PREDICTING THE RATE OF DECLINE IN EARLY ALZHEIMER DISEASE:

THE ROLE OF NEUROCOGNITIVE PERFORMANCE FEATURES

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PREDICTING THE RATE OF DECLINE IN EARLY ALZHEIMER DISEASE: THE ROLE OF NEUROCOGNITIVE PERFORMANCE FEATURES

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PREDICTING THE RATE OF DECLINE IN EARLY ALZHEIMER DISEASE:

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Alzheimer disease (AD) is a neurodegenerative disorder that characteristically begins with episodic memory impairment followed by other cognitive deficits over time; however, the course of illness varies, with significant variability in terms of the *rate* of cognitive decline across affected individuals. Several studies have examined demographic, clinical, biological, and neurocognitive performance markers to predict rate of AD progression, but findings are mixed. The current study utilized neurocognitive performance features along with disease-specific and

health features to determine the best prediction model for the rate of future cognitive decline in subjects with mild AD.

Ninety-six subjects with mild AD at baseline were administered a comprehensive battery of neurocognitive tests and clinical measures. Based on Clinical Dementia Ratings (CDR) of functional and cognitive decline within two years, subjects were determined to be Faster (n = 45) or Slower Progressors (n = 51). Stepwise logistic regressions using neurocognitive performance features, disease-specific, health, and demographic variables were performed in a hierarchical fashion to determine optimal predictors of rate of progression.

Several individual neurocognitive measures distinguished Faster from Slower Progressors at baseline, including Trail Making Test - A, Digit Symbol, California Verbal Learning Test (CVLT) Total Learned, CVLT Primacy Recall, and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Neuropsychological Battery Total Score. No disease-specific, health, or demographic variables predicted rate of progression; however, history of cardiac illness showed a trend. In a stepwise logistic regression of neurocognitive performance features alone, a combination model of three measures (Trail Making Test - A, Semantic Fluency, and CERAD Total) distinguished Faster from Slower Progressors with 76% accuracy. In an omnibus model including neurocognitive, disease-specific, health, and demographic variables, only Trail Making Test - A distinguished groups (68% correct classification).

Several neurocognitive performance features may play a role in predicting rate of decline in mild AD. Notably, three relatively brief and commonly used measures were found to predict differences in rate progression with good accuracy. Results from the current research provide important advances in understanding the role of neurocognitive measures in predicting rate of decline in AD.

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CHAPTER ONE

Background

Alzheimer disease (AD) is a neurodegenerative disorder manifested by worsening cognitive and functional ability over time. Individuals in the early stages of AD are likely to have a more pronounced deficit in episodic memory, and specifically, in the learning and retention of new information (Albert, 2011; Butters, Granholm, Salmona, Grant, & Wolf, 1987). Additionally, patients within the early phases of AD are more likely to have impairments in executive functioning and perceptual speed (Becker, Huff, Nebes, Holland, & Boller, 1988; Bondi et al., 2006). Mild to moderately progressed patients also commonly evidence impairment in language functioning, semantic memory, and visuospatial skills (Bäckman, Jones, Berger, Laukka, & Small, 2005). However, though the aforementioned presentation is most common, other patterns of AD may occur in which patients have primary progressive impairments in either visuospatial abilities, language, or other cognitive domains (Albert, 2011; Marra, Silveri, & Gainotti, 2000). As the disease progresses, cognitive functioning in all domains generally worsens, and leads to severe cognitive and functional impairment.

AD imparts multiple and complex effects on patients, caregivers, and society, including medical and specialized care fees, lost wages, nursing home placement, and significant emotional burden. Most of these effects begin to manifest long before death, as the course of cognitive decline significantly impacts patients' ability to function in daily life. Whereas the disease tends to follow a general pattern of memory impairment followed by other cognitive deficits over time, variability is seen in terms of the *rate* of cognitive decline. If the trajectory of an individual's disease course could be predicted, it could afford patients and caregivers a timeframe to plan for long-term care needs and financial considerations. Improved clinical

prediction accuracy could also reduce the burden on patient and caregivers by optimizing resources and adjusting family and social activities in a timely fashion. Finally, research and treatment protocols could be tailored to the progression trajectory for individual patients.

