THE EFFECTS OF CAUSATIVE AND SUSCEPTIBILITY GENES ON THE DEVELOPMENT OF ALZHEIMER'S DISEASE: A META-ANALYTIC APPROACH

By

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TABLE OF CONTENTS

LIST OF TABLES

Table Page

CHAPTER I

INTRODUCTION

Alzheimer's disease (AD) is a major public health issue that impacts an estimated 5%-10% of people in the 65-74-year range and nearly 50% of people over the age of 85 (Bachman, Wolf, & Linn, 1992). It is expected that the number of people afflicted with AD will increase exponentially as the "baby boomers" continue to age (Evans, 1990). Yet, despite the widespread prevalence and seriousness of this disorder, there remains much to learn about the effects certain genes play in the pathogenesis of AD. As a result, there has been a proliferation of genetics studies and several genes have been identified as contributing to the pathogenesis of familial early-onset AD (FAD) and late-onset AD (LOAD). As will be elaborated further at the end of this section, the purpose of the proposed study is to examine the impact of these genes on cognitive functioning, via meta-analyses of the accumulating literature.

FAD is a rare form of AD characterized by an early onset, before the age of 65, and accounts for approximately 1%-2% of the entire population of individuals suffering from AD (Tanzi et al., 1987). Many investigators believe the rates of FAD are closer to 5%, arguing that it is frequently misdiagnosed or all together underaddressed by researchers (McMurtray, Clark, Christine, & Mendez, 2006; Sampson, Warren, & Rossor, 2004). Missense mutations of the amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2) genes all cause autosomal dominate FAD on chromosomes 21, 14, and 1, respectively (Rocchi, Pellegrini, Siciliano, & Murri, 2003).

The presence of any of these mutations usually results in onset of AD before the age of 65, although mutations on chromosome 1 appear to result in wider variability with onset ranging from 40 years of age to 80 (Bird et al., 1996). In addition to earlier age of onset, mutations of these genes are also associated with an accelerated disease progression compared to late-onset AD (Ringman, Diaz-Olavarrieta, & Rodriguez, 2005).

The prevalence rates of each of these mutations are, thus far, unclear. For example, two studies examining mutations on chromosome 1 have resulted in widely discrepant estimates of 18% and 71% of all early-onset autosomal dominant AD (Chen et al., 2001; Cruts et al., 1998). However, most studies seem to agree with the idea that mutations on chromosome 14 account for the majority of familial early-onset AD (see Cummings et al., 1998, for review). The pathogenesis of these genetic mutations has also fueled the "amyloid hypothesis" as all three of these genetic mutations manipulate the same mechanism of action that results in the overproduction of Amyloid β (Ringman, 2005). Amyloid deposits produce widespread atrophy of several major structures found in the brain including the cerebral cortex and the hippocampus, which has been strongly linked to memory in previous studies (Squire, 1992).

In addition to these genetic mutations, the presence of certain alleles of Apolipoprotein E (ApoE) on chromosome 19 have been implicated as significantly increasing the risk for developing LOAD after the age of 65. ApoE is a plasma protein combined with a lipid that is responsible for carrying cholesterol and other fats through the bloodstream in order for these molecules to be broken down (Rocchi et al., 2003). ApoE is found in amyloid plaques and neurofibrillary tangles, both hallmark AD characteristics, and it is believed that it has some regulatory properties over their

deposition and formation (Harris et al., 2003). Plaque formation may even require the presence of ApoE before amyloid plaques become toxic in the brain (Lahiri, Sambamurti, & Bennett, 2004). The ApoE gene has three common allelic variations: epsilon 2 (ε2), epsilon 3 (ε3), and epsilon 4 (ε4). Every individual inherits one allele of ApoE from each of their parents. Therefore, there are six possible genotypes that can be inherited: ε2ε2, ε2ε3, ε2ε4, ε3ε3, ε3ε4, and ε4ε4 (Lahiri et al., 2004). Each of these allelic variations has been studied in their relation to onset of AD. The ε3 variant occurs most frequently throughout the general Caucasian population with an occurrence rate of 79% and it neither significantly increases nor decreases the risk of developing LOAD (Corder et al., 1996; Lahiri et al., 2004). The ε2 and ε4 variations occur significantly less with occurrence rates at approximately 8% and 14%, respectively (Seshadri, Drachman, & Lippa, 1995; Small, Rosnick, Fratiglioni, & Backman, 2004; Tischa et al., 2004). It is important to note that the ApoE allelic distribution among cognitively healthy individuals has been shown to be different across various ethnic backgrounds resulting in imprecise prevalence estimates for the entire population (Tischa et al., 2004). The ApoE ε2 allele is positively associated with survival and longevity among older adults and is therefore considered a protective factor against AD (Corder et al., 1996). Conversely, the increased risk for AD in the presence of the ε4 allele is the single most replicated finding in AD genetics research (Cacabelos, 2003). Approximately 40%-60% of all Alzheimer's disease carriers possess the ε4 allele of ApoE, which is two to three times higher than is typically found in the general population (Parker et al., 2005). A meta-analysis of all the different variants of ApoE indicated that heterozygous ApoE ε4 (ε2ε4 or ε3ε4) carriers are 3 to 4 times more likely to develop LOAD whereas Homozygous ApoE ε4 (ε4ε4)

allele carriers are 10 to 12 times more likely to develop LOAD (Farrer et al., 1997). Although it has a significant effect, the presence of ApoE ε4 remains merely a risk factor for developing AD as studies have shown that it has no effect on families that are genetically predisposed to develop FAD (Van Broeckhoven et al., 1994).

Many recent studies have started to focus on the effects of APP, PSEN1, PSEN2, and ApoE ε4 on various cognitive domains for nondemented carriers. It has been found that mutation carrying individuals scored higher on tests of object naming and object perception when compared to the LOAD group; however, individuals with LOAD scored significantly higher on measures of verbal ability (Warrington, Agnew, Kennedy, & Rossor, 2001). In addition, studies have found that mutation carrying individuals scored significantly lower on measures related to executive functioning, working memory, and visuospatial tasks when compared to noncarrying controls; however, there was no significant difference in the scores between the carriers and noncarriers on verbal memory and language scores (Ringman et al., 2005). In addition, the presence of ApoE ε4 is associated with poorer performance on tests of global cognitive functioning, episodic memory, and executive functioning (Small et al., 2004). No differences have been found for ApoE ε4 carriers on cognitive measures of primary memory, attention, visuospatial skill, verbal ability, and perceptual speed (Small et al., 2004). Furthermore, the zygosity of the ApoE ε4 carriers has a significant impact on the magnitude of cognitive deficits measured. Homozygotic ApoE ε4 carriers exhibit significantly poorer performance on global cognitive functioning and episodic memory when compared to noncarriers; however, heterozygotic carriers are not significantly different than noncarriers (Small et al., 2004). As expected, individuals carrying the ApoE ε2 allele

demonstrate better performance, as compared to ε3 homozygotes, whereas ApoE ε4 carriers perform significantly worse on cognitive measures (Small et al., 2004). This indicates that the ε2 allele has a beneficial impact on cognitive performance even in nondemented populations.

Although the existing literature includes meta-analytic studies of prominent genetic markers for AD, there are no meta-analytic studies examining the role of APP, PSEN1, and PSEN2 on cognitive factors. Therefore, it is the focus of this present study to try and sort through the extensive literature concerning AD to determine the effect size of each of the genes, both familial and late-onset AD, on various domains of cognitive functioning by conducting multiple meta-analyses. As is consistent with previous literature, it is hypothesized that ApoE ε4 will have the largest effect contributing to cognitive deficits while carriers of ApoE ε2 will score the highest on cognitive measures. In addition, the effect sizes of APP, PSEN1, and PSEN2 will be measured across various cognitive domains to determine which, if any, have the most significant impact on AD carrier's cognitive functioning. This will allow for better accuracy when diagnosing AD when genetic testing is not available or reasonable.

CHAPTER II

REVIEW OF LITERATURE

Alzheimer's disease (AD) is a major public health issue that impacts an estimated 5%-10% of people in the 65-74 year range and nearly 50% of people over the age of 85 (Bachman, Wolf, & Linn, 1992). It is estimated that over 20 million people have been diagnosed with AD worldwide (Itzhaki, Wozniak, Appelt, & Balin, 2004). In the United States alone there are over 4.5 million people diagnosed with AD and this number is expected to increase exponentially as the "baby boomers" begin to extend life expectancy (Evans, 1990).

As the most common form of dementia, AD accounts for approximately two thirds of all cases, and is characterized by irreversible, neurodegenerative damage of the brain (Hendrie, 1998). Despite the widespread prevalence and seriousness of this disorder there is currently no known cure for AD, although some pharmacological treatments, such as acetylcholinesterase inhibitors, have been found to be useful at slowing disease progression (Fu, Zhang, & Sun, 2005). The lack of an effective cure is largely because there are multiple risk factors, many of which remain unidentified, that increase the likelihood that someone will suffer from AD.

Normal aging typically results in a decrease in cortical and hippocampal volume, often causing mild declines in memory abilities, but AD is far more severe (Morrison & Hof, 1997). Characterized by insidious onset, AD is progressive and ultimately reveals multiple cognitive deficits which, in addition to impaired memory and thinking, may

include sleep disturbances, disorientation, change(s) in personality and behavior, inability to follow directions, and problems with language and communication. The current *Diagnostic and Statistical Manual of Mental Disorders* (text revision [*DSM–IV–TR*]; American Psychiatric Association, 2000) further requires that these cognitive deficits be accompanied by aphasia (disability in articulating ideas or comprehending spoken or written language), apraxia (disability in performing coordinated movements or manipulating objects), or agnosia (disability in interpreting sensory stimuli).

