THE IMPACT OF CAUSATIVE GENES ON NEUROPSYCHOLOGICAL FUNCTIONING IN

FAMILIAL EARLY-ONSET ALZHEIMER'S DISEASE: A META-ANALYSIS

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Mutations of three genes encoding amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2) have been shown to reliably result in familial early-onset Alzheimer's disease (FAD); a rare, but catastrophic, subtype of Alzheimer's disease (AD) marked by symptom emergence before age 65 as well as accelerated cognitive deterioration. The current study represents the first known meta-analysis on the association of APP, PSEN1 or PSEN2 on neurocognitive variables. A total of 278 FAD mutation-carriers (FAD-MC) and 284 cognitively healthy non-mutation-carriers (NC) across 10 independent investigations meeting inclusion criteria were chosen for the current meta-analysis (random effects design). Findings revealed an overarching trend of poorer performance by FAD-MC individuals compared to NC individuals across the majority of cognitive domains identified. Significant differences in effect sizes suggested FAD-MC individuals exhibited worse performance on measures of attention, explicit memory, fluency, primary memory, verbal, and visuospatial functioning. Findings indicative of differential sensitivity to cognitive domain impairments across FAD-MC and NC groups inform neuropsychological descriptions of individuals in preclinical phases of FAD.

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CHAPTER I

SUMMARY OF LITERATURE

The formidable public health burden embodied by Alzheimer's disease (AD) clearly impacts afflicted individuals and their families, but its influence on caregivers, health care providers, and researchers creates a cascade of societal malaise. As the financial obligation across these domains in the United States is estimated to reach approximately $226 billion in 2015, AD claims the title of the most expensive disease in America (Alzheimer's Association, 2015). By 2050, this figure is expected to exceed one trillion dollars due to total population growth and proportional growth of individuals 65 and older, the highest risk demographic for developing AD (Alzheimer's Association, 2015).

Alzheimer's disease, the most prevalent form of dementia (Wilson et al., 2012), is an age-related neurodegenerative illness. Its characteristic progression of cognitive deterioration, most prominently displayed in memory impairment, inexorably leads to loss of physical function followed by death. No cure exists and effective treatment is minimal, due in large part to the silent onset of the disease. Neuronal damage slowly accumulates over time, usually 20 years before perceptible symptoms emerge (Villemagne et al., 2013). This prevents early detection of the disease, which otherwise might allow for the curtailing or termination of symptom progression. Thus, increasing success rates for early identification and treatment is of paramount importance it was the primary motivation for the addition of a preclinical stage to the diagnostic criteria for AD (American Psychiatric Association, 2013).

Precise etiology has yet to be elucidated, though several genetic and environmental risk factors significantly increase the likelihood of developing AD. Among identified risk factors, advanced age and family history of genetic predisposition to AD most strongly affect risk

prevalence (Baumgart et al., 2015). Additionally, female gender, cardiovascular disorders, diabetes, traumatic brain injury, and long-term exposure to certain environmental contaminants have been linked with increased risk of developing AD (Ciobica et al., 2011; Herbert et al., 2013; Miyake et al., 2010; Suhahov et al., 2006; & Yegambaram et al., 2015). While empirical support for many of these risk factors is limited, extensive research, focused on a few specific gene mutations and their respective connections to familial and sporadic subtypes of AD, has produced a compelling body of evidence highlighting the powerful influence of genetics on risk profiles.

More specifically, genetic mutations can alter the normal breakdown of proteins in the brain. Prevailing theories on the mechanisms of action in AD neuropathology identify improperly metabolized protein fragments as culpable catalysts of characteristic neurodegeneration. Namely, the abnormal accumulation of extracellular amyloid plaques and intracellular neurofibrillary tau tangles results from a failure to clear these deposits faster than they are produced (Bolshette, 2014). Fragment buildup interferes with communication within and between neurons, which leads to progressive cognitive deterioration, reflective of underlying synapse loss and cell death (Hardy & Selkoe, 2002). Individuals with familial early-onset AD (FAD), in which these cognitive impairment symptoms emerge before age 65 (and occasionally as early as age 30), typically inherit a missense mutation in one of three specific genes on as many different chromosomes (Bekris, Yu, Bird, & Tsuang, 2010). This autosomal dominant inheritance form of the disease exhibits a more aggressive course of cognitive decline, with language, motor, and sensory impairments developing at a relatively young age, on rare occasion as early as age 30 (Rosselli et al., 2000). Prevalence rates of FAD are estimated to account for

approximately one percent of all AD cases, although frequent misdiagnosis may obscure the accuracy of these estimates (Alzheimer's Association, 2015).

Mutations on genes encoding amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) are evident in the majority of FAD cases (Bekris, Yu, Bird, & Tsuang, 2010). The precise function of APP remains unknown, but it may promote neuron proliferation and synaptogenesis, as well as play a role in cellular damage repair (Dawkins & Small, 2014; Thornton et al., 2006). Dominantly inherited mutations to APP genes result in the increased generation of an abnormally long form of beta amyloid ($A\beta_{42}$), a byproduct of APP proteolysis, which is more prone to aggregation and plaque formation (O'Brien & Wong, 2011). Mutations to the enzyme components carrying out this APP cleavage process, PSEN1 and PSEN2, also lead to excessive amyloid buildup. Importantly, presenilin mutations encompass 90% of all known FAD mutations (Shen & Kelleher, 2007). The inhibition of proper enzyme activity not only increases the rate of $A\beta_{42}$, but also decreases the rate of normal, more soluble $A\beta_{40}$, thus intensifying intercellular toxicity and accelerating the neurodegenerative process (Moehlmann et al., 2002). Furthermore, there is evidence that suggests $A\beta_{42}$ might further inhibit enzyme activity by nonproductively occupying cleavage sites, thus imitating the partial loss of presenilin function induced by genetic mutation, instigating a downward spiral of progressive neurodegeneration (Sambamurti et al., 2006). Additionally, partial loss of function in PSEN1 and PSEN2 reduces the effectiveness of protein cleavage in other substrates associated with intercellular communication and cell death signaling (De Strooper et al., 1999; Schroeter et al., 2003). The multidimensional influence of PSEN1 and PSEN2 on regular cellular activity helps clarify why their dysfunction elicits such a broad pattern of deterioration in various domains of cognitive functioning.

The extensive breadth and depth of literature focused on the molecular consequences of genetic mutations on AD pathology has merited reviews of genetic markers via meta-analytic studies, of which there are several (e.g., Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007; Farrer et al., 1997; Lambert et al., 2013) While research exists examining the role that such mutations have on cognitive factors, meta-analytic studies in this area are extremely limited, focusing on the late-onset subtype of AD. The effect of APP, PSEN1, and PSEN2 mutations on various domains of cognitive functioning for preclinical carriers has not been assessed through meta-analysis. Conducting a meta-analysis of this kind, as was the aim of this study, can assist in illuminating the relational nature and significance of each FAD-associated mutation on assorted cognitive domains.

