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Predicting Cognitive Decline in Older Adults

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Predicting Cognitive Decline in Older Adults

by:

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Each person whose signature appears below certifies that this dissertation in his/her opinion is adequate, in scope and quality, as a dissertation for the degree Doctor of Philosophy.

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I dedicate this dissertation to my three wonderful grandmothers, Florence Grace Jones, Eleanor Marie Farace and Alta Mae Picket, two of which developed dementia in their later life. It is my hope that this research will ultimately serve as an aid in early detection of memory disorders, permitting an opportunity for early intervention.

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ABSTRACT OF THE DISSERTATION

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The investigator sought to determine which neuropsychological tests are more likely to predict an individual's cognitive decline (i.e., normal to mild cognitive impairment, mild cognitive impairment to Alzheimer's disease) two years prior to conversion. A sample of non-decliners (N=109) compared to those who declined (N=24) in cognitive status (i.e., mild cognitive impairment or Alzheimer's disease) with a mean age of 61.44 (*SD*=11.29) was examined. Results indicate the Rey-Osterrieth Complex Figure Test, Retention Trial (RCFT Retention; *OR*=0.93, *p*=0.005) is a significant predictor of conversion to MCI and the Buschke Delay (*OR*=0.54, *p*=0.017) is a significant predictor of conversion to AD. Due to group sample size difference, additional analyses were conducted utilizing a subsample of demographically matched non-decliners. Results indicate the RCFT Retention is a significant predictor of conversion to MCI (OR=0.94, p=0.019) and AD (OR=0.90, p=0.048) and Buschke Delay (OR=0.68, p=0.027) is a significant predictor of conversion to AD. Given the results of this dissertation, it may be important for clinicians/researchers to monitor these measures for the purpose of predicting cognitive decline.

CHAPTER ONE

REVIEW OF THE LITERATURE

Alzheimer's Disease

According to the National Institute on Aging (2011), Alzheimer's disease is "a progressive, degenerative disorder that attacks the brain's nerve cells, or neurons, resulting in loss of memory, thinking and language skills, and behavioral changes." It was estimated that approximately 5.4 million Americans of all ages will have Alzheimer's disease in 2012. This figure includes 5.2 million people age 65 and older (Hebert, Scherr, Bienias, Bennett, & Evans, 2003), and 200,000 individuals under age 65 who have younger onset Alzheimer's disease (Alzheimer's Association, 2006). Most people in the United States living with Alzheimer's disease and other dementias are non-Hispanic whites; however, older African-Americans and Hispanics are proportionately more likely than older whites to have Alzheimer's disease and other dementias (Dilworth-Anderson, Hendrie, Manly, Khachaturian, & Fazio, 2008; Manly & Mayeux, 2004). Data specify that in the United States, older African-Americans are probably about twice as likely to have Alzheimer's disease and other dementias as older whites, (Potter et al., 2009) and Hispanics are about one and one-half times as likely to have Alzheimer's disease and other dementias as older whites (Gurland et al., 1999).

Risk Factors

Researchers have identified specific factors which place one at risk for developing Alzheimer's disease. The Alzheimer's Association (2012) reported that the greatest risk factor for Alzheimer's disease is advancing age, reporting that most people with

Alzheimer's disease are diagnosed at age 65 or older. Braak, Braak, Bhol & Reintjes (1996) studied 2,222 brains upon autopsy and found that neurofibrillary pathology (the hallmark of Alzheimer's disease) multiplies with age. The Alzheimer's Association (2012) reported that family history of Alzheimer's disease also places one at risk. The Multi-Institutional Research in Alzheimer Genetic Epidemiology project support this notion; 1,694 patients who met criteria for probable or definite Alzheimer's disease were examined, and it was found that lifetime risk of Alzheimer's disease in first-degree relatives was 39% by age 96 years. Furthermore, it was found that by age 80, children of conjugal Alzheimer's disease couples had a cumulative risk of 54%, 1.5 times greater than the sum of the risks to children having affected mothers or fathers, and nearly 5 times greater than the risk to children having unaffected parents (Lautenschlager et al. 1996). Individuals with the e4 form of the gene apolipoprotein E (APOE) are also at increased risk of developing Alzheimer's disease (Alzheimer's Association, 2012). APOE-e4 is one of three common forms (e2, e3 and e4) of the APOE gene, which provides the blueprint for a protein that carries cholesterol in the bloodstream. While everyone inherits one form of the APOE gene from each parent, research has found that individuals who inherit APOE –e4 are at increased risk of AD by a factor of 2.84 for each additional APOE-e4 allele (Corder et al., 1993). Hence, subjects with two APOE -e4 genes were more than eight times as likely to be affected as subjects with e2 or e3 genotypes. It was also found that with each additional APOE-e4 allele shifted onset of Alzheimer's to a younger age; mean onset was 84.3 years in subjects who did not have APOE-e4, 75.5 years in subjects with one APOE-e4, and 68.4 years in subjects with two APOE-e4 alleles. (Corder et al., 1993). The National Institute on Aging reported that

APOE -e4 is present in about 25 to 30 percent of the population and in about 40 percent of all people with late-onset Alzheimer's.

Research also indicates chronic depression as a risk factor for the development of Alzheimer's disease (Andersen, Lolk, Kragh-Sorensen, Petersen, & Green, 2006; Geerlings et al., 2000; Speck et al., 1995; Steenland et al., 2012). More specifically, Steenland et al. (2012) studied over 5,000 subjects at 30 different Alzheimer's disease centers and found that having depression throughout the six years of the study was a significant risk for developing MCI (for those who were initially cognitively intact) or Alzheimer's disease (for those who initially had MCI) compared to those that did not have depression. Geerlings et al, (2000) examined two independent samples of older people with normal cognition from the community-based Amsterdam Study of the Elderly and the Longitudinal Aging Study Amsterdam and found that those with severe depressive symptoms had 5.31 times the risk of developing Alzheimer's disease, but only in subjects with higher levels of education. They concluded that in a subgroup of more highly educated elderly people, depression may be an early manifestation of Alzheimer's disease before cognitive symptoms become apparent as cognitive symptoms may not initially manifest themselves due to the impact of cognitive reserve (e.g., higher education).

Healthcare Costs

Not only is Alzheimer's disease prevalent, it is potentially deadly and its healthcare costs are climbing. Alzheimer's disease is the sixth leading cause of death in the United States. Based on 2008 final data from the National Center for Health Statistics,

Alzheimer's disease was reported as the underlying cause of death for 82,435 people. (Miniño A, 2011). However, death certificates for individuals with Alzheimer's disease often list acute conditions as the primary cause of death rather than Alzheimer's disease (Macera, Sun, Yeager, & Brandes, 1992; Olichney, Hofstetter, Galasko, Thal, & Katzman, 1995; Wachterman, Kiely, & Mitchell, 2008). Thus, Alzheimer's disease is likely a contributing cause of death for even more Americans than indicated by government data. Aggregate payments for health care, long-term care and hospice for people with Alzheimer's disease and other dementias are projected to increase from $200 billion in 2012 to $1.1 trillion in 2050 (in 2012 dollars). Medicare and Medicaid cover about 70 percent of the costs of care (Alzheimer's Association, 2010).

Neurological Profile of AD

The National Institute of Neurological Disorders and Stroke (2012) indicates that Alzheimer's disease includes three major components of the disease process: 1) amyloid plaques, 2) neurofibrillary tangles, and 3) loss of connections between neurons responsible for memory and learning. Amyloid plaques are fragments of a protein called beta-amyloid peptide mixed with a collection of additional proteins, remnants of neurons, and bits and pieces of other nerve cells. Neurofibrillary tangles are formed by hyperphosphorylation of a microtubule-associated protein known as tau, causing it to aggregate, or group, in an insoluble form. This aggregated, insoluble tau protein (tau tangles) are found inside neurons, and cause dysfunction within neurons and ultimately lead to neuronal death. The loss of connections between neurons responsible for memory

and learning cause neuronal death; as neurons die throughout the brain, the affected regions begin to shrink.

