Relationship of Initial Symptoms and Differential Dementia Diagnosis in a Memory Disorder Clinic Sample

by

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The undersigned committee,
having examined the attached doctoral research project,
"Relationship of Initial Symptoms and Differential Dementia Diagnosis in a Memory Disorder Clinic Sample," by Eugenia Milroy Boozer, M.S.
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Abstract

Title: Relationship of Initial Symptoms and Differential Dementia Diagnosis in a Memory Disorder Clinic Sample

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Objective: The present study examines the consistency of differential dementia diagnoses based on neuropsychological testing. The accuracy rate of clinical diagnoses of various types of dementias, including Alzheimer's disease, vascular dementia, dementia with Lewy bodies, frontotemporal dementia, mixed dementia, and others, were identified. In addition, other common diagnoses made through neuropsychological testing such as mild cognitive impairment (MCI) and mood disorder were examined as part of the overall analysis. Additionally, initial reported symptoms of dementia were examined to analyze how these first complaints might ultimately relate to a clinical diagnosis.

Method: The neuropsychological testing data were catalogued from participants who received neuropsychological testing at the Memory Disorder Clinic, along with initial chief complaint symptoms that were gathered from patients' electronic medical records.

Results: patients diagnosed as within normal limits (WNL) were most often placed in the normal range across the board. For patients diagnosed with a mood disorder

or MCI, they were most often in the normal range except for executive functioning, motor processing, and learning and memory in which patients diagnosed with MCI were placed in the borderline range. Patients diagnosed with Alzheimer's disease or dementia other were most often categorized as impaired in all domains. When examining individual scores, patients diagnosed WNL performed best on majority of tests, though scores were undistinguishable from MCI or mood disorder on some measures. Patients diagnosed with a mood disorder scored significantly worse than those diagnosed WNL on several measures, suggesting a mood disorder has the potential to share neurocognitive patterns with dementia. Overwhelmingly, patients diagnosed with Alzheimer's disease (AD) performed the worst on individual learning and memory tests, along with exhibiting the largest phonemic/semantic split in the language domain. Secondary symptom complaints of mood disorder was most often associated with clinical diagnosis of a mood disorder, while secondary symptom complaints of behavior changes, psychotic symptoms, gait problems, and tremors were most often associated with a clinical diagnosis of dementia other.

Conclusion: This study highlights the importance of being consistent in making clinical diagnoses based on overall patterns of scores and considering initial symptom complaints to ensure differential diagnoses are carried out as accurately as possible.

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Introduction

As the older adult population, meaning age 65 and older, continues to increase in number in the coming years, the cognitive problems that afflict a large number of them will become more of a public health concern. Dementia is the general term for memory loss and other intellectual abilities severe enough to interfere with daily life, and Alzheimer's disease, the most common form of dementia, currently affects 5.3 million Americans, 5.1 million who are age 65 and older. By 2050, this number is expected to increase by 10 million as the baby boom generation continues to enter this age bracket (Alzheimer's Association, 2015). Additionally, it is estimated that by the end of the year 2015, 473,000 new cases of people age 65 and older will have developed Alzheimer's disease (Alzheimer's Association, 2015). In 2012, Alzheimer's disease was reported as the sixth leading cause of death following heart disease, malignant neoplasms, chronic lower respiratory disease, cerebrovascular disease, and accidents (Heron, 2015). For those ages 65 and older, Alzheimer's disease moved up to the 5th leading cause of death, and for people ages 85 and older, it was the 3rd leading cause of death (Heron, 2015). In 2013, 84,767 people had Alzheimer's disease listed as the official cause death on death certificates (Alzheimer's Association, 2015).

With such a large number of people dealing with a debilitating disease with no known cure, steps to insure both early and accurate diagnosis become critical for effective treatment planning, which may include introduction of medication to treat

symptoms and/or community resources. In addition, it is important to take measure to distinguish different types of dementia. Even though Alzheimer's disease is the most common form of dementia, several other diagnosable dementias, such as vascular dementia, frontotemperal dementia, Lewy Body dementia, and mixed dementias all have different presentations and affect different domains of cognition. Because a truly accurate diagnosis of Alzheimer's disease can only be made post-mortem (Alzheimer's Association, 2015), understanding the neuropathology and neuropsychology of dementia becomes important in terms of making diagnosis of dementia as accurate as possible while the person is still alive in order to provide the best possible treatment.

The following review of past research will provide information about clinical diagnosis of dementia, neuropathology of dementia in terms of various criteria available, and neuropsychology of dementia as described by various patterns of neuropsychological evaluations. The accuracy rates of diagnosis will be examined as well as the heterogeneity of neuropathology as can be seen in mixed dementias. Finally, descriptions of the East Central Florida Memory Disorder Clinic and the Florida Brain Bank Program, where data for this project was collected, will be provided in conjunction with summaries of past research involving these data.

Review of the Literature

Alzheimer's Disease (AD)

The most basic definition of Alzheimer's disease is a degenerative disease of the brain that causes problems with memory, thinking, and behavior that are not considered a normal part of aging (Alzheimer's Association, 2015). The initial symptom most patients tend to notice is forgetfulness that is severe enough to interfere with daily life. Examples of this would include becoming confused, getting lost in familiar places, misplacing items, and having word-finding difficulty (Alzheimer's Association, 2015). Increasing age is the biggest risk factor for acquiring Alzheimer's disease. Most people are diagnosed at age 65 or older, and as many as one third of people over the age of 85 have Alzheimer's disease (Alzheimer's Association, 2015). There are also some genetic risk factors. This means that those who have a parent, brother, or sister diagnosed with Alzheimer's disease are more likely to develop the disease than those who do not. The risk increases if more than one family member has the illness. Having a risk factor does not guarantee that someone will get the disease, but only increases the likelihood (Alzheimer's Association, 2015). Some risk genes have already been identified. For example, the APOE-Ɛ4 gene was the first identified and still has the strongest impact. The APOE-Ɛ2and APOE-Ɛ3 are also common risk genes. People who inherit a copy of the APOE-Ɛ4 gene have an increased risk of developing

Alzheimer's disease, and those who inherit two copies have an even greater risk (Alzheimer's Association, 2015).

The life expectancy for someone diagnosed with Alzheimer's disease is typically four to eight years following diagnosis, but some people can live as long as 20 years depending on other factors. The Alzheimer's Association (2015) recognizes different stages of the disease. Preclinical Alzheimer's disease begins many years before there are any behavioral symptoms. During the early stage, or mild Alzheimer's disease, the person may be able to still function independently with some memory lapses, such as forgetting familiar words or the location of every day objects. In the middle stage, or moderate Alzheimer's disease, the person may begin confusing their words, get frustrated or angry, and act in unexpected ways. They may have difficulty expressing thoughts and doing routine tasks. This stage is typically the longest. Finally, the late stage, or severe Alzheimer's disease, occurs when the individual has lost his or her ability to respond to the environment, have a conversation, or control movement. At this point, he or she require 24-hour care and become more vulnerable to life threatening infections such as pneumonia (Alzheimer's Association, 2015).

There is still much that needs to be learned about the precise biological changes that cause Alzheimer's disease, the individual differences in progression of the disease, and how it can be prevented, slowed, or stopped (Alzheimer's Association, 2015). As mentioned before, subjective cognitive decline is one of the

earliest warning signs and may be a way to better identify those who are at high risk of developing Alzheimer's disease.

Vascular Dementia (VaD)

The second most common cause of dementia after Alzheimer's disease is vascular dementia. Put simply, vascular dementia is a form of dementia brought on by conditions that block or reduce blood flow to the brain, which deprives the brain cells of oxygen and nutrients. Changes in thinking can occur suddenly following strokes that block major brain blood vessels (Alzheimer's Association, 2015). The location, number, and size of brain injury determines whether dementia will result from the stroke and how an individual's thinking and functioning will be affected. In a large retrospective autopsy study, pure vascular dementia was diagnosed in 10.8% of patients. Of these, 92% had hypertension-related pathology, 75% had a history of strokes, and 52-58% had myocardial infarction and/or cardiac decompensation (Jellinger & Attems, 2010). For vascular dementia, the initial symptoms are likely to be impaired judgment or impaired ability to make decisions, plan or organize (Alzheimer's Association, 2015). Additionally, it has been found that sleep disturbances may be predictive of increased cognitive decline and incident of vascular dementia (Elwood, Bayer, Fish, Pickering, Mitchell & Gallacher, 2010). The prevalence of vascular dementia increases with age until about ago 90, and men appear to be more frequently affected than women (Korczyn, Vakhapova & Grinberg, 2012; Middleton, Grinberg, Miller, Kawas

&Yaffe, 2011; Leys, Henon, Mackowiak-Cordoliani & Pasquier, 2005; Leys, Pasquier & Parnetti, 1998). Also, the mortality of patients with vascular dementia surpasses that of Alzheimer's disease (Korczyn, Vakhapova & Grinberg, 2012; Kalaria, et al., 2008).

The main risk factors for vascular dementia are artherosclerotic disease, abdominal obesity, insulin resistance, hypertension and dyslipidemia. Presence of the APOE-Ɛ4 gene may increase the risk for cognitive decline following a stroke. Diagnosis of vascular dementia is not as straightforward as other forms of dementia given the possibility of co-morbid changes in the brain, multiple forms of diagnostic criteria, and the reliance on imaging methods, which come with different types of criteria for defining brain abnormalities (Korczyn, Vakhapova & Grinberg, 2012). Rather than a diagnosis of pure vascular dementia, most cases co-occur with Alzheimer's disease (Korczyn, Vakhapova & Grinberg, 2012; Alzheimer's Association, 2015) with reports in the literature indicating up to 73% overlap between the two (Grinberg & Heinsen, 2010).

Frontotemporal Dementia (FTD)

Frontotemporal dementia (FTD) is an umbrella term referring to a group of disorders caused by progressive cell degeneration in the brain's frontal and/or temporal lobes (Alzheimer's Association, 2015). Memory and spatial ability is typically spared in early stages of the disease (Kramer, Jurik, Sharon, Rankin, Rosen, Johnson & Miller, 2003) and initial symptoms include distinct changes in

personality and behavior, and may include difficulty producing or comprehending language (Alzheimer's Association, 2015). More specifically, individuals with FTD may exhibit marked apathy, social withdrawal, and stereotypic behavior (Shinagawa, Ikeda, Fukuhara & Tanabe, 2006). Examples of stereotypic behavior include clock-watching, use of ritualized behavior, and preoccupation with counting and numbers (Bozeat, Gregory, Ralph & Hodges, 2000). Because of the apathy and/or aphasia presented, individuals with FTD may at first be misdiagnosed with having a memory disturbance. As the disease progresses, individuals typically experience problems related to behavior including loss of insight, disinhibition, mood changes, mental rigidity, and changes in eating behaviors (Shinagawa, Ikeda, Fukuhara & Tanabe, 2006). Most people diagnosed with this form of dementia develop symptoms at a younger age, such as around 60 years (Alzheimer's Association, 2015).

There are two main presentations of FTD, which include a progressive change in personality along with executive dysfunction (frontal variant) and progressive fluent aphasia coupled with breakdown in semantic knowledge (temporal variant) also known as semantic dementia (Bozeat, Gregory, Ralph & Hodges, 2000). Patients presenting with semantic dementia typically display more mental rigidity and depression, while the frontal variant patients tend to be more disinhibited. However, both types present as behaviorally very similar with the

main difference being marked semantic deficits in the semantic form (Bozeat, Gregory, Ralph & Hodges, 2000).

Social dysfunction including problems with emotion processing, profoundly affect those with FTD. This can lead to failure in recognizing negative emotions, such as anger, disgust, fear, and sadness. This problem is especially associated with right hemisphere atrophy, particularly inferior and lateral parts of the temporal lobe, right orbitofrontal cortex, and the amygdala. Another abnormal finding in patients with FTD is "Theory of Mind" deficits, or problems with the ability to attribute beliefs, desires, and intentions to others, along with self-referential processing and empathy. One way to measure this dysfunction is through the interpretation of sarcasm. In general, sarcastic statements are more difficult for FTD patients to interpret, and in one study, performance was strongly influenced by the ability to identify emotion, especially negative, from social interaction (Kipps, Nestor, Acosta-Cabronero, Arnold & Hodges, 2009).

Lewy Body Dementia (DLB)

Dementia with Lewy bodies (DLB) is a form of dementia that leads to a decline in thinking, reasoning, and independent function due to abnormal microscopic deposits, called Lewy bodies, that damage brain cells. The trademark initial symptom of this dementia is well-formed visual hallucinations, as well as possible sleep disturbance, slowness and gait imbalance, or other Parkinsonian movement features. It is common for those with DLB to have coexisting

Alzheimer's disease (Alzheimer's Association, 2015). However, visual hallucinations tend to be more characteristic of pure DLB (Rongve, Bronnick, Ballard & Aarsland, 2010). Other features of DLB include memory impairment, depression, and problem solving difficulty. Cognitive impairment and visual hallucinations most often occur before the Parkinsonism, which suggests cortical or forebrain changes may induce clinical signs earlier than changes in the brainstem (Auning, et al., 2011). According to the literature, DLB accounts for an estimated 20% of all dementia cases (McKeith, et al., 2005). DLB and Parkinson's disease dementia (PDD) tend to overlap considerably both clinically and pathologically, therefore, the term Lewy body dementia (LBD) encompasses both (Lippa, et al., 2007). Parkinson's disease (PD) results in problems with movement, such as slowness, rigidity, tremor, and gait changes. In PD, alpha-synuclein aggregates appear in the substantia nigra and are thought to cause degeneration of the nerve cells that produce dopamine. As PD progresses, it often results in dementia secondary to the accumulation of Lewy bodies in the cortex or the accumulation of beta-amyloid and tau tangles, similar to Alzheimer's disease (Alzheimer's Association, 2015).

Mixed Dementia

Considerable attention should be paid to the common occurrence of more than one type of dementia pathology existing simultaneously. In fact, literature has shown that about half of those diagnosed with dementia have evidence of more

than one cause (Alzheimer's Association, 2015). When this is the case, the patient is diagnosed as having a mixed dementia. Although the individual presents with abnormalities characteristic of more than one type of dementia occurring simultaneously, he or she may be similar or indistinguishable from those with Alzheimer's disease or another dementia (Alzheimer's Association, 2015). The most common type of mixed dementia is Alzheimer's disease combined with vascular dementia, followed by Alzheimer's disease with dementia with Lewy bodies, and Alzheimer's disease combined with vascular dementia and dementia with Lewy bodies (Alzheimer's Association, 2015). Past research has found vascular dementia with dementia with Lewy bodies to be a much less common form of mixed dementia (Alzheimer's Association, 2015).

