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## Investigating a Multimodal Approach to Clinical Diagnosis of Mild Cognitive Impairment and Alzheimer's Disease

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INVESTIGATING A MULTIMODAL APPROACH TO CLINICAL DIAGNOSIS OF MILD  
COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

by

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## ABSTRACT

### INVESTIGATING A MULTIMODAL APPROACH TO CLINICAL DIAGNOSIS OF MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

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An estimated 5.8 million Americans suffer from dementia due to Alzheimer's disease (AD), with that number projected to grow to 13.8 million by mid-century (Alzheimer's Association, 2019). Mild cognitive impairment (MCI) describes the stage between normal cognitive decline that comes with aging and a dementia diagnosis (Peterson, 1999). Due to a lack of a cure or particularly effective treatment, a major goal of treatment is to focus on improving quality of life (Budson & Solomon, 2016). An early and accurate diagnosis can address this goal in a variety of ways. Despite the high prevalence and immense amount of research in MCI and AD, there is still no individual assessment measure that can definitively diagnose either. A multimodal approach must be implemented by clinicians and investigated by researchers to ensure early and accurate diagnosis. This study used multivariate logistic regression to analyze how two neuropsychological screening tests, two brain structures' volumes, and an eye-tracking outcome all contributed to the diagnostic process. The two screening tests were the only unique contributors to the predictive model, and there was only slight evidence to suggest that the multimodal approach using these measures improved accuracy of diagnosis.

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This dissertation is dedicated to my wife, Jessica, who worked much harder than me over these years while keeping me going with her relentless love.

**NOMENCLATURE**

<i>A<math>\beta</math></i>	Beta amyloid
<i>AD</i>	Alzheimer's disease
<i>ADLQ</i>	Activities of Daily Living Questionnaire
<i>AHN</i>	Adult Hippocampal Neurogenesis
<i>aMCI</i>	Amnesic mild cognitive impairment
<i>ApoE4</i>	Apolipoprotein E- $\epsilon$ 4
<i>CDR</i>	Clinical Dementia Rating
<i>CSF</i>	Cerebrospinal fluid
<i>CT</i>	Computed tomography
<i>CVLT</i>	California Verbal Learning Test
<i>DFA</i>	Discriminant function analysis
<i>DSM-5</i>	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
<i>DTI-MRI</i>	Diffusion tensor imaging
<i>DV</i>	Dependent variable
<i>EEG</i>	Electroencephlogram
<i>EVMS</i>	Eastern Virginia Medical School
<i>FDG-PET</i>	Fluorodeoxyglucose positron emission tomography
<i>FEF</i>	Frontal eye field
<i>IRB</i>	Institutional Review Board
<i>IV</i>	Independent variable
<i>LR</i>	Logistic regression
<i>LV</i>	Lateral ventricles

**NOMENCLATURE**

<i>MCI</i>	Mild cognitive impairment
<i>MMSE</i>	Mini-Mental Status Examination
<i>MoCA</i>	Montreal Cognitive Assessment
<i>MRI</i>	Magnetic resonance imaging
<i>naMCI</i>	Non-amnestic mild cognitive impairment
<i>NIA-AA</i>	National Institute on Aging – Alzheimer’s Association
<i>NFT</i>	Neurofibrillary tangles
<i>NODDI</i>	Neurite orientation dispersion and density imaging
<i>OC</i>	Older control
<i>PET</i>	Positron emission tomography
<i>PiB</i>	Pittsburgh compound B
<i>ROI</i>	Region-of-interest
<i>VPC</i>	Visually paired comparison

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## CHAPTER 1

### INTRODUCTION

Alzheimer's disease (AD) accounts for approximately 75% of all dementia diagnoses in the United States and its prevalence is projected to continue to increase as the population ages (Budson & Solomon, 2016; Alzheimer's Association, 2019). An estimated 5.8 million Americans suffer from dementia due to AD, with that number projected to grow to 13.8 million by mid-century. In 2017, 121,404 deaths were caused by AD, making it the 6<sup>th</sup> leading cause of death in the United States, and the 5<sup>th</sup> leading cause of death in those over the age of 65. Between 2000 and 2017 deaths from stroke, heart disease, and prostate cancer all declined, but deaths from AD rose 145% (Alzheimer's Association, 2019).

Not only are the personal costs of AD high for patients and their loved ones, but the burden that is placed on society is enormous. Total payments in 2019 for health care for those with dementia are estimated to reach \$290 billion, and per-person Medicare costs are 23 times higher in those who suffer from AD than the general population.

Furthermore, in 2017 more than 16 million family members and caregivers (often termed the "invisible second patient") provided an estimated 18.4 billion hours of care to those suffering from dementia, indicating the emotional toll and time demands that this disease takes on those close to the patient (Alzheimer's Association, 2018).

Mild cognitive impairment (MCI) describes the stage between normal cognitive decline that comes with aging and a dementia diagnosis (Petersen et al., 1999). More specifically, it is a syndrome that is marked by cognitive decline greater than expected, but which does not interfere with day-to-day activities (Gauthier et al., 2006). Despite the high prevalence and immense amount of research in MCI and AD, there is still no individual assessment measure that can

definitively diagnose either. A multimodal approach must be implemented by clinicians and investigated by researchers to ensure early and accurate diagnosis.

## **1.1 Alzheimer's Disease and Mild Cognitive Impairment**

### **1.1.1 Diagnostic Criteria and Symptomology**

In order to correctly diagnose and treat dementia due to AD and MCI one must have defined what those terms encompass in terms of symptomology. Two of the leading criteria used to classify these terms are the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association, 2013) and the National Institute on Aging – Alzheimer's Association (NIA-AA; McKhann et al., 2011). Dementia is referred to as Major Neurocognitive Disorder in the DSM-5 and All-Cause Dementia by the NIA-AA; while MCI is referred to as Mild Neurocognitive Disorder in the DSM-5. Criteria for dementia in both are quite similar, and both include significant cognitive decline relative to normal aging (as observed by clinician, reported by the patient or a knowledgeable informant, or from neuropsychological testing). This impairment is significant enough to affect ability to independently perform everyday activities, and cognitive impairments are not better explained by delirium or a major psychiatric disorder (Budson & Solomon, 2016, pp. 40-41). In terms of MCI, the similarities are virtually the same as for dementia, but with no impairment of independent functioning.

There are hallmark symptoms of AD that can help distinguish it from other dementia-causing diseases. Perhaps the most well-known is how AD affects the memory of the patient. Specifically, episodic memory is affected and tends to follow Ribot's law: the patient suffers from anterograde and retrograde amnesia (or "rapid forgetting"), but has relatively intact remote memory (Ribot, 1881). Patients often also suffer from distortions and false memories (which can

commonly be confused with psychotic delusions or hallucinations), word-finding difficulties, and getting lost on both familiar and novel routes (Nitz, 2009; for a review of memory dysfunction see Budson & Price, 2005).

Though memory-related symptoms are typically the first to become apparent (due to the physiological progression of the disease originating in and around the hippocampus, see below), reasoning and judgment are also commonly impaired in those with AD when the frontal lobes are affected. Behavioral issues are highly variable, but among the most common are apathy and/or irritation. Personality changes are quite mild, especially early in the disease. Depression and anxiety are extremely common comorbid psychiatric symptoms, particularly in the early clinical stages of the disease. As the disease progresses, dysfunction becomes both more profound in those areas already affected and broadens to other areas of cognition (Budson & Solomon, 2016).

### 1.1.2 Physiological Markers of Alzheimer's Disease

Alzheimer's disease slowly progresses over the course of decades. Diagnosis cannot be made with certainty until a brain autopsy is performed and certain pathological hallmarks are identified, including two of the most prominent: neurofibrillary tangles (NFT; Perl, 2010) and beta amyloid (A $\beta$ ) plaques (Spires-Jones & Hyman, 2014). Neurofibrillary tangles have been a marker for AD since the first description of the disease by Alois Alzheimer in the early 20<sup>th</sup> century (Alzheimer, Stelzmann, Schnitzlein, & Murtagh, 1995; Hippus & Neundorfer, 2003). These microscopic structures are composed of the microtubule-associated protein *tau* and have been found to have a predictable pattern of distribution throughout the course of AD (Perl, 2010). Those structures of the brain that contain the most extensive deposits of NFT are the

hippocampus, the amygdala, and the deeper levels of the neocortex (Morrison & Hof, 1997). The hippocampus is affected early in Alzheimer's disease (Fox et al., 1996; Scheltens et al., 1992; Shi et al, 2009) and tends to decrease disproportionately in size as the disease progresses (Jack et al., 1997; Scahill et al., 2002). There has also been evidence that the hippocampus has a unique process called Adult Hippocampal Neurogenesis (AHN). This is the process whereby the hippocampal neurons continue to be matured and replaced throughout humans' lifetime (Tobin et al., 2019). Moreno-Jimenez et al. (2019) discovered thousands of immature neurons in healthy subjects well into their 90's, all neurons in different stages of AHN. Subjects with AD showed a decline in the number of neurons maturing, which further declined as the disease progressed. Thus, predictable distribution of NFTs and brain structure injury are highly characteristic of the progression of AD.

Another classic pathological hallmark of AD is A $\beta$  accumulation into plaques. These "senile plaques" were also first described in Dr. Alzheimer's groundbreaking paper as characteristic physiological indications of the disease. These occur extracellularly (NFTs occur intracellular) and appear to be the result of the protein fragments of A $\beta$  not being effectively cleared from the brain and clumping together, forming a "plaque" (Wildsmith, Holley, Savage, Skerrett, & Landreth, 2013).

Despite the long history between A $\beta$  and AD, the mechanisms linking the two are not completely understood. Amount of plaques in the brain has not been shown to consistently correlate with cognitive impairments (Giannakopoulos et al., 2003; Ingelsson et al., 2004). In fact, a significant amount of people have been found with large amounts of plaques in their brains yet exhibit no cognitive impairment (Perez-Nievas et al, 2013). On the other hand, the higher the A $\beta$  present, the higher the rates of decrease in delayed memory and executive function

(Clark et al, 2015). Deposition of A $\beta$  and subsequent plaques appear to follow a similar pattern of AD progression that NFTs do. In fact, Wirth et al. (2015) not only measured this same pattern of distribution, but also found that MCI patients showed the same regional variations of A $\beta$  deposition as AD patients, though not as pronounced or widespread. The authors went on to conclude that AD can in fact emerge in both A $\beta$  and non-A $\beta$  pathways, but ultimately these paths meet in prodromal AD stages and A $\beta$  becomes a marker for everyone with AD.

Krstic and Knuesel (2013) proposed a model linking A $\beta$  and NFTs. A simplified version begins with increased A $\beta$  leading to accumulation of plaques. The presence of plaques causes inflammatory conditions around the neurons that affect the tau proteins within the cells. This in turn culminates with NFTs being formed and neuronal cell death.

A review by Heneka et al. (2015) found that in addition to this “passive” system of A $\beta$  and NFTs affecting the brain there is an “active” system related to immunological failure that perpetuates the cell death. Pathological aging, trauma, and genes act as natural triggers for an innate immune response by microglial cells to begin synaptic remodeling in order to cleanse and restore neurons that are affected. A $\beta$  plaques also act as triggers, activating microglia and causing chronic neuroinflammation as the microglia attempt to clear the synapse. This inflammation is aggravated by microscopic factors such as peripheral inflammation and reduced microbial diversity, as well as full-body factors like obesity. This cleanse and remodel system is meant to work in acute situations; chronic neuroinflammation can lead to neurodegeneration, neuron death, reduced synaptic remodeling, and, ultimately, functional and structural damage to neurons. Furthermore, neuronal debris from the dead cells continue to perpetuate inflammation locally while aggravating areas around it.

