12-2021

Brevity vs. Breadth: Can Memory Disorders Be Diagnosed Using Fewer Neuropsychological Assessments?

Analise Roccaforte

Brevity vs. Breadth: Can Memory Disorders Be Diagnosed Using Fewer Neuropsychological Assessments?

by
Analise Roccaforte, M.A., M.S.

Bachelor of Science
Psychology
Radford University
2015

Master of Arts
Psychology
American University
2018

Master of Science
Psychology
Florida Institute of Technology
2020

A Doctoral Research Project submitted to the
School of Psychology at
Florida Institute of Technology
In partial fulfillment of the requirements
For the degree of

Doctor of Psychology
in
Clinical Psychology

Melbourne, Florida
December 2021

We the undersigned committee, having examined the submitted doctoral research project, “Brevity vs. Breadth: Can Memory Disorders Be Diagnosed Using Fewer Neuropsychological Assessments?” by Analise Roccaforte, M.A., M.S. hereby indicate its unanimous approval.

_____

Anthony LoGalbo, Ph.D.
Associate Professor
School of Psychology
Major Advisor

_____

Frank Webbe, Ph.D.
Professor Emeritus
School of Psychology

_____

David Wilder, Ph.D.
Professor
School of Behavior Analysis

_____

Robert A. Taylor, Ph.D.
Professor and Interim Dean
College of Psychology and Liberal Arts

Abstract

Title: Brevity vs. Breadth: Can Memory Disorders Be Diagnosed Using Fewer Neuropsychological Assessments?

Author: Analise Roccaforte, M.A., M.S.

Major Advisor: Anthony LoGalbo, Ph.D.

Object: The present study examines the clinical utility of combining a cognitive screener, Montreal Cognitive Assessment (MoCA), with a measure of adaptive functioning, Texas Functional Living Scale (TFLS), to diagnose memory disorders when differentiating between cognition within normal limits (WNL), mild cognitive impairment (MCI), and Alzheimer's disease (AD).

Method: A total of 207 Health First Memory Disorder Clinic patients, ages 64-94, were included in the study. Participants were screened using the MoCA and then they completed a brief neuropsychological evaluation, which included the TFLS. Participants were only included if they received a diagnosis of cognition WNL, MCI, or AD. They also had to meet criteria for each MoCA total and TFLS T-score cut-off for each diagnostic category (WNL: MoCA = ≥ 26, TFLS T = ≥ 44, MCI: MoCA = 19-25, TFLS T = 37-43, AD: MoCA ≤ 18, TFLS T = ≤36).

Results: Results of the present study revealed that the combined MoCA and TFLS score had statistically significant amount of agreement based on a chi-square analysis when compared to the overall diagnosis as determined by the Brief Neuropsychological Evaluation (BNE). Additionally, the MoCA and TFLS combined score was a statistically significant predictor of the diagnostic outcome. Correlational analysis revealed that the diagnosis based on the MoCA + TFLS combination score had a statistically significant moderate positive relationship with the diagnosis based on the BNE. Furthermore, the TFLS subtest that had the strongest relationship with a diagnosis of AD was the Memory subtest.

Conclusion: When differentiating between patients who have a diagnosis of cognition WNL, MCI, and AD, the MoCA and TFLS alone can give us similar information as a full battery of testing (BNE). Therefore, if this is used as an alternative mode of testing, more patients can be tested in a day, thereby reducing wait time between the initial visit and the cognitive evaluation, as well as diminishing the waitlist. As a result, diagnoses of mild cognitive impairment or Alzheimer's disease can be detected earlier, and appropriate interventions can be introduced sooner.

TABLE OF CONTENTS

List of Tables

List of Figures

Acknowledgements

Thank you to my boyfriend, TJ, who was there to de-escalate any stress that surfaced throughout this challenging and rewarding process, as well as throughout graduate school. The last four years would have been much more arduous without your love and support, and I am forever grateful for you. Thank you to my FIT friends, especially the Star Wars group, for being my hype team and helping me to continue to believe in myself. Thank you to my mom for everything you have done for me throughout my life, as well as the home-cooked meals and giant hugs that helped me get through graduate school. Thank you to my brother for reminding me to prioritize self-care. Thank you to Mr. and Mrs. Johnston for always checking in and me and asking how my project was going. Thank you to Dr. Wilder for being my third committee member and offering valuable feedback. Thank you to Dr. Webbe and Dr. LoGalbo for being the most amazing neuropsychology professors and mentors. An extra thank you to Dr. LoGalbo for all of the edits and helping this project come together. Thank you to Dr. Ben and Dr. Nadler for teaching me everything under the sun about neuropsychology (and life in general) and always making me feel like an absolute rockstar. I hope to be as knowledgeable as you all when I grow up. Thank you to Pongo for making me the happiest dog mom. Your kisses and snuggles served as little reminders to keep smiling even on the most stressful days.

Chapter 1: Introduction

Neuropsychological assessment is a performance-based evaluation consisting of a variety of different tasks in order to assess cognitive functioning. These evaluations originated in the late 19th and early 20th century when physicians wanted to determine the mental capacities of patients with a brain disease in a more detailed way than what could be accomplished by the clinical examination of that time (Benton, 1994). Neuropsychological assessments can include verbal responding (e.g., naming objects, sentence repetition), paper and pencil tasks (e.g., narrative writing, connecting dots), mental manipulation and flexibility (e.g., forming visual puzzles, learning from feedback), computer-based tests, and motor tasks (e.g., grip strength, finger tapping) (Lezak, 2012; Zillmer et el., 2008). Neuropsychological evaluations typically assess several domains of cognitive functioning, such as general intellect, attention, processing speed, reasoning, sequencing, problem solving, executive functioning, concentration, learning, memory, language, and communication (Braun et al., 2011). Additionally, these assessments can evaluate visual-spatial cognition, visual-motor praxis, motor and sensory function, mood, personality, quality of life, adaptive functioning/activities of daily living, social-emotional awareness and responsiveness, psychopathology, motivation, and effort (Braun et al., 2011).

Neuropsychological testing is unique in the way that it evaluates brain-behavior relationships in that it involves an objective approach using validated tests (Reitan & Wolfson, 2008). Furthermore, it can be useful in assessing the

lateralization and localization of impaired brain regions that may not be observable with standard neuroimaging (Snyder et al., 2006). Typically, these assessments are administered to individuals that have experienced an injury to the brain, a change in brain function or structure, or noticeable cognitive decline. Neuropsychologists receive specialized training in the administration of neuropsychological tests, assessment of the pattern and severity of cognitive impairment, and interpretation of results, while simultaneously considering the patient's age, educational background, motivational and emotional state, and a variety of other factors that could impact test performance (Barr, 2001).

The overall goals of neuropsychological assessment include describing strengths and weaknesses and identifying changes and impairments in cognitive functioning, determining biological correlates of test results, determining whether changes in functioning are associated with neurological, psychiatric, developmental, or non-neurological conditions, assessing changes over time, offering guidelines to plan for adjusting to work or school, offering guidelines and education for families and caregivers, and treatment planning and implementation (Hebben & Millberg, 2009). Because there is a lot of information to obtain from these evaluations, it is more common for them to be comprehensive. As a result, some neuropsychological assessments can take up to 8 hours and have to be scheduled across multiple appointments (Zillmer et al., 2008; AACN, 2021). More typically, testing takes from 3 to 6 hours (Bhargava, 2020). Because this is still a notable time frame, it is important for neuropsychologists to consider potential

factors which may interfere with performance and test results, such as patient fatigue, loss of motivation, and increased costs, when they are developing their test batteries and deciding how many appointments they will need to complete the battery (Zillmer et al., 2008).

Because time is valuable in the healthcare setting, there is an ongoing debate in the field of neuropsychology regarding whether screeners and shorter evaluations are as accurate in providing a diagnosis compared to more lengthy and comprehensive assessments. Roebuck-Spencer et al. (2017) summarized this debate by pointing out that the screeners and shorter assessments can be useful for early identification of people who are at risk for a disorder, an indication for a need for further evaluation, and a way to monitor the progression of symptoms. Additionally, screeners are brief, can often be administered as part of a routine clinical visit, and require minimal training for administration. Furthermore, a briefer evaluation would allow for an opportunity to assess more patients in a day, and it would be more affordable for the patient.

Screeners are a common tool in the healthcare setting. For example, the Patient Health Questionnaire is a common 9-item self-report measure that takes about 1-minute to administer and is commonly used to screen for depression (Kocalevent et al., 2013). People often encounter screening mechanisms as part of their routine medical checkups. Examples of these screeners include a pap smear, which tests for cervical cancer in women, a mammogram, which screens for early signs of breast cancer, a prostate-specific antigen test, which is a screener for

prostate cancer, or a colonoscopy, which is a screening test for colorectal cancer. Screeners are limited in that they typically do not provide a definitive diagnosis. Therefore, if any of these screening measures are abnormal, it often warrants further testing.

Although screening measures are an ideal way to gather imperative, and sometimes time-sensitive, information, they do have their pitfalls. By virtue of their brevity, they have a limited measurement range, and their floor and ceiling effects can threaten their validity (Jacova et al., 2007). This means that their range is very limited. Floor and ceiling effects are related to how well someone can perform on a certain assessment. Wang et al. (2008) explain that an asymptotic value is the greatest true value that a participant can demonstrate, but if a ceiling effect occurs, then the highest score that is achievable on the assessment will not demonstrate the participant's full capabilities. The authors point out that many widely used memory tests, including the Verbal Paired Associates from the Wechsler Memory Scales, and word list tests such as the Rey Auditory Verbal Learning Test and the California Verbal Learning Test, are vulnerable to exhibiting ceiling effects. Meanwhile, floor effects are similar in that they might not encapsulate the asymptotic value either, but in this case, the asymptotic value is lower than the lowest possible score on the assessment. For example, the lowest obtainable score on the Wechsler Adult Intelligence Scale, 3rd edition is a 45, and the range was slightly expanded for the 4th edition, making the lowest possible score a 40, in order to account for floor effects (Sattler & Ryan, 2009).

Furthermore, screeners and shorter assessments are much narrower in the scope of domains that they can assess, whereas comprehensive assessments are multidimensional, as they can evaluate levels of functioning across multiple domains (Roebuck-Spencer et al., 2017). Comprehensive neuropsychological batteries can help to more clearly identify the presence and magnitude of an impairment, as well as determine the etiology of those impairments, ultimate diagnosis, and perhaps assess functional capacities as well (Roebuck-Spencer et al., 2017). When considering a shorter assessment, it must be recognized that there can often be a trade-off between the brevity of an assessment and the reliability of its results (Schoenberg & Scott, 2011).

Despite these potential limitations, there are certain settings and patient populations in which a briefer evaluation may be preferred over a comprehensive neuropsychological evaluation. Bishop et al. (2003) emphasized the importance of neuropsychological services in medical hospitals and rehabilitation centers by describing their role in determining a patient's level of cognitive functioning, assisting in confirming a diagnosis, facilitating placement or treatment, assessing decisional capacity, and providing recommendations and treatment options. However, in a hospital setting, these evaluations are typically performed at bedside and are completed in a shorter amount of time than an outpatient neuropsychological assessment. Additionally, a patient who sustained a sport-related concussion should be assessed acutely and repeatedly in order to evaluate the severity of their injury, as well as their level of cognitive impairment and

symptomology, and gauge recovery, as symptoms typically resolve in 5-10 days (Scott, 2011; Iverson et al., 2005). Similarly, patients with ischemic and hemorrhagic strokes can show improvements in weeks, days, or even hours, so it is important to provide a brief neuropsychological assessment in order to gauge recovery. Pediatric neuropsychology is another field where shorter testing batteries are utilized. In a longitudinal study on children, White et al. (2009) limited their batteries to 95 minutes for ages 5-6, 60 minutes for age 3, 30 minutes for age 1.5-2, and 20 minutes for ages 6 months – 1 year. Similarly, when examining the elderly population, it is important to consider that they are more susceptible to experiencing conditions that can adversely impact the results of their neuropsychological testing, including fatigue, central nervous side effects due to medications, lower energy levels, and feelings of malaise associated with chronic illness (Lezak, 2012). Therefore, shorter evaluations would likely be more beneficial for this population as well.

