University of Alberta

Longitudinal Associations of Genetic Polymorphisms and Personality Traits:

Independent and Interactive Effects on Neurocognitive Performance

in Older Adults

by

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To my parents

ABSTRACT

Research has linked multifaceted neurocognitive phenotypes to genetic polymorphisms and environmental factors. This study examines associations of personality traits and single nucleotide polymorphisms (SNPs) on cognition. Structural equation modeling was used to examine (a) independent and interactive effects of six SNPs (*APOE, COMT, BDNF, CLU, CR1, PICALM*) and (b) five personality traits on (c) cognitive performance and change in (d) a five-wave (approximately 14-years) longitudinal sample of older adults (*N*=282). We observed (a) adults with high openness levels performed higher on memory and neurocognitive speed, (b) *COMT* allelic risk carriers showed shallower positive slope and *BDNF* allelic risk carriers had steeper change in memory, (c) combined allelic risk group for *APOE*x*CR1* had the worst performance on vocabulary and *APOE*x*COMT* and *APOE*x*BDNF* groups had shallower positive change on word recall, and (d) neuroticism levels moderated memory performance for *CLU* and *COMT* in the unexpected directions. Implications of findings are discussed.

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CHAPTER 1 - INTRODUCTION

Rapid emergence of dementia, in particular Alzheimer's disease (AD), is widely recognized as a growing threat to healthy and normal human aging. Commonly accepted non-modifiable risk factors for dementia include aging and the presence of particular genetic risk factors. With increased life expectancy in developed countries, discovery of early detection and treatment methods for dementia have become imperative. Recent research has linked genetic polymorphisms with multifaceted neurocognitive phenotypes observed in AD and dementia patients, as well as normal aging (NA) older adults (Deary, Wright, Harris, Whalley, & Starr, 2004; Goldberg & Weinberger, 2004; Green et al., 2008). Among the promising neurocognitive phenotypes are neurocognitive speed, memory, and executive functions. The magnitude of risk correlated with AD-related single nucleotide polymorphisms (SNPs) for normal cognitive aging may have implications for accelerated decline associated with dementia in NA (Barral et al., 2012; Chibnik et al., 2011; Harris & Deary, 2011; Thambisetty et al., 2013; Xiao et al., 2012). In this study we examine independent and interactive associations of genetic and environmental risk factors on cognition in NA.

Genes, Cognition, and Aging. Several genetic polymorphisms have been identified as risk factors for sporadic/non-familial AD. One of the most commonly studied and consistently linked risk factor for sporadic AD and dementia is the *Apolipoprotein E* (*APOE*) gene. The ε4 allele of the *APOE* gene is connected with cognitive impairment and increased risk of AD-related dementia (Brainerd et al., 2011), whereas the ε2 and ε3 alleles are shown to be neutral or

potentially protective (Corder et al., 1994; de-Almada et al., 2011; Panza et al., 2000). Researchers are also beginning to focus on other SNPs linked to sporadic AD such as *Complement receptor 1*(*CR1*; rs6656401), *Clusterin* (*CLU*; rs11136000), and *Phosphatidylinositol-binding clathrin assembly protein* (*PICALM*; rs541548) (Chibnik et al., 2011). Although more commonly associated with AD, all three genetic polymorphisms have also been linked to cognitive decline in NA. For example, carriers of the *CR1* risk allele (i.e., AA, A/G) showed an increased rate of decline on measures of global cognition, episodic memory, semantic memory, perceptual speed, and visuospatial speed in NA adults (*n* = 1666) recruited from a combination of two longitudinal studies: The Religious Orders Study (ROS) and Rush Memory and Aging Project (MAP) over an average of 7.8 and 4.3 years, respectively (Chibnik et al., 2011). Regarding *CLU*, Thambisetty et al. (2013) observed memory decline among carriers of the *CLU* risk allele (i.e., CC, C/T) in NA adults who eventually converted to mild cognitive impairment (MCI) or AD. This indicates the importance *CLU* may play in early detection of emerging neurodegenerative disease (e.g., AD) among older adults. Although inconsistent in findings, several SNPs of the *PICALM* gene (e.g., rs541548) have also been associated with a faster rate of cognitive decline (e.g., episodic memory) among carriers of the risk allele (i.e., CC, T/C) (Barral et al., 2012).

In addition, cognitive deficits observed in NA older adults may be linked to genetic polymorphisms that modulate the effects of dopamine (DA) levels and neurotrophic factors (Bäckman et al., 2006; Erickson et al., 2008). Two genetic

polymorphisms involving DA and neurotrophic levels are: *Catechol-O-methyltransferase* (*COMT*; rs4680) and *Brain-derived neurotrophic factor* (*BDNF*; rs6265), respectively (Raz, Rodriguez, Kennedy, & Land, 2009; Savitz, Solms, & Ramesar, 2006; Starr, Fox, Harris, Deary, & Whalley, 2007; Wishart et al., 2011). *COMT* homozygotes and carriers of the risk allele (i.e., G/G, G/A) have lower levels of DA in the prefrontal cortex and *BDNF* homozygotes and carriers of the risk allele (i.e., A/A, A/G) secrete lower levels of neurotrophic factors, particularly in the hippocampus. These two polymorphisms have been shown to play a crucial and magnifying role in the extent of neurocognitive deficits observed among groups of NA older adults (Nagel et al., 2008; Sapkota et al., 2013).

Personality, Cognition, and Aging. Molecular genetics and gene-association studies may facilitate identifying the degree of risk associated with alleles in selected SNPs for cognitive changes with aging (Kremen & Lyons, 2011). However, for many cognitive phenotypes and statuses, the consideration of lifestyle choices and environmental factors may usefully supplement or modify the observed roles of biological (genetic) factors. Environmental influences affecting successful aging represents a broad range of non-genetic factors. Both protective and risk factors contribute to cognitive change experienced with age (Harris & Deary, 2011). For example, demographics (e.g., education), physical characteristics (e.g., gait), and personality (e.g., traits) have all been shown to affect global cognitive decline (e.g., Mini-Mental State Exam (MMSE) (Alley,

Suthers, & Crimmins, 2007; Eaton et al., 2012; Middleton, Mitnitski, Fallah, Kirkland, & Rockwood, 2008).

Recently, behavior-genetic association studies have linked self-reported personality traits to genetic vulnerability and environmental influences (Eaton et al., 2012). Different levels of personality traits such as extroversion and neuroticism usually correspond to different types of behaviors (i.e., sociability and impulsiveness). Personality traits are shown to be relatively stable throughout adulthood and may define everyday life decisions; thus, shaping both our healthy and unhealthy behaviors and habits. For example, older adults scoring high on the neuroticism trait may be connected to the development of depression leading to poor health choices (Duberstein et al., 2008). Some studies have focused on gene (i.e., SNPs) by personality trait interactions that may play a role in moderating the level of cognitive performance with aging (Eaton et al., 2012). In the present study, we take a candidate gene approach in conjunction with personality traits to study independent and interactive effects on neurocognitive phenotypes in NA older adults at baseline and longitudinally.

Overview of Research Plan and Research Questions. In the following literature review, SNPs, personality, and cognitive associations will be further described. At this point, the three main steps of the planned research and the four main research questions are summarized. First, we used the NEO Personality Inventory (NEO-PI) to examine personality traits (Alwerdt, Small, & Dixon, 2012) associated with neurocognitive phenotypes. Second, we examined independent, interactive, and combined genetic risk effects of six different SNPs

on both personality traits and cognition. Third, using both concurrent and longitudinal design, we investigated the interactive effect of select SNPs by personality traits on cognitive performance and change.

Four research questions were examined. First, are different levels of personality traits (neuroticism, extroversion, openness to experience, conscientiousness, and agreeableness) associated with baseline performance and longitudinal stability on cognition? Second, are allelic risk carriers for *COMT* (G+), *BDNF* (A+), *CR1* (A+), *CLU* (C+), *PICALM* (C+), and *APOE* (ε4+) associated with different levels of personality traits and cognitive functioning? Third, are selected gene x gene interactions and total composite genetic risk score associated with different levels of personality traits and cognitive performance and stability? Fourth, do selected SNP x personality trait interactions influence initial and longitudinal cognitive performance (Figure 1)?

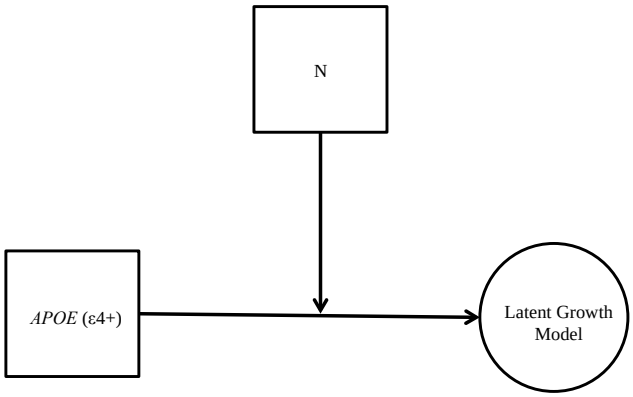


Figure 1. Conceptual model testing *APOE* (ε4+) x neuroticism (N) on latent growth model for baseline cognitive change (research question four).

CHAPTER 2 - LITERATURE REVIEW

Approximately 25 million adults worldwide are affected by Alzheimer's disease (AD) (Biagioni & Galvin, 2011) and nearly 500,000 Canadians over the age of 65 are living with a form of dementia (Alzheimer Society, 2010). The Alzheimer Society has predicted that by 2038 approximately three percent of the Canadian population will be affected by dementia (Alzheimer Society, 2010). Discovering novel protective and risk factors for early detection and treatment of dementia will improve the quality of life for older adult patients and their caregivers. Because we are only aware of the fundamental pathology of sporadic AD, which includes build-up of beta amyloid plaques and intra-neuronal neurofibrillary tangles, definite AD diagnosis is difficult (Schneider et al., 2012). The principal phenotypic characteristic of AD is the gradual decline in cognitive functions. Primary clinical characteristics include memory loss and a decline in global cognition, with early impairments in delayed recall, recognition, and executive function (EF). Family history of AD, education, gender, coexisting health factors (e.g., diabetes), and duration of AD have also been linked with the development and progression of AD (Muir et al., 2012; Schmidt, Wolf, von Ahsen, & Zerr, 2012).

Genetics, Cognition, and Aging. The role of genetic influences on normal cognitive aging and neurodegenerative diseases has been widely researched (Harris & Deary, 2011). With the initiation of genome-wide association studies (GWAS) in 2005, approximately 20,000 to 30,000 genes have been identified in the human genome. Researchers are taking candidate gene approaches to

distinguish deficits in normal cognitive aging from early signs of mild cognitive impairment (MCI) and AD-related cognitive disturbances. Regarding discovery of novel risk factors for cognitive decline observed among AD patients and NA older adults, molecular genetics (exploring independent and interactive effects of single nucleotide polymorphisms (SNPs), and neuropsychological association studies including memory and neurocognitive speed tasks have shown considerable promise.

Regarding memory, interindividual differences on memory tasks are shown to be heritable and genetic differences may be more transparent when cognitive reserve decreases as a result of aging. Differences in cognitive reserve allow some adults to cope better with neurodegenerative diseases. Thus, adults with higher cognitive reserve may reach the threshold for cognitive decline at a later age (Whalley, Deary, Appleton, & Starr, 2004). Similarly, neuroimaging studies have observed lower hippocampal and amygdala volumes in healthy older adults (age range: 65-84 years) than younger adults (age range: 22-50 years) (Malykhin, Bouchard, Camicioli, & Coupland, 2008). Interindividual differences in memory performance as a result of differences in cognitive reserve as well as changes in brain volume (e.g., hippocampus, amygdala) may be modifiable by experiences in both young and old adults through different lifestyle factors (Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012).

Different age trajectories are observed for episodic versus semantic memory performance. Semantic memory is described as knowledge memory (e.g., non-contextual) whereas episodic is memory of contextually specific experiences

(e.g., time, place) of acquired information (Tulving, 1985; Tulving, 1987). The Betula Study, a longitudinal study started in 1988, reported that decline in episodic memory was visible from 20 years of age and an increase was detected for semantic memory up to 60 years of age followed by decline in performance (Nilsson, 2003). However, other recent longitudinal studies have shown that decline in episodic memory is not observed until age 60 (Nyberg et al., 2012). Similarly, the Victoria Longitudinal Study (VLS), a three cohort longitudinal-sequential study started in the late 1980s, observed significant decline in episodic memory for adults in the 75-95 years old range as well as large interindividual differences in performance (Dixon, Small, MacDonald, & McArdle, 2012). Increased variability, both interindividual differences and intraindividual variability, is also observed with age on other cognitive performance measures, especially for speeded tasks (Hultsch, MacDonald, & Dixon, 2002). In the present study, we include episodic and semantic memory as well as neurocognitive speed to further examine cognitive domain differences associated with both genetic and lifestyle influences among older adults between 53-84 years olds.

Investigating SNPs independently and in interaction with personality traits may provide a more comprehensive understanding of the potential risk and protection factors involved in cognitive aging (Eaton et al., 2012; Kremen & Lyons, 2009). In the present study, we examine NA cognition at baseline and longitudinally using (a) personality traits based on the five factor model (i.e., Neuroticism (N), Extroversion (E), Openness to Experience (O), Agreeableness (A), Conscientiousness (C)) and (b) six SNPs that have regularly been associated

with aging- or AD-related cognitive deficits. The SNPs are *APOE* (rs7412, rs429358), *COMT* (rs4680), *BDNF* (rs6265), *CR1* (rs6656401), *CLU* (rs11136000), and *PICALM* (rs541548) (Chibnik et al., 2011; Nagel et al, 2008; Raz et al., 2009; Thambisetty et al., 2013; Wishart et al., 2011; Xiao et al., 2012). In the following literature review, we begin by describing each SNP. Each description is followed by related studies and a brief summary for each SNP. Subsequently, we describe and summarize related literature for personality traits, followed by a summary of the present study.

APOE. The most commonly and widely studied genotype for AD and dementia is *APOE*. There are vast numbers of studies with *APOE* risk and cognitive impairment (e.g., Sachs-Ericsson et al., 2010; Small, Rosnick, Fratiglioni, & Bäckman, 2004). The *APOE* genotype is involved in central nervous system repair (CNS) and function, and is differentiated by three alleles: ε2, ε3, and ε4. Carriers of ε4 allele have been associated with a higher risk of AD development (Brainerd et al., 2011) in comparison to the ε2 allele, which has been found to be protective in numerous studies (Corder et al., 1994; de-Almada et al., 2011; Panza et al., 2000). The *APOE* gene has been reported to have an antagonistic pleiotropy effect, where the gene may be beneficial at a younger age but harmful with increasing age (Jochemsen, Muller, van der Graaf, & Geerlings, 2011), thus, most studies are focusing on older adults groups to investigate *APOE*-cognition associations.

A recent study investigated cognitive function in 597 older adults (age range = 72-91 years) by examining *APOE* genotype by personality traits with the

NEO five-factor inventory (Dar-Nimrod et al., 2012). They examined the interactive effect of N (high versus low) x *APOE* (ε4+ versus ε4-) on performance of orientation, memory, and language tasks. The other four personality dimensions were included for exploratory purposes. Hierarchical regression analysis was used to investigate whether personality traits in interaction with the *APOE* (ε4+ versus ε4-) genotype would be associated with differences in cognitive performance. Carriers of the *APOE* ε4 allele in combination with higher N scores performed lower on the cognitive portion of the AD assessment scale as compared to *APOE* ε4 carriers with lower N score. A similar trend ($p = .068$) was observed for O x *APOE* (ε4 versus ε4-) (Dar-Nimrod et al., 2012). Examining *APOE* interaction with other dementia-related SNPs and personality traits may lead to identification of potential risk factors involved with cognitive decline in NA and dementia patients. The present study is the first to use both cross-sectional and longitudinal data to explore independent and interactive effects of *APOE* on personality traits and cognition in healthy older adults.