CHAPTER II

DETAILED REVIEW OF LITERATURE

Prevalence

The current and projected prevalence of Alzheimer's disease (AD) presents a daunting

public health challenge, due to its significant impact on victims, caregivers, and researchers

alike. Approximately 34 million people worldwide are currently living with AD (Barnes &

Yaffe, 2011), giving it the notorious distinction of the most common central nervous system

disorder (Prakash et al., 2015). In the United States, an estimated 5.3 million people have AD,

including 11% of those 65 and older and 32% of people 85 and older; however, it is believed that

nearly half of these Americans have not been diagnosed (Alzheimer's Association, 2015). As a

large collection of the country known as the "baby boomer" generation is beginning to reach age

65, entering elevated AD-risk territory, the number of people 65 and older will account for 20%

of the total population by 2030, a 7% increase from 2010 (Vincent & Velkof, 2010). Though

other leading causes of death in this age group (i.e., heart disease, stroke, prostate cancer) have

seen decreases in resultant mortality rates between 11%-23% since 2000, deaths from AD have

risen 71% in the same span (Alzheimer's Association, 2015).

Alzheimer's disease accounts for 60%-80% of all dementia cases (Wilson et al., 2012)

and is marked by progressive declines in cognitive function (e.g., memory impairment,

depression), subsequent physical function (e.g., difficulty speaking and walking), and ultimately

death. There is no cure at this time. This may be a consequence of relatively imperceptible

neurodegeneration that begins 20 years prior to the emergence of symptoms, thereby rendering a

cure unrealistic in the presence of insurmountable neuronal damage (Villemagne et al., 2013).

Therefore, pharmacological treatment focuses on improving symptoms, though none of the

current six FDA-approved drugs actually slow the fatal progressing of neuronal damage (Alzheimer's Association, 2015). In light of its slow and silent onset, early detection of AD is as important as it is challenging.

One of the major impediments to early detection of AD is its confusion with the normal aging process. Forgetting, problem-solving difficulties, and word-finding issues, for example, are just some signs of normal aging as well as early stages of AD; however, the pivotal discrepancy may lie in the frequency and extensiveness of these symptoms. Corresponding neurobiological changes underlie normal aging and AD, as well. Both have characteristic cortical tissue shrinkage, although it is more severe in AD due to cell loss and dead cell debris (Alzheimer's Association, 2015). Additionally, hippocampal atrophy, resulting in mild memory impairment, is associated with normal aging; however, again, this presentation is significantly more pronounced in AD (Morrison & Hof, 1997).

Increasing the chances for early detection, and successively early treatment intervention, is key for decelerating disease progression. This issue was the emphasis of a 2011 publication by the National Institute on Aging and Alzheimer's Association, which highlighted the critical importance of differentiating normal aging from preclinical AD (Sperling et al., 2011). Consequently, new diagnostic criteria now define three stages of AD: preclinical, mild cognitive impairment, and dementia, the first of which is before memory loss develops (Sperling et al., 2011). In addition to insidious onset, the current *Diagnostic and Statistic Manual of Mental Disorders* (American Psychiatric Association, 2013) requires that deficits in memory and learning and at least one other cognitive domain (e.g., executive function, language, perceptual-motor) interfere with daily functioning. This cognitive decline must also be steady, without

extended plateaus, and no evidence of mixed etiology can be present. Furthermore, evidence of Alzheimer's genetic mutation from family history can be utilized in AD diagnosis.

Risk Factors

While exact etiology remains unclear, genetic and non-genetic factors may both play a role in increasing the probability of developing AD. Unfortunately, the two most influential factors within these categories, family history of genetic susceptibility and advanced age, respectively, are not modifiable (Baumgart et al., 2015). The latter factor might explain why two thirds of all Americans with AD are women (Hebert et al., 2013), as they live longer than men (Hebert et al., 2001). Other possibilities for this gender imbalance include less educational opportunities for women historically, as there is evidence of lower education as a risk factor (Kukull et al., 2002), as well as increased vulnerability to specific gene-related risks of developing AD (Altmann et al., 2014).

There is also compelling evidence for cardiovascular and other vascular disorders impacting risk of developing AD. Studies have shown hypertension, which is known to cause increased brain atrophy and ventricular enlargement (Miyake et al., 2010), can result in the type of cognitive decline seen in AD (Ciobica et al., 2011). Moreover, high systolic blood pressure, specifically, is correlated with decrease in hippocampal volume, which has major implications for new memory formations (Launer et al., 2000). Glucose intolerance from diabetes mellitus (Ciobica et al., 2011) and high cholesterol (Solomon et al., 2007) are also associated with increased risk for developing AD.

Long-term exposure to some environmental contaminants has also been implicated in increased risk of developing AD. This is thought to be due to neuroinflammation and neuropathology provoked by the toxicity of some common pesticides, pollutants, metals, and

industrial chemicals (Yegambaram et al., 2015). Aluminum (a common ingredient in many antiperspirant products), specifically, has been incriminated as a threatening risk factor, as its exposure promotes the same amyloid accumulation seen in AD brain pathology (Bhattacharjee et al., 2014) and can cause cellular depletion in hippocampal formation (Miu, et al., 2003).

Another known risk factor increasing the likelihood of developing AD is a history of head trauma with loss of consciousness (Suhahov et al., 2006). This link is supported by evidence of tau pathology and APOE-beta deposits shown in individuals after sustaining head injuries (Jellinger, 2004). Relatedly, studies have shown larger head circumference and intra-cranial volume (ICV), or brain size, can mitigate the impact of AD symptoms (Guo et al., 2013). This finding is thought to be a protective factor due to enhanced brain reserve, or excess of total neurons (Perneczky et al., 2010). Individuals with this larger reserve, therefore, may experience wider intervals between AD onset and diagnosis, as the symptoms remain hidden for longer periods of time (Mortimer, Borenstein, & Gosche, 2005).

The research examining the heritability of AD has uncovered an abundance of evidence that genetics play a decisive role in the risk of developing AD. Several risky genes have been identified as a result of this research, some of which influence the predisposition to develop one of the two accepted subtypes of AD: familial early-onset AD (FAD) and late-onset AD (LOAD). Three specific genes and their relationships to these sub-types will be evaluated in this paper. To appreciate these genetic influences, first, a pertinent discussion of the mechanisms of action fundamental to AD is warranted.

Mechanisms of Action

The deterioration of memory, language, and physical function characteristic of Alzheimer's disease is linked with the progressive accrual of protein fragments in and around

neuronal cell bodies. Proteins improperly folding and clustering together is a normal occurrence; however, where neurotypical brains prevent excessive cluster accumulation through protective mechanisms, brains of individuals with AD fail to breakdown the clusters efficiently (Bolshette, 2014). This resultant fragment buildup interferes with inter-neuronal communication, causing malfunction and eventually cell death.

