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Genetic Moderators of Cognitive Decline in the Health and Retirement Study

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Genetic Moderators of Cognitive Decline in the Health and Retirement Study

by

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DEDICATION

This dissertation is dedicated to the wonderful people in my life who dared me to dream big and who encouraged and supported me along the way:

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ABSTRACT

The current dissertation used a gene x environment (G x E) approach to examine the independent and interactive effects of specific genetic variants and participation in physical and cognitive/social activities (PA and CSA) on cognitive performance in 4,764 participants of the Health and Retirement Study. Using three-wave data, three sets of multi-level growth models were conducted to examine baseline, longitudinal, and interactive effects of genotype (i.e., *ApoE*, *COMT*, and *BDNF*) and CSA/PA on performance across five cognitive measures: immediate, delayed and total word recall, and serial 7s and backwards counting.

At baseline, the *ApoE* ε4 allele predicted worse performance in all measures except backwards counting, and the *BDNF* Met allele predicted better recall scores. The effect of *COMT* genotype was not significant. Higher CSA/PA predicted better performance on almost all measures. One significant G x E interaction was found between *COMT* x CSA for backwards counting. Longitudinally, participation in CSA moderated the effect of time on word recall in the *ApoE* and *BDNF* models. These results support the idea that genetic and environmental factors are mechanisms of cognitive aging, but also exemplify the variability seen in genetic association studies. Further research is needed to translate such findings into clinically relevant criteria that can be used to identify individual susceptibility to cognitive decline.

CHAPTER ONE:

INTRODUCTION

Trajectories of cognitive aging are subject to high levels of heterogeneity (Dixon et al., 2007; Habib, Nyberg, & Nilsson, 2007; Small, Dixon, & McArdle, 2011). Some older adults maintain high levels of cognitive functioning throughout their lifespan (Dixon et al., 2007) while others experience notable rates of decline much earlier in life (Salthouse, 2009; Vestergren & Nilsson, 2011). A growing body of genetic association studies has attempted to identify genetic and environmental factors as likely sources of this variability, particularly in regard to the potential for these factors to modify individual susceptibility to cognitive decline. Unfortunately, the momentum of this research has been stalled by inconsistent results, replication difficulties, and small effect sizes (Payton, 2009; Raz & Lustig, 2014). Guided by the conceptual framework of the cognitive plasticity and flexibility theory (CPF; Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010) and the differential susceptibility theory (DS; Belsky et al., 2009), the current dissertation seeks to better understand the independent and interactive effects of genetic and environmental factors on age-related changes in cognitive performance in a sample of healthy older adults.

Similar to the theory of cognitive reserve (Stern, 2009), the cognitive flexibility and plasticity theory refers to an individual's potential to improve cognitive performance through deliberate acts of training, practice, or exposure to enriched environments (Lövdén et al., 2010). This potential may be governed by inherent neurological features of the brain (e.g., brain volume

or neural connectivity) that are influenced by genetic variability (Cedazo-Minguez, 2007; Payton, 2009). In relation to the cognitive flexibility and plasticity theory, the differential susceptibility theory posits that certain genotypes make individuals more or less responsive to the influence of environmental factors (Belsky et al., 2009). Together, these theories support the hypothesis that individuals with certain genotypes may be differentially susceptible (for better or worse) to environmental factors that influence age-related cognitive change. Stated another way, individuals may have genetic predispositions that dictate their responsiveness to environmental factors that influence cognitive aging. Furthermore, the magnitude of these effects may be related to the complexity or intensity of the environmental exposure.

Lifestyle activities are a type of environmental factor that has received considerable attention in the field of cognitive aging (Hertzog, Kramer, Wilson, & Lindenberger, 2008). This attention is related to the modifiable nature of lifestyle activities, as well as their potential to serve as natural interventions to promote cognitive health. The vast majority of research supports a positive relationship between participation in lifestyle activities and cognitive performance, despite a substantial amount of variability in study design, including the lack of a standardized definition or measurement of lifestyle activities (Wang, Xu, & Pei, 2012). The current dissertation will focus on two types of lifestyle activities: cognitive/social activities (CSA) and physical activities (PA), as these activities have been repeatedly associated with cognitive performance (Kraft, 2012; Mitchell et al., 2012; Small, Dixon, McArdle, & Grimm, 2012). The effects of these activities may be moderated by certain genotypes (Kim et al., 2011; Runge, Small, McFall, & Dixon, 2014; Thibeau, McFall, Wiebe, Anstey, & Dixon, 2016), and thus serve as a potential source of intraindividual variability that will be examined in this dissertation.

A number of genetic association studies have identified genetic variants that play important roles in cognitive performance. For example, variants of Apolipoprotein E (*ApoE*), a gene related to neural integrity and lipid processing (Cedazo-Minguez, 2007; Mahley, 1988), have been associated with age-related variability in cognitive processes that require complex processing, such as episodic memory and executive function (Laukka et al., 2013; Reynolds et al., 2006). Variants of Catechol-O-Methyltransferase (*COMT*) and Brain-Derived Neutrophic Factor (*BNDF*) have also been linked to variability in cognitive performance due to their roles in regulating neurotransmitter activity (Cools & D'Esposito, 2011) and neural plasticity (Matsushita et al., 2005). In particular, episodic memory and executive function appear to be influenced by variants of *COMT* (Das et al., 2014; de Frias et al., 2004; de Frias et al., 2005) as well as variants of *BDNF* (Egan et al., 2003; Gajewski, Hengstler, Golka, Falkenstein, & Beste, 2012). Recent evidence also suggests these variants moderate the potential for individuals to benefit from lifestyle factors such as CSA (Runge et al., 2014; Woodard et al., 2012) and PA (Ferencz et al., 2014; Kim et al., 2011; Thibeau et al., 2016). However, the generalization of the impact of such activities is limited by small effect sizes, replication difficulties, and insufficient statistical power (Chabris et al., 2012; Payton, 2009).

The complexity of the cognitive phenotype is a likely contributor to these limitations. For example, it is unlikely that any one gene will exhibit a large, singular effect on normal cognitive processes (Chabris et al., 2012; Goldberg & Weinberger, 2004). Most likely, cognition is a composite manifestation of multiple genetic and environmental factors. In regard to cognitive aging, the effects of gene x environment (G x E) interactions on cognition have received less attention (Payton, 2009), despite the fact that even small effects can have important clinical implications (Aguinis, Beaty, Boik, & Pierce, 2005).

The current dissertation expands on this previous research by examining the independent and interactive effects between specific genotypes (i.e., *ApoE, BDNF,* and *COMT*) and lifestyle factors (i.e., CSA and PA) on cognitive performance in a sub-sample of the Health and Retirement Study (HRS; Weir, 2012). More specifically, this research seeks to understand how genetic factors moderate the relationship between lifestyle activities and cognitive performance by evaluating genetic variants as plasticity factors that moderate individual responsiveness to environmental influences. The approach utilized multilevel modeling to estimate the independent and interactive effects of time, lifestyle activities (i.e., CSA and PA), and genotype (i.e., *ApoE, BDNF,* and *COMT*) on cognitive performance. To summarize, a greater understanding of the interactions between genes and these risk factors will provide insight regarding biological pathways and interventions that may promote healthy cognitive aging.

CHAPTER TWO:

REVIEW OF THE LITERATURE

The following section is a review of the literature pertinent to the current dissertation, including a description of the cognitive plasticity and flexibility and differential susceptibility theories as they relate to cognitive aging. A summary of previous research which examined the independent and interactive effects between genetic variants and participation in lifestyle activities on cognitive performance is also included. This section concludes with a summary of preliminary evidence that supports the theoretical and methodological approach utilized in the current dissertation and a brief statement of the research questions that will be addressed.

Theoretical Background

The cognitive plasticity and flexibility and differential susceptibility theories are well-suited to describe how genetic and environmental factors contribute to variability in cognitive performance and influence trajectories of cognitive aging. Briefly, the cognitive plasticity and flexibility theory conceptually supports the hypothesis that engagement in lifestyle activities promotes cognitive health by stimulating beneficial neuroplastic changes within the brain. Comparatively, the differential susceptibility theory postulates that neuroplasticity is dictated by genetic variability, such that an individual's genetic make-up may moderate this activity-cognition relationship. Together, the theories provide the conceptual framework to explain how genetic and environmental mechanisms contribute to heterogeneity in cognitive aging.

Cognitive Plasticity and Flexibility Theory

The neurobiological concepts of the cognitive plasticity and flexibility theory are similar to those of brain reserve and cognitive reserve (Stern, 2009). Brain reserve refers to the overall capacity of the brain to execute cognitive functions (Stern, 2009) and is likely to be determined by genetic factors (Deary, Corley, et al., 2009; Fritsch et al., 2007). Similarly, cognitive reserve represents the ability of the brain to operate efficiently despite the accumulation of structural and neural damage that occurs as a result of natural aging, and can be influenced by exposure to complex, stimulating activities, such as educational courses or occupational tasks (Stern, 2009).

Cognitive plasticity refers to the individual's potential to optimize cognitive abilities through actions that require complex thinking. Exposure to enriched environments promotes beneficial plastic changes in the brain that subsequently improve neural efficiency and processing. Appropriate levels of cognitive stimulation may therefore play a significant role in the preservation or enhancement of cognitive performance. Similar to cognitive reserve, cognitive plasticity is subject to inter- and intra-individual variability (Dixon et al., 2007; Finkel & McGue, 2007; Ram, Gerstorf, Lindenberger, & Smith, 2011). Notably, beneficial plastic changes only occur after being exposed to appropriately complex stimuli for a sufficient period of time (Lövdén et al., 2010); however, defining stimuli that meet these criteria is difficult at the individual level. These inherent differences in neurobiological structure and function are aspects of cognitive flexibility, which represents the extent to which cognitive performance can be improved. More specifically, individuals may require varying degrees and intensities of cognitive stimulation before beneficial plastic changes are experienced. As with brain reserve, cognitive flexibility may be influenced by genotype, including detrimental genetic variants

previously associated with cognitive decline (Harris & Deary, 2011). The extent to which these factors influence the trajectory of cognitive decline, however, is still unclear (La Rue, 2010).

Differential Susceptibility Theory

In terms of cognitive aging, the framework of cognitive plasticity and flexibility is complemented by the differential susceptibility theory. The differential susceptibility theory utilizes G x E interaction analyses to examine individual differences in response to environmental stimuli, which can be behavioral, physiological, or genetic in nature (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011). Based on aspects of developmental and evolutionary psychology, the differential susceptibility theory proposes that individuals with highly reactive, heritable phenotypes are more susceptible to the influences of environmental factors (Boyce & Ellis, 2005). More recently, the concept of "genetic plasticity" was incorporated into the differential susceptibility theory (Belsky et al., 2009). Genetic plasticity refers to the presence of unique genetic markers that make individuals more or less responsive to environmental influences (Belsky et al., 2009). As such, individuals with certain genetic variants may experience positive behavioral outcomes when immersed in enriched environments or worse outcomes when placed in less advantageous environments (Boyce & Ellis, 2005). It may also be possible that individuals may be genetically predisposed to be less responsive to environmental influences (i.e., their behavioral outcomes are less dependent on external factors). The differential susceptibility theory has been extensively used as a theoretical foundation to evaluate G x E interactions to predict adverse outcomes, including some types of mental illness (Ellis et al., 2011). In terms of cognitive aging, G x E interactions can evaluate cognition in terms of gains, losses, or the preservation of cognitive performance.

In sum, the concepts of cognitive plasticity and flexibility and differential susceptibility serve as a theoretical framework to examine how genetic and environmental factors influence cognitive performance, both independently and interactively. The current dissertation expands upon these concepts to address several aspects of cognitive aging. First, it is still uncertain which genetic profiles are most susceptible or resilient to cognitive decline, particularly in general populations of healthy older adults. Second, the extent to which these genetic variants moderate the influence of environmental factors (e.g., lifestyle activities) remains unclear. It is possible that certain variants predispose individuals to be differentially susceptible to environmental influences. Finally, it is unclear whether these independent or interactive relationships are limited to specific cognitive domains. Collectively addressing these issues will help identify individuals at risk for accelerated rates of cognitive decline. It will also help determine whether exposure to environmental factors (e.g., more frequent participation in PA or CSA) can help delay the onset or trajectory of these changes.

Lifestyle Activities and Cognitive Aging

The following section will review research that has examined the relationship between lifestyle activities and cognitive aging. Generally, most research has demonstrated a positive association between cognitive performance and participation in physical activities (Kramer & Erickson, 2007; Rockwood & Middleton, 2007) and cognitive activities (Lövdén et al., 2010). Moreover, these benefits do not appear to be limited to specific activities; having an overall active lifestyle has also been shown to be advantageous (Newson & Kemps, 2005). Cross-study comparisons are challenging, however, due to a number of confounding factors such as a lack of

standardized definitions and assessments of activity categories, differences in methods of cognitive measurement, and variability across study samples.

Physical Activity and Cognitive Performance

The beneficial relationship between PA and cognition has been established through randomized clinical studies that have used fitness training (both aerobic and strength conditioning) as an intervention (Colcombe & Kramer, 2003; Kramer, Erickson, & Colcombe, 2006). While these studies support a causal relationship between interventions that follow structured protocols (e.g., participating in 45 minutes of aerobic exercise 3 times a week for 12 weeks) and cognitive performance, it is not possible to draw similar conclusions for participation in more general PA. Additionally, the strength of the associations between cognition and general PA are obscured by the absence of standardized definitions or measurements of PA. However, in general, PA has been used as an umbrella term to describe purposeful body movement (Ballesteros, Kraft, Santana, & Tziraki, 2015). This comprehensive definition may be particularly suitable when referring to studies where it is not feasible to use a standardized measure of PA, such as participant-reported levels of PA or observational studies.

In a systematic review of observational studies which examined the relationship between PA and cognitive function ($k = 23$), and PA and risk of dementia ($k = 22$), approximately 70% of studies reported a protective effect of PA despite differences in study design, population, assessment of cognitive ability, and measures and definition of physical activity (Wang, Xu, et al., 2012). Additional evidence comes from studies that have associated lower levels of PA with worse cognitive performance and increased risk of dementia (Kim et al., 2011; Kraft, 2012; Woodard et al., 2012). For example, in a longitudinal study of 732 adults over the age of 65,

Kim et al. (2011) found that individuals who reported lower baseline levels of PA were significantly more likely to develop dementia or other forms of cognitive decline compared to those who reported higher levels of baseline activity. This preservation of cognitive ability may be related to multiple physiological effects that occur in response to being active.

PA stimulates a number of physiological changes that directly impact cognition, such as increased production of neurogenesis-promoting brain derived neurotropic factor (BDNF) protein in regions of the brain associated with episodic memory (Dickerson & Eichenbaum, 2010; Kim et al., 2011). Additional PA-related benefits include increased blood flow and oxygenation to the brain (Fritsch et al., 2007) as well as other physiologic mechanisms related to neuronal survival and neurogenesis (Kraft, 2012). For example, in a small intervention study of older adults aged 55-80 years, regular PA (i.e., three 40-minute walking sessions per week) over the course of a year was associated with significant increases in blood serum BDNF levels (Voss et al., 2013). The increased BDNF levels were correlated with improved connectivity between brain regions associated with memory and cognition, including the hippocampus (Voss et al., 2013). It is also possible that increased production of BDNF may contribute to increased hippocampal volume as well, which may play a key role in the preservation of cognitive health.

In a sample of 1,479 adults aged 65 and older, Erickson, Raji, et al. (2010) found significant associations between more frequent baseline PA (i.e., walking six to nine miles per week) and greater volume in the prefrontal, temporal, and hippocampal regions of the brain after nine years of follow-up. Participants with greater brain volume were also significantly less likely to experience cognitive impairment later in life (Erickson, Raji, et al., 2010). Frequent PA over time may therefore help preserve cognitive abilities that are more susceptible to biological aging, such as processing speed, working memory, and attention (Fritsch et al., 2007).

Despite the robust nature of these results, it is important to note that the interpretation of these effects of PA may vary by study design. For example, in a study of cognitively healthy adults over the age of 65, Steinberg et al. (2015) reported significant associations between cognitive performance and the amount of energy expended during PA (e.g., higher PA intensity corresponds with higher levels of energy expenditure), yet this relationship was not seen when PA was defined by duration or frequency. This is a clear example of how the definition of PA may influence study results. Furthermore, one must consider the effect of PA on cognitive performance across multiple time points in order to determine whether the effect is temporary or persists over time. In a similar fashion, the physiological pathways activated by PA are also thought to be activated by complex mental or social activities (Kraft, 2012); there is evidence that engaging in such activities also has a beneficial effect on cognition.

Cognitive/Social Activities and Cognitive Performance

Overall, similar results have been seen in studies that investigated CSA and cognition and those that have investigated PA. Most studies have supported a positive association between CSA and cognition, despite inconsistent methodological approaches and varying definitions of CSA. A meta-analysis of studies that examined the relationship between CSA and cognitive decline ($k = 9$) or the risk of dementia ($k = 9$) indicated that CSA generally had a protective effect against cognitive decline and dementia, regardless of differences in study design, population, definition or measurement of outcomes (Wang, Xu, et al., 2012).

As with PA, the act of engaging in CSA may trigger beneficial neuroplastic changes within the brain, including increased neurogenesis and decreased atrophy of brain regions associated with memory (Nithianantharajah & Hannan, 2006). A lifetime of engagement in

cognitively-stimulating activities has been associated with decreased hippocampal atrophy in older adults (Valenzuela, Sachdev, Wen, Chen, & Brodaty, 2008), which is thought to help prevent cognitive decline and the onset of dementia (Valenzuela & Sachdev, 2007; Wilson et al., 2002). It is important to note that the benefits of CSA are not always observed, and may be restricted to specific population subgroups. For example, Woodard et al. (2012) evaluated the effect of participating in seven CSA (i.e., viewing television, listening to radio, reading newspapers, reading magazine, reading books, playing games, and going to museums) as preventative factors for cognitive decline. The researchers concluded that such activities were only beneficial for individuals who presented a genetic risk for accelerated cognitive decline (Woodard et al., 2012). As a whole, however, the results of these studies must be interpreted with caution, as they represent associations rather than a causal relationship between lifestyle activities and cognitive change.

A positive correlation between frequency of participation in CSA and cognitive performance provides little information about the causal relationship between the two variables (Salthouse, Berish, & Miles, 2002). For example, it is not possible to discern whether participation in lifestyle activities is implicitly responsible for cognitive improvements, or whether external factors (i.e., physical health) influence activity level and cognition, or whether individuals with higher cognitive abilities are more likely to participate activities that are more challenging than individuals with lower cognitive abilities (Salthouse et al., 2002).

This latter concept, known as preserved differentiation (Salthouse, Babcock, Skovronek, Mitchell, & Palmon, 1990), posits that active individuals have inherently higher levels of cognitive functioning compared to inactive individuals, and the cognitive differences between these two types of individuals persist over time but follow similar trajectories of decline (Bielak,

Anstey, Christensen, & Windsor, 2012; Salthouse et al., 1990). Evidence of this effect comes from Bielak et al. (2012), who evaluated the relationship between self-reported participation in over 50 different activities and cognitive performance in a large 8-year cohort study of three age groups (20-24 years, 40-44 years, and 60-64 years at baseline; n = 7,485). Regardless of age group, individuals who reported greater baseline activity reported higher scores in episodic memory, working memory, vocabulary, and perceptual speed over time compared to less active individuals (Bielak et al., 2012). More specifically, baseline activity level predicted differences in cognitive ability between individuals, but not rates of cognitive change within each individual (Bielak et al., 2012). Similarly, Mitchell et al. (2012) found that higher frequency of baseline CSA was associated with better baseline cognitive performance, but this baseline level did not predict cognitive change over time. It is possible that the beneficial effects of lifestyle activities are most pronounced during early development stages, leading to individual differences in cognitive performance that persist throughout the lifespan (Fritsch et al., 2007).

There is also evidence that continued participation in CSA may be particularly important for preserving cognitive function, especially in old age. In a 12-year (5-wave) longitudinal study of 952 older adults (age range = 55 – 94 at baseline), Small et al. (2012) found that higher participation in CSA was associated with less decline in episodic memory and verbal speed. Additionally, changes in CSA and PA levels were found to be strong indictors of changes in episodic and semantic memory (Small et al., 2012).

Efforts have also been made to evaluate the impact of CSA on cognitive performance through experimental studies. For example, the goal of the Senior Odyssey Program (Stine-Morrow, Parisi, Morrow, & Park, 2008) evaluate the impact of a cognitive training program that focused on broad cognitive processes, including those used to solve complex problems (e.g,

executive functioning). Although the experimental group was quite small (n = 87) and covered a wide range of ages (59 – 93 years of age, M = 73.0), the results indicated that participants experienced significant improvements in executive function (Stine-Morrow et al., 2008). Another example includes the Experience Corps Program® (Carlson et al., 2008), where participants (n = 128, M = 70.1 years of age) committed to tutoring elementary school students for approximately 15 hours per week throughout the course of a school year following the successful completion of a 32-hour training program. Participants with impairments in executive function at baseline assessment showed a significant improvement (42%) in executive function at the end of the study. This idea is supported by evidence from the Synapse Study (Park et al., 2013), where older adults who engaged in complex types of CSA (e.g., learning digital photography, kitting) demonstrated significant improvements in episodic memory compared to older adults who only participated in passive types of CSA (e.g., listening to classical music).