COMT. The *COMT* (rs4680) Val158Met polymorphism increases COMT enzymatic activity that in turn decreases dopamine (DA) levels primarily in the prefrontal cortex (Chen et al., 2004). This traditionally studied *COMT* polymorphism at codon 158 on chromosome 22q11 results in the *COMT* homozygotes for the A allele having greater DA levels compared to the G allele homozygotes. Thus, carriers of the G allele may be at higher risk for cognitive deficits including executive function (EF) than homozygotes for the A allele (Nagel et al., 2008; Sapkota et al., 2013; Wishart et al., 2011). Researchers

arguing that similar to the inverted U-shaped curve for cognitive functioning a comparable curve is also present for DA regulation in the prefrontal cortex (Goldman-Rakic, 1998; William & Goldman-Rakic, 1995). In addition to lowered levels of DA in humans (Harris et al., 2005), high levels of DA have been linked to decreased cognition in monkeys and rats (Murphy, Arnsten, Goldman-Rakic, & Roth, 1996). Harris and colleagues (2005) studied the effect of *COMT* rs4680 polymorphism on cognitive function and personality traits using the International Personality Item Pool (IPIP) 50-item questionnaire in a group of NA adults (average age = 79 years) controlling for gender and childhood IQ. They found that heterozygotes for the G/A allele had the highest score on both a measure of the verbal declarative memory domain (i.e., logical memory) and the intellect/imagination personality trait compared to both risk (G/G) and no-risk (A/A) homozygotes. Although they examined interactions between the *COMT* and *APOE* polymorphism, they did not find any significant associations with either cognition or personality. Differences in DA levels among *COMT* groups may play an important role in distinguishing between cognitive differences and personality traits in NA adults (Harris et al., 2005). In the present study, we examine independent and interactive effects of *COMT* by personality traits on three different cognitive domains (viz., neurocognitive speed, episodic and semantic memory).

BDNF. BDNF is mostly present in the hippocampus and prefrontal cortex, and plays an important role in memory and long-term potentiation. It may also help to decrease the negative effects of beta amyloid exposure. The BDNF

(rs6265) Val66Met polymorphism located at 11p13 (Houlihan et al., 2009) is involved in decreased BDNF secretion and may be associated with normal cognitive decline and impairment leading to AD-related dementia (Komulainen et al., 2008; Raz et al., 2009; Wishart et al., 2010). In contrast to the *COMT* allelic risk, the A allele is considered to be the risk allele in *BDNF*. Conflicting results are seen with regard to BDNF plasma levels, *BDNF* polymorphisms, and personality trait scores. For example, a recent study did not find significant associations between BDNF plasma levels and the BDNF polymorphism but that only men (age range = 38–98 years old) with lower BDNF plasma concentration scored lower on neuroticism and higher on conscientiousness and extroversion as measured by the NEO-PI revised (NEO-PI-R), presenting gender differences (Terracciano et al., 2010). In contrast, two studies observed adults with anxiety (mean age = 39±14.6 years old) and neuroticism (age range = 25-40 years old) scores to be significantly higher among adults homozygous for the G allele (Lang et al., 2005; Sen et al., 2003). Both low and high BDNF plasma levels, as well as *BDNF* polymorphisms appear to play a role on personality trait levels. Regarding *BDNF*-cognition associations studies, a recent meta-analysis examined 23 publications with a combined total of 7095 individuals and did not observe significant associations with all of the five most commonly studied phenotypes: general cognition, memory, executive function (EF), visual processing skills, and cognitive fluency (Mandelman & Grigorenko, 2012). With contradictory findings in the literature for BDNF allelic risk on personality-cognition associations (Mandelman & Grigorenko, 2012), the present study examines interactive effects

of *BDNF* allelic combinations with other SNPs to distinguish any possible moderation effects between personality traits and cognitive change in older adults.

CLU, PICALM, CR1. The *CLU, PICALM*, and *CR1* polymorphisms have not previously been studied with personality traits. However, all three SNPs have been connected with cognitive deficits and AD-related cognitive phenotypes. We include these SNPs to specifically explore any independent and interactive associations with cognition and personality, as well as moderating effects of gene x personality on cognitive performance.

CLU. The *CLU* (rs11136000) gene is involved in amyloid clearance, apoptosis, brain atrophy, and disease progression in AD patients. In addition, *CLU* allelic risk carriers (C+) have shown 1.16 greater odds of developing sporadic AD than no risk homozygotes (T/T) (Bertram et al., 2007). Braskie and colleagues (2011) examined 398 healthy young adults between 20-29 years using mixed model regression to test associations between *CLU* allelic risk and white matter integrity. Carriers of the *CLU* allelic risk showed lower white matter integrity which may lead to an increased risk for developing AD and dementia in old age. Similarly, healthy older adults (age = 56-86 years old) from the Baltimore Longitudinal Study were also genotyped for the *CLU* SNP and followed for an average of 7.5 years. Neuropsychological testing measures included six different domains: memory, world knowledge, verbal fluency, attention and working memory, and EF. Overall, decline in memory performance was observed among carriers of *CLU* risk allele (C+) who went on to develop MCI or AD (Thambisetty et al., 2013). Furthermore, significant associations for late-onset AD have been

observed among European-American families with *CLU* allelic risk carriers (Wijsman et al., 2011).

PICALM. Recent GWAS have discovered that *PICALM* rs3851179 located on chromosome 11 is involved in the production of amyloid beta peptide and linked to the formation of amyloid plaques, indicating a connection to AD (Harold et al., 2009; Seshadri et al., 2010; Xiao et al., 2012). The PICALM protein is involved in directing the trafficking of a soluble N-ethylmaleimide sensitive fusion attachment receptor (SNARE) protein, which plays a role in the fusion of synaptic vesicles leading to neurotransmitter release at the presynaptic membrane, important for memory formation and neuronal function. Along with plaques and tangles, AD brains also exhibit a reduction in synaptic density that is correlated with cognitive decline. Therefore, a number of *PICALM* SNPs may directly impact PICALM function through synaptic vesicle cycling and increasing the risk for AD (Harold et al., 2009). One study compared 349 AD patients, 359 sex and age matched controls, and 105 centenarians to examine the distribution of *PICALM* rs3851179 alleles. Within centenarians there was a significant difference in genotype distribution for the AD and control group. Higher frequency (47.2%) of the A allele was present among healthy centenarians, suggesting that the A allele may be linked to reduced risk of developing AD and play a role in increased longevity (Piaceri et al., 2011). Similarly, older men (age range = 92-93 years old) homozygotes for the no allelic risk (A allele) performed better then G carriers on an average composite score from five different measures of cognition (i.e., fluency, forward and backward digit span, immediate and delayed word recall)

(Mengel-From, Christensen, McGue, and Christiansen, 2011). In addition, allelic risk (G+) carriers for the *PICALM* rs7110631 had a higher rate of decline on global cognition among NA participants from the Religious Orders Study and Rush Memory and Aging Project (Chibnik et al., 2011).

CR1. The *CR1* gene located on chromosome 1 at the locus 1q32 in a genetic cluster of complement related proteins is directly involved in the clearance of amyloid beta peptide from the brain and the circulatory system. There are four co-dominant alleles of different sizes and variation. *CR1* rs6656401 has been shown to have highest association with late onset AD with an odds ratio of 1.19. Some longer forms of *CR1* may be protective and reduce the effect of the complement cascade activity, which is increased in AD pathology (Crehan et al., 2012). *CR1* rs6656401 allelic risk (A+) carriers from the Religious Orders Study and Rush Memory and Aging Project showed a faster decline over 7.8 and 4.3 years, respectively, on global cognition as measured by the MMSE compared to adults with no allelic risk (Chibnik et al., 2011).

Personality. Genetic predisposition is one component that affects cognitive abilities; another important factor is personality traits. Personality traits encompass a wide range of behaviors individuals are likely to engage in and have previously been used to predict divorce rates, longevity, and cognitive decline (Eaton et al., 2012). Based on related research, the present study examines interactive effects of genetic polymorphisms to investigate personality traits as well as independent and interactive effects of SNPs by personality traits to study differences in cognition among NA older adults.

The Gingko Evaluation of Memory (GEM) clinical trial examined 602 adults (age range: 72–91 years) on cognitive decline (measured with the MMSE) and personality traits (measured with the NEO-Five Factor Inventory (NEO-FFI), a 60-item self-reported questionnaire). They used random effects linear regression with random intercept and random slope model to examine whether lower N and higher O and C would predict better cognitive functioning over a seven-year period. Adults with lower O and higher E and N levels had overall worse cognitive performance over seven years. Adults with higher N levels alone showed a steeper rate of cognitive decline and those with higher C levels showed a more gradual decline overall (Chapman et al., 2012).

In addition, SNPs linked to longevity may also be involved in influencing human personality, mood states, and depression. For example, the Lothian Birth Cohort of 1936 (n =1,000; age = 70 years) were examined for a specific set of longevity genes to test any associations with personality traits. Only the synaptojanin-2 (SYNJ2) SNP was associated with agreeableness and symptoms of depression (Luciano et al., 2012). With regards to SNP-personality traits associations, phenotypic variances for N and E have previously been examined by genome wide arrays simultaneously explained by SNPs from 12,000 individuals between the ages of 14-86 years old using linear model analysis. Approximately 6% and 12% of the phenotypic variance for N and E, respectively, is explained by common SNPs (Vinkhuyzen et al., 2013).

Among personality traits assessments, researchers have used different measures including the NEO personality inventory (NEO-PI) with the five-factor

model, the tridimensional personality questionnaire (TPQ), and the Munich Personality Test (MPT). A reliable and strong method of personality assessment is essential when investigating interactive associations with SNPs on cognition. For example, when the TPQ was used to study associations between the *APOE* ε4 allele and personality traits in a group of females (n = 135; age = 19-21 years old), no significant differences were found between *APOE* risk and all three traits (novelty seeking, harm avoidance, and reward dependence) (Tsai, Yu, & Hong, 2004). However, when the MPT was used in probable AD German patients (n = 56; age = 75.9 ± 7.9 years old), they showed higher N levels compared to controls with Parkinson's disease (PD) (Meins & Dammast, 2000). Although these differences may be due to other factors, the type of personality assessment should be carefully reviewed. Based on existing literature, the NEO-PI has shown only small changes over time in the levels and stability of personality (Costa & McCrae, 1985; Small, Hertzog, Hultsch, & Dixon, 2003). Therefore, in the present study, we chose to use the NEO-PI. Interindividual differences and broad types of personality traits can be successfully covered within the NEO-PI five-factor model including the five basic dimensions: neuroticism (N), extraversion (E), openness to experience (O), agreeableness (A), and conscientiousness (C). Higher N scores represent an increased level of psychological distress and are a feature seen among psychiatric patients including depressed patients. Higher E scores indicate generally more sociable characteristics and involvement in extracurricular activities. Adults scoring higher on the O scale tend to be imaginative, appreciate art and beauty, have a rich emotional life, are behaviorally

flexible, and intellectually curious. The level of A trait represents trusting, sympathetic, and cooperative characteristics. Finally, higher C scores represents goal oriented, competence, self-disciplined, and orderly characteristics. These five basic dimensions of the NEO-PI represent a comprehensive portrayal of adult personality and also cover several detailed facets within the N, E, and O domains. Psychologists have suggested that clinicians may benefit from routine assessment with the NEO-PI to further understand their older patients with regards to their cultural background and life choices comprising of both healthy and unhealthy decisions (see Costa & McCrae, 1992). In addition, high E, O, A, C and low N profiles have also been associated with overall subjective well-being (Weiss, Bates & Luciano, 2008); whereas, high N scores have regularly been associated with increased AD risk (Duberstein et al., 2011).

Another study examined differences in personality traits and behavioral and psychological symptoms (BPS) in 52 MCI patients versus 83 cognitively healthy adults over 55 years old using the revised NEO-PI. As hypothesized, logistic regression revealed that the MCI group had higher N levels, and lower levels of E, O, A, and C. In addition, higher levels of C were shown to be less associated with MCI patients (Rubio, Antonietti, Donati, Rossier, & von Gunten, 2013). Examining personality differences may help with early diagnosis of MCI-related dementia (Rubio et al., 2013).

Small and colleagues (2003) used longitudinal confirmatory factor analyses to examine personality trait (NEO-PI) stability over a six-year period (two-wave) in older adults (n = 223; age range = 55 to 85 years old) from the

VLS. Using latent models, they found a significantly high stability rate over the six-year period for N, E, and O (i.e., $r > 0.80$ correlations) with A and C correlations approaching $r = 0.70$ (Small et al., 2003). Personality traits may be related to cognition in NA older adults; specifically changes in neurocognitive speed, episodic memory, and semantic memory. Subsequently, Alwerdt and colleagues (2012) examined personality traits using the NEO-PI for 978 participants from the VLS to model change in cognition over a 12-year period. They observed that personality traits were related to cognitive performance at baseline but not longitudinally. Adults with high O and A levels had overall superior baseline cognitive performance (Alwerdt et al., 2012).

A similar study examined the association between development of AD and personality traits among adults 72 years and older over a six-year period. Participants with (a) high N and (b) low O or (c) low C scores were at a greater risk for AD (Duberstein et al., 2011). Likewise a combination of low N and high E scores were associated with the lower risk of dementia and low N scores alone were enough to lower dementia risk in socially isolated older adults (Wang et al., 2009). Thus, combined personality traits at extreme ends maybe associated with lower dementia risk.

Higher N level has shown to be associated with decreased hypothalamic pituitary adrenal-axis function, which may help prevent brain atrophy and cognitive decline (McCleery & Goodwin, 2001). Whereas, individuals with higher O levels may be involved in higher number of cognitive daily activities which may lead to higher cognitive reserve and maintained performance over time

on cognitive tasks. Similarly, low O levels have previously been linked to AD. There have been no concrete theories for how or why high or low A levels may be associated with cognitive performance (Chapman et al., 2012). Differences in personality traits may affect the choice of cognitive activities in older adults; thus, the importance of personality traits must be further explored with genetic risk factors for cognitive decline and dementia.

The Present Study

The present study uses a genotyped subsample from the Alwerdt et al. (2012) report. We include personality traits, AD- and NA-related SNPs, and three cognitive domains (i.e., episodic memory, semantic memory, and neurocognitive speed). The four main research questions and predictions are as follows. First, we examine personality trait (i.e., N, E, O, A, C) associations with cognition at baseline and over approximately 14-year period. Based on the literature, we predicted adults with (a) higher levels of N to have poorer cognitive performance at baseline and over time and (b) higher levels of O to have better cognitive performance. Second, we investigate independent effects of all six SNPs (*COMT* (G+), *BDNF* (A+), *CR1* (A+), *CLU* (C+), *PICALM* (C+), and *APOE* (ε4+) on (a) personality trait at baseline and (b) cognition at baseline and over time. We predicted allelic risk carriers will perform more poorly on all three cognitive domains than non-risk allelic carriers. Third, we test select gene x gene interactions and combined genetic risk score on cognitive change over time. We predicted that adults with the combined allelic risk and highest risk score would show the worst performance. Fourth, we examine the interactive effects of select

personality trait by SNPs on cognition at baseline and longitudinally. We expected adults with higher levels of N in addition to allelic risk for SNPs to have the worst overall performance. To our knowledge, this is the first study to examine gene by personality interactions on cognition among older adults over approximately 14 years.

CHAPTER 3 - METHOD

Participants

Participants from the Victoria Longitudinal Study (VLS), a large-scale and multifaceted investigation of biomedical, health, and neurocognitive aspects of aging, were enrolled through advertisements and received a small honorarium for their participation. Written informed consent was obtained from all participants and all VLS data are collected with the approval from the human/institutional research ethics board. A subsample (N = 282) with genetic data from the Alwerdt and colleagues (2012) VLS report on NEO-PI and cognition are included in the present study. The subsample comprises two VLS cohorts followed over approximately 14 years (five waves): Sample 1 (n = 60; age range: 58-73 years old; 70% female) and Sample 2 (n = 222; age range: 53-84 years old; 63.5% female) (see Table 1). Mean interval years between waves for Sample 1 were (a) wave one to two = 3.00 (b) wave two to three = 3.00, (c) wave three to four = 3.00, and (d) wave four to five = 3.41 and Sample 2 were (a) wave one to two = 3.32, (b) wave two to three = 3.21, (c) wave three to four = 4.60, and (d) wave four to five = 4.56. Total time over five waves for Sample 1 was 13 years and Sample 2 was 14 years. The overall total mean years over five waves for the combined sample as used in the present study was 14.05 years. Some participants had missing data on some of the cognitive measures and genetic data for *APOE, CLU, CR1,* and *PICALM* (see Table 2a-b). Both cross-sectional and longitudinal analyses include the full subsample representing two VLS cohorts. Further information regarding the general participant recruitment and testing procedures

Table 1
Descriptive Characteristics (M and SD) for genetic and personality trait measures for each sample and total population.

