n* = 316 [66.7%] women). This included *n* = 101 non-returning adults (*M* age at W1 = 71.3, *SD* = 8.74, range = 55.05 – 95.2 years, *n* = 69 [68.3%] women, and *n* = 1 adult without W1 data. Returning participants were similar to non-returning participants in age, education, and gender distribution. In addition, genotype percentages within the three allelic combinations were quite similar (returnees/non-returnees): AA (13.5/14.9%), AG (64.6/67.3%), GG (21.9/17.8%) and T2D proportions were almost identical (7.8/8.9%). The standard T2D diagnostic procedure identified *n* = 37 (7.8%) adults with T2D (*M* age = 76.0, *SD* = 7.76, range = 60.5 – 91.1 years, *n* = 21 [56.8%] women). The remainder constituted the W2 normal aging group of *n* = 437 (*M* age = 74.2, *SD* = 8.51, range = 57.3 – 94.5 years, *n* = 295 [67.5%] women). Table 3-1 presents additional demographic data organized by genetic allelic combination and wave. The 4-year retention rate was about 80% with equivalent ratios of the two groups at both waves. The longitudinal statistical

models do not implement listwise deletion, so all participants contributed data at either one or both waves.

Executive Function Measures

Hayling sentence completion test. This task, which indexed inhibition (Burgess and Shallice, 1997), consisted of two sets of 15 sentences, each having the last word missing. Section A required completing the sentence quickly, and measured initiation speed. Section B required completing the sentence with an unconnected word quickly, and measured response suppression. Response speed on both sections and errors on Section B were used to derive an overall scaled score for each participant on a scale ranging from 1 (impaired) to 10 (very superior).

Stroop test. This task taps inhibitory processes by requiring the respondent to ignore the automatic response of reading a printed word and to instead name the color of ink in which the word is printed (Taylor et al., 1997). The performance score was the interference index and reflected slowing in response to interference in Part C ([Part C_{time} – Part A_{time}]/Part A_{time}). Lower scores indicated better performance.

Brixton spatial anticipation test. This task (Burgess and Shallice, 1997) was a rule-attainment (or shifting) task based on the Wisconsin Card Sorting Task (Berg, 1948). Participants are required to deduce simple and changing patterns, measuring their ability to abstract logical rules (Andrés and Van der Linden, 2000). The total errors were recorded and these errors (maximum 54) were

converted to scaled scores. An overall standardized scaled score based on a scale ranging from 1 (impaired) to 10 (very superior) was used for analysis.

Color trails test part 2. Indexing shifting, the Color trails test part 2 (D'Elia et al., 1996) was similar to the Trail Making Test (Reitan and Wolfson, 1992) but minimized the influence of language. Part 2 required participants to connect numbers from 1 to 25 alternating between pink and yellow circles and disregarding the numbers in circles of the alternate color. The latency score for Part 2 was used for analysis. Lower scores indicate better performance.

DNA Extraction and *IDE* Genotyping

Saliva was collected according to standard procedures from Oragene DNA Genotek and stored at room temperature in the Oragene® disks until DNA extraction. DNA was manually extracted using the manufacturer's protocol and quantified using a NanoDrop® ND-1000 Spectrophotometer (Wilmington, DE). Genotyping was carried out by using a PCR-RFLP strategy to analyze the allele status for *IDE* (rs6583817). Briefly, SNP-containing PCR fragments were amplified from 25 ng of genomic DNA using specific primers (Fwd: 5'-AATATATGGGCAAATATTAAGTGCAC-3'; Rev: 5'-CAGTTGTGGGAATATATT CCTGAG-3'). Reactions were setup in 96-well plates using the QIAgility robotic system (QIAgen). RFLP analysis was performed on a high resolution DNA screening cartridge on a QIAxcel capillary electrophoresis system (QIAgen) using the protocol OL700 after digestion of the PCR amplicons with the restriction enzymes DdeI (NE Biolabs) for 4 hours at

37°C. The analysis was confirmed upon migration of the restriction fragments on 10 or 15% acrylamide gels for the SNP.

For genetic analyses the *IDE* genotypes were categorized by the presence of an A allele (A+ = A/A, homozygous minor allele, and G/A, heterozygous allele) or the absence of an A allele (A- = G/G, homozygous major allele). No effect on EF performance was observed; therefore, the alternative configuration (presence or absence of an G allele) was used for analyses. *IDE* genotypes were categorized by the presence of a G allele (G+ = G/G, homozygous major allele, and G/A, heterozygous allele) or the absence of a G allele (G- = A/A, homozygous minor allele).

Statistical Analyses

Statistical model fit for all analyses was determined using standard indexes: (a) χ^2 for which a good fit would produce a non-significant test ($p > .05$) indicating that the data are not significantly different from the estimates associated with the model, (b) the comparative fit index (CFI) for which fit is judged by a value of ≥ .95 as good and ≥ .90 as adequate, (c) root mean square error of approximation (RMSEA) for which fit is judged by a value of ≤ .05 as good and ≤ .08 as adequate, and (d) standardized root mean square residual (SRMR) for which fit is judged by a value of ≤ .08 as good (Kline, 2011).

Analyses for research goal 1 (EF latent model) and research goal 2 (invariance testing across two waves). First, we used Mplus 6 (Muthén and Muthén, 2010) to conduct confirmatory factor analysis. We tested two models (a) a single factor model and (b) a 2-factor model consisting of inhibition (Hayling,

Stroop) and shifting (Brixton, Color Trials test part 2). Second, we tested longitudinal (two-wave) measurement invariance including (a) configural invariance, the same indicator variables load onto the latent variable used to test the model across time, (b) metric invariance, factor loadings are constrained to be equal for each latent variable indicating that the latent variable is measuring the same construct, (c) scalar invariance, indicator intercepts are constrained to be equal allowing mean differences to be evident at the latent mean level, and (d) residual invariance, indicator residuals are constrained to be equal accounting for error variability and thus group differences are based on their common variability. We estimated factor scores for EF in Mplus and used these in subsequent latent growth models.

Analyses for research goal 3 (EF latent growth models) and research goal 4 (path analyses with *IDE* and T2D). We coded age as a continuous factor and computed latent growth models with individually-varying ages. We centered the age variable at 75, an inflection point for many cognitive domains (Small et al., 2011). To identify the functional form of change, we determined the best-fitting unconditional growth model by testing in sequence (a) a fixed intercept model, which assumes no inter- or intraindividual variation, (b) a random intercept model, which models interindividual variation but no intraindividual change, (c) a random intercept fixed slope model, which allows interindividual variation in initial performance but assumes all individuals change at the same rate, and (d) a random intercept random slope model, which models interindividual variation in both initial performance and change over time (Singer

and Willett, 2003). After the best unconditional growth model was determined, predictors of change were examined by regressing intercept and slope separately on *IDE* genotype (Model 1) and T2D status (Model 2). Next, we added intercept and slope regression pathways for *IDE* genotype, T2D status, and *IDE* genotype xT2D status to test our moderation hypothesis (Model 3).

Results

Research Goal 1 (EF Latent Model) and Research Goal 2 (Invariance Testing Across Two Waves)

We performed confirmatory factor analyses for EF. Regarding research goal 1, the one-factor EF model fit the data well for both W1 and W2. In contrast, the two-factor model could not be estimated at either wave, resulting in the absence of a positive definite variance-covariance matrix (see Table 3-2 for model goodness of fit indexes). Therefore, as observed in earlier research, we accepted the single-factor model for normal older adults. Regarding research goal 2, we conducted invariance testing on the single-factor model. The model holding indicator factor loadings equal across W1 and W2 fit the data well, thus indicating metric invariance. Fixing intercepts to be equal across time resulted in significantly poorer fit to the data according to the χ^2 difference test, although the other fit indexes were adequate. We conducted tests of partial scalar invariance by freeing intercepts for each indicator in turn. These analyses supported a model with intercepts fixed to be equal across time for inhibition (Stroop and Hayling) but not shifting (Color Trails test part 2 and Brixton) tasks. Overall, we observed metric invariance for the single-factor EF model, but only partial scalar

invariance. This result showed that the model measured the same EF construct across time, but that the manifest variables marking EF shifting exhibited mean differences across time outside of the latent differences. Latent variable reliability was indicated in three ways: (a) significant factor loadings for all four manifest variables at each wave of data (range = .31 to .75), (b) metric invariance across the two waves of data (χ^2 = 23.97, *df* = 20, *p* = .244; RMSEA = .019 (.000-.042); CFI = .995; SRMR = .029), and (c) adequate bivariate correlations across indicator variables for the two waves (range *r* = 0.4 to 0.7).

Research Goal 3 (EF Latent Growth Model) and Research Goal 4 (Path Analyses with *IDE* and T2D)

We performed latent growth modeling using estimated EF factor scores. The best fitting unconditional growth model for EF was established as a random intercept, random slope latent growth model (see Table 3-3 for model goodness of fit indexes). Next, building on this model of change over time, three additional models were tested to determine if *IDE* genotype or T2D status predicted EF initial performance or change. Finally, we tested a moderation model to examine if *IDE* genotype mitigates the negative effects of T2D status.

As shown in Table 3-3, Model 1 was used to test if *IDE* predicted EF initial performance (at the age 75 centering point) or change. The intercept and slope of EF was regressed on *IDE* genotype. We first tested the presence of the *IDE* minor allele (A+ or A-), which produced no difference in initial performance of EF (*M*s = .063 and .001 respectively, *p* > .05) or rate of EF decline (*M*s = -.021 and -.022 respectively, *p* > .05). However, the *IDE* major allele (G+ or G-) predicted

performance of EF (see Figure 3-1). Specifically, at the stipulated intercept (age 75) adults with a G allele (the G+ group) performed significantly better (*M* = .058) than those without a G allele (G- group; *M* = -.248). In addition, as shown in Figure 3-1, *IDE* genotype predicted linear change in EF performances. Specifically, adults with a G allele exhibited significantly less decline (*M* = -.019) in EF performance than those without a G allele (*M* = -.037). Furthermore, a significant dose-response effect for EF performance level at age 75 years was observed. Participants with A/A performed the poorest (*M* = -.133), those with A/G performed better (*M* = .005), and those with G/G performed best (*M* = .143, *p* = .043). There was no dosage affect for EF change (*p* > .05).

Model 2 tested if T2D predicted EF initial performance or change. The intercept and slope of EF was regressed on T2D status. T2D status predicted initial performance of EF (Figure 3-2). Specifically, adults with T2D performed significantly worse (*M* = -.285) than adults without T2D (*M* = .040) (see age 75 model intercept in the figure). However, adults with and without T2D showed no differences in the rate of EF decline (*M*s = -.024 and -.021, respectively; *p* > .05). Model 3 tested whether the effect of T2D on EF is lessened in individuals with at least one G *IDE* allele. First, EF intercept and slope were each regressed on both *IDE* and T2D status. Second, EF intercept and slope were regressed on *IDE*, T2D status, and *IDE* x T2D status. This model produced non-significant results for the *IDE* x T2D status variable for both initial EF performance, *b* = .040, *p* = .924 and change over time, *b* = .026, *p* = .631. In addition, the previously significant effect of *IDE* on EF change was no longer significant, *b* = .016, *p* = .052, and the effect

of T2D status on initial EF performance was no longer significant, b = -.366, p = .343. Therefore, the presence of an *IDE* G allele did not moderate the negative effects of T2D on EF.

Discussion

The aim of this research was to explore (a) the concurrent and longitudinal associations of one novel genetic (*IDE* rs6583817) and one metabolic-health (T2D) factor and (b) whether these factors acted independently or interactively in influencing concurrent level of performance and two-wave change in a key cognitive phenotype (EF) of aging. Of special interest was whether the possession of a G allele of this *IDE* variant would (a) exert a risk reduction or positive effect on EF performance and change or (b) moderate the countervailing expectation for a risk elevation or negative effect of T2D. Our expectations reflected these independent and interactive possibilities. We examined these issues using a large sample of older adults followed longitudinally over four years, with data analyzed using leading edge latent growth mixture models.

Regarding research goals 1 (EF latent model) and 2 (two-wave invariance testing), the confirmatory factor analyses revealed that, as expected, a single-factor model fit the data best. This model exhibited metric invariance overall and partial scalar invariance for the inhibition dimension. Our findings provide further evidence for a single-factor EF latent variable for normal aging, and are consistent with the differentiation/de-differentiation theory of typical aging in the EF phenotype. However, we note that this theory has not been tested on the same people over an extended longitudinal period (de Frias et al., 2006; Luszcz, 2011)

and we could not test the EF factor structure at the genetic level (Kremen et al., 2009; Vasilopoulos et al., 2012). Moreover, recent neurocognitive evidence indicates that it may apply differentially across the spectrum of cognitively impaired, normal, and sustained healthy aging, as associated with individualized lifetime levels of biological vulnerability and environmental risk or protective factors (de Frias et al., 2009; Dixon, 2010; Lindenberger et al., 2008).

For research goals 3 (EF latent growth model) and 4 (path analyses with *IDE* and T2D), we observed that there is indeed a potential protective effect the *IDE* G allele on the EF phenotype—both concurrently and longitudinally. Concurrently, at the age 75 centering point (Figure 3-1), the presence of an *IDE* G allele (our *IDE* G+ group) was associated with better EF performance. In fact, the dosage effect showed that each additional G allele resulted in better concurrent EF performance. Longitudinally, adults with a G allele exhibited reduced EF decline rates as compared with adults who did not possess the G allele. This *IDE* (rs6583817) variant was previously associated with increased level of IDE transcription and reduced risk of AD in a synthetic *in vitro* system (Belbin et al., 2011; Carrasquillo et al., 2010). The present research is the first to link this *IDE* polymorphism to actual cognitive performance and change in non-demented older adults. The results indicated a potential protection function for normal cognitive aging, as associated with the *IDE* major allele (G). We did not observe such an association for the minor allele (A), which had been reported as a potential protection factor for classification with neurodegenerative disease (i.e., AD). The increase of IDE messenger RNA related to the minor allele (A) reported by

Carrasquillo and colleagues would translate to a decrease in both insulin and Aβ. Conceivably, a decrease in Aβ would result in a decreased risk of AD. At the same time, a decrease in insulin would have a deleterious effect on EF, as increases in insulin have been linked to better EF performance (Awad et al., 2004). The minor and major allele of this *IDE* variant may be correspondingly specialized, with (a) the former affecting AD-related neurobiology and (b) the latter associated with prefrontal neurobiological changes, as phenotypically reflected in EF performance and change. Further research can examine whether (a) *IDE* targets two main peptides (insulin and Aβ) with the cognitive effects potentially contingent on brain region and physiological condition (e.g., aging), (b) *IDE* (rs6583817) major and minor alleles differentially affect other basic cognitive resources (e.g., speed) or risk of AD, (c) other *IDE* polymorphisms affect EF performance in normal aging, (d) other *IDE* variants interact with (or counteract) the present *IDE* variant, and (e) this *IDE* variant interacts with other biological (e.g., vascular) markers.

As expected from complementary univariate (manifest variable) studies (Biessels et al., 2008; Yeung et al., 2009), our findings show a clear link between T2D and decreased EF performance. This study contributes the novel information that T2D predicts level of performance but not accelerated decline in EF. The inference from this result is that T2D may have a (a) relatively early (perhaps pre-diagnosis) impact on EF or (b) moderated impact, by multiple individual-level factors (biological, environmental, severity, therapeutic) or (c) later acceleration in EF decline possibly occurring as a function of pre-clinical neurodegenerative

decline. The present results should be interpreted in the context of a sample of a population that would include older adults with mild to moderate cases of T2D, and for whom access to national health care may indicate that the disease is relatively controlled. Our finding that the *IDE* variant did not moderate the effects of T2D may be in part due to this lack of severe T2D. Further research using other *IDE* variants and with participants with more severe T2D symptomatology would elucidate another facet of the long term effects of T2D on cognitive phenotypes in aging.

There are several strengths and limitations associated with this study. First, the VLS data set includes only one of several possible *IDE* genotypes with linkages to common neurodegenerative (AD) and bio-health (T2D) conditions. However, the genotype tested (rs6583817) has only recently been investigated in relation to AD and has unique promise both in terms of strength of association and the potential valence of influence. Future research should examine moderating and interacting influences (both risk and risk-reduction) of other *IDE* variants, genomic (e.g., *APOE*) factors, environmental-lifestyle (e.g., physical exercise) influences, and biological (e.g., pulse pressure) modifiers (e.g., Lindenberger et al., 2008). Second, our T2D participants were identified with a strict and standard multi-step process but the assessment did not include continuously distributed and relevant biomarkers (e.g., glycated haemoglobin [HbA1c]), which were unavailable but could have provided additional theoretical and diagnostic information (e.g., Raz et al., 2008). However, the present diagnostic procedures are well-developed, documented, validated, and appropriate

to samples of older adults with relatively managed (mild to moderate) T2D conditions. Third, our goal was to examine a subgroup of aging adults who have not yet begun detectable transitions in neurodegenerative disease. Therefore, as noted, the present VLS sample is community-dwelling, fairly well-educated, and with access to national health care services. Not only is this likely to represent a growing proportion of the aging population, it provides a conservative test of the hypotheses concerning health-biological influences on prefrontal-related executive functions in older adults. That the sample may reflect late-life survivorship is reflected in the fact that about 8% had T2D and the allelic distribution of *IDE* showed some selectivity, in that the AG heterozygotes were present in a greater than expected frequency, relative to the GG homozygotes. Fourth, we focused on a prominent cognitive phenotype (EF) but both other basic (e.g., speed) and complex (e.g., episodic memory) are related to AD and EF—and possibly to this *IDE* variant in aging—and should be studied in future research. However, we note that among the strengths of this study are (a) that the EF factor was comprised of four standard and strong neuropsychological manifest variables empirically contributing to a latent variable and (b) that the EF phenotype was examined longitudinally with age as a continuous variable, resulting in an investigation of concurrent and longitudinal EF performance and change across a band of approximately 40 years.

In sum, the present study examined the effects of *IDE* (rs6583817) and T2D on EF level and change independently and together. We found that *IDE* and T2D are independently and differentially associated with EF performance in older

adults. The associations are (at cross-section) in a common direction in that both factors produce expected risk-related group differences at the age intercept. The associations are differential in that the longitudinal EF decline patterns show (a) similar functions for both healthy and T2D participants but (b) steeper decline (for the *IDE* G- group) and unique substantial preservation (for the *IDE* G+ group). Our specific analyses of *IDE* interactions with T2D showed that this variant neither protected (the G+) nor exacerbated (the G-) the observed decrements and declines of EF by T2D versus normal aging groups. Possession of an *IDE* G allele exhibited a previously unobserved positive effect on both EF level at age 75 years and change across time. Our research is the first to link *IDE* to cognitive performance and change in non-demented older adults.