Several demographic, clinical, biomedical and neurocognitive patient characteristics associated with *risk* of developing AD have shown promise in predicting future *rate* of cognitive decline, though results are mixed (Adak et al., 2004; Cosentino et al., 2008). Integrated approaches including features from all of these patient characteristic domains have examined the relationships between these factors and may better predict rate of future decline than any of these markers alone (Sona et al., 2011). Notably, although only a few studies have examined neurocognitive performance, findings show promise. For example, deficits in executive functioning, attention, and processing speed have been linked to rate of cognitive decline, and may have more efficacy than biomarkers (Lee et al., 2006; Lopez et al., 2010). However, there is no consensus among these findings in terms of predicting course of illness (Atchison, Massman, & Doody, 2007; Doody et al., 2010; MacDonald, Karlsson, Fratiglioni, & Bäckman, 2011), and some neurocognitive risk factors for developing AD (e.g., verbal episodic memory performance) have been only minimally examined.

The lack of consensus regarding neurocognitive predictors may relate to the types of neurocognitive variables utilized thus far, which may be insensitive to distinguishing rates of progression (Storandt, Grant, Miller, & Morris, 2002). For example, summation variables such as "total learned" are often used to assess memory performance, though such global or composite scores may mask distinguishing underlying performance characteristics. A *process approach* (e.g. see Kaplan, 1988) utilizing qualitative aspects of memory and cognition may enhance our ability to predict the rate of cognitive decline in AD. For example, several qualitative features

such as intrusion and recognition errors during word-list recall as well as higher recall of the most recently presented stimuli (recency effect) have been identified as valuable in predicting progression from healthy aging and mild cognitive impairment (MCI) to AD (Ahmed, Mitchell, Arnold, Nestor, & Hodges, 2008; Lekeu et al., 2010; Lonie et al., 2010; Myers, Kluger, Golomb, Gluck, & Ferris, 2008). It follows that such variables may play a significant role in predicting the rate of cognitive decline from early to later stages of AD, although the potential contribution of these factors has not been evaluated.

This study seeks to reduce these gaps in our understanding of the rate of cognitive decline in early AD: first by examining the role of qualitative neurocognitive performance characteristics; then by evaluating the incremental contribution of quantitative neurocognitive performance; and finally, integrating these features with demographic, clinical, and biomarker features to determine the best prediction model for the rate of future cognitive decline. The remainder of this chapter is a review of the existing literature and a discussion of promising, but uninvestigated features, regarding prediction of the rate of cognitive decline in AD.

Risk Factors for Developing Alzheimer Disease

Alzheimer disease begins many years before presentation of cognitive symptoms and clinical evaluation. Further, diagnosis is predicated on the patient or others recognizing symptoms and presenting for diagnosis, which could occur long after symptoms actually appear. Research in finding the earliest possible makers of the disorder has identified transitional phases between normal function and AD including preclinical impairment (primarily including biomarker changes; Sperling et al., 2011) followed by mild cognitive impairment (a stage where cognitive impairment in one or more domains is present, but daily functioning is intact; Petersen, 2009).

The presence of preclinical changes or MCI is not necessary or sufficient to predict conversion to dementia or cognitive decline, as some individuals progress to dementia, some remain stable, and some improve (Jack et al., 2010; Mitchell & Shiri-Feshki, 2009). Despite this variability in diagnosis and prognosis, understanding risk factors for developing AD is valuable as these factors may contribute to predicting rate of progression of AD once it is diagnosed.