Risk Factors

There are several known risk factors that have been shown to increase the likelihood of developing AD. Several studies have indicated that women are at a significantly higher risk for developing dementia than men, especially at very old ages (Bachman et al., 1992; Fratiglioni et al., 1997). In part, this finding reflects the fact that women, on average, live longer than men. However, even in studies that have controlled for age, women appear to be at a slightly greater risk for AD than men (Schoenberg, Anderson, & Haerer, 1985). One possible explanation that has been offered for this discrepancy is that women may have greater susceptibility to a specific genotype that increases the likelihood of developing AD (Payami et al., 1996).

Other studies have shown that cardiovascular disorders, like hypertension, significantly increase the risk of developing AD (Skoog & Gustafson, 2003). More specifically, high systolic blood pressure has been associated with an increased risk for hippocampal atrophy which greatly increases the chances of developing AD (Launer et al., 2000). The hippocampus is a part of the brain critically involved in the formation and storage of memories (Squire, 1992). Other known vascular factors and conditions that

increase the risk for developing AD include: diabetes, hypercholesterolemia, hyperhomocystinemia, and transient ischemic attacks (Iadecola & Gorelick, 2003; Michikawa, 2003).

Contaminants in the environment have also been linked to increasing the risk of developing AD. For example, aluminum and aluminum containing products, such as deodorant, have been strongly linked with AD (Graves et al., 1990). Furthermore, studies have shown that prolonged exposure to different types of aluminum can result in large cellular depletions during hippocampal formation (Miu, Andreescu, Vasiu, & Olteanu, 2003). In addition, aluminum is found in abundance within the neuritic plaques and neurofibrillary tangles that are typically associated with AD (Harrington & Wischik, 1995).

A history of head trauma has also been shown to increase the likelihood of developing AD (Mayeux et al., 1993), but only in combination with specific genotypes (Mayeux et al., 1995). In addition to head trauma, some studies have indicated that the circumference of the head and size of the brain are correlated with development of AD. Individuals with smaller heads have a greater risk for AD even after adjusting for confounding variables such as weight, height, and gender; however the genotype still plays an important synergistic role (Graves, Mortimer, & Bowen, 2001). Likewise, individuals with larger brains may be able to mask the effects of AD for a longer period of time before being officially diagnosed (Mortimer, Borenstein, & Gosche, 2005).

There has also been a substantial body of research looking at the effects of genetics as a risk factor for developing AD. One indication that genetics likely play an integral role in AD was the observation that people with Down's syndrome almost

invariably get AD if they survive into middle age (Lott & Head, 2005). Because Down syndrome is caused by trisomy on chromosome 21, researchers began to investigate the relationship between chromosomes and AD (Lott & Head, 2005). With the proliferation of genetics studies, it is now widely held that there are at least two distinct sub-types of Alzheimer's disease: familial early-onset AD (FAD) and late-onset AD (LOAD). Each of these sub-types, and the genetic underpinnings, will be reviewed. However, it is important to first understand the relevant mechanisms of action before investigating which genes on specific chromosomes are contributing to the different types of AD.

Mechanisms of Action

Alzheimer's disease is known to result when brain proteins fail to fold regularly and clump together, thereby interfering with normal neuronal activity. Two kinds of abnormal proteins have been identified as related to Alzheimer's disease: *amyloid* and *tau*. *Amyloid* produces neuritic plaques, structures formed from degenerating axons and dendrites, in various synapses found throughout the brain (Kalat, 2003). *Tau* produces neurofibrillary tangles, structures formed from degenerating structures found within neuronal cell bodies. The amount of *amyloid* and *tau* buildup present in an individual's brain can be directly influenced by their genetic makeup (Kalat, 2003).

Most cases of AD are complex in that they appear to be inherited in a non-Mendelian fashion; several genes may interact to cause the disease (Parker et al., 2005). Although several of these genes have been identified, scientists believe that there are multiple genetic combinations that have yet to be explored. Thus far, research indicates that there are four chromosomes typically involved in the pathogenesis of AD. Three of these chromosomes (21, 14, and 1) are found as missense mutations (the meaning of a

readable genetic message has changed due to a substitution on one base of DNA) that cause autosomal dominate FAD (Rocchi, Pellegrini, Siciliano, & Murri, 2003). Autosomal dominance refers to one parent carrying a genetic mutation on one of the identified chromosomes resulting in a 50% chance that the child will also develop FAD (Rocchi et al., 2003). Therefore, if both parents suffer from FAD the child will almost always (greater than 99%) develop the disorder as well. Although these genetic mutations have very high specificity, the vast majority of AD carriers only develop the disorder later in life (Rocchi et al., 2003). Furthermore, some carriers are known to be sporadic and occur in families without a specific autosomal dominant pattern of inheritance (Cummings, Vinters, Cole, & Khachaturian, 1998).

The fourth chromosome (19) that has been heavily implicated in AD progression significantly increases the risk that an individual will develop the disease. Carriers of certain allelic combinations on this chromosome most typically develop AD after the age of 65 (Kalat, 2003).

Although genes play a vital role in many of the cases of AD, it is important to note that environmental factors also significantly contribute to onset and progression of the disease. In the largest population-based twin study of AD to date (2006), researchers found that the concordance rates of AD varied with age of onset for the disorder suggesting there are non-genetic lifestyle factors that can affect both risk and timing of AD (Gatz et al., 1997). In addition, cross-cultural studies have shown that the Yoruba people of Nigeria have a much lower incidence of AD than do Americans, including African Americans (Hendrie, 2001). The Yoruba do not develop AD even if they have the same allelic combinations of certain chromosomes that increase the risk in

Americans. It is currently believed that this decreased vulnerability is the result of the Yorubas' low-calorie, low-fat, low-sodium diet.

Familial Early-Onset AD (FAD)

FAD is a rare form of AD characterized by an early onset, before the age of 65 (Kalat, 2003). This is typically problematic for both the individuals suffering from FAD and their families as they are still actively involved in providing and caring for the member of their family with AD. The prevalence rates of FAD have been estimated to affect only 1%-2% of the entire population of people suffering from AD (Tanzi et al., 1987). However, many investigators argue that the rates of FAD should be significantly higher than what is reported due to the difficulty in differentially diagnosing FAD. Recent studies illustrate this point by showing that FAD is frequently misdiagnosed as a different form of dementia or is all together under addressed by researchers in their investigations of AD (McMurtray, Clark, Christine, & Mendez, 2006; Sampson, Warren, & Rossor, 2004).

Amyloid precursor protein, Presenilin-1, and Presenilin-2

FAD is, to date, known to result from genetic mutations on three chromosomes: 21, 14, and 1. Other genes have been implicated as contributing to FAD, but these are the most widely researched genes at this time. These mutations impact the encoding for the amyloid precursor protein (APP) on chromosome 21, the presenilin-1 (PSEN1) protein on chromosome 14, and the presenilin-2 (PSEN2) protein on chromosome 1 (Rocchi et al., 2003). The presence of any of these mutations usually results in onset of AD before the age of 65, although mutations on chromosome 1 appear to result in wider variability with onset ranging from 40 years of age to 80 (Bird et al., 1996). The

variability of impact associated with a mutation on chromosome 1 has been interpreted as suggestive of incomplete penetration. In addition to earlier age of onset, mutations of these genes are also associated with an accelerated disease progression compared to late-onset AD (Ringman, Diaz-Olavarrieta, & Rodriguez, 2005).

There are other anomalous symptoms that are not present in LOAD, but are frequently found in FAD including: spastic paraparesis or quadriparesis (weakness of the lower or combined lower and upper extremities), early myoclonus (a condition of abnormal contraction of muscles or portions of muscles), seizures, or a presentation with predominantly frontal lobe dysfunction (Ringman, 2005). These discrepant effects could reflect the aggressive nature of FAD or, perhaps, the impact of the younger age of the brain at the onset of the disorder (Ringman, 2005).

The prevalence rates of each of these mutations are, thus far, unclear. For example, two studies examining mutations on chromosome 1 have resulted in widely discrepant estimates of 18% and 71% of all early-onset autosomal dominant AD (Chen et al., 2001; Cruts et al., 1998). However, most studies seem to agree with the idea that mutations on chromosome 14 account for the majority of familial early-onset AD (see Cummings et al., 1998, for a review). The pathogenesis of these genetic mutations has also fueled the "amyloid hypothesis" as all three of these genetic mutations manipulate the same mechanism of action that results in the overproduction of Amyloid β (Ringman, 2005).

Brain cells contain a large protein called amyloid precursor (APP) that is cleaved to form a smaller protein, 40 amino acids long, referred to as $A\beta_{40}$ (Kalat, 2003). Some individuals have a genetic mutation in which APP is cleaved into a slightly longer chain

of amino acids known as $A\beta_{42}$ (Kalat, 2003). The extra proteins are believed to clump together over time and damage the membranes of axons and dendrites (Lorenzo et al., 2000). The majority of people afflicted with AD accumulate amyloid plaques containing $A\beta_{42}$ before the onset of behavioral symptoms (Selkoe, 2000). Amyloid deposits produce widespread atrophy of several major structures found in the brain including the cerebral cortex and the hippocampus, which has been strongly linked to memory in previous studies (Squire, 1992).

Several mutations of the APP gene on chromosome 21 have been described in patients with FAD. These mutations occur at the cleavage sites in the precursor protein at the beginning and end of the peptide (Cummings et al., 1998). The mutated APP gene affects the production of Aβ in numerous ways, but appears to significantly increase the levels of the highly toxic $A\beta_{42}$. (Hardy, 1997). The actual function of APP in healthy brains is still poorly understood. However, it has been suggested that APP may function as an autocrine factor by stimulating cell proliferation and cell adhesion as well as supporting nerve growth factor on neurite outgrowth (Rocchi et al., 2003). Both of the presenilin mutations on chromosomes 14 and 1 are very similar in their structure and they both increase the production of Aβ, particularly $A\beta_{42}$. PSEN1 and PSEN2 mutations regulate the levels of $A\beta_{40}$ and $A\beta_{42}$ because they both have γ-secretase activity, the enzyme involved in transmembrane metabolism of APP (Haass & De Strooper, 1999; Li et al., 2000).