The predominant model of AD progression consists of six neuropathological stages. Stages 1 and 2 include NFTs in the transentorhinal cortex and the hippocampus, which translates clinically to mild AD (Braak & Braak, 1991). Additionally, the severity and location of NFTs in the brain in cases of AD has been shown to correlate with the severity of the dementia, leading to the theory that the accumulated burden on the brain is what accounts for the stage-like progression of AD (Arriagada et al., 1992; Bierer et al., 1994). A review of A $\beta$  and *tau* fluid biomarkers (e.g., oral fluid, cerebrospinal fluid [CSF], ocular fluid, olfactory fluid, blood) found that none of these have been established in early diagnostic protocols. Instead, it is recommended that they be used to confirm an AD diagnosis once symptoms are clinically identifiable (Lee et al., 2019). Another more current attempt at identifying a biomarker (pathogen associated with chronic periodontitis) that could aid in early diagnosis was shown to be associated with A $\beta$ , but not with plaques (Dominy et al., 2019). The extent and specifics of the impacts of NFTs in relation to AD is not entirely understood at this time and other factors such as beta amyloid plaques certainly contribute (Perl, 2010).

### 1.1.3 Mild Cognitive Impairment

Mild cognitive impairment describes the stage between normal cognitive decline that comes with aging and a dementia diagnosis (Petersen, 1999). More specifically, it is a syndrome that is marked by cognitive decline greater than expected, but which does not interfere with day-to-day activities (Gauthier et al., 2006). Traditionally seen as a transitional period, MCI was a term created in order to assist clinicians to provide a diagnosis for patients who are not aging normally, but do not yet meet criteria for AD (For recent reviews of the progression of MCI and AD see Peterson, 2011, and Sperling et al., 2011). Diagnosis as early as possible in both MCI



and AD progression is essential as it has been shown to be beneficial for the patient and his or her family and caretaker in a number of areas, including broader medication options, getting connected earlier with support systems, and the ability to make final preparations while the patient is still of sound mind (Alzheimer's Association, 2018). Speed and accuracy of diagnosis is critical when it comes to providing the highest quality of care to this population.

Patients with MCI can be classified into four different categories. The categories depend on whether the patient has shown poor memory performance on neuropsychological tests, which is termed amnesic MCI (aMCI), versus non-amnesic MCI (naMCI) if performance impairment was in cognitive domains other than memory (e.g., language, executive functions, etc.). The other criterion relies on whether the impairment is only in one area (single-domain) or in more than one area (multiple-domain). Therefore, the four possible clinical subtypes are aMCI single domain, aMCI multiple domain, naMCI single domain (where memory is intact while cognitive impairment is in another domain), and naMCI multiple domain (see *Figure 1*; Petersen et al., 2014). Furthermore, research will commonly label patients with MCI who eventually progress to AD as *preclinical* or *prodromal* AD, while those who remain in the MCI diagnosis over time are categorized as *stable* MCI.

**Figure 1***Types of Mild Cognitive Impairment*

		Memory Impairment	
		Yes	No
Number of Domains Affected	Single	aMCI, single domain	naMCI, single domain
	Multiple	aMCI, multiple domain	naMCI, multiple domain

There is evidence that certain types of MCI (especially aMCI) may fall on the same continuum as AD, but it is still a debate whether MCI should be considered prodromal AD or its own separate diagnosis. In their review, Petersen and Negash (2008) found that the typical rate in which patients with aMCI progress to AD is between 6-15% per year. Some patients with MCI (all subtypes) actually improve to normal at a rate of approximately 5% per year, but even within this group a subgroup improved and then subsequently declined, which is suggestive of instability in the progression to dementia rather than a direct and smooth progression. Several other factors affect the rate of progression, such as being a carrier of the Apolipoprotein E- $\epsilon$ 4 (ApoE4) allele and having rapid hippocampal atrophy.

#### 1.1.4 Comorbidity in Alzheimer's Disease

Approximately 65% of dementia is caused by AD alone, but many patients experience comorbid diseases. Common overlapping conditions include ischemic infarction (stroke),

Parkinson's disease, dementia with Lewy bodies (Perl, 2010), and frontotemporal dementia (Budson & Solomon, 2016). The boundaries that separate these conditions in terms of clinical presentations can be blurry, but suggested criteria for diagnosing the different disorders both clinically and neuropathologically are available (Baner et al., 1993; McKeith et al., 1999). This makes the clinical process even more complex and requires looking at a patient's condition(s) from multiple perspectives using a combination of measures.

## **1.2 Clinical Diagnostic Procedures**

Currently, there is no single definitive test for MCI or AD; the diagnostic process involves the clinician gathering and interpreting information from multiple sources (Albert et al., 2011). The current diagnostic procedure for MCI and AD is interdisciplinary and complex. Elements of a clinical evaluation for MCI and dementia include: history of present illness, medical history, current and past relevant medications, social history (education, occupational, learning disorders, etc.), family history of memory loss (25-40% of AD patients have a first-degree relative with AD [Jayadev et al., 2008]), physical and neurological examination, cognitive exam, laboratory studies, and neuroimaging. It is recommended to use a two-step approach to evaluate patients that are thought to possibly have MCI or dementia by 1) investigating three main areas: function, cognition, and mood/behavior; and, 2) determining the disease or diseases that are the cause (Budson & Solomon, 2016, Chapter 3).

Functioning can be ascertained through interviews with family members and/or caregivers, interview with the patient, and from several available questionnaires (e.g., the Activities of Daily Living Questionnaire [ADLQ]; Johnson et al., 2004). Cognition can be assessed through interviews and neuropsychological testing. Cognitive domains that should be

assessed are memory, language, visuospatial skills, and executive functioning. Typical mood and behavioral symptoms such as apathy, depression, anxiety, irritability, and delusions should also be given special attention.

Typically, a battery of tests assessing for MCI/AD includes, but is not necessarily limited to, a magnetic resonance imaging (MRI) of the brain to see and measure anatomical details and rule out alternative disorders (e.g., tumor, stroke, or bleeding), and neuropsychological screening exams to test cognitive functioning. Biomarker analyses such as cerebrospinal fluid (CSF) analysis for A $\beta$  and tau protein, Pittsburgh compound B (PiB), and F18 tracers used in positron emission topography (PET) scans for amyloid, have proven their clinical utility and have begun making an impact on the standard of care (e.g., Hansson et al., 2006; Ikonovic et al, 2008). While promising, it is still recommended to use biomarkers to confirm a diagnosis and not as a primary diagnostic tool. They can be difficult to access, expensive, and/or unnecessarily distressing to a patient (e.g., A $\beta$  plaques can be detected and this does not mean an AD diagnosis is applicable; Lee et al., 2019; Weller & Budson, 2018).

### **1.3 Neuropsychological Measures**

#### **1.3.1 Mini-mental Status Examination (MMSE)**

The MMSE (Folstein, Folstein, & McHugh, 1975) was developed to be a quantitative screening measure used to measure the cognitive status in adults ages 18-85. Originally developed in 1975, it has undergone “minor modifications” by the authors since then. The MMSE assesses orientation, immediate and short-term memory, attention, calculation, language, and praxis. This assessment tool is available in 73 different languages and is estimated by its publisher (Psychological Assessment Resources, PAR, Inc.) to take 15-20 minutes to administer

and score. A two-year longitudinal study found that the combination of MMSE and California Verbal Learning Test (CVLT) scores was the best predictor of progression to AD in a group of MCI patients (Pozueta et al., 2011). Those who scored 26/30 or greater at baseline on the MMSE and 4/16 or greater on the long delay total recall on the CVLT had a negative predictive value of 93.9% over the subsequent two years. Patients who scored below these cutoff scores had an 80.95% positive progression prediction to AD over the same two years. This suggests that differentiating prodromal AD from stable MCI is highly predictive based on episodic memory difficulties and overall cognitive difficulties. Qiao et al. (2019) found that MMSE scores correlated with FDG-PET imaging of *tau* protein in bilateral cerebral cortex areas.

A meta-analysis of longitudinal studies in the 1990s found that the annual rate of decline on the MMSE among AD patients was 3.3 points (Han et al., 2000), while another study found that the average monthly decline in MMSE scores among AD patients was 0.24 points, which was accelerated when the patient had eight or more years of education, arterial hypertension, type II diabetes, and/or no acetylcholine medication treatment (Roselli et al., 2009).

The MMSE has been found to have difficulty detecting MCI. In addition to this, the MMSE has also been found to be considerably biased by factors of age, education, cultural background, and socioeconomic status (Lancu & Olmer, 2006). Despite these weaknesses, a current review and meta-analysis found the MMSE to have high sensitivity and specificity for detection of dementia (0.81 and 0.89, respectively; Tsoi et al., 2015). Another review found the MMSE to have highly variable sensitivity (27-89%) and specificity (32-90%) for baseline scores to predict conversion from MCI to AD (Arevalo-Rodriguez et al., 2015). A different comprehensive review by Tombaugh and McIntyre (1992) suggests the clinical uses of the MMSE should be as a supportive tool (rather than a sole criterion for diagnosis) to classify

severity of cognitive impairment using the following cut-off levels: no cognitive impairment = 24-30; MCI = 18-23; severe cognitive impairment = 0-17, though other research has shown that these cutoff scores should take into account other factors, such as age and education level (e.g., Crum et al., 1993).

### 1.3.2 Montreal Cognitive Assessment (MoCA)

The MoCA (Nassredine et al., 2005) is a neuropsychological screening test used to help clinicians attain a quick overview of major cognitive functions. It has been shown to be effective in discriminating dementia from normal cognitive decline (Gluhm et al., 2013), especially in MCI and AD populations (Defrancesco et al., 2010; Freitas et al, 2013; Julayanont et al., 2014). The current climate has clinicians integrating the MoCA into their standard of care for a few reasons: 1) the MoCA is available for free online (until September 2020; [www.mocatest.org](http://www.mocatest.org)); 2) requires minimal training to be able to administer and score; 3) the MoCA is more sensitive to detecting MCI than the MMSE (this is especially true if the patient is 60 years or older, Ciesielska et al., 2016; Petersen et al., 1999; Petersen et al., 2001; Pinto et al., 2018; Qiao et al., 2019); 4) the MoCA reliability and validity literature has become much more robust since the creation of the measure; and, 5) MoCA researchers have created corrected normative data in a number of areas, for example in middle age and elderly populations (e.g., Larouche et al., 2016), different ethnicities (e.g., Rossetti et al., 2011), and intersectionality such as age and education (e.g., Malek-Ahmadi et al., 2014).

The MoCA has a number of tasks testing different cognitive domains, including a declarative memory task. One study found that there was no significant association between performance on the MoCA memory subscale and hippocampal volume, but this may have been

due to the study not including an impaired cohort and, therefore, encountering a confounding “ceiling effect” from healthy controls (Paul et al., 2011). This finding does not appear to be repeated or supported anywhere else in the literature, particularly when impaired cohorts are included among experimental groups. In contrast, correlations between the MoCA and total brain volume atrophy identified by MRI were found in an elderly population after accounting for various demographics (Del Brutto et al., 2015) while hippocampal and total gray matter volume were found to be two of the three best predictors of cognitive performance on the MoCA (Gupta et al., 2015). It has been suggested that, since not all subsets of the MoCA are fundamental to the diagnosis of MCI, perhaps shortened versions of the MoCA would provide comparative accuracy. However, this was not found to be the case in a cross-sectional study (Cecato et al., 2015).

In terms of measuring functionality, the MMSE and MoCA were both found to be significantly correlated with accident probability and reaction time while in a driving simulator on both rural and urban scenarios among MCI patients (there was no correlation found in healthy older controls; Beratis et al., 2018). Furthermore, the MoCA was found to have a relatively stronger correlation than the MMSE.