Neuropsychology and Geriatrics

Geriatric neuropsychological assessment is one of the fastest growing areas within clinical neuropsychology (Tuokko & Hadjistavropoulos, 1998), in part due to the importance of neuropsychological testing in narrowing and specifying the differential diagnosis of dementias. It involves individuals that are 65 years of age and older. The most common application of neuropsychological assessment involving the geriatric population includes differentiating between a cognitive disorder and normal aging (Welsh-Bohmer & Attix, 2005). There is an important

difference between cognitive change due to typical aging and cognitive decline due to a pathological process (Zimmerman & Brickman, 20009). Neuropsychological studies are particularly useful for conveying cognitive deficits associated with a neurodegenerative process, such as Alzheimer's disease (AD), and how these deficits are different from age-related cognitive decline (Salmon & Bondi, 2010). Normative data samples are collected and then used as individual comparison standards, with the assumption that normal individuals will show minimal variability in the performance of a task and deviations from this norm are due to abnormal conditions, such as a neurodegenerative disease.

Cognitive screeners and more detailed neuropsychological evaluations are both used when evaluating neurodegenerative diseases. Jacova et al. (2007) reported that brief cognitive tests are utilized to obtain a global index of cognitive functioning when assessing for dementia, while full batteries of neuropsychological testing are performed to determine a patient's level of functioning across multiple domains. They both can be useful in tracking cognitive changes that may occur over time (Cohen et al., 2019). As Roebuck-Spencer et al. (2017) point out, it is important to assess for multiple cognitive domains when formulating a diagnosis, and this is especially important for differentiating between normal aging, mild cognitive impairment, and dementia.

Normal Aging

Even among individuals experiencing normal aging without dementia, a measurable level of cognitive decline occurs (Cohen et al., 2019). As a person ages,

age-related changes in cerebral white matter involving hyperintensities occur in the brain as well (Gunning-Dixon & Raz, 2000). These white matter hyperintensities are related to global cognitive declines, and certain domains of cognitive functioning including processing speed, executive functioning, and working memory are particularly sensitive to these hyperintensities (Gunning-Dixon & Raz, 2000). Tuokko & Hadjistavropoulos (1998) argue that it is incredibly important for practitioners and other medical professionals to understand the distinction between cognitive changes in normal aging versus cognitive changes that are greater than expected for age. When someone experiences cognitive deficits that extend beyond what is typical for normal aging, further diagnostic evaluation and treatment intervention is necessary. Radvin and Katzen (2013) point out that the optimal neuropsychological battery assesses learning and memory, executive functioning, language, and visuospatial skills, as well as attention and processing speed, as these domains are frequently impaired by a variety of brain disorders and could serve as a more general marker for impairment. Normal aging most commonly involves cognitive changes in areas of attention, processing speed, aspects of language, working memory, and aspects of executive functioning, which will be described in more detail below.

Attention is responsible for governing the information flow and processing, as it facilitates, increases, or inhibits other cognitive processes (Snyder et al., 2006). In terms of attention, sustained attention and primary attention span are typically preserved in normal aging, while it is possible to have a decline in divided

attention, or the ability to concentrate on more than one piece of information at a time (Craft et al., 2018). This distinction is important because sustained attention is required for everyday activities including hobbies and pursuits, as well as safety-critical tasks like driving (Staub et al., 2012). Declines in attention switching, or the ability to shift attention from one set of stimuli to another set of stimuli, are also a consequence of normal aging.

The two main aspects of language are language comprehension and language production. In normal aging, older adults have increased difficulties with language production compared to language comprehension (Abrams & Farrell, 2011). More specifically, vocabulary and syntactic abilities remain well-preserved, while there is commonly a decline in spontaneous word-finding and verbal fluency (Craft et al., 2018). The most common cause of impaired communication in older adults is not associated with a language impairment; it has to do with age-related hearing loss, which typically affects approximately 30% of the geriatric population (La Rue, 1992).

In terms of memory, a normal aging older adult may experience a decline in retrieval efficiency (Cohen et al., 2019). This is because older adults are more likely to encode new information in a less meaningful way making their new memories less distinctive, and therefore, harder to retrieve (Glisky, 2007). Furthermore, older adults have a reduced ability to ignore irrelevant information and a decreased use of strategies that improve learning and memory (Harada et al.,

2013). Additionally, older adults have greater difficulty with combining contextual information into a coherent memory representation (Luo & Craik, 2008).

Executive functions include multiple skills such as planning, inhibition, task switching, memory updating, cognitive flexibility, and performance monitoring (Phillips & Henry, 2008). Complex neural networks and multiple cognitive processes are involved in each of these functions, making it unlikely that age will influence each of these functions in the same way (Phillips & Henry, 2008). In normal aging, individuals have more difficulties with predetermining, or planning, a complex course of action with the expectation of achieving a certain goal (Allain et al., 2005). In other words, normal aging negatively impacts one's capacity to mentally represent complex plans, but it does not interfere with their ability to execute these plans (Allain et al., 2005).

Visuospatial skills are often well-preserved in normal aging older adults; however, complex copying tasks, as well as mental rotation and assembly may be more challenging for an older adult as compared to a younger adult (Craft et al., 2018). Visual construction skills also decline over time (Harada et al., 2013). Additionally, increased visual impairment and decreased visual acuity are more common in older aged adults, which may cause them to compensate for their declining sensory abilities (Glisky, 2007). By doing this, it is possible that the way they perform cognitive tasks might be less efficient (Glisky, 2007). This also explains why there is often a decline in measures dependent on motor speed (e.g., reaction time) in older adults (Tuokko & Hadjistavropoulos, 1998).

In terms of structural and functional changes in the brain which may occur with normal aging, white matter changes and neuronal death can occur (Harada et al., 2013). Decreases in grey matter are also observed, but white matter decreases are much greater in normal aging (Harada et al., 2013). Minor deposition of beta-amyloid peptide and neurofibrillary tangles are seen in normal aging, as well as ventricular enlargement, hippocampal atrophy, and loss of synapses, neurons, neurochemical input, and neuronal networks (Welsh-Bohmer & Attix, 2005). Diffuse and widespread tissue loss, or atrophy, expansion of CSF-filled cavities, and mild shrinkage of brain parenchyma also occur in normally aging adults (Driscoll et al., 2009).

Mild Cognitive Impairment

Mild cognitive impairment (MCI) is a term used to describe when an individual is experiencing cognitive decline that is greater than that observed in normal aging, but not severe enough to be considered dementia. Importantly, the degree of cognitive impairment associated with MCI does not negatively impact a person's ability to perform activities of daily living (Gauthier, 2006). The rationale for early identification of MCI is that if cognitive decline is detected at this stage, interventions could potentially prevent further damage to the central nervous system associated with neurodegenerative processes (Petersen & Negash, 2008). There are four types of MCI: amnestic/single domain, amnestic/multiple domain, non-amnestic/single domain, and non-amnestic multiple domain. If the memory domain is impaired, then the diagnosis would be considered an amnestic subtype of

MCI. If only one cognitive domain is impaired, then it would be considered a single domain MCI versus a multiple domain MCI, where more than one cognitive domain is impaired. Petersen and his colleagues also developed a clinical characterization when diagnosing MCI, and the criteria includes subjective memory concerns, objective impairment in memory on neuropsychological testing, absence of dementia, and absence of functional complaints (Petersen et al., 1999).

MCI also has the potential to revert back to cognition being within normal limits or progress to dementia. Koepsell and Monsell (2012) found that in a sample of 3,020 people with MCI, 16% reverted back to cognition within normal limits, 64% still had MCI, and 20% progressed to dementia at a follow-up visit one year later. Factors that influence the progression of MCI to dementia are still currently being researched. Currently, the apolipoprotein E-ε4 (ApoE4) allele has been established as a risk factor for the progression of MCI to AD (Petersen & Negash, 2008). The presence of excessive beta-amyloid in patients with mild cognitive impairment can also be a predictor of progression to AD (Harada et al., 2013). Diabetes and metabolic syndrome were also associated with an increased risk of progressing from MCI to dementia (Gao et al., 2018). Furthermore, patients with more severe memory impairment, atrophy of the hippocampal formation, and cerebrospinal fluid tau level are additional risk factors for this course (Petersen & Nagash, 2008).

Sugarman et al. (2018) found that several factors associated with normal cognition progressing to MCI are similar to ones that influence the progression of

MCI to dementia, including possession of the ApoE4 allele, depression, type II diabetes, tobacco use, physical inactivity, and poor diet. Depression, anxiety, irritability, apathy, sleep disturbance, and other neuropsychiatric factors have also been correlated with a diagnosis of MCI. Furthermore, Sugarman et al. (2018) noted that successful treatment of depression in older adults had neuroprotective effects, with a depressed sample demonstrating an increase in left hippocampal volume following prolonged antidepressant use.

Factors such as younger age, higher education level, having participated in leisure-time activities more often, and having a higher baseline mini-mental status examination (MMSE) have been associated with reverting back from MCI to cognition within normal limits (Gao et al., 2018). Additionally, factors such as higher neuropsychological test scores, higher global cognitive functioning, non-amnestic MCI subtypes, single domain MCI, absence of the ApoE4 allele, larger hippocampal volume, fewer white matter hyperintensities, and fewer Alzheimer biomarkers have been shown to be predictive of MCI reversion to normal cognition (Pandya et al., 2017). Sachdev et al. (2013) also found that people who revert back to normal cognition from MCI have better control of blood pressure, greater openness to experience, better visual acuity, and better olfaction. They are also more likely to engage in mental activities, like reading books.

Dementia

Dementia is the umbrella term for neurodegenerative disorders, including AD, Lewy body dementia, frontotemporal dementia, vascular dementia, and several other less common conditions. For people in the world who are 65 years of age or older, it is estimated that approximately 50 million of them have dementia, and it is projected that the incidence rate of dementia will be 152 million by 2050 (WHO, 2020). Age is the greatest risk factor for dementia (Guerreiro & Bras, 2015). The age of onset for dementia is middle adulthood to late adulthood. Because dementia is an umbrella term, it can include a wide range of deficits, including memory loss, problems with attention, concentration, judgment, problem-solving, and other cognitive functions, as well as visuospatial difficulties. Functional and behavioral changes also commonly occur (Duong et al., 2017).

There is currently no cure for dementia. However, treatment of dementia usually targets the presenting symptoms. Common treatments include memory medications, compensatory strategies, and disease-modifying treatments. Memory medications include cholinesterase inhibitors (e.g., donepezil, memantine). These medications inhibit acetylcholinesterase, which is any enzyme that destroys the neurotransmitter, acetylcholine. Acetylcholine is involved in memory functions, which is why its preservation is important. Yiannopoulou and Papageorgiou (2013) point out that although memory medications do not cure dementia, they have been useful in slowing the progression. However, use of these medications is preferred in the early stages of dementia, as they may not be as efficacious in the later stages.

Compensatory strategies for cognitive and functional impairments may include the use of a calendar, journal, alarm, list, or sticky note reminder. Disease-modifying treatments include modulation of cholesterol and vascular risk-factors, decreasing oxidative stress, anti-inflammatory drugs, and drugs interfering with tau and amyloid beta deposition.

Alzheimer's Disease

AD accounts for 60-80% of dementias (Alzheimer's Association, 2018). The disease was first discovered in 1906, but the causes of it were not well-understood until decades later (Lowenstein, 2013). The Diagnostic and Statistical Manual of Mental Disorders, 5th edition defines AD as a neurocognitive disorder, indicating that there is significant cognitive decline as compared to the patient's premorbid level of functioning in one or more cognitive domain, including complex attention, executive functioning, learning and memory, language, perceptual-motor, or social cognition, that is preferably documented by standardized neuropsychological assessment (American Psychiatric Association, 2013). The cognitive deficit does not occur exclusively in the context of delirium, and it cannot be better explained by another mental disorder (American Psychiatric Association, 2013). The American Psychiatric Association (2013) further classifies the neurocognitive disorder as *major* if the cognitive deficit interferes with capacity for independence of everyday activities and, in the context of AD, if at least two domains are impaired. Probable AD is diagnosed when there is evidence of a causative AD genetic mutation from family history or genetic testing, clear

evidence of decline in learning and memory and at least one other cognitive domain, and a steadily progressive, gradual decline in cognition without evidence of a mixed etiology.