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Table 3-1

Descriptive Statistics for Sample by IDE *Genotype and Longitudinal Wave*

Indicator	*IDE* genotype			
	G+ (G/G & G/A)		G- (A/A)	
	W1	W2	W1	W2
n[a]	495 (122 & 373)	410 (104 & 306)	79	64
Age *M*(*SD*)	69.8 (8.48)	73.9 (8.36)	72.3 (8.65)	76.9 (8.75)
Range	53.2 – 95.2	57.3 – 94.1	54.6 – 89.3	58.9 – 94.5
Gender (% women)	67.7	67.8	62.0	59.4
T2D (% with T2D)	7.9	7.8	8.9	7.8
Hayling *M*(*SD*)	5.62 (1.42)	5.49 (1.49)	5.47 (1.42)	5.23 (1.40)
Stroop[b] *M*(*SD*)	1.25 (.706)	1.31 (.910)	1.41 (.828)	1.44 (.892)
Brixton *M*(*SD*)	4.96 (2.13)	5.42 (2.00)	4.56 (2.17)	4.98 (2.12)
Color Trails[b] *M*(*SD*)	91.9 (28.9)	99.1 (38.6)	99.3 (35.0)	107.1 (41.7)
EF factor scores *M*(*SD*)	.008 (.805)	.051 (1.20)	-.244 (.873)	-.331 (1.38)

Note. Hardy-Weinberg equilibrium $\chi^2 = 54.09$ at W1, therefore the genotypic distribution for *IDE* is not in Hardy-Weinberg equilibrium. G+ = presence of a G allele; G- = absence of a G allele; W1 = Wave 1; W2 = Wave 2; T2D = type 2 diabetes; EF = executive function.
[a] For G+ *n* is for total G (G/G & G/A). [b] Lower scores indicate better performance.

Table 3-2

Goodness of Fit Indexes for Executive Function Confirmatory Factor Analysis Models and Measurement Invariance Testing

	AIC	BIC	χ^2	*df*	*p*	RMSEA	CFI	SRMR
Model								
One factor EF (W1)	5866.575	5914.454	3.529	3	.309	.019 (.000-.075)	.995	.023
Two factor EF (W1)	Residual covariance matrix not positive definite[a].							
One factor EF (W2)	5214.349	5260.123	1.756	3	.6249	.000 (.000-.063)	1.00	.028
Two factor EF (W2)	Residual covariance matrix not positive definite.							
One factor EF (W1 and W2)	10505.045	10626.967	11.821	16	.7562	.000 (.000-.028)	1.00	.019
Equal indicator loadings	10504.623	10613.482	17.398	19	.5629	.000 (.000-.033)	1.00	.027
Equal intercepts	10563.543	10659.339	82.318	22	<.001	.069 (.054-.085)	.931	.054
Equal intercepts STRP & HAY	10509.190	10613.695	23.966	20	.2439	.019 (.000-.042)	.995	.029

Note. AIC = Akaike information criteria; BIC = Bayesian information criteria; RMSEA = Root Mean Square Error of Approximation; CFI = Comparative Fit Index; SRMR = Standardized Root Mean Square Residual; EF = Executive Function; W1 = Wave 1; W2 = Wave 2; STRP = Stroop.; HAY = Hayling.

[a] Positive definite is required for estimation of the model and indicates that the data matrix consists of (a) a non-singular (invertible) matrix, (b) all eigenvalues,> 0, (c) a determinant (serial product of the eigenvalues) > 0, and (d) all correlations and covariances being within bounds (e.g., no negative variances or correlations >1; Kline, 2011).

Table 3-3

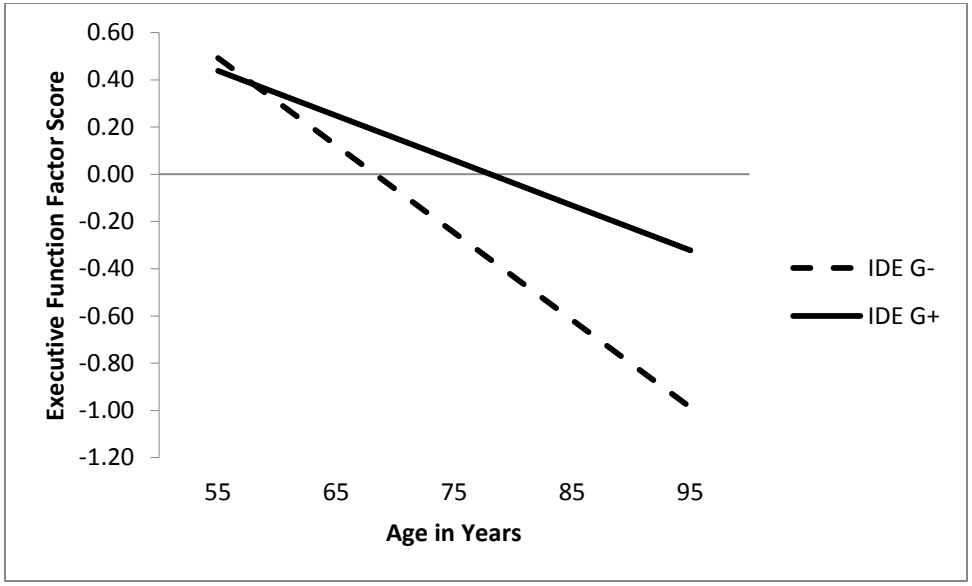
Goodness of Fit Indexes for Executive Function Latent Growth Models

Model	H0 value	-2LL	Parameters Free	AIC	BIC	Intercept		Slope	
						M	*S*	*M*	*S*
Fixed intercept	-1470.253	2940.506	3	2946.506	2959.57	.022	-	-	-
Random intercept	-971.301	1942.602	4	1950.601	1968.019	-.028	.668**	-	-
Random intercept Fixed slope	-905.567	1811.134	5	1821.134	1842.906	-.199**	.473**	-.036**	-
Random intercept Random slope	-722.631	1445.262	7	1459.262	1489.742	.014	.785**	-.022**	.002**
						b		*b*	
Model 1 (A+/A-)[a]	-722.244	1444.488	9	1462.489	1501.678	-.062		-.001	
Model 1 (G+/G-)[b]	-719.114	1438.228	9	1456.228	1495.417	.306**		.018*	
Model 2[c]	-716.752	1433.504	9	1451.503	1490.693	-.325*		-.003	
Model 3[d]									
IDE, T2D	-713.260	1426.520	11	1448.521	1496.419	.302*/-.326*		.018*/-.003	
IDE, T2D, & *IDE* x T2D	-712.257	1424.514	13	1450.514	1507.120	.305*/-.366/.040		.016/-.025/.026	

Note. H0 = Loglikelihood value; -2LL = -2 (H0) = -2 log likelihood; AIC = Akaike information criterion; BIC = Bayesian information criterion; *M* = Mean; *S* = Sample variance; A+ = presence of an A allele; A- = absence of an A allele; G+ = presence of a G allele; G- = absence of a G allele; T2D = type 2 diabetes; *b* reported as *IDE*/T2D and *IDE*/T2D/*IDE* x T2D.

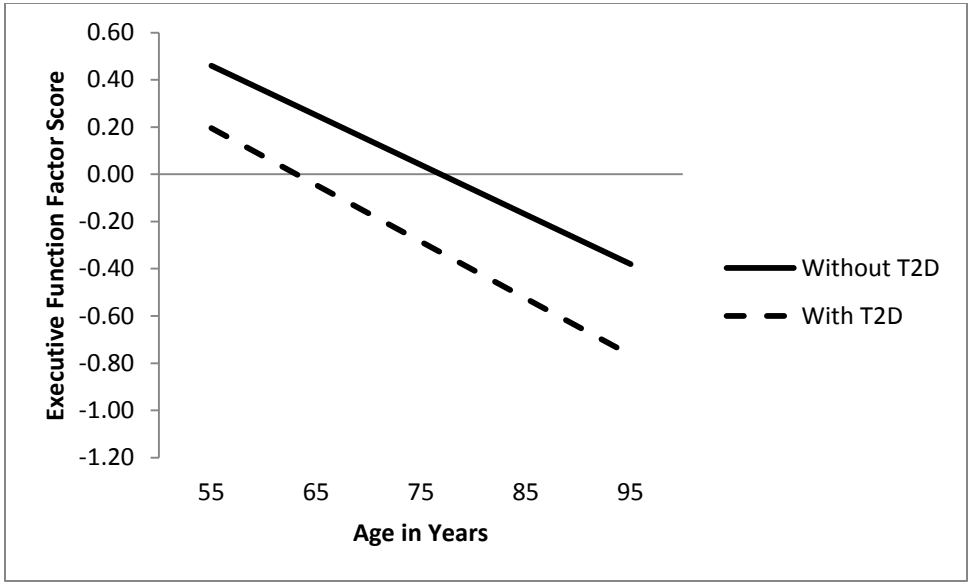
[a]Model 1 = EF intercept and slope regressed on *IDE* testing the A allele was non-significant and was dropped from analyses. [b]Model 1 testing the G allele was retained for all further analyses. [c] Model 2 = EF intercept and slope regressed on T2D. [d] Model 3 = EF intercept and slope regressed on *IDE* and T2D and then EF intercept and slope regressed on *IDE*, T2D, and *IDE* x T2D. Model 3 had an intercept-slope correlation of .037**.

* $p < .05$. ** $p < .01$.



	IDE G-	Regression Estimates	*IDE* G+
Intercept	-.248**	.306	.058
Slope	-.037*	.018	-.019

Figure 3-1. Predicted growth curve for executive function factor scores using *IDE* genotype (i.e., G- = no G allele, G+ = at least one G allele) as a predictor with age as a continuous variable centered at 75 years.
*$p < .05$. **$p < .01$.



	Without T2D	Regression Estimates	With T2D
Intercept	.040*	-.325	-.285
Slope	-.021	-.003	-.024

Figure 3-2. Predicted growth curve for executive function factor scores using T2D status (i.e., Without T2D, With T2D) as a predictor with age as a continuous variable centered at 75 years.
*$p < .05$.

Chapter Four (Study 2)

IDE (rs6583817) Polymorphism and Pulse Pressure are Independently and Interactively Associated with Level and Change in Executive Function in Older Adults

Cognitive deficits increase with age but the dynamics of when, how, and why the decrements accumulate are among the key questions of cognitive aging research (Dixon, Small, MacDonald, & McArdle, 2012; Hertzog, 2008). The timing, trajectories, and etiologies of aging-related cognitive decrements vary between people, across cognitive domains, and seem to occur later and more differentially than once thought (e.g., Schaie, 2013; Small, Dixon, & McArdle, 2011). Although both cross-sectional and longitudinal studies offer much insight into patterns of normal cognitive aging, studies with both biological markers (biomarkers) and multiple waves of observation are especially well-equipped to address these issues. Both modifiable (lifestyle, health related) and non-modifiable (genetic) factors may influence differences in cognitive performance and changes, with the influences potentially operating both independently and interactively (Dahle, Jacobs, & Raz, 2009; Dixon, 2011; Fotuhi, Hachinski, & Whitehouse, 2009; Harris & Deary, 2011; Lindenberger et al., 2008; Nagel et al., 2008; Small, Dixon, McArdle, & Grimm, 2012; Song, Mitnitski, & Rockwood, 2011; Waldstein et al., 2008). Whereas the independent influences of these factors on concurrent cognitive health are important to identify and describe, further progress may accrue by examining the role of gene x environment (health) interactions with both concurrent and longitudinal data.

One cognitive domain that is influenced by several of the aforementioned factors is executive function (Luszcz, 2011). Briefly, executive functions (EF) are cognitive processes required in order to execute plans, solve problems, and partake in goal directed endeavors (West, 1996). EFs are known to decline with advancing age and are thought to have direct links to neurodegeneration of the prefrontal cortex (Luszcz, 2011; Turner & Spreng, 2012). Clinically, performance on some EF tests is predictive of future development of mild cognitive impairment (Nathan, Wilkinson, Stammers, & Low, 2001) and Alzheimer's disease (AD; Grober et al., 2008; Rapp & Reischies, 2005). Conceptually, EF is made up of functions primarily reflecting aspects of inhibition, shifting, and updating. The developmental trajectory of EF is evidenced by apparent shifts in structure and level across the lifespan (de Frias, Dixon, & Strauss, 2006; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000; Wiebe, Espy, & Charak, 2008; Wiebe et al., 2010). Although generally unidimensional within older adults, differences in EF structure (and level) have been observed across groups of healthy (e.g., cognitively elite) aging, normal aging, and mild cognitive impairment (de Frias, Dixon, & Strauss, 2009). Increasingly, research has shown that EF performance patterns are affected or modified by a host of biological, neurobiological, health, and environmental factors (de Frias et al., 2006; Grober et al., 2008; Lindenberger et al., 2008; Luszcz, 2011; McFall et al., 2013; Nathan et al., 2001; Rapp & Reischies, 2005; Wishart et al., 2011; Yeung, Fischer, & Dixon, 2009).

In this study we address the aging of EF as it is related to specific health (PP an indicator of vascular health) and biological (genetic) factors (Luszcz, 2011; Turner & Spreng, 2012). Regarding health, research shows that overall vascular health declines with age and may be a direct contributor to cognitive (including EF) deficits and even dementia (Qiu, Winblad, & Fratiglioni, 2005; Raz, Rodrigue, & Acker, 2003; Vasan et al., 2001). More specifically, increases in blood pressure, related to declining vascular health, have been associated with reduced brain tissue volume, especially prefrontal structures and, not surprisingly, decreases in EF performance (Dahle et al., 2009; Elias, Elias, Robbins, & Budge, 2004; Raz et al., 2003; Waldstein et al., 2008). Notably, some aspects of vascular health may be modifiable and indeed maintenance of good vascular health in older adulthood may be correspondingly protective of cognitive functioning as evidenced by preserved brain tissue (Colcombe et al., 2003) and the possible postponement of dementia onset (Qiu et al., 2005; Staessen, Richart, & Birkenhäger, 2007).

Numerous aspects and indicators of vascular health may be studied in research on cognitive aging. As noted, we focus on PP which is conceptually linked to arterial stiffening. This vascular change increases with age and is associated with increases in systolic blood pressure and decreases in diastolic blood pressure (Franklin et al., 1997; Mattace-Raso et al., 2006; Raz, Dahle, Rodrigue, Kennedy, & Land, 2011). In addition, arterial stiffening has been found to have an independent effect on cardiovascular disease (Dart & Kingwell, 2001; Mitchell et al., 2007; Schiffrin, 2004) and cognitive performance in older non-

demented adults (Dahle et al., 2009; Waldstein et al., 2008). Arterial stiffness may be measured by directly by pulse wave velocity, but PP is considered a proxy (Waldstein et al., 2008). PP is calculated as systolic minus diastolic blood pressure. Typically, it shows a steep age-related increase in older adults and is considered a better predictor of declining vascular health than systolic blood pressure (Raz et al., 2011). Several researchers have reported PP associations with EF deficits (Dahle et al., 2009; Raz et al., 2011; Waldstein et al., 2008) and an increased risk of Alzheimer's disease or dementia (Qui, Winblad, Viitanen, & Fratiglioni, 2003).

Whereas PP is a prominent and modifiable health factor influencing cognition aging, genetic influences are relatively time-invariant and non-modifiable influences. Researchers have recently explored associations of selected genetic polymorphisms not only to cognitive impairment and dementia (e.g., *Apolipoprotein E* (*ApoE* ε4); Brainerd, Reyna, Petersen, Smith, & Taub, 2011) but also to normal cognitive differences and decline (Deary, Wright, Harris, Whalley, & Starr, 2004; Harris & Deary, 2011; Kremen & Lyons, 2011). Of recent and growing interest is the *insulin degrading enzyme* gene (*IDE*), for which variants have been linked to increased risk of type 2 diabetes (T2D), dementia, and AD (Bartl et al., 2011, Belbin et al., 2011; Carrasquillo et al., 2010). While IDE is most commonly recognized for its role in the degradation of insulin, this enzyme has also been linked to the processing of the glycemia-regulating peptides amylin and glucagon (Bennett, Duckworth, & Hamel, 2000; Shen, Joachimiak, Rosner, & Tang, 2006) and the human amyloid precursor protein (amyloid beta,

Aβ; Kurochkin & Goto, 1994). Neurogenetic research has identified an *IDE* linkage peak for such major aging-related diseases as T2D and late onset AD. Several *IDE* haplotypes have been identified and individual SNPs have been associated with either an increased or decreased risk of developing T2D or AD (Bartl et al., 2011). The *IDE* alleles associated with T2D risk may be due to the lowered expression of IDE, which may result in hyperinsulinemia and consequent cognitive deficits (Awad, Gagnon, & Messier, 2004; Umegaki, 2012). Alternatively, *IDE* SNPs associated with decreased risk of AD may be due to higher IDE expression and Aβ level decreases (Blomqvist et al., 2005; Kurochkin & Goto, 1994; Qiu & Folstein, 2006). Three genetic variants of *IDE* (rs6583817, rs5786996; rs4646953) have been identified as having the strong association with increased levels of IDE expression and decreased Aβ levels (Belbin et al., 2011; Carrasquillo et al., 2010). In our research, we have focused on one of these especially promising *IDE* (rs6583817) SNPs, which has a minor A allele and a major G allele. To our knowledge, the first gene association study with this variant observed increased IDE expression and decreased Aβ levels (Belbin et al., 2011; Carrasquillo et al., 2010). In a recent study we observed a positive effect of the major G allele on EF performance (McFall et al., 2013). Specifically, normal older adults possessing one or more major (G) alleles had higher levels of EF at age 75 years and less change over a four-year period than adults with the minor allele (A). Our findings supported the hypothesized mechanism that the *IDE* G allele was associated with decreased levels of insulin degrading enzyme, and that this translated to more insulin in the prefrontal cortex and better EF performance

(for a review of the molecular mechanism relating *IDE* with EF function in older adults see Bartl et al., 2011; Belbin et al., 2011; Carrasquillo et al, 2010; McFall et al., 2013). The link between increases in brain insulin to improvements in EF performance has been documented (Awad et al., 2004; for basic insulin-brain-cognition reviews see Biessels, Deary, & Ryan, 2008; Craft & Watson, 2004; Seaquist, Latteman, & Dixon, 2012). In the previous study, McFall and colleagues (2013) found that *IDE* did not predict risk of T2D diagnosis, but whether it is associated with a more basic vascular health marker—and through vascular health to cognition in aging—is as yet unknown but plausible. Other genetic variants associated with cognitive aging have been linked to vascular health (e.g., *ApoE, COMT*, and *ACE;* Anstey & Christensen, 2000; Haan, Shemanski, Jagust, Manolio, & Kuller, 1999; Hagen et al., 2007; Mahley & Rall, 2000; Raz et al., 2011; Smith, 2002; Sternäng et al., 2009), with growing interest in examining both independent and interaction associations (Lindenberger et al., 2008; Raz, Rodrigue, Kennedy, & Land, 2009) leading to magnifying or mitigating effects on cognitive phenotypes.