To summarize the results of the literature regarding cognitive performance and lifestyle activities, the general belief that 'more is better' is based on the findings of studies that report a positive association between better cognitive function and higher levels of participation in physical and cognitive activities (La Rue, 2010). Although some researchers question the validity of the claim that engaging in such activities delays cognitive decline, there is no evidence that participation in these activities have a deleterious effect (Salthouse et al., 2002). It has been proposed that a greater understanding of the genetic etiology of cognition may help identify individuals who are inherently predisposed to experience more or less beneficial effects from lifestyle activities (Fratiglioni, Paillard-Borg, & Winblad, 2004; La Rue, 2010). This has led to increased efforts to identify key associations between genes and cognition.

Evaluating the Genetic Etiology of Cognition: Methodological Approaches

The purpose of the following section is to briefly review the current methodology used to analyze the genetic etiology of cognition, with the goal of more easily summarizing the results and limitations of the current literature. The first step in identifying the genetic etiology of cognition, which represents a highly complex phenotype, involves providing sufficient evidence that supports the genetic basis of a phenotype, such as establishing familial aggregation and heritability. Familial aggregation is established when the relatives of a person with a specific phenotype are more likely to express that same phenotype compared to relatives of a person without that phenotype (Hernandez & Blazer, 2006). Heritability is established by estimating the proportion of a phenotype that is attributable to genetic variance compared to the proportion that is attributable to environmental variance (Deary, Johnson, & Houlihan, 2009). Heritability estimates for cognitive abilities have ranged from 66% for general cognitive abilities (Plomin, Haworth, Meaburn, Price, & Davis, 2013), and 77% for memory and 79% for verbal ability (Finkel, Reynolds, McArdle, & Pedersen, 2005). Together, these results suggest that up to 80% of the variability in cognitive ability can be related to genetic factors. Once patterns of familial aggregation and heritability have been established, the next step involves identifying the genes and mutations associated with the phenotype. This can be accomplished through genetic association studies such as candidate gene studies or polygenic studies.

Candidate gene studies and polygenic studies are hypotheses-driven approaches that differ primarily by the number of genes that are investigated. Candidate gene studies identify a specific gene variant *a priori* that is thought to influence the etiology of a phenotype, and use a population-based case-control or cohort samples to compare the number of individuals with and without that phenotype (Tabor, Risch, & Myers, 2002). Polygenic studies investigate multiple

genetic variants that are also identified *a priori*. For example, *BDNF* and *COMT* are often investigated together since they both play a role in neurotransmitter production. Polygenic studies can also refer to genome-wide association studies (GWAS), which are hypothesis-free studies that consider *all* genetic variables within a genome (Lvovs, Favorova, & Favorov, 2012).

Both types of studies are preferable over linkage analysis for detecting genetic associations of complex phenotypes due to the accepted fact that such phenotypes are likely influenced by many genes, each of which have a comparatively small impact (Cordell & Clayton, 2005). Despite this, such studies are often criticized for their limitations (Raz & Lustig, 2014). The results of association studies can also be difficult to interpret and replicate since not all individuals who inherit a genetic risk variant will develop the associated phenotype (i.e., incomplete penetrance), whereas individuals without that genetic variant may develop the phenotype due to environmental exposure or other random causes (i.e., phenocopy; Lander & Schork, 1994; Payton, 2009; Raz & Lustig, 2014). The following section summarizes the results of gene association studies that have utilized candidate gene and polygenic approaches to examine the effects of three genes (*ApoE, BDNF,* and *COMT*) on cognition.

Candidate Genes and Cognitive Performance

Many of the genetic association studies in cognitive aging have focused on genes related to neurotransmitters (i.e., *BDNF* and *COMT*) and processing of lipoproteins (i.e., *ApoE*). Although other genes have been investigated, such as clusterin (*CLU*) and hosphatidylinositorl-binding clathrin assembly protein (*PICALM*) genes (Ferencz et al., 2014), this section will focus on the effects of *ApoE, BDNF,* and *COMT,* as these represent some of the most widely investigated genes related to cognition and will also be examined in the current dissertation.

Apolipoprotein E

The primary function of *ApoE* is to regulate the transport of lipids (e.g., cholesterol and triglycerides) and to stimulate neuronal repair and regeneration in the brain (Cedazo-Minguez, 2007; Mahley, 1988). *ApoE* exists in three allelic isoforms: ε2, ε3, and ε4. Since the discovery of the link between *ApoE* ε4 and Alzheimer's disease (AD; Poirier et al., 1993), the *ApoE* gene has become one of the most widely researched susceptibility genes for neurological conditions (Payton, 2009). The association between *ApoE* ε4 and AD has been consistently replicated (Hirschhorn, Lohmueller, Byrne, & Hirschhorn, 2002), but there is still debate as to whether the negative effects of *ApoE* ε4 extend to normal cognition (Goldberg & Weinberger, 2004).

In cognitively healthy individuals, the effects of *ApoE* ε4 appear to be most evident in abilities that require complex processing (e.g., working memory), but these effects vary depending on age of the research sample. For example, in a cross-sectional cohort study of older adults without dementia (n = 2,848; age range 60 – 102 years; $M_{\text{baseline age}}$ = 72.84 years), significant associations were found between *ApoE* ε4 and measures of perceptual speed and episodic memory, but not for measures of semantic memory or verbal fluency (Laukka et al., 2013). Conversely, in an unrelated sample of non-demented adults (n = 563; age range 32 – 74 years; $M_{\text{baseline age}}$ = 51.06), *ApoE* ε4-carriers did not differ significantly from non- ε4 carriers in any cognitive measure; in fact, *ApoE* ε4-carriers outperformed non-ε4 carriers in reasoning ability (de Frias, Schaie, & Willis, 2014). Additional evidence of the effects *ApoE* ε4 increasing with age have been found in longitudinal cohort studies.

In a 5-year longitudinal study of non-demented older adults (n = 417; age range 74 – 93 years; $M_{\text{baseline age}}$ = 79.13); *ApoE* ε4-carriers and non-ε4 carriers had similar levels of cognitive functioning at the initial assessment, but *ApoE* ε4-carriers exhibited significantly faster 4-year

rates of decline in episodic memory, executive function, and verbal fluency (Salmon et al., 2013). This exacerbated rate of decline may be related to a negative, dose-dependent effect of the *ApoE* ε4 allele. In a 13-year longitudinal study of aging twins (n = 478; $M_{\text{baseline age}}$ = 64.96), Reynolds et al. (2006) compared baseline ability and rates of cognitive change in *ApoE* ε4 homozygotes (ε4/ ε4), heterozygotes (one ε4 allele), and non- ε4 carriers. Interestingly, *ApoE* ε4 heterozygotes had higher working memory scores at baseline, but declined more rapidly over time than *ApoE* ε4 homozygotes and non-e4 carriers (Reynolds et al., 2006).

Meta-analyses have confirmed the majority of these results (Small, Rosnick, Fratiglioni, & Backman, 2004; Wisdom, Callahan, & Hawkins, 2011). *ApoE* ε4-carriers generally performed worse than non-ε4-carriers on all cognitive measures, but were significantly worse for measures of episodic memory, perceptual speed, executive functioning, and global cognitive ability (Wisdom et al., 2011). Moreover, meta-regression analyses have indicated that the effects of *ApoE* ε4 on episodic memory and global cognitive ability increase significantly with age (Wisdom et al., 2011).

Catechol-O-Methyltransferase

The Catechol-O-Methyltransferase (*COMT*) gene encodes the COMT protein, whose enzymatic activity degrades dopamine in neuronal synapses (Green, Kraemer, DeYoung, Fossella, & Gray, 2013; Sambataro, Pennuto, & Wolf, 2012). Dopamine is an essential neurotransmitter that plays a role in the ability to execute complex cognitive tasks, including working memory and information processing (Cools & D'Esposito, 2011; Störmer, Passow, Biesenack, & Li, 2012). Cognition is influenced by dopamine in an inverted-U-dose-dependent manner: negative effects are seen when dopamine levels are too high or too low (Cools &

D'Esposito, 2011; Nagel et al., 2008; Störmer et al., 2012). A SNP in *COMT* leads to a substitution of the amino acid, Valine (Val), with another amino acid, methionine (Met), at codon 158. This substitution alters the enzymatic activity of the COMT protein, which subsequently alters the rate of dopamine degradation (Nagel et al., 2008). This altered rate of degradation is thought to contribute to changes in cognitive function.

The enzymatic activity of homozygous Met-carriers (Met/Met) is approximately 3 to 4 times lower than that of homozygous Val-carriers (Val/Val) or heterozygous Val/Met carriers (Cools & D'Esposito, 2011; Nagel et al., 2008). This difference is thought to contribute to a linear relationship between *COMT* genotype and cognition, with Met/Met carriers demonstrating higher levels of cognitive function (attributed to increased availability of dopamine), followed by Met/Val carriers, and with Val/Val carriers demonstrating the lowest levels of cognitive function (Cools & D'Esposito, 2011). However, while the detrimental effect of the *ApoE* ε4 allele has been robustly demonstrated across multiple studies, the relationship between *COMT* and cognition performance is not as clear, particularly in samples of cognitively healthy older adults.

This lack of clarity may be attributable to evidence that the influence of the *COMT* genotype varies by cognitive domain. For example, in two 5-year longitudinal studies of individuals aged 50 to 60 years, Met/Met carriers exhibited greater declines in episodic memory in the first study (de Frias et al., 2004), but Val/Val carriers had more severe declines in executive function in the second study (de Frias et al., 2005). This suggested that the Met allele may be protective for executive function ability, whereas the Val allele is protective of cognitive abilities related to memory. Das et al. (2014) found that Met carriers had significantly faster reaction time scores as compared to Val/Val carriers. These differential effects are likely influenced by the areas of the brain activated by cognitive tasks. The Met allele, which is

associated with increased availability of dopamine in the prefrontal cortex, may be positively associated with cognitive activities that activate that area of the brain (e.g., executive function or reaction time). Conversely, the Val allele decreases dopamine in the temporal lobe, which may be advantageous for cognitive tasks that activate the temporal lobes (e.g., episodic memory).

Brain-Derived Neurotropic Factor

Located on chromosome 11, the *BDNF* gene encodes the BDNF protein, which plays an essential role in neuronal stimulation and protection (Matsushita et al., 2005). BDNF protein concentrations are highest in the hippocampus, an area of the brain that plays a key role in learning and memory (Kim et al., 2011). A SNP in *BDNF* results in the amino acid substitution of Val to Met at codon 66 (val66Met). The *BDNF* Met allele has been associated with decreased production of BDNF protein (Kim et al., 2011), smaller hippocampal volume (Erickson, Prakash, et al., 2010; Lim et al., 2013), and appears to influence executive functions (Das et al., 2014; Gajewski et al., 2012) and episodic memory (Egan et al., 2003; Erickson et al., 2008; Nyberg, Lovden, Riklund, Lindenberger, & Backman, 2012) in older adults. However, the results of these studies are largely inconsistent, especially in regards to the impact of *BDNF* variants on cognitive performance in older adults.

The detrimental impact of the Met allele first reported by Egan et al. (2003) found associations between worse episodic memory performance and Met-carriers in a fairly large sample (n = 641; average approximate age = 35 years). Met-carriers have also been shown to perform worse on tasks measuring executive function (Erickson et al., 2008) and perceptual speed (Miyajima et al., 2008; Raz, Rodrigue, Kennedy, & Land, 2009). These results may be attributable to age-related declines in the production of the BDNF protein (Hattiangady, Rao,

Shetty, & Shetty, 2005). This concept is further supported by evidence from an 11-year longitudinal study. In this sample, (n = 376, M_{age} = 83.9 years), baseline scores on a measure of perceptual speed did not vary by *BDNF* genotype, but any Met-carriers experienced significantly steeper rates of decline than Val/Val carriers (Ghisletta et al., 2014).

In a manner similar to the *COMT* gene, the effects of *BDNF* genetic variants may become more apparent in age, as evidenced by a number of studies that have failed to identify a detrimental effect of the Met allele in younger samples. For example, Hansell et al. (2007) found no effects of *BDNF* genotype on working memory in a sample of adolescent twins and their siblings (n = 785, M_{age} = 16.4 years). This age-dependent effect was seen in a study of 382 younger (M_{age} = 25.6 years, age range 20 – 31) and 566 older adults (M_{age} = 65.8 years, age range = 60 – 71 years), where only the older Met-carriers performed worse in an episodic memory task (Li et al., 2010).

Summary of Genetic Association Studies

Collectively, the results of these genetic association studies results support the association between specific genes and cognition, but are plagued by inconsistencies that are likely attributable to variability in study design, sample, and assessment of cognitive ability (Payton, 2009). Interpretation of the results of these studies is further complicated by the multifactorial, complex nature of the cognitive phenotype, as well as the fact that some genetic variants may be more advantageous for different cognitive domains (Nyberg et al., 2012). Given this complexity, it is unlikely that any single genes (or even groups of similar genes) will demonstrate relatively significant effects on normal cognitive processes (Chabris et al., 2012; Goldberg & Weinberger, 2004); therefore, it is essential to consider the impact of additional factors that influence

cognition, such as environmental factors. It is very likely that interactions between genes and environmental factors, as well as interactions between genes, produce cognitive effects that are not apparent when examining the lone impact of a singular gene (Hirschhorn, Lohmueller, Byrne, et al., 2002). As such, there has been a increased interest in a sub-class of association studies that investigate G x E interactions.

Gene x Environment Studies of Cognition

The previously described studies have provided evidence of effects of genetic markers and lifestyle activities on cognitive outcomes. However, as with all complex phenotypes, cognition is most likely the result of multiple interactions between genetic and environmental factors. The effects of such interactions are estimated by a sub-class of genetic association studies known as G x E interaction studies, which seek to provide a unique understanding of how complex phenotypes are influenced by a combination of genetic factors and exposure to different environments (Ellis et al., 2011). These studies have been a central focus of recent research in terms of understanding the genetic etiology of cognitive aging.

Emerging evidence suggests that variants of *ApoE* gene may constrain the beneficial relationship between participation in lifestyle activities and cognitive performance. In a longitudinal study of Swedish adults aged 75 years old at baseline, C. Ferrari et al. (2013) examined the modifying effect of high education and high frequency of participation lifestyle activities (including CSA) for *ApoE* ε4 carriers. Notably, there were no statistically significant differences between *ApoE* ε4 carriers and non-ε4 carriers in regard to their likelihood of participating in lifestyle activities. Higher levels of participation in lifestyle activities decreased the risk of dementia and AD by approximately 40% in *ApoE* ε4 carriers (C. Ferrari et al., 2013).

This suggested that individuals with the ε4 allele may be differentially susceptible to the benefits of lifestyle activity compared to non-ε4 carriers. Unfortunately, it is not possible to examine the effects of CSA since these activities were grouped with other non-related activities.

Obisesan, Umar, Paluvoi, and Gillum (2012) examined the interactions among PA and *ApoE* genotype in a cross-sectional analysis of adults aged 60 years and older (n = 1,799). Compared to *ApoE* ε4 carriers, physically active non-ε4 carriers reported better overall cognitive function in multiple domains, including recall, memory, and learning. Additional evidence of an *ApoE* x PA effect comes from a separate longitudinal study of older adults (n = 2,480, M_{age} = 71.69 years old at baseline). In this study, Ferencz et al. (2014) investigated the cumulative impact of several genetic risk factors (including *ApoE* ε4) and regular physical activity on episodic memory. Individuals who engaged in regular light, moderate, or intense levels of physical activity outperformed inactive individuals; however, no differences in episodic memory were seen between physically active individuals with a high genetic risk score (GRS) and physically active individuals with a low GRS. These results suggest that physical activity may counteract the detrimental effects of genetic risk factors. Collectively, these results highlight the potential for physical activity to mitigate the detrimental effect of the *ApoE* ε4 allele, but additional research is clearly needed to confirm these findings as well as to identify other genetic variants that may be moderated by lifestyle activities.

Preliminary Evidence to Support the Proposed Dissertation

The current dissertation is an extension of preliminary research that examined the potential benefit of participating in CSA on cognitive performance among participants from the Victoria Longitudinal Study (VLS) with or without the *ApoE* ε4 allele (n = 278, M_{age} = 66.5

years). Higher participation in complex cognitive activities was associated with better concurrent cognitive performance in measures of episodic memory, semantic memory, and verbal fluency (Runge et al., 2014). This result supports the CPF theory, which stipulates that cognitive stimulation produces beneficial plastic changes within the brain that contribute to enhanced cognitive performance. Similar to previous research (e.g., C. Ferrari et al., 2013), results from this study also indicated that the cognitive abilities of *ApoE* non-ε4 carriers were more likely to be influenced by frequent participation in complex lifestyle activities, as compared to *ApoE* ε4 carriers (Runge et al., 2014). These results support the conceptual framework of the CPF and DS theories that certain genotypes (e.g., the *ApoE* ε4 allele) may predispose individuals to be differentially responsive to the effects of environmental stimulation.

Although the results of the current study were interesting, there were a number of limiting factors that could impact their interpretation. First, the analyses were constrained to one genotype, whereas existing evidence suggests that additional polymorphisms (e.g., *COMT* and *BDNF*) may also influence cognitive performance in older adults. Second, the VLS sample is highly selective in terms of health and educational attainment, making generalizations to the broader population difficult. Finally, the observed effects were limited to baseline observations; there were no significant interactions between genotype, participation in CSA, and longitudinal changes in cognitive performance. Whether these results may be related to differential effects among genotype, or to the lack of sufficient follow-up period to detect genotypic influences for changes in cognitive performance, will be investigated through the use of the HRS dataset.

Proposed Research Questions

This dissertation proposes to evaluate previously identified genotypes as factors that increase an individual's differential susceptibility in response to environmental factors (i.e., PA and CSA), specifically focusing on G x E interactions that identify between-individual differences in cognitive performance. The following research questions will be examined:

Question 1: How will frequency of participation in two types of lifestyle activities (PA and CSA) influence cross sectional differences and longitudinal changes in cognitive performance? It is predicted that higher frequency of participation in both types of activity at baseline will be associated with better cognitive performance at baseline as well as less cognitive change over time.

Question 2: How will cross sectional differences and longitudinal changes in cognitive performance be influenced by variants of the *ApoE, COMT,* and *BDNF* genes? It is predicted that the presence of detrimental variants will be associated with worse cognitive performance at baseline and greater cognitive change over time.

Question 3: How will the presence or absence of genetic variants moderate the benefit of participation in both types of lifestyle activity? It is predicted that the presence of detrimental genetic variants will constrain the cognitive benefits of participation in lifestyle activities (CSA/PA).

CHAPTER THREE:

METHOD

Study Sample

The study sample included ongoing respondents of the HRS, which is a longitudinal study of US adults over the age of 50. The HRS is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan (UM). Data collection occurs in 2-year cycles via telephone and face-to-face interviews. Hispanics and Black adults are oversampled. Spouses of HRS participants are also included, regardless of their age. More in-depth information regarding the methodological details of the HRS are available elsewhere (Langa et al., 2005; Wallace & Herzog, 1995). Since its inaugural wave in 1992, approximately 38,000 respondents have joined the HRS. In 2006 and 2008, a subsample of the HRS study population consented to provide DNA samples as a part of the HRS genetic initiative, sponsored by the NIA (grant numbers U01AG009740, RC2AG036495, and RC4AG039029) and conducted by UM.

The current dissertation utilizes respondents of the HRS genetic initiative subsample who also were selected to respond to the HRS Psychosocial and Lifestyle Questionnaire in 2008. Specifically, respondents had to meet the following inclusion criteria: (a) selected and consented to provide DNA samples for the HRS genetic initiative in 2006 and 2008; (b) provided genetic data that passed quality control filters as specified by the Center for Inherited Disease Research (CIDR) and the Genetics Coordinating Center (CGC) at the University of Washington; (c) aged

50 years or older; (d) selection to complete a core HRS interview (i.e., selected to complete all survey components versus selected to complete a partial interview); (e) selection to complete the HRS Psychosocial and Lifestyle Questionnaire in 2008; and (f) respondents who self-identified as White/Caucasian or Black/African American race (both Hispanics and non-Hispanics were eligible). After applying these exclusion criteria, the final sample included 4,764 respondents. Figure 1 depicts a flow chart of respondents who met these inclusion criteria.