Two types of abnormal structures have been identified as culpable fragment buildups in AD: plaques, found outside cell bodies, and tangles, found inside neuronal cell bodies (Bloom, 2014). The extracellular plaques consist of beta-amyloid protein fragments and are formed between neurons from decaying axons and dendrites (Kalat, 2003). The neurofibrillary tangles consist of tau proteins, similarly formed from decaying structures, but within neuronal cell bodies. There is evidence that the failure to clear amyloid deposits quickly enough to prevent plaque buildup may trigger the creation of excess tau tangles, and that both protein accumulations are responsible for instigating the neurodegenerative processes in AD (Hardy & Selkoe, 2002). Whether these pathogenic malfunctions arise in an individual is largely determined by their genetics (Tanzi & Bertram, 2005).

No one causal gene for AD has been identified, and in the majority of cases, AD is linked to several genes and their interactions with each other (Parker et al., 2005). Despite the twofold risk increase in first-degree relatives of individuals with late onset Alzheimer's Disease (LOAD), the disease is not usually inherited in a Mendelian manner (Bekris, Yu, Bird, & Tsuang, 2010). Substantial research has focused on four genes strongly tied to AD susceptibility, although up to 20 genes of interest have been implicated in some studies (Chouraki & Seshadri, 2014). Three of these four genes, located on chromosomes 21, 14, and 1, respectively, are associated with autosomal dominant inheritance of familial Alzheimer's disease (FAD). This means the

inheritance of only one copy of a missense mutation (i.e., an abnormal substitution of one of the chemical pairs on a gene's DNA sequence) from either carrier-parent nearly guarantees the offspring will develop FAD (95%-100%, depending on which gene) (Bekris, Yu, Bird, & Tsuang, 2010). Those who develop AD as a result of mutations on these three genes make up approximately 1% of AD cases (Alzheimer's Association, 2015). The fourth aforementioned gene, located on chromosome 19, is implicated in the over 90% of individuals with LOAD; however, its increased AD risk is associated with sporadic inheritance of specific genotypes, not mutations (Bekris, Yu, Bird, & Tsuang, 2010).

With familial diseases, shared lifestyle and environmental factors may contribute to increased risk, in addition to genetic factors (Alzheimer's Association, 2015). There are large differences in prevalence rates across race. Elderly African-Americans and Hispanics, for example, are twice and one and one half times more likely, respectively, to develop AD compared to elderly Caucasians (Gurland et al., 1999). Genetic differences do not seem to account for these variance discrepancies, suggesting comorbid health conditions, such as cardiovascular disease, and lower socioeconomic status may be largely responsible (Chin, Negash, & Hamilton, 2011).

<center>Familial Early-Onset Alzheimer's Disease</center>

Familial early-onset Alzheimer's disease (FAD) is a hereditary form of AD, with family history evidence usually spanning across multiple generations, in which symptoms emerge before age 65, and sometimes, though rarely, as early as age 30 (Bekris, Yu, Bird, & Tsuang, 2010). In contrast to sporadic late-onset AD (LOAD), FAD is characterized by a more aggressive course of cognitive decline, with earlier signs of aphasia (impairment in producing or comprehending language), apraxia (impairment in planning or executing motor movements), and

agnosia (impairment in interpreting sensory stimuli) (Rosselli et al., 2000). Prevalence rates of

FAD range from 1% to 2% of all AD cases (Tanzi et al., 1987); however, this figure is difficult

to accurately estimate due to frequent misdiagnosis and difficulty assessing family history.

Additionally, the percentage of under-diagnosis for LOAD may be greater than for FAD, as the

latter is less vulnerable to confusion with normal aging, further obscuring prevalence estimates

within all AD cases. The majority of all FAD cases exhibit genetic mutations on genes for

amyloid precursor protein (APP), presenilin 1 (PSEN-1), or presenlin 2 (PSEN-2) (Bekris, Yu,

Bird, & Tsuang, 2010).

<div align="center">Amyloid Precursor Protein</div>

Amyloid precursor protein (APP) is present in many types of cells, but large

concentrations are found in brain tissue. Though its precise function is still unknown, APP may

play a key role in neuron proliferation and synaptogenesis, as it is highly expressed during early

nervous system development (Dawkins & Small, 2014). Alternatively, it has been argued that

APP serves a more protective role, as there is evidence that it is up-regulated in mature brains

following traumatic brain injury (Thornton et al., 2006). In the latter hypothesis, individuals with

genetically mutated overexpression of APP would therefore exhibit over-primed responses to

cell damage, generating a harmful protein surplus, which then begins a chronically destructive

cycle (Hardy, 2009). Regardless of APP's exact role in healthy brains, elements of its

prototypical overexpression in FAD pathology are distinctly incriminating.

APP is rapidly and continuously metabolized in the central nervous system (Bateman et

al., 2006). The proteolysis of APP often generates a smaller peptide byproduct called beta

amyloid (Aβ), which is typically 40 amino acids long; however, inherited mutations to the genes

on chromosome 21 encoding APP can result in an increased generation of Aβ that is 42 amino

acids long ($A\beta_{42}$) (O'Brien & Wong, 2011). $A\beta_{42}$ is comparatively more toxic, less soluble, and more susceptible to aggregation over time (Shen & Kelleher, 2007). This aggregation is central to the amyloid hypothesis, which posits that the characteristic neurodegeneration in FAD is the result of a process initiated by the accumulation of beta-amyloid plaques in the brain (Hardy, 2009).

Brains of most elderly individuals exhibit some accumulation of $A\beta$, but individuals with FAD form excessive plaques before age 65, due to genetic mutations (Shen & Kelleher, 2007). There are 32 different APP missense mutations that are known to cause FAD (O'Brien & Wong, 2011), which accounts for approximately ten percent of all identified FAD mutations (Shen & Kelleher, 2007). Most of these APP mutations occur around the γ-secretase cleavage site, affecting the length and production rate of $A\beta$ (O'Brien & Wong, 2011). This APP cleavage process is mediated by the γ-secretase enzyme, which is comprised of four proteins, including presenilin-1 (PSEN1) and presenilin-2 (PSEN2). Mutations to genes encoding PSEN1 and PSEN2 account for the other 90% of known FAD mutations (Shen & Kelleher, 2007).

Presenilin-1 and Presenilin-2

The essential protein subcomponents of γ-secretase, namely presenilin-1 (PSEN1) and presenilin-2 (PSEN2), largely determine the length of peptides formed by APP cleavage (De Strooper et al., 1999). Many mutations to the genes encoding PSEN1 and PSEN2 can inhibit proper γ-secretase activity, leading to an increased production of $A\beta_{42}$ and a concurrent decreased production of the shorter, more soluble, and less toxic $A\beta_{40}$ (Moehlmann et al., 2002). This pattern of abnormal extracellular $A\beta$ accumulation yields amyloid plaques found in brains of individuals with AD (Shen & Kelleher, 2007). PSEN1, mapped onto chromosome 14, has also been linked to membrane budding and intracellular signaling during apoptosis (cell death)

(Squire, 2009). The structurally similar PSEN2, mapped onto chromosome 1, has likewise been associated with these integral cellular activities (Squire, 2009). While 90% of all identified autosomal dominant mutations resulting in FAD involve presenlin-encoding genes, 179 of these (93%) are specifically linked to PSEN1 (Obrien & Wong, 2011).