The literature examining the relationship between MoCA and imaging techniques is somewhat mixed, though when studies focused on the hippocampi and used techniques similar to those used in the current study the results were consistently supportive of a correlation. For example, one study found that while other MoCA subtests showed little to no correlation with imaging measures, MoCA memory scores were significantly correlated with severity of atrophy in multiple sclerosis patients (Ashrafi et al., 2016). Another study found that total MoCA scores trended modestly, but were not significantly correlated, with subcortical hyperintensities in an

elderly population (Paul et al., 2011). This same study found that the hippocampus did not have a significant correlation with the Delayed Recall subtest. The authors suggested that the limited range of scores on Delayed Recall might explain this result, as well as the fact that no cued memory subtest data was collected. Furthermore, the authors did not find a significant difference in neuroimaging variables between those that scored in the impaired range (< 26 total) on the MoCA and those who were not in the impaired range, suggesting that their sample lacked sensitivity commonly seen in other studies. Finally, in a multidisciplinary approach to diagnosis, MoCA was deemed to have high diagnostic value and correlated well with imaging techniques including MRI (Freitas et al., 2013).

## **1.4 Magnetic Resonance Imaging Volumetric Measures**

### **1.4.1 Magnetic Resonance Imaging**

Magnetic resonance imaging uses a tissue's natural magnetic properties to construct a two-dimensional image. Briefly, hydrogen protons in our bodies are deflected off of their natural magnetic spins (with an added radio wave) and then allowed to return back to their natural state. During the realignment, the proton releases a different radio wave which is captured by receiver coils in the MRI machine. These waves are then used to construct an image (different tissues have different recovery times) of the tissues within the targeted body part (Berger, 2002).

Volumetric MRI is used to measure the size of various brain structures in addition to total brain volume. As shown in a number of studies, if the hippocampal volume is significantly smaller than what would be expected, it is often correlated with impairment in memory (Erickson et al., 2011; Grundman et al., 2003; Peterson et al., 2000; Rempel-Clower, Zola, Squire, & Amaral, 1996). While this is most certainly true in the MCI/AD population (see



below), it is also true in other populations. For example, when looking at brain volume and memory function affected by hypoglycemic events, Kirchoff et al. (2013) observed reductions in grey matter volume in the hippocampus, thalamus, and pallidum in patients with anterograde amnesia when compared to healthy controls. Chaddock et al. (2010) found that even children show the correlation of hippocampal volume with memory. In their study they found that higher bilateral hippocampal volumes in healthy children aged 9-10 were found to be positively associated with performances on relational memory tasks. Furthermore, while using region-of-interest (ROI) analysis on MRI images in non-demented older adults, Erickson et al. (2009) were able to conclude that larger hippocampal volume paired with higher physical fitness levels were correlated with better spatial memory performance.

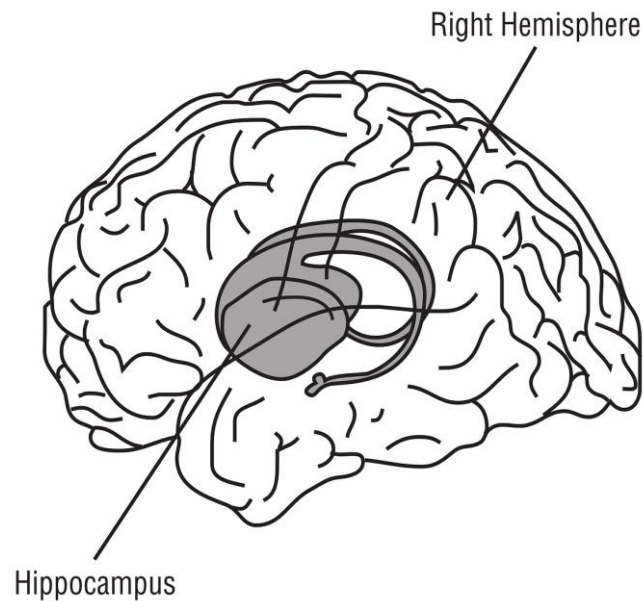
#### 1.4.2 Hippocampus

The hippocampus is a brain structure responsible for a number of cognitive tasks but is particularly essential to the declarative memory process (Squire, 1992). This role has been shown by examining how rats react to “reference memory” and “working memory” maze tasks after lesions to the hippocampus were made (Olton & Paras, 1979). At a neuronal level, firing patterns of the neurons in both animals and humans showed that the hippocampus is a key component in basic processes of declarative memory, and that damage to the structure is correlated with impaired memory (Eichenbaum, 2004). A study that looked more closely at structures that make up the hippocampi examined the relationship between specific areas of the hippocampi and different types of memory in a healthy elderly sample. They found that normal aging showed greater reduction in the hippocampal head compared to the tail. Right hippocampal tail volume atrophy correlated with poorer spatial memory (using the Groton Maze

Learning Test) while left hippocampal body volume was associated with delayed verbal memory (Chen et al., 2010). The hippocampus has been shown to have an integral role in animal and human memory behavior in a number of other studies (e.g., Fortin et al., 2002; Olton & Becker, 1979; Squire, 2004).

**Figure 2**

*The Hippocampus and its Location in the Brain*



Another study looking at performance on a retention memory task administered to children and adolescents (ages 8-19) found that long-term retention (1-week) ability was predicted by bilateral hippocampal volume. This, the authors interpret, is suggestive that

consolidation of memory traces is related to the hippocampus (Ostby et al., 2012). While these studies in healthy, young controls have found correlation between hippocampus integrity and memory ability, there is perhaps even more literature within the field of AD research supporting this claim.

As discussed earlier, it appears that AD follows a certain trajectory. During the disease progression the rate of atrophy in hippocampal structure and decline in cognitive ability appear to have strong correlation. The estimated annual hippocampal atrophy due to normal aging is 1.6-1.7% after the age of 65 (Jack et al., 2000), while in stable MCI this number rises to 2.8%, in MCI patients who progress to AD 3.7%, and AD patients 3.5-4% (Jack et al., 1998). Mormino et al. (2009) found results consistent with the popular model that AD follows the sequence of A $\beta$  deposition, hippocampal atrophy, and, finally, episodic memory decline in elderly participants. In one study, MCI and AD groups showed atrophy in the hippocampus at six months and at an even more accelerated rate of atrophy at one-year intervals. These rates of hippocampal loss were shown to be moderated by an indicator of A $\beta$  plaques (low cerebral-spinal fluid A $\beta$ <sub>1-42</sub>) and therefore indicative that hippocampal loss is part of a complex AD pathology (Schuff et al., 2009). A large longitudinal study began with 518 elderly participants who were free of clinical dementia at baseline. At four follow-up sessions spanning ten years, decline in hippocampal volume was predictive of the onset of clinical dementia and specifically predictive of decline in delayed word recall (den Heijer et al., 2010). A recent study found that the hippocampal volumes affected progression to MCI and AD more among women than in men (Burke et al., 2018). It appears the progression of AD and decline of cognitive abilities are paralleled with hippocampal atrophy.

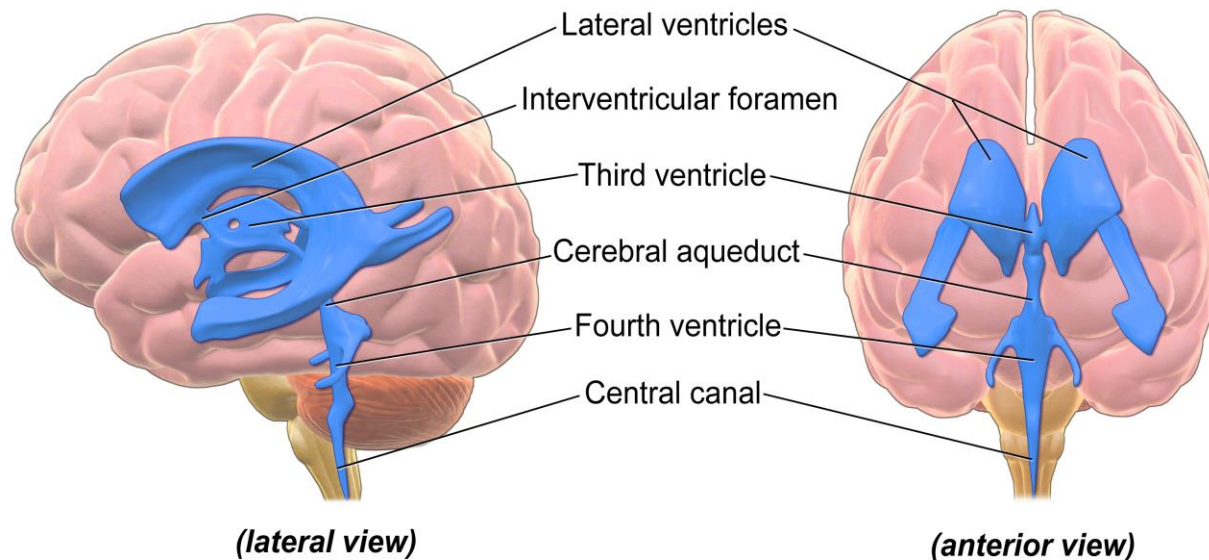
Another study found that hippocampal atrophy, when compared to A $\beta$  deposition, is a more accurate indicator of neurodegeneration in MCI and AD patients (Jack et al., 2010). There are even differences observed among the different types (or domains) of MCI, as one study reported hippocampal volumes were significantly smaller in a primarily amnesic MCI group (those more likely to progress to AD) when compared to normal controls and naMCI groups (Jak et al., 2009).

Regional hippocampal atrophy was positively correlated with more severe diagnosis (i.e., mild versus moderate AD), MMSE scores, and global and sum-of-boxes clinical dementia rating scores (CDR; Morra et al., 2009a). In a follow-up publication to this study, the investigators found that the rates of hippocampal volume loss were steeper the more severe a participant's diagnosis (normal diagnosis = 0.66% atrophy per year; MCI = 3.12% atrophy per year; AD = 5.59% atrophy per year; Morra et al., 2009b). Hippocampal volume (measured using MRI) was predictive of memory decline. Reduced activity of fornix, the predominant outflow tract of the hippocampus, function (measured using diffusion tensor imaging [DTI-MRI]), was also found to be correlated with memory decline, as well. Hippocampal volume and fornix function were both shown to have better than 90% accuracy when predicting which participants would progress to AD (Mielke et al., 2012). Using neurite orientation dispersion and density imaging (NODDI), Vogt et al. (2020) showed that in patients with MCI gray matter density was significantly lower than healthy controls in the temporal and parietal regions of the brain. Comparatively, patients with dementia due to AD were shown to have the same regions with lower density, along with frontal regions. Diffusion tensor imaging in those with MCI and mild AD showed correlations between microstructures and cognition for both A $\beta$  positive and negative participants (Reas et al., 2020).

In summary, hippocampal structural integrity has been shown to be closely related to performance on declarative memory tasks in a variety of studies. Specifically, the more hippocampal atrophy the poorer the performance on memory tests. Two theories competing on defining how the hippocampi function in memory are the Cortical Reallocation Theory and the Multiple Trace Theory. The Cortical Reallocation Theory states that the hippocampal role is to trace memory formation and consolidation for both semantic and episodic information. After this, the hippocampi transfer all the data to the neocortex. According to this theory, damage to the hippocampus will only affect recent memory since information is “passed on” to the neocortex and does not require hippocampal input after this (Alvarez & Squire, 1994; Meeter & Murre, 2004; Squire, 2004). The Multiple Trace Theory posits that the hippocampal formation encodes all information and then forms memory traces that involve both the hippocampus and the neocortex (Moscovitch et al., 2005; Nadel & Moscovitch, 1997). Due to the temporal gradient in memory decline and deterioration recognition that occurs with damage to the hippocampal formations, the Multiple Trace Theory appears to be more compatible with the known science (Leyhe et al., 2009).