Measures

Cognition and Memory

The HRS are widely cited as excellent sources of data for use in examining cognitive trends and abilities of the aging US population (McArdle, Fisher, & Kadlec, 2007). Initial interviews are conducted face-to-face, and the majority of successive interviews are conducted via telephone unless respondents are older than 80 years of age. The cognitive battery of the HRS has been evaluated for internal consistency and validity (Langa et al., 2005), and performance on these measures has been shown to be stable from wave to wave, after controlling for cohort effects and test-retest bias (Rodgers, Ofstedal, & Herzog, 2003).

Episodic memory. The episodic memory domain was assessed by an immediate and delayed word recall task. These tasks are drawn from four categorized word recall lists of 10 English nouns that do not overlap in content. Word lists are randomly assigned to respondents at the initial interview. Longitudinally, each respondent is assigned a different set of words for each four successive waves of data collection. This counterbalanced approach ensures that each respondent is assigned to each word list only once over 4 waves of data collection, with

approximately 8 years passing before a respondent is reassigned to the same set of words as their initial interview.

Immediate word recall. To assess immediate word recall, the interviewer read a list of 10 words to each respondent, and respondents verbally recalled as many words as possible. The number of correctly recalled words is scored, with higher scores indicating better performance.

Delayed word recall. Approximately 5 minutes after the immediate word recall test, during which respondents answered questions about their emotional state and completed two mental status tasks (i.e., counting backwards and serial 7s), respondents were asked to recall the nouns previously presented as part of the immediate recall task. The number of correctly recalled words is scored, with higher scores indicating better performance.

Total word recall. The total word recall score represents the sum of the immediate and delayed word recall tasks, with scores ranging from 0 to 20 for HRS waves 1996 and onward.

Attention. The attention domain evaluated knowledge and orientation, and included the serial 7s subtraction task and backwards counting from 20.

Serial 7's. Respondents are asked to subtract 7 from 100 and continue counting backwards by 7s for five total trials. The number of correct subtractions is scored (0 – 5), with high scores indicating better performance.

Backwards counting. Respondents are asked to count backwards as quickly as possible for 10 total continuous numbers, starting with the number 20. A score of two points is given if the task is completed correctly on the first try; one point if answered correctly on the second try; zero points are given if the answer is incorrect on the first and second try.

Lifestyle Activities

Measures of lifestyle activities included two items from the HRS Health questionnaire and 18 items from the Lifestyle and Stress sub-module of the HRS Psychosocial and Lifestyle Leave-Behind questionnaire (LB). The two items from the Health questionnaire are part of the HRS Core interview, which is administered to HRS respondents every two years. These items measure self-reported frequency of participation in vigorous physical activity and light physical activity, scaled on a 5-point Likert scale (1 = every day to 5 = never). The LB was first launched in 2006, and was administered to a random (50%) subsample of participants who completed the face-to-face interview. In 2008, HRS participants who had not completed a face-to-face interview in 2006 were rotated into data collection. Longitudinal data is available in 4-year intervals, with the 2010 wave containing the first longitudinal data from the 2006 participants, and the 2012 wave containing the first longitudinal data from the 2008 participants.

Since the inaugural fielding of the LB, the 18 items of Lifestyle and Stress sub-module have undergone several revisions. The 2006 questionnaires included 8 dichotomous (yes/no) items that assessed whether respondents engaged in various activities, including taking a vacation within the US, going on day trips, owning a cell phone, and using the internet and/or email. In 2008, this measure was expanded to include 18 items measured by a 6-point Likert scale (1 = daily to 6 = not in the last month). These items covered a wider range of activities and frequency of participation, including playing sports or exercising, walking 20 minutes or more, attending an educational or training course, reading books or magazines, and playing word games. In 2010, two additional items were added to the list and the response scale was changed to 7-point scale, adding a "Never/Not relevant" category. A full list of activities, stratified by wave and year of data collection, is provided in Table 1.

Considering the methodological discrepancies across the different versions of the LB questionnaire and the rotated sample design, the current dissertation utilized items from the 2008 version of the LB questionnaire, in addition to the two items from the Health questionnaire. Using conventions from the HRS (Smith et al., 2013), composite scores were generated from the type and frequency of activities of the LB questionnaires. More specifically, the items directly referring to physical activity (i.e., play sports or exercise, walk for 20 minutes or more, engage in vigorous physical activity, engage in light physical activity) were categorized as "Physical Activities." All other items were categorized as "Cognitive/Social Activities." Regardless of when participants were originally recruited into the HRS, their self-reported frequency of participation in PA or CSA in 2008 served as the baseline lifestyle activity score for the current study. The scores were scaled according to frequency of self-reported participation, with higher scores representing higher levels of self-reported frequency of activity participation (see section on *Data Preparation and Statistical Analyses* for more details).

Genotyping

The genotyping process occurred in two stages. First, the DNA samples were genotyped using the Illumina Omni2.5-v1_D protocol. After this initial stage, an annotation issue within this manifest contributed to the reverse coding of the A/B alleles for 18,763 strand ambiguous SNPs (i.e., those with A/T or C/G alleles). In response to this error, the genotypes of the ambiguous SNPs were imputed using the IMPUTE2 software (Howie, Donnelly, & Marchini, 2009) at GCC. This process uses the haplotypes of a densely genotypes reference sample to impute the probability of the three genotypes (e.g., AA, AB, or BB) at each SNP for each individual in the sample population (CIDR Health Retirement Study Imputation Report).

Familial relatedness among HRS participants were calculated using a kinship coefficient and accounted for during the imputation process when possible (J. Faul, Smith, & Zhao, 2014). A more detailed description of the imputation process as well as quality control measures are available through dbGaP (database of Genotypes and Phenotypes; phs000428.v1.p1 and phg000207.v1); however, a brief description of the processes are necessary to justify the exclusion of certain genetic samples as well as to describe the quality of the imputed data.

Imputation quality control measures. Prior to the imputation process, several quality control filters were applied to the data (N = 12,507). Samples were excluded if they had a missing call rate (MCR) greater than 2% (n = 53). Additionally, to ensure a non-related population sample, samples were excluded if they demonstrated familial relatedness (n = 87). Minor allele frequency (MAF) was not included as a filter prior to imputation, with the exception of monomorphic SNPs (i.e., a SNP that exists in homozygous form, such as AA or BB, for a given population). After the application of these filters, 12,367 genotypes were imputed. Two additional measures of imputation quality were provided for all SNPs: measures of *information* and *certainty*. *Information* is a numeric estimation (range: 0 to 1) of the association between the observed statistical information and the allele frequency estimate and *certainty* represents the posterior probability (as a percentage with a range of 0 to 1) of best-guess phenotypes (J. Faul et al., 2014). It is recommended that SNPs with i*nformation* and *certainty* levels below .8 be excluded from analyses. These criteria were applied for the SNPs of interest for the current dissertation (i.e., *BDNF, COMT,* and *ApoE*) and resulted in the removal of 103 participants, yielding an initial sample of 12,264 participant profiles.

Estimation of Hardy-Weinberg equilibrium. The results of this PCA were also used to calculate an exact test of Hardy-Weinberg equilibrium (HWE) in the two largest population

samples: self-identified white (n = 8,652) and self-identified black (n = 1,519). The samples included in the HWE test were from individuals who were unrelated and had a MCR of less than 2%. The results indicated that both populations deviated from HWE, with a deviation of approximately .01 and .001. Further analyses of these results suggested that the deviations were not related to population structure; however, it was recommended to set a HWE significance threshold of p = .0001 for subsequent analyses (Weir, 2012).

Data Preparation and Statistical Analyses

A series of analyses were conducted a priori to evaluate data quality in the current sample, including calculations of sample size and statistical power, whether the genotypes were within HWE, the creation of a lifestyle activity composite scores, and the assessment of missing data. After the *a priori* analyses, multi-level modeling (MLM) was used to examine the independent and interactive effects of PA, CSA, and genotype on individual differences in baseline cognitive performance and rates of cognitive change over time. Also referred to as mixed effects models or latent growth models (Bauer, Preacher, & Gil, 2006; Luke, 2004; McArdle, 2009; Preacher, Curran, & Bauer, 2006), MLM permits researchers to predict the value of an outcome variable that depends on the function and interactions of multiple predictor variables (Luke, 2004; McArdle, 2009).

Sample Size and Statistical Power

Power analysis and sample size considerations for G x E analyses are not well articulated. Evidence for G x E interactions increases dramatically when scanning through millions of possible genetic interactions (increasing the risk for a Type I error); however, studies can be

underpowered if genetic variants are insufficiently represented in the sample population (McArdle & Prescott, 2010). Power calculations were conducted a priori using G*power3 (F. Faul, Erdfelder, Lang, & Buchner, 2007) to estimate the sample size needed to detect the effects of two-way (e.g., G x E) and three-way (e.g., G x E x Time) interactions for cognitive outcomes. Power analyses revealed that a minimum sample size of 1,199 participants would be required to detect a small effect size (.10) with 80% power in two-way (or higher) interactions between groups (i.e., fixed effects) at the 5% significance level. In MLM, it has been estimated that a 4-fold increase in sample size is required to detect a 3-way interaction effect of the same magnitude as a 2-way interaction effect (Heo & Leon, 2010). The sample used in the current dissertation (n = 4,764) is sufficiently large enough to detect independent effects (i.e., genotype, participation in lifestyle activities) and interactive effects (i.e., G x E, G x E x time).

Evaluation of Hardy-Weinberg Equilibrium

Chi-square goodness of fit tests were used to calculate whether the observed allele frequencies within the sample were significantly different from the populations-based expected allele frequencies. The genotype distributions for each race and the results of the chi-square tests are reported in Table 2. The estimates for the current sample fall within the recommended p = .0001 significant threshold (Weir, 2012), and suggest that observed genotype frequencies of the sample are not significantly different from what would be expected in the general population. The *COMT* allele frequencies depart from HW equilibrium for blacks, with fewer observed *COMT* non-Val carriers than expected (p < 8.18e-7). This result could potentially be attributed to a number of factors, including chance, errors in the genotyping process, lack of power, population stratification, or a combination of these reasons (Hosking et al., 2004); however, there

is little guidance on how to identify the underlying cause of departure of HW (Wittke-Thompson, Pluzhnikov, & Cox, 2005). Thus, the analyses involving all genotypes, including *COMT*, were conducted using a diverse sample (whites and blacks together) as well as a stratified samples (whites and blacks only) to estimate if this departure from HW contributed to substantially different results.

The *ApoE* genotypes were categorized as *ApoE* ε4 carriers and *ApoE* non-ε4 carriers. Given the evidence associating the detrimental effects of the ε4 allele, the *ApoE* ε4 carriers were considered carriers of the "at-risk" *ApoE* genotype (Reynolds et al., 2006; Runge et al., 2014; Wisdom et al., 2011). The *COMT* genotypes were categorized as *COMT* any-Val carriers and *COMT* non-Val carriers. Given the evidence associating the detrimental effects of the Val *COMT* allele (de Frias et al., 2005; Greenwood, Lin, Sundararajan, Fryxell, & Parasuraman, 2014; Papenberg et al., 2014), the *COMT* any-Val carriers were classified as the "at-risk" *COMT* genotype. The *BDNF* genotypes were categorized as *BDNF* any-Met carriers and *BDNF* non-Met carriers. The Met allele of *BDNF* is considered detrimental (Das et al., 2014; Egan et al., 2003; Kim et al., 2011), thus the any-Met carriers are referred to as the "at-risk" *BDNF* genotype.

Measurement of Lifestyle Activities

CSA and PA levels were measured by the 18 items from the 2008 LB questionnaire plus two items regarding physical activity from the Health questionnaire. All items were rescaled such that higher responses were indicative of higher participation levels. The Cronbach's alpha coefficient for the 20 items was .71, indicating moderate levels of internal consistency and reliability among the items (Bland & Altman, 1997). Individual item-test correlation (ITC)

coefficients were evaluated to determine if the removal of individual items would increase the alpha coefficient to a more acceptable level (e.g., .8 or higher). ITC coefficients ranged between .24 and .55, with two items demonstrating ITCs below .30 (.23 and.29, respectively). The removal of these items would only increase the overall alpha by .003; therefore, all items were retained to create the composite measures of PA and CSA. Composite measures have the ability to reduce measurement error and to represent complex concepts by combining multiple variables into a single measure (Hair, Black, Babin, & Anderson, 2010). Although the most common approach is to take the average of the items in the scale (Hair et al., 2010), one of the primary objectives of the current dissertation was to examine the effects of different types of lifestyle activities. Thus, two composite scores were generated: one representing the composite score for PA and a second representing the composite score for CSA.

Description of Multi-Level Models

The multi-level analyses were modeled with the measurement observations for each wave (Level 1) nested within individuals (Level 2). As such, the intercepts of each cognitive measure were modeled as a function of individual characteristics. The Level 1 (L1) component represents inter-individual change in cognitive performance from 2008 to 2012 and the Level 2 (L2) component represents between-person differences in cognitive performance (Singer & Willett, 2003). Each model also estimates two error components: The L1 variability, or the amount of variance that occurs within each individual from wave to wave, and the L2 variability, or the amount of variance between individuals. As recommended by Aguinis, Gottfredson, and Culpepper (2013), the significance of the parameter estimates were evaluated based on the range of the confidence intervals (i.e., lower-bound intervals that do not include zero are significant).

The overall improvement in model fit was estimated by computing the change in explained variance at L1 and L2 (i.e., pseudo R^2; Raudenbush & Bryk, 2002).

Prior to analyses, cognitive performance scores were converted to T-scores (M = 50, SD = 10) to allow comparisons across tasks. Tasks that demonstrated significant non-normal distributions (i.e., Serial 7's and Backwards Counting) were log-transformed to the base of 10, as recommended for positively skewed distributions (Howell, 2010).

Unconditional model (Model A). Performance on each cognitive measure was initially evaluated using unconditional models (Model A). Model A allows for the calculation of baseline between-person differences in cognitive performance or within-person changes in cognitive performance over time. Model A also provides the intraclass correlation coefficient (ICC), or the measure of the proportion of variance in cognitive performance score that can be attributed to differences between individuals (Luke, 2004). An ICC greater than 25% suggests that the variability between individuals can be explained by differences in between-person predictors (Singer & Willett, 2003).

Unconditional growth model (Model B). The next model that was estimated was an unconditional growth model, which allows for cognitive scores to change, or vary, over multiple time points (i.e., time is the only predictor of change). By adding in the potential for scores to change over time, three additional sources of variability are estimated: within-person variability, between-person variability in baseline cognitive performance, and between-person variability in slope or rate of change. The evaluation of these variance components help clarify whether significant individual differences exist due to differences in initial status or in rates of change over time (Singer & Willett, 2003).

Conditional growth model (Model C). Model C is a conditional growth model with random intercepts and random slopes, and represents the first model to examine sources that have the potential to explain variability at baseline and change in performance for five measures of cognitive ability: immediate word recall, delayed word recall, total word recall, serial 7s, and backwards counting. Age at baseline, sex, race, and years of education, time, genotype, and baseline participation in CSA and PA served as fixed time-invariant effects at the individual (L2) level. Ethnicity was not included as a covariate due to the small portion of the sample that identified as Hispanic (<7%). In this model, the effect of time is also fixed. The purpose of this model is to determine whether the intercepts (i.e., means scores) of cognitive performance are predicted by L2 variables while assuming the effect of time is constant across all individuals. Non-zero slope parameter estimates suggest the effect of time significantly influences strength of relationship between the predictor variables and cognitive performance (Aguinis et al., 2013).

Random intercepts with random slopes and cross-level interactions (Model D). Model D examined the cross-level baseline and longitudinal effects between type of activity, genotype, and time based on previous research that has noted such interactions between genotype and cognition (Runge et al., 2014). While some researchers advise against testing for cross-level interaction effects if the slope variance between individuals is not different from zero, others argue that one should proceed with cross-level interaction models if there is strong rationale for a specific hypothesis (Aguinis et al., 2013). The purpose of these two final models are to determine whether the variance in slopes between individuals can be explained by interactions between these two predictor variables as well as to compare the parameter estimates generated by two different covariance structures.

Estimation of covariance parameter structure. Due to the longitudinal nature of the data, all models were fitted with a first-order auto-regressive (AR-1) covariance structure. Longitudinal data are more likely to exhibit proximal autocorrelation between measurement waves, a phenomenon that occurs when adjacent waves of measurement are more highly correlated than non-adjacent waves (Goldstein, Healy, & Rasbash, 1994; Shumway & Stoffer, 2011; Singer & Willett, 2003). This violates the assumption of independence and homogeneity for within-individual variability and may result in biased standard error estimates in unstructured covariance structures (Kwok et al., 2008; Shumway & Stoffer, 2011).

Model that are fitted with the AR(1) covariance structure yield a parameter estimate known as the auto-correlation coefficient (ρ), which represents the correlation between the first and second measurement waves (Shumway & Stoffer, 2011). The presence of significant ρ is an indication that there is significant variability in the error structure after accounting for the fixed and random effects that occur within the model (Singer, 1998). If there are weak correlations between the time points for the AR(1) model, then it is reasonable to assume independence between the residuals (Shumway & Stoffer, 2011).

CHAPTER FOUR:

RESULTS

Demographic Characteristics

Respondent demographic characteristics are shown in Table 3, stratified by genetic risk category for each gene (i.e., *ApoE*, *COMT*, and *BDNF*). Independent sample t-tests, Pearson's chi-square tests, and analyses of variance (ANOVA) were used, where appropriate, to examine the relationship between participant characteristics (i.e., age at 2008, years of education, sex, race, and risk status for *ApoE* ε4, *COMT*, and *BDNF*) and vital status (i.e., whether the participant was alive) at the 2012 follow-up. The results of these analyses are first presented as a collective summary of the sample, then as comparisons between genetic risk status for each single gene (e.g., *ApoE* ε4 carriers compared to *ApoE* non-ε4 carriers).

Collective Summary of Demographic Characteristics

Overall, respondents were an average of 69.73 years old in 2008 (SD = 9.52), predominately female (n = 2,828; 59.36%), non-Hispanic (n = 4,439; 93.18%), white (n =4,199; 88.14%), and averaged nearly 13 years of education (SD = 4.11). Compared to individuals who died prior to the 2012 follow-up wave, individuals who were alive were significantly younger at 2008 (M = 68.78, SD = 9.13 versus M = 76.52, SD = 10.02, respectively), t (4,762) = 18.96, p <.001. Individuals who were alive also reported significantly more years of education (M = 12.87, SD = 3.99) compared to those who died (M = 12.17, SD = 4.82), t (4,762) = -3.84, p

<.001. The difference in the proportion of men and women who were alive in 2012 compared to 2008 was significant, .85 versus .90, (X^2 (1, N = 4,764) = 21.60, p < .001).

Between-Genotype Comparisons

Prior to the between-genotype comparisons, the genotypes for *ApoE*, *COMT*, and *BDNF* were categorized as "at-risk" genotypes and "low risk" based on the literature examining the relationship between each genotype and cognitive performance. The categorizations of each genotype can be viewed in Table 3. Significant relationships were found between each genotype and race; however, this is expected considering allele frequencies vary across subpopulations of different ancestry (i.e., population stratification).

There were no significant differences between *ApoE* ε4 carriers and *ApoE* non-ε4 carriers in regard to baseline age, sex, ethnicity, years of education obtained, vital status, or self-reported frequency of participation in CSA or PA. Significant relationships were found between *ApoE* genotype and race, X^2 (1, N = 4,764) = 20.71, p < .001, with a higher percentage of blacks possessing the at-risk *ApoE* ε4 allele than whites (approximately 35% compared to 26%, respectively).

COMT non-val carriers were significantly younger than *COMT* any-Val carriers, t (4,762) = -2.33, p = .02. Significant relationships were found between *COMT* genotype and race, X^2 (1, N = 4,764) = 141.07, p < .001, with a higher percentage of whites possessing the at-risk *COMT* Val allele compared to blacks (approximately 76% compared to 53%, respectively). A significant relationship was also found between *COMT* genotype and ethnicity, X^2 (1, N = 4,764) = 7.27, p = .007, with a higher percentage of non-Hispanics possessing the Val allele compared to Hispanics (approximately 74% compared to 67%, respectively). No significant relationship

was found between *COMT* genotype, sex, years of education, vital status, or self-reported frequency of participation in baseline PA or CSA.

There were no significant differences between *BDNF* any-Met carriers and *BDNF* non-Met carriers in regard to baseline age, sex, or ethnicity. *BDNF* non-Met carriers reported significantly fewer years of education compared to *BDNF* Met-carriers, t (4,762) = -2.40, p = .016. As with *ApoE* and *COMT*, a significant relationship between *BDNF* genotype and race was found, X^2 (1, N = 4,764) = 190.54, $p < .001$, with a greater percentage of whites possessing the at-risk *BDNF* Met allele than blacks (approximately 36% compared to 7%, respectively). No significant differences were found between *BDNF* Met-carriers and non-Met carriers in regard to self-reported frequency of baseline PA. Met-carriers were significantly more likely to engage in baseline CSA than non-Met carriers, t (4,762) = -2.03, p = .04, with Met-carriers reporting an average of 2.61 units of activity compared to 2.56 units of activity for non-Met carriers.