The gradual process of brain deterioration due to these amyloid plaques and neurofibrillary tangles begins in a few limbic areas of the cortex and then spreads in a predictable, nonrandom manner across the hippocampus and neocortex. According to researchers, this sequence of changes shows little individual variation and thus provides the basis for distinguishing six stages in the development of neurofibrillary tangles (Braak & Braak, 1991). Braak & Braak (1991) determined six stages characterizing the progression and location of tau tangles in the brain. Braak stage one is the point at which tau protein starts to gather into tau tangles. The tau tangles have begun to form in the transitional entorhinal region in the medial temporal lobe. This is a "relay station" between the cortex and the hippocampus, which is critical for memory. There are no external symptoms at this stage; however, from this point, further decline is inevitable. By Braak stage two, tau tangles have accumulated further and have caused some neurons to die. At this stage, the tau tangles are much more extensive in the transitional entorhinal region and have begun to kill neurons here. In the hippocampus and neocortex, tau protein is also beginning to aggregate at this stage, but has not yet formed tangles. Cognitive testing at this stage would show minimal impairment. Tangles at this level or worse are found in the brains of about 60% of individuals over the age of 65. By Braak stage 3, the tau tangles have begun to cause extensive neuronal death. The tau protein has formed extensive tangles in the transitional entorhinal region, has also aggregated and begun to form tangles in the hippocampus, and is beginning to aggregate in the neocortex. At this stage, tau tangles and neuronal death have likely caused some memory

impairment, but only about 10% of patients at this stage will be diagnosed as suffering from dementia. Approximately 45% of individuals who are 80 years old have reached this stage. By Braak stage 4, the tau tangles have formed extensively in the transitional entorhinal region and the hippocampus where they have caused neuronal death, and they are starting to form in the neocortex. The neocortex is the largest part of the brain, and is involved in higher functions such as sensory perception, conscious thought and language. Even though the tau tangles still occupy only a small portion of the brain, they have caused significant memory and cognitive impairment. Seventy-percent of patients with this level of tangles in their brain will be diagnosed as suffering from dementia. At Braak stage 5, the tau tangles have caused extensive neuronal death, giving rise to severe memory and cognitive impairment. Tangles have expansively formed in the transitional entorhinal region, the hippocampus, and the neocortex. Approximately 80% of patients with this level of tangles will be diagnosed as suffering from moderate to severe dementia. By Braak stage 6, tau tangles have formed extensively in the transitional entorhinal region, the hippocampus, and the neocortex. The tau tangles have caused extensive neuronal death. All patients with this many tangles in their brain will be diagnosed as suffering from severe dementia. These individuals will be completely unable to take care of themselves and will have trouble recognizing family members. In sum, tau protein tangles initially begin to accumulate in the entorhinal region ("relay station" between the hippocampus and neocortex), the tangles then spread to the hippocampus (memory center) and neocortex (responsible for higher functions such as sensory perception, conscious thought and language).

Although the advancement of Alzheimer's disease initiates via brain deterioration in a few limbic areas of the cortex and then spreads in a predictable, nonrandom manner across the hippocampus and neocortex in men and women, women are disproportionally affected (Thies & Bleiler, 2013). The prevalence of AD is significantly higher in women compared to men. Recent estimates suggest that almost two-thirds of the individuals diagnosed with AD are women (Hebert et al., 2003). A reason for the higher prevalence among women may be that they live longer, on average, than men (Plassman et al., 2007; Seshadri et al., 1997). In contrast to these studies, the Cache County Study, did report a higher incidence of AD in men than women until age (van Amelsvoort, Compton, & Murphy, 2001), after which women had a higher incidence than men (Miech et al., 2002). Similarly, the Mayo Clinic Study of Aging recently reported that the rate of progression from MCI to AD was similar in men and women aged (Cosgrove, Mazure, & Staley, 2007; Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997; Good et al., 2001; Gur, Gunning-Dixon, Turetsky, Bilker, & Gur, 2002; Luders, Gaser, Narr, & Toga, 2009; Pfefferbaum et al., 2013; van Amelsvoort et al., 2001; Witte, Savli, Holik, Kasper, & Lanzenberger, 2010), but higher in women than men after age 80 (Roberts et al., 2014). However, in patients with AD, brain volumes have been found to decline faster in women than men (Skup et al., 2011).

In the context of cerebral metabolic deficits associated with cognitive impairment in dementia, two studies have shown that men have more pronounced cerebral metabolic deficits compared to women at the same level of cognitive impairment, suggesting that the greater brain reserve in men may be helping them withstand more pathology than women at the same level of dementia severity (Perneczky, Diehl-Schmid, Forstl,

Drzezga, & Kurz, 2007; Perneczky, Drzezga, Diehl-Schmid, Li, & Kurz, 2007). Furthermore, three studies reported women with one ε4 allele had about a four-fold risk of AD, whereas men with one ε4 allele showed little increased risk (Bretsky et al., 1999; Farrer et al., 1997; Payami et al., 1996). The *APOE* ε4 allele also has a greater deleterious effect on hippocampal pathology, functional connectivity changes in the default mode network, cortical thickness, and memory performance in women compared with men at different stages of AD (Damoiseaux et al., 2012; Fleisher et al., 2005; Liu et al., 2010). Additionally, a large autopsy study found that amyloid plaque and neurofibrillary tangle pathology was greatest among women who were ε4 carriers (Corder et al., 2004).

Neuropsychological Profile of AD

The neuropsychological profile of Alzheimer's disease typically includes decline in memory, language and semantic knowledge, working memory, attention, and visual spatial abilities, ultimately impacting all aspects of cognitive functioning.

Evidence has demonstrated that patients with Alzheimer's disease have impairments in episodic memory. These impairments have been displayed with various cognitive procedures, such as free recall, recognition, and paired-associate learning (Salmon, 2000). It is hypothesized that these deficits are primarily due to dysfunction in the consolidation or storage of new information. One such study found that recall after a 10-minute delay on a list learning task accurately classified 90% of early Alzheimer's disease participants (Welsh, Butters, Hughes, Mohs, & Heyman, 1991). Furthermore, empirical evidence has implicated factors that may be contributing to impairments in consolidation. For example, several studies demonstrated that those with Alzheimer's

disease have a heightened susceptibility to interference, likely due to decreased inhibitory process (Bayles & Tomoeda, 1983; Delis et al., 1991; Fuld, Katzman, Davies, & Terry, 1982; D. Jacobs, Salmon, Troster, & Butters, 1990).

A second impairment commonly seen in those with Alzheimer's disease is within the cognitive domain of language. Specifically, studies have shown that those with Alzheimer's disease show reduced performances on tests of object naming (Bowles, Obler, & Albert, 1987; Hodges, Salmon, & Butters, 1991; Martin & Fedio, 1983), verbal fluency (Butters, Granholm, Salmon, Grant, & Wolfe, 1987; Martin & Fedio, 1983; Monsch et al., 1992), and semantic categorization (Aronoff et al., 2006). This may be due to the deterioration of components that support language such as the structure and content of semantic memory. As the dementia process progresses neurologically to include the temporal, frontal, and parietal cortices, knowledge for specific information and ideas and the relationships between them may be interrupted (Hodges & Patterson, 1995). Several studies have demonstrated impairment of semantic memory through examining fluency, confrontation naming, sorting, word-to-picture matching, and definition generation. Evidence for a deterioration of semantic memory in Alzheimer's disease comes from several studies that assessed knowledge of particular concepts across different modes of access and output (e.g., fluency, confrontation naming, sorting, word-to-picture matching, and definition generation). Because deficits have been observed across varying modalities of language tests, it has been hypothesized that loss of knowledge regarding the presented information is the contributing factor rather than an inability to retrieve such information (Chertkow & Bub, 1990; Hodges, Salmon, & Butters, 1992). These researchers found that those with Alzheimer's disease were impaired on all tasks of

semantic memory; furthermore, answers were consistent across tests, such that when a specific item was incorrectly or correctly answered on one task, it was likely to be answered in the consistently in other tasks that assessed the same information in a different way. In sum, researchers have concluded that the information within these tests is no longer existent among those with Alzheimer's disease—rather than merely inaccessible.

Executive functioning, working memory, and attention are also reduced in those with Alzheimer's disease, which is commonly attributed to neurofibrillary tangle burden in the prefrontal cortex. Evidence suggests that those with Alzheimer's disease have reduced functioning on problem solving tests that require mental manipulation (Bondi, 1993; Grady et al., 1988; Lange, Sahakian, Quinn, Marsden, & Robbins, 1995; Waltz et al., 2004). Reduced mental manipulation performance may also be conveyed on working memory tasks (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991; Collette, Van der Linden, Bechet, & Salmon, 1999). Furthermore, those with Alzheimer's disease frequently have reduced performance on complex attention tasks that rely on the appropriate use of attentional resources or that require adequate shifting of attention (Parasuraman R., 1993; Perry & Hodges, 1999). In sum, the working memory and attentional impairments observed in those with Alzheimer's disease are secondary to the executive deficits.