#### 1.4.3 Lateral Ventricles

The lateral ventricles (LV) are brain structures that are part of the ventricular system in the brain. The ventricular system is mainly composed of the left and right LV and the third and fourth ventricles along with connecting structures (see *Figure 3*).

**Figure 3***The Human Ventricular System in the Brain*

Ventricles are cavities filled with CSF, which is produced by the ventricular linings and continuously flows through the entire central nervous system. The purpose of CSF is to cushion the brain, carry and distribute nutrients, and collect waste. Hippocampal atrophy is known to occur in other dementias (e.g., frontotemporal dementia; van de Pol et al., 2006), so combined assessment of the hippocampal volume and the LV may prove to be essential in accurate diagnosis. Killiany et al. (2000) performed a three-year longitudinal study that investigated a number of measures of brain structures, including LV, and were able to discriminate with 100% accuracy healthy controls from AD patients; discriminate controls from those with memory impairments that progressed to AD with 93% accuracy; and discriminate controls from those with memory complications that did *not* progress to AD over the three years with 85% accuracy.

A considerable amount of research has been conducted investigating LV, hippocampi, and other medial temporal lobe structures simultaneously due to the nature of these structures being adjacent. Change in shape of one can affect the other (e.g., a shrunken hippocampus physically provides greater space for the LV). Apostolova et al. (2012) found that healthy controls had the least hippocampal atrophy and LV enlargement, which was significantly less than MCI patients, who, in turn, had significantly less than AD patients. Another study mirrored these results and found that AD patients had greater ventricular enlargement than MCI patients and healthy controls, while MCI patients who progress to AD after six months had greater ventricular enlargement than stable MCI patients (Nestor et al., 2008). In a three-year longitudinal study of computed tomography (CT) scans, there were significant cross-sectional and longitudinal differences between rate of change in LV volume in AD patients (9% rate of change) and healthy controls (2%; de Leon et al., 1989).

Another approach to try and find diagnostically significant data in volumetric scans has been to map the shape of the LV and their surrounding structures. Qiu et al. (2009) found that the largest surface inward-deformations (i.e., shrinking) in MCI and AD patients were in the anterior hippocampal sections and the basolateral complex of the amygdala. The most pronounced surface outward-deformations (i.e., enlargements) in that same patient sample were in the LV. Ferrarini et al. (2006) found significant differences in the shapes of the LV when comparing healthy controls to AD patients. The hope for this branch of research is to eventually map out specific differences in order to provide guidelines for diagnostic consideration.

## 1.5 Eye Tracking in Alzheimer's Disease

Ocular movements in MCI and AD are unique and hold potential to provide crucial clinical information. In a review, hippocampal and medial temporal lobe structures were found to not only be involved in memory functionality, but also in visual processes. Deficits in visual short-term memory (specifically iconic memory, attention processes, and inhibitory control) can all be represented in eye movement patterns. Ultimately, this could help in predicting progression from healthy to MCI to AD (Pereira et al., 2014).

### 1.5.1 Ocular Abnormalities in Alzheimer's Disease

In their review, MacAskill and Anderson (2016) highlight microsaccade abnormality in AD. Microsaccades are tiny, horizontal rapid eye movements that serve to interrupt periods of fixation. Typically they are horizontal, but in amnesic MCI and AD patients they appear to be more oblique in shape. This shows promise for future diagnostic markers in eye tracking data.

Another review was able to group ocular changes that occur in relation to AD into saccades, smooth pursuit, and pupillary response (Molitor, Ko, & Ally, 2015). Saccades are the fast, darting movements that enable us to shift our gaze to a different target. These can either be directed towards a target (prosaccades) or away from a target (antisaccades). The activity in the frontal eye field (FEF; a structure that is part of the dorsal attentional network) and parietal eye field trigger saccades. Impairment in the FEF has been correlated with AD and can result in difficulties seeing relevant objects (Boucart et al., 2013). Abnormal prosaccades in AD are often hypometric, meaning they do not reach the target fully, or go entirely the wrong way. This is suggestive of both perseveration (returning to the target area from previous stimuli) and of



inhibitory dysfunction. When observing saccadic abnormalities in MCI and AD, eye tracking could distinguish between aMCI and naMCI (Wilcockson et al., 2019).

Antisaccades are suppressions of reflexive prosaccades and are also initiated by the FEF. Alzheimer's disease patients were found to make more incorrect saccades towards the target when instructed to make antisaccades, and also made fewer corrections after making these errors. These difficulties are also likely due to impairment in the inhibitory response. Another study's results were supportive of antisaccade abnormality as a marker for deterioration in the ability to voluntarily suppress automatic responses in favor of alternative behaviors in AD. This was found by investigating the neural correlates of controls and aMCI patients (Alichniewicz et al., 2013). The neural correlates suggest greater decreased activation in the FEF in amnesic MCI compared to controls, again likely due to decreases in inhibitory functions. Uncorrected antisaccadic errors in AD were shown to strongly correlate with spatial working memory, which suggests that impairment of inhibitory control in eye movements can potentially be used as a mark of working memory dysfunction in AD (Crawford et al., 2013). Antisaccade abnormality is correlated with neuropsychological testing, including the MMSE, as was the case with prosaccades (Molitor, Ko, & Ally, 2015).

In MCI patients, prosaccades are relatively intact while antisaccade results are mixed, possibly reflecting the range of MCI clinical categories. Though the results of the MCI patients and ocular changes were mixed, patients with aMCI showed greater impairment in antisaccadic movements (Molitor, Ko, & Ally, 2015).

One of the most popular tasks for assessing eye movement is the visual paired comparison (VPC) task. This task usually consists of a familiarization phase where subjects are presented with two identical visual stimuli that are next to each other on a computer screen. After

looking at a number of these pictures for a specified amount of time there will be a delay and, after this, the subject will go on to the test phase. During the test, subjects are presented with pictures of old stimuli next to new stimuli, also side-by-side. Eye movements are monitored and control subjects usually spend approximately 70% of the time looking at the new stimuli (termed *novelty preference*). The VPC requires no language production, minimal motor demands, and has been used across a number of species and age groups in humans from infants to the elderly (Crutcher et al., 2009). Chau et al. (2015) reported that lower novelty preference correlated with lower scores on the MMSE, and that AD patients had lower novelty preference compared to healthy controls. This suggests novelty preference can help differentiate between healthy cognition and impairment using a less cognitively demanding measure of selective attention.

Another study comparing MCI patients, controls, and Parkinson's disease patients found that when there was a two second delay between familiarization phase and test phase the three groups did not differ (all groups fixated on the novel picture >71% of the time), but when the delay was lengthened to two minutes the MCI group performed significantly different than the other two groups (53% fixation to >70% fixation, respectively; Crutcher et al., 2009). In a three-year longitudinal study Zola et al. (2013) found that VPC novelty preference scores could predict up to three years prior to a clinical diagnosis controls who progressed to MCI and MCI patients who progressed to AD.

## **1.6 Purpose and Significance of the Study**

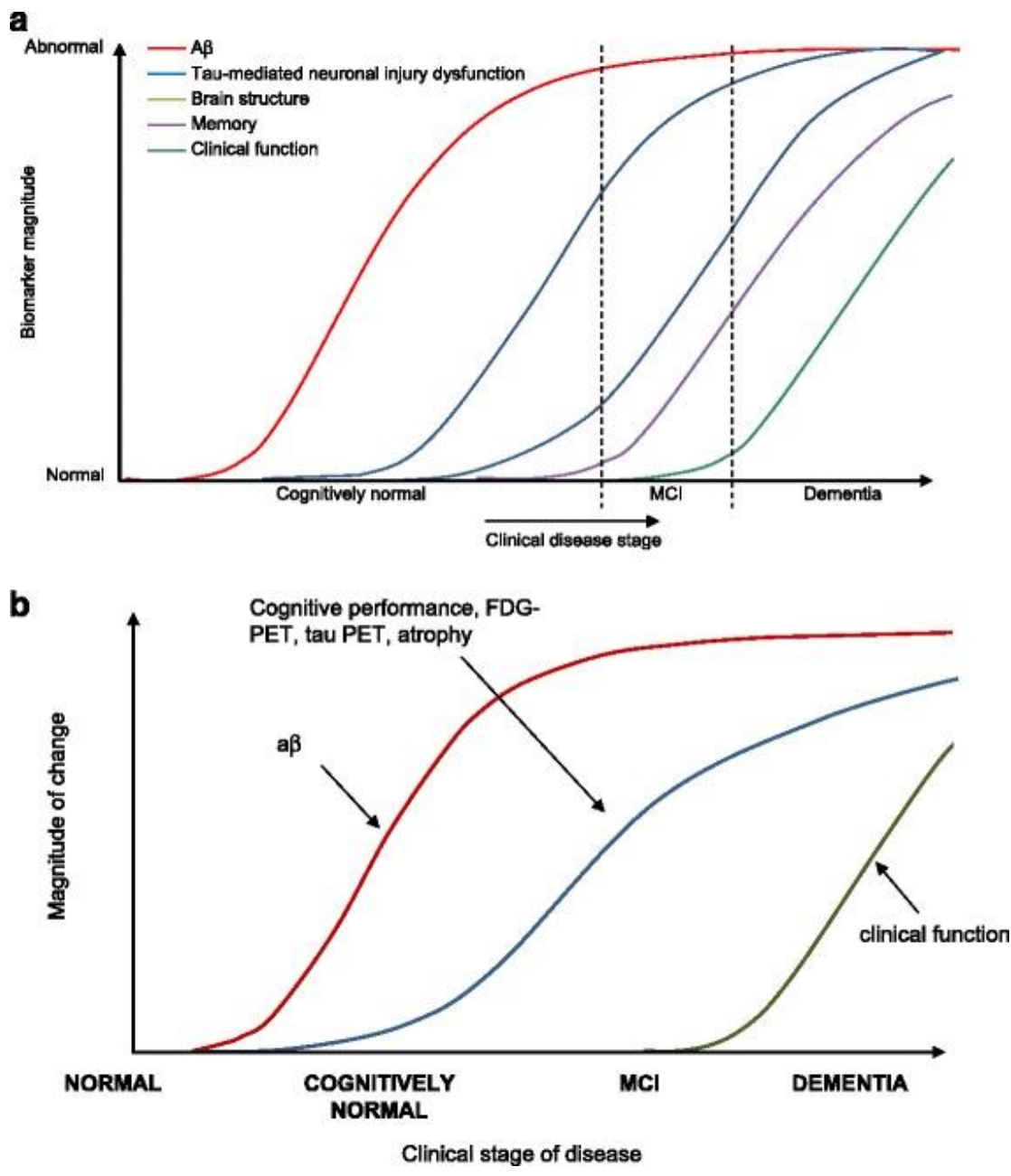
The previously described relatively lengthy and insidious progression that AD follows combined with the chimerical nature of the diagnosis, which requires data from a number of sources and assessment tools, and lack of cure or truly effective treatments all highlight the vast

importance of early and accurate diagnosis. Current pharmacological treatments can only “turn back the clock” on memory dysfunction to roughly where the patient was performing at six to 12 months prior (Budson & Solomon, 2016). A major goal of treatment for AD, therefore, is to focus on improving *quality* of life rather than *quantity* of life. On the social scale, early and accurate diagnosis of AD can relieve the burden by an estimated \$7.9 trillion in care costs (Alzheimer’s Association, 2018). At a more personal level, a diagnosis that is early and accurate provides the patient and their family a chance to become informed, prepare for the eventual decline, and complete/set-up important matters (e.g., power of attorney, in-home care, nursing home care, wills, etc.) while the patient is still able to understand fully, contribute, and make informed decisions. Furthermore, an early diagnosis gives patients and their loved ones the opportunity to try to achieve or wrap up recent or life goals while possible: travelling, finishing memoirs, spending more time with grandchildren, etc.