Accurately diagnosing individuals with various types of dementia becomes difficult with the possibility of mixed dementia. For instance, differentiating between Alzheimer's disease, vascular dementia, and mixed dementia is complicated both by symptom overlap and lack of well-defined diagnostic criteria (Zekry & Gold, 2010). According to the literature, prevalence rates for mixed dementia vary quite widely, anywhere from two to 60% (Zekry, Hauw & Gold, 2002; Jellinger, 2002). Another study found one third of Alzheimer's disease patients reached clinical criteria for a second type of dementia, either frontotemporal or dementia with Lewy bodies. There was little overlap between FTD and DLB (Piguet et al., 2009). Additionally, clinical testing, identification of

biomarkers, and neuroimaging may all fail to distinguish pure Alzheimer's disease and vascular dementia from mixed dementia cases, especially when there are microscopic infarcts only identified after autopsy (Zekry & Gold, 2010). The risk factors for mixed dementia encompass the risk factors of all pathologies involved. For example, for mixed dementia including Alzheimer's disease and vascular dementia, the vascular risk factors, such as hypertension, are particularly important (Zekry & Gold, 2010).

Clinical Diagnosis of Dementia

Differentiating between different types of dementia in a clinical setting can be a difficult task. To assist with making accurate diagnoses, clinical guidelines are available as the result of a consensus of consortium of experts. For example, beginning in 1983, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) joined together to establish criteria for describing the clinical diagnosis of Alzheimer's disease. The final report was published in 1982 (McKhann, Drachman, Folstein, Katzman, Price & Stadlan, 1984). Across multiple studies in the years following the initial report, these criteria have proven to be reliable for the diagnosis of probable Alzheimer's disease with a sensitivity of 81% and specificity of 70% (Knopman et al., 2001).

More recently, in 2011, experts met due to a need for criteria revision in order to incorporate modern innovations in clinical, imaging, and laboratory

assessment. They came to the agreement that the criteria should be flexible enough to be used by general healthcare providers without access to neuropsychological testing, advanced imaging, and CSF measures (McKhann et al., 2011). The criteria was divided into the following sections: all-cause dementia, probable Alzheimer's disease dementia, probable Alzheimer's disease with increased level of certainty, possible Alzheimer's disease dementia, probable Alzheimer's disease dementia with evidence of the Alzheimer's disease pathophysiological process, possible Alzheimer's dementia with evidence of Alzheimer's disease pathophysiological process, and considerations related to the incorporation of biomarkers into Alzheimer's disease dementia criteria.

According to the NINCDS-ADRDA criteria (McKhann et al., 2011), all-cause dementia is diagnosed when there are cognitive or behavioral symptoms that interfere with the ability to function at work or at usual activities, represent a decline from pervious levels of functioning and performing, and are not explained by delirium or major psychiatric disorder. Cognitive impairment is detected and diagnosed through a combination or history-taking from the patient and knowledgeable informant and an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. The cognitive or behavioral impairment involves a minimum two of the following domains: impaired ability to acquire and remember new information (symptoms include repetitive questions or conversations, misplacing personal belongings, forgetting

events or appointments, and getting lost on a familiar route) impaired reasoning and handling of complex tasks, poor judgment (symptoms include poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities) impaired visuospatial abilities (symptoms include inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body) impaired language functions (symptoms include difficulty thinking of common words while speaking, hesitations, speech, spelling, and writing errors) changes in personality, behavior, or comportment (symptoms include uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors).

As far as distinguishing between various types of dementia, some recommendations have been made following the third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (Robillard, 2007). For probable Alzheimer's disease dementia, it was noted that the NINCDS-ADRDA criteria provided very good sensitivity, but at the expense of specificity. This reflects the issue that there are(?) common features between different types of dementia (Robillard, 2007).

For vascular dementia, the common criteria utilized is the State of California Alzheimer's Disease Diagnostic and Treatment Center criteria (Chui et al., 1992), the National Institute of Neurological Disorders and Stroke, and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NENDS-AIREN) (Roman et al., 1993), the Hachinski Ischemic Score (HIS) (Hachinski et al., 1975), and the criteria provided in the DSM-IV (American Psychiatric Association, 2000). All of these criteria have poor sensitivity and high specificity. The lack of sensitivity can be explained by considerable overlap between vascular and Alzheimer's disease dementia. The experts proposed a more descriptive approach to the diagnosis of vascular dementia, which would take into account the neuropsychological profile of dementia, neuroimaging, and vascular risk factors (Robillard, 2007).

The sensitivity of dementia with Lewy bodies diagnosis has been the subject of controversy (Litvan et al., 2003) due to original reports that stated the presence of Lewy bodies in any distribution was sufficient for diagnosis (Kosaka, 1978; Kosaka, Yoshimua, Ikeda & Budka, 1983). Overall, diagnosis of dementia with Lewy bodies has low sensitivity and high specificity (Robillard, 2007).

The original Lund-Manchester criteria for frontotemporal dementia has been found to have low specificity (Robillard, 2007). These criteria are divided into two major sections: clinical diagnostic features of frontotemporal dementia and

neuropathological diagnostic features of frontotemporal dementia. The clinical diagnostic features are further divided into the following categories: behavioral disorders, affective symptoms, speech disorders, spatial orientation and praxis preserved, physical signs, and investigations. Also included are supportive diagnostic features, such as onset before 65, diagnostic exclusion features, and relative diagnostic exclusion features. The neuropathological diagnostic features are subdivided into "frontal lobe degeneration type", "Pick type", and "motor neuron disease type". For each of these, the criteria are organized into gross changes, distribution of microscopic changes, microscopic characteristics of grey matter, and microscopic characteristics of white matter. Finally, diagnostic exclusion features are included for the neuropathological diagnostic features (Englund et al., 1994).

The Third Canadian Consensus Conference approved several recommendations for the diagnosis of dementia (Robillard, 2007). The first recommendation made was that the diagnosis of dementia remains clinical given the evidence of good diagnostic criteria currently in use. Further, the sensitivity of clinical diagnosis for possible or probable Alzheimer's disease based on the NINCDS-ADRDA criteria remained high with low specificity, so they recommended continued use of these criteria. They concluded that mild Alzheimer's disease could be diagnosed with a high degree of specificity when the presenting clinical picture is one of memory impairment. The currently available

vascular dementia diagnostic criteria have variable accuracy, therefore, an integrative approach to vascular dementia diagnosis based on all available evidence (history, vascular risk factors, physical exam, clinical course, neuroimaging, and cognitive impairment pattern) is recommended. They recommended that dementia with Lewy bodies should be diagnosed when this pattern of dementia occurs before or concurrently with Parkinsonism, given the considerable overlap of the clinical features of dementia with Lewy bodies and Parkinson's disease dementia. Due to the frequency of coexistence between Alzheimer's disease and Lewy body neuropathology, the experts noted that it is impossible at this time to propose clinical guidelines that would separate the two diagnoses with high specificity. Finally, for patients presenting primarily with progressive decline in language or praxis, or prominent changes in behavior or personality, frontotemporal dementia should be considered (Robillard, 2007).

CERAD Criteria

Another important step in improving accurate diagnosis of dementia was the funding of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) in 1986. The purpose of this consortium was to develop standardized, reliable, and valid assessments of AD for use for all AD centers established by the National Institute on Aging (NIA), provide training in their use, and amass CERAD-based data from carefully evaluated patients and controls (Fillenbaum et al., 2008). CERAD consisted of three critical elements: an administrative core,

headed by the principle investigator, a methodology and data management center, and a series of task forces. The neuropsychology measures chosen were recognized as assessing cognitive functions implicated in AD. Considerable attention was given to developing standardized procedures for administering and scoring magnetic resonance imaging in AD and in modifying the protocol in response to pre-testing. However, inter-rater agreement was overall disappointing and ultimately not recommended (Fillenbaum et al., 2008). The CERAD guidelines have been recommended by the autopsy committee of the College of American Pathologists and form the basis for the consensus guidelines on the autopsy diagnosis of dementia with Lewy bodies (Powers, 1995).

Since its creation in 1986, CERAD neuropathology criteria have been and continue to be used in a substantial number of studies, both in the US and abroad. An overview of publications that have used CERAD measures indicates that CERAD has had two major effects. First, it has provided accepted standards for the clinical, neuropyshcological, and neuropathologic diagnosis of AD and it has provided validated, normed measures that have been broadly used and that permit comparison across studies and settings. When compared to the NINCDS-ADRDA criteria, the CERAD criteria are stricter regarding the duration of memory loss but more lenient regarding older age. After the first 10 years of the CERAD, further development of the neuropathology protocol ceased. As a consequence, the Neuropathology Task Force was unable to modify the battery to more appropriately

reflect changes seen with other dementias and to incorporate the use of appropriate markers (Fillenbaum et al., 2008).

In a more recent study examining differential diagnosis of patients attending a specialist early onset dementia clinic, researchers explored the usefulness of measurements through an examination of the relationship between clinical and pathological diagnoses in a consecutive series of patients who came to post-mortem. In particular, they focused on the differentiation between early onset degenerative dementia Alzheimer's disease and FTD (Snowden et al., 2011). They found the measurements of crucial importance in making a diagnosis were the nature and time course of evolution of symptoms, the relative weighting of physical, cognitive, and the behavioral symptoms, signs, and precise characteristics of cognitive change. The results of this study indicated a strong concordance between clinical diagnosis at the time of patients' initial referral and ultimate pathological diagnoses. This confirmed that pathological diagnosis can be predicted on clinical grounds with a high degree of accuracy.

DSM Criteria

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (American Psychiatric Association, 2013) can serve as another guide towards diagnosing dementia. The major change between the DSM-IV and the DSM-5 was the introduction of Neurocognitive Disorders (NCD) as a category. This change supported literature on the continuum of cognitive decline and efforts

to diagnose NCD further upstream, before clinical manifestations of the dementia syndrome occur through expansion of the diagnostic criteria to include mild NCD, which correspond to Mild Cognitive Impairment (Chong & Sahadevan, 2005; Geda & Nedelska, 2012). The revised DSM-5 sought to enable recognition of the neurocognitive impairment as a focus of diagnosis and treatment even before progression to functional impairment onset (Ganguli et al., 2011). Another important change in the DSM-5 is that memory deficit was no longer requisite for inclusion in the category of NCD, given the inclusion of attention, executive function, language, perceptual-motor, and social cognition among any of the cognitive domains that may be impaired, and specific emphasis that decline be assessed clinically with standardized neuropsychological testing (Tay et al., 2015).

In a study by Tay et al. (2015) involving diagnosis of patients attending a memory clinic, the frequency of dementia diagnoses among early symptomatic patients increased by almost 40% with operationalization of the DSM-5 criteria for major NCDs. A distinguishing feature of the DSM-5 relates to the specification and definition of the implicated cognitive domains, with less restrictive inclusion of the domains for which impairment has to be demonstrated to fulfill a diagnosis of major NCD. The move toward dropping memory impairment as a requisite for diagnosis of major NCD in DSM-5 was consistent with increasing recognition for relative preservation of memory in non-AD dementias. This is further supported by demonstrated impairment in only the nonamnestic domains among almost half of

MCI patients who failed to qualify for DSM-IV dementia diagnosis but were subsequently reclassified as major NCD with the DSM-5 criteria (Tay et al., 2015).

With several different ways to diagnose and classify dementia, it can be difficult to decide which system to utilize. Domenech & Azpiazu (2015) suggest that an individual can be characterized using one of three approaches: categorical, dimensional, or a combination of both. A categorical approach is based on the presence or absence of symptoms that satisfy certain criteria or not. The dimensional approach also takes into account the degree in which symptoms are present or absent, and a combination of both approaches allows diagnostic models that use both representations in dimensions and categories, having a greater predictive validity than either approach alone. It is suggested that future classification approaches should adopt and incorporate significant and continuous dimensions that can be conceptualized as diagnostic specifiers in terms of genetic factors, neural substrates, biomarkers, background, personality traits, cognitive and affective deficits, the development of the disorder, and the response to therapy (Domenech & Azpiazu, 2015)

Neuropathology of Dementia

Alzheimer's Disease

The two hallmarks of the neuropathology of Alzheimer's disease are neurofibrillary tangles and "senile plaques." Other changes include amyloid

angiopathy, brain atrophy, synaptic pathology, white matter rarefaction, granulovacuolar degeneration, neuron loss, TDP-43 proteinopathy, and neuroinflammation (Nelson et al., 2012). The pathologic processes underlying sporadic Alzheimer's disease include intraneuronal formation of abnormal tau protein and extracellular deposition of β-amyloid protein (Nelson, Braak & Markesbery, 2009). Alzheimer's disease-related lesions develop at certain sites within the brain and then progress according to a predictable sequence to other areas. Intraneuronal lesions associated with Alzheimer's disease occur before puberty or in early young adulthood (Braak & Del Tredici, 2011). Therefore, the earliest stages of Alzheimer's disease may exist long before presentation of cognitive symptoms.

Neurofibrillary tangles are found in almost every class of brain disease and are universal in normal aging subjects. They are also considered a secondary response to injury. Widespread neocortical neurofibrillary tangles are almost always associated with severe cognitive impairment in more than one disease state (Nelson et al., 2012). Neurofibrillary tangles are composed of abnormal fibrils measuring about 10 nm in diameter that occur in pairs and wound in a helical fashion with a regular periodicity of 80 nm (Kidd, 1963; Wisniewski, Narang & Terry, 1976). The primary component of the neurofibrillary tangle is the microtubule-associated protein tau, which is abnormally phosphorylated with phosphate groups attached to specific sites on the molecule (Lee et al., 1991).

For unknown reasons, vulnerable projection cells in the human brain begin to produce an abnormally phosphorylated tau protein that does not bind to microtubules and lies free, in high concentrations, in cytosol. Abnormal tau tends to form nonbiodegradable aggregates, which accumulate intraneuronally and are initially referred to as “pretangles”. This pretangle material can evolve into rigid fibriolar and argyrophilic neuropil threads in dendritic processes and neurofibrillary tangles in cell bodies (Braak & Del Tredici, 2012). Based on this process of neurofibrillary tangles, the progression of Alzheimer’s disease has been divided into six stages known as Braak and Braak staging (Braak & Braak, 1991). Stage I consists of cortical neurons that are susceptible to Alzheimer’s disease that occupy the laterally adjoining transentorhinal region of the temporal lobe. During stages I and II, tau lesions are mainly localized within the entorhinal region of the temporal lobe, particularly within the superficial entorhinal layer of medium-sized multipolar neurons. In stage III, pathology is restricted to a few regions in medial portions of the temporal lobe. In stage IV, most areas of the neocortex remain uninvolved. Cortical pathology remains somewhat less extensive, but still severe in stage V, and occurs when the individual is no longer in possession of a fully functional cerebral cortex, and is nearly always demented. At this point, a clinical diagnosis of Alzheimer’s disease is usually made. Finally, stage VI represents the end-stage of Alzheimer’s disease when all cortical regions display severe lesions (Braak & Del

Tredici, 2012). These stages were devised by mapping out the extent and distribution of lesions in brain specimens with no clinical data available at the time. Although not all Alzheimer's disease patients progress precisely along these stages, they do represent a useful concept and provide a format for neuropathologists to use in evaluating the development of Alzheimer's disease (Perl, 2010).