Morrison and colleagues (1991) have proposed that visuoperceptual deficits in those with Alzheimer's disease may be related to deteriorated association between distinct and intact cortical information process systems (Morrison, Hof, & Bouras, 1991). Additional research has supported this notion; studies have shown that those with

Alzheimer's disease have reduced performance on a visual search task where they were required to quickly identify targets on the basis of the combination of two or more features that are processed in different cortical regions (e.g., color and shape). Those with Alzheimer's disease have greater response times compared to controls than when required to identify targets solely on the basis of a single feature (Foster, Behrmann, & Stuss, 1999; Treisman, 1996). Subsequent studies showed that this deficit in "feature-binding" (Foster et al., 1999; Treisman, 1996) could not be attributed to the different attentional demands inherent in conjunction versus single-feature visual search tasks (Tales et al., 2002). In sum, research suggests that the visuoperceptual deficits observed in those with Alzheimer's disease is related to problems with information processing between cortical regions rather than deficits within the region itself.

Although neuropsychological profiles of men and women are similar, it is important to note that consistent cross-sectional difference at all ages is that women perform better on verbal memory tasks and men perform better on visuospatial tasks (Proust-Lima et al., 2008; van Hooren et al., 2007).

Mild Cognitive Impairment

It is evident that Alzheimer's disease is prevalent, deadly, and costly. Neurocognitively, there are changes that healthcare professionals may identify early in the disease process to initiate intervention opportunities—the question is, how early on is this possible? The literature is saturated with data regarding Mild Cognitive Impairment (MCI); oftentimes classifying it as the pre-dementia stage. Mild Cognitive Impairment is a distinct classification that falls between healthy aging and dementia (Petersen et al.,

1999). The literature in the field defines MCI as having a memory complaint, normal activities of daily living (ADLs), normal general cognitive functioning, abnormal memory for age, and absence of dementia (Petersen et al., 1999; Tierney et al., 1996). Petersen and colleagues (1999) found that memory function distinguishes those who are aging normally from those who have MCI; while the other cognitive domains are comparable. They also found that when compared to those with mild Alzheimer's disease, those with MCI were similar with regards to memory function, but those with mild Alzheimer's disease were more impaired in other cognitive domains. Criteria and guidelines for diagnosis of Alzheimer's disease, published in 2011, suggest that in some cases MCI is actually an early stage of Alzheimer's (Albert et al., 2011; Jack et al., 2011; McKhann et al., 2011; Sperling et al., 2011). In sum, MCI is a distinct classification of cognitive impairment and those who develop MCI with primarily amnestic features are more likely to develop Alzheimer's disease. It is estimated that approximately 10-15% of individuals diagnosed with MCI convert to AD every year (e.g., Levey et al., 2006).

Studies indicate that as many as 10 to 20 percent of people age 65 and older experience MCI (Hanninen, Hallikainen, Tuomainen, Vanhanen, & Soininen, 2002; Lopez et al., 2003; Roberts et al., 2008). As mentioned above, further cognitive decline is more likely among individuals whose MCI involves amnestic features than in those whose MCI does not involve amnestic features. Over one year, most individuals with MCI who are identified through community sampling remain cognitively stable, while some, primarily those without memory problems, experience an improvement in cognition or revert to normal cognitive status (Ganguli et al., 2011). However, nearly one third of all people who report MCI symptoms will develop Alzheimer's disease in three

or four years (Petersen et al., 1999). Therefore, it is important that people experiencing cognitive decline are identified by their healthcare practitioner to implement early intervention and facilitate reversion to normal cognitive status or, at the minimum, halt the progression of cognitive decline. It is important to note that this early identification is also critical for researchers in the field. It is critical to study those who develop Alzheimer's disease at the earliest stages to better understand the progression, thus facilitating the development of treatment. Studies have found that early intervention (at the Mild Cognitive Impairment stage), a healthy diet (e.g., increased fish, omega-3 supplements) and participating in cognitively stimulating activities (reading, writing, crossword puzzles, board or card games, group discussions or playing music) may delay the progression to dementia (Blasko et al., 2012; Cheng et al., 2013; Lee et al., 2013; Miller et al., 2012; Roberts et al., 2008; Roberts et al., 2012; Wenisch et al., 2007).

Assessment of Conversion to MCI and Alzheimer's Disease

According to the American Health Assistance Foundation, at the present time, an autopsy is needed in order to definitely diagnose Alzheimer's disease. However, while a person is alive, physicians can correctly diagnose Alzheimer's disease about 90 percent of the time based collectively on neuroimaging, neuropsychological tests, laboratory tests, and symptoms reported. However, as stated previously, it is important to detect those who may develop Alzheimer's disease before the disease process has more fully actualized. With regards to neuroimaging, recent studies have shown that PET scans using specific tracers (FDDNP and C-PIB) have been successful in the early classification of cognitive decline. More specifically, these tracers have the ability to

accurately classify those who are aging normally, have mild cognitive impairment, and dementia of the Alzheimer's type (Bateman et al., 2012; Ercoli et al., 2012; Klunk et al., 2004; Small et al., 2006; Small et al., 2012; Wolk et al., 2012). While these findings are hopeful, it is unclear as to when such techniques will be used on clinical, rather than research, populations and how accessible and feasible such scans will be for patients at the early stages of cognitive decline.

Of particular importance to the neuropsychologist are neuropsychological measures, specifically with regards to their effectiveness in detecting cognitive decline. When assessing for changes in cognitive functioning early on, neuropsychological batteries have been shown to detect such changes. However, neuropsychological batteries can be costly and time-consuming for the patient and thus it may not be efficient in providing such testing as a "screener" for early signs of cognitive decline. Certain "screeners" have been used in order to determine whether one has dementia (e.g., Mini Mental Status Exam, Montreal Cognitive Assessment). One study examined whether the Montreal Cognitive Assessment (MoCA) and Mini Mental Status Exam (MMSE) could detect MCI. The results indicated that the MMSE had a sensitivity of 18% to detect MCI, whereas the MoCA detected 90% of MCI subjects (Levey, Lah, Goldstein, Steenland, & Bliwise, 2006). Thus, these results suggest that the MoCA is a more sensitive measure for detecting MCI as compared to the MMSE. Another study has found similar results (Q. H. Guo et al., 2010). However, the ability of either of these tests to detect the earliest signs of cognitive decline (those present prior to MCI) and those found specifically among those who may develop Alzheimer's disease is not yet known.

There may be specific neuropsychological tests that have the ability to accurately classify patients who will convert from normal aging to amnestic mild cognitive impairment or from amnestic mild cognitive impairment to dementia of the Alzheimer's type. Researchers have determined that several different neuropsychological tests have the ability to predict such conversion. For example, verbal memory of lists of words such as the California Verbal Learning Test (Albert, Moss, Tanzi, & Jones, 2001; Beck, Gagneux-Zurbriggen, Berres, Taylor, & Monsch, 2012; Rabin et al., 2009; Silva et al., 2012), Auditory Verbal Learning Test (Landau et al., 2010), Rey Auditory Verbal Learning Test (Tierney, Yao, Kiss, & McDowell, 2005), Neurological Assessment Battery List Learning Test (Gavett et al., 2010), and the Buschke Selective Reminding Task (Devanand et al., 2008; Grober, Lipton, Hall, & Crystal, 2000; Masur, Sliwinski, Lipton, Blau, & Crystal, 1994; Sarazin et al., 2007; Tabert et al., 2006); verbal memory of word pairs such as the Semantic Object Retrieval Test (Kraut et al., 2007) and Wechsler Memory Scale's Verbal Paired Associates (Venneri et al., 2011); verbal memory of short stories with Wechsler Memory Scale's Logical Memory (Rabin et al., 2009), verbal long-term memory with the Wechsler's Adult Intelligence Scale's Information (Tierney et al., 2005), and verbal memory when cued with the RI-48 Test (Hanseeuw & Ivanoiu, 2011); visual memory such as the immediate recall of the figures from Wechsler Memory Scales (Albert et al., 2001) and the Rey-Osterrieth Complex Figure Test (Alladi, Arnold, Mitchell, Nestor, & Hodges, 2006; Borroni et al., 2006; Guo, Zhao, Chen, Ding, & Hong, 2009) ; executive functioning tests such as Trails B (Albert et al., 2001; Chen et al., 2000; Dickerson, Sperling, Hyman, Albert, & Blacker, 2007; Ewers et al., 2012; Zhou, Nakatani, Teramukai, Nagai, & Fukushima, 2012), digit symbol

(Tabert et al., 2006), Stroop Color Naming (Balota et al., 2010), and digit span (Kurt, Yener, & Oguz, 2011); and language tests such as Animals verbal fluency (Bennett et al., 2002; Lonie et al., 2009) and the Boston Naming Test (D. M. Jacobs et al., 1995; Kraut et al., 2007) . Based on these findings, there are deficits evident in three main cognitive domains that seem to predict conversion to dementia of the Alzheimer's type: verbal and visuospatial *memory*, *executive function* and *language*, with most of the research focusing on verbal memory of lists and contextual information.