In addition to APP, γ-secretase is responsible for cleaving many other substrates, such as Notch proteins, known to regulate intercellular signaling and development (De Srooper et al., 1999). As PSEN mutations decrease the effectiveness of this cleaving process, it is possible that affected Notch substrates may be contributing to the neuronal damage seen in FAD (Hardy, 2009). Furthermore, mutated forms of PSEN1 have been shown to inhibit the transcriptional functionality of Notch, as well as APP, thereby impairing the formation of normal intercellular connections (Schroeter et al., 2003). These ensuing synaptic and dendritic malfunctions trigger eventual cell death, thus providing a catalytic series of events that might explain the cognitive deterioration seen in AD better than solely plaques or tangles (Terry et al., 1991).

Studies of mutated adult mice brains have demonstrated that loss of function in PSEN1 and PSEN2 causes impairment in various domains of neural functioning, including: hippocampal memory formation, neurogenesis, molecular signaling, and synaptic plasticity (Handler, Yang, & Shen, 2000; Saura et al., 2004). Further supporting its multifaceted influence on disease pathology, most PSEN1 missense mutations are scattered across chromosome 14's genetic sequence, instead of localized to one specific area of functioning (Saura et al., 2004). Considering the range of possible mutations and affected domains, even partial loss of PSEN-function can negatively impact multiple levels of normal cellular activity. Moreover, such partial dysfunction can elicit a cyclical pattern of progressively greater loss of PSEN-function, and, as

proposed by the presenlin hypothesis, eventual AD pathology (Sambamurti et al., 2006; Shen & Kelleher, 2007).

According to the presenilin hypothesis, almost all variations of APP, PSEN1, and PSEN2 mutations result in elevated levels of $A\beta_{42}$ (Sambamurti et al., 2006). The excess of these abnormally long peptides increases their probability of inertly occupying the active cleavage site after their formation, thereby interfering with normal γ-secretase activity (Shen & Kelleher, 2007). Essentially, this sequence simulates the inhibiting effect of a mutated PSEN on γ-secretase, as it increases production of $A\beta_{42}$ and decreases production of $A\beta_{40}$, thus perpetuating the cycle and causing neurodegeneration (Shen & Kelleher, 2007). While this theory offers an appealing alternative to the amyloid hypothesis, some argue that it lacks sufficient empirical support (Hardy, 2009).

Hypotheses

At present, there are no meta-analytic studies on the association of APP, PSEN1 or PSEN2 on neurocognitive variables, despite their strong implication in familial Alzheimer's disease. Thus, the current study sought to carefully cull the extensive literature concerning AD to determine the effect size, via meta-analysis, of each of these genes on various domains of cognitive functioning. It was specifically hypothesized that mutation associated with APP, PSEN1, or PSEN2 would be significantly associated with cognitive functioning.

CHAPTER III

METHOD

A keyword search of the electronic databases PsycINFO, MEDLINE, and PubMed for studies published between January 1991 and November 2016 was performed. The search was conducted using the following terms: Alzheimer's disease, 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. Additionally, the following journals were hand-searched for relevant studies: *Psychology and Aging, Neurology, The Journal of the International Neuropscyhological Society, Archives of Neurology,* and *Neurobiology of Aging.* All abstracts and table of contents were reviewed to identify any missed studies. Given that 1991 marked the first differential linkage of APP mutations on chromosome 21 to familial Alzheimer's disease (Goate et al., 1991), in that chromosome 21 APP markers were found to be absent in late-onset AD families, all studies examined for inclusion in the current meta-analysis occurred after this date. Similarly, the discovery of PSEN1 and PSEN2 genetic mutations and their connection to familial AD was first discovered after 1991 (Levy-Lahad et al., 1995; Sherrington et al., 1995), thus falling within the chosen search date range. Final articles were chosen based on proper inclusion criteria.

Additionally, all citation lists for potential final studies were searched for relevant references, which were subsequently screened for possible inclusion. Consultation was sought from experts in geriatric and memory research. Executing each step in this search process thoroughly ensured that reported effect sizes accurately reflected the current literature.

Inclusion Criteria

All studies eligible for inclusion in the meta-analysis were written in English and were required to have included participants who exhibited APP, PSEN1, or PSEN2 genotypes. Additionally, cognitive performance was required to have been included in each chosen study as a standardized measurement for analysis. Studies were required to have included comparison groups consisting of individuals with no history of cognitive impairment or brain injury. As this meta-analysis was contingent upon effect sizes, chosen studies included requisite statistical information necessary for these calculations. Such statistics included: means and standard deviations; p values, various effect sizes, or F values; and sample sizes. Efforts were made to contact authors and retrieve data of potential studies that fell short of inclusion criteria strictly due to lack of the aforementioned data.

Outcome Measures

Cognitive functioning was assessed with multi-modal approaches in studies chosen for meta-analysis. Performances from each test were grouped into similar cognitive domains. The organization of these cognitive domains reflected current literature on neuropsychological assessment, generating the following groups: attention, executive functioning, explicit memory, fluency, global cognitive, primary memory, processing speed, verbal, and visuospatial. All tests included in the final meta-analysis were categorized according to these domains. This cataloging is reflected in Table 1, in which all of the measures included in the analyses are sorted into their respective cognitive domains.

Table 1

Classification of Measures to Cognitive Domains

Cognitive Domain	Measures
Attention	Graded Difficulty Arithmetic; X-target; Digits (total)
Executive Functioning	Stroop Color/Word (Interference); Trail-Making Test B; Simon; Wisconsin Card Sorting Task; 2-back test; Kramer Card Sorting; WISC-III WMIQ; Tower of London; Color Trails 2 Test; various switching and working memory tasks
Explicit Memory	RMT (words/faces); WMS-logical memory (immediate/delayed); Rey Auditory Verbal Learning Test; Rey-Osterrieth Complex Figure; Pair Binding (intact, mixed, new); Memory Verbal Prose-delayed recall; ADP-delayed recall; CERAD-word list delayed recall; WMS-R index verbal memory; WMS-R index visual memory; WMS-R index general memory; WMS-R index delayed memory; FCRT; CERAD-visual recall; WMS-visual reproduction; BVRT; various word memory tasks (recall & recognition)
Fluency	Controlled Oral Word Association Test; Letter fluency; Animal naming; Vegetable naming; Category fluency; Object naming; 5-Point Nonverbal Fluency
Global Cognitive	WAIS-R Full-Scale IQ; WASI IQ; HAWIE-R Total IQ; WISC-III Total IQ; Clinical Dementia Rating; MMSE
Primary Memory	Corsi Span; Digit Span Forward and Backward; Spatial Span Forward and Backward
Processing Speed	Digit Symbol Coding; Trail-Making Test A; Stroop Word; Stroop Color; WISC-III PSIQ; Color Trails 1 Test; Symbol Search; various measures of reaction time
Verbal	WAIS-R Vocabulary; WAIS-R Information; WAIS-R Similarities; Boston Naming Test; Graded Naming Test; National Adult Reading Test; HAWIE-R Verbal IQ; WISC-III VIQ; Auditory Comprehension subtest of the Boston Diagnostic Aphasia Examination;
Visuospatial	Paper folding; Visual Object and Space Perception Battery; CERAD-prax; Luria Mental Rotation; WISC-III PIQ; Perception Digital Test; Judgment of Line Orientation; WAIS-III cubes; Figure classification; WAIS-R Block Design; Rey-Osterrieth copy