The overarching goal of the current study is to examine the independent and interactive effects of PP and *IDE* (rs6583817) genotype on executive function (EF) performance and longitudinal change in a group of typically aging older adults. We used a relatively large sample of older adults (n = 599) with *IDE* genotype information to explore four research goals. Using confirmatory factor analysis within a structural equation modeling context we examined the first two research goals. Research goal 1 was to estimate an EF latent variable using four

measures related to two EF domains and to test this model for longitudinal measurement invariance across three waves. Research goal 2 was to determine the best fitting latent growth models for EF and for PP. Using conditional growth models we explored two additional research goals. Research goal 3 was to determine how EF performance patterns of change in older adults (aged 53-95 years) were affected independently by PP and *IDE* (rs6583817). Research goal 4 was to determine if any *IDE* allele-EF relationship was modified by PP.

Method

Participants

Participants were community-dwelling adults (initially aged 55-95 years) drawn from the Victoria Longitudinal Study (VLS). The VLS is a longitudinal sequential study designed to examine older adult development in relation to biomedical, genetic, health, cognitive and neuropsychological aspects (see Dixon & de Frias, 2004). The VLS and all present data collection procedures were in full and certified compliance with prevailing human research ethics guidelines and boards. Informed written consent was provided by all participants. Using standard procedures (e.g., Dixon et al., 2012; Small et al., 2011), we assembled longitudinal data consisting of three samples and all available waves (up to three) since the early 2000s. The executive function tasks required for this study were installed in the VLS neuropsychological battery at this point. Therefore, the first included wave for each sample was the first exposure to the executive function tasks (i.e., S1W6; S2W4; S3W1). This study assembled (a) Sample 1 (S1) Waves 6 and 7, (b) Sample 2 (S2) Waves 4 and 5, and (c) Sample 3 (S3) Waves 1, 2, and

3. The mean intervals between the waves of data collection were 4.44 (W1-W2) and 4.46 (W2-W3) years. For terminological efficiency, the respective earliest wave of each sample became Wave 1 (W1 or baseline) for the current study, the respective second wave became Wave 2 (W2), and the respective third wave became Wave 3 (W3). The design stipulated that whereas S3 participants could contribute data to all three waves, S1 and S2 participants contributed data to W1 and W2 (the third wave not available). Accordingly, the present W3 sample has a relatively larger representation of participants in their 60s and 70s and a relatively smaller representation of those in their 80s and 90s. This consideration is balanced by the advantage of testing genetic-health in EF across an accelerated longitudinal period of nearly 9 years (M = 8.9 years). Demographic information is presented in Table 4-1.

Given the necessity for both genetic and longitudinal data in this study, these factors defined the initial opportunity in sample recruitment. VLS genotyping occurred in the 2009-2011 period and was limited by funding arrangement to about 700 continuing VLS participants. After initial evaluations, the eligible source sample consisted of 683 participants with genetic data. Several exclusionary criteria were then applied to this source sample: (a) a diagnosis of Alzheimer's disease or any other dementia, (b) a Mini-Mental Status Exam (MMSE; Folstein, Folstein, & McHugh, 1975) score of less than 24, (c) a self-report of "severe" for potential comorbid conditions (e.g., epilepsy, head injury, depression), (d) a self-report of "severe" or "moderate" for potential comorbid diseases such as neurological conditions (e.g., stroke, Parkinson's disease), and

(e) insufficient EF data. The final sample for this study consisted of *n* = 598 adults. For W1 there were 597 adults, including 394 women and 203 men (*M* age = 70.6 years, *SD* = 8.61, range 53.2 – 95.2). For W2 there were 490 adults, including 321 women and 169 men (*M* age = 74.7 years, *SD* = 8.51, range 57.3 – 94.5). For W3 there were 278 adults, including 186 women and 92 men (*M* age = 74.9 years, *SD* = 7.17, range 62.4 – 94.9). In this accelerated longitudinal design, a total of 262 adults contributed data to all three waves, 272 to W1 and W2, 16 to W1 and W3, 93 to W1 only, and 1 to W2 only. The retention rates for each available and defined interval are as follows (a) S1 W1-W2 = 84%, (b) S2 W1-W2 = 77%, (c) S3 W1-W2 = 84%, (d) S3 W2-W3 = 89%, and (e) S2 W1-W3 = 77%. As noted, defined intervals are determined by availability, which in this instance is limited only by data collected and processed in this ongoing longitudinal study. For these analyses listwise deletion was not used; instead, all missing data were estimated by multiple imputations using Mplus 7 (Muthén & Muthén, 2010). Specifically, for this study 50 imputations of the data set were generated and pooled for further analyses (for further description of imputations and pooling see Enders, 2011; Graham, Olchowski, & Gilreath, 2007, Muthén & Muthén, 2010; Rubin, 1987).

Executive Function Measures

All EF tests have been used widely and frequently within the VLS, with established measurement and structural characteristics (e.g., Bielak, Mansueti, Strauss, & Dixon, 2006; de Frias et al., 2006, 2009) and demonstrated sensitivity

to health, genetic, and neurocognitive factors (e.g., McFall et al., 2013; Yeung et al., 2009) in various older adult populations.

Hayling sentence completion test. This task, which indexed inhibition (Bielak et al., 2006; Burgess & Shallice, 1997), consisted of two sets of 15 sentences, each having the last word missing. Section A required completing the sentence quickly, and measured initiation speed. Section B required completing the sentence with an unconnected word quickly, and measured response suppression. Response speed on both sections and errors on Section 2 were used to derive an overall scaled score for each participant on a scale ranging from 1 (impaired) to 10 (very superior).

Stroop test. This task taps inhibitory processes by requiring the respondent to ignore the automatic response of reading a printed word and to instead name the color of ink in which the word is printed (Taylor, Kornblum, Lauber, Minoshima, & Koeppe, 1997). In Part A, the participant named as quickly as possible the color of 24 dots printed in blue, green, red, or yellow. Part B was similar to Part A except that the dots were replaced by common (noncolor) words (e.g., when, hard, and over), printed in lower case. The respondent was instructed to name the color in which the word was printed and to ignore the verbal content. In Part C, the colored stimuli were the color names (i.e., blue, green, red, and yellow) printed in lower case with the ink color being incongruent to the color name. The performance score was the interference index and reflected slowing in response to interference in Part C ([Part C_{time} – Part A_{time}]/Part A_{time}). Lower scores indicated better performance.

Brixton spatial anticipation test. This task (Bielak et al., 2006; Burgess & Shallice, 1997) was a rule-attainment (or shifting) task based on the Wisconsin Card Sorting Task (Berg, 1948). Participants are required to deduce simple and changing patterns, measuring their ability to abstract logical rules (Andrés & Van der Linden, 2000). The total errors were recorded and these errors (maximum 54) were converted to scaled scores. An overall standardized scaled score based on a scale ranging from 1 (impaired) to 10 (very superior) was used for analysis.

Color trails test (part 2 CTT-2). Indexing shifting, the CTT (D'Elia, Satz, Uchiyama, & White, 1996) was similar to the Trail Making Test (Reitan & Wolfson, 1992) but minimized the influence of language. Part 2 required participants to connect numbers from 1 to 25 alternating between pink and yellow circles and disregarding the numbers in circles of the alternate color. The latency score for Part 2 was used for analysis. Lower scores indicate better performance.

Pulse Pressure

Pulse pressure (PP), a reliable proxy of the arterial stiffness aspect of vascular health, was calculated as follows: PP = systolic – diastolic blood pressure. For all analyses PP was used as a continuous variable and was centered at 52 mmHg, the approximate population mean at baseline. For the current study, we wished to develop a sample of typically aging older adults and thus those with self-reported high blood pressure and blood pressure medication were included in the analyses. Serious high blood was reported at baseline by only 5 participants (0.8% of the sample) and blood pressure medication use was reported by n = 158 (26.4% of the sample).

DNA Extraction and Genotyping Saliva Collection

Saliva was collected according to standard procedures from Oragene-DNA Genotek and stored at room temperature in the Oragene® disks until DNA extraction. DNA was manually extracted from the saliva sample mix using the manufacturer's protocol and quantified using a NanoDrop® ND-1000 Spectrophotometer (Wilmington, DE). Genotyping was carried out by using a PCR-RFLP strategy to analyze the allele status for IDE (rs6583817). Briefly, SNP-containing PCR fragments were amplified from 25 ng of genomic DNA using specific primers (Fwd: 5'-AATATATGGGCAAATATTAAGTGCAC-3'; Rev: 5'-CAGTTGTGGGAATATATTCCTGAG-3'). Reactions were set up in 96-well plates using the QIAgility robotic system (QIAgen). RFLP analysis was performed on a high resolution DNA screening cartridge on a QIAxcel capillary electrophoresis system (QIAgen) using the protocol OL700 after digestion of the PCR amplicons with the restriction enzymes DdeI (NE Biolabs) for 4 hours at 37°C. The analysis was confirmed upon migration of the restriction fragments on 10 or 15% acrylamide gels for the SNP.

For genetic analyses the *IDE* genotypes were categorized by the presence of an A allele (A+ = A/A, homozygous minor allele, and G/A, heterozygous allele) or the absence of an A allele (A- = G/G, homozygous major allele). For the A+/A- allele analyses, no effect on EF performance was observed (EF performance at age 75 years $p > .05$; EF change $p > .05$); therefore, the alternative configuration (presence or absence of a G allele) was used for analyses. Subsequently, *IDE* genotypes were categorized by the presence of a G allele (G+ = G/G,

homozygous major allele, and G/A, heterozygous allele) or the absence of a G allele (G- = A/A, homozygous minor allele). See Table 4-2 for descriptive statistics by *IDE* allele and wave. Although there are several potentially interesting IDE variants in this emerging literature, this is the one available in the VLS.

Statistical Analyses

Analyses pertaining to our research questions included confirmatory factor analysis and latent growth modeling. Statistical model fit for all analyses was determined using standard indexes: (a) χ^2 for which a good fit would produce a non-significant test ($p > .05$) indicating that the data are not significantly different from the estimates associated with the model, (b) the comparative fit index (CFI) for which fit is judged by a value of $\geq .95$ as good and $\geq .90$ as adequate, (c) root mean square error of approximation (RMSEA) for which fit is judged by a value of $\leq .05$ as good and $\leq .08$ as adequate, and (d) standardized root mean square residual (SRMR) for which fit is judged by a value of $\leq .08$ as good (Kline, 2011).

Research Goals (RG)

RG 1: EF latent model and 3-wave invariance testing. First, we used Mplus 7 (Muthén & Muthén, 2010) to conduct confirmatory factor analysis. We tested two models (a) a single factor model and (b) a 2-factor model consisting of inhibition (Hayling, Stroop) and shifting (Brixton, CTT). Second, we tested longitudinal (three-wave) measurement invariance including (a) configural invariance, for which the same indicator variables load onto the latent variable used to test the model across time, (b) metric invariance, for which factor loadings

are constrained to be equal for each latent variable indicating that the latent variable is measuring the same construct, (c) scalar invariance, for which indicator intercepts are constrained to be equal allowing mean differences to be evident at the latent mean level, and (d) residual invariance, for which indicator residuals are constrained to be equal accounting for error variability and thus group differences are based on their common variability. We estimated factor scores for EF in Mplus and used these in subsequent latent growth models. In addition for all further analyses, we used multiple imputations to estimate missing values for pulse pressure, age, and EF factor scores. The procedure stipulated that 50 datasets were generated and pooled before analyses were conducted.

RG 2: Latent growth models for EF and PP. We coded age as a continuous factor and computed latent growth models with individually-varying ages. Age was centered at 75 years of age, as this is the approximate center point of the 40 year band of data (i.e., 53-95 years) and because it is an observed meaningful point in cognitive aging (Dixon et al., 2012; Schaie, 2013; Small et al., 2011). We used the best fitting latent model for EF and measures of PP at each of the three waves. To identify the functional form of change, we determined the best-fitting unconditional growth model by testing in sequence: (a) a fixed intercept model, which assumes no inter- or intraindividual variation; (b) a random intercept model, which models interindividual variability in overall level but no intraindividual change; (c) a random intercept fixed slope model, which allows interindividual variation in level but assumes all individuals change at the same rate; and (d) a random intercept random slope model, which models

interindividual variation in initial level and change (Singer & Willett, 2003). Maximum likelihood estimation was used for these and all subsequent models in order to permit statistical tests of fixed and random effects (Singer & Willett, 2013). The deviance statistic was used to compare nested models.

RG 3 and RG4: Conditional growth models using PP and *IDE* (RG3) and PP moderation effects on *IDE*-EF relationship (RG4). Using the best unconditional growth model identified for EF, predictors of change were added to the model. The intercept and slope were regressed separately on *IDE* genotype and PP measured at W1. Next, in order to test the moderation effects of the *IDE*-EF relationship, we used a conditional growth model for EF with PP as a predictor using the two *IDE* genotype groups (G+/G-).

Results

Following the analyses reported in this section we tested the potential role of reported use of blood pressure medication as a covariate in the models. Consistently, all model fit statistics were significantly poorer with no changes to the observed result patterns. Therefore, analyses leading to the following results do not include this covariate.

RG 1: EF Latent Model and 3-wave Invariance Testing

Using confirmatory factor analysis we tested two EF models. The one-factor model of EF fit the data well for W1, W2, and W3. In contrast, the two-factor model could not be estimated at any of the three waves, resulting in the absence of a positive definite variance-covariance matrix (see Table 4-3 for model goodness of fit indexes). Therefore, as observed in earlier VLS research with different

samples (e.g., de Frias et al., 2006, 2009) we accepted the single-factor model for normal older adults. Next, we conducted invariance testing on the single-factor model. The model holding indicator factor loadings equal across W1, W2, and W3 fit the data well, thus indicating metric invariance. Fixing intercepts to be equal across time resulted in significantly poorer fit to the data according to the χ^2 difference test. We conducted tests of partial scalar invariance by freeing intercepts for each indicator in turn. These analyses supported partial scalar invariance for Hayling. Overall, we observed metric invariance for the single-factor EF model and partial scalar invariance indicating that this model measured the same EF construct across time, but the manifest variables marking EF, except Hayling, exhibited mean differences across time outside of the latent differences.

RG 2: Latent Growth Models for EF and PP

Executive function (EF). Using age (centered at 75) as the metric of change, we performed latent growth modeling using estimated EF factor scores. The best fitting unconditional growth model for EF was established as a random intercept, random slope latent growth model (see Table 4-4 for model goodness of fit indexes). First, this model indicated that older adults significantly vary in EF performance at age 75 (b = 1.16, p < .001). Second, the model revealed a significant decline in EF performance across time (M = -.011, p < .001). Third, older adults showed significantly variable patterns of decline (b = .002, p < .001).

Pulse pressure (PP). Using age (centered at 75) as the metric of change, we performed latent growth modeling using PP measures at each wave. For PP the preferred model was a random intercept, fixed slope model (see Table 4-4 for

model goodness of fit indexes). First, this model indicated that at age 75 years adults have levels of PP that are significantly different from the centering point of 52 mmHg (M = .299, p < .001). Second, older adults showed significant variation in PP level (b = .813, p < .001). Third, there was a significant increase in PP across time (M = .053, p < .001) for this older adult group, which was similar across individuals.

RG 3: Conditional Growth Models Using PP and *IDE*

PP. We tested two conditional growth models with PP as a predictor of EF level and change. The first model used the PP growth model in parallel process with EF growth model. Notably, time-varying PP did not significantly predict EF performance at age 75 (b = -.071, p > .05) nor did time-varying PP predict three-wave change in EF performance (b = -.001, p > .05). Therefore, we next tested a model in which the initial level of PP (at W1) was used as a predictor of both EF performance at age 75 and three-wave EF change (see Table 4-5). This model revealed two important findings. First, it showed that lower initial levels of PP, centered at the group mean of 52, resulted in significantly better EF (p < .001). Second, lower initial PP levels predicted less 9-year EF decline (p < .001, see Figure 4-1). Specifically, adults with PP at the centering point (i.e., PP = 52 mmHg) had better EF performance (M = .167) than adults PP above the centering level (EF M = -.047). Moreover, adults with PP at the centering point exhibited significantly less longitudinal decline in EF (M = -.017) than adults with higher PP levels (EF M = -.030).

***IDE* (rs6583817).** We tested *IDE* as a predictor of EF level at age 75 and rate of EF change (see Table 4-5). Two interesting results were observed. First, *IDE* significantly predicted the level of EF performance at age 75 years ($p < .05$). Specifically adults with a G allele (the G+ group) had better EF performance (M = .195) than adults without a G allele (EF M = -.113; see Figure 4-2). Second, *IDE* genotype did not significantly predict the rate of EF change (b = .012, $p > .05$). The observed slope was in the expected direction, but somewhat lower than that observed in a previous 2-wave study (i.e., b = .018, p = .027; McFall et al., 2013).

RG 4: PP Moderation Effects on *IDE*-EF Relationship

In order to examine our moderation hypothesis, we tested a model in which PP at W1 predicted (a) level of EF at age 75 and (b) three-wave change in EF over time based on the *IDE* G allele groupings (G+/G-; see Table 4-5). The pattern of results confirmed the moderation hypothesis. First, PP significantly predicted both level of EF (b = -.251, $p < .001$) and three-wave change in EF (b = -.015, $p < .001$) for the G+ group. Second, in contrast, PP did not significantly predict level of EF (b = -.092, $p > .05$) or change in EF (b = -.003, $p > .05$) for the G- group. This interaction, which demonstrates moderation by *IDE* genotype, is displayed in Figure 4-3.

Discussion

The goal of this research was to explore the independent and interactive effects of one modifiable vascular health factor (PP) and one genetic polymorphism (*IDE* [rs6583817]) on EF performance and change patterns across three waves of data in a group of older adults. For Research Goal 1 (EF latent

model and 3-wave invariance testing), we observed two main and expected findings: (a) a one-factor model of EF provided the best fit to the data for this large group of normal aging adults and (b) this one-factor model demonstrated both metric and partial scalar invariance over the three longitudinal waves. The unidimensional EF structure has been observed in our previous work with normal aging groups (de Frias et al., 2006) and was also reported for a mild cognitive impairment group (de Frias et al., 2009). In the latter study the single-factor representation was one of two models that fit the EF data for a comparison group characterized as cognitively elite older adults, so it is widely applicable to normal aging. In the present study we used two aspects of EF; updating may be incorporated into this line of research in the future but no basic measurement differences would be expected.

For Research Goal 2 (latent growth models for EF and PP), we observed several interesting findings. Regarding the growth models for EF, we detected: (a) a significant amount of variability in EF performance at the centering age of 75 years, (b) a significant decline across 9 years, and (c) a significant degree of variability in the trajectory of decline in EF over the 9 years. The fact of concurrent and change-related variability—combined with the general trajectory of decline—points to the potential operation of selective and individualized risk or protection factors. These may include elements of biological vulnerability, health burden, or lifestyle supports or compromises—all of which may operate independently or in combination to produce differential EF performance and long-term change in normal aging (Dixon, 2011; Fotuhi et al., 2009; Lindenberger et

al., 2008). These results are integral to the further research goals of this study. Regarding the growth models for PP, we observed (a) a significant amount of variability in PP level at the centering age of 75 years and (b) a significant increase in PP over the 9 years that was at a consistent rate for all adults in the sample. The increase in PP observed in this sample is in agreement with other studies indicating general age-related decreases in vascular health (Dahle et al., 2009; Davenport, Hogan, Eskes, Longman, & Poulin, 2012; Franklin et al, 1997; Raz et al., 2011).