Verbal Memory

Between the tests that have been developed to assess verbal learning, the Selective Reminding Test (SRT; Buschke, 1973) is the only measure that provides a distinctive form of feedback (Ruff, Light, & Quayhagen, 1989). On each subsequent trial after the first presentation of the entire list, which usually consists of 12 unrelated words, only the words that were not previously recalled are presented by the examiner. However, the subject must still attempt to recall the entire word list, with the learning criterion of SRT being the recall of all 12 words for two consecutive trials or the completion of 12 trials in case of unattainable performance. After the learning trials, cued recall, and multiple recognition trials, a 30-min delayed free recall trial is administered. Due to the multiple-trial list-learning procedure with selective reminders and the separate scores derived, the SRT allows the differentiation of retention, storage, and retrieval information (Lezak, Hokvieson, & Loring, 2004), as well as the simultaneous assessment of several components of memory and learning (Spreen & Strauss, 1998). Scores include Total Recall, Long-term Storage, Long-term Recall, Short-term Recall, Consistent Long-term

Recall, Random Long-term Recall, words given by the examiner the next recall attempt (Reminders), words that are not in the word list presented (Intrusions), as well as Cued Recall, Multiple-choice Recall, and Delayed Recall.

Given that selective reminding is a procedure, not a specific test, many versions have been developed since its introduction by Buschke (1973), varying, for example, the number of trials [12-trial or six-trial version (Larrabee, Trahan, Curtiss, & Levin, 1988; Larrabee, Trahan, & Levin, 2000), or mode of administration (oral or visual presentation of word list; Masur, Fuld, Blau, Thal, Levin, & Aronson, 1989). Moreover, the Selective Reminding Test has been used in different cultural environments (for example, Hebrew Selective Reminding Test by Gigi, Schnaider-Beeri, Davidson, & Prohovnik, 1999, and Spanish Selective Reminding Test by Campo & Morales, 2004). Age and sex-related influences on Selective Reminding Test performance have been found, while differences attributed to level of education are generally unclear. Increasing age is associated with a decline of performance. Females generally outperform males. Despite the inconsistencies reported, more highly educated subjects tend to show better performance (Spreen & Strauss,1998; Lezak, et al., 2004).

There are few known studies that utilize the Buschke Selective Reminding Test to predict conversion to Alzheimer's disease (e.g., Devanand et al., 2008; Tabert et al., 2006); however, the results are promising. Specifically, Tabert et al. examined 148 patients who complained of memory problems (who were compared to 63-matched controls), the percent savings from immediate to delayed recall on the Selective Reminding Test and the Wechsler Adult Intelligence Scale–Revised Digit Symbol Test were the strongest predictors of time to conversion. The combined predictive accuracy of

these 2 measures for conversion by three years was 86%. Furthermore, in the three-year follow-up patient sample (33/126 converters), Devanand et al. (2008), found that the Pfeffer Functional Activities Questionnaire (FAQ; informant report of functioning), University of Pennsylvania Smell Identification Test (UPSIT; olfactory identification), Selective Reminding Test (SRT) immediate recall (verbal memory), MRI hippocampal volume, and MRI entorhinal cortex volume combined, demonstrated 90% specificity and 85.2% sensitivity, and the three clinical predictors (SRT immediate recall, FAQ, and UPSIT) showed 81.3% sensitivity. More research is needed in order to better understand its ability to determine those who will develop Alzheimer's disease. This test is of particular interest because in addition to measuring verbal memory, it also involves working memory and executive functioning. The words within the list are not easily categorized and thus, it requires the examinee to create categorization.

Visual Spatial Memory

The Rey Complex Figure Test, RCFT (Meyers, Bayless, & Meyers, 1996) Osterrieth, 1945; Rey, 1941), measures visuospatial and visuoconstructional abilities, perceptual organization and planning (executive functioning), and visual memory. The patient is presented a stimulus card containing a complex figure which is composed of basic shapes and elements. He or she is asked to copy this drawing as precisely as possible on a blank sheet of paper. Without prior warning, the patient is then asked to draw the figure again from memory after a three-minute delay and again after a 30-minute delay (Immediate Recall and Delayed Recall).

Alladi et al. studied 124 patients with memory deficit who were non-demented by using the RCFT Complex Figure Test, and found that the MCI discrimination rate of delayed recall was 72%. Furthermore, Guo and colleagues (2009) found that the RCFT Complex Figure Test also predicted conversion from MCI to Alzheimer's disease among a sample of Chinese patients; however, they found that the RCFT accurately classified only 27% of patients and found that a list learning task was better at predicting conversion among this population. Although few studies have examined the RCFT Complex Figure Test as a predictor of conversion to Alzheimer's disease, the results suggest it may in fact be adequate in doing so. The Rey Complex Figure Test is of particular interest because, like the SRT, it likely measures executive functioning; the test requires the patient to recall the complex figure by drawing it, this involves organizing and planning in addition to visuospatial memory.

Executive

Measures of cognitive flexibility are recognized as effective tools for assessing executive dysfunction among those with Alzheimer's disease, along with other brain degenerative disorders. As mentioned previously, there are verbal and visual memory tasks that may require some executive abilities. One common tool utilized specifically to measure executive functioning is the Trail Making Test B (TMT-B). The Trail Making Test was originally designed as part of the Army Individual Test Battery (1944) and is now included in several general and specific-purpose neuropsychological test batteries (Reitan, 1994). The TMT-B involves drawing a line, connecting alternating numbers and letters in sequence (i.e., 1-A-2-B and so on). The time to complete the 'trail' is recorded.

The Trail Making Test B has been shown to be a powerful predictor of conversion to Alzheimer's disease. For instance, Chapman et al. (2010) examined individuals with MCI who later converted to Alzheimer's disease; the Trail Making Test B was the second most effective predictor of conversion, second to a memory test. Furthermore, Rozzini et al. (2007) examined 119 subjects who met criteria for MCI-amnestic only and found that the Trail Making Test B predicted conversion to Alzheimer's disease even better than memory tests (Rozzini et al., 2007).

Language

Tests of verbal fluency are widely used to assess cognitive functioning and are viewed as sensitive measure of language dysfunction in Alzheimer's disease. Depending on the type of fluency task, participants are asked to retrieve words that start with a specific letter (e.g., FAS: phonemic fluency) or words that belong to a semantic category (e.g., animals, clothing), typically, over a one minute period. It has long been known that naming is impaired at an early stage in Alzheimer's disease (Bayles, Tomoeda, & Trosset, 1990; Martin & Fedio, 1983); however, this is true also of phonemic fluency (Adlam, Bozeat, Arnold, Watson, & Hodges, 2006) and impaired semantic fluency has been viewed as a sign of early semantic degradation in pre-symptomatic Alzheimer's disease patients (Chen et al., 2001) and those with Mild Cognitive Impairment (Adlam et al., 2006). Indeed, Adlam et al. (2006) recently reported that semantic fluency was the only test of semantic functioning that significantly differentiated individuals with Mild Cognitive Impairment from healthy controls. A major finding in the Alzheimer's disease literature has been the documentation of a differentially greater semantic than phonemic

fluency impairment (Henry et al., 2004). It has been widely argued that semantic fluency is disproportionately impaired in Alzheimer's disease, while phonemic fluency is usually less impaired (Crossley, D'Arcy, & Rawson, 1997; Martin & Fedio, 1983; Monsch et al., 1992; Salmon, Heindel, & Lange, 1999) or even intact (Butters et al., 1987). The relatively greater impairment of semantic over phonemic fluency in Alzheimer's disease has been used to differentiate AD from other dementias such as fronto-temporal dementia (Rascovsky, Salmon, Hansen, Thal, & Galasko, 2007).