Note. WMS-R = Wechsler Memory Scale-Revised; MMSE = Mini Mental Status Exam; RMT = Recognition Memory Test; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; FCRT = Free and Cued Selective Reminding Test; BVRT = Benton Visual Retention Test; WISC-III = Wechsler Intelligence Scale for Children; PSIQ = Processing Speed IQ; VIQ = Verbal IQ; WMIQ = Working Memory IQ; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WASI = Wechsler Abbreviated Scale of Intelligence; HAWIE-R = Hamburg-Wechsler-Intelligenztest fur Erwachsene; ADP = aprendizaje de palabras

Statistical Analyses

Procedural instructions outlined in Hedges and Olkin (1985) for random-effects designs served as the basis for this meta-analysis. This method details how data from included studies can be combined and transformed into an effect size estimate known as Hedge's *g*. This statistic represents the difference between carrier groups (i.e., individuals with known APP, PSEN1, or PSEN2 genotypes) and control groups divided by a pooled standard deviation. Hedges and Olkin (1985) showed that the standardized mean difference resulting from this calculation is effective in correcting for biases in small sample sizes. Effect sizes, resulting from standardized mean differences within each mutation weighted by respective sample sizes, were used to combine results from each study for APP, PSEN1, and PSEN2 mutations, as well as for identified risk factors. This weighting is necessary as larger sample sizes yield more accurate estimates of variance than smaller samples (Lipsey & Wilson, 2001). For chosen studies that employed a repeated-measures design, only baseline data was included in the meta-analysis.

Homogeneity of data as well as marked inconsistencies across studies is important to assess before interpretations can be made. To ensure that magnitudes of effect sizes were trustworthy, the chi-square statistic, Q, was calculated. When significant, this statistic indicates the assumption of homogeneity has been violated, and other unaccounted factors may be responsible these perceived effects (Hedges & Olkin, 1985). Likewise, the I^2 index was calculated to assess inconsistency in the results. This index describes the proportion of variance across studies contributed by chance (Higgins, Thompson, Deeks, & Altman, 2003). In analyzing moderators, heterogeneity of data across studies and within each category was assessed by calculating the Q_W statistic. Also, differences between these categories were measured through calculating the Q_B statistic, the results of which help determine whether moderators exist and are

significantly impacting data. Statistical procedures outlined here mimic previous meta-analyses examining differences in cognitive performance based on genetic mutations (Bäckman, Jones, Berger, Laukka, & Small, 2005; Small et al., 2004). These analyses were achieved through the statistical software Comprehensive Meta Analysis, Version 2.0 (Borenstein, Hedges, Higgins, & Rothstein, 2005).

Moderator Variables

As previously mentioned, moderating variables can skew magnitudes of effect sizes of interest, thereby resulting in inaccurate interpretations of the meta-analytic data. Therefore, the possibility of potential moderators must be carefully investigated. Calculating the Q_W and Q_B statistics for heterogeneity within and between categories, respectively, helps with assurance that different studies yield similar effect sizes; however, more steps must be taken to rigorously evaluate whether moderating variables are polluting these interpretations (Hall & Rosenthal, 1991). Yet, in the case of cognitive impairments associated with APP, PSEN1, and PSEN2 genetic mutations, potential moderators of interest are difficult to address. This difficulty is attributed to the strong hereditary dominance inherent within each of these mutations. Specifically, inheriting any of these mutations from either parent leads to a 50% chance that the child will develop familial Alzheimer's disease (FAD; Rocchi et al., 2003). This genetic influence, therefore, was expected to overshadow the impact of any potential moderators.

Publication Bias

Meta-analyses are commonly depicted as accumulations of all available data in certain areas of interest. This view is obviously flawed, as even exhaustive literature searches miss out on identifying potentially viable studies, in addition to unpublished data that is inaccessible in these searches. This criticism of meta-analyses, referred to as the "file-drawer" problem

(Rosenthal, 1979), accurately points out that these studies, which often have insignificant statistical results, are locked away in "file drawers" of researchers. Therefore, effect sizes can often be overestimates of true effects. This possible publication bias was addressed by calculating the fail-safe N on each study's average weighted effect size across cognitive domains, which determined how many non-significant studies needed to be included to nullify the results.

CHAPTER IV

RESULTS

Study Characteristics

The complete list of studies chosen for final inclusion in the meta-analysis is presented in Table 2 below. Initial electronic literature search terms generated a total of 394 studies. An additional 54 studies were identified for review via hand-searching of five relevant journals, bringing the initial total to 448; however, many of these were systematically eliminated due to lack of human subjects, absence of psychometric cognitive measures, cohort redundancy, concurrent cognitive deficits exhibited in participants, or insufficient statistics reported. For multiple studies sharing overt overlap in participant pools, only the those studies with the largest sample sizes and most extensive ranges of cognitive measures were selected, so as to decrease observation dependency and maximize representative accuracy of the original cohort samples. Specifically, 393 studies were excluded due to lack of human subjects or topic salience. Of the remaining 55 full text studies reviewed for data inclusion, 33 more were eliminated as a result of participants' histories of disqualifying cognitive comorbidities (e.g., traumatic brain injury, various alternative dementias) or an absence of empirically validated psychometric cognitive measures. Following careful inspection of the research methods and participant similarities, eight more studies were excluded due to redundant sampling from shared databases or overlap of specific mutations in de-identified participants, rendering more narrow individual delineation impossible. Furthermore, an additional four studies were excluded due to lack of statistics needed for effect size calculations. Efforts were made to contact the authors of these respective studies and obtain the requisite data; however, only two authors responded, both of who offered the requested information, which was ultimately never received due to conditional complications

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(i.e., wanting to be senior author on this manuscript, asking for university level legal representation to sign a data use agreement). Altogether, data on relevant cognitive variables was acquired from 562 individuals across 10 studies.

Given the relatively small number of studies gathered for final analyses, in addition to the high proportion of those studies failing to delineate data according to respective APP, PSEN1, and PSEN2 genotypes, the originally proposed method (i.e., three separate group analyses) was insufficiently powered. Therefore, genotypes were collapsed into one overarching FAD Mutation Carrier variable. Moreover, symptomatic levels of mutation carrier participants within each original genotype group were also collapsed into this new composite variable. Consequently, final analyses were executed on FAD Mutation Carrier and Non-Carrier variables.