Senile plaques are extracellular deposits of β -amyloid peptides and are found in high proportion in all elderly persons, but the subtype neuritic plaques are more likely to be associated with cognitive impairment. These are complex structures defined by the presence of a central core accumulation of a 4-kD protein with a beta-pleated sheet configuration called BA4 (Masters et al., 1985; Beyreuther & Master, 1990; Kang et al., 1987). Neurotic plaques are ABPs surrounded by degenerating axons and dendrites that often contain hyperphophorylated tau aggregates (Nelson et al., 2012). Tau lesions are present from the beginning to end phage of Alzheimer's disease (Braak & Del Tredici, 2012).

In addition to senile plaques, the BA4 protein also tends to deposit in the walls of the cerebral cortical blood vessels, which can cause vascular amyloid deposition, also known as congophilic angiopathy. When the degree of vascular involvement is severe, tendency for spontaneous vascular rupture leading to a focal accumulation of blood in the brain tissue can occur. These hemorrhages tend to

occur in the white matter of the frontal and/or occipital poles, often small and multiple, and may be microscopic in size (Perl, 2010).

When examining the autopsied brains of individuals diagnosed with Alzheimer's disease, both gross and microscopic changes can be viewed. Most notably, these brains will demonstrate extensive and widespread distribution of both neurofibrillary tangles and senile plaques. Grossly, Alzheimer's disease brains show at least a modest degree of cerebral cortical atrophy primarily in the frontotemporal association cortex. Associated loss of brain tissue generally leads to a symmetrical dilation of the lateral ventricles. Finally, there is significant atrophy of the hippocampus with an associated selective dilation of the adjacent temporal horn of the lateral ventricle. By using one of a variety of silver impregnation staining techniques, such as the modified Bielschowski technique, neurofibrillary tangles can be viewed (Perl, 2010). Many studies have confirmed a correlation between the presence of senile plaques, neurofibrillary tangles, and cognitive status antemortem. In more advanced Alzheimer's disease, the neuroanatomic distribution of neurofibrillary tangles correlates with the location at which the neurons die and with the cognitive domains affected in the patients (Nelson et al., 2012).

Frontotemporal Dementia

Frontotemporal lobar degeneration (FTLD) is the pathological term for FTD (Josephs et al., 2011). The term encompasses a heterogeneous group of diseases that overlap in gross and histological features, all of which are associated with

varying degrees of atrophy, neuronal loss, and gliosis of the frontal and temporal lobes. There are three main proteins identified in the mechanism of neurodegeneration in these diseases are microtubule associated protein tau, the transactive response DNA binding protein of 43 kD (TDP-43), and the tumor associated protein fused in sarcoma (FUS). The majority of FTLDs can be subclassified into FTLD-tau, FTLD-TDP, and FTLD-FUS based on the biochemical signature of the abnormally deposited protein (Josephs et al., 2011).

The behavioral variant of FTD (bvFTD) can be associated with many different FTLD pathologies. For example, bvFTD associated with FTLD-TDP type 3 tends to have a typical age of onset and patients are not hypersexual, stereotypic or hyperphagic. Presence of apraxia of speech is tightly associated with FTLD-tau (Deramecourt et al., 2010; Josephs et al., 2006). The clinical syndrome of semantic dementia has been found to be highly associated with FTLD-TDP type 2 pathology and patients commonly present with aphasia associated with left anterior medial temporal lobe atrophy (Chan et al., 2001; Mummery et al., 2000).

Up to 50% of bvFTD cases have some family history of FTD, which suggests a strong familial aggregation within the FTLD spectrum of disorders (Cerami et al., 2012). The most frequent genetic mutations of FTD involve microtubule-associated protein tau (MAPT) and progranulin (GRN) genes both associated with high phenotypic variability as well as newly identified large hexanucleotide repeat expansion in the first intron of C9OFT72 mutation (Cerami

et al., 2012). Though the clinical presentation in MAPT mutation carriers is mostly consistent with bvFTD, with a mean onset in the 50s, primary progressive aphasias and late age at onset have been reported. GRN occurs in about 5-10% of cases and the age of onset along with clinical features is widely heterogeneous. For C9ORF72, the most common clinical phenotype is bvFTD, which is also widely heterogeneous, even within the same family. Mood and psychotic disorders have been described among the clinical presentations of patients with this mutation (Cerami & Cappa, 2013). A study that examined the characteristics of 32 patients with mutations in the C9ORF72 gene of patients with clinical syndromes of FTLD found a strong association of the mutation with psychotic symptoms such as delusions, hallucinations, paranoid ideation, and disordered thinking (Snowden et al., 2012). When diagnosing bvFTD, focal lobar atrophy on conventional brain MRI or CT has a relevant role. In the beginning, patients usually present a focal degeneration of pregenual anterior cingulate cortex (pACC) and frontoinsular cortex. These represent the basic components of the social and emotional processing network (Seeley et al., 2008). Further, metanalysis has shown prominent regional gray matter loss in the anterior medial frontal cortex, extending to other frontal regions, and in other brain areas such as insula and subcortical striatal regions (Pan et al., 2012).

As the disease progresses, the degeneration becomes more evident based on four anatomically definite bvFTD subtypes as described by Whitwell et al. (2009).

The frontal dominant type is defined by the presence of medial and lateral frontal lobe atrophy. The frontotemporal type has extended frontal and temporal lobe atrophy. The temporal type is described as having predominant involvement of the medial and lateral temporal lobe. Finally, the temporofrontoparietal type produces a wide atrophic pattern involving the temporal lobes as well as the frontal and parietal regions (Whitwell et al., 2009). Specific gene mutations may influence the neuroanatomical pattern of atrophy seen in bvFTD, showing prevalent frontal symmetric atrophy in MAPT and C9ORF72 mutated patients and asymmetric in GRN mutation carriers (Whitwell et al., 2013). Additionally, microstructural changes in white matter tracts within the frontal lobe or connecting frontal and temporal brain regions have been reported in bvFTD (Zhang et al., 2009).

Lewy Body Dementia

As the name implies, Lewy body dementia (LBD) is neuropathologically characterized by numerous Lewy bodies and neuritis, along with neuronal cell loss in the central and autonomic nervous systems (Kosaka, 2014). Lewy bodies are spherical, intracytoplasmic eosinophilic neuronal inclusions with a dense hyaline core and clear halo (Hancock, 2012). They are composed of alpha-synuclein, a 149-kDa protein encoded by the SNCA gene, the function of which is not well understood (Kosaka, 2014). Additionally, Lewy bodies are made of ubiquitin, a-crystalin, β -crystalin and various enzymes (Hancock, 2012). Lewy body dementia pathology initiates in the brainstem and propagates upward to the cerebral cortex

(Braak & Del Tredici, 2008). However, in the cerebral type of LBD, numerous Lewy bodies have been found in the cerebral cortex in spite of only a few in the brainstem nuclei, which suggests in these cases that the Lewy pathology occurs in the cerebral cortex and propagates downward to the brainstem (Kosaka et al., 1996). In some cases, Lewy pathology may also begin from Auerbach's plexus of the lower esophagus or the olfactory bulb (Wakabayashi et al., 1988; Sengoku et al., 2008).

It is the relatively widespread presence of Lewy bodies that differentiates LBD from other dementia syndromes at postmortem examination. Most gray matter atrophy can be seen in the temporal, parietal, occipital lobes, and in the region of the basal forebrain (Beyer et al., 2007; Burton et al., 2002; Sanchez-Castaneda et al., 2009; Whitwell et al., 2007). There is relative preservation of temporal lobe structures compared to subjects with Alzheimer's disease (Barber et al., 2000) along with relatively preserved whole brain volume that may be due to preservation of synapse integrity and neuronal counts (Hancock, 2012). Early pathological changes incur in the amygdala, alongside other limbic structures, and are now considered to precede the more global cognitive changes (Braak et al., 2003). Burton et al. (2012) conducted a study to examine the relationship between in vivo MRI volumes and underlying neuropathology in autopsy-confirmed LBD cases. They found a relationship between amygdala volume on MRI and the burden of Lewy body-associated pathology. The researchers suggested it is possible the

atrophy of the amygdala in LBD may be associated with visual hallucinations (Burton et al., 2012).

Another common neuropathological feature of LBD is the loss of dopaminergic neurons in the substantia nigra pars compacta that project to the striatum (Schulz-Schaeffer, 2010). In a study investigating the influence of nigral neuronal loss as well as nigral (α-synuclein, tau) and striatl (α-synuclein, tau and amyloid β) pathology on striatal I-FP-CIT SPECT uptake in autopsy confirmed cases of LBD, α-synuclein burden showed a trend towards a negative correlation with the number of nigral neurons. This suggests a reduction of nigral neurons occurs in LBD and indicates probability of I-FO-CIT SPECT in distinguishing LBD from other forms of dementia such as Alzheimer's disease (Colloby et al., 2012).

Vascular Dementia

Vascular alterations that cause cognitive impairment are diverse and include systemic conditions affecting global cerebral alterations involving cerebral blood vessels, most commonly small size arterioles or venules. Considering the vital importance of the cerebral blood supply for the structural and functional integrity of the brain, it is not surprising that alterations in cerebral blood vessels have a profound impact on cognitive function (Iadecola, 2013). The most common neuropathological abnormalities are multiple infarcts and lacunae in subcortical regions, mainly cerebral white matter and basal ganglia, strategic infarcts in the

thalamus and the hippocampus, and infarcts in frontier territories of large cerebral blood vessels vulnerable to one-time episodes of cerebral hypoperfusion (Hauw, De Girolami & Zekry, 2007; Jellinger, 2002; Jellinger, 2008; Love, Louis & Eillison, 2008). For example, high-grade stenosis or occlusion of the internal carotid arteries is associated with chronic ischemia and can lead to cognitive impairment even in the absence of ischemic lesions (Balestrini et al., 2013; Cheng et al., 2012; Johnston et al., 2004). Stroke doubles the risk for dementia, and approximately 30% of stroke patients go on to develop cognitive dysfunction within three years (Allen et al., 2011; Leys et al., 2005; Pendlebury & Rothwell, 2009).

Besides a single stroke, multiple infarcts caused by multiple arterial occlusions over time are well known to impair cognition, sometimes referred to as multi-infarct dementia (Iadecola, 2013). The most prevalent vascular lesions associated with cognitive impairment are related to alterations in small vessels in the hemispheric white matter (Jellinger, 2013). White matter damage resulting from such lesions consists of vacuolation, demyelination, axonal loss, and lacunar infarcts, and the expansion of white matter lesions correlates with the evolution of the cognitive impairment (Maillard et al., 2012). These are commonly associated with cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia, and smoking (Gorelick et al., 2011; Wardlaw et al., 2013). Additionally, vascular injuries resulting from cardiac arrest, hypoxic encephalopathy, and anaesthesic

accidents can be causative of acute global cerebral cortical damage and dementia (Ferrer, 2010).

In addition, microscopic infarcts and hemorrhages are independent predictors of cognitive dysfunction, but are commonly associated with other vascular pathologies such as leukoaraiosis, lacunar infarcts, large infarcts, and hemorrhage (Smith et al., 2012; van Norden et al., 2013). Cortical microbleeds are frequently associated with cerebral amyloid angiopathy, whereas microbleeds in deep regions tend to be associated with white matter disease secondary to vascular risk factors (De Reuck, 2012; Park et al., 2013). One study by Strozyk et al. (2010) found that as the severity of leukoencephalopathy increased, so did the risk of causes of dementia, including vascular dementia. They also found large infarcts were associated with antemortem clinical diagnosis of vascular dementia. This suggests that accumulating macroscopic vascular pathology, regardless of type, contributes to the diagnosis of dementia, and does so in the presence of other neurodegenerative pathology. While cognitive correlates of cortical infarcts and lacunes have been reported in demented and non-demented older adults, the contributions of other types of vascular lesions, such as cerebral amyloid angiopathy, leukoencephalopathy and microinfarcts, to cognitive impairment states are less well known (Strozyk et al., 2010).

There is substantial evidence that white matter changes are related to vascular disease. One hypothesis is that these changes are related to chronic

hypoperfusion in the territory of small perforating arteries (O'Sullivan et al., 2002; Markus et al., 2000). Cerebral microbleeds are radiological lesions due to small collections of old blood products that have previously leaked from cerebral vessels affected by small vessel pathologies, mainly lipohyaline degeneration or amyloid angiopathy (Greenberg at al., 2009). Cerebral microbleeds are commonly found in patients with vascular dementia, and are defined according to standard criteria (Pettersen et al., 2008; Cordonnier et al., 2006). Cerebral microbleeds may influence cognitive function through direct structural damage to surrounding tissue, functional disturbances in surrounding tissue, or because of disturbed small vessel reactivity and function (Werring, Gregoire & Cipolotti, 2010). In various studies, cerebral microbleeds have been found in 85% of memory clinic patients (Seo et al., 2007) and 65% of patients diagnosed with vascular dementia (Cordonnier et al., 2006).

Some rare genetic mutations are also associated with vascular cognitive impairment. The most common is CADASIL syndrome that is caused by a frame shift mutation of Notch-3 that either creates or eliminates a cysteine residue (Chabriat et al., 2009). Other hereditary pathologies include familial CAAs caused by mutations or duplications of APP, the cerebral autosomal recessive arteriopathy with subcortical infarcts and leukencephalopathy (CARASIL) caused by mutation of the TGFB repressor HTRA1, the autosomal dominant retinal vasculopathy with cerebral leukodystrophy caused by frame shift deletions in the exonuclease

TREX1, and mutations of the COL4A1 gene encoding the type IV collagen alpha 1 chain (Frederico et al., 2012; Gorelick et al., 2011; Lanfranconi & Markus, 2010).

Neuropsychology of Dementia

Alzheimer's Disease

Due to the difficulty of distinguishing among different types of dementia pre-mortem, clinicians must rely on neuropsychological tests to assist with diagnosis. Much research has been done, and continues to be conducted, to further refine neuropsychological batteries. Through this research and clinical work, certain patterns of test scores can help define certain types of dementia. Typically, this type of research and diagnosis must be made using comprehensive, standardized testing, as opposed to mental status testing or brief assessment protocols. Otherwise, it may be too difficult to detect subtle cognitive differences between groups (Walker, Meares, Sachdev & Brodaty, 2005).