Approximately 6.2 million Americans are currently living with AD, and 72% of them are 75 years of age or older (Alzheimer's Association, 2021). The Alzheimer's Association (2021) also estimates that one in nine people ages 65 and older, or 11.3%, have AD, and on average, people survive 4-8 years after an AD diagnosis; however, some people live as long as 20 years with the diagnosis, which emphasizes the slow, uncertain progression of this condition. Additionally, it is estimated that the nation-wide cost of AD and other dementias is $355 billion dollars, with $239 billion being attributed to Medicare and Medicaid payments. Furthermore, nearly half of all caregivers who provide help for older adults do so for someone living with AD or another dementia. Anand et al. (2016) found that caregiver stress is much higher when caring for someone with AD as compared to other chronic disorders, and this is likely related to their cognitive decline and increased dependence with activities of daily living.

While the clinical manifestations of AD can be observed when someone is still alive, neuropathological underpinnings of the disease within the brain cannot be detected until an autopsy is performed. The neuropathological changes that occur in AD include alterations in the production and processing of amyloid β-protein, as well as extracellular amyloid plaques, intracellular neurofibrillary tangles, loss of neurons and synapses, and reactive microgliosis (Mayeux & Stern,

2012). Microgliosis occurs when microglia, the key cellular mediators of the neuroinflammatory process that make up the immune system of the central nervous system, respond to the amyloid β deposition (Streit et al, 2004). However, in AD, microglia are ineffective in breaking down amyloid β deposits (Streit et al, 2004). Dystrophic neurites, an abnormal neuronal process characterized by microscopic and expansion of tissue degeneration, are also a characterization of AD; however, despite decades of research, the mechanism of their development and ways to prevent their formation are still unknown (Yan, 2018; Sharoar et al., 2019). AD is also associated with extensive volume loss in the temporoparietal regions, with parietal lobe atrophy being more pronounced in early-onset AD and medial temporal lobe volume loss being more pronounced in late-onset AD (Harper et al., 2016). These more global structural changes can often be observed prior to death via brain imaging, such as computerized tomography (CT) or magnetic resonance imaging (MRI).

There are both non-modifiable and modifiable risk factors related to the development of AD. The strongest known non-modifiable risk factors for AD include age, family history, and genetics (Alzheimer's Association, 2021). Older adults with a history of moderate traumatic brain injury are also 2.3 times more likely to develop AD (Alzheimer's Association, 2021). While it is not well-understood whether epileptic seizures increase the risk of AD or if they are an effect of the disease, it is known that these two neurological conditions share mutual molecular and cellular mechanisms (Edwards et al., 2019). Cardiovascular

risk factors, including diabetes, hypertension, heart disease, atherosclerosis, and hyperlipidemia, have also been associated with an increased risk of AD, as they affect the cerebrovascular network, which plays a pivotal role in maintaining the activity and integrity of the brain by regulating constant blood flow (van Kan et al., 2009; Edwards et al., 2019).

Modifiable risk factors include sleep patterns, diet, and physical inactivity. Edwards et al. (2019) also point out that sleep-wake cycle disturbances cause increased daytime sleepiness, reduced nocturnal sleep, and sleep fragmentation, which are symptoms commonly seen in AD. Therefore, the association between aging, cognition, and sleep disorders has suggested that increased sleep disturbances may lead to an increased risk of developing AD. Additionally, sleep increases the rate of amyloid beta clearance in the brain through the glymphatic system, and sleep-deprivation increases cerebrospinal fluid tau levels, both of which are associated with AD. Diet is a modifiable risk factor for AD, with elevated saturated fatty acids being associated with an increased risk and elevated monounsaturated fatty acids and polyunsaturated fatty acids being associated with a reduced risk of cognitive decline (Solfrizzi et al., 2011). Consumption of low-sugar fruits, non-starch vegetables, vegetable oils, and a diet excluding foods with added sugar are considered healthy for the brain (Solfrizzi et al., 2011). Physical inactivity has been shown to result in decreased hippocampal volume and brain neuroplasticity (Edwards et al., 2019).

Psychosocial factors including lower education, decreased cognitive stimulation, lower occupational status, lack of social interaction, absence of hobbies, and poor overall well-being has also been shown to negatively impact the onset of AD (Zhang et al., 2000). Stress can also influence development of AD due to its biological effects. Specifically, stress leads to an over-activation of the hypothalamus-pituitary-adrenal (HPA) axis, which causes an increase in the release of cortisol, and has been associated with cell death in the hippocampus, the brain region that is most commonly affected by AD neuropathology (Edwards et al., 2019). Because these risk factors are modifiable it is important for patients to be well-educated about them so that they can make lifestyle adjustments in an attempt to decrease their chance of developing AD.

Neuropsychological Assessment of Alzheimer's Disease

Neuropsychologists administer tests to older adults when assessing cognitive functioning, and they examine the pattern of testing results in the process of diagnostic formulation toward determining the presence of dementia, and AD specifically. If cognitive impairments are not observed, testing can still serve as an objective baseline that helps to monitor for possible progression and/or response to treatment (Loewenstein, 2013). Clinical interviewing, assessment of behavioral changes, family history, psychological functioning, and adaptive functioning may also be assessed. Information regarding medical history is gathered to see if other medical conditions or medications can be interfering with cognitive functioning.

When conducting a comprehensive neuropsychological assessment, certain patterns on testing might emerge that would be indicative of dementia. As previously mentioned, multiple domains of cognitive functioning are assessed. The medial temporal lobes and cortical networks are the brain regions that are negatively impacted by AD, and they are involved in learning and memory, as well as executive functioning (Buckner, 2004). Therefore, these two cognitive domains are most commonly impaired in patients with AD. Additionally, damage to the medial temporal lobe structures results in an inability to learn new information and recall the information after a delay (Weintraub et al., 2012). Therefore, common patterns of testing that may emerge include a flat learning curve during memory tests, meaning that individuals with AD do not benefit from repetition of information, as well as impaired retention of verbal and visual information following a delay. In terms of language and spontaneous production of words, phonemic fluency, or producing words that start with a certain letter, is typically more well-preserved than semantic fluency, producing words in the same category (Weintraub et al., 2012). On tests of expressive language involving narrative writing, patients with AD commonly make significantly more writing errors, mention significantly fewer categories of information, and produce short, simplistic phrases rather than a coherent account of connected ideas (Henderson et al., 1992).

In terms of executive functioning, patients with AD tend to exhibit impairments in problem solving and tests that require mental manipulation, including the Tower of London, the Modified Wisconsin Card Sorting Test, and

Trail Making Test Part B (Weintraub et al., 2012). Changes in visuospatial functions in AD are associated with visual construction, visual perception, and visual orientation (Weintraub et al., 2012). A clock drawing task can quickly assess multiple cognitive constructs including understanding of verbal instructions, spatial orientation, abstract thinking, planning, executive functioning, and visuospatial skills, and therefore it is commonly used in the assessment of dementia (Aprahamian et al., 2009). Common errors on this task include spacing errors, straying from the perimeter, planning errors, and setting the hands to the incorrect time. Among patients with AD, time-setting errors occurred in more than 50% of patients, an inability to denote the accurate time by use of hands was found to be a stronger indicator of cognitive impairment compared to visuospatial difficulties (Esteban-Santillan, 1998).

When screening for AD, multiple cognitive domains can still be assessed; however, fewer and often simpler items are used. Items that are frequently used to assess mental status in patients that are being screened for dementia include orientation (e.g., year, season, date, day, month, city, state, and clinic), concentration and attention (e.g., counting backwards, months of the year backwards), memory (e.g., learning, delayed recall), remote memory (e.g., date of birth, name of current president), abstract thinking (e.g., finding similarities between objects), language (e.g., naming, repetition), and apraxia (e.g., copying a geometric figure) (Knight, 2013). Multiple cognitive assessment screeners exist that can be used to quickly assess for dementia, but the Montreal Cognitive

Assessment (MoCA) is one of the most commonly used measures, and it is the most sensitive measure when assessing for AD (Jacova et al., 2007).

Montreal Cognitive Assessment (MoCA)

The MoCA is a measure of global cognitive functioning. There are 8 cognitive domains assessed including visuospatial/executive (5 points), naming (3 points), memory (for learning purposes), attention (6 points), language (3 points), abstraction (2 points), delayed recall (5 points), and orientation (6 points). Davis et al. (2015) found that the MoCA correctly identified 94% of patients with dementia across clinical settings when using the cut-off score of less than 26 out of 30. Nasreddine et al. (2005) found that scores of 19-25 are in the MCI range, and a score of 18 or less is likely suggestive of dementia. The MoCA shows superior psychometric properties as compared to other cognitive functioning screeners, and it has higher diagnostic accuracy when discriminating between MCI and dementia, as well as higher sensitivity to cognitive decline in longitudinal monitoring (Freitas et al., 2013). The MoCA also has more emphasis on tasks of frontal executive functioning and attention than other cognitive screeners, making it more sensitive for detecting non-AD dementias (Smith et al., 2007).

Julayanont and Nasreddine (2017) suggest that the MoCA assesses a broad range of cognition, including visuomotor and visuoperceptual skills as well as mental flexibility, with the inclusion of a brief version of the trail making test, and these abilities mainly rely on frontal lobe function. Spatial planning and visuomotor coordination are involved in copying a figure of a cube, which rely on fronto-

parieto-occipital cortices. A clock drawing task is also a component of the MoCA, and the semantic dysfunction of AD could play a role in anomia on the object naming portion of the MoCA. Digit span forward measures retention of auditory stimuli and articulatory rehearsal, while digit span backwards requires working memory and central executive processing. Greater activation of the dorsolateral prefrontal cortices and left occipital visual regions are involved in digit span backward as compared to digit span forward. Letter A tapping measures sustained and focused attention, as well as speed to respond to externally paced stimuli. Individuals with MCI and normal cognition have comparable performance on this task, but individuals with AD showed impaired performance on this task (Nasreddine et al., 2005).

Components of the MoCA have additional correlations with functional integrity of brain structures as well. For example, FMRI studies have demonstrated activation in the bilateral premotor, posterior parietal, and prefrontal cortices of the brain during the serial 7 subtraction subtest, which involves mental calculation (Julayanont and Nasreddine, 2017). The authors also reported that the sentence repetition task assesses attention and concentration, as well as language skills that are supported by the left temporo-parieto-frontal circuit, while the letter fluency task requires working memory, searching strategy, and inhibition of irrelevant words and is thus involved primarily with frontal lobe functioning. The similarities portion of the MoCA examines verbal abstract reasoning and conceptual thinking, and decreased activity in the temporal lobe and left angular gyrus in AD patients

was correlated with impairments on this test (Woo et al., 2010). The delayed recall portion of the MoCA examines memory, and patients with AD typically perform poorly on this task in terms of spontaneous recall and they additionally do not benefit from cuing and tend to have more intrusion errors compared to patients with other neurodegenerative disorders, such as Huntington's and Parkinson's disease (Julayanont and Nasreddine, 2017). Lower scores on the delayed recall portion of the MoCA is also associated with smaller hippocampal volume (Ritter et al., 2017). The final section of the MoCA is orientation, and impairments in orientation have been found to be one of the best independent predictors of functional status, which involves the ability to independently perform activities of daily living (ADLs), in patients with AD (Razani et al., 2009).

Activities of Daily Living

Activities of daily living refer to the basic tasks of everyday life (Wiener et al., 1990). Basic activities of daily living (BADLs) include relatively simpler tasks such as eating, bathing, dressing, and toileting. Instrumental activities of daily living (IADLs) include more complex and higher-order cognitive processes required to function in daily life, such as managing medications and finances, driving, using the telephone, cooking, and exercising good judgment (Monaci & Morris, 2012). Because AD involves early neurodegeneration in the medial temporal lobe structures, the first clinical manifestations are typically difficulties with short-term memory, misplacing items, forgetting appointments, repeating oneself in conversations, and worsening ability to recall recent events

(Loewenstein, 2013). As AD progresses over time, impairments occur in multiple cognitive domains, and the individual loses their ability to independently perform IADLs (Loewenstein, 2013). Meanwhile, basic activities of daily living (BADLs) initially remain relatively intact unless they are negatively impacted by another medical condition.