To determine whether the association of genotype and cognition difference by race, separate two-way ANOVA were conducted to evaluate the mean group differences in cognitive task performance between genotype, race, and the interaction between genotype and race. The results (presented in Table 4) indicate the main effects of genotype were not significant. While the main effect of race was significant for all cognitive tasks, there were no significant interactions between race and genotype. The main effect of race was controlled by entering it as a covariate in the conditional MLMs (Models C and D in subsequent section).

Multi-Level Models Examining the Independent and Interactive Effects of Lifestyle Activity, Genotype, and Covariate Predictors on Cognitive Performance

Four sets of MLMs were conducted to examine the concurrent, longitudinal, and interactive effects of genotype and baseline participation in CSA and PA on performance in five cognitive measures (immediate recall, delayed recall, total recall, serial 7s, and backwards counting). Each set included an unconditional means model (Models A), an unconditional growth model (Models B), a conditional growth model (Models C), and a conditional growth model with cross-level interactions (Models D). The primary difference between each MLM set is the genotype that was included as a predictor variable in Models C and D: Each set examined the impact of an individual gene (i.e., *ApoE, COMT,* and *BDNF*). Due to the absence of predictor variables in Models A and B, the results of these models are uniform across the three sets of MLMs. These results are reported in the subsequent section to serve as a baseline index to compare the results of Models C and D for each set. The results of Models C and D for each set are presented in Tables 5a – 5b, 6a-6b, and 7a-7b, respectively.

Models A and B: Unconditional and Unconditional Growth Models

The ICC estimates for Models A were .51, .54, .57, and .67 for the immediate, delayed, total recall, and serial 7's tasks, respectively. These estimates suggest that 51 – 67% of the variability in these scores was related to between person variations. The ICC for the backwards counting task was the lowest among the cognitive measures at 25% but this estimate is still large enough to explore between-individual predictors as potential sources of variability at the between-person level (Singer & Willett, 2003). Adding time as a fixed predictor in Models B generally improved overall model fit from Models A. Scores for immediate, delayed, and total

recall decreased significantly by .34, .36, and .41 units per year, respectively. Scores for the serial 7s task decreased by .01 log-units while the backwards counting task increased significantly by approximately .01 log-units.

When examining the variance parameters of Models A, significant between-individual variability is present at the intercept and slope for all measures. When comparing the within-individual variance estimates from Models A to those of Models B, modest reductions are found. More specifically, the effect of time accounts for approximately 10% of the within-individual variation for the immediate and delayed recall tasks, 12% for the total recall task, and 9% for backwards counting task. For the serial 7s task, the effect of time is not different from zero. The estimates of the between-individual variance parameters increased slightly from Models A to Models B, resulting in negative parameters for the amount of explained between-level variance. This result suggests that the sources of variability are likely to be concentrated at the between-individual levels (Singer & Willet, 2003). The auto-correlation coefficients of Models B were not significant and relatively small, ranging from -.13 to -.16 for the recall tasks and .03 and -.01 for the serial 7's and backwards counting tasks, respectively.

Set 1, Models C: Conditional Growth Models with *ApoE*, Activity, and Covariate Predictors

Models C in Table 5a and 5b include the results for the conditional growth models that included *ApoE* genotype, baseline CSA and PA, and covariates as predictor variables. Compared to Model B, the addition of covariates (i.e., age, sex, race, years of education), *ApoE* genotype, and frequency of participation in CSA and PA significantly improved model fit for all cognitive measures. Significant main effects for *ApoE* genotype and baseline participation in CSA and PA

were seen for all cognitive measures except for the backwards counting task. *ApoE* ε4-carriers scored between .96 – 1.16 units below the mean for immediate, delayed, and total recall tasks, and .02 log-units lower on the serial 7s task. Individuals who reported higher levels of baseline CSA scored approximately .65 - .70 units above the mean for the immediate, delayed, and total recall tasks, as well as a .01 log-unit increase in scores for the backwards counting task. Similar effects were seen for PA activity levels, with increased PA predicting higher word recall scores by 1.11 – 1.20 units and higher serial 7s scores by .01 log-units.

Among the covariates that influenced cognitive performance, older age was associated with worse performance on all cognitive tasks except backwards counting. For every one-year increase in age, the expected scores for immediate, delayed, and word recall decreased by .46 to .59 units, and the expected scores for the serial 7s task decreased by approximately .01 log-units. Female gender was associated with better scores on the three recall tasks, with scores 3.27 to 3.58 units higher than male scores. For the serial 7's tasks, female scores were approximately .04 log-units lower than male scores. Gender was not significantly associated with performance on the backwards counting task. Race and years of education were the only covariates that significantly influenced all cognitive measures. The average performance scores for black participants were significantly lower than those of white participants, ranging from 1.42 to 2.93 units lower for the three recall tasks, and .10 and .14 log-units lower for the backwards counting and serial 7s tasks. In regard to education, the scores for immediate, delayed, and total recall tasks increased by .51, .46, and .51 units per each year of education obtained beyond 12 years (i.e., high school graduate). Scores in the serial 7's and backwards counting tasks increased by .01 log-units for each additional year of education obtained.

When examining the variance parameters, the addition of the predictor variables explained an additional 18 - 26 % of the between-individual variability across all cognitive scores except for the backwards counting task. The predictor variables also explained small percentages of the within-individual variability for immediate, delayed, and total recall score (1-4%) and the backwards counting task (5%). In regard to the serial 7s tasks, the additional variance explained at the within- and between-individual levels was no different from zero. Significant slopes (i.e., rate of within-individual change) were found for immediate, delayed, and total recall (τ_{11} =2.17, τ_{11} =1.18, and τ_{11} =1.63, respectively) and backwards counting (τ_{11} =.01). The slope for the serial 7s task was not significant (τ_{11} = 7.38e-07). The auto-correlation coefficients of Models C were significant for the immediate, delayed, and total recall tasks but not the serial 7s or backwards counting tasks. These parameters indicate that individual scores on the recall tasks were much more likely to vary over time, whereas individual scores on the serial 7s and backwards counting tasks were more stable. However, the strength of these correlations is relatively small. When evaluating the model fit parameter estimates as well as the variance parameter estimates, the inclusion of the predictor variables resulted in a substantially improved model fit for all cognitive tasks.

Set 1, Models D: Conditional Growth Model with Cross-Level Interactions Between *ApoE*, Activity, and Covariate Predictors

Model D include the same predictor variables as Model C, but allows for cross-level interactions between the predictor variables while allowing the effect of time to vary randomly between individuals. The main effects of the covariates (age, gender, race, and years of education) in Models D were nearly identical to those seen in Models C. The relationship

between baseline cognitive performance and *ApoE* genotype were not significant; however, higher baseline levels of CSA and PA were associated with significantly better cognitive performance in the three word recall tasks and the serial 7s task.

Baseline participation in CSA significantly predicted performance in the backwards counting task, but this relationship was not seen for PA. Longitudinally, significant interaction effects were found between baseline CSA activity and time for immediate recall, total recall, and backwards counting. This interaction represents the effect of time on immediate and total recall performance across individuals when participation in baseline CSA increases by one unit. The negative direction of these interaction estimates also indicates that the effect of time is less strongly associated with cognitive performance in individuals who report higher levels of baseline CSA compared to individuals who report lower levels of baseline CSA. In regard to immediate recall scores, the effect of time is expected to be 1.71 for the average participant, but even though this estimate is not significant, the relationship between time and immediate recall scores becomes weaker by -.33 units as an individual's baseline participation in CSA increases by one unit. Similarly, for backwards counting, the main effect for time is not significant, but the relationship between time and backwards counting scores weakens by .01 log-units for each log-unit increase in baseline CSA levels. Finally, there was a significant main effect of time as well as the interaction effect between time and baseline CSA for total recall. The average total recall score is expected to increase by 1.25 units per year but this relationship weakens by .22 units for every one unit increase in baseline CSA.

When examining the variance parameters, the inclusion of the cross-level interactions among predictor variables did not account for any additional within-individual variability for any of the cognitive tasks. In regards to explaining between-individual variation in cognitive scores,

the inclusions of the cross-level interactions among the predictor variables explained an additional 1-4% of the variability for the three recall tasks, but did not explain any additional variability for the serial 7s and backwards counting tasks. The auto-correlation coefficients remained unchanged from Models C. Overall, when comparing the estimates for the differences in explained within- and between-person variance, the addition of the cross-level interaction factors in Models D offer little to no improvement in overall model fit.

Set 2, Models C: Conditional Growth Models with *COMT*, Activity, and Covariate Predictors

Models C in Table 6a and 6b include the results for the conditional growth models that included *COMT* genotype, baseline CSA and PA, and covariates as predictor variables. Compared to Model B, the addition of covariates (i.e., age, gender, race, and years of education), *COMT* genotype, and frequency of participation in CSA and PA significantly improved model fit for all cognitive measures.

In regard to the main effects of the covariates, older age was associated with poorer cognitive performance on all measures except backwards counting. For every one-year increase in age, predicted scores decreased by .45 to .58 units for the word recall tasks and by .01 log-units for the serial 7s task. Gender was significantly associated with all cognitive tasks except backwards counting. The average female scores were higher than male scores on the three recall tasks by 3.34 to 3.63 units, but lower on the serial 7's tasks by .04 log-units. The effect of education was significant, with each additional year of education corresponding with better scores for all measures. The effect of race was also significant for all measures, with black participants scoring significantly lower than whites by 1.51 – 3.03 units for the word recall tasks

and .11 – .14 log-units for the serial 7s and backwards counting tasks. Finally, the effect of time was significant for immediate recall only, where each wave of measurement was associated with a .80 increase in immediate recall performance.

No significant main effects of COMT genotype were found for any cognitive measure. Baseline participation in CSA and PA had significant main effects on all measures except for the backwards counting task. Individuals who reported higher levels of baseline CSA scored approximately .62 - .67 units above the mean for the immediate, delayed, and total recall tasks, as well as a .01 log-unit increase in scores for the serial 7s task. Higher levels of PA predicted better scores by 1.08 – 1.18 units for the recall tasks and by .01 log-units for the serial 7s task.

When examining the variance parameters, an additional 18 – 26% of the between-individual variability was explained by the inclusion of the predictor variables into the models for the three recall tasks and the serial 7's task. The change in between-individual variability for the backwards counting task was not different from zero. The inclusion of the predictor variables explained small percentages of the within-individual variability for the three recall tasks (1-4%) and the backwards counting task (5%), but not for the serial 7s task. The rate of within-individual change was significant for immediate, delayed, and total recall (τ_{11} =2.13, τ_{11} =1.35, and τ_{11} =1.80, respectively) and backwards counting (τ_{11} =.01), but not for the serial 7s task (τ_{11} = 2.92e-06). The presence of significant auto-correlation coefficients for the immediate, delayed, and total recall tasks indicate that scores on these tasks were more likely to fluctuate over time, although the correlations are fairly weak. The non-significant auto-correlation coefficients for the serial 7s and backwards counting tasks suggest that performance on these tasks were more stable. When evaluating the model fit parameter estimates as well as the

variance parameter estimates, the inclusion of the predictor variables resulted in a substantially improved model fit for all cognitive tasks.

Set 2, Models D: Conditional Growth Model with Cross-Level Interactions Between *COMT*, Activity, and Covariate Predictors

The main effects of the covariates (age, gender, race, and years of education) in Models D were similar to those seen in Models C. The main effect of *COMT* genotype was not significant for any cognitive measure. Higher levels of baseline CSA and PA predicted significantly better performance on all cognitive measures except for the backwards counting task. A significant baseline interaction effect was found for *COMT* genotype and CSA participation for the backwards counting task. The sample was stratified by *COMT* genotype to further explore the effects of the presence or absence of the *COMT* Val allele. The results indicate that the effect of baseline participation in CSA significantly predicted baseline backwards counting scores for *COMT* any-Val (i.e., at-risk) carriers only. Consistent with the proposed hypothesis, *COMT* any-Val carriers who reported more frequent participation in CSA tended to have higher backwards counting scores (b = .02, p = <.001); this effect was not seen for non-Val carriers (b = -.01, p = .53). The effect of time on backwards counting scores was weakened by higher levels of CSA for *COMT* any-Val carriers (b = -.02, p <.001) but not for non-Val carriers (b = .004, p = .68).

Longitudinally, one significant interaction effect was seen for *COMT* genotype and performance on the serial 7s task with *COMT* any-Val carriers scoring .03 log-units lower over time compared to *COMT* non-Val carriers. This interaction represents the effect of time on serial 7s performance as the genetic risk of *COMT* increases by one unit (i.e., low-risk carriers

compared to at-risk carriers). Given that time has a significant main effect on serial 7s performance, with the average participant scoring .03 log-units higher per log-unit increase in time, the negative interaction between *COMT* genotype and time indicates the relationship between time and serial 7s scores weakens by .03 log-units for carriers of the at-risk *COMT* genotype.

When examining the variance parameters of the collective sample, the inclusion of the cross-level interactions among predictors decreased the amount of within-individual variability for the recall tasks, but explained an additional 3-4% of between-individual variability for immediate and total recall. For the serial 7s and backwards counting tasks, the amount of additional explained within-individual and between-individual variability was not different from zero. The auto-correlation coefficients are nearly identical those found in Models C.

Overall, when comparing the estimates for the differences in explained within- and between-person variance, the addition of the cross-level interaction factors in Models D offer little to no improvement in overall model fit.

Set 3, Models C: Conditional Growth Models with *BDNF*, Activity, and Covariate Predictors

Models C in Table 7a and 7b include the results for the conditional growth models that included *BDNF* genotype, baseline CSA and PA, and covariates as predictor variables. Compared to Model B, the addition of covariates (i.e., age, gender, race, and years of education), *BDNF* genotype, and frequency of participation in CSA and PA significantly improved model fit for all cognitive measures.

As with the models investigating *ApoE* and *COMT*, older age was associated with poorer cognitive performance on all measures except backwards counting. Performance in the word recall tasks and serial 7s task decreased by .45 – .58 units and .01 log-units, respectively, for each one-year increase in age. Female scores on the recall tasks were significantly higher compared to male scores (3.33 – 3.49 units), but significantly lower than males on the serial 7s task (-.04 log-units). No significant gender effects were found for backwards counting. Significant effects of education were found across all measures, as each additional year of education predicted an increase in score by .46 – .51 units for the recall tasks and .01 log-units for the serial 7s and backwards counting tasks. Significant effects were also found for race, as black participants were predicted to score significantly lower than whites by 1.42 – 2.88 units for the word recall tasks and .12 – .14 log-units for the backwards counting and serial 7s tasks. Time had a significant effect for performance in the immediate recall task only, where measurement wave predicted a .80 unit increase in score.

Significant main effects of *BDNF* genotype and type of activity were found for several cognitive tasks. In regard to genotype, *BDNF* any-met carriers scored .48 units higher on delayed recall and .01 log-units higher on serial 7s and backwards counting than *BDNF* non-met carriers. In regard to the effect of each activity, the effect of higher levels of baseline participation in CSA and PA were significant for measures except backwards counting. More specifically, performance in the word recall tasks increased by .62 - .67 units for each unit increase in CSA activity and 1.09 – 1.18 units for each unit increase in PA. Similarly, a .01 log-unit increase in scores for the serial 7s task was significantly predicted for each unit increase in CSA and PA.

In regard to the variance parameters, the inclusion of the predictor variables increased the amount of between-individual variability explained by 17 – 19% for the three word recall tasks and 26% for the serial 7s task. The amount of additional between-individual variance explained for the backwards counting task was not different from zero. The amount of variance explained at the within-individual level ranged from 1 – 4% for the three recall tasks, as well as the backwards counting task. The amount of additional within-person variance explained for the serial 7s task was not different from zero. The presence of significant slopes for all cognitive tasks indicated that the variability of within individual scores increased the immediate, delayed, and total recall tasks (τ_{11} =2.19, τ_{11} =1.43, and τ_{11} =1.87, respectively) as well as the backwards counting (τ_{11} =.01) and the serial 7s task (τ_{11} = 2.81e-06). The auto-correlation coefficients were significant for the three recall tasks, but not the serial 7s or backwards counting task. These results indicate that performance on the recall tasks were more likely to fluctuate across measurement waves, whereas performance on the serial 7s and backwards counting tasks was more stable across measurement waves. Overall, the inclusion of the predictor variables resulted in a substantially improved model fit for all cognitive tasks.

Set 3, Models D: Conditional Growth Model with Cross-Level Interactions Between *BDNF*, Activity, and Covariate Predictors

The main effects of the covariates (age, gender, race, and years of education) in Models D were similar to those seen in Models C. In regard to the main effect of *BDNF* genotype, any-Met carriers scored significantly higher on the delayed and total recall tasks (2.52 and 2.50 units) as well as the serial 7s and backwards counting tasks (.01 log-units) compared to *BDNF* non-Met carriers. The main effects of baseline CSA and PA were significant for cognitive measures

except for the backwards counting. For each unit increase in CSA, the predicted scores increased by 0.81 – 2.52 units for the recall tasks, .01 log-units for the serial 7s task, and .03 log-units for the backwards counting task. Similar increases were seen for each unit increase in PA for all tasks except backwards counting. The baseline interaction effects between *BDNF* genotype and activity type were not significant.

Several longitudinal effects were found. First, the interaction effect between baseline CSA activity and time was significant for immediate recall, total recall, and backwards counting. More specifically, the significant effect of time for immediate and total recall scores weakens by .43 and .29 units as an individual's baseline participation in CSA increases by one unit. Similar results are seen for the backwards counting task, where the effect of time on backwards counting scores is reduced by .01 log-units for each log-unit increase in CSA. A single three-way interaction between time, *BDNF* genotype, and CSA was found. To further understand the relationship between *BDNF* genotype and CSA, the analyses were stratified by genotype.

For *BDNF* any-Met carriers, the effect of higher baseline participation in CSA on backwards counting scores was not significant (b = .002, p = .897). Longitudinally, the relationship between CSA levels and time was also not significant (b = -.002, p = .86). However, a different pattern of results was found for *BDNF* non-Met carriers. Primarily, the effect of baseline CSA participation was significant, such that backwards counting scores increased by .02 log-units for every unit increase in CSA (p = .009). The interaction between time and CSA participation was also significant (b = -.01, p = .007), and indicates the effect of time on backwards counting scores became weaker when baseline participation in CSA increased by one unit.

In regard to the variance parameters of Models D, the inclusion of the cross-level interactions among the predictor variables explained an additional 8 – 9% of the within-individual variability for the recall tasks, but these additional parameters decreased the amount of explained between-individual variance. The amount of additional explained within-individual and between-individual variability was not different from zero for the serial 7s and backwards counting tasks. The auto-correlation coefficients are nearly identical those found in Models C. Overall, when comparing the estimates for the differences in explained within- and between-person variance, the addition of the cross-level interaction factors in Models D offer little to no improvement in overall model fit.

CHAPTER FIVE:

DISCUSSION

The current dissertation examined how environmental and genetic factors influenced cross-sectional differences and longitudinal change in cognitive performance in a group of select older adults, including whether the presence of detrimental genetic variants made individuals differentially responsive to environmental factors (e.g., lifestyle activities). The following discussion will describe how the results of the analyses relate to the proposed questions and hypotheses. Specifically, performance in five cognitive measures was associated with: (a) baseline participation in physical activities (PA) and cognitive/social activities (CSA); (b) the presence of risk alleles from three genetic polymorphisms, Apolipoprotein E (*ApoE*), Catechol-O-Methyltransferase (*COMT*), and Brain-derived Neutrophic Factor (*BDNF*); (c) the interactive effects between the types of activity and risk alleles. Finally, the following discussion will conclude with an overall summary of the results, including limitations and future directions.

Question 1: How does frequency of participation in two types of lifestyle activities (PA and CSA) influence individual cognitive performance?

In line with the cognitive plasticity and flexibility framework (Lövdén et al., 2010), it was hypothesized that increased frequency of baseline participation in PA and CSA would predict significantly better baseline and longitudinal cognitive performance in measures of episodic memory and attention. As predicted, the positive influence of these lifestyle activities were seen across all models, after controlling for age, race, gender, and years of education. Both

types of activity significantly predicted baseline cognitive performance in nearly all measures with greater activity being associated with better performance. Longitudinally, the protective effect of CSA on cognitive performance was evident for the measures of immediate word recall, total recall, and backwards counting. No longitudinal effects of PA were found. The implications of these results are described in further detail in the following sections. Generally, these findings support the majority of research investigating the relationship between various types of lifestyle activities and cognitive health in aging populations (Prakash, Voss, Erickson, & Kramer, 2015; Wang, Xu, et al., 2012; Woodard et al., 2012), but not all have found a relationship with cognitive change.