For example, with Alzheimer's disease, studies have shown that patients with Alzheimer's disease typically perform worse in the memory domain compared to other types of dementia (Reed et al., 2007). In a study comparing healthy persons with those with mild frontotemporal dementia and those with Alzheimer's disease, those with mild Alzheimer's disease performed worse on tests of memory (Walker et al., 2005). Again, another study found that patients with Alzheimer's disease were more impaired on tests of episodic memory when compared with patients who had frontotemporal dementia (Diehl et al., 2005). Specifically regarding phonemic

and semantic tests of language, studies have shown that patients with Alzheimer's disease typically perform worse on semantic measures (Rogers, Ivanoiu, Patterson & Hodges, 2006). Therefore, with Alzheimer's disease, performance on neuropsychological testing typically shows a significant impairment in the memory domain compared to other domains.

Vascular Dementia

The typical expression of vascular dementia is executive dysfunction, manifested as impaired attention, planning, difficulties in complex activities, and disorganized thought, behavior, or emotion. This applies mainly to patients with subcortical white matter disease and frontal lobe lesions (Sachdev et al., 2004; Nordlund et al., 2007). Cognitive changes following strokes depend on their location. For example, slower reaction times are expected results of lesions in the frontal lobes or subcortical damage affecting the cortico-basal ganglionic-thalamic circuits (Korczyn, Vakhapova & Grinberg, 2012). Executive function is more impaired in vascular dementia than in early AD, while memory encoding and consolidation are more impaired in AD. In one study, on a letter-sequencing task (LST), the vascular dementia group demonstrated greater difficulty on portions of the LST thought to be more dependent on executive functioning, and had more omission and commission errors during sequencing and recognition tasks. Finally, vascular dementia patients had greater difficulty with the temporal aspects of memory than patients with AD (Hampstead et al., 2010). However, another study

found sizeable executive functioning and working memory impairment in patients with mild-moderate AD and vascular dementia with no differences between the disease groups (McGuinness, Barrett, Craig, Lawson & Passmore, 2010).

Neuropsychological tests indicate compromises in semantic memory, and reveal difficulties in verbal fluency tasks, which also reflect problems in executive functions (Pimentel, 2009). Findings reveal that VaD patients exhibit less impairment in episodic memory than AD patients, but present greater degree of impairment in attention, executive and motor functions. Compromise in phonemic verbal fluency has also been observed in VaD, while individuals with AD show deficits in semantic fluency. There is substantial overlap of cognitive alterations among AD and VaD, although each dementia type has distinct distinguishing characteristics (Pimentel, 2009).

No single test can distinguish mixed dementia from either vascular dementia or pure AD, therefore, comparing the neuropsychological profile of patients with vascular dementia, and those with AD show inconsistent differences from one study to another (Laukka et al., 2004). Cognitive deterioration up to three months after a stroke is consistent with vascular dementia (Roman et al., 1993)). Subcortical vascular dementia patients may have slow mentation, as opposed to memory decline, and fluctuating alertness is frequent in vascular brain disease. There also may be abrupt deficits in language problems or behavioral changes, as

opposed to a slow progression seen in other forms of dementia (Korczyn, Vakhapova & Grinberg, 2012).

Frontotemporal Dementia

In a critical review of frontotemporal dementia, Hornberger and Piguet (2012) report that episodic memory processing is relatively intact in FTD. Patients with the subtypes of behavioral variant frontotemporal dementia (fvFTD) and progressive non-fluent aphasia are reported to perform within normal limits on standard memory tests. Relative intactness of episodic memory appeared to be a useful diagnostic marker to distinguish early frontotemporal dementia from AD, in which early episodic memory disturbance remains the most common clinical feature. In the semantic dementia variant, a more complex picture emerges, with preservation of some components of episodic memory, notably recognition-based visual memory and recall of recent autobiographical events. Impaired performance on verbal, but not visuospatial memory, tests, combined with a loss of semantic knowledge, should raise the strong possibility of semantic dementia. Historical and current evidence shows that some patients with FTD can have episodic memory problems similar to AD, which can make a diagnostic distinction difficult, particularly early in the disease course. Other features supportive of this diagnosis include preservation of visual memory, particularly under forced-choice recognition format and preserved memory for temporal information and for recent autobiographical events. There is evidence that patients with behavioral variant

FTD and AD can present with similar anterograde memory deficits on neuropsychological testing (Hornberger & Piguet, 2012).

Delayed recall memory tests, in particular tests involving verbal material (i.e., word lists), emerge as a good predictor of behavioral variant FTD and AD diagnosis (Hornberger et al., 2010). In addition, one study found that patients with FTD had higher numbers of rule violations on the Tower Test than patients with AD and controls (Carey et al., 2008). Patients with FTD were also impaired on a digit span task, and inhibition of dominant responses (Hornberger, Piguet, Kipps & Hodges, 2008) and overall did poorly in the D-KEFS (Huey et al., 2009). Another study found that patients with AD were characterized by relative significant deficits with respect to the fvFTD group in short story, Rey figure, attentive matrices, and street completion test. Early deficits in executive functions cannot exclude a diagnosis of AD. Even though executive functions are routinely assessed in cases of frontal lobe damage, this should not be the focus of differential diagnosis of AD and fvFTD (Giovagnoli, Erbetta, Reati & Bugiani, 2008). The FTLD constellation of disorders, and particularly in FTD, continue to be underdiagnosed and misdiagnosed, despite being fairly common in presenile neurodegenerative diseases. The role of neurocognitive testing for early diagnosis will likely be small, in that FTD is fundamentally a behavior disorder, and cognitive deficits may be difficult to document (Wittenberg et al., 2008).

Dementia with Lewy Bodies

In one study, DLB patients were impaired in visuo-construction, praxis, attention, executive function, and delayed recall (Metzler-Baddeley et al., 2010). Overall, visuospatial abilities were more impaired in those with DLB, with a trend toward relatively preserved memory (Rongve, Bronnick, Ballard & Aarsland, 2010). Additionally, the severity of deficits on tests of visuospatial ability, specifically construction, predicts the rate of ensuring global cognitive decline for patients with DLB, but not for patients with AD (Hamilton et al., 2008). Hamilton et al. (2008) found that DLB patients who exhibited severe construction deficits at baseline, declined rapidly over the subsequent two years. In addition, DLB patients with early severe visuospatial deficits experienced a greater incidence of visual hallucinations than those with less severe visuospatial deficits (Hamilton et al., 2008). Because visual hallucinations are among the strongest diagnostic predictors of DLB, the neuropsychological assessment of visual perceptual and constructional functions is critical in suspected DLB, and its differentiation from AD (Oda, Yamamoto & Maeda, 2009). The third report of the DLB consortium mentioned that a double discrimination can help differentiate DLB from AD, with relative preservation of confrontation naming and short and medium term recall as well as recognition, and greater impairment on verbal fluency, visual perception, and performance tasks (McKeith et al., 1996).

In addition to problems in the visuospatial domain, other studies have demonstrated a greater attentional impairment in DLB patients when compared to AD patients. One study found DLB patients were significantly more impaired than AD patients on all tests of attention and fluctuating attention (Ayre et al., 1998). Another study found the deficits of attention became more pronounced with increasing dementia severity, so these deficits should be interpreted within the context of overall cognitive deficits (Ballard et al., 2001). Oda, Yamamoto, and Maeda (2009) found through analysis of multiple research studies that both neuropsychological and clinical observations strongly suggest that DLB patients experience great difficulty in sustaining attention.

Mood Disorders

Because of the large prominence of patients being diagnosed with a mood disorder (i.e., depression, anxiety, bipolar disorder), either as a primary diagnoses or secondary to dementia, it is worth reporting how mood disorders can affect neuropsychological outcomes. For example, Mukherjee and Rangasawami (2014) found that patients with affective disorders were impaired across the board on attention, executive functions, and learning and memory. More specifically, they found that bipolar depressed patients performed the worst on verbal memory tasks, and showed some impairment in non-verbal memory, attention, and executive functions, when compared to normals. Finally, they found that most patients who

had a recurrent depressive disorder performed poorly in sustained attention and verbal learning and memory. Similarly, Sweeney, Kmiec and Kupfer (2000) found bipolar patients in a mixed or manic phase displayed deficits in executive functions, episodic memory, and spatial span performance. For depressed patients, they found the deficits to be more restricted to episodic memory. Finally, through meta-analysis, many studies have identified deficits across a broad range of cognitive functions in mania and depression, namely on measures of attention, executive planning, memory, and psychomotor speed (Chamberlain & Sahakian, 2006).

Clinicopathologic Studies

The ultimate goal of clinicopathological studies is to better understand the clinical and biologic importance of identified pathological features. The ideal correlation would be a linear association between the following two discrete entities: impairment of health, and severity of pathology (Nelson, Braak & Markesbery, 2009). However, this correlation is not often obtained in practice, due to various factors such as functional reserve capacity, biologic variation between individuals in both protective and pathogenic pathways, and incomplete understanding of the disease mechanisms. Following an extensive review of the literature regarding clinicopathological studies in Alzheimer's disease, Nelson, Braak, and Markesbery (2009) found there to be a correlation of amyloid plaques and cognitive decline. However, they pointed out that controversy exists about the best way to calculate the extent of amyloid plaque pathology. Despite wide

variations in study designs, certain points emerge consistently among the studies about amyloid plaques. Compared with neurofibrillary tangles (NFTs), there is a weaker direct correlation between the density of amyloid plaques and the severity of cognitive decline. The amyloid plaque subtype that seems to correlate best with the severity of cognitive decline is the neuritic plaque. Patterns seen in an aged person's brain seem to divide into three groups: 1) few plaques, few NFTs and no cognitive impairment; 2) many plaques, few NFTs and no cognitive impairment; and 3) many plaques, many NFTs and cognitive impairment (Nelson, Braak & Markesbery, 2009).

Regardless of the staining or counting method, the correlation between neocortical NFTs and antemortem cognitive decline is strong in studies that span the clinical spectrum of Alzheimer's disease. In the course of Alzheimer's disease, the development of NFTs follows a predictable pattern, which seems to correlate on one hand with where neurons die, and on the other with the cognitive domains affected in Alzheimer's disease. Nelson, Braak, and Markesbery (2009) noted several limitations found commonly with these types of studies: 1) the schema of amyloid plaques and NFTs causing Alzheimer's disease is oversimplistic and incomplete, 2) athe density of NFTs on autopsy correlates with cognitive decline severity, this does not prove that NFTs are directly neurotoxic, and 3) more questions are raised about what induces the formation of amyloid plaques and NFTs in the first place (Nelson, Braak & Markesbery, 2009).

A single clinicopathological study utilized multivariable regression analysis to yield a strong negative association between the Braak stages of NFTs and level of cognitive function, which supports the idea that the regional distribution of NFT accumulation is on a continuum that maps well to clinical status. Further, results from this study demonstrated strong and independent contributions of both neuritic plaques and NFTs to cognitive impairment over the entire clinical course of Alzheimer's disease. Finally, the data showed definitively that marked neuropathologic changes of advanced Braak stage V/VI and frequent neuritic plaques are nearly always associated with a clinically observed dementia (Serrano-Pozo et al., 2013).

Another study examining the accuracy of clinical diagnosis of Alzheimer's disease found pathological confirmation in patients with a clinical diagnosis recorded in the NACC database to be 77.67%. The researchers who examined the data discovered DLB was the dementia most commonly misdiagnosed as Alzheimer's disease. From a neuropathological point of view, it was most likely that the presence of Lewy bodies was underreported, since staining with antibodies against ubiquitin or alpha-synuclein was not a routine procedure during most years of previous studies (Shim, Roe, Buckles & Morris, 2013). Continuing systematic comparisons of the current criteria for the clinical and pathological dementia

diagnoses are essential to clinical practice and research, and may lead to further improvement of the diagnostic procedure.

In a study that utilized the same Memory Disorder Clinic and Brain Bank data as the current study, Mahaney (2009) focused on the clinical accuracy with emphasis on the implications of diagnostic overlap on accuracy rates. The researcher found that Alzheimer's disease was identified in about 50% of the cases, and about 75% of the total sample was clinically diagnosed with AD. It was found that about 25% of participants clinically diagnosed with AD had either disaffirming or complicated pathology after autopsy evaluation. The overall sensitivity and specificity of the diagnosis of AD was found to be 85% and 33%, respectively.

Mahaney (2009) also found, upon autopsy, significant Lewy body pathology emerged in 16% of the total sample, despite having no participants being clinically diagnosed with DLB. She found vascular dementia to be the third most common dementia in this sample. With regard to initial complaints, it was found that memory loss was common across all diagnostic categories, despite the findings that many dementias do not include memory loss as an early symptom (Mahaney, 2009).

The East Central Florida Memory Disorder Clinic

The East Central Florida Memory Disorder Clinic (ECFMDC) is one of 15 designated memory disorder clinics statewide and covers a service area that includes Brevard, Indian River, Osceola, Southern Volusia, and St. Lucie counties.

The clinic is a collaborative effort between Health First Aging Institute and the Florida Institute of Technology School of Psychology. The Memory Disorder Clinic has a Board of Directors, a Clinical Advisory Committee, and a Research Committee, which all provide governance, guidance, and direction to the not-for-profit agency, which is primarily funded through the State of Florida Department of Elder Affairs (http://www.ecfmdc.org/).

The mission of ECFMDC is to provide the most effective evaluation for diagnosis and treatment for Alzheimer's Disease and related disorders, to provide information to all members of the community affected by Alzheimer's disease or related disorders, and to support, educate and train both family and professional caregivers in best practices related to memory disorders. The clinic's professionals providing service include a multi-disciplinary team that includes a geriatrician, neuropsychologists, neurologist, psychiatrist, psychologist, social worker, gerontologist, and Florida Institute of Technology School of Psychology doctoral students. These professionals work together with the patient's primary care physician to provide the best quality of memory care.

Florida Brain Bank Program

The Florida Alzheimer's Disease Brain Bank is a service and research oriented network of statewide regional sites. The intent of the brain bank program is to study brains of persons clinically diagnosed with dementia, and to provide tissue for research after their deaths. Mt. Sinai Medical Center contracts annually

with the State of Florida to operate the primary brain bank. Coordinators at regional brain bank sites in Orlando, Tampa, and Pensacola assist in recruiting participants, and act as liaisons between the brain bank and participants' families. Alzheimer's Disease respite care program providers, memory disorder clinics, and model day care programs also recruit brain bank participants. Families of participants obtain two significant service benefits from the brain bank:

1. A diagnostic confirmation of the disease written in clear, understandable terms; and
2. Involvement in variable research activities both inside and outside of Florida.