Until recently, very few studies measured the differences in cognitive functioning between individuals with FAD and LOAD as they were thought to be clinically similar. However, more recent studies have started to focus on the cognitive differences between

FAD and LOAD as well as the differences of each individual mutation linked to FAD. It has been found that mutation carrying individuals scored higher on tests of object naming and object perception when compared to the LOAD group; however, individuals with LOAD scored significantly higher on measures of verbal ability (Warrington, Agnew, Kennedy, & Rossor, 2001). PSEN1, on chromosome 14, has been studied within at-risk populations in order to determine the effect of the mutation on various cognitive factors. One study found the carriers of the PSEN1 mutation scored significantly lower on measures related to executive functioning, working memory, and visuospatial tasks when compared to noncarrying controls; however, there was no significant difference in the scores between the PSEN1 carriers and noncarriers on verbal memory and language scores (Ringman et al. , 2005).

Late-Onset AD (LOAD)

The majority of AD cases have a late onset, usually developing after the age of 65 (Kalat, 2003). The symptomology present in someone with LOAD is nearly identical to individuals with FAD with the few noted exceptions above. Much like FAD, the genetics of LOAD are complex with the possible involvement of several genes and a synergistic interaction with environmental factors (Kamboh, Minster, Feingold, & DeKosky, 2006). However, no known inherited autosomal dominant genetic mutations exist in LOAD. This indicates that many of the gene markers associated with LOAD do not definitively predict the onset of AD. However, there have been several genes identified that significantly increase the susceptibility and risk associated with the onset of sporadic LOAD. Some of these genes appear to have a larger effect on LOAD, particularly genes

on chromosome 19, however there remain several other genes on multiple chromosomes currently being investigated as potentially contributing to LOAD (Kamboh, 2004).

Chromosome 6

A human leukocyte antigen (HLA) allele on chromosome 6 has been linked with an earlier age of onset for AD (Payami et al., 1997). An allele is any of the alternative forms of a gene that may occur at a given locus. The HLA is the major histocompatibility complex in humans, responsible for allowing the cells of one tissue to survive in the presence of cells of another tissue (Payami et al., 1997). Certain alleles on HLA genes may be interfering with the immune system's ability to effectively combat LOAD (Payami et al., 1997).

Chromosome 7

There has been some evidence linking nitric oxide synthase (NOS3), an enzyme located on chromosome 7 responsible for the synthesis of nitric oxide, with LOAD pathology (Marsden et al., 1993). Some studies have shown a high concentration of the NOS3 endothelial product (eNOS) found in hippocampal pyramidal neurons, a brain region that has commonly been linked to the onset of LOAD (Doyle & Slater, 1997). Also, individuals suffering from LOAD have an increased expression of eNOS in the brain (De la Monte & Bloch, 1997). It is thought that the stress caused by this increased synthesis of nitric oxide in the brain leads to neuronal death (De la Torre & Stefano, 2000). Further research has shown that a specific genotype of NOS3 is overrepresented in LOAD patients when compared to non-demented controls (Dahiyat et al., 1999).

Chromosome 9

Lipoproteins are complex particles composed of fatty lipids, making them highly soluble and permeable in the bloodstream, and proteins (Kalat, 2003). Lipoproteins deliver fats in the form of cholesterol throughout the body and are primarily characterized by their density: high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL; Rocchi et al., 2003). Several specific genotypes of these lipoproteins have been implicated on various chromosomes as possible susceptibility agents for LOAD. The very low density lipoprotein receptor (VLDL-R) gene, located on chromosome 9, is suspected to be involved in LOAD development. VLDL-R works as a receptor for apolipoproteins (Rocchi et al., 2003), a heavily implicated contributor to LOAD which will be discussed in greater depth later in this review when overviewing chromosome 19. Further evidence that VLDL-R significantly affects LOAD is supported by studies that have found VLDL-R in abundance on specific microglia that are strongly associated with senile plaques (Christie, Chung, Rebeck, Strickland, & Hyman, 1996). Although VLDL-R has received some support, there remains some controversy concerning its lack of effect for distinct populations. More specifically, it appears that certain allelic combinations of VLDL-R with apolipoprotein significantly increase the likelihood of developing LOAD in Japanese populations and European Caucasians as opposed to Caucasian populations from other countries (Okuizumi et al., 1995; Yamanaka et al., 1998).

Chromosome 10

The insulin degrading enzyme gene (IDE), located on chromosome 10, is partly responsible for the degradation and removal of Aβ that has been secreted by microglial

cells and neurons (Vekrellis et al., 2000). Therefore, it is suggested that malfunctioning IDE may be contributing to LOAD by leaving too much secreted Aβ in the brain. Other studies have found a susceptibility locus on chromosome 10 which increases the expression of Aβ deposition resulting in an increased risk for developing LOAD (Myers et al., 2000).

Chromosome 12

Several recent studies have implicated Chromosome 12 as being a site of action where multiple abnormalities can increase the risk of developing LOAD. One abnormality involves α2-Macroglobulin, a proteinase inhibitor. Protease is a type of enzyme that is responsible for breaking down proteins in the central nervous system (Qiu, Strickland, Hyman, & Rebeck, 1999). Therefore, α2-Macroglobulin serves to stop the breaking down of certain proteins found in the brain, including Aβ (Qiu et al., 1999). α2-Macroglobulin was identified as being a disease locus during a genetic linkage study with a sample of patients and controls from Northern Spain. The results of this study implicated that α2-Macroglobulin only had a significant effect on the development of LOAD if the patients were over the age of 81 (Alvarez et al., 1999). However, other studies have found that α2-Macroglobulin is not dependent on the patient's age to still have a significant effect on the development of LOAD (Dodel et al., 2000). Other studies have rejected the effects of α2-Macroglobulin as a risk-factor for LOAD all together (Gibson et al., 2000). Therefore, further research needs to be conducted to determine whether or not α2-Macroglobulin has a significant effect on LOAD.

The low-density lipoprotein receptor-related protein gene (LRP), the main ApoE receptor in neurons, is coded for by alleles on chromosome 12 (Rebeck, Reiter,

Strickland, & Hyman, 1993). LRP enables secreted amyloid precursor proteins to gain entry into a cell without passing through the cell membrane through the process of endocytosis (Kounnas et al., 1995). Due to its close proximity to α2-Macroglobulin on chromosome 12, LRP has received recent attention as a potential explanation for the disparate research linking α2-Macroglobulin with the development of LOAD. One of the LRP alleles is associated with an earlier age of onset as well as one of the neuropathological hallmarks of AD, a significantly greater abundance of neuritic or senile plaques (Cummings et al., 1998). However, as is consistent with the research focusing on the role α2-Macroglobulin plays in the development of LOAD, several studies have found contradicting results when examining LRP. Some studies have found that it takes different variations in the involvement of one or both polymorphisms in order to significantly contribute to LOAD development (Verpillat et al., 2001). Other studies have had difficulty replicating the finding that LRP has any effect on LOAD at all (Hatanaka et al., 2000).

A small number of recent studies have focused on the transcriptional factor gene on chromosome 12, LBP-1c/CP2/LSF, and its effects on the development of LOAD. LBP-1c/CP2/LSF was examined because it is proximally similar to LRP on chromosome 12 and LBP-1c/CP2/LSF controls the expression of α2-Macroglobulin (Rocchi et al., 2003). Two studies have independently confirmed that a specific allele of LBP-1c/CP2/LSF exerts a protective effect against the development of sporadic or LOAD. It is suggested that the absence of this protective allele may actually increase the risk of developing LOAD, although this has yet to be addressed in a research study (Lambert et al., 2001; Taylor et al., 2001).

Chromosome 19

Chromosome 19 includes the gene that has the strongest support for increasing the susceptibility to develop LOAD. There is near universal acceptance among AD researchers that certain allelic combinations of apolipoprotein E significantly increase the risk of LOAD as well as modifying the risk for other factors including the genes that contribute to FAD. Apolipoprotein E (ApoE) is a plasma protein combined with a lipid that is responsible for carrying cholesterol and other fats through the bloodstream in order for these molecules to be broken down (Rocchi et al., 2003). It has also been associated with neuronal repair as it is aids in the relocation of cholesterol during neuronal growth and after injury (Mahley, 1988; Menzel, Kladetzky, & Assmann, 1983). ApoE is synthesized primarily by the liver, neurons and astrocytes in the brain, as well as macrophages (a type of white blood cell that destroys bacteria) and monocytes (Siest et al., 1995). ApoE is found in amyloid plaques and neurofibrillary tangles and it is believed that it has some regulatory properties over their deposition and formation (Harris et al., 2003). Plaque formation may even require the presence of ApoE before amyloid plaques become toxic in the brain (Lahiri, Sambamurti, & Bennett, 2004).

The ApoE gene has three common allelic variations: epsilon 2 (ε2), epsilon 3 (ε3), and epsilon 4 (ε4). Every individual inherits one allele of ApoE from each of their parents. Therefore, there are six possible genotypes that can be inherited: ε2ε2, ε2ε3, ε2ε4, ε3ε3, ε3ε4, and ε4ε4 (Lahiri et al., 2004). Each of these allelic variations has been studied in their relation to onset of AD. The ε3 variant occurs most frequently throughout the general Caucasian population with an occurrence rate of 79% (Lahiri et al., 2004). The ε2 and ε4 variations occur significantly less with occurrence rates at

approximately 8% and 14%, respectively (Seshadri, Drachman, & Lippa, 1995; Small, Rosnick, Fratiglioni, & Backman, 2004; Tischa et al., 2004). It is important to note that the ApoE allelic distribution among cognitively healthy individuals has been shown to be different across various ethnic backgrounds resulting in imprecise prevalence estimates for the entire population (Tischa et al., 2004).