Table 2

Characteristics of Studies Included in the Meta-Analysis

First Author	Year	Cognitive Domains	n, FAD-MC	n, FAD-NC	Participant Age[1]
Basun	2008	EF, EM, F, GC, M, PS, V, VS	6	5	56.9[2]
Fleisher	2012	EM, F, GC, PS	30	20	36.4
Lee	2013	EF, EM, GC, PS, V, VS	21	10	34.6
Liang	2016	AT, EF, EM, F, GC, PM, PS, V, VS	20	62	40.4
Mondadori	2006	AT, EF, EM, F, GC, V, VS	2	21	23.1
Quiroz	2016	EX, GC, PS, V, VS	18	19	13.0
Sala-Llonch	2014	AT, EF, EM, F, GC, PS, V, VS	24	14	42.3
Schöll[3]	2012	EM, GC	2	7	59.7[4]
Storandt	2014	EF, EM, F, GC, PM, PS, V	147	96	39.3
Villemagne	2009	GC	8	30	64.8
		Total n	278	284	

Note. FAD-MC = Familial Alzheimer's Disease mutation carrier (APP/PSEN1/PSEN2); FAD-NC = Familial Alzheimer's Disease mutation non-carrier; Cognitive domains: AT = attention, EF = executive functioning, EM = explicit memory, , F = fluency, GC = global cognitive ability, M = motor, PM = primary memory, PS = processing speed, V = verbal, VS = visuospatial
[1]Participant ages estimated from available data
[2]Age data only available for FAD-MC
[3]Only mutation carriers unique to Schöll 2012 sample were analyzed
[4]Age data only available for FAD-NC

Effect Sizes

The current meta-analysis ultimately generated 57 total effect sizes from nine cognitive

domains. Each effect size stemmed from standardized mean differences within each collapsed

mutation, weighted by respective sample size. These weighted effect sizes (*d*-values) are

presented in Table 3 for each of the aforementioned cognitive domains.

Table 3

Effect Sizes for Nine Domains of Cognitive Functioning

Domain	*k*	Sample Size		*d*	95% CI	*r*	*Q*	I^2 (%)
		FAD-MC	FAD-NC					
Attention	3	46	97	-.89**	-1.29, -.49	-.41	1.55	0
Executive Functioning	7	293	228	.09	-.27, .45	.05	7.15	16.09
Explicit Memory	8	252	235	-1.15**	-1.56, -.74	-.50	7.31	4.29
Fluency	6	229	218	-.48**	-.68, -.28	-.23	.50	0
Global Cognitive	10	277	284	-.25	-.78, .29	-.12	8.94	0
Primary Memory	3	173	163	-.67*	-1.17, -.16	-.32	1.83	0
Processing Speed	7	266	226	.12	-.12, .37	.06	5.90	0
Verbal	7	238	227	-.53**	-.73, -.34	-.26	3.66	0
Visuospatial	6	236	206	-.51**	-.84, -.17	-.25	4.90	0

Note. k = number of studies; FAD-MC = Familial Alzheimer's Disease Mutation Carrier
(APP/PSEN1/PSEN2); FAD-NC = Familial Alzheimer's Disease Non-Carrier; *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

FAD mutation carriers demonstrated inferior performance compared to FAD non-carriers on

seven domains, while slightly outperforming non-carriers, albeit insignificantly, on two domains

(i.e., executive functioning and processing speed). Of those domains in which FAD mutation

carriers exhibited comparatively lower effect sizes, significant differences were found in the

following neurocognitive functioning domains: attention (*k* = 3, *d* = -.89, 95% confidence

interval = -1.29, -.49, *p* < .001), explicit memory (*k* = 8, *d* = -1.15, 95% confidence interval = -

1.56, -.74, *p* < .001), fluency (*k* = 6, *d* = -.48, 95% confidence interval = -.68, -.28, *p* < .001),

primary memory ($k = 3$, $d = -.67$, 95% confidence interval = -1.17, -.16, $p < .05$), verbal ($k = 7$, $d = -.53$, 95% confidence interval = -.73, -.34, $p < .001$), and visuospatial ($k = 6$, $d = -.51$, 95% confidence interval = -.84, -.17, $p < .001$). Broadly, these effect sizes range from medium to large, according to Cohen's benchmarks (1988). In Figure 1, the results of the current meta-analysis are also visually displayed in nine forest plots corresponding to each cognitive domain, within which each study's aggregated effect size and 95% confidence interval for that domain are shown.
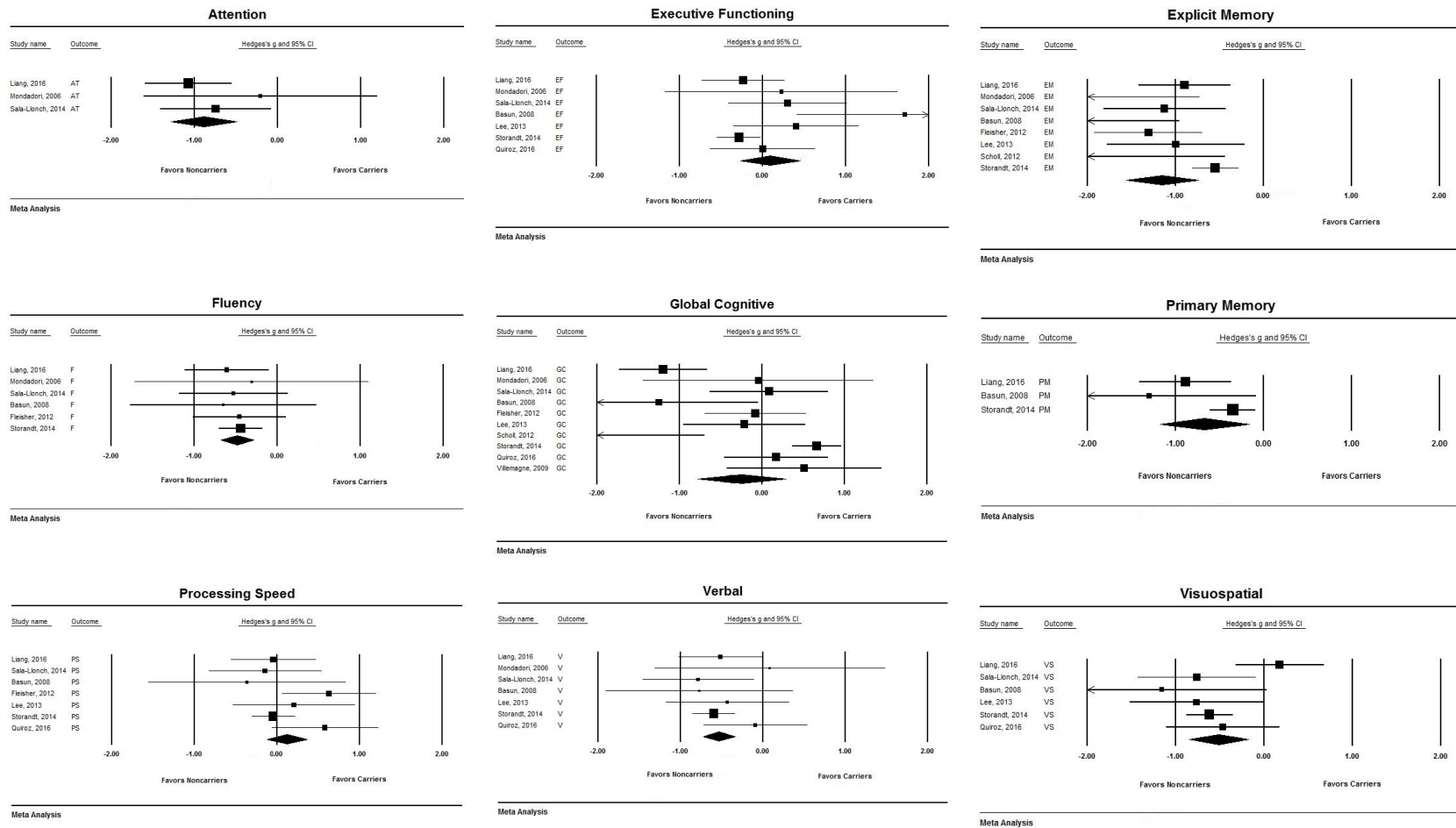
Figure 1. Forest plots for all nine cognitive domains.