Many investigations have examined the relationship between patient demographic and clinical factors and diagnosis with AD. The primary risk factor associated with the diagnosis of AD is increasing age, with prevalence doubling every 5 years after age 65 (Williams, Plassman, Burke, Holsinger, & Benjamin, 2010). In a 2,117 subject cohort from the Framingham Study, incidence of probable AD increased from 3.5 per 1,000 at ages 65-69 to 72.8 per 1,000 by age 80-85 (Bachman et al., 1993). In addition, other demographic factors such as education and ethnicity may affect the likelihood of developing AD. For example, several investigations have found low levels of education to be associated with AD diagnosis (Mortimer, Snowdon, & Markesbery, 2003; Ott et al., 1999; Stern et al., 1994; Zhang et al., 1990), and educational attainment below 7 years, appears to be an important risk factor (Barnes & Yaffe, 2011; Ott et al., 1999). However, some studies have found higher levels of education to be a risk factor for diagnosis (McDowell, Xi, Lindsay, & Tierney, 2007; Musicco et al., 2009; Tyas et al., 2007). Racial and ethnic group membership also may differentially affect the risk for developing AD. For example African Americans appear to have a higher likelihood for diagnosis than Caucasians (Hendrie et al., 1995; Tang et al., 2001), but Native Americans may be less likely to develop AD (Hendrie et al., 1993; Rosenberg et al., 1996). Clinically, subjective memory complaints (patient or informant reported memory problems), overall patient health, history of traumatic brain injury, and significant lifetime depression have been linked to later diagnosis of AD in some

studies, but findings are mixed in others (Gatz, Tyas, John, & Montgomery, 2005; Jonker, Geerlings, & Schmand, 2000; Jorm et al., 2004; Lye & Shores, 2000; Palmer et al., 2007; Song, Mitnitski, & Rockwood, 2011). In sum, increasing age and very low education appear to be promising risk factors for AD, and while other demographic and clinical factors may also affect the probability of developing AD, findings are less clear.

In terms of biomedical characteristics, genetic inheritance may play an important role in the development of AD. The probability of AD increases with the presence of the apolipoprotein E (ApoE) allele type ε4, which may be associated with up to 50% of AD cases in the United States (Adak et al., 2004; Bertram & Tanzi, 2008; Devanand et al., 2005; Forlenza et al., 2010; Gómez-Tortosa et al., 2011; Raber, Huang, & Ashford, 2004; Wilson et al., 2002). Additionally, the risk for developing AD may incrementally increase with the presence of two versus one ε4 alleles (Lucotte, Turpin, & Landais, 1994; Poirier & Davignon, 1993). However, more recent studies have found that this risk factor may be modified by demographic factors such as age, ethnicity, and sex (Chui & Gatz, 2005; Farrer et al., 1997; Weiner et al., 2003). In contrast, the ApoE ε2 allele seems to serve as a protective factor against AD (Talbot et al., 1994). Overall, while several studies have supported ApoE genotype as a risk factor AD the extent of the relationship in all populations is still unclear.

In addition to genetic factors, changes in brain structure have been associated with increased risk for development of AD. For example, in a sample of 35 healthy individuals, structural brain imaging analyses demonstrated that decreased total brain volume, decreased hippocampal volume, and rate of ventricular volume increase were significantly associated with the later development of cognitive impairment (Silbert et al., 2003). In other investigations, decreased entorhinal volume, and the slope of volumetric decline were linked with later

diagnosis of AD (Adak et al., 2004; Stoub et al., 2005). Positron emission tomography studies using radiotracers that measure beta-amyloid accumulation have also reported relationships between degree of beta-amyloid accumulation and higher likelihood of diagnosis of AD (Mormino et al., 2009; Pike et al., 2007; Sperling et al., 2011; Villemagne et al., 2008). Overall, biomedical markers appear to play an important role in understanding risk factors for developing AD. However, these measurements are costly and difficult to obtain clinically, and not all individuals exhibiting these risk factors will have cognitive decline consistent with a diagnosis of AD (Jack et al., 2010).

As with clinical, demographic and biological factors, several investigations have examined the role of neurocognitive assessments in predicting development of AD (Cervilla, Prince, Joels, Lovestone, & Mann, 2004). Decreased global cognition, as assessed by a brief screening measure, the Mini-Mental State Examination (MMSE; Folstein, Robins, & Helzer, 1983) and a comprehensive neurocognitive assessment, the Consortium to Establish a Registry for Alzheimer's Disease cognitive battery (CERAD; Morris, 1988), has been significantly associated with cognitive decline consistent with a diagnosis of AD (Bäckman et al., 2005; Rossetti, Cullum, Hynan, & Lacritz, 2010; Small, Herlitz, Fratiglioni, Almkvist, & Backman, 1997). Concordant with the nature of the disease, measures of episodic memory have been found to be significant neurocognitive predictors of AD. Guarch, Marcos, Salamero, Gasto, and Blesa (2008), for example, compared individuals that progressed to probable AD (i.e., "progressors") with non-progressors on a broad neuropsychological battery and found that progressors had lower scores on all measures except working memory at baseline. In a logistic regression analysis, performance on delayed verbal memory predicted the progression group with 80% accuracy; however, the progression group consisted of only 10 subjects, which greatly limits