The ApoE ε3 allele is the most common form found in the general population and it is believed to play a neutral role in the development of LOAD (Corder et al., 1996). In other words, it neither significantly increases nor decreases the risk associated with the development of LOAD. The ApoE ε2 allele is positively associated with survival and longevity among older adults (Corder et al., 1996). Therefore, ApoE ε2 is a protective factor against developing LOAD; however, it is the rarest allele of ApoE on chromosome 19 (Corder et al., 1996).

The ApoE ε4 allele is a powerful risk factor for the development of LOAD. The increased risk for AD in the presence of the ε4 allele is the single most replicated finding in AD genetics research (Cacabelos, 2003). It is believed that ApoE ε4 affects the development of LOAD because it increases the production of Aβ and significantly increases the number of neuritic plaques found in the brain; however, it appears that ApoE ε4 does not affect the level of neurofibrillary tangles that are commonly associated with patients suffering from AD (Gomez-Isla et al., 1996). In addition, ApoE ε4 carriers have smaller hippocampal volumes than that of noncarriers which could impact their episodic memory performance (Cohen, Small, Lalonde, Friz, & Sunderland, 2001).

Recently, researchers have begun studying the interaction between ApoE ε4 and the herpes simplex 1 virus (HSV-1), responsible for common cold sores, and its effects

on LOAD (Itzhaki et al., 2004). HSV-1 typically remains latent in individuals who carry it and only visibly expresses itself occasionally. It appears that carriers of ApoE ε4 are more susceptible to HSV-1's expression whereas carriers of ApoE ε2 experience the effects of HSV-1 less than is typical of the population (Itzhaki et al., 2004). As a result, the virulent pathogen HSV-1 is more active and damaging in the brain of ApoE ε4 carriers and may be contributing to LOAD. One case study indicated that viral inflammation, such as that caused by HSV-1, can result in the neurofibrillary tangles and degeneration in the brain commonly associated with both FAD and LOAD (Ball, 2003). In addition, some studies have shown that carriers of both ApoE ε4 allele and HSV-1 are more likely to develop LOAD than populations with either HSV-1 with a different allele of ApoE or ApoE ε4 with no HSV-1 (Itzhaki et al., 2004). ApoE ε4 carriers also have more HSV-1 DNA in the brain regions that are most commonly associated with AD, lending further support to the interaction of ApoE ε4 and HSV-1 as a risk factor (Itzhaki et al., 2004). Further research still needs to be conducted to determine if HSV-1 is a correlate or a causal mechanism in the development and onset of AD.

Approximately 40%-60% of all Alzheimer's disease carriers possess the ε4 allele of ApoE, which is two to three times higher than is typically found in the general population (Parker et al., 2005). One study assessed the risk associated with developing LOAD in the presence of ApoE ε4. The overall lifetime risk of developing LOAD increases from 14% to 29% in the presence of at least one ApoE ε4 and reduced to 9% if no ε4 is present (Seshadri et al., 1995). A meta-analysis of all the different variants of ApoE indicated that heterozygous ApoE ε4 (ε2ε4 or ε3ε4) carriers are 3 to 4 times more likely to develop LOAD whereas Homozygous ApoE ε4 (ε4ε4) allele carriers are 10 to

12 times more likely to develop LOAD (Farrer et al., 1997). In addition, the ε4 allelic variation was shown to be a significant risk factor across diverse ethnic populations in both men and women, although women appear to be at a slightly higher risk (Farrer et al., 1997). Although having only one copy of the ApoE ε4 allele significantly increases the likelihood that an individual will develop LOAD, many people carry two copies of the ε4 allele and show no signs of LOAD. Therefore, it is believed that the presence of ApoE ε4 is a risk factor, but is neither necessary nor sufficient to cause the disease (Farrer et al., 1997). Further support for ApoE ε4 as simply a risk factor was provided by a study that found that ApoE ε4 had no significant effect on families that are genetically predisposed to develop FAD (Van Broeckhoven et al., 1994).

Several studies have also looked at the effects of ApoE ε4 on nondemented populations to see if it impacts various domains of cognitive performance (Bretsky, Guralnik, Launer, Albert, & Seeman, 2003; Small et al., 2000). More specifically, studies have found that ApoE ε4 carriers have difficulty on cognitive tasks pertaining to episodic memory functioning and executive functioning (Wilson, Bienias, Berry-Kravis, Evans, & Bennett, 2002). In addition, no significant differences were found for ApoE ε4 carriers on tasks related to primary memory or visuospatial functioning (Yip, Brayne, Easton, & Rubinsztein, 2002). Regardless of these results, there remain large discrepancies in the literature concerning the effect of ApoE ε4 on cognitive performance. Some studies have reported that ApoE ε4 has a significant effect on cognitive performance among cognitively impaired individuals, but not cognitively healthy individuals (Small, Basun, & Backman, 1998). Other studies have observed significant effects of ApoE ε4-related difficulties among cognitively healthy older adults

(Wilson et al., 2002). One reason for this discrepancy is that some studies have failed to control for age (Small et al., 2004). This is a necessary control because ApoE ε4, as a risk factor for developing LOAD, loses its potency with age (Farrer et al., 1997).

A different meta-analysis combined all of the relevant literature to reconcile the differences among these studies (Small et al., 2004). This study looked at the effects of ApoE ε4 on certain cognitive domains while examining age as a possible modifying variable. In addition, this study examined the widely reported protective effects of ApoE ε2 as a protective factor against developing LOAD. More specifically, this study examined whether ApoE ε2 conveys a similar advantage to cognitive performance as it does to increased longevity (Small et al., 2004).

The results of the meta-analysis indicated significant group differences between ApoE ε4 carriers and non-carriers across several domains of cognitive functioning. More specifically, the presence of ApoE ε4 was associated with poorer performance on tests of global cognitive functioning, episodic memory, and executive functioning (Small et al., 2004). In contrast, no differences were found for ApoE ε4 carriers on cognitive measures of primary memory, attention, visuospatial skill, verbal ability, and perceptual speed. These findings are consistent with previous literature that ApoE ε4 only affects specific domains of cognitive functioning while others remain unaffected (Cohen et al., 2001; Wilson et al., 2002). There remains some question as to whether ApoE ε4 affects a carrier's visual attention or working memory when compared to non-ε4 carriers (Parasuraman, Greenwood, & Sunderland, 2002). Like previous studies, this meta-analysis found that age had an inverse relationship with the magnitude of ApoE ε4-related deficits although the effect was very small. Furthermore, the zygosity of the

ApoE ε4 carriers had a significant impact on the magnitude of cognitive deficits measured. The homozygotic ApoE ε4 carriers exhibited significantly poorer performance on global cognitive functioning and episodic memory when compared to noncarriers; however, heterozygotic carriers were not significantly different than noncarriers (Small et al., 2004). As expected, individuals carrying the ApoE ε2 allele demonstrated better performance, as compared to ε3 homozygotes, whereas ApoE ε4 carriers performed significantly worse (Small et al., 2004). This indicates that the ε2 allele has a beneficial impact on cognitive performance even in nondemented populations.

Hypotheses

Although the existing literature includes meta-analytic studies of prominent genetic markers for AD, particularly of ApoE allele combinations, there are no meta-analytic studies examining the role of APP, PSEN1, and PSEN2 on cognitive factors. Therefore, it is the focus of the proposed study to try and sort through the extensive literature concerning AD to determine the effect size of each of these genes, within both familial and late-onset AD, on various domains of cognitive measures by conducting meta-analyses of the literature.

As is consistent with previous literature, it is hypothesized that ApoE ε4 will have the largest effect contributing to cognitive deficits while carriers of ApoE ε2 will score the highest on cognitive measures. In addition, the effect sizes of APP, PSEN1, and PSEN2 will be measured across various cognitive domains to determine which, if any, have the most significant impact on AD carrier's functioning. This will allow for better accuracy when diagnosing AD when genetic testing is not available or reasonable.

CHAPTER III

METHOD

Literature Search

An electronic database search using PsycINFO, MEDLINE, and PubMed was performed for published studies in English from January 1991 to August 2008. Studies published after 1991 were selected as this was the first time that mutations of APP on chromosome 21 were identified as resulting in Alzheimer's disease (Goate et al., 1991). In addition, this time period covers the universe of articles looking at genetic mutations and genetic risk factors for Alzheimer's disease as ApoE ε4-related deficits, PSEN1, and PSEN2 were discovered shortly after APP (Corder et al., 1993; Levy-Lahad et al., 1995; Sherrington et al., 1995). These computer searches included search terms such as: Alzheimer's disease, Apolipoprotein E, APOE, amyloid precursor protein, APP, presenilin, PS1, PS-1, PS2, PS-2, PSEN, chromosome (21, 19, 14, 1), genetic, cognitive performance, memory, neuropsych, nondemented, preclinical, and cognition.

In addition to using electronic databases, the reference lists of the studies identified during the computer search were thoroughly examined to identify additional studies. Also, the abstracts and table of contents of several relevant journals, such as *Psychology and Aging*, *Neurology*, *Neuropsychological Abstracts*, *Archives of Neurology*, and *Neurobiology of Aging* were hand searched to locate any potentially missed studies. Finally, informal consultation was sought from experts in geriatric populations in order to identify any additional studies or journals relevant to the research

questions. All of these methods of literature retrieval were conducted to ensure an exhaustive review of the literature and subsequent results are representative of true effect sizes.

Eligibility Criteria

All studies selected for inclusion needed to have partitioned their participants into either the ApoE, APP, PSEN1, or PSEN2 genotypes in order to be included in the meta-analysis. In addition to identifying the participants' genotype, the studies needed to include at least one standardized measure of cognitive performance to be analyzed. The studies also must have included participants that were cognitively intact with no diagnosed cognitive impairments or traumatic brain injuries documented. Finally, the studies needed to include sufficient statistical information to allow for effect sizes to be calculated. This included: means and standard deviations; *p* values, various effect sizes, or *F* values; and sample sizes. Authors of studies that otherwise met the inclusion criteria, but were missing relevant statistics, were contacted in order to retrieve the relevant information for the analyses.