Alzheimer’s disease pathophysiological changes begin many years prior to clinical symptoms, and appear to be on a continuum, not in discrete stages as the diagnostic modifiers may suggest. Considering this, biomarkers should always be considered during the diagnostic process (Aisen et al., 2017; see *Figure 4*).

Figure 4

Change in Biomarkers Over Time in Relation to Clinical Stages and Symptomology



Note. Reproduced from Aisen et al., 2017. <http://creativecommons.org/licenses/by/4.0/>

Zhang et al. (2011) used a combination of biomarker evidence to attempt to classify healthy controls, MCI, and AD patients from a large database. By using a multimodal approach, they were able to obtain a classification accuracy of 93.2% in distinguishing AD patients from controls while achieving only 76.4%, 81.8%, and 66% accuracies from individual biomarker tests of structural MRI, fluorodeoxyglucose positron emission tomography (FDG-PET), and CSF, respectively. The same pattern was observed when distinguishing MCI from controls by finding 76.4% accuracy for the combined approach while only reaching a maximum of 72% accuracy for the individual approaches. Not only do these results support obtaining biomarker data, but also emphasize the importance of gathering data from a multitude of sources for accurate diagnosis. There have been recent proposals of new artificial intelligence-based diagnostic algorithms aimed at improving diagnosis by using multimodal approaches (e.g., by integrating MRI and FDG-PET imaging, Huang et al., 2019; by combining voxel-based morphometry measures from MRI of different brain regions, Gupta et al., 2019), but while promising these are in the infancy of research.

Instead of focusing on a single element of the diagnostic process, this study proposes to investigate clinical patterns across multiple measures in MCI and AD patients and compare these to healthy older controls (OC). Investigating multiple aspects of the clinical process will provide data gathered in a process that most patients will experience during a clinical visit. Providing insight into interactions between multiple clinical assessment measures to clinicians with limited access to certain tools (e.g., if a rural doctor's patients have no easy access to an MRI machine) could improve their diagnostic accuracy. Furthermore, results will likely re-emphasize the importance of a multimodal approach to the diagnostic procedure.

## 1.7 Statement of Problem and Hypotheses

This study seeks to answer the following questions: what are the relationships between performance on popular neuropsychological screening tests, volume of relevant brain structures, eye tracking data during a memory task, and how do these data contribute to identifying patients with MCI or AD versus healthy controls?

### **Hypotheses:**

- 1) The measures (MoCA total score, MMSE total score, hippocampal volume, LV volume, and eye tracking ratio) will accurately predict and uniquely contribute to which diagnostic group participants fall.
- 2) The predictive power of all the measures combined will be significantly greater than any individual measure's unique predictive power.
- 3) Expanding on Hypothesis 2, the more measures that are included in the predictive model, the more accurate the model will be in its predictions.

## CHAPTER 2

### METHODS

#### 2.1 Participants

Subjects were recruited from the Glennan Center for Geriatrics and Gerontology Memory Consultation Clinic at Eastern Virginia Medical School (EVMS) in Norfolk, VA. The Glennan Center specializes in evaluation of memory and other cognitive impairments and requires referral by a primary care physician or family member. The MCI participants had a clinical diagnosis of aMCI single- or multi-domain. Participants in the AD group had a clinical diagnosis of mild AD. The initial clinical diagnosis was made after one or two sessions with the participants. It should be noted that this was *not* the etiological diagnosis, which was determined after the clinician received all results from all measures. Control participants were primarily family members recruited while accompanying patients to the Glennan Center or through word-of-mouth. Those who are not recruited in this manner were family members of patients referred from Dr. David Spiegel's (the Principal Investigator) practice at EVMS. Control participants went through the same battery of tests as patients and no MCI or AD diagnosis was present.

All subjects were 60 years or older and recruited from the region surrounding the memory clinic in Southeast Virginia. All subjects' primary language was English, and they had sufficiently intact hearing to complete the neuropsychological measures. In order to undergo an MRI, a subject could not have any implanted metallic objects (e.g., cardiac pacemaker) that may disrupt their results. Informed consent was obtained and, if the patient was too impaired to properly consent, a legally authorized representative consented with the subject's assent. All data related to this study was de-identified in Excel sheets on a password protected computer behind

locked doors at the Glennan Center. All physical data was kept in a locked filing cabinet after being de-identified and will be destroyed upon completion of the study.

## **2.2 Procedures**

During the initial consultation, patients were administered a brief neurocognitive screening as part of the standard clinical evaluation. The MMSE was first and the MoCA the last measure in a battery that typically took approximately 45-60 minutes. Testing was administered by either a clinical or research staff member who had been trained in the administration and scoring of the measures.

Exclusionary criteria included history of stroke, traumatic brain injury resulting in loss of consciousness, seizure disorder (and/or currently on seizure medications), significant ophthalmological or visual problems, claustrophobia, which could preclude an MRI, implanted or embedded medical device (e.g., pacemaker) or other metal (e.g., shrapnel), or surgery for a cerebral aneurysm.

Diagnosis of probable AD at the stage of MCI or dementia was made based on the recommendations from the National Institute on Aging – Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease (Albert et al., 2011; McKahn et al., 2011). Eligible patients were approached by the clinician or a research staff member at the end of their clinical evaluation to inform them about the study and seek their consent to participate.

After their clinical appointment concluded, participants first completed vision and hearing tests measured by the Snellen chart, the Hearing Handicap Inventory Screening Questionnaire, and a brief demographic questionnaire utilized in “Development of a Clinically Practical Protocol for the Evaluation of EEG-based Neurometrics, IRB # 14-02-EX-0026,”



which had already been approved by the EVMS Institutional Review Board. They also underwent consent/assent procedures at this time. Participants were then scheduled for one visit to complete both an electroencephalogram (EEG; results not part of this study) and VPC eye tracking evaluation.

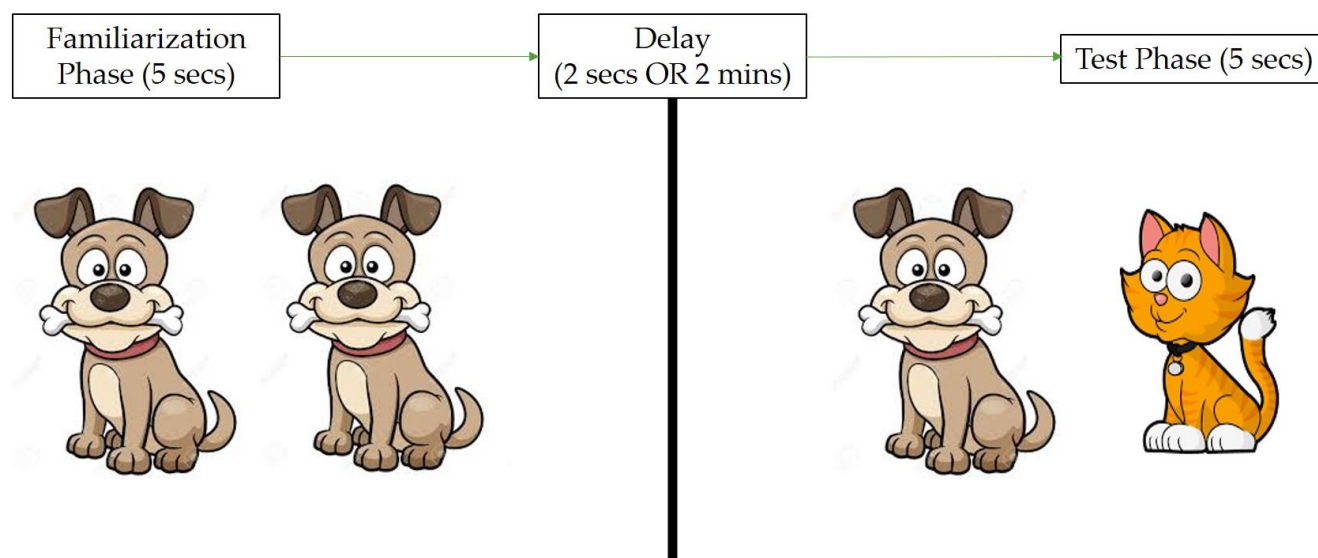
After the EEG neurometric profile was compiled, a VPC task was administered using an infrared eye tracker, as well as a webcam-based eye tracker. The task functioned using standard web browsers on typical desktop computers equipped with attached webcams. The VPC task required that the participant look at stimuli as they appear on the computer screen. First, during a brief 30-second calibration phase, the participant watched a ball as it moved around the screen. This data was used later to map images of the participant's eyes captured during the task onto screen coordinates.

The entire VPC testing procedure lasted approximately five minutes, including the calibration session. Subjects were administered one trial of four blocks (delay order: 2-minute delay, 2-second delay, 2-second delay, 2-minute delay). Each trial consisted of two phases; a familiarization phase followed by a test phase. In both phases, the participants were instructed to look at the monitor, "as if watching television." During the familiarization phase, two identical pictures were presented side-by-side on the monitor for five seconds. The monitor then would go dark for a delay interval of either two seconds or two minutes. Then, in the test phase, two pictures were presented side-by-side for five seconds. One of the images was identical to the image presented during the familiarization phase and the other was a novel image. The side of presentation of the novel picture was selected pseudo-randomly and presented equally often on the left or right side of the monitor. After the test phase of the trial, the monitor darkened for 20 seconds until the beginning of the next trial. In order to ensure subject attention for test trials that

had two-minute delays, the experimenter verbally alerted all subjects that there will be “approximately ten seconds before the next pair of images” (see *Figure 5*).

**Figure 5**

*Visual Paired Comparison Task Example*



Those participants who did not have an MRI of brain as part of their clinical work up were referred to the local MRI and CT Diagnostics Imaging Center to receive a structural MRI using the scanning protocol recommended for allowing later NeuroQuant analysis. An MRI was scheduled to occur within two weeks of the Glennan Center evaluation. Imaging of the brain was performed with a 3.0-Tesla MRI scanner (General Electrics) using a standard dementia MRI protocol, including T1 weighted FSPGR 3D, with 3D volumetric analysis using NeuroQuant technique.

The NeuroQuant computer automated analysis routinely provides volume data on 40 brain regions on each side of the brain, for a total of 80 volume measurements. However, this analysis provides comparisons to a normal-control group for only three brain regions (averaged across left and right sides). These regions include hippocampi, lateral ventricles and inferior lateral ventricles. The specific procedures for this analysis can be found at the NeuroQuant website (<http://www.cortechslabs.com/products/>). An example of the NeuroQuant outputs can be found in *Figure 6*.