Boston Naming Test (BNT) introduced in 1983 by Drs. Edith Kaplan, Harold Goodglass, and Sandra Weintraub, is a widely used neuropsychological assessment tool to measure confrontational word retrieval (a type of semantic fluency) in individuals with aphasia or other language disturbance caused by stroke, Alzheimer's disease, or other dementia disorders. The BNT contains 60 line drawings graded in difficulty from "bed" (easy, high frequency) to "abacus" (difficult, low frequency) that the patient must name. Like other semantic based tests (e.g., Animals), the patient must produce words; however, with the BNT the patient must produce the exact word, rather than having a choice of words within a category. With regards to conversion to Alzheimer's disease, the BNT may have particular predictive ability due to its assessment of long-term memory. Research has found that the BNT is an effective predictor of conversion to Alzheimer's disease (Howieson et al., 2003; Kraut et al., 2007); however, the studies are few.

Because the Buschke Selective Reminding Test, RCFT Complex Figure Test, Trail Making Test B, semantic fluency (i.e. Animals), the Boston Naming Test and their associated cognitive domains (verbal memory, visuospatial memory, executive

functioning, and language) have individually demonstrated the ability to predict conversion to Alzheimer's disease, the current study seeks to investigate the ability of these tests together, to predict conversion from normal aging to MCI and MCI to Alzheimer's disease.

Aims & Hypotheses

Aim 1: To determine what neuropsychological measures best predict conversion from normal aging to Mild Cognitive Impairment and Mild Cognitive Impairment to probable Alzheimer's disease among older adults.

- Hypothesis 1.1: Individually, the Buschke Selective Reminding Test (Total), Rey-Osterrieth Complex Figure Test (Delay), Boston Naming Test, Trail Making Test B, and Animals verbal fluency test will predict conversion from normal aging to MCI.
- Hypothesis 1.2: Based on the outcome of 1.1, a multivariate model will be developed in which the significant tests together will predict conversion from normal aging to MCI.
- Hypothesis 1.3: Individually, the Buschke Selective Reminding Test (Total), Rey-Osterrieth Complex Figure Test (Delay), Boston Naming Test, Trail Making Test B, and Animals verbal fluency test will predict conversion from MCI to AD.
- Hypothesis 1.4: Based on the outcome of 2.1, a multivariate model will be developed in which the significant tests together will predict conversion from MCI to AD.

Aim 2: To determine whether depression predicts conversion to a more severe cognitive disorder (MCI or AD).

- Hypothesis 2.1: Incidence of depression as measured by the Hamilton Depression Scale at time of testing will predict conversion from normal aging to MCI.
- Hypothesis 2.2: Incidence of depression as measured by the Hamilton Depression Scale at time of testing will predict conversion from normal aging to AD.

CHAPTER TWO

METHODS AND PROCEDURES

Participants

The present study examined data from a convenience sample of 130 individuals, based on the availability of follow-up neuropsychological data. This convenience sample was drawn from a larger longitudinal study of mild age-related memory loss designed to determine neuropsychological, neuroimaging, and genetic predictors of subsequent cognitive decline. DNA was obtained from blood samples, and APOE genotypes were determined with the use of standard techniques. Investigators blind to the genetic findings performed all of the clinical procedures. Written informed consent was obtained in accordance with the procedures set by the UCLA Institutional Review Board.

Recruitment

Participants from the larger study were recruited through advertisements and physician referral that emphasized middle-aged and older people with memory complaints and family histories of dementia.

Inclusion/Exclusion

Any subjects with a neurological, medical, or psychiatric condition that could affect memory or other cognitive processing were excluded. Subjects with major depression at baseline were excluded. Standardized laboratory screening tests for a dementia evaluation and magnetic resonance imaging (MRI) scans were performed to uncover potentially treatable causes of mental impairment. To eliminate people with

conditions that could reduce memory performance, those with neurological and medical disorders or major depressive disorder were excluded from participation. The participants were also excluded if they scored less than 25 on the Mini-Mental Status Exam, which represented the criteria used for participants to be 'asymptomatic.' These methods of exclusion were based on a review of medical history, laboratory tests, and a psychiatric interview and evaluation.

Instrumentation

Verbal Memory

Buschke Selective Reminding Test

The Buschke Selective Reminding Test (SRT) measures verbal learning and memory using a multiple-trial list-learning paradigm. The SRT involves reading to the subject a list of words and then having the subject recall as many of these words as possible. Each subsequent learning trial involves the selective presentation of only those items that were not recalled on the immediately preceding trial. The SRT distinguishes between short-term and long-term components of memory by measuring recall of items that were not presented on a given trial. The rate at which subjects learn can also be evaluated. Alternate forms reliability among those with Alzheimer's disease is good (.92); however, in other populations is variable (.48-.85).

Visual Memory

Rey-Osterrieth Complex Figure Test

The Rey-Osterrieth Complex Figure Test (RCFT) assesses visual-spatial

constructional ability and visual memory. It also permits assessment of a variety of cognitive processes including planning, organizational skills, and problem solving strategies, as well as perceptual, motor, and episodic memory functions. The examinee is asked to copy the Rey-Osterrieth figure and is then asked to recall it from memory 3 minutes and 30 minutes after the copy trial. The internal consistency of the Rey Figure was evaluated by treating each detail as an item and computing split-half and alpha coefficients (Berry et al., 1991; Fasteneau et al., 1996). Both split-half and coefficient alpha reliabilities were greater than .60 for the copy condition and greater than .80 for recall conditions in adults, suggesting that all of the details tap into a single factor. Test-retest reliability for Immediate Recall r = .76, Delayed Recall r = .89 and Recognition Total Correct r = .87) in a sample of 12 normal subjects after a retest interval of about 6 months. However, Berry et al. (1991) retested elderly individuals after 1 year and found that the copy condition was not reliable across this interval. Reliabilities of the immediate-recall and 30-minute-delay trials were also low (.47 to .59). Others have reported somewhat higher reliabilities for this population (Mitrushina and Satz, 1991). The RCFT Copy, 3-minute Recall and 30-minute Recall and Recognition Total Correct scores were significantly correlated with tasks requiring memory and constructional ability (BVRT Total Correct, RAVLT Trial 5, Form Discrimination, Hooper, Trails B, and the Token Test). Scores on the RCFT are moderately correlated to performance on visual-spatial subtests (Wechsler Intelligence Test's Block Design and Object Assembly; e.g., Poulton & Moffitt, 1995; Tombaugh et al. 1992; Wood et al., 1982).

Executive Functioning

Trail Making Test B

The Trail Making Test (TMT) is a measure of attention, speed and mental flexibility. The test requires the examinee to connect, by making pencil lines, 25 encircled numbers and letters in alternating order. The TMT test-retest reliability varies with the age range and population studied but is for the most part adequate. In older adults 1-year-test-retest reliabilities were sufficient (.67–.72).

Language

Semantic Fluency (Animals)

The Semantic Fluency test evaluates the spontaneous production of words under restricted search conditions. The examinee is asked to produce as many animal names as possible within a one-minute interval. The test-retest reliability of Semantic Fluency when using the category *Animals*, is high; Bird et al. (2004) found that only 10% of his sample (retested 1 month post initial assessment) had a change in score that fell outside the reliability coefficient indices.

Boston Naming Test–2

The Boston Naming Test–2 (BNT–2) is a visual naming task involving 60 black and white drawings of common objects. The BNT–2 was originally published by Kaplan et al. (1978). The stimuli to be named for the BNT–2 are line drawings of objects with increasing difficulty, ranging from simple, high-frequency vocabulary words (e.g., *comb*) to rare words (e.g., *abacus*). The test-retest reliability over short intervals is high (r = 91;

SEM = 1.02). The BNT–2 correlates highly with other language measures of its kind; Visual Naming Test of Multilingual Aphasia Examination (*r* = .76 to .86, Axelrod et al. 1994).

IQ

Wechsler Test of Adult Reading

The Wechsler Test of Adult Reading (WTAR) is an assessment of premorbid functioning in adults. It requires the examinee to read aloud irregularly spelled words. The test includes 50 words that become progressively irregular. The WTAR shows excellent internal consistency with coefficients ranging from .90 to .97 for the U.S. standardization sample. The test-retest reliability tends to be fairly stable over time. According to the manual, 319 participants completed the test on two separate occasions, spaced 2 to 12 weeks apart with an average interval about 35 days. Test-retest correlations were very good (>.90) and practice effects were minimal.

Mood

Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (Ham-D) is designed for adults and is used to rate the severity of their depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation or retardation, anxiety, weight loss, and somatic symptoms. The scale contains 17 items pertaining to symptoms of depression experienced over the past week. A score of 0-7 is considered to be normal. Scores of 20 or higher indicate moderate, severe, or very severe depression. Internal reliability of the Ham-D is

estimated to be from 0.46 to 0.97. In terms of inter-rater reliability, Pearson's r is estimated to be from 0.82 to 0.98. Retest reliability is estimated to be from 0.81 to 0.98. Established criteria are met for convergent, discriminant, and predictive validity.