Outcome Measures

The studies included in the meta-analysis assessed their participants' cognitive functioning using different measures for similar cognitive functions. Therefore, all of the cognitive tests were organized into several broad domains of cognitive functioning. These domains are based on the typical taxonomy found in the neuropsychological assessment literature (Lezak, Howieson, Loring, Hannay, Fischer, 2004). The cognitive domains in which the individual measures were categorized include: attention, episodic memory, executive functioning, global cognitive ability, perceptual speed, primary

memory, verbal ability, and visuospatial functioning. Table 1 contains examples of many of the tests that were included in the analyses and their respective cognitive domain categorization.

Table 1
Classification of Measures to Cognitive Domains

Cognitive Domain	Measures
Attention	Paced Auditory Serial Addition Test; Stroop Color; Stroop Word; Two-Back Task (zero back condition); Trailmaking-A
Episodic Memory	Auditory Verbal Learning Test; Benton Visual Retention Test; Buschke Selective Reminding Test; California Verbal Learning Test; Fuld Object Recognition Test; Randt Short Story Memory Test; Wechsler Memory Scale; various tests of immediate recall, delayed recall, and recognition.
Executive Functioning	Arithmetic; Mazes; Stroop Color/Word (Interference); Trailmaking-B; Two-Back Task; various switching tasks
Global Cognitive Ability	Heim AH4-Part 1; Mattis Dementia Rating Scale; Mini-Mental State Examination; Modified Mini-Mental State Examination; Wechsler Adult Intelligence Scale- Full Scale IQ Score
Perceptual Speed	Digit Symbol Coding, Symbol Digit Modalities Test, various measures of reaction time
Primary Memory	Digit Span Forward and Backward
Verbal Ability	Boston Naming Test; Controlled Oral Word Association Test; Spot the Word Test; National Adult Reading Test; Wechsler Adult Intelligence Scale- Verbal IQ measures; various tests of category and letter fluency
Visuospatial Skill	Block Design; Clock Test; various measures of construction and figure copying

Statistical Analysis

Studies that met the inclusion criteria were analyzed following the methods and procedures proposed for a random-effects design by Hedges and Olkin (1985). When compared to other meta-analytic methods, this approach has been shown to be more reasonable and convergent with previous findings pertaining to various topics in the literature (Johnson, Mullen, & Salas, 1995). The data from each study was used to calculate an effect size estimate, Hedge's *g*, which is the difference between the AD groups (APP, PS1, PS2, or ApoE ε4-carriers) and the control group (non-carriers) divided by the pooled standard deviation. Therefore, Hedge's *g* represents the standardized mean difference between the AD and control groups in each study and was chosen because it corrects for biases due to small sample sizes (Hedges & Olkin, 1985). The effect size, *d*, was used to pool the results across studies for each of the genetic mutations and risk factors. It represents the standardized mean difference between studies within each mutation, weighted by the sample sizes of the individual studies (Hedges & Olkin, 1985). Weighting the studies affects the variance estimate for each study because variance estimates for studies with larger sample sizes are more precise than those for studies with smaller effect sizes (Lipsey & Wilson, 2001). Negative effect sizes indicate poorer performance on the cognitive measures for the AD groups when compared to non-carriers. Also, several studies used multiple cognitive measures for one domain (e.g., PASAT and Trails A to measure attention). As a result, an averaged effect size of the measures for each domain was obtained for each study following the procedures outlined by Cohen (1988). The initial baseline data was used in the meta-analysis for studies that administered cognitive measures at multiple time points.

The chi-square statistic, Q, was also calculated to test for homogeneity of results across studies. If significant, it indicates that there may be other characteristics affecting the magnitude of the effect sizes (Hedges & Olkin, 1985). In addition to the Q-statistic, the I^2 index was calculated as a measure of the degree of inconsistency in the study results. It represents the percentage of variance across studies that is not attributed to chance alone (Higgins, Thompson, Deeks, & Altman, 2003). For the moderator analysis, Q_W was calculated as a measure of the heterogeneity of studies within categories. In addition, Q_B was calculated to represent the difference between categories of the moderator variable. If significant, Q_B indicates that the moderating variables are significantly affecting the results. All of the outlined statistical procedures are consistent with previous meta-analyses that examined the effects that ApoE and mutations for AD have on nondemented individuals' cognitive performance (Bäckman, Jones, Berger, Laukka, & Small, 2005; Small et al., 2004). All analyses were conducing using the statistical software Comprehensive Meta Analysis, Version 2.0 (Borenstein, Hedges, Higgins, & Rothstein, 2005).

Moderator Variables

In addition to calculating overall effect sizes, potential moderating variables that are associated with the magnitude of effect sizes were included for examination. While a test of heterogeneity increases confidence that the studies share a common effect size, it is still necessary to fully address the effect of potential variables' impact on the effect sizes observed (Hall & Rosenthal, 1991). Therefore, two moderating variables that typically influence ApoE-related cognitive deficits were examined; age and the zygosity of ApoE ε4 carriers. Several studies have shown that increases in age significantly

decrease the magnitude of the effect attributed to ApoE ε4 (Farrer et al., 1997; Small et al., 2004). Therefore, age was treated as a continuous variable to plot the magnitude of the observed effect sizes between ApoE ε4 carriers and ApoE ε4-noncarriers'cognitive performance. In addition to age, ApoE ε4 zygosity (homozygous or heterozygous) and the potential compensatory effects of ε2 zygosity were examined for the analyses.

For the meta-analysis, no moderating variables were examined as possibly affecting the effect size magnitude of APP, PSEN1, and PSEN2 genetic mutations. This is largely because the inheritance of any one of these genetic mutations from only one parent results in a near 50% likelihood that the offspring will develop FAD as well (Rocchi et al., 2003). Therefore, unlike ApoE ε4 carriers, it is thought that there are very few potential moderators on the effect size magnitude from genetic mutations, including the presence of ApoE ε4. While the inheritance of a genetic mutation from both of the parents resulting in further cognitive deficiencies associated with only one mutation is possible, the actual sample size of participants identified in the relevant studies was too small to include as a moderating variable in the analyses.

Publication Bias

One common criticism of meta-analyses is that they have historically overestimated effect sizes as a result of the "file-drawer problem." The file-drawer problem is the result of publication bias in which the set of available studies in peer-reviewed journals is not representative of all studies ever conducted on that topic (Rosenthal, 1979). There are many studies that are unpublished because their results are not statistically significant and are sitting in researchers' "file drawers." To examine the possibility of publication bias, the fail-safe N was calculated on the mean weighted effect

sizes contributed by each study (collapsing across the cognitive domains) to determine the number of nonsignificant studies that would need to be included to nullify the results. Rosenthal (1979) recommends testing this estimated fail-safe N value against $5k + 10$ (k = number of studies), a conservative estimate of the existing unpublished null-finding studies. Rosenthal (1979) indicates that the meta-analysis results are an accurate estimate of the true effect size if the fail-safe N is relatively large when compared to the estimated number of unpublished or unretrieved studies.

CHAPTER IV

RESULTS

Study Characteristics

Table 2 displays the characteristics of the studies included in the ApoE meta-analysis. Originally, 176 studies were identified for inclusion in the analyses. Many of these studies were conducted by the same researchers on the same cohort resulting in multiple publications. To avoid dependency in the observations, the most comprehensive study from that research group was included. Comprehensive studies included the largest sample sizes and widest breadth of cognitive measures and are thought to be the best representation of the original research sample. As a result, 49 studies were eliminated after examining the characteristics of the study and the respective participant samples. 22 additional studies were eliminated as the participants had documented cognitive deficits including, but not limited to: different types of dementia, Parkinson's disease, and traumatic brain injury. 39 studies were missing relevant data to calculate the effect sizes and were contacted for the necessary information; 11 authors responded to the request with the data; 7 authors refused to send the data; the remaining 21 authors never responded to the request for the information. In total, cognitive test results were obtained from 40,942 cognitively healthy individuals across 77 studies.

Only five studies focusing on APP, PSEN1, and PSEN2 were identified to be included in the analyses. Of those five studies, three were by the same authors and the

remaining two collected data from the same extended family. As a result of the dependency in observations, analyses were only conducted on ApoE.

Table 2
Characteristics of Studies Included in the Meta-Analysis

First author	Year	Cognitive Domains	*n*, ε4 present	*n*, ε4 absent	Participant Age
Alexander	2007	EF, EM, PM, PS, VA	91	324	28
Askar	2005	EF, EM, VA	17	61	62.3
Bartzokis †	2006	EM, GC	12	53	66.1
Bathum †	2006	GC	138	597	92
Baum	2006	GC	40	189	78.3
Berr	1996	EM	274	869	65
Blair	2005	EM, PS, VA	2418	5477	56.8
Bondi	1999	AT, EF, EM, GC, PM, PS, VA, VS	43	90	69.5
Bookheimer	2000	EM	16	14	62.5
Bunce	2005	EM, PM, VS	49	118	82.8
Burkhardt	2004	EM, GC	64	117	66.1
Calhoun-Haney	2005	GC	22	28	71.9
Caselli	2002	EF, EM, GC, PM, VA, VS	84	42	55.1
Deary	2002	GC	121	345	79.1
Deeny	2008	GC	25	52	59.8
den Heijer	2002	GC	261	688	72.3
Dik	2000	EM	213	653	73.2
Driscoll	2005	AT, EF, EM, GC, VS	16	16	78.2
Espeseth	2008	AT, EF, EM, GC, PS	37	59	64.5
Ewers	2008	GC	6	31	66.7
Flicker	2004	EM, GC, PS	74	225	78.9
Flory	2000	EM, GC, PM	61	159	45.5
Frisoni	2005	GC	4	21	69
Gilbert	2004	EM, GC, VA	19	19	71.4
Helkala	1995	AT, EF, EM, GC, VA, VS	278	634	73.9
Hofer	2002	EM, PS, VA	95	339	75.9
Houston	2005	AT, EF, EM, GC, VA, VS	24	28	76.2
Hu	2006	GC	106	349	74.1
Hwang	2006	GC	20	91	75
Irie	2008	GC, PS	602	1945	74.7
Jessen	2007	EM	213	839	80.1
Johnson	2006	AT, EF, EM, VA	11	53	55
Jorm	2007	EM, GC, PM, PS, VA	1757	4638	42.7
Juva †	2000	GC	68	245	85
Kim	2002	EM, GC, VA, VS	74	392	70.1
Klages	2003	EM, GC	42	167	76.8
Kryscio	2006	AT, EF, EM, VA	137	330	Not Reported
Lehmann †	2006	EM	666	1451	72.5
Levy	2004	EM, PS, VA, VS	61	115	59.4