	Sample 1	**Sample 2**	**Total**
n	60	222	282
Age (years)	64.27 (3.39)	65.05 (5.88)	64.88 (5.45)
Education (years)	13.67 (3.02)	15.22 (2.98)	14.89 (3.05)
Gender (M/F)	18/42	79/143	97/185
Personality			
Neuroticism	77.48 (20.14)	77.09 (20.91)	77.17 (20.72)
Extroversion	101.97 (16.67)	101.06 (16.58)	101.25 (16.57)
Openness to Experience	113.43 (14.50)	116.06 (18.38)	115.50 (17.64)
Conscientiousness	50.03 (6.77)	50.12 (8.21)	50.10 (7.91)
Agreeableness	50.42 (5.74)	51.24 (6.28)	51.07 (6.17)
Genes			
APOE	ε4- = 47; ε4+ = 12	ε4- = 155; ε4+ = 54	ε4- = 202; ε4+ = 66
COMT	A/A = 10; G+ = 50	A/A = 53; G+ = 169	A/A = 63; G+ = 219
BDNF	G/G = 38; A+ = 22	G/G = 149; A+ = 73	G/G = 187; A+ = 95
CLU	T/T = 5; C+ = 55	T/T = 37; C+ = 184	T/T = 42; C+ = 239
PICALM	T/T = 24; C+ = 36	T/T = 98; C+ = 123	T/T = 122; C+ = 159
CR1	G/G = 30; A+ = 30	G/G = 66; A+ = 155	G/G = 96; A+ = 185

Note. n = Total number. M = Mean. SD = Standard deviation. *APOE* = Apolipoprotein E (ε4- = no risk/ ε4+ = risk). *COMT* = Catechol-O-methyltransferase (A/A = no risk/G+ = risk). *BDNF* = Brain-derived neurotrophic factor (G/G = no risk/A+ = risk). *CLU* = Clusterin (T/T = no risk/C+ = risk). *PICALM* = Phosphatidylinositol-binding clathrin assembly protein (T/T = no risk/C+ = risk). *CR1* = Complement receptor 1(G/G = no risk/A+ = risk).

Table 2
Descriptive characteristics (M and SD) *for all cognitive tasks for (a) Sample 1, and (b) Sample 2.*
(a)

	Sample 1				
	Wave 1	**Wave 2**	**Wave 3**	**Wave 4**	**Wave 5**
n	60	59	58	57	54
Episodic Memory					
Word List Free Recall	19.55 (3.55)	19.21 (3.69)	19.16 (3.26)	19.01 (3.35)	18.23 (3.75)
Semantic Memory					
Fact Recall	21.22 (4.70)	20.85 (5.13)	20.32 (5.07)	20.64 (4.84)	19.54 (5.46)
Vocabulary	45.47 (5.53)	44.68 (5.36)	45.14 (4.92)	45.11 (4.65)	44.11 (5.09)
Neurocognitive Speed					
Sematic Verification (Log)	3.48 (.12)	3.45 (.10)	3.46 (.10)	3.48 (.10)	3.47 (.12)
Lexical Decision (Log)	2.99 (.10)	2.97 (.09)	3.00 (.10)	3.00 (.09)	3.00 (.10)

Note. n =Total number. M = Mean. SD = Standard deviation. Log = Logarithmic scale.

(b)

Sample 2					
	Wave 1	**Wave 2**	**Wave 3**	**Wave 4**	**Wave 5**
n	222	207	197	182	146
Episodic Memory					
Word List Free Recall	18.67 (3.79)	19.08 (3.87)	18.49 (4.06)	17.54 (4.48)	16.03 (4.99)
Semantic Memory					
Fact Recall	21.63 (6.21)	21.86 (6.46)	21.56 (6.26)	21.10 (7.09)	19.77 (7.21)
Vocabulary	44.74 (5.84)	45.03 (5.33)	44.63 (5.43)	44.03 (5.33)	43.81 (5.43)
Neurocognitive Speed					
Sematic Verification (Log)	3.48 (.11)	3.47 (.10)	3.48 (.10)	3.50 (.11)	3.54 (.12)
Lexical Decision (Log)	3.00 (.11)	2.97 (.11)	2.98 (.11)	3.00 (.12)	3.04 (.14)

Note. n = Total number. M = Mean. SD = Standard deviation. Log = Logarithmic scale.

have been published (Dixon & de Frias, 2004; Small et al., 2003).

DNA Extraction and Genotyping. Saliva was collected according to standard procedures from Oragene-DNA and stored at room temperature in 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. Genotyping was carried out by using a PCR-RFLP strategy to analyze the allele status for the following six SNPs: *APOE* (rs7412, rs429358), *COMT* (rs4680), *BDNF* (rs6265), *CR1* (rs6656401), *PICALM* (rs541548), and *CLU* (rs11136000) (see Table 1).

Allelic Distributions for *BDNF, COMT, APOE, CR1, CLU,* and *PICALM.* Genotyping for *BDNF* resulted in 187 individuals who were G/G carriers, 83 individuals who were G/A carriers, and 12 individuals A/A carriers. For *COMT* there were 63 individuals who were A/A carriers, 154 A/G carriers, and 65 G/G carriers. For *APOE* 6 individuals were ε2/ε2 carriers, 23 ε2/ε3 carriers, 14 ε2/ε4 carriers, 172 ε3/ε3 carriers, 61 ε3/ε4 carriers, and 6 ε4/ε4 carriers. For *CR1* there were 96 individuals who were G/G carriers, 147 individuals who were G/A carriers, and 38 A/A carriers. For *CLU* there were 101 individuals who were C/C carriers, 138 individuals who were T/C carriers, and 42 individuals who were T/T carriers. For *PICALM* there were 122 individuals who were T/T carriers, 98 who were T/C carriers, and 61 C/C carriers. Distribution of allelic risk by sample is represented in Table 1.

The genotype frequencies for four of the examined genotypes did not differ significantly from Hardy-Weinberg equilibrium: *BDNF* rs6265 ($\chi^2 = 2.22$, *p*

= 0.136); *COMT* rs4680 ($\chi^2 = 0.57$, $p = 0.450$); *CR1* rs6656401 ($\chi^2 = 2.41$, $p = 0.121$); *CLU* rs11136000 ($\chi^2 = 0.21$, $p = 0.645$). However, the *PICALM* rs541548 ($\chi^2 = 12.73$, $p < 0.001$) and *APOE* rs429358 ($\chi^2 = 25.74$, $p < 0.001$) were not in Hardy-Weinberg equilibrium. For purposes of analyses we included two allelic combinations for all six genotypes as being a carrier of one allelic risk is considered to be at risk: *COMT* (risk: G/G, A/G, and no risk: A/A), *BDNF* (risk: A/A, A/G, and no risk: G/G), *APOE* (risk: ε4+, and no risk: ε4-), *CR1* (risk: A/A, A/G, and no risk: G/G), *CLU* (risk: C/C, C/T, and no risk: T/T), *PICALM* (risk: C/C, C/T, and no risk: T/T).

Measures

Cognition. Cognitive functions were assessed for three different domains: episodic memory (word list free recall), semantic memory (vocabulary and fact recall), and neurocognitive speed (lexical decision and semantic verification).

Word List Free Recall. From a pool of six equivalent lists, two different but comparable lists of 30 English words (i.e., six taxonomic categories with five words each; Dixon et al., 2004) were used. Participants were given two minutes to study the list and five minutes to write down their answers. The total numbers of words correctly recalled from each list was used as a final score.

Vocabulary. The total number of correct answers from three 18-items series of tests in the Educational Testing Service kit (Ekstrom, French, Harman, & Dermen, 1976) with 54 multiple-choice vocabulary questions was obtained for a final score.

Fact Recall. Two versions of a general information test (40-items each) taken from a normed battery (Nelson & Narens, 1980) were administered. The test required recall from multiple domains including science, history, literature, sports, geography, and entertainment. Participants had to write down their answers. The total numbers of facts correctly recalled from each version were averaged to obtain a final score.

Lexical Decision (LEX). In a total of 60 trials (30 words and 30 non-words), participants had to read on the computer screen and then correctly specify on the keyboard whether a string of five to seven letters resulted in an English word (e.g., *island* vs *nabion*). Participants' response latencies were recorded in milliseconds and the average latency for correct specification was used as the final score.

Semantic Verification (SEM). Across 50 total trials with plausible and nonsensical sentences, participants read each sentence from the computer screen and indicate whether the sentence was plausible or nonsensical (e.g., *the tree fell to the ground with a loud crash* vs *the pig gave birth to a litter of kittens this morning*) on the keyboard. Participants' response latencies were recorded in milliseconds and the average latency for correct specification was used as the final score.

Personality. Personality data on the five-factor model was collected using the NEO-PI.

NEO-PI. The NEO-PI (Costa & McCrae, 1985) was used at baseline for all participants to assess the five domains of personality traits: neuroticism (N),

extraversion (E), openness to experience (O), agreeableness (A), and conscientiousness (C). The questionnaire consisted of 181 statements (e.g., I am known as a warm and friendly person). Participants were required to answer based on how much they agreed with each statement from strongly disagree to strongly agree on a 5-point Likert scale. The questionnaire had two forms consisting of the participant's self-response and a second response by a relative. In the present study we only use the participant's self-response. The N, E, and O domains included six subscales measured by eight items each. Specifically, N included anxiety, hostility, depression, self-consciousness, impulsiveness and vulnerability. E had warmth, gregariousness, assertiveness, activity, excitement seeking, and positive emotions. The O domain consisted of openness to fantasy, aesthetics, feelings, actions, ideas, and values. The other two domains with eighteen items each did not have additional sections in the NEO-PI (Costa and McCrae, 1985) version as used in the present study (Small et al., 2003).

Data Preparation

SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to combine data sets for 282 adults with personality data at Wave 1 from both Sample 1 and Sample 2 in the VLS. Measures for all three cognitive domains across five waves and genetic data were included. All SNPs were mean centered to reduce collinearity between the product terms and predictors. Allelic risk were coded as -0.56 and no allelic risk as 0.44 to easily multiply gene-by-gene interactions and avoid overlap. Gene x gene interactive effects were multiplied and coded as .19 (0.44 x 0.44; no allelic risk), -0.25 (-0.56 x 0.44; at least one

allelic risk), and 0.31 (-0.56 x -0.56; combined allelic risk).

Cognitive measures for each wave were examined for a normal distribution. We only used mean latency of correct responses with any response plus or minus three standard deviations removed. Therefore, any extreme outliers above three standard deviations that may be due to error (i.e., accidental key press, tasks interruptions) were not included. Lexical decision and semantic verification scores were log transformed due to high skewness and kurtosis. All values for neurocognitive speed measures in the text refer to the log transformed scores. After log-transformation, all five waves of data for semantic verification was not significant ($p > 0.05$) for the Kolmogorov-Smirnov test of normality indicating that the data are normally distributed. Log-transformed scores for only wave one and wave two of lexical decision latency scores met the Kolmogorov-Smirnov normality distribution test.

Statistical Analysis

Descriptive statistics were calculated using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA) (see Table 1; Table 2). Path analysis and structural equation modeling (SEM) was used to analyze all research questions using Mplus Version 7 (Muthen & Muthen, 2012). All missing values for cognitive measures were assumed to be missing at random (MAR) and handled using maximum likelihood (ML) and missing predictor values were handled using list wise deletion in Mplus. Only one participant was lost due to list-wise deletion.

Confirmatory Factor Analysis. Confirmatory factor analysis (CFA) was used to examine loadings of all manifest variables on latent variables of episodic

memory, semantic memory, and neurocognitive speed. The two indicators of episodic memory were word recall list 1 and word recall list 2. The two indicators of semantic memory were fact recall and vocabulary, the neurocognitive speed latent variable were semantic verification and lexical decision. The first model tested all observed variables on one latent variable of cognition to refute the one-factor model. The second model tested a three factor CFA model to confirm that the data provides a good model fit to the three latent variables.

The final three-factor CFA model was then used to test longitudinal invariance between Waves 1 (baseline) - 5 (year 14). Longitudinal invariance is tested beginning with configural invariance, followed by metric, scalar, and residual invariance, taking into consideration each successive level of invariance obtained. Failure to obtain at least configural invariance for semantic memory and neurocognitive speed constructs lead to examination of each manifest variable separately.

Latent Growth Models. Because we were not able to obtain invariance for two (semantic memory and neurocognitive speed) of our three latent constructs, latent growth models (LGM) were examined for each manifest variable separately (word recall, fact recall, vocabulary, semantic verification, lexical decision) over five waves to arrive at a final best-fitting model of change. We adopted a model building approach and started with a simple (null) model, and added parameters at each step to arrive at a baseline model of change. Although starting with the null model is not realistic, it is the first step to a model building approach (i.e., to start with the simplest model). The strategy to find the

best-fitting model of change is to keep adding parameters until there is no further improvement in fit or no degrees of freedom are left. The null model assumes that there is no change over five waves, followed by the addition of fixed intercepts, random intercepts, fixed slope, random slope, fixed quadratic and random quadratic. First, in the null model, the variances for the intercepts were fixed across adults to 0. Second, in the random intercepts model, individuals were allowed to vary in intercept variance by removing the fixed intercept at 0. Third, a fixed linear slope was added to the baseline model by fixing the slope to 0 across all adults. The fixed linear slope assumed that all participants were changing in performance at the same rate. Fourth, adults were allowed to vary in their slope performance by removing the fixed linear slope constraint, and adding a random intercept and random linear slope model of change. Fifth, a fixed quadratic was added to the random intercept and random linear slope model, where both the intercepts and the slope were allowed to vary across individuals, but the curvilinear change was fixed across all participants. In this model, the factor loadings from the linear slope were squared to determine the factor loadings for the quadratic slope factor. Finally, the last model of baseline change tested was the random intercept, random linear slope and random quadratic model, where everyone was allowed to vary in intercept, slope and quadratic change over approximately fourteen years.

The best fitting baseline change model was determined by examining several fit statistics. The chi-square test of model (χ^2; $p > .05$) allowed for an overall indication of good model fit. Additional absolute/comparative fit indices

were also examined to determine a good model fit to the data (Kline, 2011): the root mean square error of approximation (RMSEA ≤ .05), comparative fix index (CFI ≥ .95), and the standardized root mean square residual (SRMR ≤ .08). Following the examination of model fit, the χ^2difference statistic was calculated to detect any improvement in fit with the addition of free parameters at each step.

Time Invariant Predictors. After the finalization of the best fitting model of change, each personality trait (N, E, O, A C) and each categorical SNP (*APOE*, *COMT*, *BDNF*, *CLU*, *CR1*, *PICALM*) was added as a time invariant predictor to assess the effect of personality trait and allelic risk on intercept, change in linear slope, and quadratic over approximately 14 years. Baseline age was added as a covariate on intercept and slope in all analyses. Due to the large span of time in the present study (up to 14 years), we include age as a covariate only to rule out any differences in cognitive performance and changes associated with age.

Research Question 1 and 2. A total of five models (five manifest variables) were tested for both personality traits (research question 1) and SNPs (research question 2). Intercept and slope were regressed on all six SNPs and personality traits. Allelic risk carriers were coded as -0.56, and no risk homozygotes were coded as 0.44. Both the significant standardized and unstandardized regression coefficients of each predictor were examined to determine effect on intercept, slope, and quadratic over approximately 14 years.

Research Question 3. Results from research question 1 and 2 were used to select SNPs with significant main effects on cognitive performance, or personality. Only SNPs with independent effects and the *APOE* SNP were used to

test gene x gene interactions to determine any moderating effects on select cognitive and personality measures. Interactive associations of the select SNPs were examined with all available genotypes (*APOE, COMT, BDNF, CLU, CR1, PICALM*). Product terms were calculated to examine any significant gene x gene interactions. Additionally, to test the effect of combined genetic risk for six SNPs, a composite score of genetic risk was calculated by adding the allelic risk (coded as 1) and no risk (coded as 0) for each individual. Higher score represented higher genetic risk. Intercept and slope for each cognitive measure was regressed on composite score of genetic risk to determine the effect of aggregate risk.

Research Question 4. For gene x personality interactions associations, similar to research question 3, we selected SNPs with significant independent effects on cognition to examine interactive effects with all personality traits on select manifest variables. Based on the supporting literature and in addition to the selected SNPs (regardless of significant main effects), any moderating effects of N were also examined with all SNPs on word recall and vocabulary to assess episodic and semantic memory. A total of 21 models were analyzed. Product terms were calculated to represent the interaction between each SNP and personality trait (e.g., N x *APOE*).

CHAPTER 4 – RESULTS

Descriptive characteristics were calculated for all SNPs and personality traits by sample (see Table 1) and cognitive measures by sample and wave (see Table 2a and 2b). First, we determined latent growth models of change for the five cognitive measures across five waves of measurement. Second, we examined each research question with the final best-fitting baseline model of change for episodic memory (word recall), semantic memory (fact recall, vocabulary), and neurocognitive speed (lexical decision, semantic verification).