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Moderator Analyses

An assessment of the heterogeneity of effect sizes across each cognitive domain was conducted via the Q statistic, which obeys the chi-squared distribution and is considered a conservative approach that is influenced by sample size. All nine domains failed to indicate significant heterogeneity of effect sizes, and, thus, also implied an absence of any significant influence from potential moderating variables. As discussed previously, the hereditary dominance of APP, PSEN1, and PSEN2 genetic mutations eclipses the impact any conceivable moderator might impose on effect sizes; therefore, no moderators were identified or analyzed for influence on effect sizes. While the true function of the Q statistic in this case is to test the null hypothesis of a commonly shared effect size among all studies analyzed, it should not be utilized as a measure of the amount of actual variance; that is, nonsignificant results could either represent insignificant amounts of observed variation across accurate studies, or considerable observed variance across inexact studies (Borenstein, Hedges, Higgins, & Rothstein, 2009).

The I^2 statistic was computed to assess the heterogeneity of effect sizes across each cognitive domain as a proportion of observed variance to total variance. Given the relatively small number of studies included in the meta-analysis, the I^2 statistic is valuable, as it is does not directly depend on the number of studies included. All but two cognitive domains (i.e., executive functioning and explicit memory) yielded I^2 values of zero. The domains of executive functioning ($I^2 = 16.09\%$) and explicit memory ($I^2 = 4.29\%$) indicated some proportions of observed variance greater than zero. According to benchmarks offered by Higgins et al. (2003), I^2 values around 25%, 50%, and 75% are considered low, moderate, and high, respectively; however, these benchmarks are derived from a survey of several meta-analyses of clinical trials, which might not translate to all types of meta-analyses (Borenstein, Hedges, Higgins, &

Rothstein, 2009). It is also important to note that low values of I^2 do not necessarily signify a narrow distribution of observed effects, but could be equally likely to reflect a widespread variation of effects across studies with more error.

Publication Bias

A visual depiction of the statistical approach to assessing the extent of publication bias is presented as a funnel plot of effect sizes and their associated standard errors in Figure 2. In situations where publication bias is present, many studies will appear at the bottom and toward the outsides of the "funnel," indicating large effect sizes, but small confidence levels of the estimates due to relatively small sample sizes. Figure 2 shows a broadly symmetrical scattering of effect sizes within the funnel. Additionally, the calculated fail-safe N was found to be 20, twice as many studies than were found to meet inclusion criteria. Together, these observations suggest the current results are largely independent from any potentially confounding effects generated by a publication bias within this field.
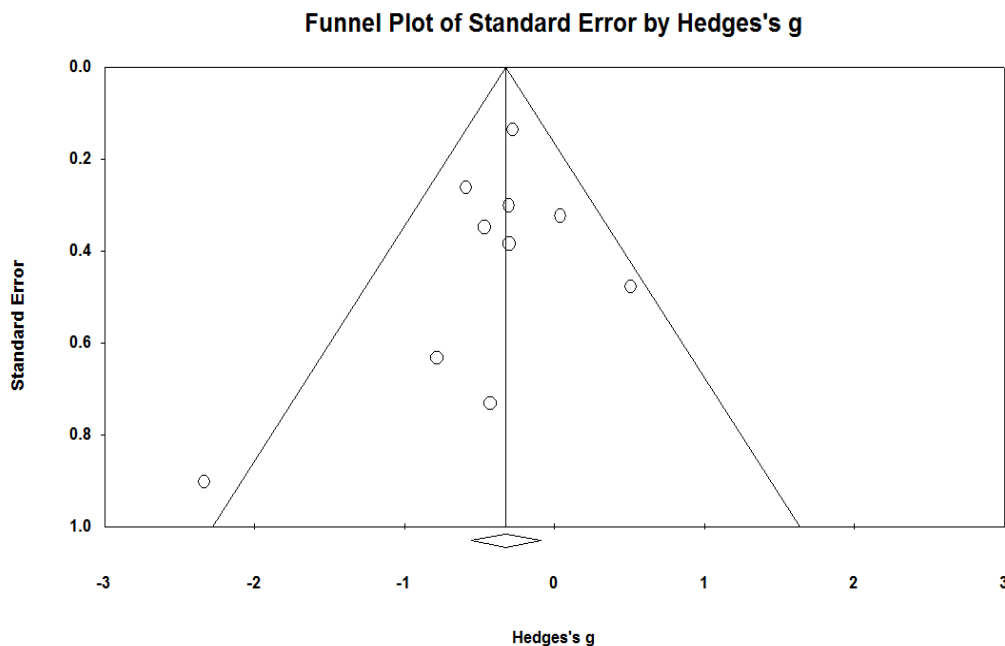
Funnel Plot of Standard Error by Hedges's g

Standard Error (y-axis): 0.0, 0.2, 0.4, 0.6, 0.8, 1.0

Hedges's g (x-axis): -3, -2, -1, 0, 1, 2, 3

Figure 2. Funnel plot assessment of publication bias.

CHAPTER V

DISCUSSION

The current meta-analysis establishes the first statistical summarization of the effect sizes

of cognitive domain performance reflected in the existing literature comparing carriers of APP,

PSEN1, and PSEN2, both asymptomatic and symptomatic, and unimpaired non-carriers. As

certain deficits in other forms of AD have been shown to be capable of detection before making

a diagnosis of symptomatic AD (Acosta-Baena et al., 2011), contributing to the body of

knowledge describing the cognitive characteristics of FAD can potentially improve our

understanding of the relationship between the genotypes in question and progression of the

disease, as well as resultantly improve early detection methods. Despite certain methodological

drawbacks, the current meta-analysis reflects initial efforts to help inform which aspects of

neuropsychological functioning are differentially affected by the mere presence of these

missense mutations in asymptomatic and early symptomatic stages of the disease progression.