Moffat	2000	GC	13	13	69.1
Mondadori	2007	EM	13	21	22.3
Moore	2005	GC	19	16	74.5
Mosconi	2008	EM, GC, PS, VA	13	15	59
Newman	2000	GC, VA	29	29	59.4
Nilsson	2006	GC, EM	777	1918	58.8
O'Brien	2004	AT, EF, EM, GC, PM, VA	13	25	72.9
O'Hara	1998	EM, GC, PS, VA	22	61	74
Payton †	2006	AT, EM, GC, PS, VA	185	555	62.9
Peavy	2007	EM, GC	29	55	78.4
Persson	2006	GC, VA	30	30	66.3
Plassman	1997	EM, GC, PS, VA	6	14	62.5
Pomara	2005	EM, GC, VA	24	40	66.1
Reiman	1996	EM, EM, GC, PM, VA, VS	11	22	56
Reynolds	2006	EM, PM	160	386	65
Riley	2000	EM, GC, VA, VS	34	207	81
Robson	2002	AT, EM, GC, VA	34	52	59
Rosen	2002	EF, GC, PM	21	21	62.2
Sager	2005	EF, EM, GC, VA, VS	204	248	53
Salo	2001	EM, GC, VA	12	34	89
Savitz	2007	AT, EF, EM, PM, VA	60	165	47.9
Schmidt	1996	EF, EM, PM, PS, VA	39	175	60.5
Small, B. J.	2000	AT, EF, EM, GC, VA	91	322	72.9
Small, B. J.	1998	EM, GC, PM, VA, VS	20	54	81.8
Small, G.	2000	EM, GC	27	27	66.4
Smith	1998	GC	90	251	79.7
Steed	2001	AT, EF, EM, PS	30	81	64.5
Sun	2007	AT, EM, GC, VA, VS	4	26	68.8
Swan	2006	EF, EM, PS	70	256	78.9
Tagarakis	2007	EM, GC, PM	33	104	69.5
Tardiff	1997	EF, EM, PM, PS	17	48	61.3
Tohgi	1997	GC	14	40	58.7
Tupler	2007	EM, GC	73	90	65.8
Wang	2006	EM, GC	4	16	75.1
Wilson, Bienas	2002	GC	158	511	75.5
Wilson, Schneider	2002	EM	186	542	75.9
Wishart	2006	AT, EF, EM, VA	13	22	66.6
Yaffe	1997	EF, GC, PS	271	1479	71.1
		Total *n*	11108	29834	

Note. ε4 = epsilon 4 allele of the apolipoprotein E gene; Cognitive domains: AT = attention, EM = episodic memory, EX = executive functioning, GC = global cognitive ability, PM = primary memory, PS = perceptual speed, VA = verbal ability, VS = visuospatial functioning.

† Participant ages were estimated from available data.

Effect Sizes

A total of 227 effect sizes were extracted across all eight cognitive domains. Table 3 displays the mean weighted effects sizes (*d*-values) for each of the eight cognitive domains calculated across all of the studies included in the analyses. ApoE ε4 carriers performed more poorly than ApoE non-ε4 carriers on all of the cognitive domains; significant differences were found on episodic memory (k = 56, d = -.14, 95% confidence interval = -.21, -.07, $p < .001$), global cognitive functioning (k = 55, d = -.05, 95% confidence interval = -.10, -.004, $p < .05$), executive functioning (k = 22, d = -.06, 95% confidence interval = -.12, -.004, $p < .05$), and perceptual speed (k = 18, d = -.07, 95% confidence interval = -.13, -.01, $p < .05$). Although the observed effect sizes are small according to Cohen's conventions (1988), some of the observed effects are larger than previously reported findings (Small et al, 2004).

Table 3

Effect Sizes for the Eight Domains of Cognitive Functioning

Domain	*k*	Sample Size		*d*	95% CI	*r*	*Q*	I^2 (%)
		ApoE ε4+	ApoE ε4-					
Episodic Memory	56	8,991	22,728	-.14**	-.21, -.07	-.07	241.07**	77.19
Global cognitive ability	55	4,782	13,666	-.05*	-.10, -004	-.03	72.63*	25.65
Verbal ability	33	5,953	14,638	-	-.05,	-.002	36.72	12.86

				.003	.05			
Executive functioning	22	1,535	4,387	-.06*	-.12, -.004	-.03	18.08	0
Perceptual Speed	18	5,831	15,896	-.07*	-.13, -.01	-.04	34.11**	50.17
Primary Memory	15	2,459	6,371	-.11	-.33, .11	-.06	125.61**	88.85
Attention	15	974	2,454	-.03	-.11, .05	-.02	7.26	0
Visuospatial functioning	13	902	1,992	-.02	-.11, .06	-.01	8.57	0

Note. k = number of studies; ApoE = apolipoprotein E; ε4+ = ε3/ε4, ε4/ε4; ε4- = ε2/ε2, ε2/ε3, ε3/ε3; d = mean weighted effect size, *CI* = confidence interval, r = effect size expressed as correlation coefficient, Q = within domain homogeneity, I^2 = percentage of heterogeneity due to study differences.
* $p < .05$. ** $p < .01$.

Moderator Analyses

The results indicated significant heterogeneity of effect sizes for episodic memory ($Q = 241.07$, $p < .001$), global cognitive ability ($Q = 72.63$, $p < .05$), perceptual speed ($Q = 34.11$, $p < .01$), and primary memory ($Q = 125.61$, $p < .001$), indicating that moderator variables are influencing the results.

Meta-regression was used to measure the impact of increasing age on the observed effect sizes between ApoE-ε4 carriers and ApoE non-ε4 carriers on episodic memory, global cognitive ability, and perceptual speed (Figures 1, 2, and 3 in Appendix A, respectively). Increasing age was a significant predictor of larger effect sizes for both episodic memory ($Q_m = 6.67$, $p < .01$) and global cognitive ability ($Q_m = 5.16$, $p < .05$); however, age was not a significant predictor of effect size changes for perceptual speed ($Q_m = .38$, $p = .54$). This indicates that the differences observed between ApoE-ε4 carriers and ApoE non-ε4 carriers on episodic memory and global cognitive ability become larger as the carriers age.

Table 4 displays the mean weighted effect sizes (*d*-values) when controlling for ApoE ε4 zygosity on measures of episodic memory and global cognitive ability. The six remaining cognitive domains were not examined as a result of too few studies reporting the cognitive results according to ApoE ε4 zygosity. ApoE ε4 homozygote carriers (ε4/ε4) performed significantly poorer than ApoE non-ε4 carriers on measures of episodic memory (k = 12, d = -.18, 95% confidence interval = -.34, -.02, $p < .05$); however, no significant differences were found between ApoE ε4 heterozygote carriers (ε3ε4) and ApoE non-ε4 carriers on measures of episodic memory (k = 12, d = -.04, 95% confidence interval = -.09, .01, p = .12). In addition, no significant differences were found between ApoE ε4 homozygote carriers and ApoE ε4 heterozygote carriers on measures of episodic memory (Qb = 2.73, p = .10). On measures of global cognitive ability, no significant differences were found between ApoE ε4 homozygote carriers and ApoE non-ε4 carriers (k = 7, d = -.14, 95% confidence interval = -.31, .03, p = .11). Likewise, ApoE ε4 heterozygote carriers did not perform significantly different than ApoE non-ε4 carriers on measures of global cognitive ability (k = 7, d = .02, 95% confidence interval = -09, .14, p = .72). Finally, no significant differences were found between ApoE ε4 homozygote carriers and ApoE ε4 heterozygote carriers on measures of global cognitive ability (Q_b = 2.33, p = .13).

Table 5 displays the mean weighted effect sizes (*d*-values) when comparing the presence of ApoE ε2 against ApoE ε4 on measures of episodic memory and global cognitive ability. The six remaining cognitive domains were not examined as a result of too few studies reporting the presence of ApoE ε2. ApoE ε2 carriers (ε2/ε2, ε2,ε3) did not perform significantly different than the control group (ApoE ε3/ε3) on measures of

episodic memory (k = 6, d = .09, 95% confidence interval = -.05, .22, p = .20). Likewise, no significant differences were found between ApoE ε4 carriers (ε3/ε4, ε4/ε4) and the control group (ApoE ε3/ε3) on measures of episodic memory (k = 6, d = -.08, 95% confidence interval = -.17, .02, p = .11). However, ApoE ε2 carriers performed significantly better than ApoE ε4 carriers on measures of episodic memory (Q_b = 3.88, p < .05). On measures of global cognitive ability, ApoE ε2 carriers did not perform significantly different than the control group (k = 4, d = .05, 95% confidence interval = -.17, .28, p = .65). Likewise, ApoE ε4 carriers did not perform significantly different than the control group on measures of global cognitive ability (k = 4, d = .001, 95% confidence interval = -.11, .11, p = .99). Finally, ApoE ε2 carriers did not perform significantly different than ApoE ε4 carriers on measures of global cognitive ability (Q_b = .16, p = .69).