For Research Goal 3, we tested conditional growth models using PP and *IDE* in order to examine the independent effects of these factors on EF performance and change. We found a series of interesting results. First, older adult carriers of an *IDE* G allele were advantaged in EF performance (at the centering age of 75 years) as compared with those with the AA allele combination (homozygotes). Second, *IDE* genotype predicted level of EF performance, but not rate of change in this group of normal older adults. In the only previous study of which we are aware, we observed the same results for the concurrent association test, but apparently different results for the rate of change tests (McFall et al., 2013). In that study, older adults with a G allele (i.e., G+ group) experienced lower decline than those without a G allele over two waves of measurement. A likely qualification and explanation for this variation in results is evident. The slope values are not dramatically different: The two-wave slope data for the G+ group from the earlier study indicated $b = .018$ ($p = .027$) whereas the present three-wave slope was slightly lower $b = .012$ ($p > .05$). There could indeed be real

adjustments in the effects of *IDE*-specific modification of EF slope over longer (about 9 years), as compared with shorter (about 4 years) periods of aging. Further longitudinal work—combined with other key genetic variants related to EF or general cognitive integrity—may shed light on the longer term prospects for the aging functions of EF. It is also possible that an unavoidable methodological characteristic of the present design influenced this slight shift in slope. As we noted above, in the present study the third wave of data was restricted to one of the three contributing VLS samples. This resulted in relatively fewer than expected participants in wave 3, but also a slightly younger than expected age range. It is therefore possible that the minor leveling off of the slope occurred between W2 and W3 and was related to the corresponding leveling off of the age range of the third wave. These substantive and methodological facts will be evaluated using upcoming new longitudinal data. For now, this interpretive uncertainty is not critical to the next (fourth) research goal. One other result pertaining to Research Goal 3 should be noted: We found evidence that adults with higher PP experienced decreased EF performance at age 75 and more decline over time. The best PP-related predictor and moderator of EF performance and change was the initial level of PP (at baseline). Time-varying PP was not related to time-varying EF in this study. Although PP varied over waves, it may not have varied dramatically enough to differentially affect EF change.

Unique to this research was the opportunity to examine a potential PP moderation of the *IDE*-EF relationship as pursued in Research Goal 4. The results (see Figure 4-3) show that indeed baseline PP (centered at 52mm Hg) moderated

the *IDE*-EF relationship. Specifically using G+/G- grouping and at the centering age of 75, the G+ group had higher EF performance than did the G- group. When PP was added to this model as a predictor, group results were indeed different. For the *IDE* G- group PP did not significantly alter either the level of EF performance at age 75 or 9-year EF change. In contrast, adults in the G+ group exhibited a different pattern. Specifically, adults with a G allele and lower levels of PP had higher levels of EF performance at age 75 and less 9-year EF change. As PP increased, the G+ group exhibited significant EF changes—viz., a decrease in EF performance at age 75, when compared to their healthier (in terms of PP) counterparts, and a more pronounced EF 9-year decline. In fact, adults at a high average PP (i.e., 72 mm Hg) showed an increase in EF decline, in a pattern similar to that displayed by adults without the protective *IDE* G allele. Overall, the results of the RG4 analyses show the important result that older adults with a G+ allele produce the best EF group performance, both concurrently and over time—if they also have healthier levels of PP. In contrast, adults with the G+ allele and less healthy levels of PP experience detrimental cognitive effects, as shown by decrements in EF performance at age 75 years and a steeper decline in EF over 9 years. A growing number of studies have reported results supportive of a perspective sometimes referred to as a differential-susceptibility hypothesis (e.g., Belsky et al., 2009). Although often rendered in terms of gene-environment interactions—with environment referring to a variety of extra-personal and other influences—we observed consistent results in a specific interaction between a selected genetic variant and a basic biological-health influence. More specifically,

older adults possessing the *IDE* (rs6583817) major (G) allele are particularly susceptible to health-environmental factors, perhaps especially some vascular health markers such as PP (e.g., Davenport et al., 2012; Fotuhi et al., 2009; Raz et al., 2009; Raz et al., 2011; Song et al., 2011). Notably, from a clinical and public health perspective, these results appear not in cognitively impaired or highly at risk (e.g., for dementia) patients, but for normal older adults, with varying but generally typical or managed ranges of PP.

Among the other (and unmeasured in this study) factors that could affect the degree of decline or preservation of EF performance in older adults are changes in insulin resistance in the brain (see Biessels et al., 2008; Craft & Watson, 2004, for potential biological mechanisms). The *IDE* (rs6583817) minor (A) allele has been reported to increase the amount of *IDE* expression, resulting in a decrease in insulin and Aβ (Carrasquillo et al., 2010). As noted by other researchers (Belbin et al., 2011; Carrasquillo et al., 2010), this could result in a lowered risk of Alzheimer's disease and conceivably, due to decreased insulin in the brain, lower cognitive abilities. According to this model, the *IDE* major (G) allele is related to a decrease in *IDE* expression resulting in an increase of insulin in the brain. Increases in insulin have been linked to increases in cognitive performance and indeed insulin may become even more important to cognitive performance with advancing age (Awad et al., 2004; Seaquist et al., 2012). Decreases in EF performance have been linked to reduced cerebral blood flow and white matter lesions where the prefrontal cortex is especially vulnerable (Raz, et al., 2003; Saxby, Harrington, McKeith, Wesnes, & Ford, 2003; Waldstein et al., 2008). The

increased insulin level associated with the *IDE* G+ allele may account for some of the cognitive preservation observed with normal aging (Raz et al., 2003) but poorer vascular health as measured by PP may increase cognitive vulnerability to the point that even preserved or enhanced insulin levels can no longer provide sufficient support (Craft & Watson, 2004).

As has been suggested in multiple domains, the present research confirms that maintenance of vascular health is essential for cognitive health in older adulthood (Colcombe et al., 2003; Elias et al., 2004; Qiu et al., 2005; Waldstein et al., 2008). Although vascular health is a relatively modifiable risk factor in neurocognitive aging, both hypertension medication and lifestyle choices (e.g., physical exercise, diet) require extended compliance and may vary in their effects by endemic factors (e.g., gender; Davenport et al., 2012). In this study we observed that one of the conditions may also be basic and unmodifiable genetic factors. Specifically, PP interacts in its effect on EF performance and long-term change with a recently identified genetic polymorphism of growing interest across the spectrum of normal aging to Alzheimer's disease. Further research on the interactions of such varied conditions as lifestyle activities and genetic factors may further clarify their combinatorial roles in neurocognitive aging (Colcombe et al., 2003; Fotuhi et al., 2009; Raz et al., 2003).

There are several limitations and strengths associated with this study. First, the VLS has only one of several *IDE* genotypes that could be associated with neurodegenerative diseases (i.e., Alzheimer's and related disorders) and cognitive-related health conditions (i.e., T2D). This particular genotype

(rs6583817) has just recently been investigated in relation to AD but has been relatively unexplored in regard to normal cognitive aging. Although the results of research with this polymorphism are very promising, a broader representation of the *IDE* group would be valuable for future research. Second, this study considers arterial stiffness, which is one aspect of the larger domain of vascular health and is associated with cognitive performance in older adults. Although a direct measure of arterial stiffness (pulse wave velocity) is not available in the VLS, systolic and diastolic blood pressure are available and therefore the recommended proxy of pulse pressure was used. The effect of vascular health and genetics on cognition in older adults would benefit from a broader representation of normal and clinical vascular health. Third, the present sample is relatively large and covers three waves over about 9 years, but a design characteristic should be noted, as it affected the n and age characteristics of W3. The design characteristic is that at the time of this study (a) S1 and S2 have not yet been tested on their corresponding W3 and (b) only S3 contributed to W3. Attrition rates for each definable interval (two waves of data on the same sample) were reported and excellent—and the accelerated longitudinal approach was successful—but a more complete design would have included some W3 participants from all three samples. Notably, however, this design characteristic did not seem to affect the results: From the invariance testing to the change-related analyses, the 3-wave data were quite informative. One potential and slight leveling effect was noticed and reported and should be investigated further in future research. Fourth, our study is designed to evaluate the effects of genetics and health factors in a

relatively normal older adult sample. To represent typical aging, we deliberately included older adults with varying levels of blood pressure and even self-reported hypertension medication. In general, at intake, the VLS samples are designed to be relatively healthy (e.g., free of known neurodegenerative disease), community dwelling, and broadly educated. The goal is to observe aging-related changes in biological and neurological health and evaluate their impact on cognitive performance and change. We note, however, that all participants have access to national health care. Although this group may not be representative of all older adults, it may represent a conservative estimation of the moderation effects of environmental factors (i.e., aspects of vascular health) on genetic-cognition relationships.

There are also several strengths associated with this study. First we used contemporary statistical approaches to analyze a series of research goals that systematically built the case for the final set of analyses. Second, we examined the effect of continuously measured age in an accelerated longitudinal design that allowed us to look at the effects of PP and *IDE* (rs6583817) across three data collection points spanning about 9 years. Third, our sample was relatively large (i.e., W1 n = 598) and well-characterized. That this group comprised a band of 40 years of aging is important to note. Fourth, our EF latent variable was composed of four standard and strong neuropsychological manifest variables. Fifth, we examined a novel genetic variant, related to vascular disease and AD, in a relatively healthy group of older adults. We observed potentially protective effects in normal neurocognitive aging.

In conclusion, the goal of this study was to examine the independent and interactive effects of vascular health, as measured by PP and *IDE* (rs6583817) on EF level for both (a) a centering age of 75 years and (b) change across about 9 years. Whereas the *IDE* (rs6583817) major (G) provided apparent protection from the decrements in EF associated with aging, decreased vascular health had a detrimental effect on EF patterns. Furthermore, the protective effects of the G allele were strongly influenced by the negative effects of decreasing vascular health. This fact may imply that the maintenance of vascular health is even more important for adults who possess specific allelic combinations of key cognitive aging genes (e.g., *IDE,* rs6583817). Future research will determine the extent to which vascular health—and potentially numerous other aging-related health factors—may have substantial direct and moderating influences on cognitive phenotypes of aging.

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Table 4-1.

Participant Characteristics Categorized by Time Point

	W1	W2	W3
n	597	490	278
Gender (% Women)	66.0	65.5	66.9
Age	70.6 (8.62)	74.7 (8.51)	74.9 (7.17)
Range	53.2-95.2	57.3-94.5	62.4-94.9
Years between waves		4.44 (.54)	4.46 (.71)
Education	15.3 (2.97)	15.4 (3.01)	15.4 (3.17)
Health to perfect[a]	1.79 (.715)	1.84(.719)	1.85 (.796)
Health to peers[b]	1.58 (.692)	1.63 (.648)	1.66 (.732)
Pulse Pressure (mmHg)	52.2 (11.5)	55.6 (12.9)	55.3 (12.4)
Range	32.8 – 171.4	26.2 – 120.9	29.0 – 95.5
Correlation with age	.444	.418	.378
Smoking Status (%)	*n* = 514	*n* = 418	*n* = 277
Present	3.7	2.6	1.1
Previous	51.4	53.8	53.8
Never	44.9	43.5	44.8
Alcohol Use (%)	*n* = 514	*n* = 418	*n* = 277
Presently	88.3	89.2	89.5
Previous	3.9	8.1	9.0
Never	7.8	2.6	1.4

Note. Results presented as *Mean* (*Standard Deviation*) unless otherwise stated. Age and education presented in years. Smoking and drinking status are reported in percentages of participants who responded to the question. [a] Self-reported health relative to perfect. [b] Self-reported health relative to peers. Self-report measures are based on 1 “very good” to 5 “very poor”.

Table 4-2

Descriptive Statistics for Sample by IDE *Genotype and Longitudinal Wave*

	IDE genotype					
	G+ (G/G & G/A)			G- (A/A)		
	W1	W2	W3	W1	W2	W3
n[a]	519	427	255	79	63	23
Age	70.1 (8.52)	74.2 (8.40)	74.7 (6.98)	73.4(8.73)	77.9 (8.62)	76.8 (9.00)
Range	58.0-82.9	57.2-94.1	62.4-92.9	54.6-90.7	58.9-94.5	63.2-94.9
Gender (% women)	67.1	67.0	67.5	59.5	55.6	60.9
Pulse Pressure	51.8 (10.5) (8.75)	55.4 (13.1)	55.1 (12.4)	55.0 (16.5)	57.1 (11.5)	58.4 (12.1)
Range	32.8-99.2	26.2-120.9	29.0-95.5	33.8-171.4	33.8-82.0	38.6-80.2
Systolic blood pressure	127.3 (21.6)	127.1 (16.0)	126.6 (14.8)	128.7 (20.3)	129.8 (15.0)	130.5 (15.3)
Diastolic blood pressure	75.6 (19.2)	71.8 (9.05)	71.6 (8.53)	73.7 (9.54)	72.7 (9.24)	71.9 (8.17)
Hayling	5.57 (1.46)	5.45 (1.51)	5.61 (1.37)	5.39 (1.41)	5.28 (1.31)	5.13 (1.60)
Stroop[b]	1.28 (.737)	1.33 (.923)	1.21 (.727)	1.44 (.876)	1.54 (1.07)	1.39 (.674)
Brixton	4.89 (2.16)	5.42 (2.00)	5.64 (1.93)	4.53 (2.19)	4.91 (2.19)	5.45 (2.02)
Color Trails[b]	92.9 (29.2)	99.8 (39.0)	100.7 (38.7)	103.4 (39.6)	109.2 (42.2)	99.3 (31.9)
EF factor scores	.014 (.823)	.082 (1.19)	.442 (.956)	-.277 (.932)	-.301 (1.32)	.177 (1.02)

Note. Results presented as *Mean* (*Standard Deviation*) unless otherwise stated. Hardy-Weinberg equilibrium $\chi^2 = 54.09$ at W1, therefore the genotypic distribution for *IDE* is not in Hardy-Weinberg equilibrium. W1 = Wave 1; W2 = Wave 2; W3 = Wave 3.
[a] For G+ *n* is the total G (G/G & G/A). [b] Lower scores indicate better performance.

Table 4-3

Goodness of Fit Indexes for Executive Function Confirmatory Factor Analysis Models and Measurement Invariance Testing

	AIC	BIC	χ^2	*df*	*p*	RMSEA	CFI	SRMR
Model								
One factor EF (W1)	9442.891	9491.202	32.502	3	<.000	.128 (.019-.170)	.786	.121
Two factor EF[a] (W1)	Non-positive definite.							
One factor EF (W2)	8079.871	8126.009	10.951	3	.0120	.074 (.030-.123)	.963	.088
Two factor EF[a] (W2)	Non-positive definite.							
One factor EF (W3)	4376.223	4416.245	9.987	3	.0187	.091 (.033-.156)	.919	.088
Two factor EF[a] (W3)	Non-positive definite.							
One factor EF (W1, W2, W3)	20862.182	21077.468	62.349	41	.0174	.030 (.013-.044)	.985	.078
Equal indicator loadings[b]	20865.389	21080.675	65.556	41	.0088	.032 (.016-.045)	.983	.086
Equal intercepts	20970.994	21159.919	183.161	47	<.001	.070 (.059-.080)	.907	.110
Equal intercepts STRP & HAY	20868.560	21075.059	72.727	43	.0031	.034 (.020-.047)	.980	.089

Note. AIC = Akaike information criteria; BIC = Bayesian information criteria; RMSEA = Root Mean Square Error of Approximation; CFI = Comparative Fit Index; SRMR = Standardized Root Mean Square Residual; EF = Executive Function; W1 = Wave 1; W2 = Wave 2; STRP = Stroop; HAY = Hayling.
[a] Model not identified. [b] Best fitting model used for Factor Score Analysis.

Table 4-4

Absolute Fit Indexes for Executive Function and Pulse Pressure Latent Growth Models

Model	-2LL	AIC	BIC	*D*	Δ*df*
			Executive Function (EF)		
Fixed intercept	4003.216	4007.217	4003.216	-	-
Random intercept	2522.664	2528.664	2541.844	1480.5	1*
Random intercept Fixed slope	2499.658	2507.657	2525.231	23.0	1*
Random intercept Random slope[a]	1811.242	1823.242	1849.603	688.4	2*
			Pulse Pressure (PP)		
Fixed intercept	6133.836	6141.836	5952.256	-	-
Random intercept	5591.604	5601.604	5623.572	540.2	1*
Random intercept Fixed slope[a]	5241.314	5253.314	5279.675	348.29	1*
Random intercept Random slope[b]	5207.978	5223.977	5259.126	29.3	2*

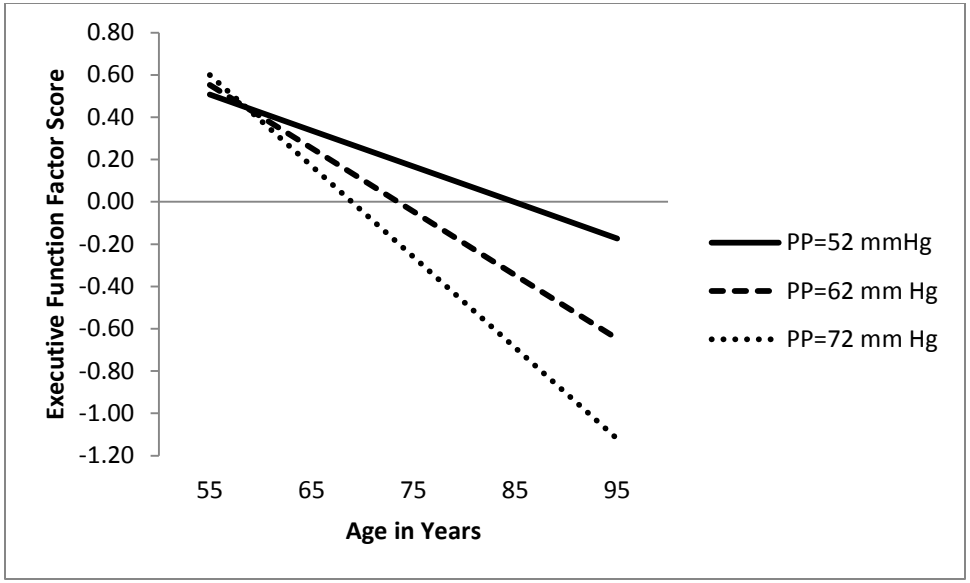
Note. -2LL = -2 log likelihood; AIC = Akaike information criterion; BIC = Bayesian information criterion; *D* = deviance statistic; *df* = degrees of freedom.
[a] Preferred model. [b] The variance of the slope was not significant, therefore this model was not retained despite the significant deviance test.
* $p < .001$.