Figure 6

Example NeuroQuant Reports

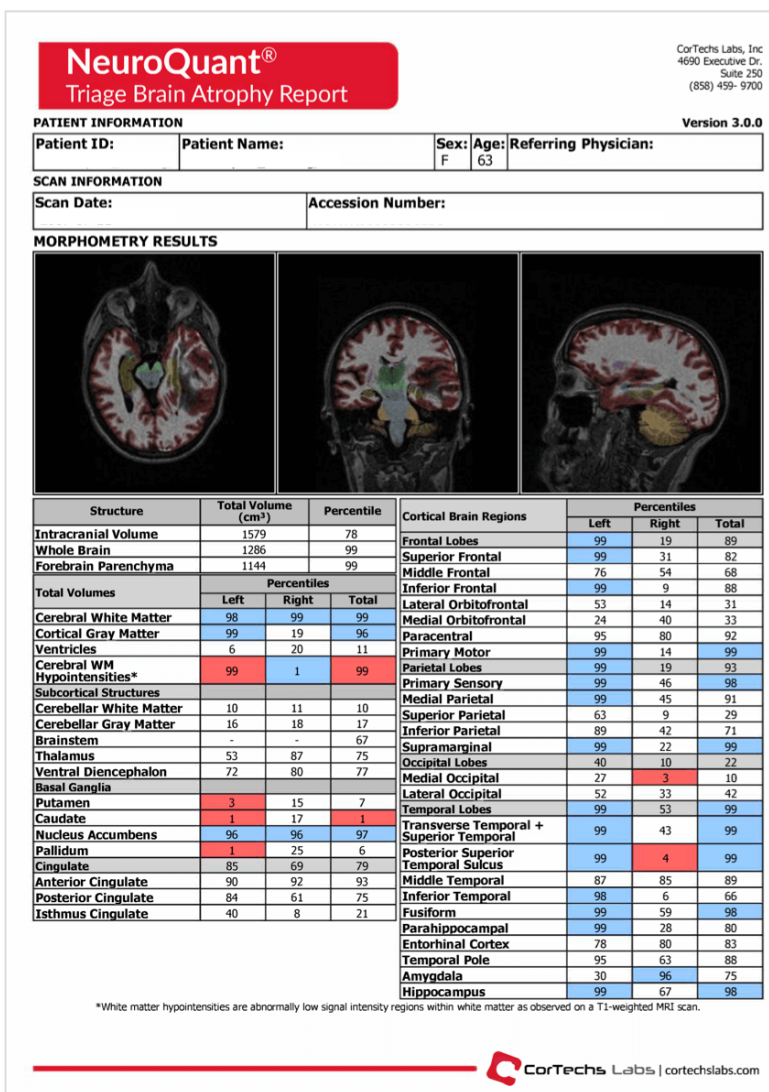
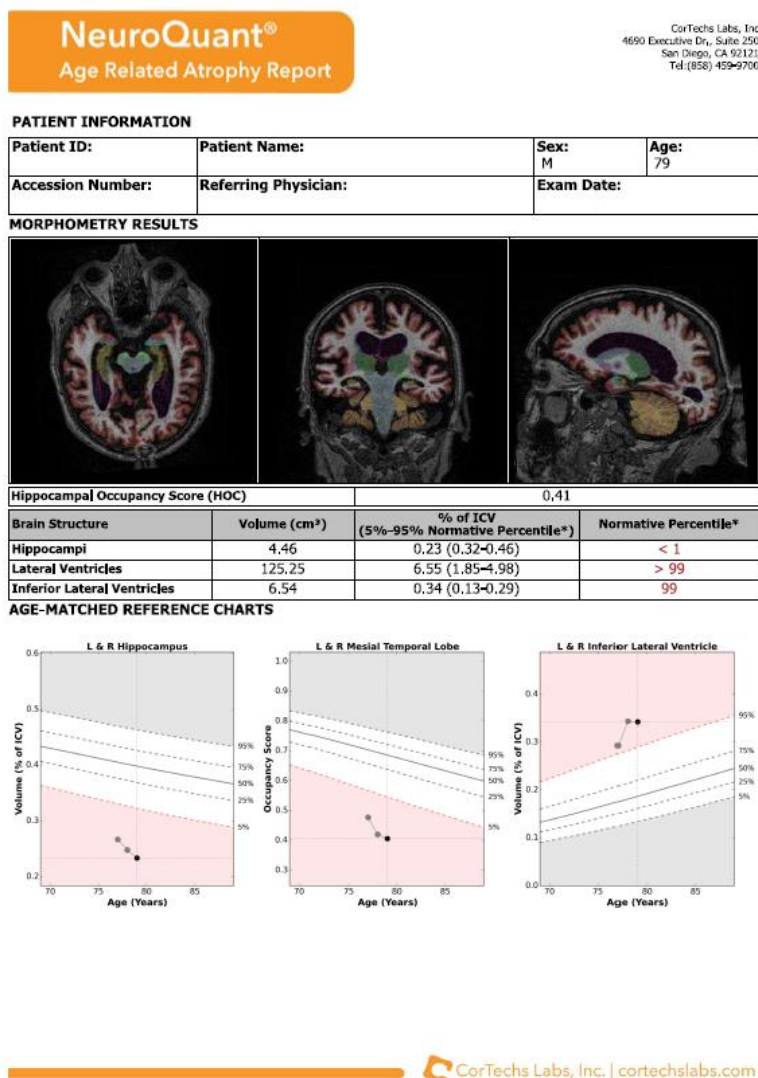


Figure 6 Continued



The cost of imaging studies for participants was covered by research funding if the imaging was not done as part of the routine clinical work-up. For those participants who had an MRI as part of their clinical work up, the research team members obtained MRI data from the participants' electronic medical records (Allscripts) for further analysis.

### 2.3 Measures

Diagnostic work up for each participant included a 120-minute standardized baseline assessment by interviewing and examining the patients, administration of a 60-minute battery of neuropsychological tests that assessed all major cognitive domains. and interview of a proxy close to the patient. This process included a review of medical records, clinical interviews with patient and family (or close acquaintances, if available), neuropsychological battery, neurological exam, medical exam, and other tests the director deemed necessary (e.g., MRI, FDG-PET scan).

For independent variables, the total MoCA scores and total MMSE scores were used from the neuropsychological tests. These scores are both out of a maximum score of 30. With regards to the volumetric measures, the hippocampal volume and LV volume numbers provided by the NeuroQuant analysis were used. These volumes were in centimeters cubed units and were the results of the 3D volumetric post-processing of MRI scans. Finally, eye tracking data provided a novelty preference ratio which was used as the fifth independent variable.

Data was collected from a total of 69 participants. Following the removal of three cases (described in Results section), *Table 1* shows the demographic data. In addition to the demographics, data on the five predictors (MMSE, MoCA, Hippocampal Volume [HV], Lateral Ventricular Volume [LVV], and Eye-Tracking Ratio [ETR]) were gathered. There was a significant difference between groups on age,  $F(2) = 3.84, p = 0.03$ , which is expected given the previously mentioned gradual cognitive decline model of Alzheimer's disease. There were no significant differences between groups among education,  $F(2) = 0.80, p = 0.45$ , or gender,  $F(2) = 0.36, p = 0.70$ .

**Table 1***Demographic Data of 66 Participants*

Diagnostic Category	<i>n</i>	Age	Education	Gender (percent male)
Older Control (OC)	13	68.31 (5.22)	15.11 (1.69)	44.44
Mild Cognitive Impairment (MCI)	23	73.61 (9.21)	14.90 (2.44)	53.33
Alzheimer's Disease (AD)	30	76.39 (8.78)	14.17 (2.48)	72.22
<i>Total</i>	66	73.53 (8.78)	14.66 (2.36)	59.52

*Note.* Mean(SD) format unless otherwise stated.

**Table 2***Descriptive Data of Five Predictors*

Diagnostic Category	<i>n</i>	MMSE	MoCA	HV	LVV	ETR
OC	13	28.62 (2.10)	26.69 (2.10)	6.31 (0.72)	46.82 (29.00)	0.56 (0.11)
MCI	23	25.48 (2.43)	21.45 (3.28)	6.05 (1.32)	47.62 (26.13)	0.55 (0.09)
AD	30	21.74 (2.26)	18.10 (2.40)	5.60 (0.79)	48.44 (29.88)	0.08 (0.04)
<i>Total</i>	66	24.78 (3.35)	21.41 (4.14)	5.92 (1.08)	47.77 (27.55)	0.54 (0.08)

*Note.* Mean(SD) format.

## CHAPTER 3

### RESULTS

#### 3.1 Assumptions and Data Cleaning

Analyses were completed according to suggestions from Tabachnick and Fidell (2018) and Peng, Lee, and Ingersoll (2002). Prior to analyses, variables were examined using R (version 3.6.3) for accuracy of data entry, missing values, fit between their distributions, and the assumptions of multivariate analysis. To improve pairwise linearity and reduce the extreme skewness and kurtosis, LVV and ETR variables were logarithmically transformed. These transformed variables were then compared to the original data and were not significantly different, therefore the original data was kept for analyses.

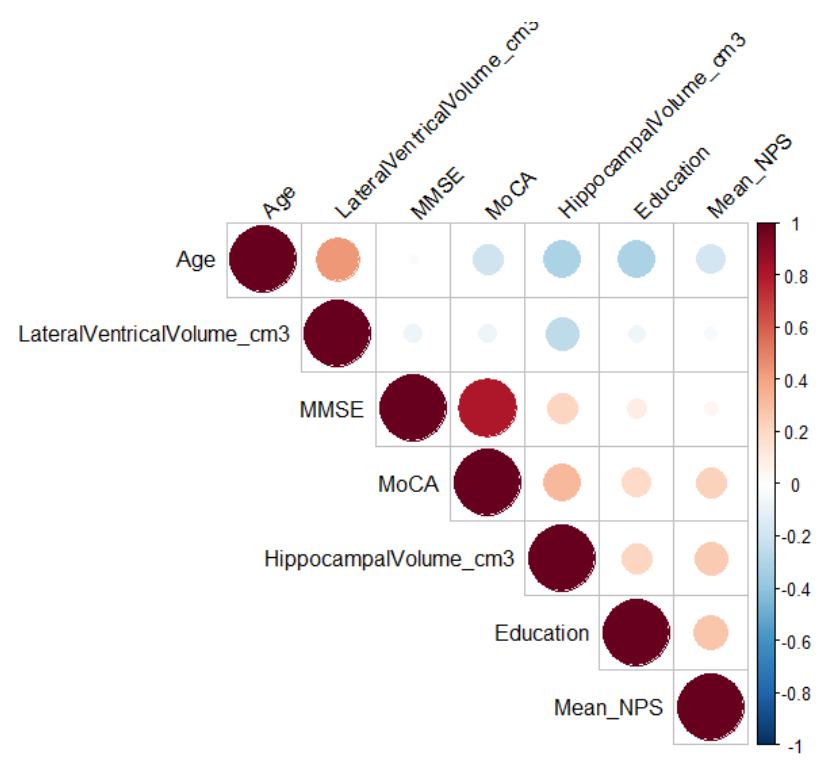
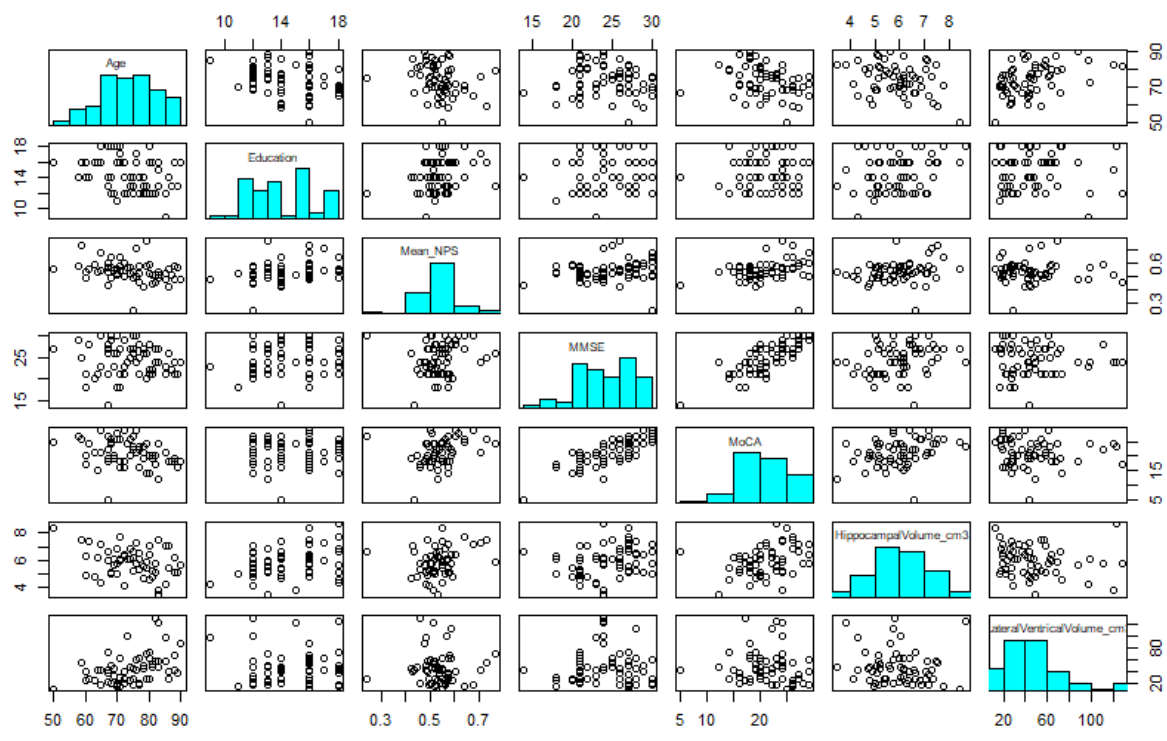
Three cases were left out of analysis, one from each diagnostic group. Two cases, one with an extremely low  $z$ -score in ETR and one case in MoCA, were found to be univariate outliers. One other case was identified through Mahalanobis distance as a multivariate outlier with  $p < .001$ . All three outliers were deleted, leaving 66 cases for analysis.