generalizability. In a longitudinal study of 52 community-dwelling individuals, impaired initial performance on a visual memory task was associated with a twofold increase in relative risk of developing AD within 1-3 years (Kawas et al., 2003).

Just as initial impairment on specific neurocognitive tests has been associated with later development of AD, a *combination* of neurocognitive measures may similarly assist in predicting future diagnosis of AD. For example, Guarch, Marcos, Salamero, & Blesa (2004) found that immediate and delayed verbal and nonverbal memory scores combined with associative learning and vocabulary was significantly associated with diagnosis of dementia two years later in individuals with memory complaints (N=43). In a larger epidemiological investigation of 263 healthy subjects, verbal memory and language test scores significantly predicted incidence of dementia in non-demented elderly at a five-year follow-up, while verbal episodic memory significantly predicted dementia at ten-year follow-up (Tierney, Yao, Kiss, & McDowell, 2005). Schmid, Taylor, Foldi, Berres, and Monsch (2013) compared 29 cases of incident dementia to 29 normal controls and found that qualitative neuropsychological factors including number of intrusions (‘recalled’ words that were not actually on the list) and response bias (the decision rule used when faced with an uncertain choice) on a verbal learning task were significant predictors of diagnosis of dementia in combination with other clinical and demographic factors. Thus, it is reasonable that assessment of neurocognitive performance may be valuable in estimating risk of developing AD.

In sum, findings regarding a number of risk factors show promise; however further investigation is necessary to consistently predict future diagnosis of AD. Despite our growing understanding of risk factors for developing AD, little is known about the rate of cognitive

decline once AD is diagnosed, and these early risk factors may play an important role in predicting prognosis.

Rate of Cognitive Decline in AD

In most patients, the disease tends to follow a general pattern of memory impairment followed by other cognitive deficits. However, there is great variability in the rate of cognitive decline. The factors associated with faster versus slower decline have been investigated to help predict a patient's trajectory of cognitive decline.

Our ability to predict who will decline at what rate is very limited due to inconsistent findings between studies. These discrepancies are likely due to methodical differences between studies in the definition and measurement of "faster" and "slower" cognitive decline as there is no consensus in these definitions (Soto et al., 2008). In addition, several studies examining population-based cognitive decline have found outcomes to be dependent on the measurement tools used. For example, on a global measure of cognitive functioning, the MMSE, the average rate of decline is 2-4 points per year (Morris, 2003). On a more sensitive clinical rating of global cognitive and functioning, the Clinical Dementia Rating Scale (CDR) Sum of Boxes (Morris, 1993), the average patient score increases by 1.5 points per year (reflecting worsening status) (Aisen, Petersen, & Thal, 2008; Williams, Storandt, Roe, & Morris, 2012). However, while these anchors may be useful as population-based markers of rate of decline, these ranges may be misleading in individual patients as they fail to accurately capture unique patient characteristics.

The results from several investigations have suggested that the rate of cognitive decline is often non-linear, with patients declining at different rates depending on the stage and severity of dementia (Brooks & Yesavage, 1995; Doody, Massman, & Dunn, 2001; Haxbya, Raffaelea, Gillettea, Schapiroa, & Rapoporta, 1992; Ito et al., 2011; Morris, 2003; Stern et al., 1994). To

complicate the picture further, as Holmes and Lovestone (2003) commented, there is great interindividual variability in the rate of decline. In particular, some patients progress at a faster rate than others, which may be critical in determining prognosis and in treatment planning (Kraemer, Tinklenberg, & Yesavage, 1994). Thus, the model for the rate of cognitive decline may need to be specific to the stage of AD as well as to factors unique to individual patients.