Procedures

After complete description of the study to the subjects, written informed consent was obtained in accordance with the UCLA Human Subjects Protection Committee procedures. At both their initial and follow-up visits, all subjects underwent diagnostic evaluation including physical and medical examination, laboratory screening blood tests that ruled out medical conditions possibly affecting cognition, medical history assessment, and neuropsychological testing. Subjects were asked to return for follow-up at a two-year interval.

Data Analysis and Procedures

SPSS 17 was used for all analyses for the purposes of using neuropsychological and mood assessments within a battery to predict conversion from normal to either MCI or AD. The data was first cleaned and screened for missing data eliminating participants with missing data of interest. Frequency analyses were conducted for all demographic variables of interest in the study. Conversion outcomes were dichotomously coded as either converted normal/MCI or AD or normal converted to MCI. Univariate logistic regression analysis was used to determine conversion to MCI and AD for all neuropsychological tests. Multivariate models were constructed based on significant variables after applying the bonferroni correction method to variables in Hypothesis 1.1

and 1.3 for each multivariate analysis. In order to correct for error caused by group size discrepancy between decliners and non-decliners, a second set of univariate binary regressions were conducted utilizing a demographically (gender, age, education and ethnicity) matched sub-set of non-decliners.

Statistical Analysis

Aim 1: To determine what neuropsychological measures best predict conversion from normal aging to Mild Cognitive Impairment and Mild Cognitive Impairment to probable Alzheimer's disease two years prior to conversion among older adults.

- Hypothesis 1.1: Individually, the Buschke Selective Reminding Test (Total, Delay, and Recognition), Rey-Osterrieth Complex Figure Test (Copy, Delay, and Retention), Boston Naming Test, Trail Making Test B, and Animals verbal fluency test will predict conversion to MCI. To test hypothesis 1.1 individual, six univariate logistical regressions were conducted.
- Hypothesis 1.2: After applying the bonferroni correction method to significant predictors from Hypothesis 1.1, a multivariate logistic regression model was constructed to predict conversion to MCI. To test hypothesis 1.2, the following neuropsychological tests were used within the model, Buschke Total, Buschke Delay, RCFT Retention and Trails B.
- Hypothesis 1.3: Individually, the Buschke Selective Reminding Test (Total, Delay, and Recognition), Rey-Osterrieth Complex Figure Test (Copy, Delay, and Retention), Boston Naming Test, Trail Making Test B, and Animals verbal

fluency test will predict conversion to AD. To test hypothesis 1.1, six univariate logistical regressions were conducted.

- Hypothesis 1.4: After applying the bonferroni correction method to significant predictors from 1.3, a multivariate logistic regression model was constructed to predict conversion to AD. To test hypothesis 1.3, the following neuropsychological tests were used within the model, the Buschke Total, Buschke Delay, Buschke Recognition, RCFT Copy and RCFT Delay.

Aim 2: To determine if depressive symptoms predict conversion to a more severe cognitive to disorder (MCI or AD) two years prior to conversion.

- Hypothesis 2.1: Incidence of depression as measured by the Hamilton Depression Scale at time of testing will predict conversion to MCI. To test hypothesis 2.1 a univariate logistical regression model was constructed to predict conversion of MCI based on depression scores.
- Hypothesis 2.2: Incidence of depression as measured by the Hamilton Depression Scale at time of testing will predict conversion to AD. To test hypothesis 2.2 univariate logistical regression model was constructed to predict conversion of AD based on depression scores.

CHAPTER THREE

RESULTS

Sample Characteristics

Descriptive characteristics of the sample can be found in Table 1.

Table 1

Descriptive Characteristics of the Sample (n=130)

	Total n=130	Convert to MCI		Convert to AD	
		No Conversion (n=61)	Conversion to MCI (n=15)	No conversion (n=121)	Conversion to AD (n=9)
Male	59% (n=55)	(n=23)	47% (n=7)	(n=48)	67% (n=6)
Female	41% (n=78)	(n=38)	53% (n=8)	(n=73)	33% (n=3)
Ethnicity					
Latino	3% (n=4)	0% (n=0)	0% (n=0)	3% (n=4)	0% (n=0)
Asian American	5% (n=6)	3% (n=2)	0% (n=0)	5% (n=6)	0% (n=0)
African American	5% (n=7)	0% (n=0)	0% (n=0)	6% (n=7)	0% (n=0)
Caucasian	87% (n=116)	97% (n=59)	100% (n=15)	86% (n=104)	100% (n=9)
Education	16.39 (SD=2.97)	16.67 (2.94)	15.72 (SD=3.24)	16.45 (3.03)	15.78 (SD=2.77)
Age	61.44 (SD=11.30)	60.84 (1.38)	65.20(SD=11.42)	60.69 (11.15)	68.56 (SD=9.98)

Aim 1

The first aim was to determine what neuropsychological measures best predict conversion from normal aging to Mild Cognitive Impairment and Mild Cognitive Impairment to probable Alzheimer's disease two years prior to conversion among older adults. Correlation analyses were conducted to determine whether there was significant shared variance among the measures.

Table 2.

Correlations between Neuropsychological Tests

	RCFT Copy	RCFT Delay	RCFT Retain	RCFT Recog	Buschke Total	Buschke Delay	Buschke Recog	Boston	Trails B	Animals
Rey Copy	1.00	0.408**	0.256**	0.270**	0.278**	0.246**	0.115	0.409**	-0.461**	0.161
Rey Delay	0.408**	1.00	0.596**	0.60	0.245**	0.218**	0.185**	0.286**	0.258**	0.220*
Rey Retain	0.256**	0.596**	1.00	0.028	0.385**	0.387**	0.207*	0.299**	0.343**	0.217*
Rey Recog	0.270**	0.60	0.028	1.00	0.94	0.117	0.002	0.045	0.161	0.144
Buschke Total	0.278**	0.245**	0.385**	0.94	1.00	0.860**	0.600**	0.239**	-0.392**	0.325**
Buschke Delay	0.246**	0.218**	0.387**	0.117	0.860**	1.00	0.630**	0.159	-0.320**	0.307**
Buschke Recog	0.115	0.185**	0.207*	0.002	0.600**	0.630**	1.00	0.259**	-0.246**	0.270**
Boston	0.409**	0.286**	0.299**	0.045	0.239**	0.159	0.259**	1.00	-0.479**	0.369**
Trails B	-0.461**	0.258**	0.343**	0.161	- 0.392**	-0.320**	-0.246**	-0.479**	1.00	-0.266**
Animals	0.161	0.220*	0.217*	0.144	0.325**	0.307**	0.270**	0.369**	-0.266**	1.00

Hypothesis 1.1

Hypothesis 1.1 was partially supported. The results of the 10 individual univariate logistical regressions showed the Buschke Selective Reminding Test (Total & Delay), Rey-Osterrieth Complex Figure Test (Retention) and Trail Making Test B individually predicted conversion to MCI after applying the bonferroni correction method. Results from these tests are found in Table 3.

Table 3.

Univariate Binary Logistic Regression Predicting Conversion from Normal Aging to MCI (61 non convertors, 15 converted to MCI)

Variable	Wald *(df=1)*	*p*	Odds Ratio (OR)
RCFT Copy	0.003	.959	1.005
RCFT Delay	0.220	.639	0.983
RCFT Retention	13.663	.000**	0.913
RCFT Recognition	1.070	.301	3.080
Buschke Total -	8.508	.004**	0.944
Buschke Delay	13.439	.000**	0.645
Buschke Recognition	5.812	.016	0.256
Boston	4.518	.034	0.824
Trails B	9.604	.002**	1.049
Animals	0.389	.533	0.961

***Significant at the .005 level (after applying the bonferroni correction method)*

Hypothesis 1.2

After applying the bonferroni correction method to significant predictors from Hypothesis 1.1, the multivariate logistic regression model showed the Buschke Recognition and RCFT Retention as the only significant predictors of conversion to MCI. Results from these tests are found in Table 4. Specifically, individuals who were only able to retain 30% (SD=2.71) of visual information after a delay (RCFT Retention) were more likely to develop MCI at time 2 when compared to individuals who were able to retain 54% (SD=3.22) or more of the same visual information. Furthermore, those that converted to MCI recognized, on average, approximately 92% of the words they were presented with initially, where as those that did not convert, on average, recognized approximately 100% of the words.

Table 4.