Table 4-5

Absolute Fit Indexes for Executive Function Conditional Latent Growth Models

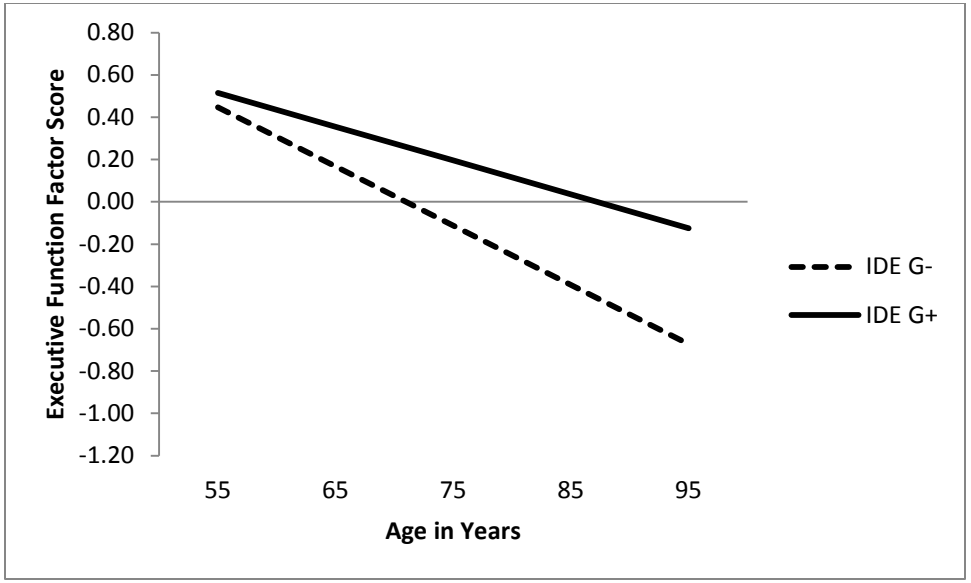
Model	-2LL	AIC	BIC
Predicted by PP (W1)	2171.26	2187.26	2222.41
Predicted by *IDE* (G+/G-)	2207.24	2223.24	2258.39
Predicted by PP (W1) for *IDE* (G+/G-) group	2153.40	2185.40	2255.70

Note. -2LL = -2 log likelihood; AIC = Akaike information criterion; BIC = Bayesian information criterion.



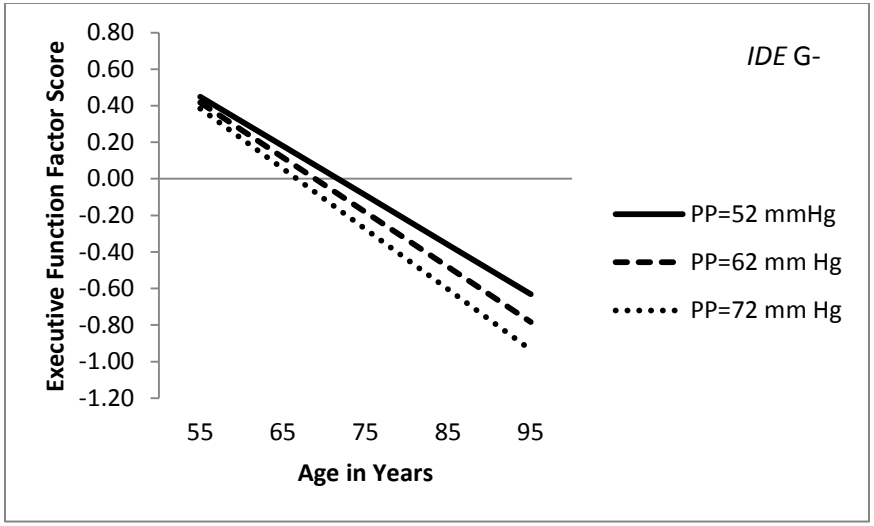
	PP 52	Regression Estimates	PP 62	PP 72
Intercept	.167**	-.214***	-.047	-.261
Slope	-.017**	-.013***	-.030	-.043

Figure 4-1. Predicted growth curve for executive function factor scores using pulse pressure (PP, measured in mm Hg) at W1 as a predictor with age as a continuous variable centered at 75 years.
*p < .05. **p < .01.***p < .001.

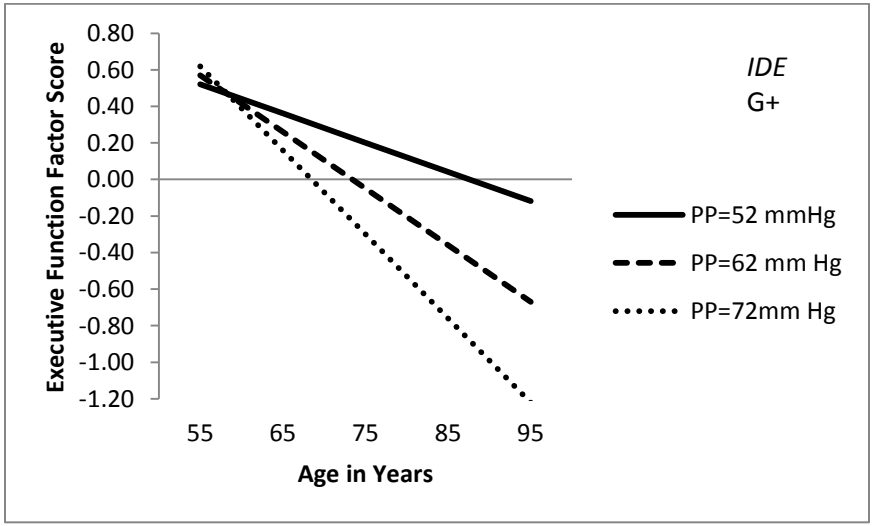


	IDE G-	Regression Estimates	*IDE* G+
Intercept	-.113	.308*	.195
Slope	-.028**	.012	-.016

Figure 4-2. Predicted growth curve for executive function factor scores using *IDE* genotype (i.e., G- = no G allele, G+ = at least one G allele) as a predictor with age as a continuous variable centered at 75 years.
*$p < .05$. **$p < .01$.



	PP 52	Regression Estimates	PP 62	PP 72
Intercept	-.091	-.092	-.183	-.275
Slope	-.027*	-.003	-.030	-.033



	PP 52	Regression Estimates	PP 62	PP 72
Intercept	.201***	-.251***	-.050	-.301
Slope	-.016**	-.015***	-.031	-.046

Figure 4-3. Predicted growth curve for executive function factor scores by *IDE* genotype (i.e., G- = no G allele, G+ = at least one G allele) using pulse pressure as a predictor with age as a continuous variable centered at 75 years.
*$p < .05$. **$p < .01$. ***$p < .001$.

Chapter Five (Study 3)

Genetic (*ApoE*) and Vascular Health (Pulse Pressure) Influences on the Aging of Declarative Memory: Selective Protective Effects for ε2 Carriers in Level and Change of Episodic Memory

Individual differences in cognitive performance and trajectories of change are substantial and uniquely informative about actual descriptive patterns of many aspects of cognitive aging (Hertzog, 2008), including declarative memory (Anstey, 2012; Dixon, Small, MacDonald, & McArdle, 2012). These individual differences in cognitive performance and change are thought to be due to a variety of influences reflecting mechanisms often sorted into biological (e.g., genetic) and environmental (e.g., health or lifestyle) factors (Harris & Deary, 2011; Mitnitski, Song, & Rockwood, 2013; Plassman, Williams, Burke, Holsinger, & Benjamin, 2010; Song, Mitnitski, & Rockwood, 2011). In turn, these factors may reflect two underlying theoretical processes, primary and secondary aging, respectively (see Anstey, 2012; Birren & Cunningham, 1985). Whether these factors serve "risk" or "protective" roles, they may operate both independently and interactively in determining the level and shaping the trajectories of the phenotypic expression, including brain structure and function, performance indicators, and clinical outcomes (e.g., Fotuhi, Hachinski, & Whitehouse, 2009; Harris & Deary, 2011; Josefsson, de Luna, Pudas, Nilsson, & Nyberg, 2012; Kalpouzos & Nyberg, 2012; Lindenberger et al., 2008). In the present study, we adopt a gene x environment (health) approach to examining potential mechanisms of individual differences in concurrent level and longitudinal change in declarative memory performance

among older adults. Accordingly, we target a genetic polymorphism and a major vascular health factor, both of which may be related independently and interactively with long-term memory change in aging. Specifically, we test the effects of *Apolipoprotein E* (*ApoE*) and pulse pressure (PP) for interactive effects on both episodic and semantic memory performance and change in a longitudinal sample of older adults.

Overall, declarative memory (DM) exhibits a general pattern of aging-related decline, but the two principal domains of DM reflect different systems of memory (episodic and semantic) that may display contrasting patterns of aging effects (Nilsson, 2003; Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012; Nyberg et al., 2003; Rönnlund, Nyberg, Bäckman, & Nilsson, 2005; Small, Dixon, & McArdle, 2011; Tulving, 1987). Semantic memory (SM) is the accumulation of general world or cultural knowledge, as reflected in the ability to recall political facts or definitions of vocabulary. Researchers have observed maintenance and even increases in SM ability well into old age (Dixon et al., 2012; Nilsson, 2003; Old & Naveh-Benjamin, 2008; Rönnlund et al., 2005). In addition, SM deficits are thought to be relatively dependent on environmental (non-biological) factors such as education level (Nyberg, Bäckman, Erngrund, Olofsson, & Nilsson, 1996). In comparison, episodic memory (EM) requires remembering of new and personally experienced information, such as names of people you have just met or words you have just heard. Although clearly influenced by selected neural and other biological factors (e.g., Nyberg et al., 2012), a variety of health and environmental may also operate to determine EM

performance and longitudinal changes (e.g., Anstey, 2012). In general, EM changes may occur earlier than SM changes, but recent longitudinal results suggest that even the former may appear to be more gradual than once thought (Dixon et al., 2012; Nilsson, 2003; Nyberg et al., 2012; Rönnlund et al., 2005; Schaie, 2013). At a latent variable level, DM is potentially separable into two related dimensions, SM and EM (Nyberg et al., 2003). With aging, these two DM domains may be differentially affected by a host of environmental, health, and genetic factors (Anstey & Christensen, 2000; Nilsson et al., 2006; Rönnlund et al., 2005). In the current study, we test the latent variable characteristics of DM (SM, EM), and examine the independent and interactive influences of selected environmental and genetic factors.

Vascular health is among the prominent environmental influences on normal memory aging. Pulse pressure, which is conceptually linked to arterial stiffening, is one measure of vascular health used in aging research. The vascular change measured by PP increases with age and is associated with increases in systolic blood pressure and decreases in diastolic blood pressure (Franklin et al., 1997; Mattace-Raso et al., 2006; Raz, Dahle, Rodrigue, Kennedy, & Land, 2011). Arterial stiffening has been found to have an independent effect on cardiovascular disease (Dart & Kingwell, 2001; Mitchell et al., 2007; Schiffrin, 2004) and cognitive performance in older non-demented adults (Bender & Raz, 2012a; Dahle, Jacobs, & Raz, 2009; McFall et al., in press; Waldstein et al., 2008). Arterial stiffness is measured directly by pulse wave velocity, but PP is considered a proxy of pulse wave velocity (Waldstein et al., 2008). PP is

calculated as systolic minus diastolic blood pressure. Typically PP shows a steep age-related increase in older adults and is considered a better predictor of declining vascular health than systolic blood pressure (Raz et al., 2011).

Several researchers have reported PP (and other vascular health) associations with memory deficits in typically aging older adults (Waldstein et al., 2008), increased β-amyloid burden (Rodrigue et al., 2013), and an increased risk of Alzheimer's disease or dementia (Qiu, Winblad, Viitanen, & Fratiglioni, 2003). Memory deficits associated with poor vascular health (i.e., as measured by high systolic or high diastolic blood pressure) were observed for EM tasks (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003; Saxby, Harrington, McKeith, Wesnes, & Ford, 2003). Raz and colleagues (2011) reported that when age, sex, and genetic variants were taken into account, PP and EM correlations were no longer significant. Higher levels of PP were negatively associated with level of EM performance in a group of middle-aged adults (Pase et al., 2010), supporting the idea that the memory decrements may start in midlife. In addition, persons with high PP exhibited accelerated EM decline in comparison to their counterparts with lower PP (Waldstein et al., 2008). In contrast, other researchers observed no group differences between hypertensive and normotensive adults on tasks of working memory, associative memory, and free recall (Dahle et al., 2009). Bender and Raz (2012a) found no main effects of PP on EM. Researchers have reported that vascular health has no effect on SM tasks (Elias, Elias, Robbins, & Budge, 2004).

The relationship *ApoE* has to the development of mild cognitive impairment (Brainerd, Reyna, Petersen, Smith, & Taub, 2011), β-amyloid burden (Rodrigue et al., 2013), and late onset AD (Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007) has sparked a growing interest in both (a) associations with normal or predictably impaired memory aging and (b) potential interactive effects (with other genes or environments) on producing memory decline (Jochemsen, Muller, van der Graaf, & Geerlings, 2012; Wisdom, Callahan, & Hawkins, 2011). Researchers are actively exploring associations among *ApoE* and cognitive changes in non-demented older populations (Berlau, Corrada, Head, & Kawas, 2009; Jochemsen et al., 2012; Lindahl-Jacobsen et al., 2012), other cognition or health specific genes (Ferencz et al., 2013; Josefsson et al., 2012; Laukka et al., 2013; McFall et al., 2013), and gene x environment interactions (Bender & Raz, 2012a, 2012b; McFall et al., in press).

ApoE consists of three isoforms, *ApoE2*, *ApoE3*, and *ApoE4*, and the corresponding ε2, ε3, and ε4 alleles. A gene that codes for a lipid-carrying protein known to be involved in cell maintenance and repair, *ApoE* modulates the efficiency of neuronal repair and plasticity (Lind & Nyberg, 2010; Mahley, 1988). The ε3 allele is the most common and is considered the 'normal' form. The ε2 has been identified as the allele associated with lower levels of cholesterol, heart disease, and risk of dementia and Alzheimer's disease (Berlau et al., 2009; Corder et al., 1993; Fotuhi et al., 2009; Mahley & Rall, 2000). It has also been associated with better cognitive performance in non-demented populations (Anstey & Christensen, 2000; Deary et al., 2004; Lindahl-Jacobsen et al., 2012; Small,

Rosnick, Fratiglioni, & Bäckman, 2004; Wilson, Bienias, Berry-Kravis, Evans, & Bennett, 2002; Wisdom et al., 2011). In contrast, the ε4 variant has been linked to decreased vascular health (Bennet et al., 2007; Smith, 2002), cognitive decrements in global functioning, EM, executive functioning, and perceptual speed (Laukka et al., 2013; Small et al., 2004; Wisdom et al., 2011), increased mortality risk (Lindahl-Jacobsen et al., 2012), and is the largest known risk factor for mild cognitive impairment and sporadic AD (Brainerd et al., 2011). In general, although there are mixed results associated with *ApoE* and EM, carriers of ε4 have exhibited episodic memory decrements when compared to non-ε4 carriers (Anstey & Christensen, 2000; Caselli et al., 2011; Laukka et al., 2013; Lee et al., 2008; Nilsson et al., 2006; Schiepers et al., 2012; Small et al., 2004; Sternäng et al., 2009). Other researchers have found that *ApoE* in interaction with environmental (i.e., health and lifestyle) factors explained more of the variance associated with EM. For example, *ApoE* ε4 carriers have poorer memory performance when they also have poorer vascular health (Bender & Raz, 2012a; Caselli et al., 2011; Ferencz et al., 2013; Sternäng et al., 2009; Yasuno et al., 2012; Zade et al., 2010). In contrast, the limited literature of the effect of *ApoE* on SM has resulted in small or non-significant findings (Nilsson et al., 2006; Reynolds, Gatz, Berg, & Pedersen, 2007). However, *ApoE* effects for SM have been reported in interaction analyses: Sternäng and colleagues (2009) have reported differentially poorer cognitive performance for older women with a ε4 allele and high cholesterol.

A growing emphasis in the study of both normal cognitive aging and neurocognitive degenerative diseases has been on the examining of risk and protective factors that may operate independently and interactively in producing variations in phenotypic trajectories and clinical outcomes. Many of these factors, evaluated independently, are not sufficient or necessary for producing normal cognitive decline, mild cognitive impairment, or dementia (e.g., Anstey & Christensen, 2000; Dolcos, MacDonald, Braslavsky, Camicioli, & Dixon, 2012; Gomar, Bobes-Bascaran, Conejero-Goldberg, Davies, & Goldberg, 2011; Lindenberger et al., 2008). Accordingly, it is becoming increasingly apparent that cognitive decline and dementia are the result of many factors that in combination lead to varying degrees of decline (e.g., Buckner, 2004; Fotuhi et al., 2009; Luck et al., 2013; Wikgren et al., 2012). Recently, some researchers have focused on the interactive or synergistic effects of predictors, including gene x gene and gene x environment factors that have been associated with cognitive phenotypes of aging (Harris & Deary, 2011). For example, interactions of *catechol-o-methyl transferase* (*COMT*) and *brain-derived neurotropic factor* (*BDNF*) genes (Lindenberger et al., 2008) and *COMT* and *ankyrin repeat and kinase domain containing 1* (*ANKK1*) genes (Wishart et al., 2011) were associated with worse cognitive outcomes for older adults. Other genes such as *translocase of outer mitochondrial membrane 40* (*TOMM40*; Ferencz et al., 2013), *phosphatidylinositol-binding clathrin assembly protein* (*PICALM*), and *clusterin* (*CLU*; Barral et al., 2012) synergistically affect episodic memory when analyzed in interaction with *ApoE*. In addition, interactions of *ApoE* with lifestyle

characteristics (e.g., body mass index, physical fitness, smoking status, and education) have been reported to affect select cognitive phenotypes in non-demented older adult samples (Josefsson et al., 2012; Plassman et al., 2010; Raz, Rodrigue, Kennedy, & Land, 2009; Zade et al., 2013) as well as risk of dementia or Alzheimer's disease (Kivipelto et al., 2008; Luck et al., 2013).

In summary, although DM declines with aging the enduring questions of when, how, and why (Dixon et al., 2012) point to several relevant research directions. First, do the two primary memory domains within DM (i.e., EM and SM) follow similar or different age-related performance and change patterns? Second, to what extent is the variability associated with performance in these two declarative memory domains produced by independent and interactive effects of selected biological and environmental factors? Understanding the interactions of genes and health conditions in the aging of DM may (a) account for substantial unexplained variance associated in performance and change, (b) lead to the detection of theoretically relevant effects that appear less independently due to real inter-dependence among multiple factors, and (c) promote further insights into the underlying mechanisms of memory performance and change in normal aging.