Brain bank participants must be pre-registered, so families must plan ahead, as a comprehensive application must be completed, and medical records must be collected, especially from the neurologist or other specialists who made the initial diagnosis. Upon the death of the patient, a final pathology report is provided to the family, and the patient's physicians and the brain issue becomes available to researchers worldwide. The diagnoses are a critical piece of the family's medical history and will become more important as new treatments become available (http://www.elderaffairs.state.fl.us/doea/BrainBank/index.php).

Statement of Purpose

The first objective of this study is to identify how consistently diagnoses are made based on patterns of individual scores, as indicated by previous research, on participants who were seen for neuropsychological evaluation at the East Central Florida Memory Disorder Clinic. Based on research completed by Mahaney (2009), the main diagnoses given were Alzheimer's disease, Vascular Dementia, Dementia with Lewy Bodies, and Frontotemporal Dementia. Mixed dementia and other diagnoses were examined as well. The importance of this objective is to examine the impact of dementia with multiple neuropathological processes, and the importance of accurate clinical diagnosis to align with certain treatment interventions.

A similar objective of this study is to examine the overall broad patterns of neuropsychological evaluation scores in a brief battery to observe how differential diagnoses are made based on these patterns. Finally, this study will be reviewing the earliest reported symptoms of dementia, and then analyzing how closely those complaints predict a clinical diagnosis. Again, this information becomes useful when formulating a treatment plan as early as possible.

Hypotheses

1. Neuropsychological domains identified as impaired will be different among neuropathological diagnoses. Specific sub-hypotheses are as follows:

a. Alzheimer's disease group will show more impairment in memory and language domains compared to others.
b. Additionally, semantic fluency will be more impaired than phonemic fluency within the Alzheimer's disease groups.
c. For the diagnoses categorized as dementia other, neuropsychological impairments will be more pronounced in the domains of executive functioning, attention, and visuospatial abilities.
d. The MCI group will have scores lower than WNL and mood disorder in all domains.
e. Patients in the mood disorder category will perform worse than those patients in the within normal limits category across domains.

2. Initial behavior complaint symptoms will differ among clinical neuropsychological diagnoses. Specific sub-hypotheses are as follows:
    a. Alzheimer's disease group will show the greatest amount of memory loss initial complaint symptom, based upon the typical clinical course.
    b. The dementia other group will show the greatest amount of changes in personality and behavior, sleep, and psychotic complaints as the initial symptom based upon the typical clinical course.

c. The mood disorder group will show more changes in mood complaints as the initial symptom (i.e., depression or anxiety).

Method

Participants

A convenience sample of 983 participants referred to the East Central Florida Memory Disorder Clinic for neuropsychological evaluation was selected for the larger analysis of identifying correlations between domains of impairment and clinical diagnosis, as well as correlations of specific test scores and clinical diagnosis. Participants were self, family, or doctor-referred for evaluation and treatment of various memory disorders. Participants involved in the current study completed a brief neuropsychological evaluation and were given a diagnosis based on a clinical case review.

The total sample (N = 983) included 422 males and 561 females ranging in age from 39 to 95, with a mean age of 78.11 at the time of evaluation. Years of completed education ranged from 3 to 22, with a mean of 13.70 years. Much of the total sample identified as Caucasian descent (N = 895; 91%), followed by those of African American descent (N = 49; 5%), Asian descent (N = 4; 0.4%), and Native American descent (N = 14; 1.4%). Some participants selected "Other" as their race (N = 16; 1.6%) or chose not to respond (N = 5; 0.5%). Of the total number of participants, 25 (2.5%) identified as Hispanic ethnicity, while the majority identified as Non-Hispanic (N = 897; 91.3%), Other (N = 3; 3%), or chose not to respond (N = 58; 5.9%). See Figures 1 and 2 for distribution of race and ethnicity.

Documentation of all demographic information was gathered from each participant at the time of evaluation through self-report and/or patient chart.

Figure 1. Race

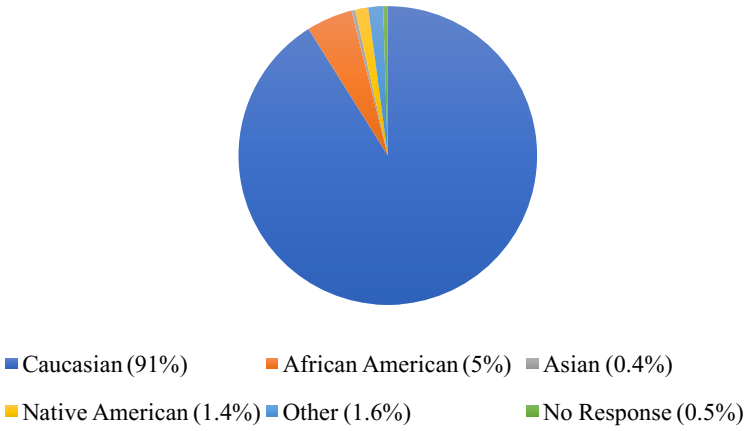
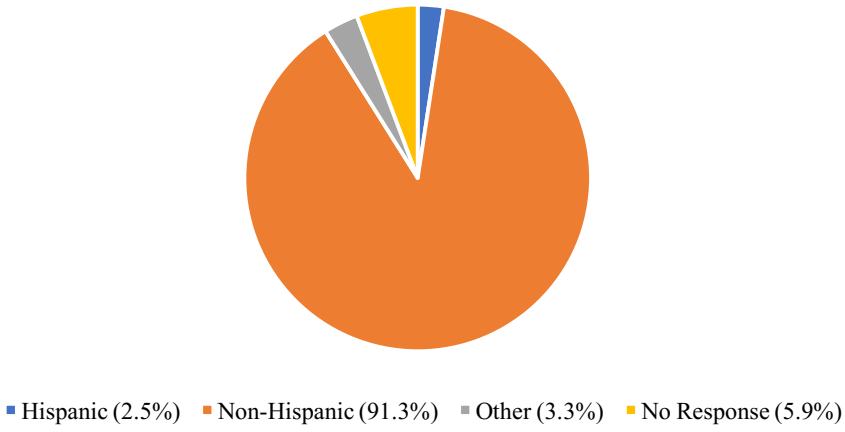


Figure 2. Ethnicity



Clinical diagnoses for participants were determined at the time of case reviews by a multi-disciplinary team composed of a neurologist, geriatrician, social worker, neuropsychologist, and doctoral level psychometrists, based on evaluation

scores, patient and informant history, medical evaluation, and neuroimaging. It should be noted a percentage of patients in the study went on to receive re-evaluations anywhere from six months to a year or more, following their initial evaluation, and may have incurred a change in clinical diagnosis. However, patient re-evaluations are not included in this study to avoid duplication of participants, and due to the use of alternate subtests chosen for the testing battery.

All participants were included in the analysis investigating initial behavioral characteristics based on data gathered from each patient's electronic medical record.

Procedure

The primary analysis included participants who completed a brief neuropsychological battery of tests, and subsequently were given a clinical diagnosis based on scores. All testing data were recorded and stored in an electronic database for all patients, along with related demographic data and diagnoses. Most scores obtained were either scaled scores, T-scores, or Z-scores corrected for age and/or education level and sex. The testing battery used from January 2011 until November 2013 consisted of the following: Controlled Oral Word Association Test (COWAT); Multilingual Aphasia Examination (MAE) Sentence Repetition; Trail Making Tests A and B; Symbol Digit Modalities Test (SDMT); Cognitive Screening Test (CST); Victoria Stroop Test; Clock Drawing Test (Free and Copy); Shepherd Serial List Learning Test; and the Executive

Interview (EXIT – Brief Edition). After November 2013, the MackSF4, a brief version of the Boston Naming Test, in which the patient must correctly identify 15 common objects, replaced the MAE Sentence Repetition test in the language domain. The testing battery from January 2011 until December 2014 utilized the Cognitive Screening Test (CST; Headminder, Inc.) for visual learning and memory, at which time it was replaced with the Rey-Osterrieth Complex Figure test (Rey-O). It was also at this time the Rey-O Copy task replaced the Clock Copy task in the visuospatial domain. Finally, a select group of participants were given the Boston Naming Test (BNT) in place of the MackSF4 if significant naming aphasia was suspected. However, the BNT is not included in these statistical analyses due to the small number of patients. See Appendix A for full descriptions of each test.

Patients' clinical diagnoses were divided and coded into the following categories: Within normal limits (WNL), mood disorder (based on primary diagnosis of either depression, anxiety, or both), mild cognitive impairment (MCI), probable Alzheimer's disease, and dementia other. The "dementia other" category was created to capture infrequently diagnosed dementia such as mixed dementia, Parkinson's disease dementia, dementia of undetermined etiology, vascular dementia, dementia with Lewy bodies, and frontotemporal dementia. It was necessary to combine these diagnoses into one category to increase statistical power.

Information about patients' initial symptom complaints was gathered from the first doctor's visit note, and coded into the following categories: memory loss, mood (based on mention of present anxiety, depression, or bipolar disorder), sleep (described as REM sleep disorder, insomnia, or other sleep problems), gait (noted as unsteady, frequent falls, or balance concerns), behavior (most often described as aggressive or acting out behavior, inappropriate sexual behavior, or any other behavior changes), psychotic (based on symptoms of psychosis such as hallucinations or delusions), tremor, personality change (most often noted by a family member), and weakness.

Results

Because some testing scores are recorded as raw score not corrected for age and education level, these factors were analyzed separately to examine any differences in diagnoses directly related to age and education. Next, the effect of gender on diagnosis for each diagnostic category was analyzed. Then overall frequencies of diagnoses were examined and recorded, along with the relationship of domain impairment and clinical diagnosis. The remaining results analyzed differences of individual scores and clinical diagnosis, which were divided by respective domains: language, attention and concentration, executive functioning, motor-processing speed, visuospatial, and learning and memory. Finally, analyses of initial patient complaint and clinical diagnosis were examined.

Age of Patients and Diagnosis

A one-way ANOVA was conducted to examine the relationship of patient age at time of testing and diagnose, and this relationship was found to be significant, F (4, 873) = 31.20, p <0.001. Bonferroni post-hoc test revealed no significant difference in age between patients diagnosed WNL and those diagnosed with a mood disorder, though patients diagnosed as WNL were significantly younger than patients diagnosed with MCI, Alzheimer's disease, and dementia other. There was no significant difference in age of patients diagnosed with MCI and those diagnosed with Alzheimer's disease and dementia other. There was also no significant difference in patients diagnosed with Alzheimer's disease and

dementia other. However, patients diagnosed with Alzheimer's disease were significantly older than patients diagnosed with WNL or a mood disorder. See Table 1 for mean ages.

Table 1. Patient age

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	75.31	7.90	4	31.20	<0.001
Mood Disorder	115	73.14	9.20			
MCI	162	79.58	6.52			
Alzheimer's disease	311	81.13	6.71			
Dementia other	196	79.31	7.30			

Years of Education and Diagnosis

A one-way ANOVA was conducted to examine relationship of years of education and diagnosis, and this relationship was found to be significant, F (4, 873) = 4.08, p = 0.003. Bonferroni post-hoc test revealed patients diagnosed with Alzheimer's disease had significantly fewer years of education than patients diagnosed as WNL and those diagnosed with MCI. No other significant differences were found between groups. See Table 2 for mean years of education.

Table 2. Years of education

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	14.41	2.48	4	4.08	0.003
Mood Disorder	115	13.89	2.17			
MCI	162	14.20	2.72			
Alzheimer's disease	311	13.40	2.80			
Dementia other	196	13.59	2.93			

Sex and Diagnosis

A chi-square test was performed to examine broad relationships between diagnostic category and sex. A significant difference was found between diagnosis and patient sex, X^2 (4, N = 878) = 33.59, $p < 0.001$, where more females than males were diagnosed with WNL, a mood disorder, Alzheimer's disease, and dementia other. More males than females were diagnosed with MCI. See Table 3 for chi-square results of sex and diagnosis.

Table 3. Sex and diagnosis

Sex	WNL	Mood	MCI	AD	Dem. other
Female Count	59	91	77	176	99
Expected	53.7	65.8	92.6	177.8	112.1
Male Count	35	24	85	135	97
Expected	40.3	49.2	69.4	133.2	83.9

Clinical Diagnosis

Out of a sample of N = 878 included in the five diagnostic categories, the most common diagnosis was Alzheimer's disease with 31.6% (N = 311), followed by dementia other with 19.9% (N = 196), then MCI with 16.5% (N = 162), mood disorder with 11.7% (N = 115), and WNL with 9.6% (N = 94). See Table 4 for percentages and frequencies of clinical diagnosis.

Table 4. Clinical diagnoses

Diagnosis	Frequency	Percent
Alzheimer's Disease	311	31.6%
Dementia Other	196	19.9%
MCI	162	16.5%
Mood Disorder	115	11.7%
WNL	94	9.6%

Clinical Diagnosis based on Domain

A chi-square test was performed to examine broad relationships between diagnostic category and domain of impairment. A relationship was found between diagnosis and level of impairment in the language domain, X^2 (8, N = 877) = 192.13, $p < 0.001$, where patients diagnosed as WNL, a mood disorder, or MCI performed most often in the normal range, and those diagnosed with Alzheimer's disease and dementia other were most often in the borderline range. See Table 5 for chi-square relationships in the language domain.

Table 5. Level of impairment in language domain and diagnoses

Diagnosis		Normal	Borderline	Impaired	Total
WNL	N	78	14	2	94
	%	19.6	4.6	1.2	10.7
Mood disorder	N	80	30	5	115
	%	20.1	9.8	2.9	13.1
MCI	N	102	50	9	161
	%	25.6	16.3	5.2	18.4
Alzheimer's disease	N	91	127	93	311
	%	22.9	41.5	43.8	35.5
Dementia other	N	47	85	64	196
	%	11.8	27.8	37.0	22.3

There was also a relationship found between diagnosis and level of impairment in the attention and concentration domain, X^2 (8, N = 869) = 289.37, p < 0.001, where patients diagnosed with WNL, a mood disorder, or MCI were more

likely to be in the normal range, whereas those diagnosed with Alzheimer's disease and dementia other were more likely to score within the impaired range. See Table 6 for chi-square relationships in the attention and concentration domain.

Table 6. Level of impairment in attention and concentration domain and diagnoses

Diagnosis		Normal	Borderline	Impaired	Total
WNL	N	85	8	1	94
	%	23.6	3.4	0.4	10.8
Mood disorder	N	80	22	13	115
	%	22.2	9.4	4.7	13.2
MCI	N	92	57	13	162
	%	25.6	24.4	4.7	18.6
Alzheimer's disease	N	76	92	138	306
	%	21.1	39.3	50.2	35.2
Dementia other	N	27	55	110	192
	%	7.5	23.5	40.0	22.1

There was a relationship between diagnosis and level of impairment in the executive functioning domain, X^2 (8, N = 873) = 366.67, p < 0.001, where patients diagnosed with WNL or a mood disorder were more likely to score in the normal range, those diagnosed with MCI more likely to score within the normal or borderline range, and those with Alzheimer's disease or dementia other were more likely to score within the impaired range. See Table 7 for chi-square relationships in the executive functioning domain.