Multivariate Logistic Regression Predicting Conversion from Normal Aging to MCI (61 non convertors, 15 converted normal to MCI)

Variable	Wald *(df=1)*	*p*	Odds Ratio (OR)
Buschke Total	0.988	.320	1.050
Buschke Delay	0.774	.379	0.792
Buschke Recog	4.359	.037**	0.057
RCFT Retain	8.665	.003**	0.875
Trails B	0.032	.057	1.062

***Significant at the .05 level*

Hypothesis 1.3

Hypothesis 1.3 was partially supported. The results of the six individual univariate logistical regressions showed the Buschke Selective Reminding Test (Total, Delay and Recognition), RCFT (Copy, Delay and Retention) and Trails B predicted conversion to AD. Results from these tests are found in Table 5.

Table 5.

Univariate Binary Logistic Regression Predicting Conversion from Normal Aging/MCI to Probable Alzheimer's Disease (121 non convertors, 9 converted to probable AD)

Variable	Wald *(df=1)*	*p*	*Odds Ratio (OR)*
Buschke Total	12.883	.000**	0.927
Buschke Delay -	12.578	.000**	*0.550*
Buschke Recognition	12.012	.001**	*0.382*
RCFT Copy	9.786	.002**	*0.722*
RCFT Delay	8.234	.004**	*0.780*
RCFT Retention	6.717	.010	*0.936*
Boston Naming Test	0.862	.353	*0.943*
Trails B	7.142	.008**	*1.018*
Animals	3.171	.075	*0.859*

***Significant at the .005 level (after applying the bonferroni correction method)*

Hypothesis 1.4

After applying the bonferroni correction method to significant predictors from hypothesis 1.3, the multivariate logistic regression model showed the Buschke Delay as the only predictor of conversion to AD. Results from these tests are found in Table 6. Specifically, individuals who were not demented at time one but recalled only approximately 2 out of 12 words from a list (Buschke Delay=1.89, SD=2.71) were more likely to develop dementia by time 2 when compared to individuals who were able to recall approximately 8 out of 12 words on this same task (Buschke Delay=8.40, SD=3.22).

Table 6.

Multivariate Logistic Regression Predicting Conversion from Normal Aging/MCI to Probable Alzheimer's Disease (121 non convertors, 9 converted to probable AD)

Variable	Wald *(df=1)*	*p*	Odds Ratio (OR)
Buschke Total	0.662	0.416	1.037
Buschke Delay	5.689	0.017**	0.537
Buschke Recognition	0.331	0.565	0.765
RCFT Copy	2.931	0.087	0.781
RCFT Delay	0.480	0.488	0,924

***Significant at the .05 level*

To correct for error caused by group size discrepancy between converters and non-converters, a second set of univariate binary regressions were conducted utilizing a demographically (gender, age, education and ethinicity) matched sub-set of non-converters. The demographic characteristics of these groups are found in Tables 6 and 7.

Table 7.

Comparison demographic data from demographically matched non-converters and converters to MCI

	Non-converters (N=15)	Converted to MCI(N=15)
Male	N=7	N=7
Female	N=8	N=8
Ethnicity		
Asian American	N=1	N=0
Caucasian	N=14	N=15
Education	15.53 (SD=2.774)	15.73 (SD=3.240)
Age	64.33 (SD=10.118)	65.20 (SD=11.416)

Table 8.

Comparison demographic data from demographically matched non-converters and converters to AD

	Non-converters (N=(9)	Converted to AD (9)
Male	N=5	N=6
Female	N=4	N=3
Ethnicity		
Asian American	N=1	N=0
African American	N=2	N=0
Caucasian	N=7	N=9
Education	16.67 (SD=4.664)	15.78 (SD=2.774)
Age	67.67 (10.087)	68.56 (SD=9.976)

These tests showed that the RCFT Retention was a significant predictor of conversion to MCI. Specifically, individuals who were only able to retain 31% (SD=15.8) of visual information after a delay (RCFT Retention) were more likely to develop MCI at time 2 when compared to individuals who were able to retain 51% (SD=21.2) or more of the same visual information. Furthermore, the results revealed that the Buschke Delay and the RCFT Retention were significant predictors of conversion to AD. Specifically, individuals who were not demented at time one but only retained 30% (SD=14.3) of visual information after a delay (RCFT Retention) were more likely to develop dementia at time 2 when compared to individuals who were able to retain 51% (SD=17.3) or more of the same visual information. Furthermore, those individuals who were not demented at time one but recalled only approximately 2 out of 12 words from a list (Buschke Delay=2.0, SD=2.7) were more likely to develop dementia by time 2 when compared to individuals who were able to recall approximately 7 out of 12 words on this same task (Buschke Delay=7.0, SD=4.1). Results of these analyses may be found in Table 8 and 9.

Table 9.

Univariate Binary Logistic Regression Predicting Conversion from Normal Aging to MCI (15 non convertors, 15 converted to MCI)

Variable	Wald (df=1)	*p*	Odds Ratio (OR)
Total Buschke	0.421	.516	0.988
Delay Buschke	1.839	.175	0.864
Recog Buschke	0.393	.531	0.815
Copy RCFT	0.617	.432	1.085
Delay Rey-O	0.001	.980	0.999
Retain Rey-O	5.520	.019**	0.940
Recog RCFT	0.357	.550	2.154
Boston	0.200	.655	1.030
Trails B	0.355	.551	1.046
Animals	0.355	.551	1.046

***Significant at the .05 level*

Table 10.

Univariate Binary Logistic Regression Predicting Conversion from normal/MCI to AD (9 non convertors, 9 converted to AD)

Variable	*Wald (df=1)*	*p*	*Odds Ratio*
Total Buschke	3.267	.071	.944
Delay Buschke	4.910	.027**	.675
Recog Buschke	1.932	.165	.534
Copy RCFT	3.392	.066	.767
Delay Rey-O	3.603	.058	.755
Retain RCFT	3.897	.048**	.899
Recog RCFT	0.233	.630	.625
Boston	0.097	.755	.976
Trails B	0.889	.346	1.010
Animals	0.986	.321	.903

***Significant at the .05 level*

Aim 2

The second aim was to determine whether depressive symptoms predict conversion to a more severe cognitive disorder (MCI or AD) two years prior to conversion.

Hypothesis 2.1

Hypothesis 2.1 was not supported. The results of the univariate binary logistical regression model indicated that depression scores from the Hamilton Depression Scale did not significantly predict conversion to MCI. Results of this analysis are found in table 10.

Table 11.

Univariate Binary Logistic Regression Predicting Conversion from Normal Aging to MCI (61 non convertors, 15 converted normal to MCI)

Variable	Wald *(df=1)*	*p*	Odds Ratio
Hamilton Depression	.055	.815	1.024

Hypothesis 2.2

Hypothesis 2.2 was not supported. The results of the univariate binary logistical regression model indicated that depression scores from the Hamilton Depression Scale do not significantly predict conversion to AD. Results from these tests are found in Table 11.

Table 12.

Univariate Binary Logistic Regression Predicting Conversion from Normal Aging/MCI to Probable Alzheimer's Disease (121 non convertors, 9 converted to probable AD)

Variable	Wald *(df=1)*	*p*	Odds Ratio
Hamilton Depression	.129	.719	1.042

CHAPTER FOUR

DISCUSSION

Purpose of the Study

The current study sought to establish which neuropsychological measures best predict future cognitive decline. More specifically, the purpose of this study was to determine the ability of the Buschke Selective Reminding Test, Rey Osterrieth Complex Figure Test, Trail Making Test B, semantic fluency (i.e. Animals), the Boston Naming Test and their associated cognitive domains (verbal memory, visuospatial memory, executive functioning, and language), to predict conversion to a more severe cognitive status (e.g., normal aging to MCI, MCI to probable Alzheimer's disease).

Findings

The current study revealed that two measures served as predictive indicators of conversion to a more severe cognitive status (e.g., MCI, AD). More specifically, the Rey Osterrieth Complex Figure Test's (RCFT) retention score and the Buschke Selective Reminding Test's delayed recall score and recognition score were sensitive in predicting conversion to MCI and dementia of the Alzheimer's type. When assessing the entire study sample, the RCFT retention score predicted conversion from normal aging to MCI. Those who converted to MCI on average retained approximately 30% of what they initially encoded from the complex figure, while those who remained stable recalled roughly 54%. Furthermore, those that converted to MCI recognized, on average, approximately 92% of the 12 words they were presented with initially, where as those that did not convert, on average, recognized approximately 100% of the words. The

Buschke SRT delayed recall score predicted conversion from normal aging or MCI to dementia of the Alzheimer's type. Those who converted to dementia of the Alzheimer's type accurately recalled approximately two of twelve words while participants that remained stable accurately recalled approximately eight out of twelve words. When examining the demographically matched subsample, conversion to MCI was predicted by the RCFT and conversion to dementia of the Alzheimer's type was predicted by both the RCFT and the Buschke SRT.