The overarching goal of the current study was to examine the independent and interactive effects of PP and *ApoE* on both EM and SM performance and longitudinal change in a group of typically aging older adults. We used a relatively large sample of genotyped older adults (n = 570 at baseline) to explore four research goals. For the first two research goals we used confirmatory factor

analysis within a structural equation modeling context. Research goal 1 was twofold: (a) to use six measures related to two memory domains (i.e., EM, SM) to estimate a latent DM variable and (b) to test this model for longitudinal measurement invariance across three waves. Research goal 2 was to determine the best fitting latent growth models for EM and SM and PP. Using conditional growth models we explored two additional research goals. Research goal 3 was to determine how EM and SM performance patterns in older adults (aged 53-95 years) were affected independently by PP and *ApoE*. Research goal 4 was to determine if PP and *ApoE* interactively affected EM and SM. Based on previous findings, we expected there to be independent effects of PP and *ApoE* on EM but not on SM. We expected to see EM decrements associated with ε4 carriers and EM benefits associated with ε2 carriers. We also expected that PP would exacerbate the effect that *ApoE* has on EM for ε4 but not for ε2 carriers.

Method

Participants

Participants were community-dwelling adults (initially aged 53-95 years) drawn from the Victoria Longitudinal Study (VLS). The VLS is a longitudinal sequential study designed to examine older adult development in relation to biomedical, genetic, health, cognitive and neuropsychological aspects (see Dixon & de Frias, 2004). The VLS and all present data collection procedures were in full and certified compliance with prevailing human research ethics guidelines and boards. Informed written consent was provided by all participants. Using standard procedures (e.g., Dixon et al., 2012; Small et al., 2011), we assembled a selected

longitudinal data set consisting of three samples with up to three available waves collected in the period beginning in the early 2000s. Specifically, this data set consisted of participants from (a) Sample 1 (S1) Waves 6 and 7, (b) Sample 2 (S2) Waves 4 and 5, and (c) Sample 3 (S3) Waves 1, 2, and 3. The mean intervals between the waves of data collection were 4.45 (W1-W2) and 4.49 (W2-W3) years. For terminological efficiency, the respective earliest wave of each sample became Wave 1 (W1 or baseline), the respective second wave became Wave 2 (W2), and the respective third wave became Wave 3 (W3). The design stipulated that whereas S3 participants could contribute data to all three waves, S1 and S2 participants contributed data to W1 and W2 (the third wave not available). Accordingly, the present W3 sample has a relatively larger representation of participants in their 60s and 70s and a relatively smaller representation of those in their 80s and 90s. This consideration is balanced by the advantage of testing genetic-health associations for memory across an accelerated longitudinal period of nearly 9 years (M = 8.9 years). Demographic information is presented in Table 5-1.

Given the necessity for both genetic and longitudinal data in this study, these factors defined the initial opportunity in sample recruitment. VLS genotyping occurred in the 2009-2011 period and was limited by funding arrangement to about 700 continuing VLS participants. After initial evaluations, the eligible source sample consisted of 683 participants with genetic data. Several exclusionary criteria were then applied to this source sample: (a) a diagnosis of Alzheimer's disease or any other dementia, (b) a Mini-Mental Status Exam

(MMSE; Folstein, Folstein, & McHugh, 1975) score of less than 24, (c) a self-report of "severe" for potential comorbid conditions (e.g., epilepsy, head injury, depression), (d) a self-report of "severe" or "moderate" for potential comorbid diseases such as neurological conditions (e.g., stroke, Parkinson's disease), and (e) EM or SM data missing from two or more waves. The remaining sample with full genetic data at W1 consisted of 600 adults. Due to the conflict between the reported protective effect of ε2 on memory and the reported risk associated with ε4, we wished to assess the independent effect of ε2 and ε4. Therefore, adults with *ApoE* genotype ε2/ε4 (n = 30) were removed. Consequently, W1 consisted of 570 adults, including 372 women and 198 men, (M age = 70.6 years, SD = 8.69, range 53.2 – 95.2). W2 consisted of 468 adults, including 303 women and 165 men, (M age = 74.7 years, SD = 8.58, range 57.3 – 94.5). W3 consisted of 272 adults, including 184 women and 88 men, (M age = 74.9 years, SD = 7.30, range 62.4 – 94.9). In this accelerated longitudinal design, a total of 257 adults contributed data to all three waves, 211 adults contributed to W1 and W2 only, 15 adults contributed only to W1 and W3, and 87 adults contributed only to W1. The retention rates for each available and defined interval are as follows (a) S1 W1-W2 = 83%, (b) S2 W1-W2 = 78%, (c) S3 W1-W2 = 84%, (d) S3 W2-W3 = 92%, and (e) S2 W1-W3 = 77%. As noted, defined intervals are determined by availability, which in this instance is limited only by data collected and processed in this ongoing longitudinal study. For these analyses listwise deletion was not used; instead, all missing data were estimated by multiple imputations using Mplus 7 (Muthén & Muthén, 2010). As per practice in the VLS lab, 50

imputations of the data set were generated and pooled for further analyses (for further description of imputations and pooling, see Enders, 2011; Graham, Olchowski, & Gilreath, 2007; Muthén & Muthén, 2010; Rubin, 1987).

Memory Measures

Memory tests used for the current study have been widely used and documented within the VLS (and other studies), with established measurement and structural characteristics and demonstrated sensitivity to health and neurocognitive factors in various older adult populations (e.g., Anstey, 2012; Dixon et al., 2012; Dixon et al., 2004; Josefsson et al., 2012; Kalpouzos & Nyberg, 2012; MacDonald, DeCarlo, & Dixon, 2011).

Episodic memory measures.

Word recall. This task consisted of immediate free recall of two lists of 30 English words selected from the total set of six structurally equivalent (but content diverse) lists (Dixon et al., 2004). The word recall task is administered in a rotated design so as to eliminate context-related practice effects. Over three waves no participant sees the same list twice. Each list consisted of 6 words from each of five taxonomic categories (e.g., birds, flowers) typed on a single page in unblocked order. Participants were given 2 min to study each list and 5 min to write as many words as they could recall. The number of correctly recalled words averaged across the two lists was used for analysis.

Rey auditory verbal learning (REY). This task was used to assess verbal learning and memory (Lezak, 1983; Vakil & Blachstein, 1993). The participant listened to 15 nouns read aloud and immediately after recalled aloud as many of

these nouns as possible. This was repeated for 5 trials with the same list (A1-A5). Then a second list (B1) of 15 unrelated nouns was read aloud to the participant and immediate recall was required. Finally, the participant was asked to recall the first list (A6). List B1 was used to measure free recall and A6 was used to measure recall after interference. The number of nouns recalled from B1 and A6 were used for analyses.

Semantic memory measures.

Fact recall. This task consisted of six sets of 40 equivalent but different general information questions (e.g., "What is the last name of the author of the book 1984?") that were content balanced in terms of science, history, art, sports, geography and entertainment (Nelson & Narens, 1980). The fact recall task is administered in a rotated design so as to eliminate context-related practice effects. Over three waves no participant sees the same list twice. Participants answered two sets of questions per testing session and the task was self-paced. The correct responses from each of the two tests (fact recall 1, fact recall 2) were used for analysis.

Vocabulary. This task used 54 multiple choice items (recognition) taken from the Kit of Factor Referenced Cognitive Tests (Ekstrom, French, Harman, & Dermen, 1976). Participants were given 15 minutes to choose the word that most closely matched the meaning of the presented word. The number of correctly recognized words was used for analysis.

Pulse Pressure (PP)

PP, a reliable proxy of the arterial stiffness aspect of vascular health, is calculated as follows: PP = systolic blood pressure – diastolic blood pressure. For all analyses PP was used as a continuous variable and was centered at the sample mean of 52.0 mmHg. Increases in PP are considered to be an indication of decreases in vascular health. The current study was designed to consider typically aging adults and therefore we included those adults reporting relatively high blood pressure and blood pressure medication use. However, cases of each were relatively rare. Serious high blood pressure was reported at baseline by 4 participants (0.7% of the sample) and blood pressure medication use was reported by 153 adults (28% of the sample). More than 90% of participants' actual blood pressure levels were considered normal or prehypertensive. See Table 5-2 for a comparison of actual blood pressure levels in this sample.

DNA Genotyping

Saliva was collected according to standard procedures from Oragene-DNA. Saliva was stored at room temperature in the Oragene® disks until DNA extraction. DNA was manually extracted from 0.8 ml of saliva sample mix using the manufacturer's protocol with adjusted reagent volumes. Briefly, samples were incubated for 2.5 hours at 50°C after inversion. Samples were transferred to a centrifuge tube and mixed with Oragene® purifier, incubated on ice for 10 min, then centrifuged at 15,000g for 5 min to pellet the denatured protein. The supernatant was transferred to a new tube and DNA was precipitated by adding an equal volume of 100% ethanol. The DNA pellet was washed with 70% ethanol,

dried, and re-suspended with 10 mM Tris, pH 8.0; 1 mM EDTA buffer. DNA was incubated at 50°C for 1 hour with occasional vortexing followed by incubation at 4°C overnight to ensure complete re-hydration before quantification using a NanoDrop® ND-1000 Spectrophotometer (Wilmington, DE).

Genotyping were carried out by using a PCR-RFLP strategy to analyze the allele status for *ApoE* (determined by the combination of the SNPs rs429358 and rs7412). Briefly, SNP-containing PCR fragments were amplified in 25 ul of 1X PCR reaction mix containing 25 ng genomic DNA, 12.5 pmol of each specific primers (Fwd: 5'-GGCACGGCTGTCCAAGGA-3'; Rev: 5'-GCCCCGGCCTGGTACACTGCC-3'), 6.25 nmol of each dNTP, 1.25U Taq DNA polymerase (NEB), 1.5 mM $MgCl_2$ and 10% DMSO. Reactions were setup in 96-well plates using the QIAgility robotic system (QIAgen). RFLP analysis was then performed on a high resolution DNA screening cartridge on a QIAxcel capillary electrophoresis system (QIAgen) using the protocol OL700 after digestion of the PCR amplicons with the restriction enzymes HhaI (NE Biolabs) for 16 hours at 37°C. The analysis was confirmed upon migration of the restriction fragments on 10 or 15% acrylamide gels for each SNP.

For genetic analyses the *ApoE* genotypes were categorized according to the presence or absence of either the ε2 or the ε4 allele to test for protection or risk effects. Specifically, three groups were used: (a) ε2+, consisting of ε2/ε2, ε2/ε3; (b) ε3, consisting of ε3/ε3; and (c) ε4+, consisting of ε4/ε4, ε3/ε4. The number of adults in each group were $n = 72$ for ε2+, $n = 355$ for ε3, and $n = 143$ for ε4+.

Statistical Analyses

Analyses pertaining to our research questions included confirmatory factor analysis and latent growth modeling. Statistical model fit for all analyses was determined using standard indexes: (a) χ^2 for which a good fit would produce a non-significant test ($p > .05$) indicating that the data are not significantly different from the estimates associated with the model, (b) the comparative fit index (CFI) for which fit is judged by a value of ≥ .95 as good and ≥ .90 as adequate, (c) root mean square error of approximation (RMSEA) for which fit is judged by a value of ≤ .05 as good and ≤ .08 as adequate, and (d) standardized root mean square residual (SRMR) for which fit is judged by a value of ≤ .08 as good (Kline, 2011). Specific applications are described in the following research goal sections.

Analyses for RG 1: DM (EM, SM) latent model and invariance testing across three waves. We used Mplus 7 (Muthén & Muthén, 2010) to conduct confirmatory factor analysis. We tested two models (a) a one-factor DM model (word recall, REYB1 [free recall], REYA6 [recall after interference], fact recall 1, fact recall 2) and (b) a two-factor DM model consisting of EM (word recall, REYB1 [free recall], REYA6 [recall after interference]) and SM (fact recall 1, fact recall 2, vocabulary). Next, we tested EM and SM outside the DM latent variable. Next, we tested longitudinal (three-wave) measurement invariance for an EM model and an SM model including: (a) configural invariance, for which the same indicator variables load onto the latent variable used to test the model across time; (b) metric invariance, for which factor loadings are constrained to be equal for each latent variable indicating that the latent variable is measuring the same

construct; (c) scalar invariance, for which indicator intercepts are constrained to be equal allowing mean differences to be evident at the latent mean level; and (d) residual invariance, for which indicator residuals are constrained to be equal accounting for error variability and thus group differences are based on their common variability. We estimated factor scores for EM and SM in Mplus which were then used in subsequent latent growth models. In addition, for all further analyses, we used multiple imputations to estimate missing values for pulse pressure, age, EM, and SM factor scores. By VLS procedure, 50 datasets were generated and pooled before analyses were conducted.

Analyses for RG 2: Latent growth models for EM, SM, and PP. We coded age as a continuous factor and computed latent growth models with individually-varying ages. Age was centered at 75 years of age, as this was the approximate center point of the 40-year band of data (i.e., 53-95 years) and because 75 is an observed meaningful point in cognitive aging (Dixon et al., 2012; Schaie, 2013; Small et al., 2011). We used the best fitting latent model for EM, SM, and PP at each of the three waves. To identify the functional form of change, we determined the best-fitting unconditional growth model by testing in sequence: (a) a fixed intercept model, which assumes no inter- or intraindividual variation; (b) a random intercept model, which models interindividual variability in overall level but no intraindividual change; (c) a random intercept fixed slope model, which allows interindividual variation in level but assumes all individuals change at the same rate; and (d) a random intercept random slope model, which

models interindividual variation in initial level and change; (Singer & Willett, 2003).

Analyses for RG 3 and RG 4: Conditional growth models of EM and SM using PP and *ApoE* (RG3) and testing PP moderation effects of *ApoE*-EM and *ApoE*-SM relationships (RG4). Using the best unconditional growth models identified for EM and for SM, we ran EM and SM as parallel processes in order to examine the differences our predictors might have on these two DM domains. We then added predictors of change to the model. The intercept and slope for EM and SM were regressed separately on *ApoE* genotype and PP measured at W1. Next in order to test the moderation effects of the *ApoE*-EM, *ApoE*-SM relationship, we used a conditional growth model with PP as a predictor using three *ApoE* (ε2+, ε3, ε4+) genotype groups (see McArdle & Prescott, 2010).

Results

RG 1: DM (EM, SM) Latent Model and Invariance Testing Across Three Waves

For simplicity of reporting, all fit indices and abbreviations are in Table 5-3. Using confirmatory factor analysis we tested a one-factor DM model consisting of word recall, REYA6, REYB1, fact recall 1, fact recall 2, and vocabulary (see Table 5-3 for model goodness of fit indexes). The one-factor DM model did not fit the data well. We then tested a two-factor DM model; an EM factor consisting of word recall, REYA6, and REYB1 and a SM factor consisting of fact recall 1, fact recall 2, and vocabulary. The two-factor model fit the data adequately. We tested a single-factor EM model consisting of word recall, REYA6, and REYB1

and then a single-factor SM model consisting of fact recall 1, fact recall 2, and vocabulary (see Table 5-3). Both of these single factor models fit the data adequately. These models therefore showed configural invariance (Con). We then conducted further invariance testing beginning with metric invariance (Met) for the EM-Con model and the SM-Con model. The EM-Met model tested equal indicator factor loadings across W1, W2, and W3 and resulted in a significantly poorer fit to the data than the unrestrained EM-Con model according to the χ^2 difference test ($\Delta\chi^2 = 12.62$, $\Delta df = 4$, $p = .013$). However, the model was still adequate using the standard indexes (described above), thus indicating metric invariance. Using the EM-Met model we tested for scalar invariance (Scal). The EM-Scal model testing equal intercepts across time resulted in significantly poorer fit to the data than the EM-Met model, ($\Delta\chi^2 = 186.56$, $\Delta df = 4$, $p = <.001$). Overall, we observed configural and metric invariance for the single-factor EM model (see EM-Con, EM-Met, EM-Scal models in Table 5-3). For the SM model, the SM-Met model testing equal indicator factors loadings to be equal across W1, W2, and W3 resulted in model that was not significantly worse than the unrestrained SM-Con model according to the χ^2 difference test ($\Delta\chi^2 = 3.56$, $\Delta df = 4$, $p = .468$). The SM-Scal model testing equal intercepts across time resulted in significantly poorer fit to the data than the SM-Met model, ($\Delta\chi^2 = 15.69$, $\Delta df = 4$, $p = .004$). Overall, we observed configural and metric invariance for the single-factor SM model (see SM-Con, SM-Met models in Table 5-3). The resulting models measured the same EM and SM construct across time and manifest variables marking EM and SM were the same. Both models had partial scalar

invariance by methodological design (i.e., to calculate factor scores for EM, word indicator intercepts were constrained; for SM, fact recall 1 intercepts were constrained) indicating that EM (except for Word) and SM (except for fact recall 1) exhibited indicator mean differences across time outside of the latent differences.

RG 2: Latent Growth Models for EM and SM and PP

EM and SM. Using age (centered at 75) as the metric of change, latent growth models were tested using estimated EM and SM factor scores independently. The best fitting unconditional growth model for EM was established as a random intercept, random slope latent growth model (see Table 5-4). The best fitting unconditional growth model for SM was established as a random intercept, fixed slope latent growth model. We then tested the best fitting models for EM and SM as a parallel process model. This model fit the data well and was used for all subsequent models (see Table 5-4). Specifically, adults varied significantly in their EM performance at age 75 (b = 1.203, p < .001) and their SM performance at age 75 (b = 1.035, p < .001). There was significant 9-year decline in EM performance (M = -.012, p < .001) and adults exhibited significant individual differences in EM decline (b = .001, p < .001). There was no significant 9-year decline in SM performance (b = -.004, p > .05) and this pattern was the same for all adults, as indicated by the non-significant random slope model.

Pulse pressure (PP). The best fitting unconditional growth model for PP was established as a random intercept, fixed slope latent growth model (see Table 5-

4). Specifically, PP levels were significantly different from the group mean at age 75 (M = .295, p < .001) and adults differed significantly in their PP levels at age 75 (b = .811, p < .001). There was a significant 9-year increase in PP (M = .055, p < .001) for all adults in the same pattern, as indicated by the non-significant random slope model.

RG 3: Conditional Growth Models of EM and SM Using PP and *ApoE*

We tested two conditional growth models with PP as a predictor of EM and SM level and change. First, we tested the effect of time-varying PP on time-varying EM and SM. This time-varying PP model was not identified. Second, we tested a model in which the baseline level of PP (at W1) was used as the predictor of time-varying EM and SM (see Figure 5-1). The baseline PP model resulted in two significant EM related findings: the baseline level of PP significantly predicted both (a) level of EM performance at age 75 (b = -.125, p < .05) and (b) rate of 9-year EM change (b = -.008, p < .001). Specifically, adults with the mean level of baseline PP (i.e., PP = 52.0 mmHg) performed better on EM tasks (M = .033) at age 75 than adults with PP 10mm Hg higher (M = -.092). In addition, adults with the mean level of PP at baseline exhibited less 9-year decline (M = -.013) than adults with PP 10 mmHg higher (M = -.021). In contrast, baseline PP did not predict level of SM performance at age 75 (p > .05) or rate of SM change (p > .05).

Second, we tested a growth model using *ApoE* (ε2+, ε3, ε4+) and observed the patterns of EM and SM level at age 75 and rate of EM and SM change. This

model did not significantly predict EM or SM performance at age 75 years (p > .05) nor did it significantly predict the rate of EM or SM 9-year change (p > .05).