The findings of the current meta-analysis revealed significant differences between

individuals possessing APP, PSEN1, or PSEN2 familial Alzheimer's disease mutation genotypes

(FAD mutation carriers) and individuals who do not carry these particular mutations (FAD non-

carriers) across six domains of cognitive functioning. Specifically, groups of FAD mutation

carriers exhibited significantly lower aggregated scores on standardized measurement groupings

of attention, explicit memory, fluency, primary memory, verbal and visuospatial functioning,

compared to FAD non-carrier groups. Notably, the range of weighted mean differences between

FAD carrier and non-carrier groups stretched from small (.12 for processing speed domain) to

large (-1.15 for explicit memory domain) standard deviations suggesting differential impacts of

carrier status. The domains representing executive functioning, global cognitive, and processing speed were not observed to be significantly different between groups.

It is difficult to judge the consistency of these findings against the existing literature, given the lack of comparable analyses conducted with this population; however, some analogous patterns of poor performance are observed in studies characterizing the typical progression of late-onset Alzheimer's disease (LOAD), in which episodic memory and language are often the first areas to sustain deficits in early asymptomatic (Lopera et al., 1997; Storandt, Balota, Aschenbrenner, & Morris, 2014). Such observations are broadly commensurate with results of the current analysis, as the largest effect size difference was observed in the explicit memory domain and differences within the verbal domain were also significant. While the percentage of observed variance in these domains not due to chance is very low and likely zero, the magnitudes and directions of the effects are consonant with expectations. The same can be said for visuospatial, primary memory, fluency, and attention; all of which are domains in which FAD carrier groups predictably performed significantly worse compared to non-carrier groups based soley on effect size differences.

Conversely, the largest proportion of real observed variance within the meta-analytic model lies in the executive functioning domain. Yet, the effect size differences in this domain were not significant between groups, a result that is inconsistent with observations in the literature that activities dependent upon executive functions are considerably negatively impacted (Lopera et al., 1997). Similarly, processing speed is another domain typically more sensitive to insult than other domains, but that failed to indicate significant differences between groups, with a weighted mean difference estimate actually indicative of better performance in the FAD carrier group, albeit insignificantly. Again, limited proportions of variance explained by

group differences weakens potential interpretative extrapolations, but one would expect to see opposite trends based on existing knowledge of cognitive domain vulnerability to dementia progression generally.

While calculated overall effect sizes are the primary statistical focus of a meta-analytic review, it is also important to discuss the extent to which moderator variables influence the magnitude of these effect sizes. Given the hereditary influence inherent in autosomal dominant Alzheimer's disease, impact from potential moderating variables is likely negligible. By definition, dementia is a progressive disease over time. Thus, severity increases with age. The inherent nature of dementing conditions, in part, played a role in the decision to employ a random-effects model meta-analysis, in that this model already accounts for variations of true effects, including those attributable to age. Furthermore, the non-significant results for tests of heterogeneity generated in this analysis increases confidence that chosen studies share common effect sizes (Hall & Rosenthal, 1991).

One goal of all meta-analyses is to accurately represent the entirety of all studies ever conducted within a given field. Therefore, assessing the presence of publication bias is crucial to avoiding systemic errors in a meta-analysis intended to be cumulative. When studies with smaller sample sizes are preferentially published according to the magnitude of their effect sizes, a publication bias emerges. The current results fail to provide support for a publication bias. Considering only 10 studies met inclusion criteria for the current meta-analysis, in addition to the exceptionally small population of unique individuals identified and cognitively evaluated for their rare FAD mutations, it is perhaps less likely that 20 studies were missed in the literature search compared to similarly sized fail-safe Ns calculated in other meta-analyses examining more common research targets within larger bodies of literature. In light of these considerations,

the "file drawer" problem, while pertinent, is arguably not persuasive enough to deplete

confidence extracted from the symmetrical funnel plot, which suggests the current results are

largely independent from any potentially confounding effects generated by a publication bias

within this field.

Limitations

Among the most salient limitations to the current meta-analysis are the psychometric

measures at the core of data collection across studies. While a multi-modal approach has the

advantage of breadth of coverage, it is plagued in this case with inconsistencies in validity and

reliability of the psychometric instruments utilized. For example, some studies employed more

empirically validated tests to capture domain performance, while others used less validated

measures but on comparable numbers of participants, thus being treated equally in terms of

statistical influence in the meta-analysis. Additionally, some measures inherently assess more

than one cognitive domain at a time, thereby contaminating designated domains with

confounding variables.

Another limitation is the relatively small sample size of studies chosen for final inclusion.

This is largely a byproduct of the scarcity of identified members of the population of interest. As

APP mutations specific to FAD were only first identified in 1991, and similarly for PSEN1 and

PSEN2 in 1995, there has not been a substantial amount of time for which individuals could be

identified and recruited for quantitative research. Moreover, since efforts have been made to

establish registries identifying individuals at risk for FAD (e.g., DIAN, PICOGEN, API) for the

purpose of describing, and ultimately preventing, the course of the disease from preclinical

phases onward, different studies have drawn samples from these de-identified databases, which

creates a challenge for ensuring independency of observations in systematic reviews like the

current study. Consequently, the literature, though having vastly expanded in the last 10 years, still remains somewhat limited, and also impacted the decision to collapse all three genotypes, as well as levels of symptomatology within those genotypes, into one all-encompassing FAD mutation-carrier variable, further limiting the interpretability of results.

Finally, these aforementioned limitations influenced the decision to utilize a random effect model of meta-analysis, described by Hedges and Olkin (1985). This approach allows for inherent variability within the methods of each study. As such, it generates a more conservative estimate of aggregated data, much less likely to provide significant estimates compared to the alternative fixed effect model. Under the latter design, it is assumed that the actual effect size for all studies is the same (Borenstein, Hedges, Higgins, & Rothstein, 2009). As this allows for wider range of weights, some significant results from studies with larger samples can much more significantly impact the summary estimates generated. When employing a fixed effect design in the current analysis, proportions of "true" observed effects increased dramatically across all cognitive domains.

Future Directions

Given the rate at which research in this area has grown over the last 10 years, more concentrated analyses focused on more rigidly defined domains of cognitive functioning should be conducted once sufficient levels of independent data emerges in the literature. Relatedly, as more data becomes available for research (e.g., from aforementioned registries), exploration of possible discrepancies in data across demographic information (e.g., gender, education) might help better illuminate protective factors. Furthermore, a meta-analysis discriminating between APP, PSEN1, and PSEN2, as originally proposed for the current study, might help shed light on the differential impact of these specific genetic mutations on neuropsychological functioning.

Also, when amount of available data permits, separating out asymptomatic from somewhat symptomatic, but non-demented, mutation-carrier individuals will elucidate the extent to which these mutations affect cognitive performance in preclinical phases of the disease. As the nature of the interaction between genotype and disease progression is slowly unveiled through studying individuals at risk for familial early-onset Alzheimer's disease, the possibilities for minimizing and ultimately preventing the catastrophic consequences of FAD and related dementias will ascend exponentially.

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