Physical Activity and Cognitive Performance

In the current dissertation, there was evidence of the beneficial effect of baseline PA on concurrent cognitive performance, after controlling for age, gender, race, and years of education. More specifically, each unit increase of participation in PA corresponded with increases in word recall scores and serial 7s scores by approximately 1.00 – 1.30 units and .02 – .03 log-units, respectively. These results are consistent with those from other cross-sectional studies (Ballesteros, Mayas, & Reales, 2013; Huang, Dong, Zhang, Wu, & Liu, 2009; Middleton, Barnes, Lui, & Yaffe, 2010), although it is important to note these effects may vary by population characteristics (Huang et al., 2009) or study design (Steinberg et al., 2015).

Although the current dissertation identified concurrent effects of PA, no longitudinal effects were found, which contradicts the results of most studies that consistently support the protective relationship between PA and cognitive performance. A recent meta-analysis of 247 cross-sectional and cohort studies (n > 300 participants per study) investigated the association

between various modifiable risk factors and cognitive performance and/or dementia (Beydoun et al., 2014). Twenty-four of these 247 studies represented cohort studies that included PA as a primary risk factor for cognitive decline, and approximately 88% of these studies reported evidence of the protective relationship between higher levels of PA and cognitive health (Beydoun et al., 2014). Additionally, it is possible that other aspects of the current dissertation (e.g., the select nature of the study sample or the definition of PA) may contribute to study bias (see *Limitations* for more information).

Nevertheless, the results of the current dissertation support the notion that PA may improve cognitive performance to a moderate extent. This may be particularly important for tasks that involve the prefrontal cortex and hippocampus (Prakash et al., 2015). These areas of the brain, which play a key role in memory and attention, are particularly susceptible to the effects of aging (Cabeza, Nyberg, & Park, 2005). In line with the cognitive plasticity and flexibility theory (Lövdén et al., 2010), PA may stimulate neurocognitive plasticity factors that are associated with cognitive performance, such as increased production of the BDNF protein, improved neuronal connectivity, and decreased hippocampal atrophy. These studies, which emphasize measurement of biomarkers or other neurological traits in relatively small study samples, provide valuable evidence regarding the physiological mechanisms of cognitive plasticity that guide the interpretation of cross-sectional general population studies, including the current dissertation. Overall, the protective effect of PA on cognitive decline and dementia has been identified across multiple studies, despite notable limitations including the absence of a standardized definitions of PA, differences in study populations, and variable use of cognitive assessments (Baumgart et al., 2015; Wang, Xu, et al., 2012).

Cognitive/Social Activity and Cognitive Performance

The results of the current dissertation support the hypothesis that baseline participation in CSA is beneficial to cognitive performance. After controlling for the effects of covariates, greater frequency of baseline CSA predicted better concurrent cognitive performance across all measures. These results are similar to those from other cross-sectional studies which have examined the relationship between cognitive performance and various types of mental activity (Runge et al., 2014; Wilson et al., 2002). Longitudinally, the protective effect of baseline CSA was seen for measures of episodic memory (i.e., immediate and total recall) and attention (i.e., backwards counting). These results also support the findings of a number of longitudinal studies that purport the protective relationship between participation in CSA and better neurocognitive health, including cognitive decline (Valenzuela et al., 2008; Wilson et al., 2002) and incident dementia (Valenzuela & Sachdev, 2007; Verghese et al., 2003; Wang, Gustafson, et al., 2012; Wilson et al., 2002).

The beneficial effects of CSA on cross-sectional cognitive performance has been reported in several studies (Bielak et al., 2012; Mitchell et al., 2012). This result may be attributable to preserved differentiation, or the concept that individuals with higher cognitive abilities are more likely to engage in more complex lifestyle activities (Salthouse et al., 2002). As such, it is possible that between-person differences in levels of activity are simply a reflection of differences in inherent cognitive abilities (see Limitation for further discussion). However, there is also evidence that suggests that declines in activity participation precedes declines in cognitive performance (Small et al., 2012). This latter result suggests that although CSA may not necessarily improve cognitive function, it may play a crucial role in the preservation of cognitive abilities, especially in old age.

Similar to PA, the protective aspect of CSA may be the result of beneficial neuroplastic changes that are stimulated through CSA. While participation in CSA has been repeatedly correlated with increased neurogenesis and other beneficial neurological changes in animal models (e.g., Nithianantharajah & Hannan, 2006), there is little evidence of this at the human level. For example, in a small study of cognitively health adults (aged 58 – 93), higher levels of complex mental activity throughout the lifespan (including domains related to education, reading, writing, and occupation) was associated with a significantly decreased risk of cognitive decline and hippocampal atrophy (Valenzuela et al., 2008). This evidence that hippocampal volume increases in response to CSA is similar to that of PA, which may explain why both types of activities are beneficial for cognitive performance.

Further evidence of the beneficial effects of CSA have been documented in experimental studies. Results from the Senior Odessy Program (Stine-Morrow et al., 2008) and Experience Corps Program® (Carlson et al., 2008) have demonstrated that the cognitive performance (i.e., executive function) of older adults can be improved after participating in programs that increase their levels of CSA. Furthermore, it may be beneficial to design intervention studies that focus on different types of CSA. For example, Park et al. (2013) examined how participation in different types of CSA impacted cognitive function in a sample of 221 adults (aged 60 – 90 years; $M = 71.67$). During the course of the three-month program, participants assigned to the productive engagement experimental condition spent approximately 15 hours per week learning digital photography, quilting, or both digital photography and quilting (the latter spent the first half of the study learning about digital photography and the second half about quilting). Conversely, participants assigned to the receptive-engagement condition spent approximately 15 hours per week engaging in facilitator-led social activities (e.g., watching movies, cooking, or

going on field trips to museums) or participating in activities they believed to be beneficial to cognition (e.g., listening to classical music, watching documentaries, or completing word puzzles). Results indicated that participants in the productive engagement condition (i.e., those who learned about digital photography, quilting, or a combination of both) improved significantly on measures of episodic memory compared to participants in the receptive engagement condition. Overall, these results highlight the beneficial relationship between CSA and cognition. The results also indicate that it may be possible utilize types of CSA in intervention studies to maintain or even improve cognitive performance.

As previously discussed, these effects may vary from study to study due to a number of confounding factors (i.e., differences in study population, design, definition of CSA), and as such, these results of the current dissertation should be interpreted with caution. In particular, differences in study design make it challenging to interpret the results of the current dissertation. For example, much of the cognitive aging literature has focused on using complex mental activity as an intervention, such as randomly assigning participants to take a computer course (Klusmann et al., 2010) or to complete complex mental tasks like math problems or word puzzles (Tranter & Koutstaal, 2008). A recent meta-analysis concluded that participating in CSA was associated with improved memory, executive function, and composite memory scores, but the results were inconsistent across studies (Kelly et al., 2014). However, a review of studies that evaluated CSA as a broad construct (i.e., lifestyle activities) concluded that participation in CSA was associated with a reduced risk of cognitive decline and dementia, despite differences in populations and study design (Wang, Xu, et al., 2012).

In sum, PA and CSA both appear to have positive influences on concurrent cognitive performance but do not necessarily affect the rate of cognitive change over time. In terms of the

cognitive flexibility and plasticity theory, plastic changes in the brain may be stimulated by PA and CSA but unique aspects of CSA are needed to provide sufficient stimulation to produce long-term beneficial plastic changes (Lövdén et al., 2010). Moreover, the extent to which an individual can improve his or her cognitive abilities (i.e., cognitive flexibility) may be influenced by unfavorable genetic variants related to cognitive function, particularly in older adults (Harris & Deary, 2011).

Question 2: How do Variants of the *ApoE, COMT,* and *BDNF* Genes Influence Cognitive Performance?

It was hypothesized that variability in *ApoE*, *COMT*, and *BDNF* genotype would be independently associated with cognition, with the presence of detrimental risk alleles (i.e., the *ApoE* ε4 allele, *COMT* Val allele, and *BDNF* Met allele) predicting worse baseline and longitudinal cognitive performance. Under the premise of the cognitive plasticity and flexibility theory, variation in genotype may contribute to intraindividual differences in cognitive performance by influencing the integrity of neural structures (e.g., protein structure) that facilitate plastic changes within the brain. The results of the current dissertation provide partial support for this hypothesis, as the examined risk alleles were not uniformly associated with variability in cognitive performance at baseline, and few longitudinal genetic effects were found.

Of the three risk alleles, the detrimental effect of *ApoE* ε4 allele was the most robust at baseline measurement: *ApoE* ε4 carriers scored significantly lower compared to non-*ApoE* ε4 carriers on every cognitive measure except backwards counting. The presence of the *COMT* Val-allele did not significantly affect baseline performance on any cognitive measure, but weakened the effect of time on performance in the serial 7s measure. Unexpectedly, the

presence of the *BDNF* Met had a positive impact, with any-Met *BDNF* carriers outperforming *BDNF* Val/Val carriers on baseline measures of delayed and total word recall.

Apolipoprotein E and Cognitive Performance

The current finding that non-*ApoE* ε4 carriers outperformed *ApoE* ε4 carriers on baseline cognitive measures but not over time contributes a number of research studies that investigated the impact of the *ApoE* ε4 in a cognitively healthy population. The *ApoE* ε4 allele has been repeatedly implicated in the development of mild cognitive impairment (MCI) and dementia (Brainerd, Reyna, Petersen, Smith, & Taub, 2011; Dixon et al., 2014; Farlow et al., 2004; C. Ferrari et al., 2013; Packard et al., 2007; Schipper, 2011). This effect also extends to normal cognitive aging: individuals with the *ApoE* ε4 allele have performed worse on episodic memory tasks (Laukka et al., 2013), a finding that is supported by two earlier meta-analyses, which showed associations between *ApoE* ε4 carriers and worse performance in episodic memory, executive functioning, and general cognitive ability (Small et al., 2004; Wisdom et al., 2011). The results of the current dissertation support and extend these earlier findings.

Interestingly, other studies have reported adverse longitudinal, but not baseline, effects the *ApoE* ε4 allele in healthy adults (e.g., de Frias et al., 2014; Reynolds et al., 2006; Salmon et al., 2013). *ApoE* ε4 carriers performed similarly (or better) on cognitive measures compared to non-*ApoE* ε4 carriers, but still exhibited greater longitudinal cognitive declines (de Frias et al., 2014; Reynolds et al., 2006). These results suggest that the effect of the *ApoE* ε4 allele may not necessarily play a role in cognitive performance until old age, although the absence of age-comparative data makes it difficult to determine when this effect occurs.

At a neurological level, variants of the *ApoE* gene have been associated with neurological pathways that influence plasticity in brain regions associated with cognition (e.g., hippocampus, prefrontal-cortex). The ε4 allele, in particular, has been connected to maladaptive lipid metabolism and neuronal maintenance and repair (Cedazo-Minguez, 2007; Teter, 2004). In healthy populations, *ApoE* ε4 carriers are less likely to exhibit evidence of beneficial neuroplastic changes in the hippocampus compared to non-ε4 carriers in response to neural stimulation (Schönheit, Glöckner, & Ohm, 2007). Cognitively healthy ε4 carriers also have greater levels of activation in the prefrontal cortices of the brain (Wishart et al., 2006), a finding which suggests greater utilization of resources is needed for these individuals to maintain normal levels of cognitive performance. Similar evidence was reported in a meta-analysis of brain imaging studies (representing over 1300 patients) in individuals with AD or MCI (Schroeter, Stein, Maslowski, & Neumann, 2009). The current results provide additional support regarding the role of *ApoE* variants and neuroplastic variability in brain, with the negative effects of the ε4 allele contributing to concurrent, but not longitudinal, differences in cognitive performance.

Catechol-O-Methyltransferase and Cognitive Performance

The current results found no significant association between *COMT* genotype and performance in any cognitive measures, rejecting the proposed hypothesis that variants of the *COMT* gene would affect baseline cognitive performance. Longitudinally, a single *COMT* genotype effect was found: the effect of time on serial 7s performance was weakened by the presence of any-Val *COMT* allele. Initially, this may be interpreted as a beneficial result; however, performance on the serial 7s measure tended to increase significantly over time (e.g., a practice effect). Since the presence of the *COMT* Val allele weakens the relationship between

performance and time, this result suggests that although *COMT* any-Val carriers did not necessarily perform worse in the backwards counting measure over time, they benefited less from practice. These findings, while somewhat unexpected, are not exclusive to the current dissertation and reflect an inconsistent pattern of results regarding the influence of the *COMT* gene on cognition in samples of healthy older adults (Das et al., 2014; de Frias et al., 2004; de Frias et al., 2005; Nagel et al., 2008).

Previously, Das et al. (2014) found no significant baseline and longitudinal associations between *COMT* genotype and episodic memory, although it should be noted this sample was slightly younger (M = 62.60 years) and more educated (M = 14.30 years) compared to the current sample (M_{age} = 69.73 years; $M_{education}$ = 12.78 years). Other researchers have failed to find associations between *COMT* genotype and episodic memory (Stuart, Summers, Valenzuela, & Vickers, 2014) or executive function (Erickson et al., 2008) in population samples of similar age rages (e.g., 50 – 85 years). Other studies that have reported *COMT*-related differences in episodic memory and executive function noted that the detrimental effect of the Val allele became more apparent during the later decades of life (de Frias et al., 2004; de Frias et al., 2005; Nagel et al., 2008). However, these results should be interpreted with caution due to sample limitations, such as the all-male sample evaluated by de Frias et al. (2004) and (de Frias et al., 2005), as well as the small sample of older adults (n = 154) in Nagel et al. (2008).

Given the interrelated connection between the *COMT* gene and dopamine degradation in various brain regions, differences between Val and Met carriers may vary depending on which neurological pathways are activated by the cognitive task at hand. For example, Val carriers may perform more poorly on measures that require executive function, working memory, or attention (e.g., serial 7s or backwards counting), as these tasks activate the dorsolateral prefrontal

cortex (Kipps, 2004), an area of the brain with particularly high concentrations of the COMT protein (Cools de Espositio, 2011). This may, in part, explain why the Val allele appears to have a detrimental effect for certain cognitive domains. For example, in separate analyses of the same all-male sample, declines in executive function were found for *COMT* Val/Val-carriers (de Frias et al., 2005), while declines in episodic memory were reported *COMT* Met/Met-carriers (de Frias et al., 2004).

Moreover, these deficits may only be detectable in individuals with inherently lower cognitive abilities. Papenberg et al. (2014) found *COMT* Val homozygotes performed worse than *COMT* any-Met carriers on measures of episodic and working memory, but only when restricting the analyses to the lowest-performing tertile of the sample. Additionally, although this sample was cognitively healthy and excluded individuals with less than 8 years of education, the absence of more extensive clinical assessments make it difficult to confirm that these low-performing individuals were not in the preclinical stages of cognitive decline.

In sum, the general absence of an independent *COMT* genotype effect in the current results, combined with the literary evidence, suggest that the effect of the Val allele may be limited to specific cognitive domains or populations (i.e., older adults or individuals with lower cognitive abilities). Furthermore, the absence of *COMT* genetic effects may be related to the tests included in the HRS cognitive battery, which has a limited number of measures designed to evaluate executive function and has been critiqued for lacking the sensitivity to detect subtle variations in normative cognitive aging (Lachman & Spiro, 2002). The lack of an independent genetic effect, however, does not eliminate *COMT* from contributing to an overall cognitive phenotype. Interactions among additional genetic and environmental factors are likely to affect

cognitive performance in a manner is not detected when examining the independent effect of a candidate gene (Hirschhorn, Lohmueller, Pearce, Pike, & Lander, 2002).

Brain-Derived Neutrophic Factor and Cognitive Performance

Contrary to the proposed hypothesis, the *BDNF* Met allele was associated with better baseline cognitive performance on all measures except immediate word recall. No longitudinal main effects of *BDNF* genotype were found. These results contradict the results of frequently cited studies that have reported a detrimental effect of the Met-allele for episodic memory (Egan et al., 2003; Li et al., 2010), executive function (Erickson et al., 2008) and processing speed (Ghisletta et al., 2014; Miyajima et al., 2008), although these effects are not always reported (Harris et al., 2006; Stuart et al., 2014).

The results of the current dissertation are not wholly unique, as there is additional evidence of a positive relationship between the Met allele and cognitive performance. Older Met-carriers outperform non-Met carriers in general mental ability (Harris et al., 2006) and tasks that require memory-based task switching (Gajewski, Hengstler, Golka, Falkenstein, & Beste, 2011). Collectively, these discrepancies highlight the importance of accounting for the potential impact of age and overall cognitive health when examining the influence of *BDNF* on cognition.

Similar to *ApoE*, variants of *BDNF* may moderate cognitive ability by contributing to neuroplastic variability in the hippocampus and prefrontal cortex. Met-carriers typically exhibit lower levels of hippocampal and MTL activation (Hariri et al., 2003; Kauppi et al., 2013) as well as lower hippocampal and prefrontal cortex volume (Nemoto et al., 2006), although these differences do not always contribute to a significant difference in overall brain volume (Miyajima et al., 2008). Importantly, these differences do not always manifest as detectable

differences in cognitive performance. For example, in a small sample of older adults (n = 194, aged 55-75 years), Kauppi et al. (2013) noted that activation levels in the MTL of Met-carriers was significantly lower than non-Met carriers during the memory encoding process, but not the retrieval process. Ultimately, *BDNF* Met-carriers slightly underperformed non-Met carriers in memory performance, but the difference was not significant. As with the variants of the *COMT* and *ApoE* genes, these results suggest that the *BDNF* Met allele may contribute to neurological differences at the physiological level, but these differences may only be detectable in specific populations or cognitive domains.

As with the *COMT* gene, the effects of *BDNF* may vary by cognitive domain. For example, Egan et al. (2003) found the *BDNF* Met allele negatively affected memory performance in a relatively young sample (M = 35 years), but this relationship was not found with any other cognitive domain. Li et al. (2010) also reported a negative association between the Met-allele and episodic memory, but this effect was limited to older adults' (M = 65.0 years) performance in backward serial recall tasks (i.e., recalling words in the reverse order from which they were presented); there were no genetic differences between forward recall (Li et al., 2010). Similarly, in another sample of older adults (M = 63.0 years), Miyajima et al. (2008) also reported lower scores for episodic memory, processing speed, and general intelligence in Met-carriers compared to non-Met carriers. Conversely, other studies of older adults have reported no differences between Met-carriers and non-Met carriers on measures of episodic memory (Harris et al., 2006; Stuart et al., 2014).

Discrepancies regarding the effects of *BDNF* genotype are also evident in longitudinal studies. Older Met-carriers have performed worse than non-Met carriers in baseline assessments of executive function, but were more likely to maintain their executive cognitive abilities over 10

years of follow-up while non-Met carriers demonstrated greater decline (Erickson et al., 2008). Conversely, Ghisletta et al. (2014) found no baseline differences between Met-carriers and non-Met carriers in performance speed, but Met-carriers experienced greater decline after 13 years.

The contradictory results of two recent meta-analyses further exhibit the extent of the inconsistent findings regarding the impact of *BDNF* genotype. One meta-analysis of 28 studies results supported a negative relationship between the Met-allele and memory (Kambeitz et al., 2012). Comparatively, a separate meta-analysis of 23 studies (seven of which overlapped with the aforementioned study), found no relationship between *BDNF* genotype and general intelligence, episodic memory and executive function, processing speed, or cognitive fluency (Mandelman & Grigorenko, 2012). Upon closer review of the first meta-analysis, the effect became non-significant when restricting the analyses to cognitively healthy samples (d = .09, p = .06). However, the interpretability of the results of the latter meta-analysis was limited by a lack of description of the ages of the samples and the extent of other potential confounding variables (e.g., cognitive health of samples, publication bias).

Question 3: How Does Variation in ApoE, BDNF, and COMT Genotype Moderate the Effect of Participating in PA and CSA on Cognitive Performance?

It was hypothesized that the variability in genetic factors would interact with baseline levels of CSA and PA, with the presence of detrimental variants constraining the benefit of participating in both type of activity. This hypothesis was guided by preliminary evidence, which indicated that *ApoE* ε4 carriers were less responsive to the beneficial effects of participating in CSA, while non- ε4 carriers demonstrated significantly better episodic memory (Runge et al., 2014). Similar studies have also reported better cognitive performance in

physically and cognitively active *ApoE* non-ε4 carriers compared to non-ε4 carriers (Obisesan et al., 2012; Woodard et al., 2012). This provided support for combining aspects of the differential susceptibility and cognitively plasticity and flexibility theories, with detrimental genetic variants representing inherent individual susceptibility factors that constrain one's ability to develop beneficial plastic changes in response to environmental stimuli. The next section describes the interactive effects of single genetic variants (i.e. *ApoE, COMT,* and *BDNF*) and CSA and PA.