As previously discussed, ADLs are one of the major differentiators between a diagnosis of MCI and a diagnosis of AD, as essentially intact ADLs are typically present among individuals with MCI while impaired ADLs are required to diagnose AD. Therefore, assessing for ADLs is extremely useful for making this differential diagnosis. Monaci and Morris (2012) also point out that the degree of cognitive impairment is associated with ADL performance, as there is a strong association between performance on neuropsychological testing and measures of ADLs, deterioration of ADLs can help to predict the risk of developing AD, and ADL scales are effective in screening for AD. Methods of determining an individual's ability to perform ADLs can include self-report measures or objective assessments. While self-report and caregiver-report questionnaires are easy to administer and may reasonably represent real-world performance, they are susceptible to reporter bias involving potential exaggeration or minimization of difficulties (Schmitter-Edgecombe et al., 2011). Although performance-based measures involve completing tasks that may not specifically occur within the patient's actual environment, and performance on these measures could fluctuate based on motivation, cognition, and behavior, Schmitter-Edgecombe et al. (2011) argue that

performance-based measures have the benefit of being objective, quantifiable, repeatable, and norm-referenced. Performance-based measures of functional status are typically in a paper and pencil form, where daily problem-solving and real-world situations are assessed, or they are behavioral simulation tasks where patients complete the daily tasks in a laboratory environment. The Texas Functional Living Scale (TFLS) is a behavioral simulation performance-based task that assesses functional status.

Texas Functional Living Scale (TFLS)

The TFLS is a 24-item comprehensive measure of adaptive functioning comprised of 4 subscales: Time, Money and Calculation, Communication, and Memory. It includes tasks involving reading and drawing hands on a clock, calculating monetary change, writing a check, addressing an envelope, reading a phone book, following instructions to set a microwave, and delayed recall of tasks. It is used as an objective measure of performance-based instrumental activities of daily living. The TFLS has good psychometric properties including reliability, internal consistency, and convergent and discriminant validity, as well as easy administration instructions and brief administration time (Cullum et al., 2001). Having an objective measure is important because patients who are impaired may not be aware of the deficits, and thus may be less likely to report having these types of difficulties during an interview or on a self-report questionnaire. Although caregivers are typically more accurate when providing information regarding the patient's level of functioning, their reports are still vulnerable to inaccuracies that

may cause them to over- or under-report the patient's abilities (Lowe et al., 2020). These potential inaccuracies are commonly related to caregiver burden, amount of time spent with the patient, patient's degree of cognitive impairment, and misconceptions about normal aging (Lowe et al., 2020).

Current Study

Due to the millions of people being negatively impacted by AD either directly or indirectly as a caregiver, the billions of dollars being spent on the disease, and the projection that the incidence rate will triple in the next 30 years (Alzheimer's Association, 2021), it is important to be able to quickly determine whether or not someone is experiencing normal age-related cognitive changes, a mild form of cognitive impairment such as MCI, or AD. Being that AD is a time-sensitive disease in that interventions are much more useful in the earliest stages, it would be quite beneficial to accurately determine what stage the patient is in (normal, MCI, or AD) in a rapid fashion so that interventions can be introduced sooner. It also would be more affordable to participate in a briefer assessment, such as 30 minutes of cognitive testing as compared to 2-3 hours. Additionally, differentiating between MCI and AD is critical for disease monitoring and making treatment decisions, but this is rarely addressed when using brief cognitive screeners (Jacova et al., 2007). The current study seeks to determine whether a cognitive screener combined with a measure of adaptive functioning is an effective method of obtaining information regarding global cognition and daily functioning toward making an accurate differential diagnosis. Specifically, it is hypothesized

that the MoCA and TFLS alone will be as effective in predicting whether someone is diagnosed as having cognition within normal limits, meeting criteria for MCI, or meeting criteria for AD, compared to the results of a ~2-hour neuropsychological evaluation.

The primary specific aim of this study is to assess whether the MoCA and the TFLS can be used in conjunction to differentiate cognition within normal limits, MCI, and AD. Specifically, it is hypothesized that performance on the MoCA and TFLS will be predictive of diagnostic outcome, such that those with MoCA scores of 26 or higher and TFLS total scores in the average range or higher (T = ≥45) will be more likely to have a diagnosis of cognition within normal limits (Hypothesis 1); those with MoCA scores of 19-25 and TFLS total scores in the low average range (T = 37-43) will be more likely to have a diagnosis of MCI (Hypothesis 2); and those with MoCA scores of 18 or less and TFLS total scores in the below average range or lower (T = ≤ 36) will be more likely to have AD (Hypothesis 3). Additionally, this study aims to determine which subcomponent(s) of the TFLS is the strongest predictor of the final diagnosis, and it is hypothesized that scores on the memory subtest will be most predictive of AD (Hypothesis 4).

Chapter 2: Methods

Participants

A total of 207 individuals ages 64-94 (*M = 79.5, SD* = 6.4) presented to the memory disorder clinic and were included in this study. Among these, 117 (56.5%) were female and 90 (43.5%) were male. Most of the patients were Caucasian (*N* =

188, 90.8%) and non-Hispanic (*N* = 196, 94.7%). The remaining participants self-identified as Black (*N* = 13, 6.3%), Asian (*N* = 1, 0.5%), Native American (*N* = 1, 0.5%), and Other (*N* = 4, 1.9%). Following the brief neuropsychological evaluation, the majority of this sample that presented to the memory disorder clinic was diagnosed with AD (*N* = 108, 52.2%). Of the 207 patients assessed, 34 (16.4%) were diagnosed with within normal limits, and 65 (31.4%) were diagnosed with MCI. All of the participant demographics and characteristics are presented in Table 1. Inclusion criteria was comprised of participant completion of a brief neuropsychological evaluation at the memory disorder, with inclusion of the Texas Functional Living Scale and the Montreal Cognitive Assessment.

Exclusion criteria involved the participants not fitting into the MoCA and TFLS cutoffs established by Hypothesis 1-3 and receiving a diagnosis other than WNL, MCI, or AD. Of the original 466 patients in the sample, 184 (39.5%) of them were excluded because they had a diagnosis other than WNL, MCI, or AD (e.g., mixed dementia, vascular dementia, frontotemporal dementia, anxiety/depression). This resulted in a sample of 282 patients who met diagnostic criteria for inclusion in this study. Then, applying MoCA and TFLS cutoffs for categorization of scores, a total of 75 patients (26.6%) were excluded because their scores on these two measures did not conform to the parameters outlined above. For example, if an individual had a score of 26 or higher on the MoCA, but a TFLS total score in the low average range, this would represent a mismatch of scores on these two measures, and therefore that individual would be excluded. Applying this

method by final diagnosis, 39 patients (26.5%) were excluded for this reason in the AD group, 31 patients (32.3%) were excluded in the MCI group, and 5 patients (12.8%) were excluded in the WNL group.

Measures

Screener

Montreal Cognitive Assessment (MoCA); Nasreddine (1995)

The Montreal Cognitive Assessment (MoCA) was developed in 1995 by Dr. Ziad Nasreddine, and it is a brief 30-item cognitive screener that is used to assess multiple cognitive domains, including visuospatial skills, naming, memory, attention, language, abstraction, delayed recall, and orientation. The MoCA has normative data for ages 55-85. This screener is currently used in over 200 countries, and it has multiple versions, including ones to accommodate for blindness (MoCA blind) and an education level of less than 5 years (MoCA Basic). If the patient has less than 12 years of education, an additional point is added to the total. The MoCA takes about 10 minutes to administer, and a score of 26 or above is considered within normal limits.

There are 5 possible points that can be achieved in the visuospatial domain: one point for a trail making test involving numbers and letters, 1 point for copying a geometric figure, and 3 points for a clock drawing task involving contour, number, and hands. There are three possible points that a patient can get in the naming domain, and they involve naming different animals. On a verbal list learning task, there are two trials of 5 words that are given as the learning/encoding

portion of a verbal memory task. No points are awarded for this section of the test. In the attention domain, there is one possible point for a 5-number digits forward task, one possible point can be awarded for a 3-number digits backward task, one possible point can be awarded for tapping task, and three possible points can be awarded a complex task involving mental math. In the language domain, there are two possible points for sentence repetition and one for verbal fluency. Two points can be obtained in the abstract reasoning domain. There are 5 possible points that can be earned in the delayed memory section (one for each word in the learning/encoding portion of the verbal memory task), and 6 possible points in the orientation section (date, month, year, day, place, city).

Adaptive Functioning

Texas Functional Living Scale (TFLS); Cullum, Saine, & Weiner (2009)

The Texas Functional Living Scale is a performance-based screening tool that assesses adaptive functioning and provides insight into the patient's ability to perform instrumental activities of daily living. The test can be administered to people ranging from age 16-90 years of age. It is comprised of four functional domains, including time (e.g., reading a clock, drawings hands on a clock, reading a calendar, etc.), money and calculation, communication (e.g., reading a phonebook, writing a check, etc.), and memory. The TFLS consists of 24 items, and it takes approximately 15 to 20 minutes to administer. The TFLS produces a composite score for each subscale in the form of percentile ranges, and the total

raw score is converted to a standardized T-score for the overall TFLS score. A T-score of 43 or above is considered within normal limits.

Brief Neuropsychological Evaluation

The brief neuropsychological evaluation (BNE) is a more comprehensive evaluation than the screening measures, and it takes about 2-3 hours to administer. It assesses multiple cognitive domains including learning and memory, language, attention, processing speed, executive functioning, visuospatial skills, and adaptive functioning. It includes the following tests: Brief Visuospatial Memory Test-Revised (BVMT-R) (Benedict, 1996), Shepherd Verbal Learning Test (Norheim et al., 2018), Western Aphasia Battery (WAB), Digit Span subtest of the Wechsler Adult Intelligence Scale, 4th Edition (WAIS-IV) (Wechsler, 2008), Clock Drawing Test (Salmon et al., 1992), Trail Making Test (TMT) A & B (Reitan, 1994), Stroop Color and Word Test (Golden, 1978), Modified Wisconsin Card Sorting Test (M-WCST) (Nelson, 1976), Controlled Oral Word Association Task (COWAT) (Benton, Hamsher, & Sivan, 1994), Category Fluency Test (Acevedo et al., 2000), Mack SF4 (Mack, 1992), Narrative Writing Sample of the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass & Kaplan, 1972), Geriatric Anxiety Inventory (GAI) (Pachana et al., 2007), and Geriatric Depression Scale (GDS) (Sheikh & Yesavage, 1986).

The Brief Visuospatial Memory Test-Revised is a paper-and-pencil test used to assess visual memory and visuospatial functioning. The Shepherd Verbal Learning Test is a verbal memory and list-learning task that includes 10 words and

5 consecutive learning trials, a delayed recall portion after a 5-minute delay, and a recognition trial. The WAB is used to evaluate language abilities such as expressive and receptive aphasia related to a neurological disorder, and the components used in the BNE are two measures of comprehension involving yes/no questions and simple commands, as well as a measure of basic repetition. The digit span subtest measures simple auditory attention, working memory, and mental manipulation. The Clock Drawing Test is a simple tool used to assess for signs of neurological problems, including dementia, and it measures visuospatial functioning, planning, and organization, and it can provide information regarding whether or not the individual is experiencing visual neglect. The Trail Making Test is a two-part visual-motor assessment that measures attention, visual scanning, processing speed, and number sequencing (Part A), as well as more complex aspects of executive functioning including set-shifting and cognitive flexibility (Part B). The Stroop Color and Word Test is a timed test of word reading, color naming, and cognitive flexibility.