Latent Growth Model of Change for Cognitive Measures. First, as expected the fixed intercepts model (Model 0) did not fit the data well and was rejected for all cognitive measures (see Table 3). Second, a random intercepts model (Model 1) also known as unconditional means model was examined. Adults were allowed to vary in intercept, which is represented by their overall mean score on the task at baseline. All fit indices (χ^2, RMSEA, CFI, SRMR) pointed to a poor model fit. However, the χ^2 difference test showed that the random intercepts model is significantly better than Model 0 for all cognitive measures. Third, in Model 2 a fixed slope was added to the random intercepts model where the model takes into account change over time but everyone is assumed to change at the same rate. The model was still a poor fit to the data but was slightly better than the random intercepts model (see Table 3). Fourth, in Model 3 a random intercepts and random linear slope model was tested, where both the intercept and the slope were allowed to vary across individuals. A significant improvement in model fit (e.g., word recall: χ^2 difference test =

Table 3

Model fit statistics and chi-square difference test for baseline model of change for episodic memory, semantic memory, and neurocognitive speed domains.

	$\chi^2_M(df_M)$	CFI	RMSEA (90% CI)	SRMR	χ^2_D (df_D)
Model 0: Fixed Intercepts					
Episodic Memory: Word Recall	766.298(14); p = 0.00	0.00	0.437 (0.411-0.463)	0.473	--
Semantic Memory: Vocabulary	1428.28 (14); p = 0.00	0.00	0.599 (0.572-0.625)	0.603	--
Semantic Memory: Fact Recall	1454.29 (14); p = 0.00	0.00	0.604 (0.578-0.630)	0.601	--
Neurocognitive Speed: Semantic Verification	1016.433(14); p = 0.00	0.00	0.504 (0.478-0.530)	0.596	--
Neurocognitive Speed: Lexical Decision	716.937(14); p = 0.00	0.00	0.422 (0.396-0.449)	0.492	--
Model 1: Random Intercept					
Episodic Memory: Word Recall	157.720 (13); p = 0.00	0.797	0.199 (0.172-0.227)	0.172	608.578(1); p = 0.00
Semantic Memory: Vocabulary	55.165 (13); p = 0.00	0.970	0.107 (0.079-0.137)	0.132	1373.12(1); p = 0.00
Semantic Memory: Fact Recall	145.661 (13); p = 0.00	0.907	0.190 (0.163-0.219)	0.115	1308.63(1); p = 0.00
Neurocognitive Speed: Semantic Verification	152.939 (13); p = 0.00	0.857	0.195 (0.168-0.224)	0.482	863.494(1); p = 0.00
Neurocognitive Speed: Lexical Decision	117.740 (13); p = 0.00	0.845	0.169 (0.142-0.198)	0.550	599.20 (1); p = 0.00
Model 2: Random Intercept, Fixed Slope					
Episodic Memory: Word Recall	74.945 (12); p = 0.00	0.912	0.136 (0.108-0.167)	0.156	82.775 (1); p = 0.00
Semantic Memory: Vocabulary	21.810 (12); p = 0.0397	0.993	0.054 (0.012-0.089)	0.132	33.355 (1); p = 0.00
Semantic Memory: Fact Recall	89.981 (12); p = 0.00	0.946	0.152 (0.123-0.182)	0.085	55.68 (1); p = 0.00
Neurocognitive Speed: Semantic Verification	92.111 (12); p = 0.00	0.918	0.154 (0.125-0.184)	0.492	60.828 (1); p = 0.00
Neurocognitive Speed: Lexical Decision	90.891 (12); p = 0.00	0.884	0.153 (0.124-0.183)	0.632	26.849 (1); p = 0.00
Model 3: Random Intercept, Random Slope					
Episodic Memory: Word Recall	55.341 (10); p = 0.00	0.936	0.127 (0.095-0.160)	0.115	19.604 (2); p = 0.00
Semantic Memory: Vocabulary	18.122 (10); p = 0.0529	0.994	0.054 (0.000-0.092)	0.136	3.688 (2); p = 0.186
Semantic Memory: Fact Recall	145.661 (13); p = 0.00	0.907	0.190 (0.163-0.219)	0.115	1308.63(1); p = 0.00
Neurocognitive Speed: Semantic Verification	83.036 (10); p = 0.00	0.925	0.161 (0.130-0.194)	0.267	9.075 (2); p = 0.011
Neurocognitive Speed: Lexical Decision	80.586 (10); p = 0.00	0.896	0.158 (0.127-0.191)	0.286	10.305 (2); p = 0.006
Model 4: Random Intercept, Random Slope, Fixed Quadratic					
Episodic Memory: Word Recall	14.110 (9) ; p = 0.1185	0.993	0.045 (0.000-0.088)	0.084	41.231 (1); p = 0.00
Semantic Memory: Vocabulary	8.949 (9) ; p = 0.4420	1.00	0.00 (0.00-0.067)	0.128	9.173 (1); p = 0.010
Semantic Memory: Fact Recall	64.211 (9); p = 0.00	0.961	0.147 (0.115-0.182)	0.035	17.114 (1); p = 0.00

Neurocognitive Speed: Semantic Verification	18.857 (9); p = 0.0264	0.990	0.062 (0.020-0.102)	0.314	64.179 (1); p = 0.00
Neurocognitive Speed: Lexical Decision	22.730 (9); p = 0.00	0.980	0.074 (0.036-0.112)	0.254	57.856 (1); p = 0.00
Model 5: Random Intercept, Random Slope, Random Quadratic					
Episodic Memory: Word Recall	9.770 (6); p = 0.1347	0.995	0.047 (0.000-0.099)	0.054	Not positive definite
Semantic Memory: Vocabulary	7.061 (6); p = 0.3153	0.999	0.025 (0.00-0.084)	0.111	1.888 (3); p = 0.596
Semantic Memory: Fact Recall	41.590 (6); p = 0.00	0.975	0.145 (0.105-0.188)	0.035	Not positive definite
Neurocognitive Speed: Semantic Verification	14.331 (6); p = 0.0262	0.991	0.070 (0.023-0.118)	0.262	4.526 (3); p = 0.210
Neurocognitive Speed: Lexical Decision	14.980 (6); p = 0.0204	0.987	0.073 (0.027-0.120)	0.202	7.75 (3); p = 0.051

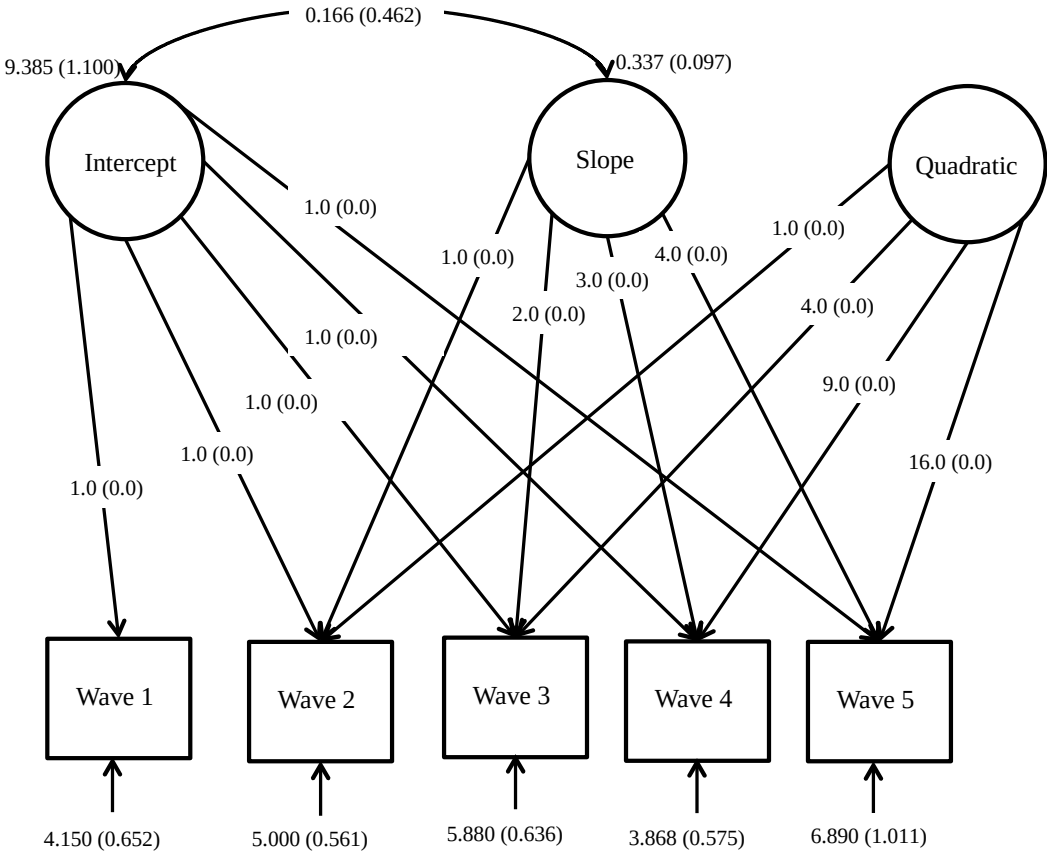
Note. χ^2_M = chi-square test of model fit. df_M = degrees of freedom for model fit. RMESA = root mean square error of approximation. CI = confidence interval. CFI = comparative fix index. SRMR = standardized root mean square residual. X^2_D = chi-square test of difference. df_D = degrees of freedom for difference in model fit.

19.604; p =0.00) was observed but the overall Model 3 was a poor fit (e.g., Word recall: χ^2 = 55.341; p = 0.00; RMSEA (90% CI) = 0.127 (0.095-0.160); CFI = 0.936; SRMR = 0.115; see Table 3).

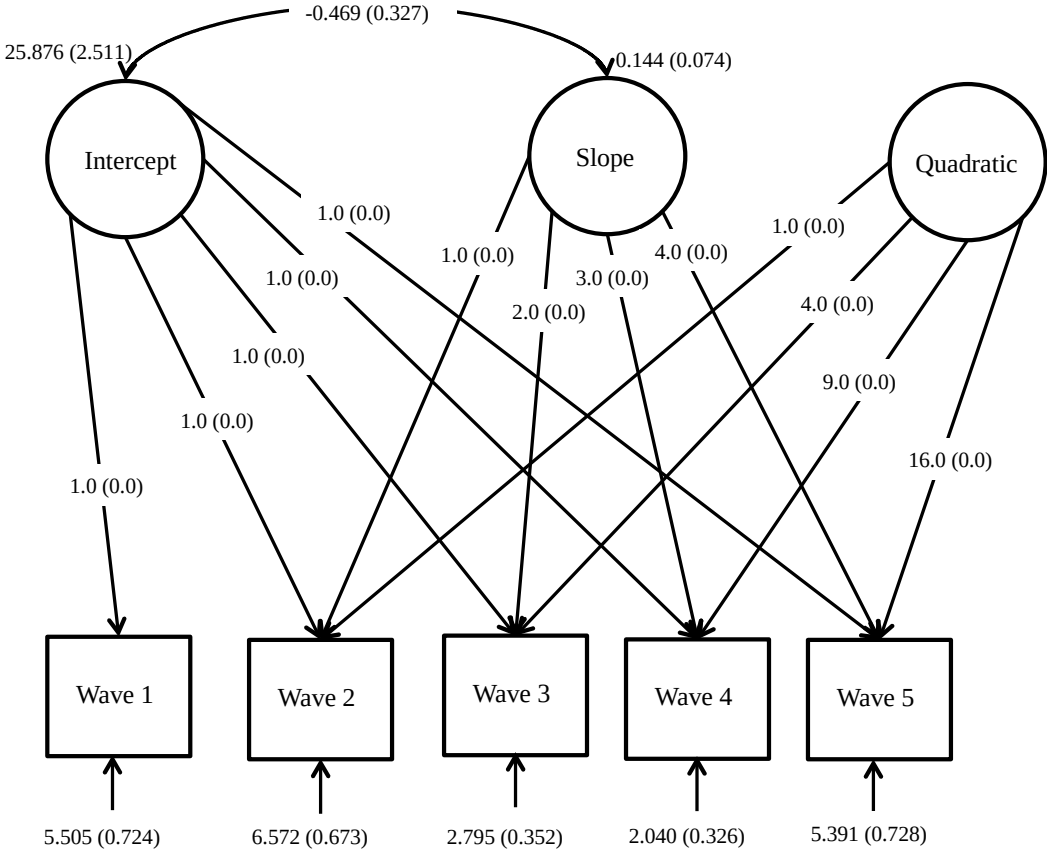
Fifth, in Model 4 a random intercept, random linear slope model, and a fixed quadratic model was examined for each cognitive measure. Adults were allowed to vary with respect to where they started out and how they changed over time but curvilinear change was the same across everyone. This model fit the data well (see Table 3). Sixth, to test any further improvement in model fit with the addition of a random quadratic, in Model 5 we tested the random intercepts, random linear slope, and a random quadratic model. The intercept, slope and quadratic were all allowed to vary across individuals. Model 5 resulted in the absence of a positive definite covariance for word recall and fact recall. In addition a significant χ^2 difference in model fit for vocabulary, lexical decision, and semantic verification was not observed. Thus, we rejected this model and accepted the fixed quadratic model (Model 4) (see Figures 2a-e). In sum older adults vary with respect to where they start out and how they change linearly over time, but do not vary in terms of their curvilinear change from wave 1 to wave 5 on word recall, fact recall, vocabulary, lexical decision, and semantic verification (Table 3).

Research Question 1. The five personality traits were examined for associations with both baseline performance and five-wave change in episodic memory, semantic memory, and neurocognitive speed. Intercept and slope were

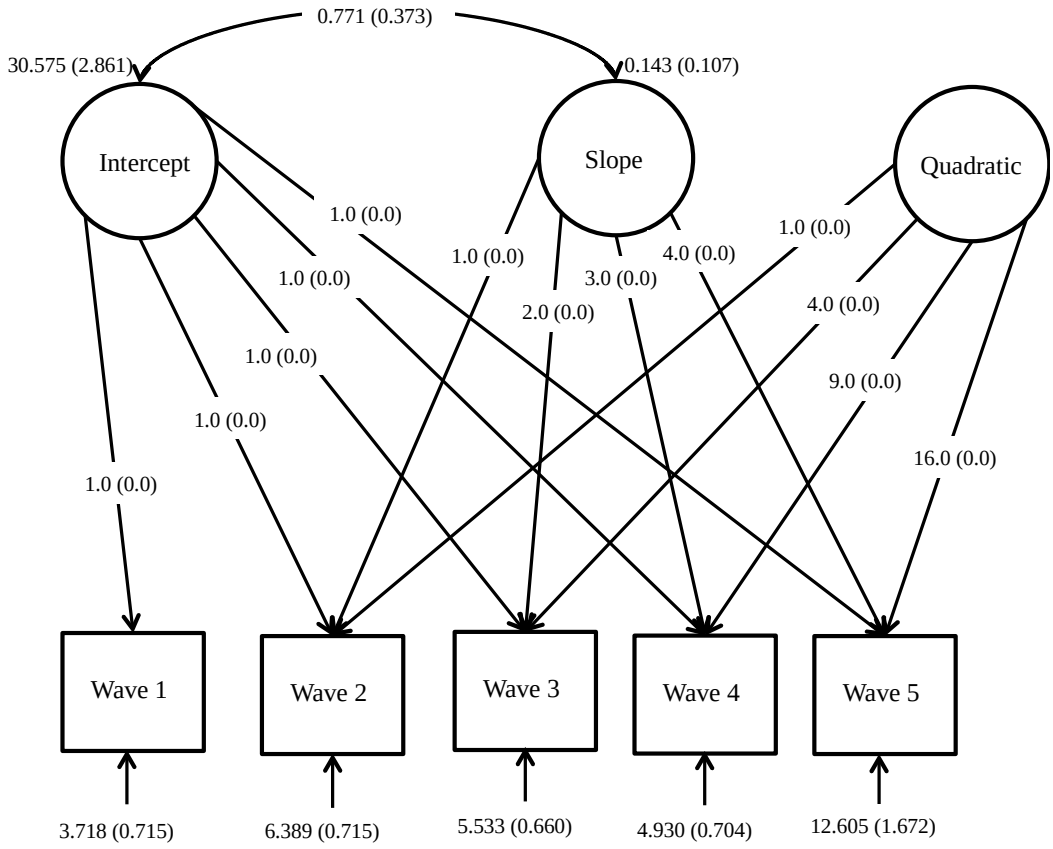
(a) Word Recall: Random intercept, random slope, and fixed quadratic model (Model 4).