Table 4
Effect Sizes for Episodic Memory and Global Cognitive Ability When Controlling for ApoE- ε4 Zygosity

Domain	k	Sample Size		d	95% CI	Q_w	Q_b
		ApoE ε4+	ApoE ε4-				
Episodic Memory							
HMZ ε4	12	592	16,046	-.18*	-.34, -.02	26.1**	2.73
HTZ ε4	12	6,001	16,046	-.04	-.09, .01	19.59	
Global Cognitive							
HMZ ε4	7	137	5,148	-.14	-.31, .03	5.71	2.33
HTZ ε4	7	1,496	5,148	.02	-.09, .14	17.03	

Note. k = number of studies; ApoE = apolipoprotein E; ε4+ = ε3/ε4, ε4/ε4; ε4- = ε2/ε2, ε2/ε3, ε3/ε3; d = mean weighted effect size, *CI* = confidence interval, Q_w = within

domain homogeneity, Q_b = between groups homogeneity; HMZ ε4 = homozygote epsilon 4 carriers (ε4/ε4); HTZ ε4 = heterozygote epsilon 4 carriers (ε3/ε4).
* $p < .05$. ** $p < .01$.

Table 5
Effect Sizes for Episodic Memory and Global Cognitive Ability When Comparing ApoE-ε2 Against ApoE-ε4

Domain	*k*	Sample Size		*d*	95% CI	Q_w	Q_b
		ε2+ or ε4+	ε3/ ε3				
Episodic Memory							
ApoE ε2+	6	270	1,460	.09	-.05, .22	1.94	3.88*
ApoE ε4+	6	659	1,460	-.08	-.17, .02	4.78	
Global Cognitive							
ApoE ε2+	4	178	1,054	.05	-.17, .28	4.51	.16
ApoE ε4+	4	456	1,054	.001	-.11, .11	1.33	

Note. *k* = number of studies; ApoE = apolipoprotein E; ε2+ = (ε2/e2, e2/e3); ε4+ = ε3/ε4, ε4/ε4; *d* = mean weighted effect size, *CI* = confidence interval, Q_w = within domain homogeneity, Q_b = between groups homogeneity.
* $p < .05$. ** $p < .01$.

Publication Bias

Figure 4 in Appendix A displays a funnel plot to visually assess for any publication bias. When publication bias is present, the funnel plot would have multiple studies with few participants and large effect sizes near the bottom of the plot. This is largely because studies with a smaller number of participants are less likely to get published unless the effect sizes are large. As can be seen in Figure 4, the effect sizes are symmetrically distributed with no publication bias visually present. In addition, the fail-safe N of 533 calculated across all 77 studies when collapsing cognitive domains exceeded the estimate of 395 unretrieved or existing unpublished studies with

nonsignificant findings. This indicates that the observed significant effects cannot be explained by publication bias during the selection of the included studies.

CHAPTER V

DISCUSSION

The results of the meta-analysis indicated statistically significant group differences between ApoE ε4 carriers and ApoE non-ε4 carriers across multiple domains of cognitive functioning. More specifically, ApoE ε4 carriers performed significantly poorer on measures of episodic memory, global cognitive ability, executive functioning, and perceptual speed. Overall, the weighted mean differences between the groups ranged from middling to small, ranging from .003 to .14 standard deviations. No significant differences were observed for the domains of attention, primary memory, verbal ability, and visuospatial skill.

The decreased performance observed on certain cognitive abilities as a result of the presence of ApoE ε4 is consistent with many other studies. Specifically, several researchers have found that ApoE ε4 carriers perform worse on measures of episodic memory (Bondi, Salmon, Galasko, Thomas, & Thal, 1999; Flory, Manuck, Ferrell, Ryan, & Muldoon, 2000; Levy et al., 2004; Nilsson et al., 2006; Wilson, Bienias et al., 2002), global cognitive ability (Deary et al., 2002; Hwang et al., 2006), executive functioning (1995; Rosen, Bergeson, Putnam, Harwell, & Sunderland, 2002; Swan, Lessov-Schlaggar, Carmelli, Schellenberg, & La Rue, 2006) and perceptual speed (Blair et al., 2005). Furthermore, nonsignificant findings is consistent with many other studies for attention (Small et al., 2004; Sun et al., 2007), primary memory (Rosen et al., 2002),

verbal ability (O'Hara Helkala et al., et al., 1998; Small et al., 2000), and visuospatial skills (Levy et al., 2004).

The analysis of possible moderators revealed that age, ApoE ε4 zygosity, and the presence of ApoE ε2 all significantly impacted the results. Concerning age, the results indicated that increases in age results in significantly larger effect size differences between ApoE ε4 carriers and ApoE non-ε4 carriers on measures of episodic memory and global cognitive ability. These findings are inconsistent with an earlier meta-analysis that found nonsignificant findings for age and effect size differences between ApoE ε4 and ApoE non-ε4 carriers on measures of episodic memory and global cognitive ability (Small et al., 2004). In addition, the magnitude and direction of the effect is also different as the previous meta-analysis found that effect sizes became smaller as the participants aged (Small et al., 2004). It is thought that this discrepancy is the result of twice as many studies being included in the present analyses which increases the chances of finding significant results.

Controlling for the moderating effects of ApoE ε4 zygosity indicated that homozygous carriers performed significantly worse than heterozygotes on measures of episodic memory when being compared to homozygote ε3 carriers. The middling sized effects are consistent with previous research that has documented the dose-effect relationship of ApoE ε4 and episodic memory (Berr et al., 1996; Caselli et al., 2002; Small et al., 2004; Yaffe, Cauley, Sands, & Browner, 1997). This study was unable to replicate the previous meta-analysis that found a significant dose-effect relationship for measures of global cognitive ability. It is thought that this is a result of fewer studies of

global cognitive ability being included in the current analyses; the same authors were contacted to obtain the data, but they did not respond with the necessary information.

Finally, the presence of ε2 was associated with higher scores than ApoE ε4 carriers on measures of episodic memory. Although the magnitude of the effect was small, the findings are still congruent with previously reported research studies (Small et al., 2004; Mondadori et al., 2007; Wilson, Bienias et al., 2002). These results complement the findings that the presence of ApoE ε2 is positively associated with survival and longevity among older adults (Corder et al., 1996).

The results of the current meta-analysis help to extend and confirm the findings of Small et al. (2004). The aforementioned study did not find significant deficits in perceptual speed while this meta-analysis detected a small effect. In addition, both meta-analyses confirm that the presence of ApoE ε4 is negatively associated with episodic memory, executive functioning, and overall global cognitive ability. Again, both analyses support the notion that the presence of ApoE ε4 does not affect attention, verbal ability, visuospatial skill, or primary memory. Also, both meta-analyses found a dose-effect relationship for ApoE ε4 alleles with homozygotic carriers performing the worst on measures of episodic memory. Finally, both analyses found a significant compensatory mechanism, albeit a small effect, with the presence of ApoE ε2 on episodic memory.

Knowing that ApoE selectively affects only certain aspects of cognition raises the possibility that ApoE is somewhat isolated from certain areas of neural functioning. Recent studies have found that carriers of ApoE ε4 have significantly smaller hippocampi and amygdalae in both the left and right hemispheres of the brain when compared to homozygote ApoE ε3 carriers (den Heijer et al., 2002). This finding could help explain

why ApoE ε4 carriers experience poorer performance on measures of episodic memory. Another recent study has shown that ApoE ε4 carriers employ a more economic use of learning-related neural resources without taxing their performance which raises the possibility that the presence of ApoE ε4 only impacts certain aspects of episodic memory (Mondadori et al., 2007). Although ApoE ε4 only exerts small effects on cognitive functioning, the increasing identification of the specific aspects of cognitive functioning that are affected could help elucidate on the mechanism of action that ApoE ε4 uses to increase the chances of developing Alzheimer's disease later in life.

The most prevalent limitation of the meta-analysis is the variability inherent in the testing instruments attempting to measure the same domain of functioning. Many of the included cognitive measures have poor psychometric properties including inconsistent reliability and suspect validity. Many of the measures tap into multiple cognitive domains simultaneously, making it difficult to isolate the effect to one specific function. Finally, most of the studies included in the global cognitive ability analyses used the Mini Mental State Examination (MMSE) as a screening device for Alzheimer's disease. The MMSE is deficit oriented making it very hard to avoid the ceiling effects to gain a more nuanced view of the differences between ApoE ε4 carriers and ApoE non-ε4 carriers on global cognitive functioning.

Another limitation is that the majority of the studies included in the analyses simply reported the scores for two groups: ApoE ε4+ and ApoE ε4-. Very few studies presented the data with it divided according to the full ApoE genotype. This makes it difficult to determine the presence of a dose-effect relationship between ApoE ε4 alleles and cognitive performance. Also, many of the studies did not report on additional

information that could have been included as moderating variables. Gender, education, and the presence of cardiovascular disease may all have an impact; however, the relatively small number of studies that documented this information made it impossible to create an accurate summary statistic.

Future research should focus on identifying which specific areas of episodic memory, global cognitive ability, executive functioning, and perceptual speed are most impacted by the presence of ApoE ε4. It is thought that multiple standardized measures with a high correlation should be administered to avoid any losses in validity. In addition, the impact of age needs to be more closely examined. Small et al. (2004) indicated that increases in age mask the effects of ApoE ε4; however, the findings from this meta-analysis indicated the opposite. Age enhanced the poorer performance exhibited by the ApoE ε4 carriers when compared to the ApoE non-ε4 carriers.

Additionally, future research should focus on determining which cognitive domains are impacted by mutations of the APP, PSEN1, and PSEN2 genes in nondemented, preclinical populations. The studies currently in the literature on this topic do not include many cognitive measures and instead focus on the chromosomal differences. Like the gains made with understanding ApoE, much can be learned about these mutations if it is known what areas of cognitive functioning they most affect.