The M-WCST is a modification of the original Wisconsin Card Sorting Test that uses 48 cards instead of the original 128, and it examines aspects of executive functioning including perseveration, ability to learn from feedback, abstract reasoning, and mental flexibility. The COWAT assesses phonemic fluency, and the category fluency test assesses semantic fluency. The Mack SF4 is a 15-item abbreviated version of the 60-item Boston Naming Test, and it consists of black and white line drawings of common objects and the goal is to provide the common

name for the object. The Narrative Writing Sample (Cookie Theft) of the BDAE is included to assess writing abilities. The GAI consists of 20 “agree/disagree” items that are designed to assess common anxiety symptoms in the geriatric population, and if the patient endorses 9 or more items, they are considered to be experiencing significant anxiety. The GDS consists of 30 “yes/no” items that assess for common depressive symptoms in a geriatric population, and if the patient endorses 10 or more items, they are considered to be experiencing notable depressive symptomatology.

Procedures

Participants were obtained from the clinical patient population at a community memory disorder clinic referred for a comprehensive evaluation. First, they participated in a clinical interview with the geriatrician and social worker. Then, they were administered a brief cognitive screener, the MoCA, with the social worker to assist in determining whether a more thorough evaluation of their cognitive functioning was warranted. If so, they were scheduled for a BNE, which was administered by a clinical psychology doctoral student under the supervision of a licensed and board-certified clinical neuropsychologist. On the day of the evaluation, the patient signed an informed consent to confirm that they agree to participate in the testing and have their test data used for research purposes. Once the informed consent is signed, the patient participated in the more comprehensive assessment that evaluates multiple domains of cognitive functioning. Total testing time took approximately 2-3 hours.

Once testing was complete, the doctoral student scored the testing and created a one-page summary sheet that included every score. On this sheet, the tests are organized by cognitive domain. An X was placed in either the "Impaired," "Mildly/Moderately Impaired," or "Within Normal Limits" range for each cognitive domain so that it was easily interpretable by other members of the medical team. Then, a multidisciplinary case review including the geriatrician, social worker, neurologist, neuropsychologist, pharmacy students, and clinical psychological doctoral students was held to review the medical history, level of functioning in terms of activities of daily living, test data, and neuroimaging. After discussing the holistic view of the patient, the members collaborated in order to develop diagnostic impressions and make recommendations based on the needs of the patient. Diagnostic impressions were based on the overall pattern of testing from the neuropsychological evaluation, brain imaging, and information collected during the initial visit with the provider or geriatrician and the social worker, which included the medical and psychosocial history, report of ADLs, onset of memory loss, and medication information.

The multidisciplinary team made their overall diagnoses using the Tenth Revision of the International Classification of Diseases and Related Health Problems (ICD-10) (WHO, 1992) diagnostic criteria. Possible diagnoses included AD, vascular dementia, dementia with Lewy bodies, frontotemporal dementia, dementia unspecified, mixed dementia, alcohol dependence with alcohol-induced persisting dementia, Parkinson's disease or dementia with Parkinsonism,

Huntington's disease, obstructive hydrocephalus, amnestic disorder, unspecified intracranial injury, cerebral infarction, MCI, unspecified neurocognitive disorder, progressive supranuclear palsy, corticobasal degeneration, aphasia, unspecified depressive disorder, unspecified anxiety disorder, adjustment disorder, and cognition within normal limits. Patients who were diagnosed with cognition within normal limits typically had average scores across cognitive domains on their neuropsychological evaluation, along with intact IADLs, and it was more likely that their neuroimaging was unremarkable. In terms of MCI, patients are diagnosed with amnestic type or non-amnestic type, as well as single domain or multiple domain. These patients had mild impairments in one or more cognitive domains, and their IADLs were intact. Diagnoses were made using all of the information presented at case review, as well as the Peterson criteria. AD diagnoses typically involved impaired IADLs, impaired cognitive domains on neuropsychological testing, and notable neuroimaging findings (e.g., enlarged temporal horns, temporal/parietal lobe atrophy).

Study Significance

The implications for this study are that the MoCA and TFLS alone would provide the same diagnosis as a 2 to 3-hour comprehensive evaluation in terms of whether an older adult has MCI, AD, or is within normal limits cognitively. This would allow for the ability to test more patients in a day, which is important considering the increasing prevalence rates of people with AD. This would also allow for quicker interventions, such as memory medications, and other

recommendations. This is especially important for people in the MCI stage that may be able to change something in their daily routine to decrease their modifiable risk factors and reduce the risk of developing AD. This would also reduce the risk of fatigue and low energy levels interfering with test results. Additionally, a shorter evaluation would be more affordable for the patient. Therefore, it would be very beneficial to know if we can get the same information in a shorter period of time, since time can be of the essence when it comes to these diagnoses.

Chapter 3: Results

Statistical Analysis

All statistical analyses were conducted using IBM SPSS version 25.0. A Chi-square test of independence was conducted to determine if the diagnostic results from the MoCA + TFLS were in agreement with the results from the 2-3 hour brief neuropsychological evaluation. Binary logistic regression was also conducted to determine if the screener diagnosis is predictive of the same diagnostic outcome as the longer battery. Individual binary logistic regressions were used to determine which subtest (Time, Money/Calculation, Communication, or Memory) of the TFLS was most predictive of a diagnosis of AD.

Hypothesis 1-3

One assumption for a chi-square test is that the two variables should be measured at an ordinal or nominal level, and both of these variables are nominal or ordinal. The second assumption is that the two variables should consist of two or more categorical, independent groups. Each variable consists of 3 independent

groups (WNL, MCI, AD). Therefore, a chi-square test of independence was performed to examine the level of agreement between the diagnosis determined by the MoCA + TFLS and the longer battery of testing (BNE). The comparison examined if MoCA scores of ≥26 and TFLS total scores of T ≥ 44 were suggestive of within normal limits as determined by the BNE, if MoCA scores of 19-25 and TFLS total scores of T=37-43 were suggestive of mild cognitive impairment as determined by the BNE, and if MoCA scores of ≤18 and TFLS total scores of ≤36 were suggestive of Alzheimer's disease as determined by the BNE. The relationship between these variables was statistically significant, X^2 (4, N = 207) = 193.06, p = <.001. The effect size for this finding (Cramer's V = .68), was large (Cohen, 1988), suggesting that there is a strong relationship between the two modes of testing. A cross-tabulation of diagnoses determined by the MoCA + TFLS and diagnoses determined by the BNE can be found in Table 2.

A binary logistic regression was performed to ascertain how well the combined screener score predicted the diagnostic outcome determined by the BNE. The statistical assumptions required to run this analysis were met. Assumption #1 for a binary logistic regression is that the dependent variable is measured on a dichotomous scale. Although there are three dependent variables (diagnoses of WNL, MCI, and AD), this assumption was met by running multiple binary logistic regressions and analyzing only two of the dependent variables at one time (e.g., WNL/MCI vs. AD, WNL/AD vs. MCI, and MCI/AD vs. WNL). Assumption #2 states that there is one or more independent variables that are either continuous or

categorical. Our screener diagnosis (MoCA + TFLS) is a categorical independent variable that meets this criterion. Assumption #3 includes the independence of observations, meaning that the dependent variable has mutually exclusive and exhaustive categories. This criterion is met because the outcome variable can only be placed in one category and not any other, and the probability of them happening is 100% because they are already predetermined by the BNE. Assumption #4 of a binary logistic regression states that there needs to be a linear relationship between any continuous independent variable and the logit transformation, or inverse, of the dependent variables. Continuous independent variables were not used in this analysis, so this assumption is met.

Hypothesis 1

When analyzing how well the MoCA + TFLS predicted the overall diagnosis for people that were cognition WNL versus everyone else (MCI and AD), the binary logistic regression model was statistically significant, $X^2(1) = 56.57$, $p = <.001$. The model explained 40.5% (Nagelkerke R^2) of the variance in the diagnostic groups and correctly classified 90.3% of cases. More specifically, 55.9% of cases that were observed to be a diagnosis of cognition WNL were also predicted by the model to be cognition WNL. Compared to cases who received a diagnosis of MCI or AD, cases that had a diagnosis of WNL had 43 times greater odds of having the same diagnosis on the MOCA + TFLS (OR = 42.56, 95% CI [13.92, 130.15]). Results of the Pearson correlation indicated that there was a significant moderate positive association between patients who were diagnosed as cognition

WNL based on the MoCA + TFLS and patients who were diagnosed as cognition WNL based on the BNE ($r(1) = .61$, $p < .001$).

Hypothesis 2

When determining how well the MoCA and TFLS combined differentiated between MCI and WNL/AD, the binary logistic regression model was statistically significant, $X^2(1) = 82.03$, $p = <.001$. The model explained 46.0% (Nagelkerke R^2) of the variance in the diagnostic groups and correctly classified 82.6% of cases. In terms of participants who were diagnosed as MCI, the model correctly predicted 81.5% of them. Overall, the model correctly classified 82.6% of cases. Based on the odds ratio, the odds of having a diagnosis of MCI as determined by the BNE are 21 times greater than chance with the MoCA + TFLS diagnosis (OR = 21.71, 95% CI [10.12, 46.67]). Results of the Pearson correlation indicated that there was a significant positive association between patients who were diagnosed as MCI based on the MoCA + TFLS and patients who were diagnosed as MCI based on the BNE ($r(1) = .62$, $p < .001$).

Hypothesis 3

A binary logistic regression was also performed to analyze how effectively the combined MoCA and TFLS score predicted the diagnostic outcome determined by the BNE when comparing WNL/MCI and AD. The logistic regression model was statistically significant, $X^2(1) = 155.43$, $p = .001$. The model explained 70.5% (Nagelkerke R^2) of the variance in the diagnostic groups and correctly classified 90.3% of cases. In terms of participants who were diagnosed as AD, 89.8% of them

were correctly predicted by the model. The odds ratio revealed that the odds of having a diagnosis of AD as determined by the BNE was 88 times greater if the MoCA + TFLS classified the patient as having AD (OR = 88.18, 95% CI [34.92, 222.71]). Results of the Pearson correlation indicated that there was a significant positive association between patients who performed poorly on the MoCA and TFLS and therefore, were diagnosed with AD and patients who were diagnosed with AD based on the BNE ($r(1) = .81$, $p < .001$).

Hypothesis 4

Lastly, four binary logistic regressions were performed to determine which subtest of the TFLS is the best predictor of a diagnosis of AD. The Time subtest explained 40.1% (Nagelkerke R^2) of the variance in the diagnostic groups and correctly classified 75.8% of cases and 67.6% of patients with AD as determined by the BNE. The Money subtest explained 44.3% (Nagelkerke R^2) of the variance in the diagnostic groups and correctly classified 75.4% of cases and 75% of patients who were diagnosed with AD. The Communication subtest explained 56.8% (Nagelkerke R^2) of the variance in the diagnostic groups and correctly classified 83.1% of patients overall and 80.6% of patients with AD. The Memory subtest explained 58.8% of the variance in the diagnostic groups and correctly classified 83.6% of patients overall and 87% of patients with AD. The Memory subtest explained the largest amount of variance. Results of the Pearson correlation indicated that there was a significant negative association between performance on all four subtests of the TFLS and patients who were diagnosed with AD as

determined by the BNE (Table 3). The Memory subtest had the strongest relationship with a diagnosis of AD ($r(1) = -.71$, $p < .001$).

Chapter 4: Discussion

With the rising prevalence rate of Alzheimer's disease and its neurodegenerative nature, it is highly beneficial to diagnose memory disorders in a quick fashion and introduce interventions earlier on. This is also important for individuals with mild cognitive impairment, as their cognitive functioning may be negatively impacted by modifiable factors and can therefore improve. As previously discussed, a major distinguishing factor between whether someone meets for criteria for MCI or AD is their ability to perform instrumental activities of daily living. Therefore, the present study aimed to determine if memory disorders could be diagnosed using a cognitive screener, the MoCA, and a measure of adaptive functioning, the TFLS, specifically when differentiating between cognition WNL, MCI, and AD.

The outcome of this study revealed that combining the MoCA and TFLS results in a statistically significant prediction of the diagnosis based on the BNE. Additionally, there was a statistically significant relationship between the diagnosis as determined by the MoCA + TFLS and the diagnosis as determined by the BNE. However, in terms of diagnoses of cognition WNL, the MoCA + TFLS combination correctly classified only 55.9% of cases, and the remaining cases were mainly misclassified as MCI. This is problematic because people would receive an inaccurate diagnosis. More specifically, there are cases of MCI that can progress to

dementia, and therefore, patients may believe that they have a neurodegenerative disease when they actually are functioning within normal limits with no signs of a neurodegenerative process. This can be extremely anxiety-provoking for the patient.