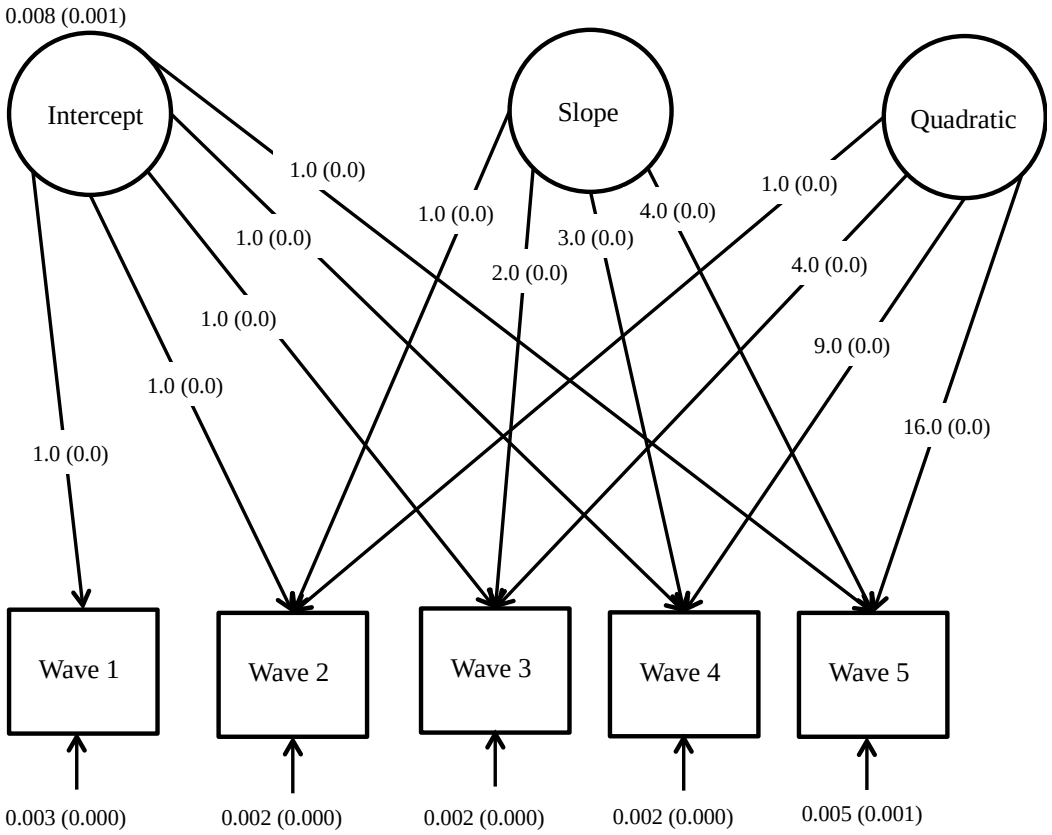
(b) Vocabulary: Random intercept, random slope, and fixed quadratic model (Model 4).



(c) Fact Recall: Random intercept, random slope, and fixed quadratic model (Model 4).



(d) Semantic Verification: Random intercept, random slope, and fixed quadratic model (Model 4).



(e) Lexical Decision: Random intercept, random slope, and fixed quadratic model (Model 4).

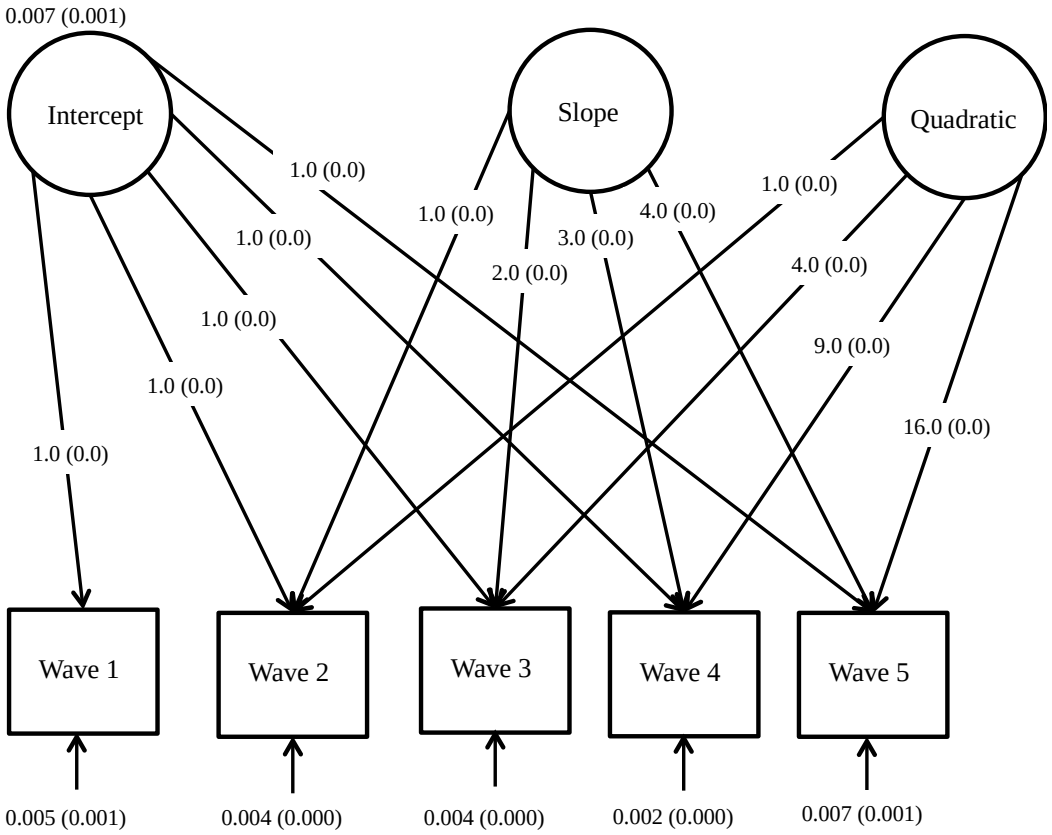


Figure 2. Final baseline latent growth model of cognitive change for (a) word recall, (b) vocabulary, (c) fact recall, (d) semantic verification, and (e) lexical decision

regressed on N, E, O, A, C, and age, as a covariate for each manifest variable (Table 4).

First, episodic memory performance was significantly predicted by O and C. Specifically, older adults with a one-unit increase in O and C showed a 0.038 (p = .003) increase and a 0.058 (p = .035) decrease, respectively, in word recall at wave 1. The traits N, E and A did not significantly predict intercept or slope for episodic memory.

Second, semantic memory performance as measured by vocabulary and fact recall were significantly predicted by N, E, O, and A on intercept. As expected, adults with a one-unit increase in O levels performed 0.144 (p < .001) higher, whereas adults with a one-unit increase E level performed 0.097 (p < .001) lower on vocabulary. Similarly, on fact recall, adults with a one-unit increase in O levels had a 0.101 (p < .001) increase in performance and adults with a one-unit increase in N, E, and A levels showed a 0.045 (p = .010), 0.091 (p < .001), 0.202 (p < .001), respectively, decrease in performance. Regarding change in linear slope, a significant difference was observed for only A on vocabulary. Adults with a unit increase in A showed a 0.019 (p = .031) decrease in rate of linear change over five waves (Figure 3).

Third, neurocognitive speed performance was significantly predicted by O levels on intercept for semantic verification. As expected, adults with a one-unit increase in O had 0.001 (p = .009) lower latency score. None of the five personality traits significantly predicted change in neurocognitive speed.

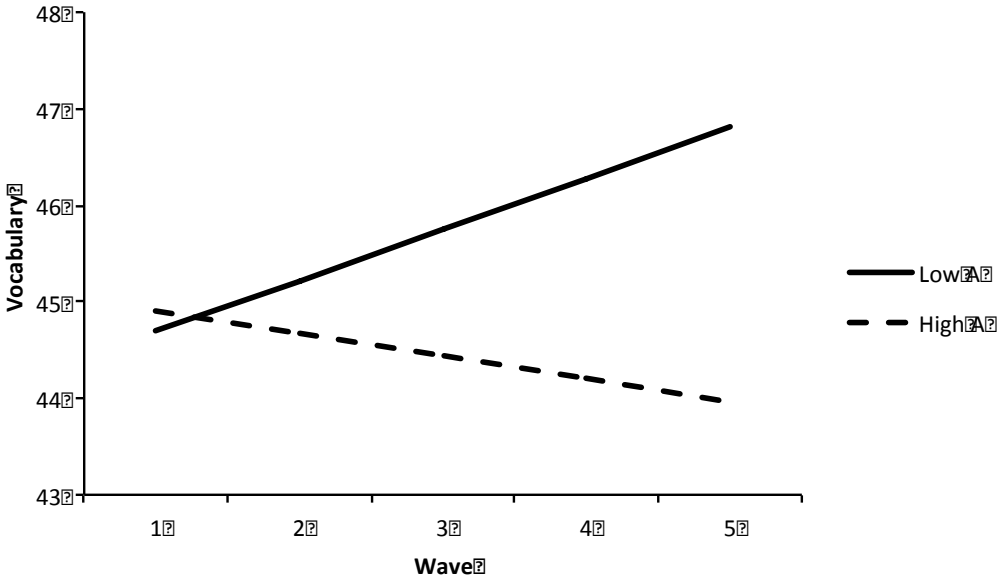


Figure 3. High in agreeableness (A) was associated with negative change in performance whereas low in A was associated with positive linear change over five waves. High and low represent 20 units above and below the mean A score.

Table 4.
Unstandardized regression coefficients and model fit indices for personality traits on three cognitive domains: episodic memory, semantic memory, and neurocognitive speed.

Episodic Memory: Word Recall					
			Model Fit Indicators		
Intercept (SE)	**Slope (SE)**	$\chi^2_M(df_M)$	**CFI**	**RMSEA (90% CI)**	**SRMR**
22.315 (4.026)***	2.556 (1.179)*	35.554 (27); p = 0.125	0.989	0.034 (0.000-0.061)	0.045
		Intercept		**Linear Slope**	
Predictors		**Est.**	**SE**	**Est.**	**SE**
Neuroticism		-0.010	0.011	0.006	0.003
Extroversion		-0.021	0.014	0.004	0.004
Openness to Experience		0.038**	0.013	-0.002	0.004
Conscientiousness		-0.058*	0.028	0.010	0.008
Agreeableness		0.048	0.035	-0.004	0.010
Age		-0.069	0.038	-0.048***	0.011
Semantic Memory: Vocabulary					
			Model Fit Indicators		
Intercept (SE)	**Slope (SE)**	$\chi^2_M(df_M)$	**CFI**	**RMSEA (90% CI)**	**SRMR**
23.447 (5.551)***	4.385 (1.031)***	26.802 (27); p = 0.475	1.000	0.000 (0.000-0.046)	0.067
		Intercept		**Linear Slope**	
Predictors		**Est.**	**SE**	**Est.**	**SE**
Neuroticism		-0.011	0.015	-0.002	0.003
Extroversion		-0.097***	0.020	-0.003	0.004
Openness to Experience		0.144***	0.018	-0.002	0.003
Conscientiousness		-0.032	0.038	-0.001	0.007
Agreeableness		0.005	0.048	-0.019*	0.009
Age		0.258***	0.052	-0.039***	0.010
Semantic Memory: Fact Recall					
			Model Fit Indicators		
Intercept (SE)	**Slope (SE)**	$\chi^2_M(df_M)$	**CFI**	**RMSEA (90% CI)**	**SRMR**
43.035 (6.328)***	2.682 (1.139)*	82.335 (27); p = 0.000	0.963	0.085 (0.065-0.107)	0.022
		Intercept		**Linear Slope**	

Predictors	**Est.**	**SE**	**Est.**	**SE**
Neuroticism	-0.045*	0.017	0.004	0.003
Extroversion	-0.091***	0.023	-0.001	0.004
Openness to Experience	0.101***	0.020	-0.002	0.004
Conscientiousness	-0.058	0.044	0.001	0.008
Agreeableness	-0.202***	0.054	-0.008	0.010
Age	-0.113	0.059	-0.032**	0.011

Neurocognitive Speed: Semantic Verification

			Model Fit Indicators		
Intercept (SE)	**Slope (SE)**	$\chi^2_M(df_M)$	**CFI**	**RMSEA (90% CI)**	**SRMR**
3.530 (0.114)***	-0.117 (0.029)***	35.467 (27); p = 0.127	0.992	0.033 (0.00-0.061)	0.157

	Intercept		**Linear Slope**	
Predictors	**Est.**	**SE**	**Est.**	**SE**
Neuroticism	0.000	0.000	0.000	0.000
Extroversion	0.000	0.000	0.000	0.000
Openness to Experience	-0.001**	0.000	0.000	0.000
Conscientiousness	-0.001	0.001	0.000	0.000
Agreeableness	0.000	0.001	0.000	0.000
Age	0.002	0.001	0.001***	0.000

Neurocognitive Speed: Lexical Decision

			Model Fit Indicators		
Intercept (SE)	**Slope (SE)**	$\chi^2_M(df_M)$	**CFI**	**RMSEA (90% CI)**	**SRMR**
2.819 (0.114)***	-0.135 (0.034)***	46.257 (27); p = 0.0119	0.973	0.050 (0.024-0.074)	0.145

	Intercept		**Linear Slope**	
Predictors	**Est.**	**SE**	**Est.**	**SE**
Neuroticism	0.000	0.000	0.000	0.000
Extroversion	0.000	0.000	0.000	0.000
Openness to Experience	-0.001	0.000	0.000	0.000
Conscientiousness	0.000	0.001	0.000	0.000
Agreeableness	0.001	0.001	0.000	0.000
Age	0.003**	0.001	0.001***	0.000

Note. Est. = regression estimate. SE = standard error. χ^2_M = chi-square test of model fit. df_M = degrees of freedom for model fit. RMSEA = root mean square error of approximation. CI = confidence interval. CFI = comparative fix index. SRMR = standardized root mean square residual.
*p<.05; **p<.01; ***p<.001.

Research Question 2. First, five personality traits and age were regressed on all six SNPs to test any genetic associations with personality. No significant genetic associations were observed with the personality traits.

Second, intercept and slope for each of the five cognitive measures were regressed on all six SNPs (Table 5). *COMT* genotype showed a significant difference in positive linear change for semantic memory performance as measured by vocabulary. Specifically, *COMT* A/A homozygotes showed a 0.268 ($p = 0.037$) higher change in positive linear slope from those with COMT allelic risk (G+) (Figure 4). Surprisingly, a significant effect of *BDNF* genotype was also observed in the unexpected direction for fact recall. *BDNF* G/G homozygotes showed less change in positive slope by 0.280 ($p = 0.020$) than BDNF heterozygotes with A+ allelic risk over five waves. *APOE, CLU, CR1*, and *PICALM* did not significantly predict intercept or linear change for semantic memory.

Both intercept and slope for episodic memory and neurocognitive speed performance were not significantly predicted by allelic risk for any of the six SNPs.

Research Question 3. First, total composite score for genetic risk was measured and examined for all cognitive measures at baseline and longitudinally. Second, interactive effects of *COMT* and *BDNF* were examined with all SNPs on cognition (vocabulary and fact recall). Third, based on the literature linking *APOE* genotype to dementia, *APOE* interactions were examined with all SNPs to examine any moderating effects of the five SNPs for *APOE* effects on one task for

Table 5.
Unstandardized regression coefficients and model fit indices for genetic risk on three cognitive domains: episodic memory, semantic memory, and neurocognitive speed.