Table 7. Level of impairment in executive functioning domain and diagnoses

Diagnosis		Normal	Borderline	Impaired	Total
WNL	N	84	9	1	94
	%	29.7	3.2	0.3	10.8
Mood disorder	N	74	29	12	115
	%	26.1	10.2	3.9	13.2
MCI	N	70	73	19	162
	%	24.7	25.7	6.2	18.6
Alzheimer's disease	N	41	108	160	309
	%	14.5	38.0	52.3	35.4
Dementia other	N	14	65	114	193
	%	4.9	22.9	37.3	22.1

There was also a relationship between diagnosis and level of impairment in

the motor-processing domain, X^2 (8, N = 871) = 253.21, p < 0.001, where patients diagnosed with WNL or a mood disorder were more likely to score in the normal range, those diagnosed with MCI more likely to score in the normal or borderline range, and those diagnosed with Alzheimer's disease or dementia other were more likely to score in the impaired range. See Table 8 for chi-square relationships in the motor-processing domain.

Table 8. Level of impairment in motor-processing speed domain and diagnoses

Diagnosis		Normal	Borderline	Impaired	Total
WNL	N	81	12	1	94
	%	21.7	5.0	0.4	10.8
Mood disorder	N	84	19	12	115
	%	22.5	7.9	4.7	13.2
MCI	N	91	58	13	162
	%	24.3	24.1	5.1	18.6
Alzheimer's disease	N	85	94	128	307
	%	22.7	39.0	50.0	35.2
Dementia other	N	33	58	102	193
	%	8.8	24.1	39.8	22.2

Likewise, there was a relationship between diagnosis and level of impairment in the visuospatial domain, X^2 (8, N = 875) = 240.32, p < 0.001, where

patients diagnosed with WNL or a mood disorder were more likely to score in the normal range, those diagnosed with MCI were slightly more likely to score within the normal range versus borderline range, and those diagnosed with Alzheimer's disease were more likely to score in the impaired range. Those diagnosed with dementia other were likely to score in the borderline or impaired range. See Table 9 for chi-square relationships in the visuospatial domain.

Table 9. Level of impairment in visuospatial domain and diagnoses

Diagnosis		Normal	Borderline	Impaired	Total
WNL	N	86	8	0	94
	%	21.6	2.9	0.0	10.7
Mood disorder	N	85	26	4	115
	%	21.4	9.6	2.0	13.1
MCI	N	87	67	8	162
	%	21.9	24.6	3.9	18.5
Alzheimer's disease	N	87	100	123	310
	%	21.9	36.8	60.0	35.4
Dementia other	N	53	71	70	194
	%	13.3	26.1	34.1	22.2

Finally, there was a relationship between diagnosis and the level of impairment in the learning and memory domain, X^2 (8, N = 876) = 794.76, p <

0.001, where patients who were diagnosed with WNL or a mood disorder were more likely to score in the normal range, those with MCI were most likely to score in the borderline range, and those diagnosed with Alzheimer's disease or dementia other were more likely to score in the impaired range. See Table 10 for chi-square relationships in the learning and memory domain.

Table 10. Level of impairment in learning and memory domain and diagnoses

Diagnosis		Normal	Borderline	Impaired	Total
WNL	N	83	10	1	94
	%	41.5	4.0	0.2	10.7
Mood disorder	N	74	30	11	115
	%	37.0	12.1	2.6	13.1
MCI	N	31	123	8	162
	%	15.5	49.8	1.9	18.5
Alzheimer's disease	N	1	33	276	310
	%	0.5	13.4	64.3	35.4
Dementia other	N	11	51	133	195
	%	5.5	20.6	31.0	22.3

Language Domain

A one-way ANOVA was conducted to examine the differences between diagnostic category for individual scores within each domain. For the language domain, phonemic scores from the COWAT test differed significantly, F (4, 870) =

29.21, $p < 0.001$. A Bonferroni post-hoc test revealed that patients diagnosed as WNL had higher phonemic scores than those diagnosed with MCI ($p = 0.43$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Further, patients diagnosed with a mood disorder scored higher than those diagnosed with Alzheimer's disease ($p < 0.001$) and dementia other ($p < 0.001$). Similarly, patients diagnosed with MCI also performed better than those diagnosed with Alzheimer's disease ($p < 0.001$) and dementia other ($p < 0.001$). Finally, patients diagnosed with dementia other scored worse than patients diagnosed with Alzheimer's disease ($p < 0.001$). See Table 11 for all mean scores.

Table 11. Phonemic scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	10.63	2.87	4	29.21	<0.001
Mood Disorder	115	9.76	2.38			
MCI	162	9.59	2.75			
Alzheimer's disease	309	8.37	2.81			
Dementia other	195	7.47	3.03			

Regarding the semantic scores, there was a statistically significant effect for diagnostic category, F (4, 873) = 123.35, $p < 0.001$. A Bonferroni post-hoc test revealed patients diagnosed WNL had higher semantic scores than those diagnosed with a mood disorder ($p = 0.003$), MCI ($p < 0.001$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Patients diagnosed with MCI scored higher than those diagnosed with Alzheimer's disease ($p < 0.001$) and dementia other ($p < 0.001$). See Table 12 for all semantic mean scores.

Table 12. Semantic scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	10.66	2.55	4	123.35	<0.001
Mood Disorder	115	9.40	2.48			
MCI	162	8.10	2.43			
Alzheimer's disease	311	5.63	2.57			
Dementia other	196	5.56	2.45			

The difference, or split, between phonemic and semantic score was examined, and there was a significant difference for diagnostic category, F (4, 873) = 23.52, $p < 0.001$. A Bonferroni post-hoc test revealed patients diagnosed WNL had a smaller split between scores compared to those diagnosed with MCI ($p = 0.001$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Patients diagnosed a mood disorder had a smaller split between scores compared to those diagnosed with MCI ($p = 0.015$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Patients diagnosed with MCI also had a smaller split compared to those diagnosed with Alzheimer's disease ($p < 0.001$). Finally, patients diagnosed with Alzheimer's disease had a larger split in scores compared to dementia other ($p = 0.026$). See Table 13 for mean split between phonemic and semantic scores.

Table 13. Phonemic/semantic split scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	-0.03	2.67	4	23.52	<0.001
Mood Disorder	115	0.04	2.72			
MCI	162	1.49	3.00			
Alzheimer's disease	311	2.68	2.98			
Dementia other	196	1.88	2.99			

The MackSF4 score was found to differ across diagnostic categories, F (4, 477) = 13.34, $p < 0.001$. Because raw scores were utilized, patient age and years of education were entered as covariates. Pairwise comparisons revealed patients diagnosed WNL had higher scores than those diagnosed with Alzheimer's disease ($p < 0.001$) and dementia other ($p < 0.001$). Similarly, patients diagnosed with a mood disorder and MCI performed better than those diagnosed with Alzheimer's disease ($p < 0.001$; $p < 0.001$) and dementia other ($p < 0.001$; $p = 0.001$). See Table 14 for MackSF4 mean scores.

Table 14. MackSF4 scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	49	13.45	2.24	4	13.34	<0.001
Mood Disorder	42	13.19	2.13			
MCI	68	12.69	1.82			
Alzheimer's disease	198	10.75	3.01			
Dementia other	127	11.30	2.71			

Finally, the MAE Sentence Repetition Z-scores were examined and showed a significant main effect for diagnostic category, F (4, 321) = 3.01, $p = 0.02$. The Bonferroni post-hoc test revealed patients diagnosed WNL scored higher than those

diagnosed with Alzheimer's disease ($p = 0.019$). See Table 15 for MAE Sentence Repetition mean scores.

Table 15. MAE sentence repetition scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	33	-0.10	1.45	4	3.08	0.016
Mood Disorder	50	-0.77	1.60			
MCI	84	-0.65	1.60			
Alzheimer's disease	102	-1.13	1.73			
Dementia other	57	-1.08	1.62			

Attention and Concentration

A one-way ANOVA was conducted to examine differences between diagnostic categories and individual testing scores within the attention and concentration domain. For the Trails A test, there was a significant difference in scores for diagnostic category, F (4, 860) = 45.19, $p < 0.001$. A Bonferroni post-hoc test showed patients diagnosed WNL performed better than those diagnosed with a mood disorder ($p < 0.001$), MCI ($p < 0.001$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Patients diagnosed with a mood disorder and MCI performed better than those diagnosed with Alzheimer's disease ($p < 0.001$; $p < 0.001$) and dementia other ($p < 0.001$; $p < 0.001$) . Finally, those diagnosed with dementia other performed significantly worse than those diagnosed with Alzheimer's disease ($p = 0.005$). See Table 16 for Trails A mean scores.

Table 16. Trails A scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	10.39	3.30	4	45.19	<0.001
Mood Disorder	115	8.28	3.41			
MCI	160	8.13	2.87			
Alzheimer's disease	304	6.57	3.47			
Dementia other	192	5.53	2.96			

For the Trails B test, there was a significant difference in scores for diagnostic category, F (4, 846) = 98.41, $p < 0.001$. Patients who were diagnosed WNL performed better than those diagnosed with a mood disorder ($p < 0.001$), MCI ($p < 0.001$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Patients diagnosed with a mood disorder and MCI scored better than those diagnosed with Alzheimer's disease ($p < 0.001$; $p < 0.001$) and dementia other ($p < 0.001$; $p < 0.001$). See Table 17 for Trails B mean scores.

Table 17. Trails B scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	10.31	3.21	4	98.41	<0.001
Mood Disorder	114	7.91	4.11			
MCI	161	6.83	3.88			
Alzheimer's disease	297	3.84	3.66			
Dementia other	185	3.04	2.99			

Regarding the SDMT Oral test, there was a significant difference in scores for diagnostic category, F (4, 851) = 67.54, $p < 0.001$. According to the Bonferroni post-hoc test, patients diagnosed WNL performed better than patients diagnosed with a mood disorder ($p = 0.024$), MCI ($p < 0.001$), Alzheimer's disease ($p <$

0.001), and dementia other ($p < 0.001$). Patients diagnosed with a mood disorder and MCI scored better than those diagnosed with Alzheimer's disease ($p < 0.001$; $p < 0.001$) and dementia other ($p < 0.001$; $p < 0.001$). See Table 18 for SDMT Oral mean scores.

Table 18. SDMT oral scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	9.71	2.83	4	67.54	<0.001
Mood Disorder	114	8.45	2.91			
MCI	162	7.62	2.80			
Alzheimer's disease	303	5.48	3.15			
Dementia other	183	4.85	2.99			

Analysis of the SDMT Written test revealed a significant difference in scores for diagnostic category F (4, 854) = 42.08, $p < 0.001$. A Bonferroni post-hoc test was conducted and it was found that patients diagnosed WNL performed better than patients diagnosed with a mood disorder ($p = 0.001$), MCI ($p = 0.007$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Patients diagnosed with a mood disorder and MCI scored better than those diagnosed with Alzheimer's disease ($p < 0.001$; $p < 0.001$) and dementia other ($p < 0.001$; $p < 0.001$). Finally, patients diagnosed with dementia other scored worse than those diagnosed with Alzheimer's disease ($p = 0.030$). See Table 19 for SDMT written mean scores.

Table 19. SDMT written scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	10.94	2.85	4	42.08	<0.001
Mood Disorder	113	9.26	3.26			
MCI	162	9.56	2.80			
Alzheimer's disease	303	7.57	3.23			
Dementia other	187	6.70	3.29			

Executive Functioning

A one-way ANOVA was conducted to examine differences between diagnostic categories and individual testing scores within the executive functioning domain. It should be noted that Trails B scores are included in this domain as well and results can be referenced above. For CST response accuracy scores, there was a significant difference for diagnostic category, F (4, 501) = 29.82, $p < 0.001$. A Bonferroni post-hot test was conducted and it was found that patients diagnosed as WNL performed better than those diagnosed MCI ($p < 0.001$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Also, patients diagnosed with a mood disorder performed significantly better than those diagnosed with MCI ($p < 0.001$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Finally, patients diagnosed with MCI had better scores than those diagnosed with Alzheimer's disease ($p = 0.004$) and dementia other ($p = 0.001$). See Table 20 for CST response accuracy mean scores.

Table 20. CST response accuracy scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	64	8.28	2.77	4	29.82	<0.001
Mood Disorder	86	8.12	2.93			
MCI	118	6.27	3.18			
Alzheimer's disease	143	4.98	2.95			
Dementia other	95	4.66	2.72			

With regard to the VST interference scores, a significant difference was found for diagnostic categories, F (4, 824) = 4.13, p = 0.003. Patients diagnosed as WNL performed better than those diagnosed with Alzheimer's disease (p = 0.020) and dementia other (p = 0.001). See Table 21 for VST interference score means.

Table 21. VST interference scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	11.10	2.86	4	4.13	0.003
Mood Disorder	112	10.10	2.98			
MCI	158	10.15	3.28			
Alzheimer's disease	292	9.84	3.73			
Dementia other	173	9.36	3.59			

For VST words scores, there was a significant difference found for diagnostic category, F (4, 837) = 32.75, p < 0.001. After a Bonferroni post-hoc test was conducted, it was found that patients diagnosed as WNL performed better than those diagnosed with a mood disorder (p = 0.003), MCI (p < 0.001), Alzheimer's disease (p < 0.001), and dementia other (p < 0.001). Patients diagnosed with a mood disorder and MCI had better scores than those diagnosed with Alzheimer's

disease ($p < 0.001$; $p < 0.001$) and dementia other ($p < 0.001$; $p < 0.001$). See Table 22 for VST word score means.

Table 22. VST word scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	9.21	2.93	4	32.75	<0.001
Mood Disorder	113	7.96	2.83			
MCI	161	7.65	2.36			
Alzheimer's disease	295	6.50	2.35			
Dementia other	179	6.21	2.22			

Analysis of VST color scores revealed a difference for diagnostic category, F (4, 828) = 40.63, $p < 0.001$. Following a Bonferroni post-hoc test, it was shown that patients diagnosed WNL performed better than those diagnosed with a mood disorder ($p = 0.002$), MCI ($p < 0.001$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Patients diagnosed with a mood disorder and MCI had better scores than those diagnosed with Alzheimer's disease ($p < 0.001$; $p < 0.001$) and dementia other ($p < 0.001$; $p < 0.001$). See Table 23 for VST color score means.