The following scatterplots show associations among all variables plus age, education, and gender:



Figure 7

Scatterplots of Variable Associations



From these scatterplots, it is apparent that most of the pairwise correlations are in an acceptable range for not violating the multicollinearity assumption. However, the value of Pearson correlation of 0.8 between MMSE and MoCA is high enough to violate this assumption. Thus, it was considered to be essential to use only one of the two variables in the predictive model and compare the results to the full model.

### 3.2 Main Analyses

A five-predictor multivariate logistic regression model was run using diagnostic group as outcome (or, dependent) variable and with several independent variables (or, predictors). For comparison purposes, the OC group was considered as a reference group. Thus, the other two groups MCI and AD were compared to the reference group. The theoretical framework of the multivariate logistic model can be given as:

$$\log \left( \frac{\Pr(\widehat{Group}=MCI)}{\Pr(\widehat{Group}=OC)} \right) = \hat{\beta}_0 + \hat{\beta}_1 X_1 + \hat{\beta}_2 X_2 + \dots + \hat{\beta}_p X_p \quad \text{Equation (1)}$$

$$\log \left( \frac{\Pr(\widehat{Group}=AD)}{\Pr(\widehat{Group}=OC)} \right) = \hat{\beta}_0 + \hat{\beta}_1 X_1 + \hat{\beta}_2 X_2 + \dots + \hat{\beta}_p X_p \quad \text{Equation (2)}$$

where  $\Pr(\widehat{Group} = MCI)$  represents predicted probability of MCI given the predictors in the model. Similar interpretation holds for other terms.  $\hat{\beta}_0$  is the estimated intercept and  $\hat{\beta}_1, \hat{\beta}_2, \dots, \hat{\beta}_p$  are the coefficients associated with predictors  $X_1, X_2, \dots, X_p$ , respectively.

Initially, this regression was carried out by the Multivariate Logistic Regression (NOMREG) procedure in SPSS version 26 in the Windows 10 environment. Results are shown in *Table 3*.

**Table 3**

*Multivariate Logistic Regression Analysis of 66 Patients' Diagnoses by SPSS NOMREG (Version 26) – Full Model*

Predictor (MCI vs OC)	$\beta$	SE $\beta$	Wald's $\chi^2$	<i>df</i>	<i>p</i>
Intercept*	43.21	21.06	4.21	1	0.04
MMSE	-0.42	0.43	0.97	1	0.33
MoCA*	-1.12	0.53	4.50	1	0.03
HV	0.12	0.03	0.05	1	0.83
LVV	0.04	7.83	1.11	1	0.29
ETR	-10.45	7.83	1.78	1	0.18

Predictor (AD vs OC)	$\beta$	SE $\beta$	Wald's $\chi^2$	<i>df</i>	<i>p</i>
Intercept**	61.33	22.14	7.68	1	0.006
MMSE*	-1.05	0.48	4.77	1	0.03
MoCA*	-1.28	0.55	5.37	1	0.02
HV	0.73	0.70	1.09	1	0.30
LVV	0.04	0.04	1.09	1	0.30
ETR	-17.70	11.08	2.55	1	0.11

Test	$\chi^2$	<i>df</i>	<i>p</i>
Overall model evaluation			
Likelihood ratio test	55.99	10	<.0001
Goodness-of-fit test			
Pearson	60.36	96	.998
Deviance	54.86	96	1.00

Pseudo R <sup>2</sup>	
Cox and Snell	0.65
Nagelkerke	0.74
McFadden's <i>p</i> <sup>2</sup>	0.51

*Note.* \*\* = *p*-value < .01, \* = *p*-value < .05.

There was a good model fit (discrimination among groups) on the basis of the five predictors,  $\chi^2$  (96, *N* = 66) = 54.86, *p* = 1.00, Nagelkerke *R*<sup>2</sup> = .75, using a deviance criterion. Two predictors (MMSE and MoCA) set statistically significant enhanced prediction, *p* < .05.

Due to the previously mentioned high correlation between the two neuropsychological predictors, the predictor MMSE was removed from the model and similar results were found for model fit,  $\chi^2 (98, N = 66) = 68.02, p = 0.99$ , Nagelkerke  $R^2 = .63$ . This was also the case when MoCA was removed from the full model,  $\chi^2 (100, N = 66) = 67.66, p = 1.00$ , Nagelkerke  $R^2 = .64$ . In both instances the remaining neuropsychological test set statistically significant enhanced prediction,  $p < .05$ .

To determine how accurate the full model was at predicting and classifying diagnoses, a machine learning approach was used to train and test the prediction model with all variables. The model was developed (or trained) using 80% of the sample. Once the model was trained, it was tested using the remaining 20% of the sample. The 80% random sample for training set consisted of 58 rows and nine columns, whereas the test set consisted of 12 rows and nine columns. The multivariate logistic regression model was run using the diagnosis as the dependent variable. Again, the OC group was considered a reference group.

**Table 4***Estimates of Coefficients for Multivariate Logistic Regression with All Predictors*

Predictor (MCI vs OC)	$\beta$	SE $\beta$	Z	p
Intercept	-7.30	6.61	-1.10	.269
ETR	14.41*	6.46	2.23	< .050
MMSE	4.72**	1.58	2.99	< .010
MoCA	-21.25***	1.44	-14.74	< .001
HV	8.87***	0.56	15.84	< .001
LVV	0.27	5.96	0.05	.963

Predictor (AD vs OC)	$\beta$	SE $\beta$	Z	p
Intercept	21.10**	6.61	3.19	< .010
ETR	-1.90	6.46	-0.29	.768
MMSE	4.16**	1.58	2.64	< .010
MoCA	-21.63***	1.44	-15.00	< .001
HV	10.10***	0.56	18.06	< .001
LVV	0.34	5.96	0.06	.955

Note. \*\*\* =  $p$ -value < .001, \*\* =  $p$ -value < .01, \* =  $p$ -value < .05. AIC = 61.05.

The trained models based on estimates shown in *Table 4* were used to predict group affiliations in the test dataset (cross-validation) and results are in *Table 5*:

**Table 5**

*Cross Table Showing Observed and Predicted Group Affiliations*

	Predicted			
Observed	1	2	3	Row Total
1	3	1	1	5
2	1	3	0	4
3	1	0	1	2

*Note.* Accuracy of the model = 63.64%, which is moderate. This may be because of several reasons, one of which is that our test dataset has only 11 non-missing values. The maximum accuracy in k-fold (k = 5) cross-validation, which is considered better in small data situations, was 68.65% (with 28 warning messages).

The predictor MMSE was removed from the model in step 1 of the machine learning approach and the cross-validation table was exactly like *Table 5* (above). The overall accuracy was 63.64%. The maximum accuracy in k-fold (k = 5) cross-validation, which is considered better in small data situations, was 62.38% (with 11 warning messages), AIC = 62.61597.

The predictor MoCA was removed from the model in step 1 of the machine learning approach and the cross-validation table was exactly like *Table 5* (above). The overall accuracy was 63.64%. The maximum accuracy in k-fold (k = 5) cross-validation, which is considered better in small data situations, was 71.64% (with 9 warning messages), AIC = 66.56079.

### 3.3 Supplemental Analyses

The k-fold cross-validation technique described previously was created by utilizing listwise deletion of cases. Out of the 66 cases, there were 11 subjects with 20 data points missing (6.28%). This was greater than the suggested threshold of 5%, so using listwise deletion may have introduced a considerable amount of bias into the results (Tabachnick & Fidell, 2018). To address this, missing values were imputed using the *mice* package in R (predictive mean matching, 100 iterations). Finally, multiply imputed datasets were analyzed using the *mice* and *nnet* packages in R. Like previous results, only MMSE and MoCA showed statistically significant contributions to the model (see *Tables 6-8*):

**Table 6**

*Pooled Multiply Imputed Multivariate Logistic Regression Analysis of 66 Diagnoses by R Version 3.6.3 Using mice and nnet Packages*

Predictor (MCI with OC as Reference)	$\beta$	SE $\beta$	Z	df	p
Intercept	46.12*	22.16	2.08	49.44	0.04
MMSE	-0.57	0.40	-1.41	50.33	0.16
MoCA	-0.99*	0.46	-2.14	50.40	0.04*
HV	-0.01	0.62	-0.02	49.01	0.98
LVV	-3.24	3.09	-1.05	49.29	0.30
ETR	1.23	11.45	0.11	47.86	0.91

Predictor (AD with OC as Reference)	$\beta$	SE $\beta$	Z	df	p
Intercept	56.69*	22.84	2.48	49.10	0.02*
MMSE	-1.16*	0.44	-2.61	50.51	0.01*
MoCA	-1.18*	0.49	-2.43	50.51	0.02*
HV	0.32	0.73	0.44	47.79	0.66
LVV	-1.39	3.53	-0.39	49.61	0.70
ETR	-5.61	14.61	-0.38	45.28	0.70

Note. \* = p value < 0.05



**Table 7**

*Pooled Multiply Imputed Multivariate Logistic Regression Analysis of 66 Diagnoses by R Version 3.6.3 Using mice and nnet Packages (Omitting MMSE)*

Predictor (MCI with OC as Reference)	$\beta$	SE $\beta$	Z	df	p
Intercept	28.26	14.81	1.91	49.41	0.06
MoCA	-1.07*	0.40	-2.66	52.15	0.01*
HV	0.25	0.54	0.46	47.88	0.65
LVV	-1.27	2.41	-0.53	48.70	0.60
ETR	3.33	11.19	0.30	49.87	0.77

Predictor (AD with OC as Reference)	$\beta$	SE $\beta$	Z	df	p
Intercept	33.73*	15.42	2.19	49.25	0.03*
MoCA	-1.48***	0.43	-3.48	52.12	0.001**
HV	0.40	0.65	0.62	47.50	0.54
LVV	-0.68	2.77	-0.25	49.22	0.81
ETR	0.83	13.32	0.06	48.55	0.95

Note. \* = p value < 0.05; \*\*=p value < 0.01

**Table 8**

*Pooled Multiply Imputed Multivariate Logistic Regression Analysis of 66 Diagnoses by R Version 3.6.3 Using mice and nnet Packages (Omitting MoCA)*

Predictor (MCI with OC as Reference)	$\beta$	SE $\beta$	Z	df	p
Intercept	27.47*	13.26	2.07	50.83	0.04*
MMSE	-1.01*	0.36	-2.83	53.56	0.006*
HV	-0.22	0.58	-0.37	48.01	0.71
LVV	-0.14	2.05	-0.07	51.20	0.95
ETR	-10.81	9.73	-1.11	51.35	0.27

Predictor (AD with OC as Reference)	$\beta$	SE $\beta$	Z	df	p
Intercept	37.13*	14.20	2.61	50.62	0.12*
MMSE	-1.69***	0.41	-4.15	53.41	0.0001***
HV	-0.02	0.69	-0.03	47.78	0.96
LVV	1.29	2.60	0.50	51.37	0.62
ETR	-20.00	12.99	-1.54	48.06	0.13

Note. \* =  $p$  value < 0.05; \*\*\* =  $p$  value < 0.001

Comparison of log-likelihood ratios for the full multiply imputed model against a model using only neuropsychological tests showed no statistically significant difference,  $t = 0.26$ ,  $p = 0.95$ . Log-likelihood ratios for the full model against MRI measures-only model showed a statistically significant difference,  $t = 3.16$ ,  $p = 0.004$ . The full model against ETR-only model also showed a statistically significant difference,  $t = 2.56$ ,  $p = 0.009$ . Finally, a regression was run with no neuropsychological tests in the model. This overall model was not statistically different from the intercept model (see Table 9).