Gene x Environmental Interactions on Cognitive Performance

Contrary to the preliminary evidence and the proposed hypothesis, few interactions were found between genotype and PA or CSA. The results of the current dissertation indicate that *COMT* and *BDNF* moderated the association between activity and cognitive performance. Specifically, older adults who carried the *COMT* Val allele (i.e., high risk) and also reported more frequent CSA had better baseline backwards counting scores. *COMT* non-Val carriers did not appear to benefit from CSA. Longitudinally, the backwards counting scores of *BDNF* non-Met carriers (i.e., a low risk) were less likely to decline if they also reported high levels of baseline CSA. There were no baseline or longitudinal interactive effects between *ApoE* and CSA or PA.

The absence of an interactive baseline or longitudinal effects between *ApoE* and CSA and PA was unexpected, particularly considering the independent effects that were found for CSA, PA, and *ApoE* in the current dissertation, as well as previous research which has indicated the *ApoE* ε4 allele generally constrains the beneficial effects of CSA or PA (Obisesan et al., 2012; Runge et al., 2014; Woodard et al., 2012). However, in regard to preventing the onset of mild cognitive impairment (MCI) or dementia, CSA and PA appear to be protective for *ApoE* ε4-

carriers. For example, Ferrari (2013) found that factors thought to promote neuroplasticity (i.e., high levels of education and participation in lifestyle activities) delayed the onset of dementia for ε4-carriers by 1.2 – 2.2 years, an effect that contributed to ε4 carriers living dementia-free for an amount of time similar to non-ε4 carriers. Subsequent research also reported that higher levels of lifetime cognitive activity was associated with a lower accumulation of beta-amyloid plaques in the brains of cognitively healthy individuals, particularly in *ApoE* ε4-carriers (Wirth, Villeneuve, La Joie, Marks, & Jagust, 2014).

In cognitively healthy populations, the presence of the ε4 allele appears to constrain the cognitive benefits of participating in CSA or PA in cross-sectional analyses. However, longitudinally, ε4-carriers who report high levels of CSA or PA have a reduced risk for dementia or cognitive decline. Taken together, these results suggest that the ε4 allele affects inherent cognitive abilities (independent of the effects of CSA and PA), but the benefits of an active lifestyle are more apparent in ε4 carriers over time.

Compared to the *ApoE* genotype, the interactive effects between *COMT* or *BDNF* and CSA and PA have not been extensively studied in aging populations. This makes it difficult to decipher the results of the current dissertation regarding the interactive effects that were found for *COMT*, *BDNF*, and CSA. Previous G x E studies regarding these particular genes have typically focused on aspects of development (e.g., exposure to adverse life events; Hygen et al., 2015; Rabl et al., 2014) or psychopathology (Nielsen et al., 2015; Rivollier, Lotersztajn, Chaumette, Krebs, & Kebir, 2014). The few studies that have examined older populations have also focused on PA alone. For example, higher levels of PA predicted better performance in cognitive domains associated with the prefrontal cortex (e.g., speed, reaction time) for *COMT* any-Val carriers, although this effect is not apparent in non-Val carriers (Mandelli & Serretti,

2013; Voelcker-Rehage, Jeltsch, Godde, Becker, & Staudinger, 2015). Most recently, Thibeau et al. (2016) found that that higher levels of PA were associated with better baseline episodic memory scores and less decline over time for *BDNF* non-Met carriers. Conversely, this association was absent for any-Met carriers, a results that suggests the *BNDF* Met allele may constrain the benefits of engaging in PA.

CHAPTER SIX:

CONCLUSION

In recognition of the heterogeneity and between-individual variability in cognitive aging, the current dissertation conducted a series of analyses using data from the Health and Retirement Study (HRS) to examine three potential sources of this variability: Genetic variants, environmental factors, and genetic and environment (G x E) interactions. Collectively, these analyses were performed to better understand the extent to which biological and lifestyle factors contribute to individual variability in cognitive aging. It is hoped that the results will contribute to future efforts to understand the biological and environmental mechanisms that promote healthy cognitive aging.

Conceptually guided by theories of neurocognitive plasticity and flexibility (Lövdén et al., 2010) and differential susceptibility (Belsky et al., 2009), the first sets of analyses examined the independent effect of lifestyle factors (i.e., baseline participation in CSA and PA) on baseline cognitive performance and cognitive change over time. Several notable results were produced. First, higher levels of participation in both types of activity had a positive influence on baseline cognition, as evidenced by better performance in nearly all cognitive measures. Second, participation in baseline CSA, but not PA, also affected the rate of cognitive change by weakening the effect of time. These results correspond with recent research indicating that engagement in CSA and PA is associated with improved cognitive performance (Bielak et al., 2012; Mitchell et al., 2012; Thibeau et al., 2016). The absence of long-term effects of PA on

cognitive performance contradicts the results of previous longitudinal research (Beydoun et al., 2014; Thibeau et al., 2016), and may be attributable to the relatively few number of questions regarding PA in the HRS Psychosocial Lifestyle Questionnaire or an insufficient follow-up period.

The second set of analyses assumed a similar theoretical and analytical approach to examine the independent effects of *ApoE, COMT,* and *BDNF* variants as predictors of baseline cognitive performance and cognitive change over time, with several key findings. First, variants of *ApoE* significantly predicted initial cognitive performance, but not rate of cognitive change, with the presence of the ε4 allele consistently predicting worse cognitive performance. This result is consistent with the majority of current research focusing on cognitively healthy populations (Laukka et al., 2013; Small et al., 2004; Wisdom et al., 2011). Second, the *BDNF* Met allele, which has typically been linked with poorer cognitive performance (Egan et al., 2003; Erickson et al., 2008), was associated with better cognitive performance. Finally, *COMT* genotype did not independently predict baseline cognitive performance, but it was associated with change over time in a measure of attention. The unexpected results of the independent effects of *BDNF* and *COMT,* may be related to limitations of the HRS cognitive battery (e.g., lack of domain-specific, sensitive measures) or unaccounted G x E interactions (Goldberg & Weinberger, 2004; Sapkota, Vergote, Westaway, Jhamandas, & Dixon, 2015; Thibeau et al., 2016).

The third set of analyses examined whether the presence of detrimental genetic variants moderated the relationship between CSA and PA and cognitive performance. Unexpectedly, few interactive effects were identified: *COMT* genotype moderated the relationship between CSA and initial cognitive performance but not rate of change over time, where individuals with the

COMT Val allele who also reported higher levels of CSA outperformed *COMT* non-Val carriers in a measure of attention. Additionally, *BDNF* genotype moderated the relationship between CSA and rate of cognitive change, but did not influence the initial CSA – cognitive performance relationship. More specifically, *BDNF* non-Met carriers who also reported higher levels of baseline CSA were more likely remain stable compared to *BDNF* any-Met carriers.

Strengths and Limitations, and Future Directions

The research described in the current dissertation has a number of strengths and limitations. One of the primary strengths is the evaluation and comparison of the independent and interactive effects of two types of lifestyle activities and multiple genetic variants on trajectories of cognitive change. This approach is particularly applicable for the investigation of cognitive phenotypes, which are likely influenced by a combination of endogenous factors and domain-specific neurobiological pathways (Deary, Wright, Harris, Whalley, & Starr, 2004; Goldberg & Weinberger, 2004). Additional strengths are related to unique features of the secondary dataset that was used in the current dissertation: The HRS is one of the few datasets that provides data on several measures of cognitive function, different types of lifestyle activities, and genetic information across multiple time points. Furthermore, the current sample is large enough to provide sufficient statistical power to detect small independent and interactive effects in multilevel models (Heo & Leon, 2010), a feature that may be absent in other studies with significantly fewer participants.

Finally, a strength of the current dissertation is the inclusion of both white and black participants (while simultaneously taking steps to control the potential confounding effect of race). This contributes to a relatively small body of literature that investigated genetic or

environmental influences on cognition in racially diverse populations (Fiocco et al., 2010). For example, in one of the few studies that specifically examined the impact of race in concordance with *COMT* genotype, Fiocco et al. (2010) found no baseline effects of COMT genotype on executive functioning performance in either race; however, a linear rate of decline was noted in whites, with Met/Met carriers demonstrating the greatest rate of decline. Conversely, black Met/Val carriers exhibited the greatest rate of decline, followed by Met/Met carriers and then Val/Val carriers. Future research should consider race as an importance facet of study design, as the effect of genotype may not always correspond with similar trajectories of decline in people of different races.

While the HRS was specifically chosen because it allowed for examination of the proposed research questions, certain aspects of the dataset nevertheless limited the interpretability of the results. First, the HRS cognitive battery has been critiqued for its limited range of cognitive domains, its ability to detect variability in normal cognitive aging, and the potential for ceiling or practice effects (Lachman & Spiro, 2002). Efforts have been made to reduce practice effects in the word recall tasks through a counterbalanced random assignment of four different word lists; however, it is not clear whether such efforts have been applied to improve the reliability and validity of the other measures. This feature may have contributed to the relative stability in cognitive performance as well as the lack of domain-specific effects seen in the current dissertation. Additional measures, such as tasks to assess executive function (e.g., verbal fluency) and speed of processing (e.g., reaction time), would need to be added to the current HRS battery to improve its sensitivity to detect small variations in normative cognitive aging (Lachman & Spiro, 2002).

A second limitation of the HRS measures is the retrospective, self-reported assessment of participant engagement in lifestyle activities in the Psychosocial and Lifestyle Leave-Behind questionnaire (LB). The use of self-report measures is a common approach to study behavior and is typically the only feasible option to collect data pertaining to participation in lifestyle activities, particularly in studies with extremely large sample sizes. However, research has shown that self-report measures can contribute to a number of biases (Podsakoff, MacKenzie, Lee, & Podsakoff, 2003). For example, the accuracy of self-reported levels of PA has been shown to differ among men and women, older and younger individuals, as well as individuals with higher body mass index (P. Ferrari, Friedenreich, & Matthews, 2007).

A third methodological limitation is related to the HRS LB questionnaire, which was designed to broadly evaluate participation in a variety of lifestyle activities as opposed to focusing exclusively on cognitive, social, and/or physical activities. The activities were categorized as CSA or PA (Smith et al., 2013) in order to address the proposed question; however, the underlying factor structure of the items remains complex and broadly defined. Future research could approach the HRS LB questionnaire as a single construct regarding participation in lifestyle activities in order, particularly since the use of robust definitions of activity may be more appropriate to promote general neurocognitive health at the population level.

Apart from these methodological issues, one must also consider the reverse-coding error that occurred during the genotyping process of the HRS genetic sample (see Methods) as a limitation. Extensive efforts were made to ensure the quality of data generated by the genotype imputation procedures (Weir, 2012), but it remains a possibility that some of the atypical results reported in the current dissertation were attributable to this reverse-coding error. It is also

possible that this error contributed to a violation of HW equilibrium for the *COMT* genotype in the black population (i.e., a greater number of observed black *COMT* any-Val carriers than expected; see Table 2). Since *a priori* analyses indicated that interactions between race and *COMT* genotype did not significantly predict performance on any cognitive measure, race was subsequently included as a covariate as recommended to control for potential confounding (Keller, 2014). To further account for the potential influence of race, the models were repeated with white and black participants only (see Appendices) with no significant differences in outcomes.

Finally, the lack of indicators of cognitive health or other disease-states within the current sample may also be considered a limitation. Although respondents who completed the HRS questionnaire via proxy were excluded from the current sample, no additional criteria were applied to verify the cognitive or overall physical health of the respondents. Independent and interactive effects of both genetic and environmental factors may become more apparent in samples that include cognitively normal and impaired individuals, or in samples with certain disease-states. For example, Dik et al. (2000) found the *ApoE* ε4 allele to predict greater cognitive declines in older adults, but this effect was limited to individuals who demonstrated levels of cognitive impairment. Further research would extend the current results by including a clinical measure of cognitive impairment to examine the baseline and longitudinal impact of genetic variants in cognitively healthy and impaired individuals, as well as other disease-states.

This research was conducted in an attempt to identify genetic and environmental factors which contribute to the etiology of cognitive aging, and how these factors influence cognition on an independent and interactive level. The current results suggest that both factors contribute to inherent differences in cognitive performance between individuals but further work is needed to

understand how these mechanisms contribute to the overall process of cognitive aging. These factors may assist in the early detection or evaluation of risk for cognitive decline by allowing researchers and clinicians to assessing a range of risk factors, instead of focusing exclusively on cognitive testing.

Table 1. Life of lifestyle activities included in the 2008 [α] Psychosocial and Lifestyle Leave-Behind Questionnaire, stratified by wave and year of data collection

Psychosocial and Lifestyle Leave-Behind Questionnaire
Care for sick/disabled adult
Do activities with grandchildren
Volunteer with youth or teens
Other volunteer or charity work
Perform activities with children
Take an educational course
Attend a meeting (sport, social, or other club)
Pray privately
Read books, magazines, newspapers
Play word games (e.g., Scrabble)
Play card/mind games (e.g., chess)
Write letters, stories, or journal
Use a computer
Perform home maintenance or garden
Bake or cook something special
Make clothes, knit, or embroider
Work on a hobby or project
Play sports or exercise
Walk for 20 minutes or more
Health Questionnaire
Engage in vigorous physical activity
Engage in light physical activity

[α] 6-point Likert-scale: 1 - not in the last month; 2 - at least once a month; 3 - several times a month; 4 - once a week; 5 - several times a week; 6 - daily

Table 2. Expected versus observed genotype frequencies by gene and race

Gene	Race	Genotype	Expected Frequencies (%)	Observed Frequencies (%)	Observed Frequencies (n)	Hardy-Weinberg Equilibrium (X^2, significance)
ApoE	CEU	Ɛ4+	0.28	0.26	1,071	14.59, p = .01
		Ɛ4-	0.72	0.74	3,128	
	ASW	Ɛ4+	0.37	0.35	195	1.62, p = .23
		Ɛ4-	0.69	0.65	370	
COMT	CEU	Val +	0.75	0.77	3,213	3.91, p = .14
		Val -	0.25	0.23	986	
	ASW	Val +	0.42	0.53	300	28.03, p = 8.18e-7*
		Val -	0.56	0.47	265	
BDNF	CEU	Met +	0.36	0.36	1,496	.82, p = .66
		Met -	0.64	0.64	2,703	
	ASW	Met +	0.09	0.07	38	3.02, p = .22
		Met -	0.91	0.93	527	

* Outside the recommended p = .0001 threshold to indicate significant differences (Weir, 2012)

CEU - White population; ASW - African American population

Table 3. Baseline demographic characteristics by genotype

	ApoE		**COMT**		**BDNF**		**TOTAL**
	ε4-	ε4+	Val-	Val +	Met -	Met +	
	low-risk	at-risk	low-risk	at-risk	low-risk	at-risk	
N	3,498	1,266	1,251	3,513	3,230	1,534	4,764
Age at 2008 Wave							
M	69.86	69.34	69.18	69.92	69.85	69.46	69.73
SD	9.72	9.21	9.37	9.65	9.62	9.50	9.59
Gender (% female)	59.32	59.48	60.19	59.07	58.89	60.37	59.36
Race (%)							
White/Caucasian	65.66	22.48	20.70	67.44	56.74	31.40	88.14
Black or African American	7.77	4.09	5.56	6.30	11.06	0.80	11.86
Ethnicity (%)							
Non-Hispanic	68.01	25.17	24.03	69.14	63.16	30.02	93.18
Hispanic	5.42	1.41	2.23	4.60	4.64	2.18	6.82
Education (years)							
M	12.68	12.77	12.65	12.83	12.68	12.99	12.78
SD	4.00	4.56	3.93	4.17	4.31	3.62	4.11

Table 4. Two-way ANOVA showing mean group differences between genotype, race, and their interaction for all cognitive tasks

	Immediate Recall				Delayed Recall				Total Recall			
	Sum of Squares	df	*F*	*p* value	Sum of Squares	df	Mean Square	*p* value	Sum of Squares	df	*F*	*p* value
ApoE genotype	185.60	1	1.88	0.17	333.87	1	66.77	0.64	375.66	1	0.77	0.57
Race	4,820.57	1	24.39	**<.001**	5,196.84	1	2,594.42	**<.001**	4,038.35	1	20.6	**<.001**
ApoE genotype x Race	148.98	1	0.75	0.47	1,456.29	1	145.63	0.14	1,138.42	1	1.16	0.31
COMT genotype	32.97	1	0.33	0.56	34.93	1	34.93	0.55	38.80	1	0.40	0.53
Race	4,278.90	1	43.38	**<.001**	9,804.87	1	9,804.87	**<.001**	8,009.06	1	81.64	**<.001**
COMT genotype x Race	192.72	1	1.95	0.76	181.93	1	181.93	0.17	212.92	1	2.17	0.14
BDNF genotype	91.43	1	0.93	0.34	30.24	1	30.24	0.58	61.37	1	0.63	0.43
Race	710.90	1	7.20	**0.01**	2,407.38	1	2,407.38	**<.001**	1,727.89	1	17.61	**<.001**
BDNF genotype x Race	53.32	1	0.54	0.46	3.69	1	3.69	0.85	21.62	1	0.22	0.64

	Serial 7s				Backwards Counting			
	Sum of Squares	df	*F*	*p* value	Sum of Squares	df	Mean Square	*p* value
ApoE genotype	488.60	1	1.04	0.39	554.96	1	110.99	0.35
Race	7,817.48	1	41.64	**<.001**	733.93	1	366.97	**0.02**
ApoE genotype x Race	1,531.45	1	1.63	0.09	851.77	1	85.17	0.57
COMT genotype	311.57	1	3.36	0.07	342.30	1	342.30	0.07
Race	24,474.67	1	263.64	**<.001**	5,572.88	1	5,572.88	**<.001**
COMT genotype x Race	93.01	1	1.00	0.32	841.53	1	841.52	0.06
BDNF genotype	22.52	1	0.24	0.62	302.82	1	302.82	0.08
Race	6,793.52	1	73.14	**<.001**	509.41	1	509.41	**0.02**
BDNF genotype x Race	2.37	1	0.03	0.87	312.79	1	312.79	0.07

Table 5a. Parameter estimates from multi-level models examining cognitive performance as a function of *ApoE* and activity: Immediate, delayed, and total word recall tasks

	Immediate Recall		Delayed Recall		Total Recall	
	Model C	Model D	Model C	Model D	Model C	Model D
Baseline main (fixed) effects						
Intercept	**85.30 (12.78)**	**84.49 (12.85)**	**78.46 (12.47)**	**77.98 (12.48)**	**80.90 (12.12)**	**80.22 (12.13)**
Time	**.83 (.38)***	1.71 (4.90)	.56 (.38)	.94 (.52)	.62 (.37)	**1.25 (.50)**
Age (covariate)	**-.59 (.18)****	**-.59 (.18)****	**-.46 (.18)***	**-.46 (.18)***	**-.52 (.17)****	**-.51 (.17)****
Gender (covariate)	**3.50 (.24)**	**3.50 (.24)**	**3.34 (.24)**	**3.34 (.24)**	**3.64 (.24)**	**3.64 (.24)**
Race	**-1.42 (.35)**	**-1.42 (.35)**	**-2.93 (.36)**	**-2.93 (.36)**	**-2.38 (.36)**	**-2.38 (.36)**
Years of education (covariate)	**.51 (.03)**	**.51 (.03)**	**.46 (.03)**	**.46 (.03)**	**.51 (.03)**	**.51 (.03)**
ApoE	**-.90 (.25)**	-.13 (1.20)	**-1.02 (.26)**	-.80 (1.21)	**-1.02 (.26)**	-.51 (1.20)
Baseline CSA	**.63 (.15)**	**.93 (.21)**	**.63 (.16)**	**.73 (.21)**	**.67 (.16)**	**.88 (.21)**
Baseline PA	**1.09 (.11)**	**1.13 (.14)**	**1.10 (.11)**	**1.17 (.14)**	**1.17 (.11)**	**1.23 (.14)**
Baseline interaction effects						
ApoE x CSA		-.06 (.40)		.02 (.40)		-.02 (.28)
ApoE x PA		-.01 (.07)		-.11 (.29)		-.11 (.28)
Longitudinal interaction effects						
Time x *ApoE*		.54 (.72)		.70 (.71)		.67 (.67)
Time x Baseline CSA		**-.33 (.12)***		-.11 (.12)		**-.22 (.11)****
Time x PA		.01 (.08)		-.03 (.08)		-.01 (.08)
Time x *ApoE* x CSA		-.14 (.24)		-.12 (.23)		-.14 (.22)
Time x *ApoE* x PA		-.13 (.17)		-.08 (.16)		-.11 (.16)
Variance components (random effects)						
Within-person (L1) variance (σ^2)	**42.92 (3.52)**	**43.05 (3.52)**	**41.33 (3.58)**	**41.44 (3.60)**	**37.05 (3.32)**	**37.18 (3.33)**
Intercept (L2) variance (τ_{00})	**45.15 (4.45)**	**44.94 (4.45)**	**47.89 (4.53)**	**47.75 (4.54)**	**50.34 (4.28)**	**50.16 (4.29)**
Auto-correlation coefficient (ρ)	**-.17 (.07)**	**-.16 (.07)**	**-.14 (.07)**	**-.14 (.07)**	**-.18 (0.8)**	**-.18 (.08)**
Additional information						
Df	14	21	14	21	14	21
-2 log likelihood (FIML)	-45,639.70	-45,629.47	-45,465.12	-45,462.36	-45,189.03	-45,182.96
AIC	91,307.39	91,300.94	90,958.25	90,966.73	90,406.07	90,407.92
BIC	91,411.73	91,457.44	91,062.58	91,123.23	90,510.40	90,564.42
Psuedo R^2 (L1)	0.04	-0.003	0.01	-0.003	0.02	-0.004
Psuedo R^2 (L2)	0.18	0.01	0.19	0.003	0.19	0.004