Table 23. VST color scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	10.57	2.81	4	40.63	<0.001
Mood Disorder	113	9.10	3.08			
MCI	159	8.23	2.74			
Alzheimer's disease	292	7.04	2.77			
Dementia other	175	6.71	2.92			

The Exit total raw scores were examined using age and years of education as covariates. Exit scores are interpreted as lower scores indicating better performance. Following analysis of these scores, a significant difference was revealed for diagnostic category, F (4, 871) = 67.57, $p < 0.001$. Pairwise comparisons showed the patients diagnosed as WNL performed better than those diagnosed with MCI ($p = 0.001$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Patients diagnosed with a mood disorder and MCI had better scores than those diagnosed with Alzheimer's disease ($p < 0.001$; $p < 0.001$) and dementia other ($p < 0.001$; $p < 0.001$). Table 24 for Exit score means.

Table 24. Exit scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	3.88	2.33	4	67.57	<0.001
Mood Disorder	115	5.06	2.91			
MCI	162	6.07	2.73			
Alzheimer's disease	311	9.90	4.33			
Dementia other	196	9.68	4.41			

Motor Processing Speed

A one-way ANOVA was conducted to examine the differences between diagnostic categories and individual testing scores within the motor processing speed domain. It should be noted that Trails A, Trails B, SDMT Oral, and SDMT Written scores are included in this domain as well and results can be referenced above. Analysis of CST Response Speed scores revealed no significant differences for diagnostic category, F (4, 499) = 1.76, $p = 0.14$.

With the VST Dots score, there was found to be a significant difference for diagnostic category, F (4, 832) = 31.72, $p < 0.001$. A Bonferroni post-hoc test was conducted and revealed that patients diagnosed WNL performed better on this test than those diagnosed with MCI ($p < 0.001$), Alzheimer's disease ($p < 0.001$) and dementia other ($p < 0.001$). Patients diagnosed with a mood disorder had better scores than those diagnosed with MCI ($p = 0.014$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Finally, patients diagnosed with MCI performed better than those diagnosed with Alzheimer's disease ($p = 0.001$) and dementia other ($p = 0.006$). See Table 25 for VST dots score means.

Table 25. VST dot scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	92	9.83	3.23	4	31.72	<0.001
Mood Disorder	113	8.92	3.08			
MCI	160	7.76	2.82			
Alzheimer's disease	293	6.60	2.94			
Dementia other	179	6.65	2.83			

Visuospatial Ability

A one-way ANOVA was utilized to analyze the differences between diagnostics categories and individual testing scores within the visuospatial domain. Analysis of the Rey-O figure copy scaled scores revealed a significant difference for diagnostic category, F (4, 114) = 5.95, $p < 0.001$. Following a Bonferroni post-hoc test, it was found that patients diagnosed with a mood disorder scored better

than patients diagnosed with Alzheimer's disease ($p = 0.001$). See Table 26 for Rey-O figure copy score means.

Table 26. Rey-O figure copy scaled scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	4	9.50	2.08	4	5.95	<0.001
Mood Disorder	11	9.36	3.61			
MCI	12	7.33	3.23			
Alzheimer's disease	59	3.86	4.24			
Dementia other	33	5.45	4.77			

A portion of patients had Rey-O figure copy scores recorded as percentages which were later coded based on percent ranges where lower percent is indicative of greater impairment. A chi-square test was performed to examine broad relationships between diagnostic category and percent range of impairment. A relationship was found between diagnosis and level of impairment in the language domain, X^2 (16, N = 214) = 55.41, $p < 0.001$, where patients diagnosed as WNL and with a mood disorder had a much higher percent of patients scoring in the >16% range, and patients diagnosed with Alzheimer's disease or dementia other had a higher percent scoring in the <1% range. See Table 27 for chi-square results for Rey-O figure copy percent impairment.

Table 27. Rey-O figure copy percent impairment

Diagnosis		>16%	11-16%	6-10%	2-5%	<1%
WNL	N	24	1	0	1	0
	%	23.1	10.0	0.0	5.9	0.0
Mood	N	14	1	0	1	0
	%	13.5	10.0	0.0	5.9	0.0
MCI	N	17	1	1	4	7
	%	16.3	10.0	14.3	23.5	9.2
AD	N	35	5	5	9	38
	%	33.7	50.0	71.4	52.9	50.0
Dem. other	N	14	2	1	2	31
	%	13.5	20.0	14.3	11.8	40.8

The free clock total raw scores were examined using age and years of education as covariates. Following analysis of these scores, a significant difference was revealed for diagnostic category, F (4, 868) = 49.62, $p < 0.001$. Pairwise comparisons showed patients diagnosed WNL performed better than those diagnosed with MCI ($p = 0.009$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Patients diagnosed with a mood disorder and MCI had significantly higher scores than those diagnosed with Alzheimer's disease ($p < 0.00$; $p < 0.001$) and dementia other ($p < 0.001$; $p < 0.001$). See Table 28 for free clock score means.

Table 28. Free clock scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	9.39	0.87	4	49.62	<0.001
Mood Disorder	114	8.59	1.96			
MCI	162	8.18	1.85			
Alzheimer's disease	311	5.78	3.15			
Dementia other	194	6.24	2.96			

Similarly, for the copy clock raw scores, age and years of education were used as covariates. Analysis of these scores revealed a significant difference for diagnostic category, F (4, 554) = 11.72, $p < 0.001$. Pairwise comparisons showed patients diagnosed WNL, with a mood disorder, and MCI score significantly higher than those diagnosed with Alzheimer's disease ($p < 0.001$; $p < 0.001$; $p = 0.002$) and dementia other ($p < 0.00$; $p < 0.001$; $p < 0.001$). See Table 29 for copy clock score means.

Table 29. Copy clock scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	65	9.69	0.58	4	11.72	<0.001
Mood Disorder	91	9.51	1.00			
MCI	123	9.33	1.00			
Alzheimer's disease	164	8.59	1.89			
Dementia other	118	8.46	2.01			

Learning and Memory

A one-way ANOVA was conducted to examine differences between diagnostic categories and individual testing scores within the learning and memory domain. Scores from the CST Learning portion were examined and there was a

statistically significant difference for diagnostic category, F (4, 491) = 62.26, p < 0.001. A Bonferroni post-hoc test revealed patients diagnosed as WNL had higher scores than those diagnosed with MCI (p = 0.001), Alzheimer's disease (p < 0.001), and dementia other (p < 0.001). Patients diagnosed with a mood disorder and MCI performed significantly better than those diagnosed with Alzheimer's disease (p < 0.001; p < 0.001) and dementia other (p < 0.001; p < 0.001). See Table 30 for CST Learning score means.

Table 30. CST learning scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	63	11.24	3.08	4	62.26	<0.001
Mood Disorder	85	9.64	3.69			
MCI	119	9.22	3.49			
Alzheimer's disease	133	4.69	3.34			
Dementia other	96	5.64	3.64			

CST Delay scores were examined and there was a statistically significant difference for diagnostic category, F (4, 508) = 90.36, p < 0.001. A Bonferroni post-hoc test revealed patients diagnosed WNL performed better than those diagnosed with MCI (p < 0.001), Alzheimer's disease (p < 0.001), and dementia other (p < 0.001). Finally, patients diagnosed with a mood disorder and MCI performed significantly better than those diagnosed with Alzheimer's disease (p < 0.001; p < 0.001) and dementia other (p < 0.001; p < 0.001). See Table 31 for CST Delay score means.

Table 31. CST delay scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	63	10.56	2.62	4	90.36	<0.001
Mood Disorder	86	9.57	3.79			
MCI	119	8.44	3.32			
Alzheimer's disease	145	3.60	2.96			
Dementia other	100	4.59	3.46			

A subset of patients was given Rey-O Immediate scaled scores which were examined and there was a statistically significant difference for diagnostic category, F (4, 114) = 25.46, $p < 0.001$. A Bonferroni post-hoc test revealed patients diagnosed WNL and with a mood disorder had better scores than those diagnosed with Alzheimer's disease ($p < 0.001$; $p < 0.001$) and dementia other ($p = 0.002$; $p < 0.001$). Patients diagnosed with MCI performed better than those diagnosed with Alzheimer's disease ($p < 0.001$), and patients diagnosed with Alzheimer's disease performed significantly worse than those diagnosed with dementia other ($p = 0.016$). See Table 32 for Rey-O immediate scaled score means.

Table 32. Rey-O immediate scaled scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	4	10.50	3.11	4	25.46	<0.001
Mood Disorder	11	10.55	4.34			
MCI	12	7.92	2.27			
Alzheimer's disease	59	3.98	1.42			
Dementia other	33	5.67	2.86			

All other patients received a T-score for the Rey-O Immediate test and analysis of these scores showed a significant difference for diagnostic category, F

(4, 208) = 43.55, $p < 0.001$. A Bonferroni post-hoc test revealed patients diagnosed as WNL performed better than patients diagnosed with MCI ($p = 0.002$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Patients diagnosed with a mood disorder and MCI scored significantly better than patients diagnosed with Alzheimer's disease ($p < 0.001$; $p < 0.001$) and dementia other ($p < 0.001$; $p < 0.001$). See Table 33 for Rey-O immediate t-score means.

Table 33. Rey-O figure immediate t-scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	26	60.96	13.57	4	43.55	<0.001
Mood Disorder	16	52.06	18.28			
MCI	30	49.37	12.44			
Alzheimer's disease	91	33.56	9.15			
Dementia other	50	33.88	9.67			

A subset of patients was given Rey-O Delay scaled scores which were examined and there was a statistically significant difference for diagnostic category, F (4, 112) = 25.35, $p < 0.001$. A Bonferroni post-hoc test revealed patients diagnosed WNL, with a mood disorder, and MCI performed better than those diagnosed with Alzheimer's disease ($p < 0.001$; $p < 0.001$; $p < 0.001$) and dementia other ($p = 0.001$; $p < 0.001$; $p = 0.012$). Finally, patients diagnosed with Alzheimer's disease performed worse than those diagnosed with dementia other ($p = 0.019$). See Table 34 for Rey-O delay scaled score means.

Table 34. Rey-O figure delay scaled scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	4	9.75	3.40	4	25.35	<0.001
Mood Disorder	11	9.27	1.65			
MCI	12	7.75	2.30			
Alzheimer's disease	58	4.10	1.42			
Dementia other	32	5.50	2.31			

All other patients received a T-score for the Rey-O Delay test and analysis of these scores showed a significant difference for diagnostic category, F (4, 204) = 45.37, $p < 0.001$. A Bonferroni post-hoc test revealed patients diagnosed as WNL performed better than those diagnosed with MCI ($p = 0.007$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Patients diagnosed with a mood disorder and MCI performed better than those diagnosed with Alzheimer's disease ($p < 0.001$; $p < 0.001$) and dementia other ($p < 0.001$; $p < 0.001$). See Table 35 for Rey-O delay t-score means.

Table 35. Rey-O figure delay t- scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	26	61.23	14.64	4	45.37	<0.001
Mood Disorder	16	48.19	18.36			
MCI	30	46.40	12.75			
Alzheimer's disease	88	29.72	9.26			
Dementia other	49	31.73	11.52			

Scores from the Shepherd Word List (delay, percent retention, recognition, and commissions) were analyzed utilizing patient age and education as covariates. For the word list delay score, there was found to be a significant difference for

diagnostic category, F (4, 865) = 310.42, $p < 0.001$. Pairwise comparisons revealed significant differences between all diagnostic categories. Patients diagnosed as WNL performed significantly better than those diagnosed with a mood disorder ($p < 0.001$), MCI ($p < 0.001$), Alzheimer's disease ($p < 0.001$) and dementia other ($p < 0.001$). Likewise, patients diagnosed with a mood disorder performed better than those diagnosed with MCI ($p < 0.001$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Patients diagnosed with MCI performed significantly better than those diagnosed with Alzheimer's disease ($p < 0.001$) and dementia other ($p < 0.001$). Finally, patients diagnosed with Alzheimer's disease performed significantly worse than those diagnosed with dementia other ($p < 0.001$). See Table 36 for word list delay score means.

Table 36. Word list delay scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	7.24	1.79	4	310.42	<0.001
Mood Disorder	115	6.05	2.36			
MCI	162	4.35	1.80			
Alzheimer's disease	308	1.00	1.30			
Dementia other	193	2.26	1.98			

Regarding the word list recognition scores, there was found to be a significant difference for diagnostic category, F (4, 859) = 68.61, $p < 0.001$. Pairwise comparisons revealed patients diagnosed WNL had better scores than those diagnosed with MCI ($p = 0.030$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Also, patients diagnosed with a mood disorder and

MCI had better scores than those diagnosed with Alzheimer's disease ($p < 0.001$; $p < 0.001$) and dementia other ($p < 0.001$; $p < 0.001$). Finally, patients diagnosed with Alzheimer's disease performed worse than those diagnosed with dementia other ($p < 0.001$). See Table 37 for word list recognition score means.

Table 37. Word list recognition scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	9.35	1.30	4	68.61	<0.001
Mood Disorder	115	8.94	1.61			
MCI	162	8.57	1.30			
Alzheimer's disease	302	6.05	2.82			
Dementia other	193	7.04	2.53			

Analysis of the number of word list commissions showed a significant difference for diagnostic category, F (4, 858) = 29.65, $p < 0.001$. Pairwise comparisons revealed patients diagnosed WNL, with a mood disorder, and MCI performed significantly better than patients diagnosed with Alzheimer's disease ($p < 0.001$; $p < 0.001$; $p < 0.001$) and dementia other ($p < 0.001$; $p < 0.001$; $p < 0.001$). See Table 38 for word list commission score means.

Table 38. Word list commission scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	0.45	1.32	4	29.65	<0.001
Mood Disorder	115	0.45	0.84			
MCI	162	0.89	1.11			
Alzheimer's disease	301	2.08	2.06			
Dementia other	193	1.78	1.81			

Finally, word list retention was also recorded as a percentage of number of delayed words out of the best number of words during the learning trial. For this portion, there was a significant difference found for diagnostic category, F (4, 864) = 193.57, $p < 0.001$. Pairwise comparisons revealed patients diagnosed as WNL performed better than patients diagnosed with MCI ($p < 0.001$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Likewise, patients diagnosed with a mood disorder performed better than those diagnosed with MCI ($p < 0.001$), Alzheimer's disease ($p < 0.001$), and dementia other ($p < 0.001$). Patients diagnosed with MCI also performed better than patients diagnosed with Alzheimer's disease ($p < 0.001$) and dementia other ($p < 0.001$). Finally, patients diagnosed with Alzheimer's disease performed significantly worse than patients diagnosed with dementia other ($p < 0.001$). See Table 39 for word list retention percentage means.