Similarly, this model improperly diagnosed one patient with AD. Had this model been the go-to diagnostic tool for this patient, it would have done them an inexcusable disservice by concluding that they have a neurodegenerative disease when the full battery of testing suggested that their cognition was within normal limits. Additionally, interventions may be introduced that are unnecessary, including cholinesterase inhibitors, that, like most medications, can cause a variety of side effects. Although there was a statistically significant relationship between the diagnoses of cognition WNL determined by the MoCA + TFLS and the diagnoses determined by the BNE, which technically supports hypothesis 1, the clinical interpretation of the results reveals that the combined MoCA + TFLS is not a good model for diagnosing cognition WNL because approximately half of the cases are misdiagnosed.

Hypothesis 2 was also supported by the data, as 81.5% of the patients diagnosed with MCI by the BNE were also diagnosed with MCI when using the MoCA + TFLS combination. The relationship between patients diagnosed with MCI according to the two diagnostic methods was also statistically significant. Clinically, approximately 20% of patients are still being misdiagnosed using the

model, with 6% being diagnosed as WNL and 8% being diagnosed with AD. Once again, this suggests that more information is needed for a more accurate diagnosis.

If someone is given a diagnosis of WNL when their full battery of testing suggests MCI, then they may not make any lifestyle changes, putting them at risk of having more severe impairments in their cognition. However, if someone is given an accurate diagnosis of MCI, then they may be motivated to improve their health and reduce the risk of their impairment progressing towards dementia. Similarly, if someone is diagnosed with AD when the full battery of tests suggest that they have MCI, they may not make any lifestyle changes under the assumption that it is too late because AD does not have reversible effects. As previously mentioned, this misdiagnosis can cause an extreme amount of unnecessary stress and result in interventions being introduced that are not needed.

When diagnosing AD, 89.8% of patients were correctly diagnosed using the MoCA + TFLS combination, and again, there was a statistically significant relationship between the diagnostic methods, which supports hypothesis 3. In the clinical context, this suggests that the model is most accurate in identifying AD. Using this model, 10% of people are still at risk of being improperly diagnosed. As a result, clinical history will be important for solidifying a diagnosis of AD. For example, if patients are having difficulty performing instrumental activities of daily living (e.g., managing finances, managing medications, and driving), and they are having significant problems with short-term memory, and the model suggests that they had AD, then a diagnosis of AD can be concluded without further testing. If

their IADLs are intact but the model suggests a diagnosis of AD, then more information is needed for an accurate diagnosis.

In terms of the subtest analysis, the Memory subtest of the TFLS was the strongest predictor of a diagnosis of AD, and this provides supporting evidence for hypothesis 4. However, it is also important to note that the Memory subtest was only marginally better than other subtests in its ability to predict AD, which was not expected being that people with AD have prominent memory deficits. The subtest that was the next strongest predictor was the Communication subtest. The Communication subtest includes many elements of IADLs, including writing a check, addressing an envelope, and following steps to set a microwave.

Because the Time and Money/Calculation subtests of the TFLS were found to be somewhat less predictive of AD compared to Memory and Communication, this suggests that aspects of IADLs measured by the Memory and Communication subtests of the TFLS may be more likely to become impaired first or relatively earlier in the course of AD. Current findings suggest that although individuals with AD may have difficulty across all aspects of IADLs measured by the TFLS, they frequently appear to have relatively better preserved skills in Time and Money/Calculation domains as compared to Memory and Communication domains. For example, the Time subtest includes 3 questions (out of 9 total points) that are related to reading a calendar and another 3-point question asking them to read a clock. Likewise, the Money/Calculation subtest includes some simple counting of American currency and more basic mental math problems. It is in the

more advanced stages of AD that poorer performance on these tasks is to be expected.

Impact of Study

Being that the MoCA + TFLS properly diagnosed almost 90% of patients with AD, it appears that this method serves as a useful tool when diagnosing this specific type of dementia. Chodosh et al. (2004) found that physicians are unaware of cognitive impairment in approximately 40% of their cognitively impaired patients, leaving these early interventions to be unimplemented. The MoCA + TFLS combination would help with this problem. The results of this study are important because they suggest that this memory evaluation can be administered in a shorter period of time, allowing for more patients to be seen in a day, patients to be evaluated more frequently, and cognitive impairment to be detected earlier.

The National Institute on Aging (2021) states that assessing cognitive impairment as an early stage can offer several benefits: if the outcome is negative, then the concerns of memory impairment can be alleviated; however, if there is concern for memory loss, next steps can be taken to identify the root cause of the impairment (e.g., medication side effects, metabolic imbalance, delirium, dementia, etc.), safety issues can be addressed, advanced directives can be put in place, caregivers can develop strategies to improve quality of life (if applicable), and compensatory strategies for memory can be utilized. In addition to earlier identification of AD, the MoCA + TFLS combination would also serve as a useful

tool for detecting memory impairment in the context of AD, and therefore, earlier implementation of these "next steps" can be established.

Considering that the MoCA + TFLS combination was not as accurate when differentiating between WNL and MCI, it is suggested that this method should primarily be used to identify whether someone has AD or not. Although the results of this study are significant, a major implication is that an accurate diagnosis cannot be made using only two neuropsychological tests in many scenarios. These results are suggestive that a full battery of tests is necessary to truly develop a holistic view of the patient and make an accurate diagnosis. Therefore, the MoCA and TFLS combination should still be treated like a screener in many cases.

For example, if a patient has a MoCA score ≤18 and a TFLS score of ≤36T, and the clinical history is suggestive of AD, then a diagnosis of AD can be inferred and will likely be correct the overwhelming majority of the time, suggesting that a more comprehensive evaluation may not be necessary. However, if either score falls above these cutoffs, further testing will likely be needed to clarify the diagnosis because these two instruments were not as accurate when differentiating between MCI and WNL. If the scores fall within these parameters, but the clinical history is not suggestive of AD, further assessment is still warranted for an accurate diagnosis. Additionally, being that approximately 1 in 4 patients were excluded from this study because they did not fit into the classification parameters for MoCA and TFLS scores defined above, the model will not always be applicable. This

demonstrates a notable limitation to using this model. This further emphasizes that this model is best utilized as a screener.

Limitations

There are notable limitations to this study. Because this study only included patients with dementia who were diagnosed with AD specifically, the ability of the MoCA and TFLS to differentiate other dementia subtypes is unknown. The MoCA + TFLS do not have a thorough enough pattern analysis to be able to make this distinction. It only the potential for diagnostic utility when determining if someone has AD or not, which means it is not generalizable to people that have MCI or the entire population of people with other memory disorders. Furthermore, it was not a good model when diagnosing WNL, as it only correctly diagnosed about half of these patients. Additionally, there are unequal sample sizes in each group, with 52% of the sample being diagnosed with AD, and 90% percent of the sample being Caucasian, making it not very diverse and less generalizable.

Another potential concern regarding the use of screeners for diagnostic purposes is that they might be administered and interpreted by individuals with limited training to do so. Test results need to be considered in the context of clinical information regarding the individual being evaluated, and other contributing factors to cognitive and functional impairment also often need to be ruled out before reaching a diagnostic conclusion. Being that it is still imperative that someone with knowledge and training in neuropsychology interpret neuropsychological results, these findings are not suggestive that this can be

bypassed. Furthermore, this faster mode of testing is only applicable in the context of AD, as other neurological injuries require a much more thorough approach. That being said, simply getting two low scores on both the MoCA and TFLS is not sufficient enough for a diagnosis of AD. The clinical history is needed, and it should be commensurate with a typical AD presentation in terms of symptom onset and progression, with the primary impairment in cognitive functioning being in the memory domain, as well as rule out of other potential contributing factors via blood work and brain scans. A neuropsychologist would be the most well-equipped to consider all of these factors and make a determination regarding whether further testing is warranted or if a diagnosis can be concluded.

Future Directions

Future directions for this study include having approximately equal groups for WNL, MCI, and AD, using a more diverse population, and trying to make the sample more generalizable overall. This would entail running a similar study with a larger sample size, as well as a more culturally diverse group. Despite a lack in a strong pattern analysis, determining how well this model would be useful in diagnosing other memory disorders besides AD would be another important area to explore being that 39.4% of the original sample was excluded because it did not fall into one of the examined categories. It would also be beneficial to further explore why 26.6% of the patients that were diagnosed with AD, MCI, or WNL did not fit into the diagnostic categories based on the MoCA and TFLS cutoffs. Additionally, future research should examine this topic from a more longitudinal perspective and

examine how well introducing interventions sooner promotes a better prognosis in the context of neurodegenerative treatment, as well as when is the impairment too significant to effectively introduce interventions.

Conclusion

With the rising prevalence rate of Alzheimer's disease and its neurodegenerative progression, it is beneficial to catch the diagnosis early on and introduce interventions sooner in an attempt to slow progression. Current procedures at most memory clinics involve patients neuropsychological testing battery being scheduled approximately 3-6-months to a year after their initial visit, and their feedback appointment is typically not scheduled for over a month after their testing session. Some clinics have wait lists for neuropsychological testing. Furthermore, the neuropsychological evaluation typically takes 2-3 hours to complete, which can be tiring for these elderly patients who are 65 years of age and older and often have medical comorbidities or physical limitations which may preclude participation in a lengthy cognitive assessment.

The MoCA and TFLS combined proved to be a relatively good predictor of diagnostic outcome when detecting AD. When using this model, patients can be tested in a shorter period of time using a battery consisting of two tests, allowing for more patients to be tested in a day. This would allow for patients to be seen sooner, receive a potential diagnosis earlier, introduce interventions faster, and hopefully have a better prognosis where disease progression can be slowed. This would likely remove the need for a wait list and decrease timeframes between the

initial visit and the testing, as well as the testing visit and the feedback session where recommendations are provided. When a disease is progressive, and therefore, time-sensitive, reducing these timeframes is imperative. Despite having no cure, this clinical information allows for neuropsychologists to better address the consequences of this disease and prolong quality of life as much as possible.

Although this model is useful when diagnosing AD, it is not as applicable when differentiating between WNL and MCI, as 41.2% of the WNL cases were misdiagnosed as MCI when using the MoCA + TFLS classification parameters. Similarly, 12% of patients with MCI were misdiagnosed as AD using this model and 6% of MCI patients were misdiagnosed as WNL. The findings suggest that this model is most appropriately used as a screener, and further testing can only be avoided if the model and clinical history are suggestive of AD. However, the major implication of this study is that when it comes to neuropsychological testing, breadth wins over brevity, as a full picture of cognitive functioning is required for accurate diagnosis.