Note: Bolded text indicates significance at $p < .001$, ** indicates significance at $p < .01$, * indicates significance at $p < .05$; CSA = Cognitive/Social Activity; PA = Physical Activity; Model C = Conditional Growth Model; Model D = Conditional Growth Model with Cross-Level Interactions

Table 5b. Parameter estimates from multi-level models examining cognitive performance as a function of *ApoE* and activity: Serial 7s and backwards counting tasks

	Serial 7s		Backwards Counting	
	Model C	Model D	Model C	Model D
Baseline main (fixed) effects				
Intercept	**4.66 (.24)**	**4.66 (.24)**	**4.62 (.51)**	**4.54 (.52)**
Time	**.01 (.01)***	.01 (.01)	.03 (.02)	.17 (.21)
Age (covariate)	**-.01 (.01)****	**-.01 (.003)****	-.01 (.01)	-.01 (.01)
Gender (covariate)	**-.04 (.01)**	**-.04 (.01)**	.01 (.008)	.01 (.008)
Race	**-.14 (.01)**	**-.14 (.01)**	**-.11 (.01)**	**-.11 (.01)**
Years of education (covariate)	**.01 (.001)**	**.01 (.001)**	**.01 (.001)**	**.01 (.001)**
ApoE	**-.02 (.01)**	-.01 (.03)	.003 (.01)	-.03 (.05)
Baseline CSA	**.01 (.004)**	**.01 (.005)***	.01 (.01)	**.02 (.01)***
Baseline PA	**.01 (.003)**	**.01 (.003)**	.003 (.004)	.001 (.006)
Baseline interaction effects				
ApoE x CSA		-.002 (.01)		.02 (.02)
ApoE x PA		.001 (.01)		-.01 (.01)
Longitudinal interaction effects				
Time x *ApoE*		-.001 (.002)		.05 (.03)
Time x Baseline CSA		.001 (.002)		**-.01 (.01)***
Time x PA		.001 (.002)		.005 (.004)
Time x *ApoE* x CSA		-.002 (.004)		-.01 (.01)
Time x *ApoE* x PA		.0002 (.003)		-.003 (.01)
Variance components (random effects)				
Within-person (L1) variance (σ^2)	**.017 (.0004)**	**.017 (.0004)**	**.095 (.01)**	**.10 (.01)**
Intercept (L2) variance (τ_{00})	**.026 (.001)**	**.026 (.001)**	**.082 (.01)**	**.082 (.01)**
Auto-correlation coefficient (ρ)	.04 (.02)	.04 (.02)	-.03 (.05)	-.03 (.05)
Additional information				
Df	14	21	14	22
-2 log likelihood (FIML)	4,137.42	4,139.52	-5,250.88	-5,243.46
AIC	-8,246.95	-8,237.04	10,529.76	10,530.92
BIC	-8142.49	-8,080.50	10,634.12	10,694.91
Psuedo R^2 (L1)	0.00	0.000	0.05	-0.005
Psuedo R^2 (L2)	0.26	0.000	0.00	0.000

Note: Bolded text indicates significance at $p < .001$, ** indicates significance at $p < .01$, * indicates significance at $p < .05$; CSA = Cognitive/Social Activity; PA = Physical Activity; Model C = Conditional Growth Model; Model D = Conditional Growth Model with Cross-Level Interaction

Table 6a. Parameter estimates from multi-level models examining cognitive performance as a function of *COMT* and activity: Immediate, delayed, and total word recall tasks

	Immediate Recall		Delayed Recall		Total Recall	
	Model C	Model D	Model C	Model D	Model C	Model D
Baseline main (fixed) effects						
Intercept	**84.44 (12.79)**	**83.71 (12.81)**	**77.66 (12.47)**	**76.90 (12.50)**	**80.11 (12.13)**	**79.30 (12.15)**
Time	**.80 (.39)***	**1.99 (.71)****	.54 (.38)	**1.69 (.59)***	.60 (.37)	**1.87 (.66)****
Age (covariate)	**-.58 (.18)****	**-.57 (.18)****	**-.45 (.18)***	**-.45 (.18)***	**-.51 (.17)****	**-.50 (.17)****
Gender (covariate)	**3.50 (.24)**	**3.50 (.24)**	**3.34 (.24)**	**3.34 (.24)**	**3.63 (.24)**	**3.63 (.24)**
Race	**-1.51 (.36)**	**-1.52 (.36)**	**-3.03 (.37)**	**-3.03 (.37)**	**-2.49 (.37)**	**-2.48(.37)**
Years of education (covariate)	**.50 (.03)**	**.50 (.03)**	**.46 (.03)**	**.46 (.03)**	**.51 (.03)**	**.51 (.03)**
COMT	-.05 (.26)	-.76 (1.18)	-.04 (.27)	.13 (1.20)	-.05 (.27)	-.31 (1.18)
Baseline CSA	**.63 (.16)**	**.81 (.34)***	**.62 (.16)**	**.82 (.35)***	**.67 (.16)**	**.87 (.34)***
Baseline PA	**1.09 (.11)**	**1.00 (.24)**	**1.10 (.11)**	**1.12 (.24)**	**1.18 (.11)**	**1.14 (.24)**
Baseline interaction effects						
COMT x CSA		.14 (.40)		-.11 (.40)		.01 (.40)
COMT x PA		.14 (.28)		.03 (.28)		.09 (.28)
Longitudinal interaction effects						
Time x *COMT*		-.27 (.71)		-.83 (.69)		-.66 (.66)
Time x Baseline CSA		-.31 (.21)		-.19 (.20)		-.27 (.19)
Time x Baseline PA		-.07 (.14)		-.19 (.13)		-.14 (.13)
Time x *COMT* x CSA		-.06 (.24)		.07 (.23)		.02 (.22)
Time x *COMT* x PA		.06 (.16)		.19 (.16)		.14(.15)
Variance components (random effects)						
Within-person (L1) variance (σ^2)	**42.99 (3.53)**	**43.10 (3.54)**	**40.94 (3.55)**	**41.03 (3.56)**	**36.87 (3.31)**	**36.97 (3.33)**
Intercept (L2) variance (τ_{00})	**45.13 (4.46)**	**44.94 (4.47)**	**48.58 (4.49)**	**48.47 (4.51)**	**50.73 (4.28)**	**50.58 (4.28)**
Auto-correlation coefficient (ρ)	**-.16 (.07)**	**-.16 (.07)**	**-.15 (.07)**	**-.15 (.07)**	**-.19 (.08)**	**-.18 (.08)**
Additional information						
-2 log likelihood (FIML)	-45,645.67	-45,637.4	-45,472.70	-45,469.66	-45,196.51	-45,190.74
Change in -2 loglikelihood	637.05	8.27	612.42	3.04	655.39	5.77
AIC	91,319.34	91,316.80	90,973.39	90,981.32	90,421.01	90,423.48
BIC	91,423.67	91,473.30	91,077.73	91,137.82	90,525.34	90,579.98
Psuedo R^2 (L1)	0.04	-0.003	0.01	-0.002	0.03	-0.003
Psuedo R^2 (L2)	0.18	0.004	0.18	0.000	0.19	0.003

Note: Bolded text indicates significance at $p < .001$, ** indicates significance at $p < .01$, * indicates significance at $p < .05$; CSA = Cognitive/Social Activity; PA = Physical Activity; Model C = Conditional Growth Model; Model D = Conditional Growth Model with Cross-Level Interaction

Table 6b. Parameter estimates from multi-level models examining cognitive performance as a function of *COMT* and activity: Serial 7s and backwards counting tasks

	Serial 7s		Backwards Counting	
	Model C	Model D	Model C	Model D
Baseline main (fixed) effects				
Intercept	**4.64 (.24)**	**4.63 (.24)**	**4.63 (.51)**	**4.64 (.51)**
Time	.01 (.01)	**.03 (.01)***	.03 (.02)	.03 (.03)
Age (covariate)	**-.01 (.003)****	**-.01 (.003)****	-.01 (.01)	-.01 (.01)
Gender (covariate)	**-.04 (.01)**	**-.04 (.01)**	.01 (.01)	.01 (.01)
Race	**-.14 (.01)**	**-.14 (.01)**	**-.11 (.01)**	**-.11 (.01)**
Years of education (covariate)	**.01 (.001)**	**.01 (.001)**	**.01 (.001)**	**.01 (.001)**
COMT	.01 (.001)	.01 (.03)	.002 (.01)	-.09 (.05)
Baseline CSA	**.01 (.004)**	.01 (.01)	.005 (.01)	-.003 (.02)
Baseline PA	**.01 (.003)**	**.01 (.01)***	.003 (.004)	-.001 (.01)
Baseline interaction effects				
COMT x CSA		-.001 (.01)		**.04 (.02)***
COMT x PA		.001 (.01)		.001 (.01)
Longitudinal interaction effects				
Time x COMT		**-.03 (.01)***		.04 (.04)
Time x Baseline CSA		-.005 (.004)		-.002 (.01)
Time x PA		.001 (.003)		.004 (.01)
Time x COMT x CSA		.001 (.005)		-.02 (.01)
Time x COMT x PA		.001 (.003)		-.001 (.01)
Variance components (random effects)				
Within-person (L1) variance (σ^2)	**.017 (.0004)**	**.017 (.0004)**	**.095 (.01)**	**.095 (.01)**
Intercept (L2) variance (τ_{00})	**.026 (.001)**	**.026 (.001)**	**.082 (.01)**	**.082 (.01)**
Auto-correlation coefficient (ρ)	.04 (.02)	.04 (.02)	-.03 (.05)	-.03 (.05)
Additional information				
-2 log likelihood (FIML)	4,133.15	4,136.13	-5,250.93	-5,242.89
Change in -2 loglikelihood	-473.38	-2.98	140.41	8.04
AIC	-8,238.31	-8,230.26	10,529.87	10,527.78
BIC	-8,133.95	-8,073.73	10,634.22	10,684.32
Psuedo R^2 (L1)	0.00	0.000	0.05	0.000
Psuedo R^2 (L2)	0.26	0.000	0.00	0.000

Note: Bolded text indicates significance at p <.001, ** indicates significance at p < .01, * indicates significance at p < .05; CSA = Cognitive/Social Activity; PA = Physical Activity; Model C = Conditional Growth Model; Model D = Conditional Growth Model with Cross-Level Interaction

Table 7a. Parameter estimates from multi-level models examining cognitive performance as a function of *BDNF* and activity: Immediate, delayed, and total word recall tasks

	Immediate Recall		Delayed Recall		Total Recall	
	Model C	Model D	Model C	Model D	Model C	Model D
Baseline main (fixed) effects						
Intercept	**84.19 (12.79)**	**82.69 (12.79)**	**77.25 (12.46)**	**75.98 (12.47)**	**79.77 (12.12)**	**78.31 (12.13)**
Time	**.80 (.39)***	**2.01 (.54)**	.54 (.38)	**1.18 (.53)***	.60 (.37)	**1.54 (.51)****
Age (covariate)	**-.58 (.18)****	**-.57 (.18)****	**-.45 (.18)****	**-.45 (.18)****	**-.51 (.17)****	**-.50 (.17)****
Gender (covariate)	**3.49 (.24)**	**3.50 (.24)**	**3.33 (.24)**	**3.34 (.24)**	**3.62 (.24)**	**3.63 (.24)**
Race	**-1.42(.36)**	**-1.42 (.36)**	**-2.88 (.37)**	**-2.86 (.37)**	**-2.35 (.37)**	**-2.34 (.37)**
Years of education (covariate)	**.50 (.03)**	**.50 (.03)**	**.46 (.03)**	**.46 (.03)**	**.51 (.03)**	**.51 (.03)**
BDNF	.27 (.25)	1.56 (1.14)	**.48 (.25)***	**2.52 (1.16)***	.40 (.26)	**2.20 (1.14)***
Baseline CSA	**.63 (.16)**	**1.03 (.21)**	**.62 (.16)**	**.81 (.22)**	**.67 (.16)**	**.97 (.21)**
Baseline PA	**1.09 (.11)**	**1.14 (.15)**	**1.10 (.11)**	**1.29 (.15)**	**1.18 (.11)**	**1.30 (.15)**
Baseline interaction effects						
BDNF x CSA		-.38 (.37)		-.22 (.38)		-.31 (.37)
BDNF x PA		-.01 (.26)		-.45 (.27)		-.31 (.26)
Longitudinal interaction effects						
Time x *BDNF*		-.62 (.68)		-.24 (.66)		-.45 (.63)
Time x Baseline CSA		**-.43 (.13)**		-.13 (.12)		**-.29 (.12)****
Time x PA		-.03 (.09)		-.10 (.08)		-.07 (.08)
Time x *BDNF* x CSA		.23 (.24)		-.03 (.21)		.09 (.21)
Time x *BDNF* x PA		.02 (.15)		.14 (.15)*		.09 (.14)
Variance components (random effects)						
Within-person (L1) variance (σ^2)	**42.89 (3.51)**	**43.12 (3.54)**	**40.81 (3.54)**	**41.09 (3.57)**	**36.76 (3.30)**	**37.04 (3.33)**
Intercept (L2) variance (τ_{00})	**45.25 (4.45)**	**44.91 (4.47)**	**48.74 (4.49)**	**48.32(4.52)**	**50.87 (4.27)**	**50.46 (4.29)**
Auto-correlation coefficient (ρ)	**-.17 (.07)**	**-.16 (.07)**	**-.15 (.07)**	**-.15 (.07)**	**-.18 (.08)**	**-.18 (.08)**
Additional information						
-2 log likelihood (FIML)	-45,645.10	-45,637.00	-45,472.09	-45,466.05	-45,195.29	-45,188.72
Change in -2 loglikelihood	637.66	8.10	613.03	6.04	656.61	6.57
AIC	91,318.19	91,316.00	90,972.19	90,974.09	90,418.58	90,419.45
BIC	91,422.53	91,472.50	91,076.52	91,130.59	90,522.91	90,575.95
Explained Within-Person Variance (L1)	0.04	-0.005	0.01	-0.007	0.03	-0.008
Explained Intercept Variance (L2)	0.18	0.008	0.17	0.009	0.19	0.008

Note: Bolded text indicates significance at $p < .001$, ** indicates significance at $p < .01$, * indicates significance at $p < .05$; CSA = Cognitive/Social Activity; PA = Physical Activity; Model C = Conditional Growth Model; Model D = Conditional Growth Model with Cross-Level Interaction

Table 7b. Parameter estimates from multi-level models examining cognitive performance as a function of *BDNF* and activity: Serial 7s and backwards counting tasks

	Serial 7s		Backwards Counting	
	Model C	Model D	Model C	Model D
Baseline main (fixed) effects				
Intercept	**4.65 (.24)**	**4.65 (.24)**	**4.64 (.51)**	**4.59 (.51)**
Time	.01 (.01)	.003 (.01)	.03 (.02)	**.07 (.02)****
Age (covariate)	**-.01 (.003)****	**-.01 (.003)****	-.01 (.01)	-.01 (.01)
Gender (covariate)	**-.04 (.01)**	**-.04 (.01)**	.01 (.01)	.01 (.01)
Race	**-.14 (.01)**	**-.14 (.01)**	**-.12 (.01)**	**-.12 (.01)**
Years of education (covariate)	**.01 (.001)**	**.01 (.001)**	**.01 (.001)**	**.01 (.001)**
BDNF	.002 (.01)	-.001 (.03)	-.01 (.01)	.02 (.05)
Baseline CSA	**.01 (.004)****	**.01 (.005)***	.005 (.01)	**.03 (.01)****
Baseline PA	**.01 (.003)**	**.01 (.003)**	.003 (.004)	-.004 (.01)
Baseline interaction effects				
BDNF x CSA		-.002 (.01)		-.02 (.02)
BDNF x PA		.002 (.01)		.01 (.01)
Longitudinal interaction effects				
Time x *BDNF*		.02 (.01)		-.03 (.03)
Time x Baseline CSA		.003 (.002)		**-.02 (.01)**
Time x PA		.001 (.002)		.004 (.01)
Time x *BDNF* x CSA		**-.01 (.004)***		.01 (.01)
Time x *BDNF* x PA		.001 (.003)		-.002 (.01)
Variance components (random effects)				
Within-person (L1) variance (σ^2)	**.017 (.0004)**	**.017 (.0004)**	**.095 (.01)**	**.095 (.01)**
Intercept (L2) variance (τ_{00})	**.026 (.001)**	**.026 (.001)**	**.082 (.01)**	**.082 (.01)**
Auto-correlation coefficient (ρ)	.04 (.02)	.03 (.02)	-.03 (.05)	-.03 (.05)
Additional information				
-2 log likelihood (FIML)	4,132.23	4,135.66	-5,250.15	-5,243.65
Change in -2 loglikelihood	-472.46	-3.43	141.19	6.50
AIC	-8,236.46	-8,229.31	10,528.30	10,529.31
BIC	-8,132.10	-8,072.77	10,632.66	10,685.85
Explained Within-Person Variance (L1)	0.00	0.000	0.03	0.000
Explained Intercept Variance (L2)	0.26	0.000	0.00	0.000

Note: Bolded text indicates significance at $p < .001$, ** indicates significance at $p < .01$, * indicates significance at $p < .05$; CSA = Cognitive/Social Activity; PA = Physical Activity; Model C = Conditional Growth Model; Model D = Conditional Growth Model with Cross-Level Interaction

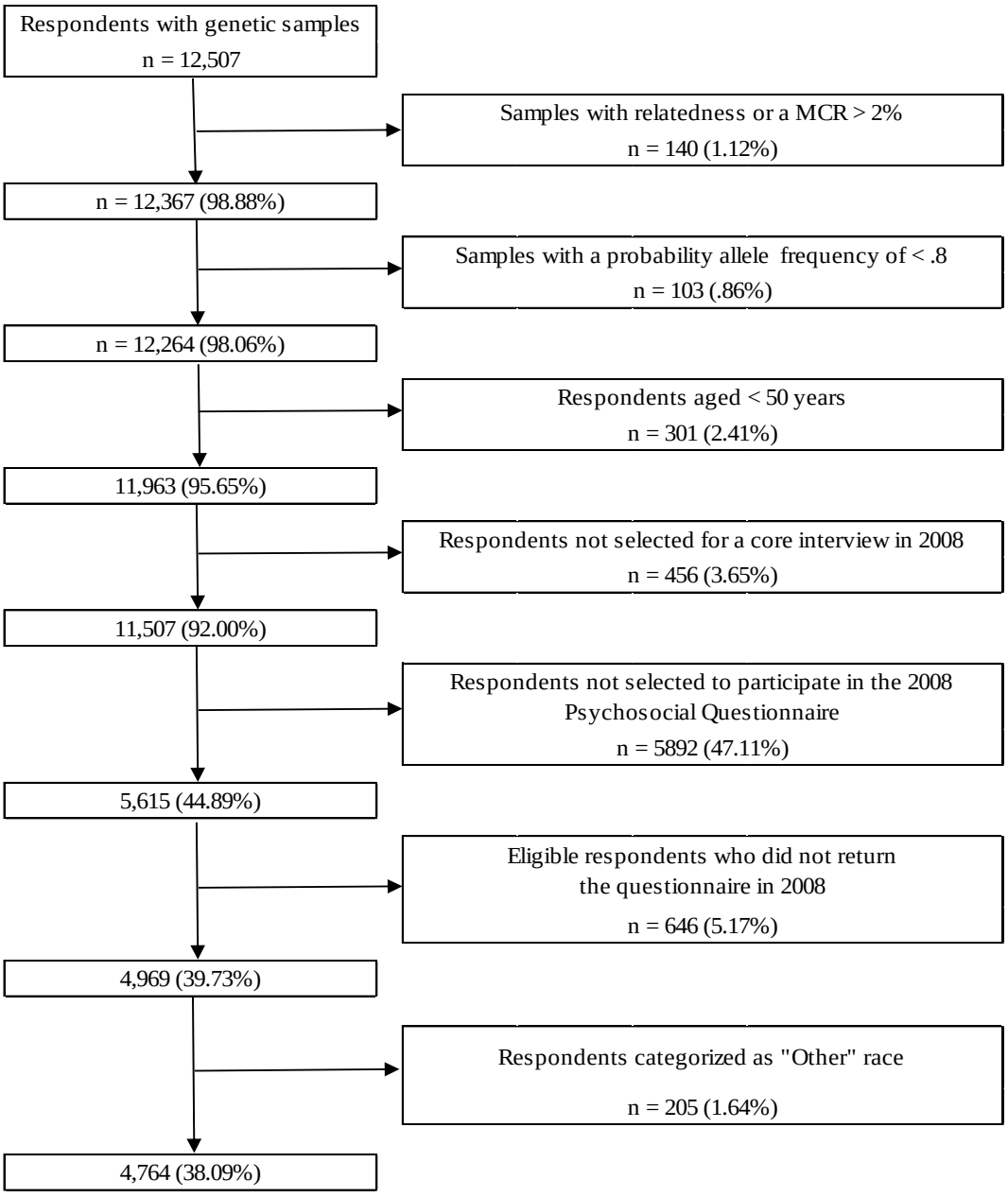

Figure 1. Flowchart of inclusion criteria

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APPENDICES

The following appendices contain the parameter estimates for the conditional growth models with each genotype, activity, and covariate predictors (Models C) and conditional growth models with cross-level interactions between genotype, activity, and covariate predictors using white participants only.