Episodic Memory: Word Recall					
			Model Fit Indicators		
Intercept (SE)	**Slope (SE)**	$\chi^2_M(df_M)$	**CFI**	**RMSEA (90% CI)**	**SRMR**
24.208 (2.654)***	3.395 (0.769)***	39.594 (30); p = 0.113	0.987	0.035 (0.000-0.061)	0.047
		Intercept		**Linear Slope**	
Predictors		**Est.**	**SE**	**Est.**	**SE**
APOE		0.963	0.0500	0.135	0.140
BDNF		-0.368	0.456	0.029	0.125
COMT		-0.082	0.537	0.009	0.146
CR1		0.271	0.464	-0.012	0.126
CLU		0.310	0.621	-0.208	0.167
PICALM		-0.716	0.446	0.184	0.122
Age		-0.082*	0.041	-0.048***	0.012
Semantic Memory: Vocabulary					
			Model Fit Indicators		
Intercept (SE)	**Slope (SE)**	$\chi^2_M(df_M)$	**CFI**	**RMSEA (90% CI)**	**SRMR**
29.528 (3.923)***	2.647 (0.678)***	40.3347 (30); p = 0.098	0.993	0.036 (0.000-0.062)	0.077
		Intercept		**Linear Slope**	
Predictors		**Est.**	**SE**	**Est.**	**SE**
APOE		0.537	0.737	0.085	0.123
BDNF		-1.264	0.675	0.046	0.110
COMT		-1.211	0.794	0.268*	0.129
CR1		0.633	0.686	0.062	0.111
CLU		0.302	0.919	-0.046	0.148
PICALM		0.040	0.659	-0.017	0.107
Age		0.236***	0.061	-0.037***	0.010
Semantic Memory: Fact Recall					
			Model Fit Indicators		

Intercept (SE)	Slope (SE)	$\chi^2_M(df_M)$	CFI	RMSEA (90% CI)	SRMR
28223 (4.338)***	2.240 (0.741)**	83.904 (30); p = 0.000	0.961	0.082 (0.062-0.103)	0.026
			Intercept	**Linear Slope**	
Predictors			**Est.**	**SE**	**Est.**	**SE**
APOE			0.230	0.816	0.224	0.135
BDNF			-0.662	0.747	-0.280*	0.120
COMT			-0.171	0.879	-0.002	0.1414
CR1			0.893	0.759	-0.070	0.121
CLU			0.383	1.016	-0.110	0.160
PICALM			-0.009	0.730	0.010	0.117
Age			-0.096	0.067	-0.032**	0.011
Neurocognitive Speed: Semantic Verification						
				Model Fit Indicators		
Intercept (SE)	**Slope (SE)**	$\chi^2_M(df_M)$	**CFI**	**RMSEA (90% CI)**	**SRMR**
3.310 (0.075)***	-0.096 (0.019)***	39.036 (30); p = 0.125	0.991	0.034 (0.000-0.061)	0.118
			Intercept	**Linear Slope**	
Predictors			**Est.**	**SE**	**Est.**	**SE**
APOE			0.003	0.014	-0.005	0.003
BDNF			0.007	0.013	0.003	0.003
COMT			0.018	0.0015	-0.004	0.004
CR1			-0.008	0.013	0.000	0.003
CLU			0.002	0.018	0.001	0.004
PICALM			0.012	0.013	0.001	0.003
Age			0.003*	0.001	0.001***	0.000
Neurocognitive Speed: Lexical Decision						
				Model Fit Indicators		
Intercept (SE)	**Slope (SE)**	$\chi^2_M(df_M)$	**CFI**	**RMSEA (90% CI)**	**SRMR**
2.757 (0.074)***	-0.095 (0.022)***	35.739 (30); p = 0.217	0.991	0.027 (0.000-0.056)	0.111
			Intercept	**Linear Slope**	
Predictors			**Est.**	**SE**	**Est.**	**SE**
APOE			0.006	0.014	-0.003	0.004
BDNF			0.011	0.013	0.001	0.004

COMT	0.021	0.015	-0.007	0.004
CR1	-0.009	0.013	0.007	0.004
CLU	0.000	0.017	0.005	0.005
PICALM	-0.001	0.012	0.002	0.004
Age	0.004**	0.001	0.001**	0.000

Note. Est. = regression estimate. SE = standard error. χ^2_M = chi-square test of model fit. df_M = degrees of freedom for model fit. RMSEA = root mean square error of approximation. CI = confidence interval. CFI = comparative fix index. SRMR = standardized root mean square residual.
*p<.05; **p<.01; ***p<.001.

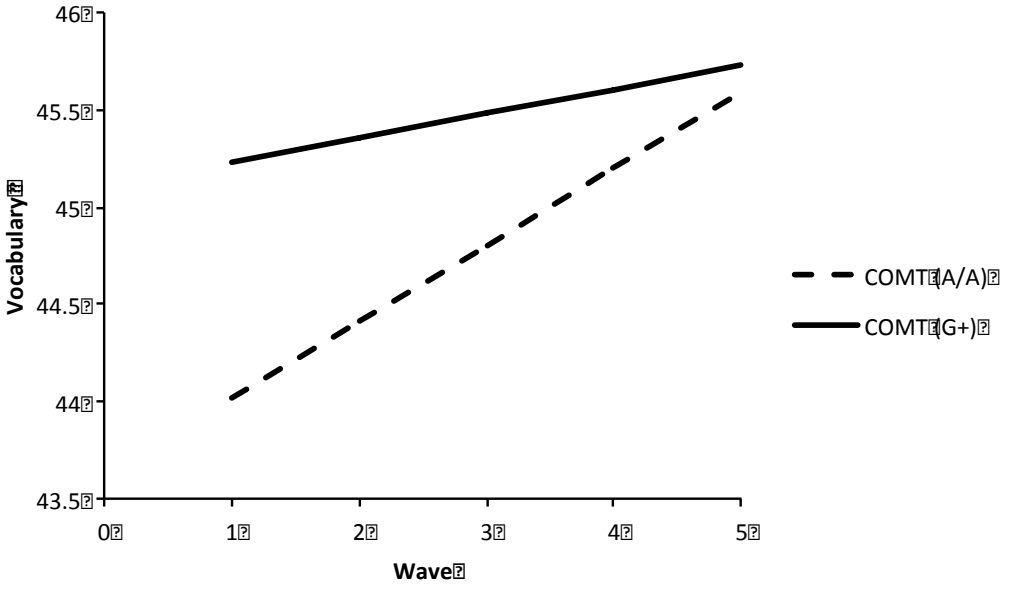


Figure 4. This shows the slope effect for *COMT* on semantic memory. *COMT* allelic risk carriers (G+) had less change, whereas *COMT* A/A homozygotes had greater rate of positive change ($\beta = 0.268$) over five waves.

each of the three cognitive domains (word recall, vocabulary, semantic verification) (Table 7a-c). Task selection for each construct was based on the best overall latent growth model fit indices (Table 3). A total of 5 models were examined for composite score of genetic risk, and 24 models for gene x gene interactions.

Composite score for genetic risk. No significant effects were observed for combined allelic risk on all five cognitive tasks (Table 6).

COMT and *BDNF*. First, independent effect of *COMT* on vocabulary was not significantly moderated by any of the five SNPs. Second, the *BDNF* x *COMT* interaction was significant (β = -5.281; p = .004) at baseline for fact recall performance. However, this result should be interpreted with caution because the model fit indices were poor (i.e., χ^2 = 77.975; p = 0.00; RMSEA (90% CI) = 0.098 (0.075-0.122); CFI = 0.961; SRMR = 0.025; see Table 7a). Poor model fit indices indicate that the results associated with this model is not reliable.

APOE. APOE x *COMT* and *APOE* x *BDNF* interactions were significant on word recall performance and a significant interaction was observed for *APOE x CR1* for vocabulary performance. There were no other significant gene x gene interactions association with cognition.

APOE x *COMT*. Carriers for *APOE* (ε4+) x *COMT* homozygotes (G+) had (β = -0.732; p = .036) smaller change in slope on word recall than did those with *APOE* (ε4-) x *COMT* (A/A) homozygotes. Unexpectedly, adults with at least one allelic risk for *APOE* or *COMT* (*APOE* (ε4+) x *COMT* (A/A)/ *APOE* (ε4-) x

Table 6.
Unstandardized regression coefficients and model fit indices for composite genetic risk on episodic memory, semantic memory, and neurocognitive speed.

	Intercept		Linear Slope		Model Fit Indicators			
Cognitive Measures	**Est.**	**SE**	**Est.**	**SE**	$\chi^2_M(df_M)$	**CFI**	**RMSEA (90% CI)**	**SRMR**
Word Recall	0.027	0.191	-0.046	0.052	21.809 (15); p = 0.113	0.991	0.041 (0.000-0.076)	0.069
Age	-0.073	0.041	-0.048***	0.012				
Vocabulary	0.285	0.281	-0.074	0.045	26.417 (15); p = 0.034	0.992	0.053 (0.015-0.086)	0.122
Age	0.237***	0.061	-0.036***	0.010				
Fact Recall	-0.032	0.309	0.047	0.050	71.207 (15); p = 0.000	0.959	0.118 (0.092-0.147)	0.039
Age	-0.094	0.067	-0.031**	0.011				
Semantic Verification	-0.007	0.005	0.001	0.001	26.944 (15); p = 0.029	0.988	0.055 (0.017-0.087)	0.190
Age	0.003*	0.001	0.001***	0.000				
Lexical Decision	-0.005	0.005	0.000	0.001	22.174 (15); p = 0.103	0.989	0.042 (0.000-0.077)	0.164
Age	0.004**	0.001	0.001**	0.000				

Note. Est. = regression estimate. SE = standard error. χ^2_M = chi-square test of model fit. df_M = degrees of freedom for model fit. RMSEA = root mean square error of approximation. CI = confidence interval. CFI = comparative fix index. SRMR = standardized root mean square residual.
*p<.05; **p<.01; ***p<.001.

Table 7.
Significant unstandardized regression coefficients and model fit indices for gene x gene interactions with significant independent associations and APOE interactive effects on measure of (a) semantic memory and (b) episodic memory.
(a)

Semantic Memory: Vocabulary								
	Intercept		**Linear Slope**		**Model Fit Indicators**			
Significant Model	**Est.**	**SE**	**Est.**	**SE**	$\chi^2_M(df_M)$	**CFI**	**RMSEA (90% CI)**	**SRMR**
1. *APOE* x *CR1*	-3.260*	1.603	-0.072	0.269	24.698 (21); p = 0.261	0.997	0.026 (0.000-0.060)	0.098
APOE	-0.318	0.845	0.074	0.142				
CR1	1.168	0.754	0.106	0.126				
Age	0.235***	0.060	-0.037***	0.010				
Semantic Memory: Fact Recall								
					Model Fit Indicators			
	Intercept		**Linear Slope**					
Significant Model	**Est.**	**SE**	**Est.**	**SE**	$\chi(df_M)$	**CFI**	**RMSEA (90% CI)**	**SRMR**
1. *BDNF* x *COMT*	-5.281**	1.827	0.367	0.298	77.975 (21); p = 0.000	0.961	0.098 (0.075-0.122)	0.025
BDNF	-2.507*	0.984	-0.144	0.160				
COMT	0.443	0.869	-0.050	0.141				
Age	-0.100	0.062	-0.033**	0.011				

Note. Est. = regression estimate. SE = standard error. χ^2_M = chi-square test of model fit. df_M = degrees of freedom for model fit. RMSEA = root mean square error of approximation. CI = confidence interval. CFI = comparative fix index. SRMR = standardized root mean square residual.
*p<.05; **p<.01; ***p<.001.

(b)

Episodic Memory: Word Recall								
	Intercept		Linear Slope		Model Fit Indicators			
Significant Models	**Est.**	**SE**	**Est.**	**SE**	$\chi^2_M(df_M)$	**CFI**	**RMSEA (90% CI)**	**SRMR**
1. *APOE* x *COMT*	0.0708	1.246	-0.732*	0.349	22.842 (21); p = 0.353	0.997	0.018 (0.000-0.056)	0.055
APOE	1.179	0.670	-0.106	0.188				
COMT	-0.274	0.585	0.159	0.163				
Age	-0.077	0.041	-0.050***	0.011				
2. *APOE* x *BDNF*	0.815	1.051	-0.630*	0.290	38.562 (21); p = 0.011	0.977	0.056 (0.026-0.083)	0.059
APOE	0.843	0.510	0.224	0.141				
BDNF	-0.643	0.496	0.186	0.136				
Age	-0.076	0.041	-0.050***	0.011				

Note. Est. = regression estimate. SE = standard error. χ^2_M = chi-square test of model fit. df_M = degrees of freedom for model fit. RMSEA = root mean square error of approximation. CI = confidence interval. CFI = comparative fix index. SRMR = standardized root mean square residual.
*p<.05; **p<.01; ***p<.001.

COMT (G+)) showed the greatest change in positive slope over five waves (Figure 5).

APOE x *BDNF*. *APOE* (ε4+) x *BDNF* (A+) allelic risk carriers also showed the smallest change in linear slope (β = -0.630; p = 0.030) and those with at least one allelic risk had the greatest increase in slope (Figure 6; Table 7b).

APOE x *CR1*. Combined *APOE* (ε4+) x *CR1* (A+) allelic risk carriers had the worst performance (β = -3.260; p = .042), followed by those with no allelic risk and adults with at least one *APOE* or *CR1* allelic risk had the best performance on vocabulary over five waves (Figure 7; Table 7b). No significant difference in slope was present.

Research Question 4. First, interactive effects of all six SNPs with N were examined on the word recall task and vocabulary (Table 8a-b).

N x *CLU*. Performance for *CLU* allelic risk carriers on vocabulary was moderated by N. Adults with higher N x *CLU* (C+) showed superior performance (β = 0.134*; p* = .001) from those with lower N x *CLU* (T/T) (Figure 8). Similarly, on the intercept for word recall, adults with higher N x *CLU* (C+) exceeded adults with lower N x *CLU* (T/T) (β = 0.078; p = .005) (Figure 9).

N x *COMT*. *COMT* allelic risk carriers (G+) x higher N scores had less change in negative slope for word recall whereas, *COMT* (A/A) homozygotes with lower N levels showed a faster rate of decline on word recall performance (β = 0.013; p = .039) (Figure 10).

Second, all personality traits were tested for interactive effects of *COMT* allelic risk on vocabulary performance and *BDNF* allelic risk on fact recall performance (Table 8b). No significant interactions were observed.

Table 8.
Significant unstandardized regression coefficients and model fit indices for select gene x personality interactions with significant independent associations and neuroticism (N) interactive effects on measures of (a) episodic memory, (b) semantic memory.
(a)

Episodic Memory: Word Recall								
	Intercept		**Linear Slope**		**Model Fit Indicators**			
Significant Models	**Est.**	**SE**	**Est.**	**SE**	$\chi^2_M(df_M)$	**CFI**	**RMSEA (90% CI)**	**SRMR**
1. N x *CLU*	0.078**	0.028	0.003	0.007	23.495 (21); p = 0.318	0.997	0.021 (0.000-0.056)	0.054
N	0.031*	0.015	0.005	0.004				
CLU	-5.708**	2.193	-0.406	0.582				
Age	-0.063	0.038	-0.050***	0.011				
2. N x *COMT*	-0.011	0.024	0.013*	0.006	30.074 (21); p = 0.091	0.988	0.039 (0.000-0.068)	0.053
N	-0.004	0.013	0.008	0.003				
COMT	0.663	1.893	-1.016	0.521				
Age	-0.063	0.038	-0.050***	0.011				

Note. Est. = regression estimate. SE = standard error. χ^2_M = chi-square test of model fit. df_M = degrees of freedom for model fit. RMSEA = root mean square error of approximation. CI = confidence interval. CFI = comparative fix index. SRMR = standardized root mean square residual.
*p<.05; **p<.01; ***p<.001.

(b)

Semantic Memory: Vocabulary								
	Intercept		Linear Slope		Model Fit Indicators			
Significant Model	**Est.**	**SE**	**Est.**	**SE**	$\chi^2_M(df_M)$	**CFI**	**RMSEA (90% CI)**	**SRMR**
1. N x *CLU*	0.134**	0.042	-0.012	0.007	23.315 (21); p = 0.327	0.998	0.020 (0.000-0.056)	0.078
N	0.073**	0.023	-0.005	0.004				
CLU	-10.298**	3.284	0.906	0.514				
Age	0.253***	0.057	-0.037***	0.010				

Note. Est. = regression estimate. SE = standard error. χ^2_M = chi-square test of model fit. df_M = degrees of freedom for model fit. RMSEA = root mean square error of approximation. CI = confidence interval. CFI = comparative fix index. SRMR = standardized root mean square residual.
*p<.05; **p<.01; ***p<.001.