Tables

Table 1

Distribution of Patient Demographics and Clinical Characteristics

Characteristic	Frequency (%)
Age (Mean+/-SD) (N= 207)	**79.5 +/- 6.45**
Years of Education (Mean+/-SD) (N= 207)	**14 +/- 2.61**
Gender (N=207)	
Female	**117 (56.5)**
Male	**90 (43.5)**
Race (N=207)	
Caucasian	**188 (90.8)**
Black	**13 (6.3)**
Asian	**1 (0.5)**
Native American	**1 (0.5)**
Other	**-**
No Response	**4 (1.9)**
Ethnicity (N = 207)	
Hispanic	**11 (5.3)**
Non-Hispanic	**196 (94.7)**
Caregiver (N = 207)	
No Caregiver	**152 (73.4)**
Caregiver	**55 (26.6)**
Caregiver's Gender (N = 55)	
Female	**31 (56.4)**
Male	**22 (40.0)**
Missing	**2 (3.6)**
Caregiver's Relationship (N = 55)	
Spouse	**27 (13)**
Child	**21 (10.1)**
Non-Relative	**5 (2.4)**
Sibling	**2 (1)**
BNE Diagnosis (N = 207)	
Within Normal Limit (WNL)	**34 (16.4)**
Mild Cognitive Impairment (MCI)	**65 (31.4)**
Alzheimer's Disease (AD)	**108 (52.2)**
MoCA Score (Mean +/- SD)	**18.8 +/- 4.99**
TFLS Score (Mean +/- SD)	**39.3 +/- 11.15**

Table 2

Crosstabulation of Diagnoses Determined by Screener and Diagnoses Determined by BNE

		Screener Diagnosis			Total
		WNL	MCI	AD	
BNE Diagnosis	WNL	19	14	1	34
	MCI	4	53	8	65
	AD	1	10	97	108
Total		24	77	106	207

Table 3

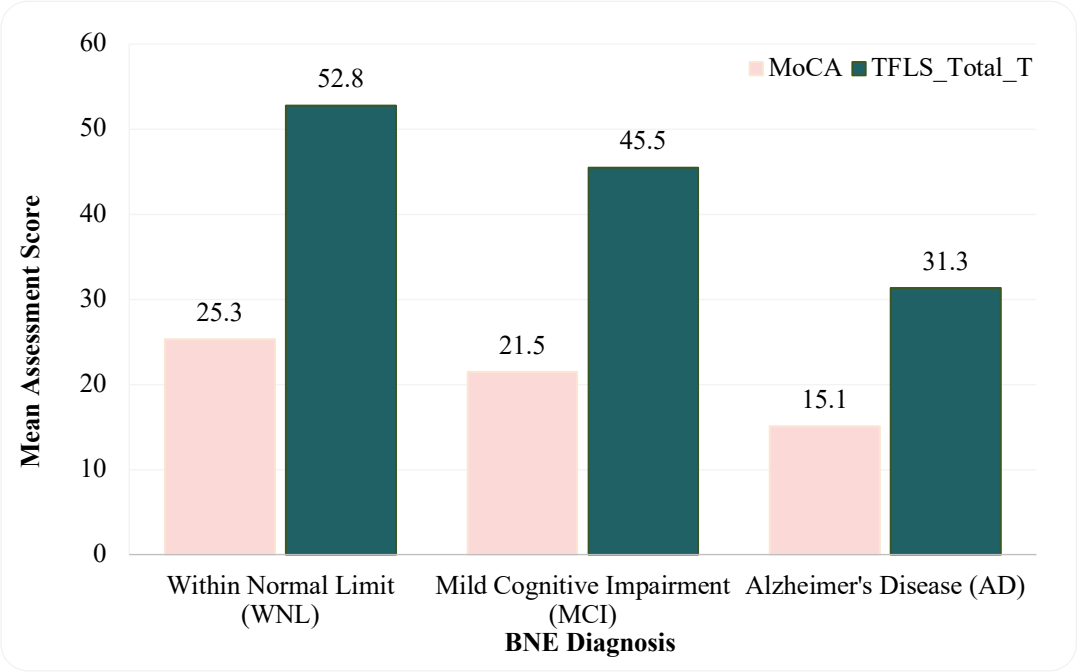
Correlations Between TFLS Subtests and AD Diagnosis Determined by BNE

Variables	1	2	3	4	5
1. AD Diagnosis	---				
2. Time	-.56**	---			
3. Money/Calculation	-.59**	.63**	---		
4. Communication	-.69**	.60**	.60**	---	
5. Memory	-.71**	.44**	.45**	.51**	---

**Correlation is significant at the 0.01 level (2-tailed).

Figures

Figure 1: Mean Scores of MoCA and TFLS for Each Diagnosis



References

Acevedo, A., Loewenstein, D. A., Barker, W. W., Harwood, D. G., Luis, C., Bravo, M., Hurwitz, D. A., Aguero, H., Greenfield, L., & Duara, R. (2000). Category fluency test: Normative data for English- and Spanish-speaking elderly. *Journal of the International Neuropsychological Society: JINS*, *6*(7), 760–769. https://doi.org/10.1017/s1355617700677032

Allain, P., Nicoleau, S., Pinon, K., Etcharry-Bouyx, F., Barré, J., Berrut, G., Dubas, F., & Gall, D. L. (2005). Executive functioning in normal aging: A study of action planning using the Zoo Map Test. *Brain and Cognition*, *57*(1), 4–7. https://doi.org/10.1016/j.bandc.2004.08.011

Arvanitakis, Z., Shah, R. C., & Bennett, D. A. (2019). Diagnosis and management of dementia: Review. *JAMA*, *322*(16), 1589–1599. https://doi.org/10.1001/jama.2019.4782

Barr, W. B. (2001). Methodologic Issues in Neuropsychological Testing. *Journal of Athletic Training*, *36*(3), 297–302.

Bennett, T. L. (2001). Neuropsychological evaluation in rehabilitation planning and evaluation of functional skills. *Archives of Clinical Neuropsychology*, *16*(2001), 237-253.

Benton, A. L. (1994). Neuropsychological assessment. *Annual Review of Psychology*, *45*, 1–23. http://dx.doi.org.portal.lib.fit.edu/10.1146/annurev.ps.45.020194.000245

Bishop, C. L., Temple, R. O., Tremont, G., Westervelt, H. J., & Stern, R. A. (2003). Utility of the neuropsychological evaluation in an acute medical hospital. *The Clinical Neuropsychologist*, *17*(4), 468–473. https://doi.org/10.1076/clin.17.4.468.27944

Braun, M., Tupper, D., Kaufmann, P., McCrea, M., Postal, K., Westerveld, M., Wills, K., & Deer, T. (2011). Neuropsychological assessment: A valuable tool in the diagnosis and management of neurological, neurodevelopmental, medical, and psychiatric disorders. *Cognitive and Behavioral Neurology: Official Journal of the Society for Behavioral and Cognitive Neurology*, *24*(3), 107–114. https://doi.org/10.1097/WNN.0b013e3182351289

Cacho, J., Benito-León, J., García-García, R., Fernández-Calvo, B., Vicente-Villardón, J. L., & Mitchell, A. J. (2010). Does the combination of the MMSE and Clock Drawing Test (Mini-Clock) improve the detection of mild Alzheimer's Disease and Mild Cognitive Impairment? *Journal of Alzheimer's Disease*, *22*(3), 889–896. https://doi.org/10.3233/JAD-2010-101182

Chodosh, J., Petitti, D. B., Elliott, M., Hays, R. D., Crooks, V. C., Reuben, D. B., Galen Buckwalter, J., & Wenger, N. (2004). Physician recognition of cognitive impairment: Evaluating the need for improvement. *Journal of the American Geriatrics Society*, *52*(7), 1051–1059. https://doi.org/10.1111/j.1532-5415.2004.52301.x

Cohen, R. A., Marsiske, M. M., & Smith, G. E. (2019). Chapter 10—Neuropsychology of aging. In S. T. Dekosky & S. Asthana (Eds.), *Handbook of Clinical Neurology* (Vol. 167, pp. 149–180). Elsevier. https://doi.org/10.1016/B978-0-12-804766-8.00010-8

Davis, D. H., Creavin, S. T., Yip, J. L., Noel-Storr, A. H., Brayne, C., & Cullum, S. (2015). Montreal Cognitive Assessment for the diagnosis of Alzheimer's disease and other dementias. *Cochrane Database of Systematic Reviews*, *10*(2015), 1-49. https://doi.org/10.1002/14651858.CD010775.pub2

Denny, A., Bartley, K., Edwards, S., Webbe, F., & LoGalbo, A. (2021). AD8 patient–informant discrepancy predicts insight and cognitive impairment in Alzheimer's disease. *Geriatric Nursing*, *42*(1), 262–267. https://doi.org/10.1016/j.gerinurse.2020.08.009

Driscoll, I., Davatzikos, C., An, Y., Wu, X., Shen, D., Kraut, M., & Resnick, S. M. (2009). Longitudinal pattern of regional brain volume change differentiates normal aging from MCI. *Neurology*, *72*(22), 1906–1913. https://doi.org/10.1212/WNL.0b013e3181a82634

Duong, S., Patel, T., & Chang, F. (2017). Dementia. *Canadian Pharmacists Journal : CPJ*, *150*(2), 118–129. https://doi.org/10.1177/1715163517690745

Edwards, G. A., Gamez, N., Escobedo, G., Calderon, O., & Moreno-Gonzalez, I. (2019). Modifiable risk factors for Alzheimer's disease. *Frontiers in Aging Neuroscience*, *11*. http://dx.doi.org.portal.lib.fit.edu/10.3389/fnagi.2019.00146

Esteban-Santillan, C., Praditsuwan, R., Veda, H., & Geldmacher, D. S. (1998). Clock Drawing Test in Very Mild Alzheimer's Disease. *Journal of the American Geriatrics Society*, *46*(10), 1266–1269. https://doi.org/10.1111/j.1532-5415.1998.tb04543.x

Etienne, V., Marin-Lamellet, C., & Laurent, B. (2008). Évolution du contrôle exécutif au cours du vieillissement normal. *Revue Neurologique*, *164*(12), 1010–1017. https://doi.org/10.1016/j.neurol.2008.03.021

Freitas, S., Simões, M. R., Alves, L., & Santana, I. (2013). Montreal Cognitive Assessment: Validation Study for Mild Cognitive Impairment and Alzheimer Disease. *Alzheimer Disease & Associated Disorders*, *27*(1), 37–43. https://doi.org/10.1097/WAD.0b013e3182420bfe

Gao, Q., Gwee, X., Feng, L., Nyunt, M. S. Z., Feng, L., Collinson, S. L., Chong, M. S., Lim, W. S., Lee, T.-S., Yap, P., Yap, K. B., & Ng, T. P. (2018). Mild Cognitive Impairment Reversion and Progression: Rates and Predictors in Community-Living Older Persons in the Singapore Longitudinal Ageing Studies Cohort. *Dementia and Geriatric Cognitive Disorders EXTRA*, *8*(2), 226–237. https://doi.org/10.1159/000488936

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., Belleville, S., Brodaty, H., Bennett, D., Chertkow, H., Cummings, J. L., de Leon, M., Feldman, H., Ganguli, M., Hampel, H., Scheltens, P., Tierney, M. C., Whitehouse, P., & Winblad, B. (2006). Mild cognitive impairment. *The Lancet*, *367*(9518), 1262–1270. https://doi.org/10.1016/S0140-6736(06)68542-5

Glisky, E. L. (2007). Changes in Cognitive Function in Human Aging. In D. R. Riddle (Ed.), *Brain Aging: Models, Methods, and Mechanisms*. CRC Press/Taylor & Francis. http://www.ncbi.nlm.nih.gov/books/NBK3885/

Guerreiro, R., & Bras, J. (2015). The age factor in Alzheimer's disease. *Genome Medicine*, *7*. https://doi.org/10.1186/s13073-015-0232-5

Gunning, F. M., & Brickman, A. M. (2010). Structural brain changes associated with normal aging. In H. J. [Ed Aizenstein, C. F. Reynolds, & M. [Ed Fernandes (Eds.), *Neuroimaging research in geriatric mental health* (pp. 101–124, Chapter xiii, 263 Pages). Springer Publishing Company (New York, NY, US). http://search.proquest.com/psycinfo/docview/742978985/CC4EAF89330647B5PQ/2

Gunning-Dixon, F. M., & Raz, N. (2000). The cognitive correlates of white matter abnormalities in normal aging: A quantitative review. *Neuropsychology*, *14*(2), 224–232. http://dx.doi.org.portal.lib.fit.edu/10.1037/0894-4105.14.2.224

Harada, C. N., Natelson Love, M. C., & Triebel, K. (2013). Normal Cognitive Aging. *Clinics in Geriatric Medicine*, *29*(4), 737–752. https://doi.org/10.1016/j.cger.2013.07.002

Harper, L., Bouwman, F., Burton, E. J., Barkhof, F., Scheltens, P., O'Brien, J. T., Fox, N. C., Ridgway, G. R., & Schott, J. M. (2017). Patterns of atrophy in pathologically confirmed dementias: A voxelwise analysis. *Journal of Neurology, Neurosurgery & Psychiatry*, *88*(11), 908–916. https://doi.org/10.1136/jnnp-2016-314978

Hartlage, L. C. (2001). Neuropsychological testing of adults: Further considerations for neurologists. *Archives of Clinical Neuropsychology*, *16*(3), 201–213. https://doi.org/10.1016/S0887-6177(00)00079-2

Harvey, P. D. (2012). Clinical applications of neuropsychological assessment. *Dialogues in Clinical Neuroscience*, *14*(1), 91–99.