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APPENDIX A

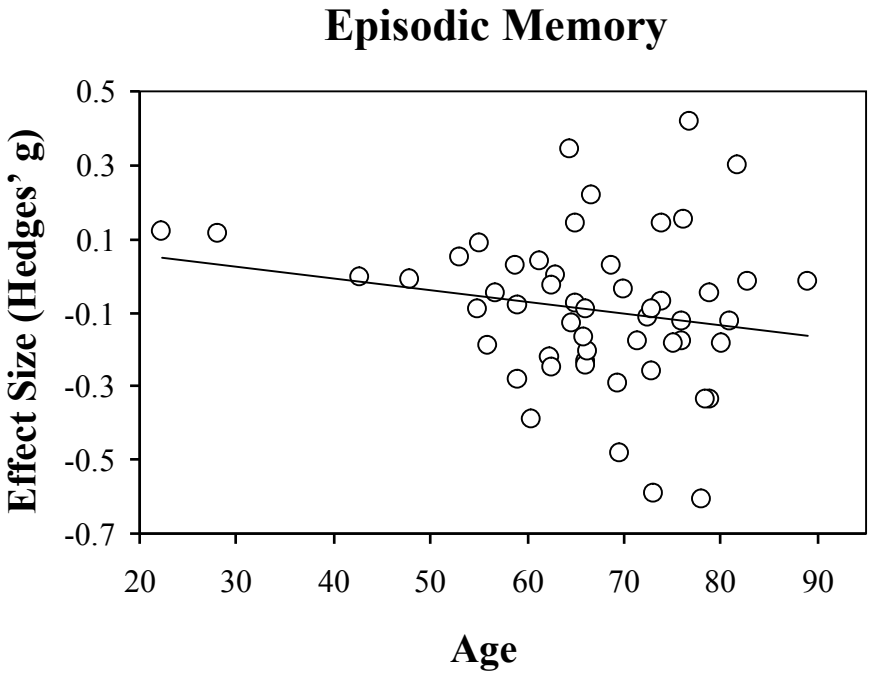

Figure 1. Scatterplot of age and effect size (Hedges' *g*) for episodic memory. Flory et al, 2000 and Levy et al, 2004 were excluded because of outlying effect sizes. Kryscio, 2006 was excluded because age was not able to be obtained. $Q_m = 6.67$, $p < .01$.

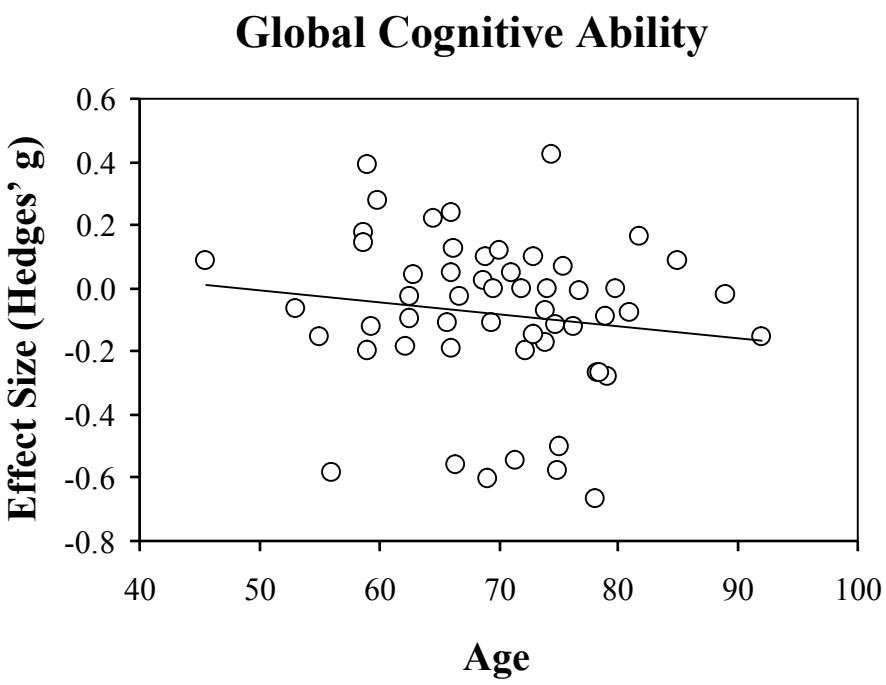

Figure 2. Scatterplot of age and effect size (Hedges' *g*) for global cognitive ability. $Q_m = 5.16$, $p = .02$.

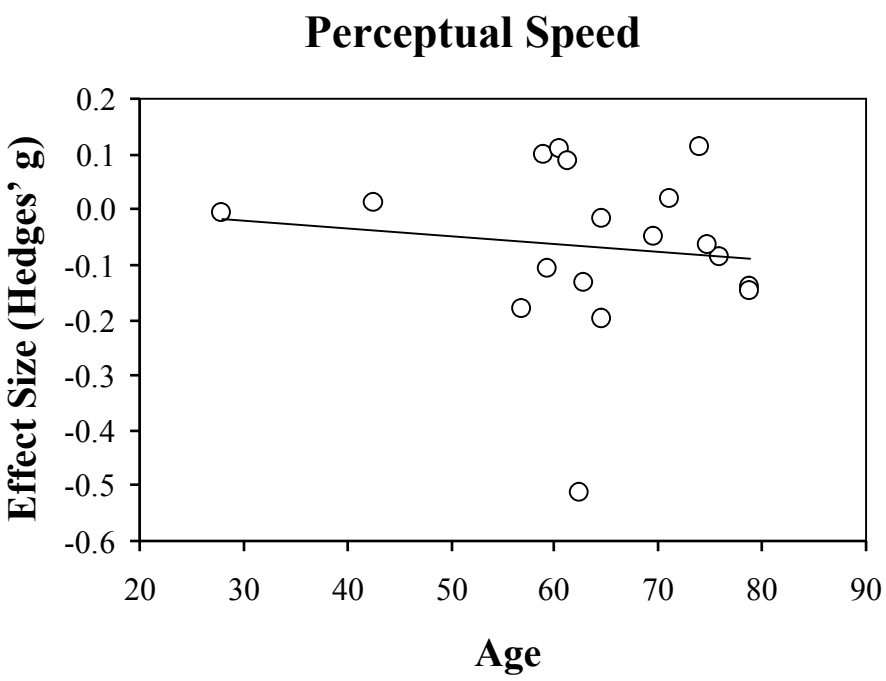

Figure 3. Scatterplot of age and effect size (Hedges' *g*) for perceptual speed. $Q_m = .38$, $p = .54$.

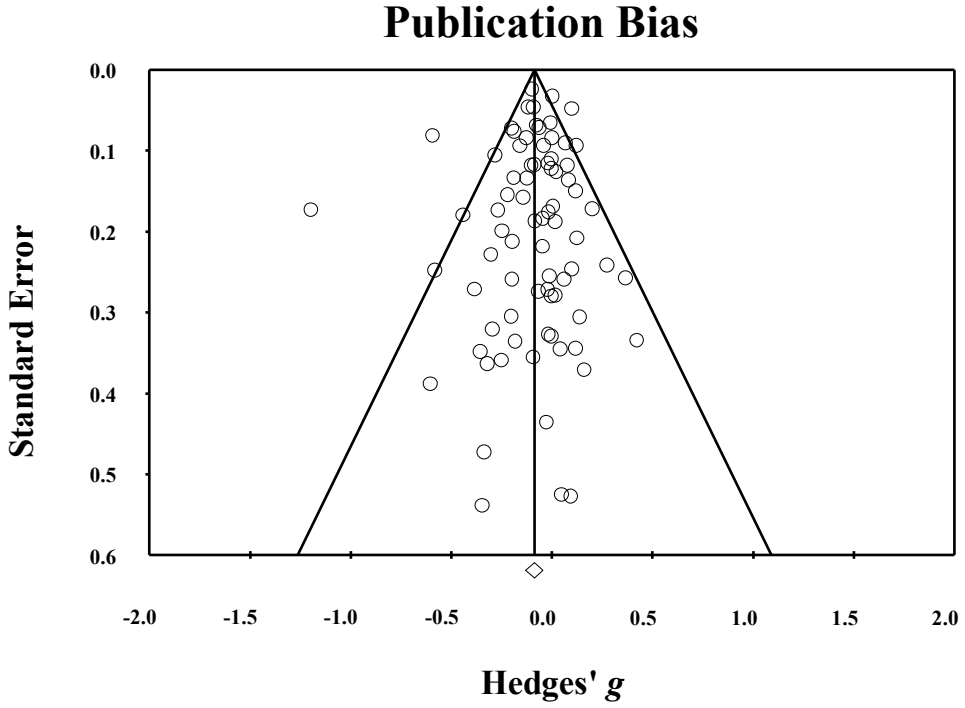

Figure 4. Funnel plot of standard error and Hedges' *g* to visually assess for publication bias. $n = 77$.

VITA

Nicholas Matthew Wisdom

Candidate for the Degree of

Master of Science

Thesis: THE EFFECTS OF CAUSATIVE AND SUSCEPTIBILITY GENES ON THE DEVELOPMENT OF ALZHEIMER'S DISEASE: A META-ANALYTIC APPROACH

Major Field: Psychology

Biographical

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Name: Nicholas Matthew Wisdom Date of Degree: December, 2008

Institution: Oklahoma State University Location: Stillwater, Oklahoma

Title of Study: THE EFFECTS OF CAUSATIVE AND SUSCEPTIBILITY GENES ON THE DEVELOPMENT OF ALZHEIMER'S DISEASE: A META-ANALYTIC APPROACH

Pages in Study: 74 Candidate for the Degree of Master of Science

Major Field: Psychology

Findings and Conclusions:

Missense mutations of the amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2) genes all cause autosomal dominate familial early-onset Alzheimer's disease (FAD). Apolipoprotein E, particularly the epsilon 4 allele (ApoE ε4), is also a known genetic risk factor for developing late-onset AD (LOAD). The presence of any of these mutations or ApoE ε4 impacts cognitive performance in nondemented individuals. Evidence of the presence and magnitude of these cognitive deficits will be examined with meta-analyses of the available literature.

ADVISER'S APPROVAL: Jennifer L. Callahan, PhD