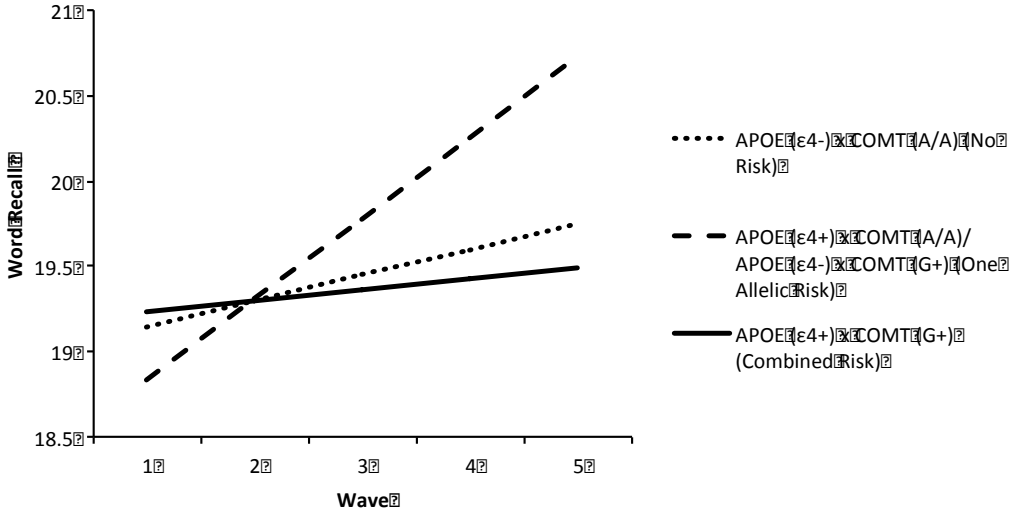


Figure 5. This shows the positive slope effect for *APOE* by *COMT* interaction for word recall (β = -0.732). *APOE* (ε4+) x *COMT* (G+) allelic risk carriers had the smallest amount of change, followed by adults with no allelic risk. Adults with at least one *APOE* or *COMT* allelic risk had the highest increase in rate of change over five waves.

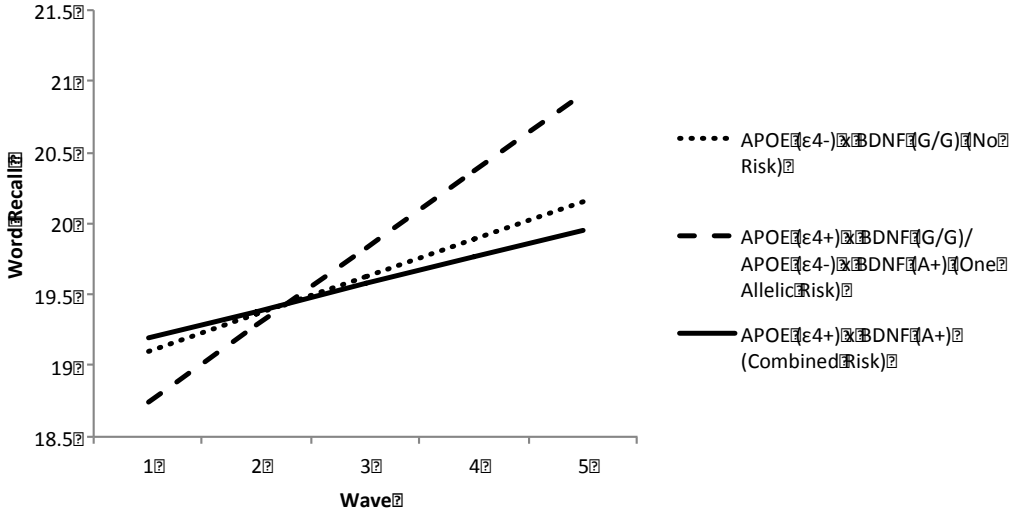


Figure 6. This shows the positive slope effect for *APOE* by *BDNF* on word recall (β = -0.630). *APOE* (ε4+) x *BDNF* (A+) allelic risk carriers showed the smallest amount of change followed by adults with no allelic risk. Adults with at least one *APOE* or *BDNF* allelic risk had the highest increase in rate of change.

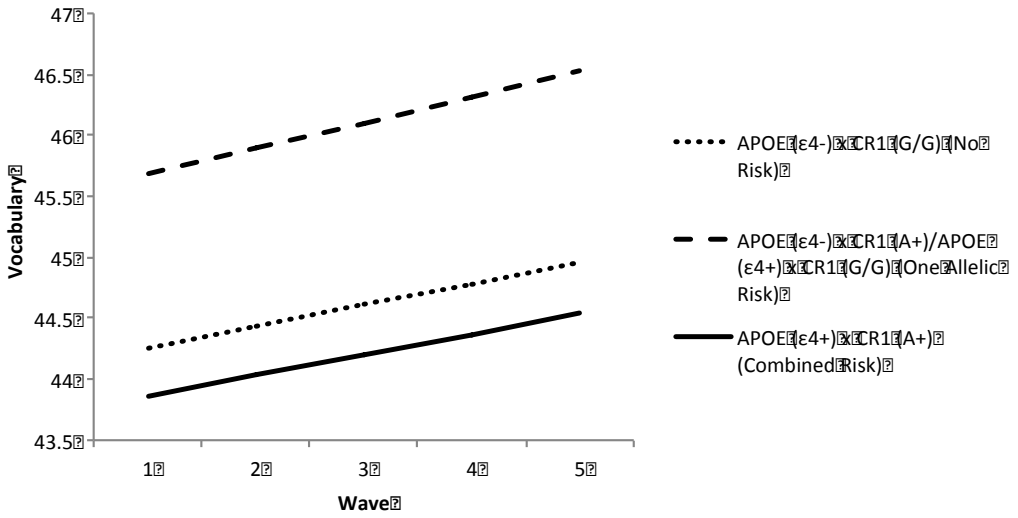


Figure 7. The figure shows *APOE* by *CR1* interaction effect on intercept for vocabulary (β = -3.260). *APOE* (ε4+) x *CR1* (A+) allelic risk carriers had the worst performance, followed by those with no allelic risk. Adults with at least one *APOE* or *CR1* allelic risk had the best performance.

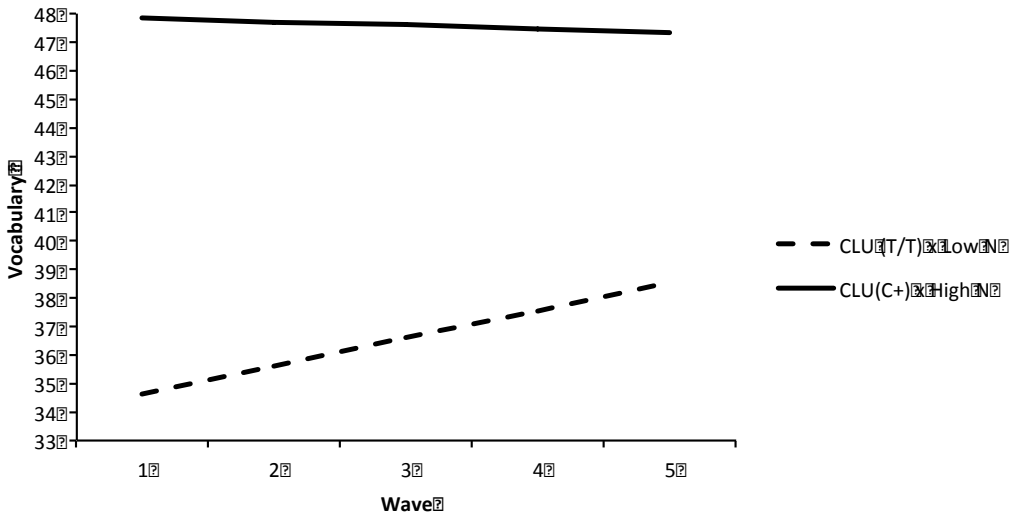


Figure 8. N levels moderated vocabulary performance for *CLU* genotype (β = 0.134). *CLU* allelic risk carriers (C+) with high N levels showed better performance than *CLU* homozygotes for no allelic risk (T/T) with low N. High and low represent 20 units above and below the mean score.

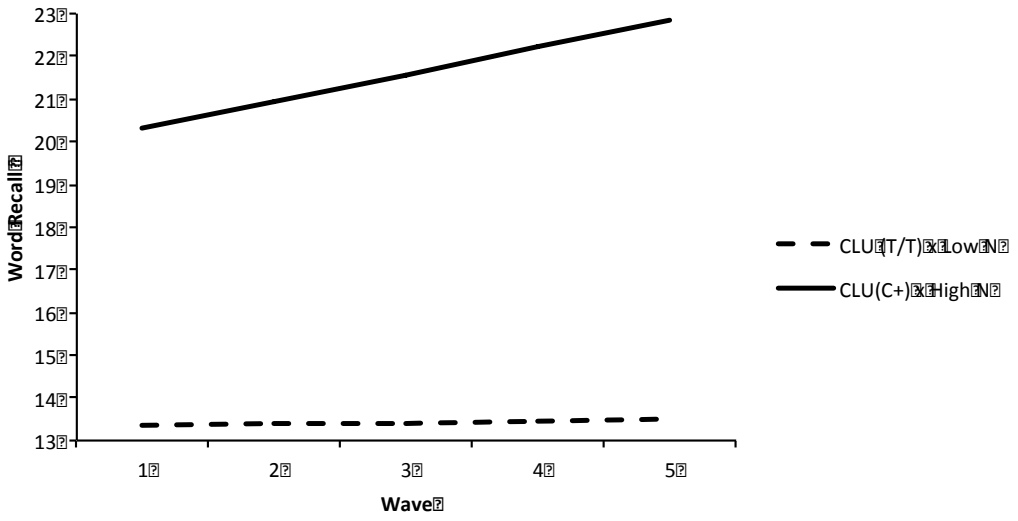


Figure 9. N levels moderated word recall performance for *CLU* genotype (β = 0.078). *CLU* allelic risk carriers (C+) with high N levels showed better performance than *CLU* homozygotes for no allelic risk (T/T) with low N. High and low represent 20 units above and below the mean score.

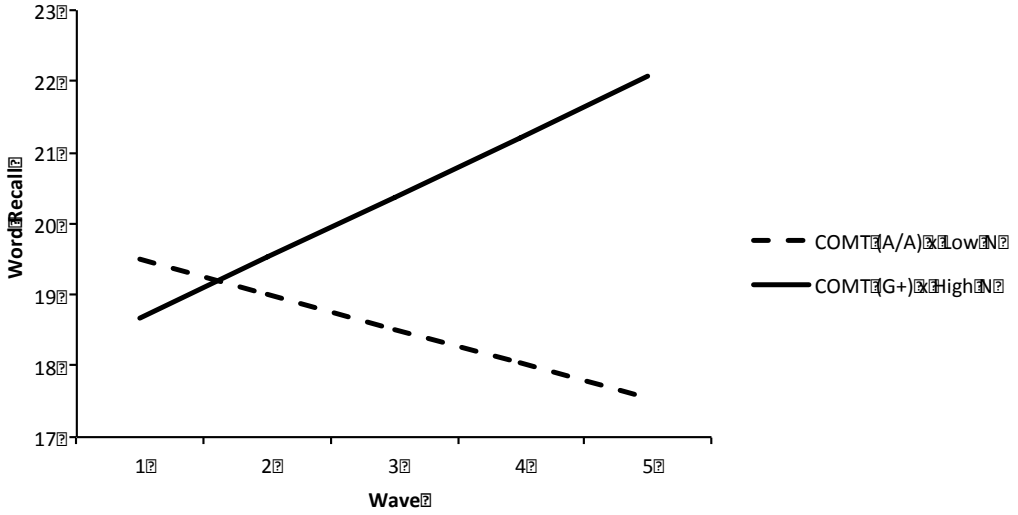


Figure 10. N levels moderated word recall performance for *COMT* genotype (β = 0.013). *COMT* allelic risk carriers (G+) with high N levels had positive change and *COMT* A/A homozygotes with low N declined. High and low represent 20 units above and below the mean score.

CHAPTER 5 – DISCUSSION

The objectives of the present study were to examine independent and interactive associations of *APOE, COMT, BDNF, CLU, CR1*, and *PICALM* in combination with personality traits to test change in declarative memory and neurocognitive speed performance in NA older adults over approximately 14 years. Previous studies have observed significant association of personality traits (Grahman & Lachman, 2012; Kato et al., 2013; Meier, Perrig-Chiello, & Perrig, 2002; Soubelet & Salthouse, 2011) and genetic risk (Barral et al., 2012; Chibnik et al., 2011; Deary, Wright, Harris, Whalley, & Starr, 2004; Goldberg & Weinberger, 2004; Green et al., 2008; Thambisetty et al., 2013; Xiao et al., 2012 Nagel et al., 2008; Wishart et al., 2010) for change in cognitive performance. However, this is the first longitudinal study examining six SNPs and personality traits together to study cognitive performance over five waves (up to 14 years). In the present study, we observed selectively supportive results for independent effects of personality traits and genetic risk and interaction effects of gene x gene and gene x personality for initial and/or change in cognitive performance. Supportive results include (a) adults with high O levels performed consistently higher on memory and neurocognitive speed tasks, (b) *COMT* allelic risk carriers showed less change in positive linear slope on word recall, (c) combined allelic risk carriers for *APOE* x *CR1* had the worst performance on vocabulary, and (d) N levels moderated word recall performance for adults with *CLU* and *COMT* allelic risk.

Regarding latent growth models of cognition, as expected there was both linear and quadratic change over 14.05 years. However, quadratic change did not differ among individuals. Random intercept, random linear slope, and fixed quadratic was the final best-fitting model for all five cognitive measures. It should be noted that models for fact recall and lexical decision did not meet all fit statistic requirements for an adequate fit (see Table 3). We still chose to examine the best possible model fit achieved for these two measures because CFI and SRMR (only for fact recall) were still acceptable and the chi-square values were not too large for the sample size in the present study (N = 282). However, we only did this to examine independent effects of personality traits and SNPs and choose not to interpret the finding for fact recall and lexical decision models for gene x gene and gene x personality interactions. Thus, the results, especially changes in performance for fact recall and lexical decision should be interpreted by taking into consideration that only the CFI and SRMR fit indices were acceptable for fact recall and only the CFI for lexical decision (see Table 3). We now discuss findings for each research question:

Research Question 1. As expected, being high in O personality trait was consistently linked to better performance at baseline for episodic memory, semantic memory, and neurocognitive speed. Previous research has linked the O trait to intelligence (Goldberg, 1993) and cognitive performance (Alwerdt et al., 2012; Grahman & Lachman, 2012; Schaie, Willis, & Caskie et al., 2004; Soubelet & Salthouse, 2011). We did not observe a significant change in performance over approximately 14 years suggesting that adults with high or low O are maintaining

their performance over time. One possibility is that adults with higher levels of O are open minded and may actively engage in creative activities and new interests throughout their lifetime, whereas those lower in O are less likely to be involved in cognitively stimulating activities; therefore, they may not benefit from these natural interventions. Although we accounted for age, adults with high O levels may also be actively engaged in a higher number of activities as they age to compensate for the loss in encoding and retrieving involved in memory tasks. In a related vein, Mitchell and colleagues (2012) combined four longitudinal studies with up to 21 years of data to examine the effect of cognitive activity on cognitive performance. They observed that adults who do not maintain their level of cognitive activity over time may be at a higher risk for cognitive decline.

As the present study only had Caucasian older adults from Canada, future studies should take this into consideration by including adults with differences in socioeconomic backgrounds and education levels to examine whether socioeconomic status and demographic modifies the strong link between high O and memory (Costa, Terracciano, & McCrae, 2001). Positive associations between high O and cognitive performance across three domains of cognition (i.e., episodic memory, semantic memory, and neurocognitive speed) implies that these adults are thinking critically and may be more cognitively engaged in not just one but a variety of activities to effectively process broad types of memory and speed information.

With regard to the O trait and brain functioning, previous research (e.g., Panksepp, 1998; Schultz, 1998) has linked the dopaminergic system to novelty

seeking and exploratory behaviors commonly observed in the O trait. DeYoung, Peterson and Higgins (2005) hypothesized that the dorsolateral prefrontal cortex (PFC) in interaction with the dopaminergic system may be responsible for the type of behaviors observed in individuals with high O levels (DeYoung et al., 2005). Previous research has shown that the O trait may be associated with dopaminergic projections to the PFC and anterior cingulate cortex, where the dorsolateral region of the PFC regulates cognitive function (i.e., working memory) (Schultz, 1998). DeYoung, Peterson and Higgins (2005) concluded that novelty-seeking behavior observed with the O trait could possibly be regulated by dopamine.