Appendix 1a. Parameter estimates from multi-level models examining cognitive performance as a function of *ApoE* and activity: Immediate, delayed, and total word recall measures for whites only

	Immediate Recall		Delayed Recall		Total Recall	
	Model C	Model D	Model C	Model D	Model C	Model D
Baseline main (fixed) effects						
Intercept	**90.59 (13.50)**	**90.20 (13.50)**	**81.67 (13.09)**	**81.42 (13.09)**	**85.93 (12.77)**	**85.611 (12.77)**
Time	**.96 (.41)***	**1.87 (.60)**	.69 (.39)	**1.13 (.55)***	**.78 (.38)**	**1.46 (.53)**
Age (covariate)	**-.69 (.19)**	**-.70 (.19)**	**-.55 (.18)***	**-.55 (.18)***	**-.63 (.18)****	**-.63 (.18)****
Gender (covariate)	**3.50 (.24)**	**3.50 (.24)**	**3.35 (.24)**	**3.36 (.26)**	**3.64 (.26)**	**3.65 (.26)**
Years of education (covariate)	**.46 (.03)**	**.46 (.03)**	**.42 (.03)**	**.42 (.03)**	**.46 (.03)**	**.46 (.03)**
ApoE	**-1.05 (.28)**	-8.31 (1.31)	**-1.16 (.26)**	-.75 (1.34)	**-1.19 (.28)**	-.86 (1.31)
Baseline CSA	**.78 (.17)**	**1.07 (.23)**	**.73 (.18)**	**.87 (.23)**	**.81 (.16)**	**1.03 (.23)**
Baseline PA	**1.08 (.11)**	**1.08 (.15)**	**1.06 (.12)**	**1.12 (.15)**	**1.15 (.11)**	**1.18 (.15)**
Baseline interaction effects						
ApoE x CSA		.13 (.43)		.02 (.40)		.07 (.43)
ApoE x PA		-.08 (.30)		-.12 (.29)		-.01 (.30)
Longitudinal interaction effects						
Time x *ApoE*		.60 (.80)		.41 (.76)		.53 (.73)
Time x Baseline CSA		**-.37 (.12)***		-.16 (.12)		**-.27 (.12)****
Time x PA		.05 (.09)		-.001 (.08)		.03 (.08)
Time x *ApoE* x CSA		-.17 (.26)		-.04 (.24)		-.11 (.24)
Time x *ApoE* x PA		-.14 (.17)		-.09 (.17)		-.11 (.16)
Variance components (random effects)						
Within-person (L1) variance (σ^2)	**42.92 (3.52)**	**39.42 (3.47)**	**36.93 (3.41)**	**37.02 (3.42)**	**32.70 (3.13)**	**32.80 (3.14)**
Intercept (L2) variance (τ_{00})	**49.55 (4.49)**	**49.31 (4.51)**	**51.89 (4.46)**	**51.78 (4.46)**	**55.42 (4.22)**	**55.26 (4.23)**
Auto-correlation coefficient (ρ)	**-.23 (.08)**	**-.23 (.08)**	**-.22 (.08)**	**-.22 (.08)**	**-.28 (.09)**	**.27 (.09)**
Additional information						
df	13	20	13	20	13	20
-2 log likelihood (FIML)	-40,275.52	-40,265.15	-40,037.58	-40,035.46	-39,850.43	-39,844.35
AIC	80,577.05	80,570.29	80,101.17	80,110.92	79,726.86	79,728.69
BIC	80,672.30	80,716.80	80,196.42	80,257.47	79,822.12	79,875.24
Psuedo R^2 (L1)	-0.03	0.08	0.03	0.00	0.05	0.00
Psuedo R^2 (L2)	0.15	0.00	0.13	0.00	0.15	0.00

Note: Bolded text indicates significance at $p < .001$, ** indicates significance at $p < .01$, * indicates significance at $p < .05$; CSA = Cognitive/Social Activity; PA = Physical Activity; Model C = Conditional Growth Model; Model D = Conditional Growth Model with Cross-Level Interactions

Appendix 1b. Parameter estimates from multi-level models examining cognitive performance as a function of *ApoE* and activity: Serial 7s and backwards counting measures for whites only

	Serial 7s		Backwards Counting	
	Model C	Model D	Model C	Model D
Baseline main (fixed) effects				
Intercept	**4.37 (.24)**	**4.38 (.25)**	**4.17 (.51)**	**4.04 (.51)**
Time	**.01 (.01)***	.01 (.01)	.02 (.02)	.28 (.21)
Age (covariate)	**-.01 (.01)****	**-.01 (.003)****	-.005 (.01)	-.003 (.01)
Gender (covariate)	**-.04 (.01)**	**-.04 (.01)**	.01 (.008)	.01 (.008)
Years of education (covariate)	**.01 (.001)**	**.01 (.001)**	**.01 (.001)**	**.01 (.001)**
ApoE	**-.02 (.01)**	-.01 (.03)	-.003 (.01)	-.01 (.05)
Baseline CSA	**.01 (.004)**	.01 (.005)*	.01 (.01)	**.02 (.01)***
Baseline PA	**.01 (.003)**	**.01 (.003)**	.003 (.004)	.002 (.006)
Baseline interaction effects				
ApoE x CSA		-.01 (.01)		.01 (.02)
ApoE x PA		.003 (.01)		-.01 (.01)
Longitudinal interaction effects				
Time x *ApoE*		.001 (.01)		.02 (.04)
Time x Baseline CSA		.003 (.002)		**-.02 (.01)***
Time x PA		.001 (.002)		.003 (.004)
Time x *ApoE* x CSA		-.001 (.005)		-.002 (.01)
Time x *ApoE* x PA		-.002 (.003)		-.003 (.01)
Variance components (random effects)				
Within-person (L1) variance (σ^2)	**.016 (.0004)**	**.016 (.0004)**	**.074 (.01)**	**.073 (.005)**
Intercept (L2) variance (τ_{00})	**.024 (.001)**	**.024 (.001)**	**.078 (.01)**	**.078 (.01)**
Auto-correlation coefficient (ρ)	.05 (.03)	.04 (.02)	**-.14 (.05)**	**-.14 (.05)**
Additional information				
df	13	20	13	21
-2 log likelihood (FIML)	3,947.26	3,951.07	-3,840.06	-3,832.71
AIC	-7,868.52	-7,862.4	7,706.12	7,707.43
BIC	-7,773.24	-7,715.56	7,801.40	7,861.34
Psuedo R^2 (L1)	0.00	0.00	0.01	0.01
Psuedo R^2 (L2)	0.14	0.00	0.00	0.00

Note: Bolded text indicates significance at $p < .001$, ** indicates significance at $p < .01$, * indicates significance at $p < .05$; CSA = Cognitive/Social Activity; PA = Physical Activity; Model C = Conditional Growth Model; Model D = Conditional Growth Model with Cross-Level Interactions

Appendix 2a. Parameter estimates from multi-level models examining cognitive performance as a function of *COMT* and activity: Immediate, delayed, and total word recall measures for whites only

	Immediate Recall		Delayed Recall		Total Recall	
	Model C	Model D	Model C	Model D	Model C	Model D
Baseline main (fixed) effects						
Intercept	**89.60 (13.51)**	**89.36 (13.54)**	**77.66 (12.47)**	**76.90 (12.50)**	**80.11 (12.13)**	**79.30 (12.15)**
Time	**.93 (.41)***	**2.08 (.80)****	.54 (.38)	**1.69 (.59)****	.60 (.37)	**1.87 (.66)****
Age (covariate)	**-.68 (.19)**	**-.68 (.19)****	**-.45 (.18)***	**-.45 (.18)***	**-.51 (.17)****	**-.50 (.17)****
Gender (covariate)	**3.48 (.25)**	**3.48 (.25)**	**3.34 (.24)**	**3.34 (.24)**	**3.63 (.24)**	**3.63 (.24)**
Years of education (covariate)	**.46 (.03)**	**.46 (.03)**	**.46 (.03)**	**.46 (.03)**	**.51 (.03)**	**.51 (.03)**
COMT	-.13 (.28)	-.96 (1.36)	-.04 (.27)	.13 (1.20)	-.05 (.27)	-.31 (1.18)
Baseline CSA	**.78 (.17)**	**1.23 (.41)****	**.62 (.16)**	**.82 (.37)****	**.67 (.16)**	**.88 (.34)***
Baseline PA	**1.08 (.12)**	**.80 (.24)****	**1.10 (.11)**	**1.12 (.24)**	**1.18 (.11)**	**1.14 (.24)**
Baseline interaction effects						
COMT x CSA		-.15 (.46)		-.11 (.40)		.01 (.97)
COMT x PA		.34 (.30)		.03 (.28)		.09 (.28)
Longitudinal interaction effects						
Time x *COMT*		-.15 (.81)		-.83 (.69)		-.66 (.66)
Time x Baseline CSA		-.35 (.24)		-.19 (.20)		-.27 (.19)
Time x Baseline PA		-.06 (.14)		-.19 (.13)		-.14 (.13)
Time x *COMT* x CSA		-.08 (.24)		.07 (.23)		.02 (.22)
Time x *COMT* x PA		.10 (.16)		.19 (.16)		.14(.15)
Variance components (random effects)						
Within-person (L1) variance (σ^2)	**39.44 (3.47)**	**39.56 (3.48)**	**40.94 (3.55)**	**41.03 (3.56)**	**36.87 (3.31)**	**36.97 (3.33)**
Intercept (L2) variance (τ_{00})	**49.46 (4.52)**	**49.25 (4.52)**	**48.58 (4.49)**	**48.47 (4.51)**	**50.73 (4.28)**	**50.58 (4.26)**
Auto-correlation coefficient (ρ)	**-.22 (.07)**	**-.22 (.07)**	**-.15 (.07)**	**-.15 (.07)**	**-.19 (.08)**	**-.18 (.08)**
Additional information						
df	13	20	14	21	14	21
AIC	80,591.20	80,587.59	90,973.39	90,981.32	90,421.01	90,423.48
BIC	80,686.45	80,734.14	91,077.73	91,137.82	90,525.34	90,579.98
Psuedo R^2 (L1)	0.05	0.00	0.01	0.00	0.03	0.00
Psuedo R^2 (L2)	0.15	0.00	0.18	0.00	0.19	0.00

Note: Bolded text indicates significance at p <.001, ** indicates significance at p < .01, * indicates significance at p < .05; CSA = Cognitive/Social Activity; PA = Physical Activity; Model C = Conditional Growth Model; Model D = Conditional Growth Model with Cross-Level Interactions

Appendix 2b. Parameter estimates from multi-level models examining cognitive performance as a function of *COMT* and activity: Serial 7s and backwards counting measures for whites only

	Serial 7s		Backwards Counting	
	Model C	Model D	Model C	Model D
Baseline main (fixed) effects				
Intercept	**4.64 (.24)**	**4.63 (.24)**	**4.63 (.51)**	**4.64 (.51)**
Time	.01 (.01)	**.03 (.01)***	.03 (.02)	.03 (.03)
Age (covariate)	**-.01 (.003)****	**-.01 (.003)****	-.01 (.01)	-.01 (.01)
Gender (covariate)	**-.04 (.01)**	**-.04 (.01)**	.01 (.01)	.01 (.01)
Years of education (covariate)	**.01 (.001)**	**.01 (.001)**	**.01 (.001)**	**.01 (.001)**
COMT	.01 (.001)	.01 (.03)	.002 (.01)	-.09 (.05)
Baseline CSA	**.01 (.004)**	.01 (.01)	.005 (.01)	-.003 (.02)
Baseline PA	**.01 (.003)**	**.01 (.01)***	.003 (.004)	-.001 (.01)
Baseline interaction effects				
COMT x CSA		-.001 (.01)		**.04 (.02)***
COMT x PA		.001 (.01)		.001 (.01)
Longitudinal interaction effects				
Time x COMT		**-.03 (.01)***		.04 (.04)
Time x Baseline CSA		-.005 (.004)		-.002 (.01)
Time x PA		.001 (.003)		.004 (.01)
Time x COMT x CSA		.001 (.005)		-.02 (.01)
Time x COMT x PA		.001 (.003)		-.001 (.01)
Variance components (random effects)				
Within-person (L1) variance (σ^2)	**.017 (.0004)**	**.017 (.0004)**	**.095 (.01)**	**.095 (.01)**
Intercept (L2) variance (τ_{00})	**.026 (.001)**	**.026 (.001)**	**.082 (.01)**	**.082 (.01)**
Auto-correlation coefficient (ρ)	.04 (.02)	.04 (.02)	-.03 (.05)	-.03 (.05)
Additional information				
df	14	21	14	21
AIC	-8,238.31	-8,230.26	10,529.87	10,527.78
BIC	-8,133.95	-8,073.73	10,634.22	10,684.32
Psuedo R^2 (L1)	0.00	0.00	0.03	0.00
Psuedo R^2 (L2)	0.26	0.00	0.00	0.00

Note: Bolded text indicates significance at $p < .001$, ** indicates significance at $p < .01$, * indicates significance at $p < .05$; CSA = Cognitive/Social Activity; PA = Physical Activity; Model C = Conditional Growth Model; Model D = Conditional Growth Model with Cross-Level Interactions

Appendix 3a. Parameter estimates from multi-level models examining cognitive performance as a function of *BDNF* and activity: Immediate, delayed, and total word recall measures for whites only

	Immediate Recall		Delayed Recall		Total Recall	
	Model C	Model D	Model C	Model D	Model C	Model D
Baseline main (fixed) effects						
Intercept	**89.43 (13.51)**	**87.94 (13.51)**	**80.49 (13.09)**	**79.06 (13.09)**	**84.76 (12.77)**	**83.23 (12.77)**
Time	**.93 (.41)***	**2.19 (.60)**	.67 (.39)	**1.28 (.57)****	**.76 (.38)***	**1.70 (.56) ****
Age (covariate)	**-.68 (.19)**	**-.68 (.19)**	**-.54 (.19)****	**-.54 (.19)****	**-.61 (.18)**	**-.61 (.18)**
Gender (covariate)	**3.48 (.25)**	**3.48 (.25)**	**3.33 (.26)**	**3.33 (.26)**	**3.62 (.26)**	**3.62 (.26)**
Years of education (covariate)	**.46 (.03)**	**.46 (.03)**	**.41 (.03)**	**.41 (.03)**	**.46 (.03)**	**.46 (.03)**
BDNF	.24 (.25)	1.92 (1.20)	.50 (.26)	**3.05 (.12)****	.40 (.26)	2.68 (1.20)
Baseline CSA	**.78 (.17)**	**1.37 (.24)**	**.73 (.18)**	**1.10 (.24)**	**.81 (.18)**	**1.31 (.24)**
Baseline PA	**1.08 (.12)**	**1.05 (.16)**	**1.07 (.18)**	**1.20 (.16)**	**1.15 (.12)**	**1.21 (.16)**
Baseline interaction effects						
BDNF x CSA		-.72 (.39)		-.63 (.40)		-.71 (.39)
BDNF x PA		.02 (.27)		-.32 (.27)		-.17 (.27)
Longitudinal interaction effects						
Time x *BDNF*		-.56 (.72)		-.23 (.69)		-.40 (.67)
Time x Baseline CSA		**-.53 (.14)**		-.20 (.13)		**-.37 (.13) ****
Time x PA		.03 (.09)		-.05 (.09)		-.01 (.09)
Time x *BDNF* x CSA		.31 (.23)		.07 (.22)		.19 (.22)
Time x *BDNF* x PA		-.03 (.16)		.09 (.15)		.03 (.15)
Variance components (random effects)						
Within-person (L1) variance (σ^2)	**39.32 (3.46)**	**39.62 (3.49)**	**36.46 (3.37)**	**36.77 (3.40)**	**32.46 (3.12)**	**32.80 (3.15)**
Intercept (L2) variance (τ_{00})	**49.61 (4.50)**	**49.13 (4.53)**	**52.72 (4.43)**	**52.21 (4.54)**	**55.92 (4.21)**	**55.39 (4.24)**
Auto-correlation coefficient (ρ)	**-.23 (.08)**	**-.22 (.08)**	**-.23 (.08)**	**-.23 (.08)**	**-.28 (.09)**	**-.27 (.09)**
Additional information						
df	13	20	13	20	13	20
-2 log likelihood (FIML)	-40,282.24	-40,272.69	-40,044.15	-40,038.34	-39,857.92	-39,849.97
AIC	80,585.38	80,585.38	80,114.29	80,116.68	79,741.84	79,739.94
BIC	80,731.92	80,731.92	80,209.55	802,636.23	79,837.10	79,886.48
Psuedo R^2 (L1)	0.05	-0.01	0.04	-0.01	0.05	0.04
Psuedo R^2 (L2)	0.15	0.01	0.12	0.01	0.14	0.01

Note: Bolded text indicates significance at $p < .001$, ** indicates significance at $p < .01$, * indicates significance at $p < .05$; CSA = Cognitive/Social Activity; PA = Physical Activity; Model C = Conditional Growth Model; Model D = Conditional Growth Model with Cross-Level Interactions

Appendix 3b. Parameter estimates from multi-level models examining cognitive performance as a function of *BDNF* and activity: Serial 7s and backwards counting measures for whites only

	Serial 7s		Backwards Counting	
	Model C	Model D	Model C	Model D
Baseline main (fixed) effects				
Intercept	**4.36 (.25)**	**4.36 (.25)**	**4.18 (0.51)**	**4.13 (.51)**
Time	.01 (.01)	.01 (.01)	.02 (.02)	**.07 (.03) ****
Age (covariate)	**-.01 (.003) ***	**-.01 (.003)***	-.005 (.007)	-.005 (.007)
Gender (covariate)	**-.04 (.006)**	**-.04 (.006)**	.012 (.008)	.012 (.008)
Years of education (covariate)	**.01 (.001)**	**.01 (.001)**	**.01 (.001)**	**.01 (.001)**
BDNF	.001 (.006)	-.02 (.03)	-.01 (.007)	-.01 (.05)
Baseline CSA	**.008 (.004) ***	.004 (.005)	.006 (.005)	**.03 (.01)**
Baseline PA	**.01 (.003)**	**.01 (.003)**	.004 (.004)	-.002 (.006)
Baseline interaction effects				
BDNF x CSA		.005 (.009)		-.02 (.01)
BDNF x PA		.002 (.006)		.01 (.01)
Longitudinal interaction effects				
Time x *BDNF*		.03 (.01)		-.03 (.03)
Time x Baseline CSA		**.01 (.03) ****		**-.02 (.007)**
Time x PA		.001 (.002)		.003 (.004)
Time x *BDNF* x CSA		**-.01 (.004) ****		.01 (.01)
Time x *BDNF* x PA		.001 (.003)		-.003 (.007)
Variance components (random effects)				
Within-person (L1) variance (σ^2)	**.024 (.001)**	**.024 (.001)**	**.073 (.005)**	**.073 (.005)**
Intercept (L2) variance (τ_{00})	**.016 (.001)**	**.016 (.001)**	**.017 (.003)**	**.017 (.003)**
Auto-correlation coefficient (ρ)	.05 (.03)	.04 (.03)	**-.14 (.05)**	**-.14 (.05)**
Additional information				
df	13	20	13	20
-2 log likelihood (FIML)	3,940.54	3,947.10	-3,838.62	-3,831.41
AIC	-7,855.67	-7,854.21	7,703.24	7,702.82
BIC	-7,760.41	-7,707.62	7,798.82	7,849.40
Psuedo R^2 (L1)	0.17	0.00	0.03	0.00
Psuedo R^2 (L2)	0.00	0.00	0.00	0.00

Note: Bolded text indicates significance at $p < .001$, ** indicates significance at $p < .01$, * indicates significance at $p < .05$; CSA = Cognitive/Social Activity; PA = Physical Activity; Model C = Conditional Growth Model; Model D = Conditional Growth Model with Cross-Level Interactions