Despite the importance of determining a disease progression timeline for clinical management and planning purposes, our ability to predict who will decline at what rate is very limited. Several demographic, disease-severity, psychiatric/behavioral, biomedical, and neurocognitive variables have shown promise, although findings regarding the utility of these predictors have been mixed and there is no consensus among these findings in terms of predicting course of illness (Atchison, Massman, & Doody, 2007; Doody et al., 2001; MacDonald, Karlsson, Fratiglioni, & Bäckman, 2011). A review of investigations that have examined risk factors for faster cognitive decline throughout the disease process follows.

Demographic

Several demographic factors have been associated with faster rate of cognitive decline in AD. Age and education have been widely explored, but results are inconsistent.

Age. While some investigations have found younger age of onset related to faster cognitive decline, overall results are mixed. For example, in a study of 127 patients with probable AD, Jacobs et al., (1994) found that onset below age 65 was associated with faster decline on the modified MMSE and Blessed Dementia Rating Scale (an informant-based behavioral rating scale; Blessed, Tomlinson, & Roth, 1968) after 2 years. Musicco et al., (2009) observed that age of onset younger than 70 was associated with faster time to loss of 5 points on

MMSE in patients with mild to moderate AD (N = 154). Moreover, in a large study of 1,062 patients, O'Hara et al., (2002) found that age below 75 at the time of initial visit (in conjunction with moderate to severe aphasia and initial MMSE score greater than 7) was associated with faster decline (>3 points/year) on the MMSE. However, other studies have not found this inverse correlation between age of onset and rate of cognitive decline. For example, Huff, Growdon, Corkin, and Rosen (1987) found that rate of decline on the Blessed Dementia Rating Scale was faster in patients with onset older than 65. The authors concluded that due to great variability in performance between groups, age of onset is not a strong predictor of rate of decline. Huff et al.'s, (1987) findings were supported by a study that found age of onset to be unrelated to rate of decline (Stern et al., 1994). Thus, while some investigations indicated that the age of disease onset might play an important role in predicting rate of decline, the strength of this feature may depend on its interaction with other patient characteristics.

Education and latent cognitive ability. Higher level of education has been associated with faster cognitive decline, but findings are complex. Viatonou and colleagues (2009) studied 250 patients with probable AD and found that educational attainment beyond secondary school, in conjunction with malnutrition, risk of depression, and caregiver burden, predicted clinically significant loss of 3 or more points on the MMSE in one year among demented subjects aged 75 or more. This finding supported an investigation of 312 community-dwelling patients with AD, which found that each additional year of education was related to incrementally faster cognitive decline (Scarmeas, Albert, Manly, & Stern, 2006). This relationship was a stronger predictor of future decline than age, gender, ethnicity, differential baseline cognitive performance, depression, and vascular comorbidity. Educational achievement and cognitive performance are highly correlated with latent cognitive ability (Wilson et al., 2009), and the extent to which the

disease has progressed in relation to previous cognitive levels may be a more important predictor than specific educational attainment (Drachman, O'Donnell, Lew, & Swearer, 1990). In a study by Bracco et al. (2007) in 85 individuals with early stage AD, higher premorbid intelligence was associated with faster memory decline. Thus, higher latent cognitive ability and level of education appear to be promising risk factors for faster rate of cognitive decline.

The findings reported above are unexpected given that higher *incidence* of AD is related to lower levels of education and lower premorbid cognitive functioning (Barnes & Yaffe, 2011). A possible explanation may be that despite the protective effects of higher levels of education and cognitive ability from developing AD, higher educational attainment may become a risk factor for faster future rate of cognitive decline once AD has been diagnosed. The theory of cognitive reserve posits that individuals with higher premorbid or longstanding cognitive ability may better utilize cognitive resources to compensate for decline and the disease process may be more advanced when eventually diagnosed (Stern, Albert, Tang, & Tsai, 1999; Tang et al., 2001; Teri, McCurry, Edland, Kukull, & Larson, 1995). Then, when reserve is eventually overcome, rate of decline may accelerate in these individuals (Wilson et al., 2009). For example, (Wilson et al., 2004) analyzed a subset of "typical AD participants," those with 16 years of education and those with 8 years of education. After 4 years, the higher educated patients evidenced more cognitive decline; however, these effects were seen later in the AD disease course. Furthermore, Hall et al. (2007) examined 117 cases of incident dementia and identified a "change point" where rate of decline begins to accelerate. The authors found that each additional year of education delayed onset of accelerated decline by 0.21 years, but that once acceleration began, decline was more rapid than those with higher levels of education.