RG 4: PP Moderation Effects of *ApoE* – EM and *ApoE* – SM Relationships

In order to examine our moderation hypothesis, we tested two moderation models. The three-group unconstrained model, used PP at W1 to predict (a) level of EM and SM at age 75 and (b) three-wave change in EM and SM. The predictions were based on three *ApoE* allele groupings: (a) ε2+, consisting of ε2/ε2, ε2/ε3; (b) ε3, consisting of ε3/ε3; and (c) ε4+, consisting of ε4/ε4, ε3/ε4. The second moderation model, the three-group constrained model, was based on the first model and used PP at W1 to predict (a) level of EM and SM at age 75 and (b) three-wave change in EM and SM based on the same three *ApoE* allele groupings, but with PP regression estimates constrained to be equal for the ε3 and the ε4+ groups.

For the three-group unconstrained model we observed differential EM patterns within the three *ApoE* groups, confirming the moderation hypothesis. First, for the ε2+ group PP did not significantly predict either level of EM performance at age 75 years (p > .05) or 9-year change in EM (p > .05). Second, for the ε3 group baseline level of PP significantly predicted both level of EM performance at age 75 years (b = -.144, p < .05) and 9-year change in EM (b = -.009, p < .001). Third, for the ε4+ group PP did not significantly predict either level of EM at age 75 (b = -.145, p > .05) and 9-year change in EM (b = -.009, p > .001). We hypothesized that the group profiles for the ε3 and ε4+ groupings were more similar than different; therefore, we tested the three-group constrained

model that constrained the PP regression estimates to be equal for the ε3 and the ε4+ groups. If the three-group constrained model was not significantly different from the previous three-group unconstrained model then we could infer that the ε3 and ε4+ group profiles were similar. As expected, the constrained model was not significantly different from the unconstrained model, Δ-2LL = .194, Δ*df* = 2, *p* > .10, and it resulted in differential *ApoE* group findings. First, for the ε2+ group PP did not significantly predict level of EM performance at age 75 years (*p* > .05) or 9-year change in EM (*p* > .05). Second, for the ε3 group baseline level of PP significantly predicted both level of EM performance at age 75 years (*b* = -.144, *p* < .05) and 9-year change in EM (*b* = -.009, *p* < .001). Third, for the ε4+ group baseline level of PP significantly and similarly predicted both level of EM performance at age 75 years (*b* = -.144, *p* < .05) and 9-year change in EM (*b* = -.009, *p* < .001). Taken together, these results indicated that PP at baseline moderates the relationship *ApoE* has with EM for ε3 or ε4+ carriers but not for ε2 carriers. This interaction, demonstrating moderation by PP for *ApoE* genotype-EM association, is displayed in Figure 5-2. As can be seen in the figure (2a), EM performance for ε2 carriers is not differentially affected by PP levels: there are no detectable memory performance differences and the change patterns across PP level are relatively modest. For ε3 carriers (see 2b), the lower PP level subgroup shows better mean performance and more shallow change patterns than the two higher vascular risk subgroups. For the ε4 carriers (see 2c), a similar pattern is observed; although each of the subgroups appears to have somewhat steeper slopes than the corresponding ε3 groups, the differences between the two patterns

are not significant. Finally, regarding SM, baseline level of PP did not significantly predict level of SM at age 75 years or nine-year SM change ($p > .05$).

Discussion

The aim of this research was to examine the independent and interactive effects of one modifiable vascular health indicator (PP) and one genetic polymorphism (*ApoE)* on performance and change patterns of memory across three waves (9 years) of longitudinal data for a group of older adults (spanning a 40-year band of aging). For Research Goal 1 (i.e., DM [EM, SM] latent model and invariance testing across three waves), we observed two main findings. First, two single-factor models of EM and SM provided the best fit for the three waves of data (see Table 5-3). These results provide confirmation that declarative memory can be usefully characterized in terms of two separate but related systems at the latent variable level, and that this might in part account for the frequently observed different performance patterns across adulthood (Nyberg et al., 2003, 2012; see also Tulving, 1987). Second, both EM and SM demonstrated configural and metric invariance. Configural invariance (i.e., all indicators load on the same factors) allowed us to assume that the model measured the same memory construct across time. Metric invariance (i.e., factor loadings are constrained to be equal across time points) allowed us to assume that the constructs were manifest in the same way across time. This meant that factor scores could be calculated using the same weighting scheme across time. Lack of scalar invariance indicated that the manifest variables marking memory exhibited mean differences across

time outside of latent differences. In sum, establishing configural and metric invariance across waves for EM and SM formally permitted us to conduct longitudinal analyses.

For Research Goal 2 (i.e., latent growth models for EM, SM, and PP), we observed several findings. First, EM and SM exhibited different patterns of variability and change in this group of older adults (see Figure 5-1). Regarding the growth of EM, adults exhibited (a) significant variability in EM performance around the centering point of 75 years, (b) significant EM nine-year decline, and (c) significant individual differences in EM decline (Nyberg et al., 2012; Rönnlund et al., 2005; Small et al., 2011). Regarding the growth of SM, adults exhibited (a) significant variability in SM performance around the centering point of 75 years, (b) no significant SM nine-year decline, and (c) a consistent pattern for all adults (i.e., no significant variance around the lack of nine-year decline). Although relatively few studies of the aging of DM have included latent variables of both EM and SM (Dixon et al., 2012; Nyberg et al., 2003; Wilson et al., 2002), the observed patterns in the present study are consistent with these and are similar to those observed with other approaches (e.g., Nilsson, 2003; Rönnlund et al., 2005; Small et al., 2011).The SM patterns observed in this study are consistent with other research in regard to the interindividual differences associated with SM (Dixon et al., 2012; MacDonald et al., 2011) and less decline than EM (Nilsson, 2003; Nilsson et al., 2006). The contrasting longitudinal patterns for these two domains suggest that DM variability (individual differences at the centering age and in longitudinal change) may be differentially dependent on primary or

secondary aging factors such as protective- or risk-related factors of biological vulnerability, health burden, or lifestyle choices (Anstey, 2012; Dixon et al., 2012; Josefsson et al., 2012; Nilsson, 2003; Nilsson et al., 2006; Nyberg et al., 2003, 2012). Specifically, EM may be affected not only directly by biological factors but also indirectly by environmental factors (e.g., health) that exacerbate the extent of deleterious influence from the declining neurobiological substrate. In contrast, SM is more dependent on secondary aging factors and may be protected by accumulating and supported environmental factors (e.g., education, cognitive activities), many of which may decline in effectiveness with aging.

For this research goal we also tested a growth model related to pulse pressure, known to reflect arterial aging. We found that older adults (a) differed significantly in their levels of PP at age 75 years, (b) exhibited a significant increase in PP across a nine-year period, and (c) exhibited the same pattern of change over the three waves. This aging-related increase in PP is consistent with other research indicating general vascular health decline with aging (Dahle et al., 2009; Dart & Kingwell, 2001; Davenport, Hogan, Eskes, Longman, & Poulin, 2012; Franklin et al., 1997; Morra, Zade, McGlinchey, & Milberg, 2013; Raz et al., 2011). For present purposes, this result is primarily useful in that it permitted us to proceed with PP as a predictor in subsequent EM and SM models. In sum, the overall observations of RG2 included three main points. First, EM exhibited interindividual concurrent variability and 9-year longitudinal decline. Second, SM exhibited interindividual concurrent variability but non-significant 9-year decline.

Third, PP exhibited interindividual concurrent variability and 9-year longitudinal increase, indicating decline in vascular health.

For Research Goal 3, we tested conditional growth models in order to determine the independent effects of PP and *ApoE* on EM and SM performance and change. Several interesting results were observed. First, higher baseline level of PP was associated with both (a) lower levels of EM performance at age 75 and (b) more EM decline over the nine-year period. Our findings support research reporting lower memory performance associated with poorer vascular health in older adults. For example, lower memory performance has been associated consistently with type 2 diabetes and hypertension (van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009) and PP (Pase et al., 2010; Waldstein et al., 2008; but see Bender & Raz, 2012a). Second, baseline PP had no effect on either centering level of SM or change in SM, although the latter may be due to the fact that relatively little 9-year change was found for SM. This supports previously reported findings for which some health factors have minor effects on SM performance (e.g., Elias et al., 2004; Nilsson et al., 1997; see also Sternäng et al., 2009). Third, although time-varying PP exhibited a significant 9-year increase, there was no effect of PP change on time-varying EM. Instead, initial level of PP accounted for the differential effect on EM change. Fourth, *ApoE* exhibited no main effects on either EM or SM level or nine-year change. Previous research on *ApoE* and DM performance in aging has produced somewhat inconclusive patterns. Our findings support studies that have reported no independent effects of *ApoE* on EM (Bender & Raz, 2012a; Bunce, Anstey, Burns, Christensen, &

Easteal, 2011; Ferencz et al., 2013; Raz et al., 2009; Sternäng et al., 2009). In contrast other research has reported independent *ApoE* effects on EM performance (Laukka et al., 2013; Wilson et al., 2002). Wilson and colleagues (2002) examined *ApoE* allele groups the same as our study and found independent effects associated with *ApoE*. Specifically, ε2 carriers exhibited consistent (or even improved) EM performance over three years whereas ε3 carriers exhibited slight EM decline and ε4 carriers exhibited the steepest decline. These inconsistent findings may be a function of differences between study designs. First, *ApoE* may independently affect some DM tasks and not others, making the inconsistencies dependent on a variety of tasks used among studies (Wisdom et al., 2011). Second, independent effects of *ApoE* may be influenced by other study specific factors such as age of the participant (i.e., heritability may increase with age), environmental factors that may have previously influenced at risk allele carriers, or differences other risk alleles in combination with *ApoE* (Harris & Deary, 2011; Plassman et al., 2010; Wisdom et al., 2011). In sum, three main points were observed for RG3. First, baseline level of PP predicted level and change in EM. Second, baseline level of PP did not affect SM. Third, *ApoE* was not independently associated with level or change in either EM or SM.

For Research Goal 4, we tested the hypothesis that PP would moderate *ApoE*-EM and *ApoE*-SM relationships. Although there were no main effects of *ApoE* on EM and SM, the gene x environment interactions based on three *ApoE* groups (i.e., ε2+, ε3, and ε4+) and PP level showed differential effects on EM (see Figure 5-2). In general, adults with centering level of PP (i.e., 52mm Hg) for any of the

three *ApoE* groups (but especially the non- ε2+ group) were similar in level of EM at age 75 and experienced more shallow negative change slopes than did their genotype counterparts with higher levels of PP. The patterns of EM change across level of vascular health were differentiated by *ApoE* status. First, the ε2+ group EM performance and 9-year change showed some decline over the 9-year period but neither the performance at age 75 nor the slope of decline was affected by level of PP. Second, in contrast, the ε3 and ε4+ groups performed at significantly lower average levels of EM at age 75 and displayed more 9-year decline in EM, increasingly so as PP levels were elevated. In fact, the fan patterns demonstrated exacerbating effects of worsening PP on EM change, and these were in contrast to the tight parallel patterns for the ε2 group. The apparent differences in levels and slopes between the ε3 and ε4 groups were not significant, according to the unconstrained and constrained moderation models we conducted. These results support and extend regarding the potential cognitively protective ε2 allele, showing that it may also moderate memory deficits and declines associated with substantial increases in the vascular risk represented by elevated PP (Deary et al., 2004; Fotuhi et al., 2009; Small et al., 2004). In contrast, those adults who do not have the ε2 allele continue to be at risk – in fact increased risk – with higher levels of PP. Less directly, perhaps, the present results may have implications for recent reports concerning the synergistic negative effect of *ApoE* ε4 and decreased cardiovascular health (Bender & Raz, 2012a). Specifically, Bender & Raz (2012a) reported no main effects of *ApoE* ε4 or PP on EM but that higher PP in a group of ε4+ carriers resulted in lower levels of EM. Other researchers reported that any

cardiovascular risk factor (e.g., hypercholesterolemia, type 2 diabetes, high systolic blood pressure) in the presence of the ε4 allele resulted in exacerbated age-related memory decline (Caselli et al., 2011; Zade et al., 2010). Similarly, Yasuno and colleagues (2012) found that adults who were *ApoE* ε4 carriers and were hypertensive experienced more decline for a cognitive composite scale of attention, memory, language, and reasoning. The relevant literature on cognitive performance associated with older adult ε2 carriers is limited, probably due to the low percentage of ε2 carriers in a normal population (see Sternäng & Wahlin, 2011). The present VLS sample permits this and future research on this important topic in neurocognitive aging. Specifically, future research on synergistic positive effects on neurocognitive performance, changes, and clinical outcomes is encouraged (e.g., Bonner-Jackson, Okonkwo, & Tremont, 2012; Wilson et al., 2002). The present research demonstrates that the ε2 protective effect can be quite robust across elevated risk levels of vascular health which, under other allelic conditions, have pernicious effects on episodic memory in aging.

The present study does not contain neuroimaging data, although such studies have begun to reveal informative results (e.g., linking hippocampal volume and ε2 versus ε4 carriers; Alexopoulos et al., 2011; Hostage, Choudhury, Doraiswamy, & Petrella, 2013). Among apparently concordant results are (a) that memory performance deficits associated with ε4 manifest primarily in the presence of (other) age-related biological burden, but (b) the protective effects of the ε2 allele may extend into very late life, despite primary aging. As is typical, however, early results are complicated. For example, in one study very old (90+ years) adult ε2

carriers seemed to be at a lower risk of dementia but an increased risk of Alzheimer's disease neuropathology (Berlau et al., 2009). Along with the possibility of preserved brain function for older ε2 carriers, the protective effects of the *ApoE* ε2 allele, even in the presence of high PP, may be due to increased levels of ApoE and therefore an increased ability to make repairs to the neuronal damage that is associated with neurobiological aging and decreased vascular health. Carriers of the ε3 or ε4 alleles have the added disadvantage of less ApoE to repair the neural damage associated with aging, such as that in an already compromised hippocampus, among the early sites of amyloid plaques in the AD cascade.

There are several limitations and strengths associated with this study. First, this study considers arterial stiffness, which is one aspect of the larger domain of vascular health and is associated with cognitive performance in older adults. Although a direct measure of arterial stiffness (pulse wave velocity) is not available in the VLS, a well-established proxy (PP) is based on the available measures of systolic and diastolic blood pressures. Despite the significant *ApoE* x PP interaction showing differential effects on EM, future research could examine a broader representation of normal and clinical vascular health measures. Second, the present sample is relatively large and covers three waves over about 9 years, but a design characteristic reported earlier should be noted again, as it affected the n and age characteristics of W3. The design characteristic is that at the time of this study (a) S1 and S2 had not yet been tested on their corresponding W3 and (b) only S3 contributed to W3. Attrition rates for each definable interval (two waves

of data on the same sample) were reported and excellent—and the accelerated longitudinal approach was successful—but a more complete design would have included some W3 participants from all three samples. Notably, however, this design characteristic did not seem to affect the results: From the invariance testing to the change-related analyses, the 3-wave data were quite informative. Third, this study is designed to evaluate the effects of a genetic and vascular health factor in a relatively normal older adult sample (see Table 5-2). To represent typical aging, we deliberately included older adults with varying levels of blood pressure and even self-reported hypertension medication. In general, at intake, the VLS samples are designed to be relatively healthy (e.g., free of known neurodegenerative disease), community dwelling, and broadly educated. The goal is to observe aging-related changes in biological and neurological health and evaluate their impact on cognitive performance and change. We note, however, that all participants have access to national health care. Although this group may not be representative of all older adults, it may represent a conservative estimation of the moderation effects of environmental factors (i.e., aspects of vascular health) on genetic-cognition relationships.

There are also several strengths associated with this study. First we used contemporary statistical approaches to analyze a series of research goals that systematically built the case for the final set of analyses. Second, we examined the effect of continuously measured age in an accelerated longitudinal design that allowed us to examine the effects of PP and *ApoE* across three data collection points spanning about 9 years. Third, our sample was relatively large (i.e., W1 n =

570) and well-characterized. That this group comprised a band of 40 years of aging is important to note. Fourth, we investigated two separate declarative memory latent variables EM and SM composed of six standard and strong neuropsychological manifest variables.

In conclusion, the goal of this study was to examine the independent and interactive effects of vascular health, as measured by PP and *ApoE* on EM and SM level for both (a) a centering age of 75 years and (b) change across about 9 years. Although decreased vascular health (i.e. PP) had a negative influence on EM, it appeared that *ApoE* ε2 provided protection from the decrements in EM associated with aging and decreased vascular health. In addition, in the absence of a ε2 allele the effects of decreased vascular health are not mitigated. This suggests that the maintenance of vascular health is even more important for adults who possess specific allelic combinations of key cognitive aging genes (e.g., *ApoE*). Future research will determine the extent to which vascular health—and potentially numerous other aging-related health factors—may have substantial direct and moderating influences on cognitive phenotypes of aging.

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Table 5-1

Participant Characteristics Categorized by Time Point

	W1	W2	W3
N Sample 1	54	45	na
Sample 2	164	128	na
Sample 3	352	295	272
Total	570	468	272
Gender (% Women)	65.3	64.7	67.6
Age	70.6 (8.69)	74.7 (8.58)	74.9 (7.30)
Range	53.2-95.2	57.3-94.5	62.4-94.9
Years between waves		4.45 (.55)	4.45 (.71)
Education	15.3 (3.01)	15.5 (3.05)	15.5 (3.10)
Health to perfect[a]	1.79 (.723)	1.83(.719)	1.84 (.814)
Health to peers[b]	1.57 (.688)	1.63 (.652)	1.67 (.747)
Pulse Pressure (mm Hg)	52.1 (11.4)	55.3 (12.5)	55.2 (12.4)
Range	32.1 – 171.4	26.2 – 102.6	33.0 – 95.5
Correlation with age	.441†	.417†	.362†
BMI (kg/m^2)	26.9 (4.25)	26.6 (4.32)	26.7 (4.50)
Range	15.0 – 48.6	16.2 – 41.0	10.0 – 39.5
Correlation with age	-.047	-.051	-.086
Smoking Status (%)			
Present	4.2	3.0	1.1
Previous	53.0	53.4	53.6
Never	42.8	43.6	45.3
Alcohol Use (%)			
Presently	88.8	89.5	89.6
Previous	4.0	8.0	8.6
Never	7.2	2.4	1.9

Note. Results presented as *Mean* (*Standard Deviation*) unless otherwise stated. Age and education presented in years. Smoking and drinking status are reported in percentages of participants who responded to the question.
[a] Self-reported health relative to perfect. [b] Self-reported health relative to peers. Self-report measures are based on 1 "very good" to 5 "very poor".
na = data not available.
† $p < .01$.