It is not surprising that tests of visual and verbal memory were sensitive in predicting conversion as the literature supports this finding. As mentioned previously, memory of lists of words such as the California Verbal Learning Test (Albert et al., 2001; Beck et al., 2012; Rabin et al., 2009; Silva et al., 2012), Auditory Verbal Learning Test (Landau et al., 2010), Rey Auditory Verbal Learning Test (Tierney et al., 2005), Neurological Assessment Battery List Learning Test (Gavett et al., 2010), and the Buschke Selective Reminding Test (Devanand et al., 2008; Grober et al., 2008; Masur et al., 1994; Tabert et al., 2006) have all been shown to be predictive of conversion to a more severe memory disorder. Similarly, researchers have identified word pair tests such as the Semantic Object Retrieval Test (Kraut et al., 2007) and Wechsler Memory Scale's Verbal Paired Associates (Venneri et al., 2011) as accurate identifiers of those who will convert. Furthermore, research has found lower scores on tests of verbal memory of short stories, such as the Wechsler Memory Scale's Logical Memory (Rabin et al., 2009), to be predictive of conversion. Researchers have also identified tests of verbal long-term memory, such as the Wechsler's Adult Intelligence Scale's Information (Tierney et al., 2005) and tests of cued verbal memory, such as the RI-48 Test (Hanseeuw & Ivanoiu,

2011) to be adequate in predicting who will convert. With regards to visual memory, researchers have found tests such as the immediate recall of the figures from Wechsler Memory Scales (Albert et al., 2001) and the Rey-Osterrieth Complex Figure Test (Alladi et al., 2006; Borroni et al., 2006; Guo et al., 2009) to predict conversion to a more severe cognitive diagnosis.

Additionally, research suggests that tau protein tangles and amyloid plaques spread in a predictable, nonrandom manner beginning in the entorhinal region ("relay station" between the hippocampus and neocortex), spreading to the hippocampus (memory center) and neocortex (responsible for higher functions such as sensory perception, conscious thought and language; Braak & Braak, 1991). The entorhinal-hippocampus system plays an important role in autobiographical, declarative and episodic memories and in particular spatial memories including memory formation, memory consolidation, and memory optimization in sleep. Because this entorhinal region is one of the first areas impacted by tau tangles—accumulating and eventually causing neuronal death—it is expected that the tests measuring functions of this region would predict conversion before tests measuring functions of domains impacted later in the disease process (e.g., language, executive functioning). Braak and Braak found that during the stage in which neuronal death has begun in the entorhinal region, cognitive testing would show minimal impairment, suggesting that such tests would likely need to be highly sensitive. However, the literature is abundant in suggesting that measures in other domains (e.g., language, executive functioning) are also sensitive in predicting conversion to a more severe memory disorder (e.g., Albert et al., 2001; Balota et al., 2010; Bennett et al., 2002; Chen et al., 2000; Dickerson, Sperling, Hyman, Albert, &

Blacker, 2007; Ewers et al., 2012; Jacobs et al., 1995; Kraut et al., 2007; Kurt, Yener, & Oguz, 2011; Lonie et al., 2009; Tabert et al., 2006; Zhou, Nakatani, Teramukai, Nagai, & Fukushima, 2012). This finding was not upheld in the present study.

There are several reasons why these findings may be lacking in the present study. For instance, the present study implemented rigorous diagnostic methods when determining conversion status including multiple sources of diagnosis (e.g., PET scan, clinical consensus by neurology, geriatric psychiatry, neuropsychology, and radiology), utilization of neuropsychological tests from each cognitive domain, and in some cases, multiple tests within a domain, and stringent statistical processes were used (examined the impact of age, education, and gender on conversion and utilized statistical corrections when running multiple tests). Other studies have utilized extensive diagnostic methods when assessing for conversion, including imaging (Artero, Tierney, Touchon, & Ritchie, 2003; Bennett et al., 2002; Borroni et al., 2006; Chen et al., 2000; Estevez-Gonzalez, Kulisevsky, Boltes, Otermin, & Garcia-Sanchez, 2003; Grober et al., 2008; Grober et al., 2000; Perri, Serra, Carlesimo, & Caltagirone, 2007; Rami et al., 2007); however, the majority of studies have not examined the measures of interest, namely the Buschke Selective Reminding Test, Boston Naming Test and the Rey Osterrieth Complex Figure Test. Few studies have been found that were similar to the current study's diagnostic rigor and assessment measures used (Devanand et al., 2008; D. M. Jacobs et al., 1995; Tabert et al., 2006). However, the participants within the Jacobs et al. study did not undergo imaging as way of confirming conversion. The Tabert et al. study included imaging as part of their conversion determination, but did not include the Rey Osterrieth Complex Figure Test within their neuropsychological battery.

Limitations

A major caveat to the current study is a relatively small sample size. Small sample size limits statistical power and may decrease the likelihood of detecting significant predictors of conversion. Other similar studies with larger sample sizes have found somewhat differing findings. For instance, Jacobs et al. (1995) in a community based sample of approximately 443 people, found that in addition to the immediate recall on the selective reminding test, the Boston Naming Test and the WAIS-III Similarities were predictive of conversion to dementia. Additionally, Chen et al. (2000), in a large sample of approximately 600 individuals, found word list delayed recall and the Trail-making Test B to predict conversion to dementia.

Another limitation of the study is sample diversity, both with regards to ethnicity and education. The current study's sample consists of mainly Caucasian, college educated individuals and thus has limited generalizability. It is important to consider that individuals of diverse demographics may differ with regards to cognitive degeneration (e.g., higher education may buffer against a cognitive degenerative disease diagnosis) and thus varying assessment measures may be a better fit to detect progression among these individuals.

Implications

The findings of the current study suggest two neuropsychological measures seem to be good at predicting conversion to a more severe cognitive status among a primarily Caucasian, college educated sample. Generalization of these findings is cautioned; however, once similar results are found among replications of this study with diverse

samples, it may be that neuropsychologists use such measures to determine whether a patient may later convert to a more severe memory disorder with the goal of intervening to delay progression (Blasko et al., 2012; Cheng et al., 2013; Lee et al., 2013; Miller et al., 2012; Roberts et al., 2008; Roberts et al., 2012; Wenisch et al., 2007). Furthermore, it is critical that those who develop Alzheimer's disease are studied at the earliest stages in order to better understand the progression, thus facilitating the development of increasingly advanced treatments.

It is important to highlight that although it is essential to determine whether an individual will convert to a more severe cognitive diagnosis, it is also imperative to recognize that the job of the provider is not simply to inform our patient of their likelihood of converting. Rather, our goal is to help inform the patient of their cognitive strengths and weaknesses as it relates to their daily functioning in order to inform coping strategies as well as intervene via cognitive training, diet, exercise, etc. Therefore, while the findings of this study serve an important role in informing later decline in cognitive status, it is not suggested that these tests be used in separation of a full neuropsychological battery, particularly when a decline in patient functioning is reported. As doing so may inhibit the provider from gathering measurable cognitive strengths and weaknesses from each cognitive domain and more importantly, offering relevant coping strategies and recommendations related to these findings.

Conclusion

In sum, the current study sought to determine which neuropsychological measures best predict future cognitive decline. Among the current study's sample, the Buschke

Selective Reminding Test and the Rey Osterrieth Complex Figure Test are sensitive in predicting conversion to a more severe cognitive disorder (e.g., MCI, probable AD) two years prior to conversion. These findings are in line with the majority of past research that demonstrates verbal and visual memory tasks to be the most predictive of conversion. However, other studies have generated some conflicting results demonstrating tests of executive functioning and language as predictors of conversion; these studies are fewer. The current study's investigators examined the Buschke SRT and Rey Osterrieth Complex Figure Test (among others: BNT, TMT B, Animals) due to the unique capability of these tests to measure multiple cognitive resources (e.g., Buschke SRT: verbal memory, working memory, executive functioning; RCFT: visual memory, executive functioning). This is the only identified study that has examined these measures together and implemented rigorous diagnostic means to determine conversion (e.g., clinical consensus, imaging, full neuropsychological battery). These findings may serve to assist both clinicians and researchers in detecting individuals who may convert to either MCI or probable AD. Future studies may seek to carry out the current methodology among more diverse samples in order to determine the sensitivity of the current study's measures among individuals of various demographics.

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