In contrast to these findings, several multivariate studies of cognitive decline included education and premorbid intelligence as predictors of rate of decline, but these were not significant in the overall model (Doody et al., 2010; Ito et al., 2011; Suh, Ju, Yeon, & Shah, 2004). Therefore, these features may be less robust predictors when compared with other factors. Overall, despite some mixed findings, latent cognitive ability and level of educational attainment may play an important role in future rate of cognitive decline.

Disease-Severity

A number of studies have examined how the rate of cognitive decline prior to initial study evaluation (i.e., "baseline") affects prediction of later rates of decline. As the severity of cognitive impairment increases, rates of cognitive decline may differ.

Pre- vs. post-diagnosis rate of cognitive decline. Current estimates indicate the disease onset of AD to be 15 years prior to diagnosis, but it may be much longer (Sperling et al., 2011). Doody et al. (2001) developed a method for estimating a rate of cognitive decline prior to diagnosis of AD, which they termed "pre-progression rate," and used this to predict the rate of future decline. They observed 298 patients with probable or possible AD, and calculated a pre-progression rate with this formula based on normative data for the MMSE and informant report: [MMSE (expected)-MMSE (initial)] / [estimated duration of symptoms]. Groups were separated into slow, intermediate, and rapid "pre-progressors" and the authors examined the duration of time to loss of 5 points on the MMSE. Rapid pre-progressors reached the 5-point loss mark earlier than slower groups; however, the actual rate of pre-initial evaluation and post-initial evaluation progression of cognitive decline was not correlated. Thus, even though patients

declining rapidly prior to diagnosis will likely continue to decline faster than other patients, the actual rate of prior decline may not be useful in predicting rate of future decline.

In a follow-up study, Doody et al. (2010) examined pre-progression rate and several other cognitive measures in 597 patients with AD who were followed for 15 years. The authors found that slow pre-progressors had longer duration of symptoms, and higher IQ and education. Slow and intermediate pre-progressors maintained better performance on a brief screening tool for overall cognitive impairment (Alzheimer's Disease Assessment Scale-cognitive subscale, ADAS-cog; Rosen, Mohs, & Davis, 1984), but the intermediate group accelerated in decline on CDR Sum of Boxes (a clinical rating of cognitive and functional impairment; Williams, Storandt, Roe, & Morris, 2012). Hallucinations and delusions were significant predictors of decline on the CDR Sum of Boxes, but age, gender, education, premorbid IQ, extra-pyramidal signs and ApoE ε4 were not significant predictors. On the ADAS-cog, age, education, premorbid-IQ, and delusions were significant covariates, but gender, hallucinations, extrapyramidal signs, and ApoE genotype were not significant in prediction of decline. Intermediate and fast pre-progressors could not be reliably distinguished in post-baseline evaluations. In other studies including multiple demographic and clinical factors, duration of symptoms prior to baseline evaluation did not reliably predict later rate of cognitive decline (Suh et al., 2004). Swanwick, Coen, Coakley, and Lawlor (1998) examined cognitive decline in 95 patients with AD and found that even though subjects with longer duration of symptoms at presentation were significantly more impaired on global measures of cognitive function, age and duration of symptoms were not predictive of rate of future decline. Further, the rate of progression over the first year did not predict subsequent annual rate of decline. Accordingly, these findings support that rate of decline prior to diagnosis may have limited utility in estimating future the rate of decline.