**Table 9***Multivariate Logistic Regression without Neuropsychological Tests*

Predictor (MCI with OC as Reference)	$\beta$	SE $\beta$	Z	df	p
Intercept	4.36	3.68	1.41	1	0.24
HV	-0.38	0.40	0.92	1	0.34
LVV	-0.003	0.02	0.04	1	0.84
ETR	-1.60	4.95	0.10	1	0.75
Predictor (AD with OC as Reference)	$\beta$	SE $\beta$	Z	df	p
Intercept	7.85	3.87	4.11	1	0.10
HV	-0.62	0.42	2.22	1	0.14
LVV	<0.001	0.02	0.001	1	0.98
ETR	-6.02	5.33	1.27	1	0.26

## CHAPTER 4

### DISCUSSION AND CONCLUSION

This section will discuss the implications of the results presented previously. First, the findings of the main and supplemental analyses will be discussed in reference to the original research questions and hypotheses, as well as convergence and divergence of existing literature. Next limitations of the study will be presented. Finally, clinical and research implications of the study will be discussed as well as recommendations for future directions.

#### 4.1 Discussion of Results

A full model including all five predictors was run and the model was significantly different from a model with no predictors (the intercept model). Interestingly, the only predictors that were statistically significant contributors to the model were MMSE and MoCA. This may have been an overrepresentation issue, as the neuropsychological tests were the only measures that were always available to the clinician to review at the time of diagnosis. However, even when the tests were removed from the regression model the remaining model was not significantly different than intercept, indicating that the measures in this neuropsychological test-less model were not particularly good predictors of diagnosis. Furthermore, removing MMSE and MoCA one at a time from the full model still left the remaining neuropsychological test the only predictor with statistical significance to the model. Finally, comparing the full model to only the neuropsychological tests showed no real improvement in accuracy of the model.

Hypothesis 1 predicted that all the measures together would accurately predict and uniquely contribute to which diagnostic group participants fall. This hypothesis was supported moderately with the different regression models ranging from approximately 62 - 71% accuracy.

Hypotheses 2 and 3 stated that the predictive power of all the measures combined would be greater than any individual measure's unique predictive power and/or combinations of fewer predictors. These hypotheses were not supported as the neuropsychological measures themselves were statistically as accurate as the full model which included all the predictors.

In general, all models were moderately predictive of actual results, though they did not reach the levels of more accurate, less accessible measures such as PiB-PET scan (approximately 96% accurate) and CSF (85-90% accurate), though these measures are recommended for confirmation of diagnosis, not initial assessment (Lee et al., 2019; Weller & Budson, 2018). When comparing the full five predictor model to models with fewer predictors (e.g., a model with only MRI measurements) the full model was more accurate with its predictions, which supports the original Hypothesis 2. However, this was not the case when the full model was compared to neuropsychological tests only, which suggests that the neuropsychological tests alone made the full five predictor model accurate. There was also considerable missing data that was slightly higher than the recommended threshold of 5% (see Tabachnick & Fidell, 2018). Multiply imputing this data and running the same regressions did not change any of the overall outcomes, implying that missing data did not significantly affect the study results.

## **4.2 Limitations**

There were multiple limitations in this study, one of them being that it is unclear how generalizable these results are to the larger population. The overall sample size when used for a five-predictor multivariate logistic regression was on the low side, which may have led to low statistical power. This may account for the non-significant findings of measures that, when based on past literature, would be expected to have a strong influence on the predictive power of the

regression model. The gender ratio of the different diagnostic groups was not congruent with previous research, as women typically are disproportionately likely to have Alzheimer's disease, while some studies show males are more likely to receive a diagnosis of MCI (Mielke, Vemuri, & Rocca, 2014). This study's sample was slightly more males in the MCI group while the AD group had almost 73% males.

The diagnostic role was performed by a sole clinician at a single site and the recruitment process of participants may have also introduced confounding variables. A portion of participants in the OC group were recruited while accompanying their loved ones to appointments at the Glennan Center. This may mean that many of the control participants were related to the MCI and AD participants. Indeed, studies have typically shown controls with a novelty preference around 70% towards the novel object while participants with MCI or AD being closer to 50% (Crutcher et al., 2009). The control sample in this study was much closer to 50% (56%) than would be expected. Research has shown that AD has a considerable genetic component (Bertram & Tanzi, 2008), so the possibility exists that the OC group in this study had a greater ratio than the general population of those who have AD but are not presenting clinically yet. The significant difference in age between the groups also may have contributed to this factor and future studies should age-match their groups to eliminate this confound.

Other limitations relate to the instruments and measures used. First, the MMSE was always administered first in the neuropsychological battery and the MoCA last. It is anomalous to give both tests in the same visit, given their considerable overlap in what they assess. The order that these measures were administered study-wide may have caused fatigue effects and/or practice effects, as well as interference, especially in the memory portions.

Another limitation with this study was the “circular reasoning” of the neuropsychological test results and diagnosis. The MMSE and MoCA were both scored immediately after administration and those results were shared with the clinician during the patients’ initial visits, ultimately aiding in his diagnostic decision. It was not surprising that both measures were significant to the predictive power of the regression models. There was concern that this methodology may have led to an underrepresentation of the other measures. However, upon further analyses, even when these measures were removed from the equation, the other measures did not produce a model that had the same accuracy.

#### **4.3 Implications for Clinicians and Future Research**

Considering these limitations, the found results have considerable implications for both clinicians and directions for future research. The multimodal approach was minimally supported. More predictors led to only slightly more accurate predictive models of diagnosis, but neuropsychological tests were the only measures that held statistical weight in terms of affecting the regression models’ accuracy. This suggests that in a clinical setting a) neuropsychological screening remains important to accurate diagnosis; and, b) the MoCA seems to be slightly more advantageous than the MMSE for accurate diagnosis, especially when it comes to diagnosing MCI accurately, which is congruent with current literature. When considering these findings, it is recommended that clinicians rely on the MoCA rather than the MMSE. The MoCA appears to be more useful for diagnosing both conditions and the normative data is on par or quickly reaching the levels of the MMSE. The MoCA developers should particularly focus on extending their normative data into older ages in order to accurately represent a broader community.

Still, predictive power of the regressions' outcomes was at levels that would allow a clinician to be confident in following up appropriately in order to confirm diagnosis of MCI or AD using methods such as biomarker testing. It should be restated that only a select number of factors were selected for this study. There may have been numerous other quantitative and qualitative factors that led to each patient's diagnosis. The "art" of diagnosing requires a clinician to decide which pieces of information he or she will give more weight to depending on the overall picture of the patient, and this is not easily quantified. Future research should continue to assess measures that are popular in assessment settings, as well as those that are more recent and/or novel. Latent variables may also be pertinent to uncovering what is truly beneficial in the assessment.

This study does provide good news since the neuropsychological screeners, which were the most impactful measures on accuracy, are readily available, low cost, and require minimal training to administer. It is recommended that clinicians continue to use as many sources as feasible to assist in their diagnostic process, including those that were not included in this study (e.g., family interview).

A future study implementing a longitudinal research design with multiple providers in various settings would be helpful for several reasons: 1) the longitudinal approach would allow more accurate comparisons of participants who truly are declining due to dementia, which would be evident over long periods of time (months or years); 2) this design would also provide a clearer picture of how a person may change over time across a number of measures; 3) increase generalizability of the study results while also giving more statistically sound results with greater power. Increasing the number and diversity of patients recruited and having more diagnosticians involved would allow for greater ability to generalize results. Furthermore, it is recommended



that research focused on communicating to clinicians which measures should hold more weight in their process, as well as which ones should be used in a more supplemental role.

The purpose of this study was to provide useful results that can translate to clinical work. The importance of neuropsychological screening tests was highlighted as crucial to accurate diagnosis. The difficulty translating complex clinical processes to research was also apparent as many of the measures that are standard assessment tools did not affect accuracy in any statistically relevant way. The highest accuracy achieved by any regression model in this study was not near the accuracy of the gold standard tests, but was still clinically relevant. The literature suggests strongly that a clinician utilize the multimodal approach to diagnosing MCI and AD. In fact, this has been and continues to be the standard of practice for more than 20 years (American Psychological Association, 2012). Practical and ethical issues need to be considered when deciding on which diagnostic assessment battery to utilize, as well as the “art” components of diagnosing a patient. Future studies should build on the methods outlined here to continue to try and identify the most important facets of diagnosing these life-altering problems.

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## VITA

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### EDUCATION

**The Virginia Consortium Program** | Norfolk, VA | Doctor of Philosophy degree in Clinical Psychology  
2014 – 2020 (expected)

**Boston University** | Boston, MA | Master of Arts degree in Psychology  
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**The University of Georgia** | Athens, GA | Bachelor of Science degree in Psychology, Minor in Sociology  
December 2008

### INTERNSHIP EXPERIENCE

**Salem VA Medical Center Psychology Internship Program** | Salem, VA

- *Major rotations in Geropsychology, Evidence-Based Psychotherapy Team/Mental Health Clinic, and Clinical Neuropsychology.*
- *Minor rotations in the Center for Traumatic Stress, Business Consultation, and Recovery from Severe Mental Illness.*
- *Integrative Behavioral Couple Therapy (IBCT) being implemented with veterans and significant others in year-long rotation in couple therapy.*

July 2019 – present

### PRACTICA EXPERIENCES

#### **Community Psychological Resources**

Community Psychological Resources | Norfolk, VA  
Supervisor: Janelle Mason, Ph.D.  
August 2018 – July 2019

#### **Glennan Center for Geriatrics and Gerontology**

**Memory Consultation Clinic**  
Eastern Virginia Medical School | Norfolk, VA  
Supervisor: Michael Stutts, PhD  
September 2014 – July 2018

#### **Office of Counseling Services**

Old Dominion University | Norfolk, VA  
Supervisor: Alex Dryden, Psy.D.  
August 2017 – May 2017

#### **Neuropsychology Program**

Eastern Virginia Medical School | Norfolk, VA  
Supervisors: Michael Stutts, PhD,  
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January – July 2017

#### **STEP Program**

Virginia Beach Public Schools | Virginia Beach, VA  
Supervisor: Lisa Conway-Sugden, PhD  
August 2015 – July 2016

#### **Old Dominion University Athletics**

Old Dominion University | Norfolk, VA  
Supervisor: Adela Roxas, PhD  
August 2014 – July 2015