He, Y. L., Zhang, X. K., & Zhang, M. Y. (2000). Psychosocial risk factors for Alzheimer's disease. *Hong Kong Journal of Psychiatry*, *10*(2), 2–7.

Iverson, G. L., Brooks, B. L., Collins, M. W., & Lovell, M. R. (2006). Tracking neuropsychological recovery following concussion in sport. *Brain Injury*, *20*(3), 245–252. https://doi.org/10.1080/02699050500487910

Jacova, C., Kertesz, A., Blair, M., Fisk, J.D., & Feldman, H.H. (2007). Neuropsychological testing and assessment for dementia. *Alzheimer's & Dementia 3*(4), 299-317. https://doi.org/10.1016/j.jalz.2007.07.011

Julayanont, P., & Nasreddine, Z. S. (2017). Montreal Cognitive Assessment (MoCA): Concept and Clinical Review. In A. J. Larner (Ed.), *Cognitive Screening Instruments: A Practical Approach* (pp. 139–195). Springer International Publishing. https://doi.org/10.1007/978-3-319-44775-9_7

Knight, R. G. (2013). *The Neuropsychology of Degenerative Brain Diseases*. Psychology Press.

Kocalevent, R.-D., Hinz, A., & Brähler, E. (2013). Standardization of the depression screener Patient Health Questionnaire (PHQ-9) in the general population. *General Hospital Psychiatry*, *35*(5), 551–555. https://doi.org/10.1016/j.genhosppsych.2013.04.006

Koepsell, T. D., & Monsell, S. E. (2012). Reversion from mild cognitive impairment to normal or near-normal cognition. *Neurology*, *79*(15), 1591–1598. https://doi.org/10.1212/WNL.0b013e31826e26b7

LaRue, A. (2013). *Aging and Neuropsychological Assessment*. Springer Science & Business Media.

Luo, L., & Craik, F. I. M. (2008). Aging and memory: A cognitive approach. *The Canadian Journal of Psychiatry / La Revue Canadienne de Psychiatrie*, *53*(6), 346–353.

Mayeux, R., & Stern, Y. (2012). Epidemiology of Alzheimer Disease. *Cold Spring Harbor Perspectives in Medicine*, *2*(8), a006239–a006239. https://doi.org/10.1101/cshperspect.a006239

McCoy, K. J. M. (2015). Clinical Neuropsychology: A Pocket Handbook for Assessment, 3rd edition, edited by Michael W. Parsons and Thomas A. Hammeke. *Archives of Clinical Neuropsychology*, *30*(4), 356–357. https://doi.org/10.1093/arclin/acv023

Monaci, L., & Morris, R. G. (2012). Neuropsychological screening performance and the association with activities of daily living and instrumental activities of daily living in dementia: Baseline and 18- to 24-month follow-up. *International Journal of Geriatric Psychiatry*, *27*(2), 197–204. https://doi.org/10.1002/gps.2709

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Nguyen, C. M., Copeland, C. T., Lowe, D. A., Heyanka, D. J., & Linck, J. F. (2020). Contribution of executive functioning to instrumental activities of daily living in older adults. *Applied Neuropsychology: Adult*, *27*(4), 326–333. https://doi.org/10.1080/23279095.2018.1550408

Pandya, S. Y., Lacritz, L. H., Weiner, M. F., Deschner, M., & Woon, F. L. (2017). Predictors of Reversion from Mild Cognitive Impairment to Normal Cognition. *Dement Geriatr Cogn Disord*, 11.

Park, D. C., & Festini, S. B. (2017). Theories of Memory and Aging: A Look at the Past and a Glimpse of the Future. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *72*(1), 82–90. https://doi.org/10.1093/geronb/gbw066

Perlmutter, M. (1978). What is memory aging the aging of? *Developmental Psychology*, *14*(4), 330–345. http://dx.doi.org.portal.lib.fit.edu/10.1037/0012-1649.14.4.330

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild Cognitive Impairment: Clinical Characterization and Outcome. *Archives of Neurology*, *56*(3), 303–308. https://doi.org/10.1001/archneur.56.3.303

Petersen, R., & Negash, S. (2008). Petersen RC, Negash S. Mild cognitive impairment: An overview. CNS Spectr 13: 45-53. *CNS Spectrums*, *13*, 45–53. https://doi.org/10.1017/S1092852900016151

Phillips, L. H., & Henry, J. D. (2008). Adult aging and executive functioning. In V. [Ed Anderson, R. [Ed Jacobs, & P. J. [Ed Anderson (Eds.), *Executive functions and the frontal lobes: A lifespan perspective* (pp. 57–79, Chapter xxxiii, 541 Pages). Taylor & Francis (Philadelphia, PA, US). http://search.proquest.com/psycinfo/docview/621801128/7415B6B99DB54E79PQ/1

Ravdin, L. D., & Katzen, H. L. (Eds.). (2013). *Handbook on the Neuropsychology of Aging and Dementia*. Springer New York. https://doi.org/10.1007/978-1-4614-3106-0

Reitan, R. M., & Wolfson, D. (2008). Can Neuropsychological Testing Produce Unequivocal Evidence of Brain Damage? I. Testing for Specific Deficits. *Applied Neuropsychology*, *15*(1), 33–38. https://doi.org/10.1080/09084280801917350

Ritter, A., Hawley, N., Banks, S. J., & Miller, J. B. (n.d.). The Association between Montreal Cognitive Assessment Memory Scores and Hippocampal Volume in a Neurodegenerative Disease Sample. *Journal of Alzheimer's Disease*, *58*(3), 695–699. https://doi.org/10.3233/JAD-161241

Roebuck-Spencer, T. M., Glen, T., Puente, A. E., Denney, R. L., Ruff, R. M., Hostetter, G., & Bianchini, K. J. (2017). Cognitive Screening Tests Versus Comprehensive Neuropsychological Test Batteries: A National Academy of Neuropsychology Education Paper†. *Archives of Clinical Neuropsychology*, *32*(4), 491–498. https://doi.org/10.1093/arclin/acx021

Rog, L. A., & Fink, J. W. (2013). Mild Cognitive Impairment and Normal Aging. In L. D. Ravdin & H. L. Katzen (Eds.), *Handbook on the Neuropsychology of Aging and Dementia* (pp. 239–256). Springer. https://doi.org/10.1007/978-1-4614-3106-0_16

Rosenberg, G. (2013). Reversion from mild cognitive impairment to normal or near-normal cognition: Risk factors and prognosis. *Neurology*, *80*(19), 1818–1818. https://doi.org/10.1212/WNL.0b013e31829430ba

Sachdev, P. S., Link to external site, this link will open in a new window, Lipnicki, D. M., Crawford, J., Reppermund, S., Kochan, N. A., Trollor, J. N., Link to external site, this link will open in a new window, Wen, W., Draper, B., Slavin, M. J., Kang, K., Lux, O., Mather, K. A., Brodaty, H., & Team, A. S. (2013). Factors predicting reversion from mild cognitive impairment to normal cognitive functioning: A population-based study. *PLoS ONE*, *8*(3). http://dx.doi.org.portal.lib.fit.edu/10.1371/journal.pone.0059649

Salmon, D. P., & Bondi, M. W. (2009). Neuropsychological Assessment of Dementia. *Annual Review of Psychology*, *60*, 257–282. https://doi.org/10.1146/annurev.psych.57.102904.190024

Sattler, J. M., & Ryan, J. J. (2009). *Assessment with the WAIS-IV*. Jerome M Sattler Publisher.

Schmitter-Edgecombe, M., Parsey, C., & Cook, D. J. (2011). Cognitive Correlates of Functional Performance in Older Adults: Comparison of Self-Report, Direct Observation, and Performance-Based Measures. *Journal of the International Neuropsychological Society*, *17*(05), 853–864. https://doi.org/10.1017/S1355617711000865

Schoenberg, M. R., & Scott, J. G. (Eds.). (2011). *The Little Black Book of Neuropsychology: A Syndrome-Based Approach*. Springer US. https://doi.org/10.1007/978-0-387-76978-3

Sharoar, M. G., Hu, X., Ma, X.-M., Zhu, X., & Yan, R. (2019). Sequential formation of different layers of dystrophic neurites in Alzheimer's brains. *Molecular Psychiatry*, *24*(9), 1369–1382. https://doi.org/10.1038/s41380-019-0396-2

Smith, T., Gildeh, N., & Holmes, C. (2007). The Montreal Cognitive Assessment: Validity and Utility in a Memory Clinic Setting. *The Canadian Journal of Psychiatry*, *52*(5), 329–332. https://doi.org/10.1177/070674370705200508

Solfrizzi, V., Panza, F., Frisardi, V., Seripa, D., Logroscino, G., Imbimbo, B. P., & Pilotto, A. (2011). Diet and Alzheimer's disease risk factors or prevention: The current evidence. *Expert Review of Neurotherapeutics*, *11*(5), 677–708. http://dx.doi.org.portal.lib.fit.edu/10.1586/ern.11.56

Staub, B., Doignon-Camus, N., Després, O., & Bonnefond, A. (2013). Sustained attention in the elderly: What do we know and what does it tell us about cognitive aging? *Ageing Research Reviews*, *12*(2), 459–468. https://doi.org/10.1016/j.arr.2012.12.001

Stephan, B. C. M. (n.d.). The neuropathological profile of mild cognitive impairment (MCI): A systematic review. *Molecular Psychiatry*, 21.

Streit, W. J., Mrak, R. E., & Griffin, W. S. T. (2004). [No title found]. *Journal of Neuroinflammation*, *1*(1), 14. https://doi.org/10.1186/1742-2094-1-14

Sugarman, M. A., Alosco, M. L., Tripodis, Y., Steinberg, E. G., & Stern, R. A. (2018). Neuropsychiatric Symptoms and the Diagnostic Stability of Mild Cognitive Impairment. *Journal of Alzheimer's Disease*, *62*(4), 1841–1855. https://doi.org/10.3233/JAD-170527

Tuokko, H., & Hadjistavropoulos, T. (2014). *An Assessment Guide To Geriatric Neuropsychology*. Psychology Press.

van Kan, G. A., Rolland, Y., Nourhashémi, F., Coley, N., Link to external site, this link will open in a new window, Andrieu, S., & Vellas, B. (2009). Cardiovascular disease risk factors and progression of Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *27*(3), 240–246. http://dx.doi.org.portal.lib.fit.edu/10.1159/000203365

Wang, L., Zhang, Z., McArdle, J. J., & Salthouse, T. A. (2008). Investigating Ceiling Effects in Longitudinal Data Analysis. *Multivariate Behavioral Research*, *43*(3), 476–496. https://doi.org/10.1080/00273170802285941

Welsh-Bohmer, K. A., & Attix, D. K. (2005). *Geriatric Neuropsychology: Assessment and Intervention*. Guilford Publications. http://ebookcentral.proquest.com/lib/fit/detail.action?docID=330557

White, R. F., Campbell, R., Echeverria, D., Knox, S. S., & Janulewicz, P. (2009). Assessment of neuropsychological trajectories in longitudinal population-based studies of children. *Journal of Epidemiology and Community Health*, *63*(Suppl_1), i15–i26. https://doi.org/10.1136/jech.2007.071530

Wu, K., Taki, Y., Sato, K., Qi, H., Kawashima, R., & Fukuda, H. (2013). A longitudinal study of structural brain network changes with normal aging. *Frontiers in Human Neuroscience*, *7*. http://dx.doi.org.portal.lib.fit.edu/10.3389/fnhum.2013.00113

Zarit, S. H., & Talley, R. C. (Eds.). (2013). *Caregiving for Alzheimer's Disease and Related Disorders*. Springer New York. https://doi.org/10.1007/978-1-4614-5335-2

Zimmerman, M. E., & Brickman, A. M. (2009). Neuropsychology of Healthy Aging. In K. T. Tashima, V. Valcour, N. C. Sacktor, & R. H. Paul (Eds.), *HIV and the Brain: New Challenges in the Modern Era* (pp. 347–367). Humana Press. https://doi.org/10.1007/978-1-59745-434-6_17