As hypothesized for semantic memory, adults with higher level of N showed poorer performance on fact recall but there was no significant change in linear slope over five waves. Similar results have been observed in previous studies (Alwerdt et al., 2012) and connection of the N trait to depression like behaviors (Duberstein et al., 2008) suggests that adults with high N levels in the present study may be less interested in cognitively stimulating activities resulting in a low level of crystalized intelligence in adulthood. Surprisingly, we did not observe significant differences in intercept or slope for episodic memory, suggesting that higher N levels with age may be protective against cognitive decline observed in older adults (Nilsson, 2003; Nyberg et al., 2012). One possible explanation for this is that with increasing age, older adults become more anxious and worrisome about realistic problems. From this perspective, high N in older age as measured by the NEO-PI may be realistic. Because personality traits

are shown to be invariant across age in older adults (Soubelet & Salthouse, 2011), additional information (i.e., changes in lifestyle) and measures should be considered to accurately reflect the level of N in older adults. For example, a recent study examined 68 centenarians with high scores on the positive attitude towards life domain as measured by the Personality Outlook Profile Scale and high self-rated health scores performed significantly better on the MMSE. Borderline significance was also observed where personality scores mediated the relationship between self-rated health and MMSE scores (Kato et al., 2013). Similar to the mediation of positive outlook for self-rated health, this unexpected finding in the present study may also be moderated by another personality trait (i.e., C or O levels) to compensate for risk contributed by high N levels. Balanced levels between personality traits among the five domains may also affect the overall cognitive performance for older adults. Exploration of interaction between personality traits on cognitive performance should be examined in future studies.

Similarly, high E was associated with poorer performance for semantic memory. Previous research has shown mixed findings regarding E levels and cognitive performance (Meier, Perrig-Chiello, & Perrig, 2002; Soubelet & Salthouse, 2011). Older adults in the present study may be highly affected by a decrease in social activities with old age and less likely to engage in cognitive activities (Brown et al., 2012). Consequently they performed poorly on measures of semantic memory and crystalized intelligence, which has been shown to increase with age (Nilsson, 2003). On the other hand, it is possible that introverted adults are not influenced by this change in social lifestyle and may be more likely

to engage in a higher number of scholarly activities. Differences in cognitive domains could affect the performance of highly extroverted individuals in tasks requiring the need to quickly perform such as neurocognitive speed. We did not observe a significant difference with regard to lexical neurocognitive speed in the present study, but future studies should examine adults with high E levels on other dimensions of neurocognitive speed tasks such as non-verbal speeded tasks (e.g., choice reaction time task).

Although we did not observe significant difference in episodic memory, previous study has linked high E and low N levels measured with the Freiburger Personality-Inventory (FPI) to better memory performance in healthy older adults (N = 287; age range: 68-95 years) (Meier, Perrig-Chiello, & Perrig, 2002). Parallel to E, high C levels were negatively related to intercept for word recall. Adults scoring high on C tend to be more organized and motivated but this might not directly influence their fluid intelligence and episodic memory performance. We did not observe any significant differences for semantic memory and neurocognitive speed because other risk factors such as SNPs may be moderating this effect.

Differences in A levels were associated with baseline performance and change on semantic memory performance. Adults with high A levels were more likely to show decreased fact recall performance at baseline and less change in positive linear slope on vocabulary over five waves. A previous study (Grahman & Lachman, 2012) has shown similar findings between poor cognitive performance and high A levels; thus, supporting that the A trait may be more

related to social interactions and less related to cognitive functioning abilities in older adults.

Connections between memory and personality are small but have been regularly observed. Based on findings from the current study, some personality traits may be useful markers of protection against cognitive decline in old age and dementia. Hence, identifying environmental risk factors connected to specific traits and behaviors should be emphasized in future studies. Changes in the environment that may modulate behaviors associated with specific personality traits leading to various protective and risk factors such as grave life events (e.g., death in the family) should also be taken into consideration.

Research Questions 2 and 3. We did not observe any significant associations between personality traits and the six SNPs. In previous studies, *COMT* has been associated with different types of personalities such as higher level of disorganization (Sheldrick et al., 2008). Sheldrick et al. (2008) found that the A/A genotype as compared with the G/G was significantly associated with higher level of disorganization, as measured by the schizotypical personality trait questionnaire (SPQ-B) in 522 healthy younger adults (mean age: 24.75 ± 5.84 years). Similar to the present study, they also did not find significant *COMT* associations with any of the five personality traits as measured by NEO-PI (Sheldrick et al., 2008). Therefore, *COMT* SNP and personality trait associations may be more relevant in adults with schizophrenia due to the critical involvement of dopamine levels in both cases, than on personality traits in NA older adults.

Regarding the *BDNF* polymorphism, a study by Sen et al. (2003), detected a small link between the *BDNF* protective allele (G/G) and higher N levels. They concluded that those with protective allele might highly be prone to depression (Sen et al., 2003). Contrary to the *BDNF* genotype, the *CR1* risk allele (A/A) has been linked to depression. Hamilton and colleagues (2012) found that the *CR1* rs6656401 and *CR1* rs3818361 SNPs were connected to a diagnosis of depression in female adults (M age = 47.4 years old). Therefore, based on the literature, future studies should include a measure of negative affect or depression to explore the connection between the six cognition-related SNPs examined in the present study.

We now discuss the independent and select interactive effects of all six SNPs examined in the present study for genetic-cognition associations, both concurrently and longitudinally. We observed supportive results for *COMT* and *BDNF* genotypes on semantic memory tasks. To our knowledge, this is the first longitudinal study examining gene x gene interactions on memory and lexical speed measures up to 14 years. However, previous studies have examined gene x gene interactive effects on neurocognitive phenotypes in cross-sectional samples with mixed findings (e.g., Nagel et al., 2008; Sapkota et al., 2013; Wishart et al., 2011). We did not find any significant independent or interactive associations for neurocognitive speed.

COMT. Carriers of the *COMT* risk allele showed less change in positive linear slope on vocabulary over 14 years, whereas those homozygous for the protective allele (A/A) showed greater change in performance (see Figure 8).

Previous studies have reported mixed findings for *COMT*-cognition associations. These include findings in the expected (Wishart et al., 2011) and unexpected (Harris et al., 2005) directions, no effect on memory and speed measures (Laukka et al., 2012), EF tasks (Dennis et al., 2010), global cognition (e.g., MMSE) (Erickson et al., 2008), and significant interactions with other dopaminergic genes (Bellander et al., 2011). The *COMT* genotype may also be highly sensitive to cognitive tasks (Bilder et al., 2008) as well as gender effects (Tsai et al., 2004). Therefore, future studies should include other cognitive domains (e.g., EF) and gender stratification for testing specificity of effects by gender (Harris et al., 2005; Soeiro-De-Souza et al., 2013).

BDNF. Surprisingly, adults with *BDNF* allelic risk (A+) had more change in positive linear slope than those with the protective allelic combination (see Figure 9). Previous studies have reported *BDNF* A+ carriers with poorer cognitive performance (Egan et al., 2003; Miyajima et al., 2008), as well as similar findings in the unexpected direction (Laukka et al., 2012). Laukka and colleagues (2012) examined the effect of five aging-dementia related SNPs, including *BDNF* on cognition with 2,694 older adults. They reported that *BDNF* carriers for the A allele showed better performance on category fluency. However, they found this unexpected effect only in adults with protective allele for *KIBRA* and *CLSTN2,* suggesting that effects of *BDNF* are moderated by other SNPs.

APOE. As predicted and widely reported (Brainerd et al., 2011; Elias-Sonnenschein et al., 2011; Verghese et al., 2011; Wisdom et al., 2011), we did not

detect a significant difference or change in performance between the protective (ε4-) and risk (ε4+) groups.

Our third research objective was to identify the effect of select gene x gene interaction to detect discrepancies observed with significant independent findings for SNP-cognition associations. We observed significant interactions between the *APOE* x *COMT* and *APOE* x *BDNF* for change in word recall performance over five waves. Adults with the combined allelic risk for both interactive effects showed the least amount of change in positive linear slope. This leads us to conclude and reinforce our hypothesis that risk-risk interactions (i.e., *APOE* x *COMT* and *APOE* x *BDNF*) may lead to highly detrimental effects on neurocognitive phenotypes in NA older adults. Specifically, we detected that older adults with combined protective alleles for both SNPs had less change in positive slope. However, in both interactions we observed a surprising finding that the presence of at least one *APOE* or *COMT* and one *APOE* or *BDNF* allelic risk was associated with the highest increase in rate of change for positive slope over approximately 14 years (see Figure 6; Figure 7).

Previous work by Harris and colleagues (2005) has shown similar findings for *COMT*, where heterozygotes with at least one allelic risk have shown superior performance over homozygotes with protective alleles. Regarding *BDNF* and neurocognitive phenotypes, mixed results have been reported (Mandelman & Grigorenko, 2012). BDNF is highly available in the hippocampus and important for maintaining plasticity and memory. Differences in environmental or other genetic factors (for example, *BDNF* may interact with *COMT* levels in the PFC

through basal ganglia-thalamocortical loops (e.g., Alexander et al., 1986), may be modulating the relationship between memory performance and *BDNF* (Mandelman & Grigorenko, 2012). In the present study, possession of at least one allelic risk was the most advantageous in both *APOE* x *COMT* and *APOE* x *BDNF* interaction effects. Carriers of at least one allelic risk showed the highest change on word recall and this effect increased with each additional wave (Figure 6 and 7).

Similarly, we also detected differences in intercept for *APOE* x *CR1* interaction on vocabulary performance. Carriers of one allelic risk showed the best performance and those with combined allelic risk had the worst score (Figure 7). We did not find significant *APOE*-related interactive effects for either *CLU* or *PICALM* in this sample. *CLU* and *PICALM* may be more receptive to environmental stimuli than gene x gene interactive effects. Consistently superior performance of heterozygotes in memory leads us to speculate the intricate and small interactive associations between SNPs. Specifically, findings that may lead us to discover genetic biomarkers involved in dementia and AD. For example, similar findings for genetic risk intensifications in a larger sample size and varied dementia/clinical populations may lead to early detection of cognitive changes.

The present study did not find any significant independent effect of *APOE, PICALM, CLU,* and *CR1* genotype on performance in any of the three cognitive domains. Effects of *APOE, PICALM, CLU* and *CR1* allelic risk may be more pronounced in adults with dementia than NA older adults. Other genes or environmental factors such as personality traits may be modifying the small

multifaceted effects of *APOE, PICALM, CLU,* and *CR1* allelic risk for neurocognitive phenotypes.

Research Question 4. We found select personality x gene interactive effects on episodic memory and semantic memory. Significant interaction of N x *CLU* on word recall and vocabulary and N x *COMT* on word recall was observed. In a previous study, by Dar-Nimrod and colleagues (2012) observed significant interaction of N x *APOE* on cognitive functioning. Surprisingly, we did not observe any interaction of personality traits with *APOE*.

N x CLU. Adults with higher N x *CLU* allelic risk (C+) had higher performance on both semantic and episodic memory domains. Specifically, C+ carriers with higher N scores had a higher performance on vocabulary and word recall tasks, whereas T/T homozygotes with lower N levels showed poorer performance. This novel finding with gene x personality traits contributes to the growing literature of mixed results with only SNPs and cognitive associations (Laukka et al., 2012; Thambisetty et al., 2013). The present study adds to different environmental factors that may be mediating cognitive performance associated with genetic risk factors. It is important to note that we did not observe a significant difference in slope, thus only baseline differences were present.

N x *COMT.* Surprisingly, adults with higher N levels were protected from cognitive decline even with *COMT* G+ allelic risk, whereas *COMT* A/A homozygotes with lower N scores had a faster rate of decline over 14 years on word recall. In the present study, we did not observe independent effect of N or *COMT* on episodic memory but we observed a significant N x *COMT* interaction

implying that N levels may be significantly moderating performance of *COMT* allelic risk carriers among older adults. Taking into account that the effect of *COMT* polymorphism is amplified in the aging brain (Sambatoro, Pennuto, Wolf, 2012), and prior studies have reported mixed effects for *COMT* allelic risk on cognition (Harris et al., 2005; Laukka et al., 2012; Wishart et al., 2011), the findings from the present study entails further investigation to distinguish the moderation of low versus high N levels in adults with *COMT* allelic risk.

The novel gene x personality findings in the present study may influence future research investigating gene-environmental effects in specific clinical (e.g., dementia, AD) and older adult population (e.g., cognitive decline) to consider including gene by personality interactions.

Strengths and Limitations

Strengths and limitations of the present study are now discussed.

First, as hoped, we were not able to achieve longitudinal configural invariance to examine three latent cognitive domains: episodic memory, semantic memory, and neurocognitive speed. One constraint for this was the availability of a minimum of only two cognitive indicators for each of our three domains. In the future, additional measures should be added to retest the possibility of examining latent factors. Second, examining manifest variables over time adds in the possibility of test-specific factors (i.e., retest effects) and measurement errors because the same tasks are used over time. Third, we only had a sample size of $N = 282$, therefore we were limited in statistical power to detect all possible significant gene x gene, and gene x personality interactions due to limited cell

sizes (see Table 9). The number of adults with allelic risk versus no risk for gene x gene combinations may have hindered any significant associations. Also, due to the sample size, we choose not to examine any moderating effects of gender or other possible moderators. Therefore, a larger sample size is recommended for future studies. Fourth, we included a healthy homogenous group of older Caucasians, which may have masked some interactive effects and may limit generalization results of this study. Social differences may affect personality trait scores and heritability of genes among different nationalities. It is also conceivable that some samples of exclusively older adults may include disproportionate representation of genotypes associated with survivability (or conversely missing survivability risk factor genotypes). As we used a subsample of participants from the Alwerdt and colleagues (2012) report with *N* = 978 older adults, we conducted post hoc comparisons to check on the concordance of personality scores between the two groups. These checks revealed similar mean personality scores and inter-correlations across the five scales. For the larger sample (Alwerdt et al., 2012) the reported means were: N = 76.58 (19.88), E = 99.74 (16.00), O = 111.56 (18.11), A = 50.23 (6.32), C = 50.32 (7.70). For the present study the calculated means were: N = 77.17 (20.72), E = 101.25 (16.57), O = 115.50 (17.64), A = 51.07 (6.17), C = 50.10 (7.94). Similar to the mean personality scores, inter-correlations across all five subscales were also very close between the two groups (see Table 10). Future studies should consider examining any sample discrepancies by including comparison to healthy younger sample, clinical populations (e.g., AD, MCI), and different ethnic groups.

Table 9.
Post-hoc power calculation for all models.

Models	**Alpha Level**	**RMSEA**	**Sample Size**	**df**	**Power**
1. Personality Models	0.05	Null = 0.05 Alt. = 0.08	282	27	0.71
2. SNP Models	0.05	Null = 0.05 Alt. = 0.08	282	30	0.75
3. Gene x Gene Models	0.05	Null = 0.05 Alt. = 0.08	282	21	0.62
4. Composite Genetic Risk Models	0.05	Null = 0.05 Alt. = 0.08	282	15	0.51
5. Gene x Personality Models	0.05	Null = 0.05 Alt. = 0.08	282	21	0.62

Note. RMSEA = root mean square error of approximation. Alt. = alternative. df = degrees of freedom. SNP = single nucleotide polymorphism.

Table 10.
Personality inter-correlations for Alwerdt et al. (2012) and the present study.

Alwerdt et al. (2012)				
	E	**O**	**C**	**A**
N	-.22*	-.02	-.25**	-.26**
E		.34**	.24**	.13**
O			-.00	.18**
C				.19**
Present Study				
	E	**O**	**C**	**A**
N	-.30**	.02	-.31**	-.26
E		.41**	.24**	.11
O			.04	.08
C				.22**

Note. N = neuroticism. E = extroversion. O = openness to experience. C = conscientiousness. A = agreeableness.
*p<.05; **p<.01

Fifth, although we included age as a covariate to rule out any cognitive changes due to age alone, future study should examine any interactions with age for three-way genetic x personality x age effects on memory and neurocognitive performance. Sixth, a major strength of the present study is that we had a longitudinal sample ranging in age from 53 to 84 years old and up to14 years of longitudinal data tested on three cognitive domains. Seventh, we had several specific questions and hypothesis regarding each research question, but a substantial number of models were exploratory in nature. Thus, future studies should carefully plan the design to reduce the number of models explored.

Conclusions

We observed some gene x personality interactions on intercept and change in memory performance over approximately 14 years in NA older adults. Our results were supportive of prior research including findings in opposite directions. Specifically, we conclude that *COMT* and *BDNF* SNPs may play an important role in moderating the effects of *APOE* allelic risk in a NA population. Supportive results for interactive effects of *CLU* x N on semantic memory and episodic memory and *COMT* x N on episodic memory suggests that these two SNPS may be highly involved in shaping neurocognitive performance and change. In the future, researchers and clinicians may be able to develop ways to mediate cognitive decline observed in dementia and old age for those with already at risk personality traits in combination with genetic risk by recommending changes in one's lifestyle.

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