Table 5-2

Blood Pressure Levels Across Time

		W1	W2	W3
Systolic Blood Pressure				
Hypotension	< 90 mm Hg	1 (.2%)	1 (.2%)	0
Normal and Prehypertension	90 – 139.9 mm Hg	453 (82.4)	360 (78.4%)	209 (80.7%)
Stage 1 Hypertension	140 – 159.9 mm Hg	87 (15.8%)	88 (19.2%)	43 (16.6%)
Stage 2 Hypertension	≥ 160 mm Hg	9 (1.6%)	10 (2.2%)	7 (2.7%)
Diastolic Blood Pressure				
Hypotension	< 60 mm Hg	32 (5.8%)	39 (8.5%)	21 (8.1%)
Normal and Prehypertension	60 – 89.9 mm Hg	485 (88.2%)	404 (88.0%)	231 (89.2%)
Stage 1 Hypertension	90 – 99.9 mm Hg	28 (5.1%)	14 (3.1%)	7 (2.7%)
Stage 2 Hypertension	≥ 100 mm Hg	5 (.9%)	2 (.4%)	0

Table 5-3

Goodness of Fit Indexes for Memory Confirmatory Factor Analysis Models and Measurement Invariance Testing

Model	AIC	BIC	χ^2	*df*	*p*	RMSEA	CFI	SRMR
One-factor DM	47029.65	47346.23	749.68	117	<.001	.095 (.089-.101)	.887	.132
Two-factor DM	46718.74	46995.74	456.77	126	<.001	.066 (.060-.073)	.941	.100
EM	24409.70	24581.17	16.13	15	.373	.011 (.000-.041)	.999	.016
EM-Con[a]	24483.62	24646.30	94.06	17	<.001	.087 (.070-.104)	.959	.071
EM-Met[b]	24488.23	24633.33	106.67	21	<.001	.082 (.067-.098)	.955	.082
Equal indicator loadings								
EM-Scal	24666.80	24794.31	293.24	25	<.001	.134 (.120-.148)	.858	.108
Equal intercepts								
EM-PScal	24586.77	24723.07	209.21	23	<.001	.116 (.102-.131)	.901	.106
Partial equal intercepts								
SM	Not positive definite							
SM-Con[a]	22308.21	22457.70	120.35	20	<.001	.091 (.076-.108)	.971	.080
SM-Met [b]	22303.77	22435.68	123.91	24	<.001	.083 (.069-.098)	.971	.073
Equal indicator loadings								
SM-Scal	22311.46	22425.78	139.60	28	<.001	.082 (.068-.095)	.968	.082
Equal intercepts								
SM-PScal	22313.98	22437.09	138.12	26	<.001	.085 (.071-.099)	.968	.080
Partial equal intercepts								

Note. AIC = Akaike information criteria; BIC = Bayesian information criteria; RMSEA = Root Mean Square Error of Approximation; CFI = Comparative Fit Index; SRMR = Standardized Root Mean Square Residual; DM = declarative memory; EM = episodic memory; SM = semantic memory; Con = configural; Met = metric; Scal = scalar; PScal = partial scalar.

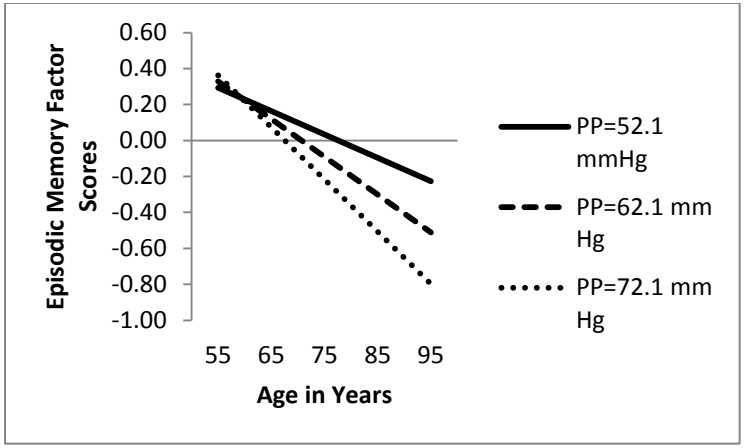
.[a] First indicator intercepts constrained for this and all consequent models. [b] Best fitting model used for Factor Score Analysis.

Table 5-4

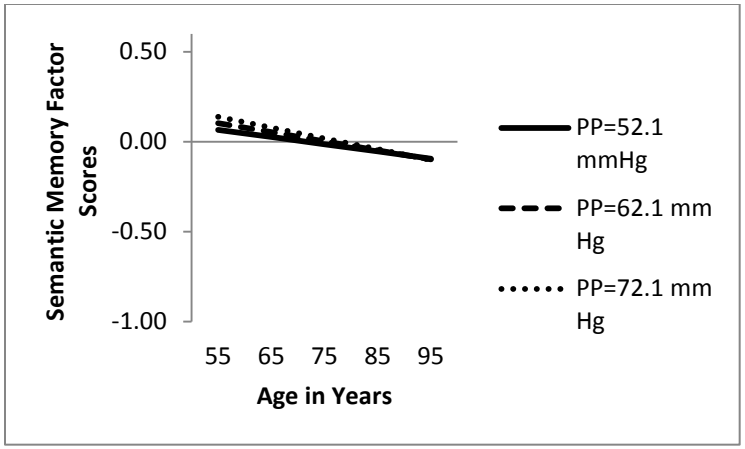
Goodness of Fit Indexes for Memory and Pulse Pressure Latent Growth Models

	Model	-2LL	AIC	BIC	*D*	Δ*df*
EM	Fixed intercept	3920.24	3928.25	3945.84	-	
	Random intercept	2013.42	2023.42	2045.41	1906.82	1*
	Random intercept Fixed slope	1941.12	1953.12	1979.50	72.30	1*
	Random intercept Random slope[a]	1416.36	1432.36	1467.36	524.76	2*
SM	Fixed intercept	3850.78	3834.78	3843.57	-	
	Random intercept	477.62	483.62	496.81	7373.16	1*
	Random intercept Fixed slope[a]	320.84	328.83	346.42	156.78	1*
	Random intercept Random slope	-420.32	-408.31	-381.93	741.16	2*
EM PAR SM[b]		1314.22	1346.22	1415.22		
PP	Fixed intercept	5614.94	5622.94	5640.32	-	
	Random intercept	4904.12	4914.13	4935.86	710.82	1*
	Random intercept Fixed slope[a]	4608.36	4620.36	4646.44	295.76	1*
	Random intercept Random slope	4567.86	4583.86	4618.62	40.50	2*

Note. -2LL = -2 log likelihood; AIC = Akaike information criterion; BIC = Baysian information criterion; *D* = deviance statistic; *df* = degrees of freedom; EM = episodic memory; SM = semantic memory; PP = pulse pressure.
[a] Best fitting model. [b] Best fitting EM and SM model as parallel processes. *$p < .001$.

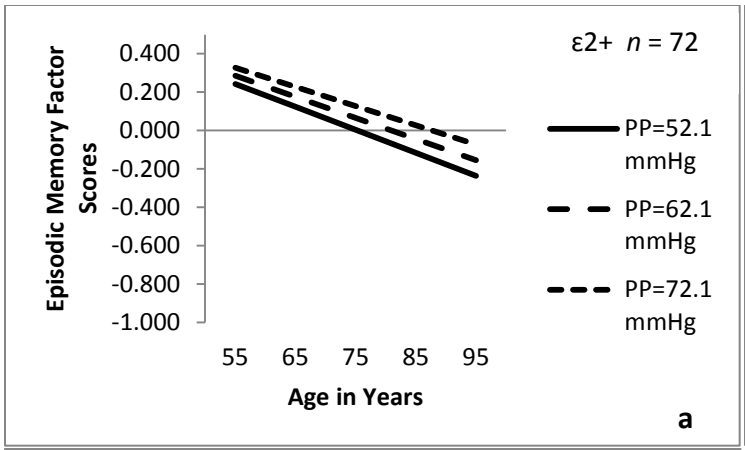


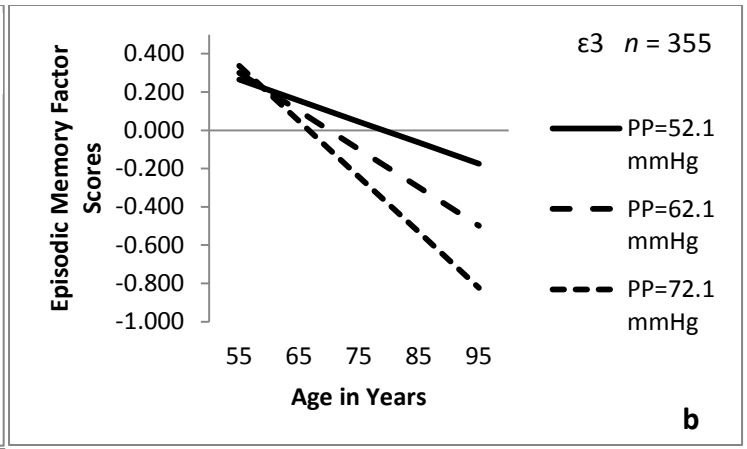
	M at PP = 52	Reg. Est.
EM Intercept	.033	-.125*
EM Slope	-.013***	-.008***

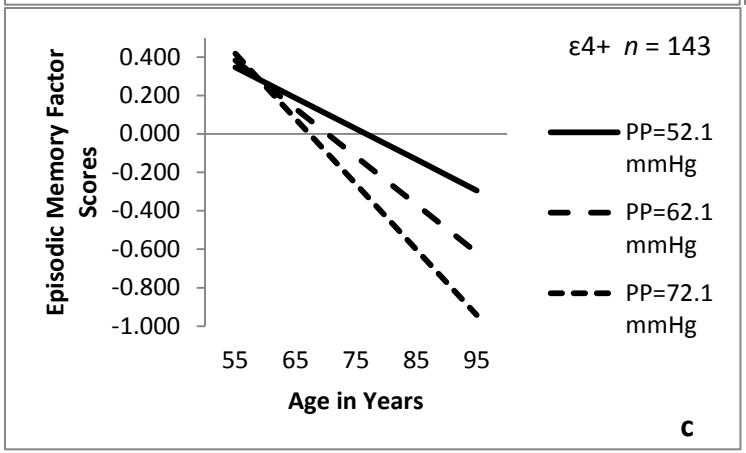


	M at PP = 52	Reg. Est.
SM Intercept	-.014	.016
SM Slope	-.004	-.001

Figure 5-1. Predicted growth curve for declarative memory factor scores (episodic memory, semantic memory) using pulse pressure (PP, measured in mm Hg) at W1 with age as a continuous variable centered at 75 years. -2 Log Likelihood = 1276.38; Akaike Information Criteria = 1316.37; Bayesian Information Criteria = 1403.28; Parameters Free = 20.
* $p < .05$. *** $p < .001$.







ApoE		*M* at PP = 52[a]	Reg. Est.[a]
ε2+	EM i	.003 | .003	.062 | .062
	EM s	-.012 | -.012	.001 | .001
ε3	EM i	.045 | .045	-.144* | -.144*
	EM s	-.011*** | -.011***	-.009** | -.009***
ε4+	EM i	.026 | .026	-.145 | -.144*
	EM s	-.016** | -.016**	-.009 | -.009***

Figure 5-2. Predicted growth curve for episodic memory factor scores by *ApoE* genotype group using pulse pressure at W1 with age as a continuous variable centered at 75 years. *ApoE* grouping = ε2+ (ε2/ε2, ε2/ε3), ε3 (ε3/ε3), ε4+ (ε4/ε3, ε4/4) with ε3 constrained to be equal to ε4+; 2 Log Likelihood = 1237.92; Akaike Information Criteria = 1357.92; Bayesian Information Criteria = 1618.66.
[a] Model 1 | Model 2. i = intercept. s = slope. $^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

Chapter Six

General Discussion and Conclusions

The aim of this research was to examine the concurrent and longitudinal association of two modifiable health (i.e., type 2 diabetes, pulse pressure) and two non-modifiable genetic (i.e., *IDE*, *ApoE*) factors and ascertain their independent or interactive influence on cognitive performance and change (i.e., executive function, episodic memory, semantic memory) of older adults.

Study 1 examined the independent and interactive effects of T2D and *IDE* on EF. Both T2D and *IDE* produced group related EF performances differences at the age intercept and *IDE* produced group differences in 6-year rate of EF change. Specifically, adults who possessed an *IDE* G allele had better EF performance and less EF decline than adults who did not possess an *IDE* G allele. Adults without T2D had better EF performance than the adults with T2D. In addition, the presence of T2D did not magnify the preservative effects of the *IDE* G allele on EF nor exacerbate the decrements of the group without an *IDE* G allele.

Study 2 examined the independent and interactive effects of PP and *IDE* on EF. Both baseline PP and *IDE* produced group related EF performance differences at the age intercept and baseline PP produced group differences in 9-year rate of EF change. Specifically, adults with an *IDE* G allele performed better on EF tasks at age of intercept than did those adults without a G allele. Adults with higher PP performed more poorly on EF tasks at age of intercept and experienced greater EF decline. The moderation analyses showed that adults with poorer vascular health as measured by PP differentially affected EF performance

in older adults with an *IDE* G allele. For these factors the allele that was associated with preserved EF performance (G) was the most impacted by increases in PP.

Study 3 examined the independent and interactive effects of PP and *ApoE* on EM and SM. Baseline PP produced group related EM performance difference at age of intercept and produced group differences in 9-year rate of EM change. Specifically, adults with higher PP performed more poorly on EM tasks at age of intercept and experienced more 9-year EM decline. Baseline PP exhibited no effect on SM performance or rate of change. *ApoE* exhibited no effect on either EM or SM performance at age of intercept or rate of change. The moderation analyses revealed that the negative effect of higher PP did not affect the *ApoE* ε2+ grouping on EM performance. However, higher PP differential affected the *ApoE* ε3/ ε4+ groupings. Specifically, higher PP had a negative impact on the EM performance at age of intercept and 9-year rate of change for older adults with a ε3 or ε4 allele. Those with a ε2 allele showed no difference in EM performance in the presence of higher PP.

Overall, four important findings came from this research. First, this research confirms the negative impact that health factors (i.e., T2D, PP) have on cognitive performance and change in normal older adults. Both T2D and PP are modifiable health factors. If these lifestyle and health conditions are controlled—or if positive interventions are implemented—their deleterious impact on older adult cognition may be less severe (Anstey & Christensen, 2000; Awad et al., 2004; Cholerton et al., 2011; Pase et al., 2010; Yasuno et al., 2012; Zade et al., 2010).

Intriguing questions remain, such as whether related interventions implemented earlier in the lifespan (e.g., midlife) might benefit later normal aging changes or even onset of cognitive impairment.

Second, a relatively novel genetic factor (i.e., *IDE*) was examined and the major allele (G) of this gene was found to have a protective effect on EF performance and change in older adults. This is the first time that this particular genetic SNP (i.e., rs6583817) has been analyzed in relation to normal cognitive aging. Although other SNPs have been associated with T2D (Bartl et al., 2011), for this allele an effect was seen for EF performance and EF change patterns but not in relation to T2D. Our findings support previous research that links this particular *IDE* variant to increased level of IDE transcription and lowered risk of AD (Belbin et al., 2011; Carrasquillo et al., 2010).

Third, the *ApoE* analyses resulted in a non-significant main effect on memory performance and change, but our three group moderation analyses (i.e., ε2+/ ε3/ ε4+) revealed statistically significant and theoretically interpretable interaction results. Whereas adults possessing the protective ε2 allele were unaffected by poor vascular health (both in terms of similar levels and stable change trajectories) carriers of the risk ε4 allele were more vulnerable to negative vascular health (both in terms of differentially lower levels of performance and steeper trajectories of decline). This is an important consideration as the effects of genes may indeed especially be expressed in the presence of specific health and/or other genetic factors (McArdle & Prescott, 2010). These findings are supported by the literature that links cardiovascular risk to *ApoE* ε4, but not ε2, with more

detrimental cognitive outcomes (Caselli et al., 2011; Deary et al., 2004; Ferencz et al., 2013; Rodrigue et al., 2013; Zade et al., 2010). Our findings support the limited ε2 allele literature that reports the maintenance or improvement of EM for ε2 carriers (Deary et al., 2004; Hyman et al., 1996; Lindahl-Jacobsen et al., 2012; Wilson et al., 2002), even in the context of poorer vascular health.

Fourth, the results of the second and third studies showed that an interaction between the modifiable health factor PP and two different genes (i.e., PP x *IDE*; PP x *ApoE*) affect older adult cognition, although in different ways. Adults in Study 2 with the protective *IDE* G allele were more vulnerable to the negative effects of decreased vascular health (i.e., higher PP) in regard to EF. In constrast, adults in Study 3 with the protective *ApoE* ε2+ were unaffected by the negative effects of higher PP in regard to EM. This highlights the importance of examining gene x environment (health) interactions in relation to identifying the groups of older adults who could most benefit most from targeted health-related interventions.

Levels and trajectories of cognitive performance with aging are determined in part by genotypic influences, but also by the impact of environmental and health factors operating concurrently or in preceding periods of the lifespan. At a public health level, the importance of controlling vascular health even when there is no genetic information available is unquestioned, but our findings highlight the importance of identifying people with genetic vulnerability for which poor vascular health might exacerbate the severity of the condition. Specifically, adults possessing a potentially protective genetic allele may be particularly susceptible

to poor health or lifestyle choices and those adults possessing a potentially risky genetic allele may improve their outcomes simply by maintaining the best possible health and lifestyle. Therefore, it is important to examine cognitive phenotypes with aging on a continuum of competence in relation to both genetic and lifestyle factors. This allows us to capture both the protective and detrimental effects of genes and environment on older adult cognition (Belsky et al., 2009) in order to provide interventions that will be most effective to particular groups of adults. The current program of research, specifically the gene x environment (health) approach, adds to the literature by identifying specific groups that would most benefit from interventions that highlight better vascular health such as lifestyle changes.

Rather than repeating the common strengths and limitations of the three studies (these have been discussed in more detail within each individual study), we turn now to a brief consideration of future directions for this research program. First, the *IDE* (rs6583817) genotype should be included in future investigations with (a) other *IDE* genotypes, (b) other genes (e.g., *ApoE*), (c) environmental-lifestyle (e.g., physical fitness) factors, and (d) health related (e.g., weight status) modifiers (see Lindenberger et al., 2008). Second, neurocognitive speed should be investigated in relation to gene x environment or gene x gene interactions models of cognitive aging. Third, as noted above other measurable health factors that are continuous rather than dichotomous should be explored (i.e., glycated hemoglobin, HbA1c; body mass index). Fourth, future analyses will benefit from the addition of data for the W3 from samples 1 and 2, which will be available in

due course. Fifth, replication of these findings should be carried out in other population (i.e., other longitudinal studies), allowing for (a) a broader age range that would include younger adults and (b) potentially more health-related diversity.

Overall, in this sample of normally aging adults there is evidence that both genetic and health-related factors are associated independently and sometimes interactively with the prominent cognitive aging phenotypes. This research highlights the importance of examining gene x environment (health) interactions and may have special implications for clinical management of biological and cognitive health for older adults.

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