Table 39. Word list retention percent scores

Diagnosis	*n*	*M*	*SD*	*df*	*F*	*p*
WNL	94	80.81	16.57	4	193.57	<0.001
Mood Disorder	115	71.85	24.48			
MCI	162	59.20	21.25			
Alzheimer's disease	308	17.05	22.04			
Dementia other	192	37.51	31.04			

Initial Symptom Complaints

Patients' chief symptom complaints and associated symptoms were categorized based on first visit note. Memory loss was documented as the chief

complaint for all but two patients ($N = 981$) whose initial symptoms were listed as a mood disorder and lower extremity weakness. Out of all patients, most reported two initial symptoms ($N = 424$) while a large majority only reported one ($N = 348$), followed by three symptoms ($N = 176$), four symptoms ($N = 32$), and five symptoms ($N = 3$). Refer to Table 40 for all frequencies and percentages of each initial symptom.

Table 40. Initial Symptoms

Initial Symptom	Frequency	Percent
Memory Loss	981	52.5%
Mood	430	23.0%
Sleep	189	10.1%
Gait	143	7.7%
Behavior	58	3.1%
Psychotic	35	1.9%
Tremor	26	1.4%
Personality	4	0.2%
Weakness	1	0.1%

Because all but two of the chief complaints were memory loss, the subsequent associated symptoms were analyzed using chi-squares to see if there were any significant differences between initial symptoms and clinical diagnosis. There was found to be a significant relationship between diagnosis and secondary symptom complaint, X^2 (24, $N = 564$) = 59.00, $p < 0.001$, where patients who reported symptoms of a mood disorder were most likely to receive a clinical diagnosis of a mood disorder. Patients who reported sleep disturbance were more

likely to be diagnosed with WNL or dementia other. Patients who exhibited a change in behavior, psychotic symptoms, or gait problems were more often diagnosed with dementia other. Patients who displayed a tremor were more often diagnosed with MCI or dementia other. Finally, patients with a personality change were more often diagnosed with dementia other. See Table 41 for chi-square relationships of secondary symptoms.

Table 41. Secondary symptoms and clinical diagnoses

Diagnosis		Mood	Sleep	Behavior	Psychotic	Gait	Tremor	Personality
WNL	N	31	11	3	2	6	1	0
	%	57.4	20.4	5.6	3.7	11.1	1.9	0.0
Mood	N	85	10	0	0	2	2	0
	%	85.9	10.1	0.0	0.0	2.0	2.0	0.0
MCI	N	57	14	2	1	13	2	1
	%	63.3	15.6	2.2	1.1	14.4	2.2	1.1
AD	N	120	20	14	7	20	2	0
	%	65.6	10.9	7.7	3.8	10.9	1.1	0.0
Dem. other	N	70	14	15	10	24	3	2
	%	50.7	10.1	10.9	7.2	17.4	2.2	1.4

There was also a significant relationship between diagnosis and tertiary symptom complaint, X^2 (20, N = 178) = 43.00, p = 0.002, where patients who

reported symptoms of a mood disorder were most likely to receive a clinical diagnosis of MCI. Patients who reported sleep disturbance were more likely to be diagnosed with WNL or a mood disorder. Patients who exhibited a change in behavior, psychotic symptoms, or tremor were more often diagnosed with dementia other. See Table 42 for chi-square relationships of tertiary symptoms.

Table 42. Tertiary symptoms and clinical diagnoses

Diagnosis		Mood	Sleep	Behavior	Psychotic	Gait	Tremor
WNL	N	2	14	0	1	6	0
	%	8.7	60.9	0.0	4.3	26.1	0.0
Mood disorder	N	2	21	0	1	10	1
	%	5.7	60.0	0.0	2.9	28.6	2.9
MCI	N	4	18	1	0	4	2
	%	13.8	62.1	3.4	0.0	13.8	6.9
Alzheimer's disease	N	3	21	4	3	11	0
	%	7.1	50.0	9.5	7.1	26.2	0.0
Dementia other	N	3	11	8	5	13	9
	%	6.1	22.4	16.3	10.2	26.5	18.4

Discussion

Analyzing the significant differences in individual testing scores by domain assists in informing overall clinical diagnosis. By examining these differences over time with a large sample, consistency of diagnoses based on previous findings can be explored and refined if necessary. These studies become particularly important as patient care and treatment plan relies heavily on differential diagnosis of dementia, especially as this cohort continues to grow over the coming years.

After analyzing broad patterns of domains and diagnosis, it was found that in the language domain, patients diagnosed WNL, with a mood disorder, or MCI were more often categorized in the normal range, while patients diagnosed with Alzheimer's disease and dementia other were more often placed in the borderline range.

Similar with attention and concentration, patients who were WNL, had a mood disorder, or MCI were more often in the normal range, but patients who were diagnosed with Alzheimer's disease or dementia other were more often in the impaired range.

Regarding executive functioning, patients diagnosed WNL or a mood disorder were more often in the normal range, while those with MCI were in either the normal or borderline range, and patients with Alzheimer's disease and dementia other were more often placed in the impaired range.

Likewise, with the motor processing domain, patients diagnosed WNL and a mood disorder were more likely in the normal range, while patients diagnosed with MCI were mostly in the normal range, but starting to be placed more in the borderline range, while patients diagnosed with Alzheimer's disease and dementia other were in the impaired range.

Interestingly, when it came to the visuospatial domain, patients diagnosed WNL and with a mood disorder were in the normal range, those with MCI were mostly in the normal range, some in the borderline range, while patients diagnosed with dementia other were typically either in the borderline or impaired range. Patients diagnosed with Alzheimer's disease were mostly placed in the impaired range. Finally, and as expected, patients diagnosed WNL and a mood disorder were most often placed in the normal range, those with MCI were in the borderline range, and patients diagnosed with Alzheimer's disease and dementia other were most often in the impaired range. This is a similar finding to past studies that have found patients with Alzheimer's disease to be most impaired in this domain (Reed et al., 2007).

Because these broad patterns are based on individual scores within the domain specific patterns of scores were examined by domain. It was unsurprising to find that patients diagnosed WNL had performed the best on most tests. However, there were some instances when scores were indistinguishable from other diagnoses. For example, in the language domain, the MackSF4 score was not

different from mood disorder or MCI. Also, the MAE sentence repetition score was indistinguishable from all other diagnoses except Alzheimer's disease. However, this test is no longer used in the testing battery, so it's inability to differentiate between diagnoses is not an issue now. Other examples of indistinguishable scores from mood disorder are the SDMT written score, CST response accuracy, and brief Exit. As with the sentence repetition score, the CST response accuracy score in the motor processing speed domain was indistinguishable from any other diagnosis and is no longer used in the battery (due to the CST testing service being discontinued). Finally, remaining scores that were statistically similar between WNL and mood disorder were Rey-O copy scaled score and t-score, free clock, CST learning and delay, word list recognition, word list commissions, and word list retention. The Rey-O delay t-score and word list commission score was additionally indistinguishable from an MCI diagnosis.

When it comes to a diagnosis of a mood disorder, it is important to note the scores that separate this diagnosis from a diagnosis of WNL, as previous research has shown that certain mood disorders, such as depression, can produce testing data suggesting a neurocognitive disorder (Mukherjee & Rangasawami, 2014; Chamberlain & Sahakian, 2006.) For example, in the language domain, patients diagnosed with a mood disorder scored worse than those WNL on phonemic and the phonemic/semantic split. These patients also scored lower than WNL on the word list delay. Otherwise, patients diagnosed with a mood disorder performed at

least better than those diagnosed with Alzheimer's disease and dementia other, while also scoring better than those diagnosed with MCI on the VST dots (motor-processing speed) and CST response accuracy (executive functioning).

As might be expected, patients diagnosed with MCI tended to produce scores that were lower than WNL and mood disorder, but higher than Alzheimer's disease and dementia other. However, certain scores were only better than patients diagnosed with Alzheimer's disease, such as the phonemic/semantic split (language) and the Rey-O immediate scaled score (learning and memory).

Similar to previous research (Rogers, Ivanoiu, Patterson & Hodges, 2006), patients diagnosed with Alzheimer's disease most notably had the largest phonemic/semantic split (language) compared to all other diagnoses. Other scores in which patients diagnosed with Alzheimer's disease scored the lowest out of any other diagnosis were Rey-O immediate t-score and scaled score, word list delay, word list recognition, and word list retention. Again, like previous research, it appears that low scores in the learning and memory domain is what differentiates Alzheimer's disease from other diagnoses. However, is should be noted that there were multiple scores in which those with Alzheimer's disease were indistinguishable from those diagnosed with dementia other. Examples of these would be the MackSF4 (language), semantic, Trails B (attention and concentration; executive functioning), SDMT oral, CST response accuracy, VST words, VST

color, brief Exit, VST dots, free clock, copy clock, Rey-O copy, CST learning, CST delay, Rey-O immediate t-score and Rey-O delay t-score.

Finally, the individual scores that separate dementia other from other diagnoses based on lowest score were phonemic (language), Trails A, and SDMT written (attention and concentration). Of course, this particular diagnostic category is most difficult to analyze given the fact that it contains multiple difference dementia diagnoses. However, the results of scores specifically from the attention and concentration domain are somewhat in line with past research that has shown Lewy body dementia (considered a "dementia other") patients to be more impaired in this domain (Ayre et al., 1998).

When examining the initial symptom complaints, it was unsurprising to find the overwhelming majority of patients were given memory loss as chief complaint, especially given that these patients are being referred to a memory disorder clinic, specifically. It was also unsurprising that a large majority of patients who presented with symptoms of mood disorders were ultimately diagnosed clinically with a mood disorder following evaluation. However, since this symptom was the second largest reported, the striking comorbidity of mood changes with dementia diagnosis should also be noted. One interesting finding was that patients who reported sleep difficulty were either diagnosed as cognitively normal or with dementia other. This could depend largely on the specific type of sleep disorder, such as insomnia versus REM sleep disorder, for instance, and leaves room for further refinement in future

studies. The finding that behavior changes, psychotic symptoms, gait problems, and tremors were more related to a dementia other diagnosis lines up with past research that frontotemporal dementia is often associated with marked personality and behavior change (Shinagawa, Ikeda, Fukuhara & Tanabe, 2006) and that Lewy body dementia is characterized by well-formed visual hallucinations (Rongve, Bronnick, Ballard & Aarsland, 2010) and Parkinson's disease dementia has movement problems as featured symptoms (Alzheimer's Association, 2015).

A major strength of this study is the large number of patients available in the database, along with the variety of different types of testing scores distributed throughout each domain. Another strength is relative stability of testing measures utilized over several years with only minimal changes made to the testing battery. In fact, based on the statistical analyses, it appears the tests removed were weaker in differentiating between diagnoses (i.e., MAE sentence repetition, CST response speed). Another strength is the consistency of diagnosis based on specific patterns of scores scrutinized by a treatment team which has a basis in previous, established research. Another strength of this study is the revelation that despite using what is considered a "brief" protocol, the patterns of scores and results were similar to previous research utilizing a full battery.

The prominent limitation of this study is the lack of neuropathological findings that would confirm the clinical diagnosis to truly know how closely the score patterns predict an accurate diagnosis. While the Florida Brain Bank Program

maintains a database of neuropathological findings, unfortunately it not easily accessed for the purpose of research projects. Another limitation is the inability to distinguish certain dementia diagnoses grouped together into one "dementia other" category because of low numbers of patients within such categories (i.e., Lewy body dementia, frontotemporal dementia). In order to truly differentiate all categories, it would be necessary to isolate these and perform separate analyses. Another similar limitation is a marked overlap in test scores and domains that can take away from the specificity of scores. This is most apparent with several test results that are statistically the same between Alzheimer's disease and dementia other, making it more difficult to distinguish between these diagnostic categories. Finally, a limitation relates specifically to the CST scores given that this is a test no longer available for clinical use. Therefore, there is no way to use this test for future data collection.

There were some limitations related specifically to gathering data for initial symptoms complaints. For example, there does not appear to be a standardized form for asking patients about these specific symptoms and patients have seen different providers for their initial appointment who likely have varying ways of obtaining information. Therefore, providers may not specifically ask patients about certain associated symptoms. Another limitation is the high comorbidity of symptom complaints which makes it difficult to distinguish which is more

prominent. For example, a sleep disorder may be secondary to a mood disorder and not necessarily a symptom of dementia.

Future research should take these limitations into consideration and more focus placed on the importance of data gathered by brain banks where neuropathological reports can provide accurate dementia diagnoses to be compared to clinical diagnoses. This would be the only way to truly ensure the ability of neuropsychological testing to more accurately predict clinical diagnoses. Because most patients who enter a memory disorder clinic are given a chief complaint of memory loss, perhaps more importance should be placed on delving into all associated symptoms in order to assist in early differentiation between Alzheimer's disease and other types of dementia. Overall, these studies need to continue to be carried out since the more precise a clinical diagnosis is made, the better a treatment plan and resources can be provided for the patient to address their specific needs, which would in turn improve quality of life. This outcome is often the best to strive for with incurable, degenerative diseases. Until medical treatments make tremendous improvements, accurate diagnostics can go a long way in assisting patients, especially when the population in question is continuing to grow along with the need for best treatment.

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APPENDIX: Neuropsychological Measures and Descriptions

1. *Controlled Oral Word Association Test (COWAT)*: A subtest of the Multilingual Aphasia Examination battery involving spontaneous production of words under restricted search conditions for both phonemic and semantic fluency tasks.
2. *Multilingual Aphasia Examination (MAE) Sentence Repetition*: A subtest of the MAE battery that requires the repetition of 14 sentences of increasing length up to 22 syllables. Vocabulary and syntax are deliberately simple, but interrogative, negative, and other forms are included.
3. *Trail Making Test A and B*: A test of visual attention and task switching consisting of two parts. Part A involves connecting a set of 25 dots as quickly as possible while maintaining accuracy, and part B requires the subject to alternate between numbers and letters in sequential order.
4. *Symbol Digit Modalities Test (SDMT)*: A test used to assess divided attention, visual scanning, tracking, and motor speed.
5. *Cognitive Screening Test (CST)*: A computerized test designed to measure response inhibition, fine motor skills and processing speed, visual learning and encoding, and delayed recall for visually presented stimuli.

6. *Victoria Stroop Test*: A measure of cognitive control that assesses the ease with which a person can maintain a goal in mind and suppress a habitual response in favor of a less familiar one.
7. *Clock Drawing Test*: A test measuring visual-spatial constructional ability (free) and delineates executive difficulties from visual-constructive deficits (copy).
8. *Shepherd Serial List Learning Test*: A measure of verbal learning and encoding along with delayed recall for verbal information. The recognition portion determines recognition of words presented in an array of distractor words.
9. *Executive Interview (EXIT – Brief Edition)*: A screening measure designed to measure overall executive function.
10. *MackSF4*: A brief test of confrontational naming based on the full version of the Boston Naming Test.
11. *Rey-Osterrieth Complex Figure test (Rey-O)*: A test to assess visual-spatial constructional ability and visual memory.