Initial severity of cognitive impairment. Severity of cognitive impairment at initial evaluation appears to be an important factor in predicting the rate of future cognitive decline in AD. Storandt, Grant, Miller, and Morris (2002) examined 289 demented and 230 nondemented individuals with incipient (i.e., MCI), very mild, and mild dementia. Initial dementia severity was significantly associated with rate of cognitive decline, with more severe groups declining faster than less severe groups. In addition, age, initial prominent language difficulties and visuospatial deficits, and fewer medications, were also significantly related with rate of cognitive decline. A model developed by Ito et al. (2011) utilizing age, ApoE ε4 genotype, gender, family history of AD, years of education, and baseline severity of cognitive impairment supported these findings (N=817). In this study, increased rate of disease progression was associated with worse baseline severity on the ADAS-cog; however, age, ApoE ε4 genotype, and gender were identified as potential covariates affecting disease progression. These findings suggest that initial dementia severity may have an important effect on future rate of cognitive decline, but a multivariate model including demographic, biomedical, and neurocognitive factors may better represent the rate of decline.

The model developed by Ito et al. (2011) also illustrated a nonlinear progression of rate of decline based upon baseline disease severity, highlighting the impact of disease severity on future rate of cognitive decline in AD. Stern and colleagues (1994) hypothesized that the rate of cognitive decline may have a bell-shaped relationship with initial disease severity. These investigators examined 111 patients with AD over one year and found that individuals with mild and severe impairment at baseline declined more slowly than individuals with a moderate degree of impairment. Gender, age at onset, and family history of dementia did not affect rate of deterioration. These findings are similar to other investigations that have found that the rate of

cognitive decline increases with disease stage initially, and then appears to decrease in the more advanced stages of the disease (Morris et al., 1993). In sum, disease severity may play an important role in predicting future rate of decline. Additionally, a cross-sectional approach based upon initial dementia severity may reduce the variability in rate of cognitive decline based on stage of disease progression, and could provide a more accurate model for the future course of decline.

Psychiatric and Behavioral

Psychiatric and behavioral factors have also been investigated in relation to the rate of cognitive decline in AD. Scarmeas et al. (2007) followed 497 patients with early stage AD semiannually for an average of 4.4 years (range = 0.1 to 14 years) and found that the presence of at least one disruptive behavioral symptom such as wandering, verbal outbursts, physical threats/violence, agitation/restlessness, and sundowning was associated with faster cognitive decline. Sundowning and agitation/restlessness were particularly associated with more rapid cognitive decline. Additionally, faster cognitive decline has been reported in patients with aggressive behavior, agitation, and sleep disturbance (Mortimer, Ebbitt, Jun, & Finch, 1992). In particular, the presence of visual hallucinations was associated with faster rate of decline in AD in some investigations (Doody et al., 2010; Wilson, Gilley, Bennet, Beckett, & Evans, 2000). Extrapyramidal symptoms and the presence of Lewy body pathology in conjunction with a diagnosis of AD have been associated with faster cognitive decline, but other investigations have found discordant results (Kraybill et al., 2005; Soto et al., 2008). The presence of behavioral symptoms related to the AD can be difficult to separate from the presence of other disease processes (such as Lewy body dementia), which makes tracking etiology of symptoms difficult

(Soto et al., 2008). Additionally behavioral and psychiatric and symptoms may appear late in the disease process (Lyketsos et al., 2011), limiting the utility of these markers in predicting future rate of cognitive decline.

Biomedical

Several biomedical factors have been investigated for their influence on the rate of cognitive decline in AD. As reviewed earlier, the ApoE ε4 genotype is a significant risk factor for AD (Adak et al., 2004). Vascular factors have also been linked to a higher likelihood of developing AD. Finally, measures derived from brain imaging and cerebrospinal fluid have been associated with future diagnosis of AD (Jack et al., 2011; Sperling et al., 2011). These findings lend support for examining the role of these factors in predicting rate of cognitive decline in AD.

Genetic. While an association between ApoE ε4 genotype and accelerated cognitive decline in AD would be reasonable to expect given the role of this genotype as a risk factor for developing dementia, results have been mixed. In some investigations the ApoE ε4 allele has been associated with faster progression of AD while others have paradoxically found that genotype ε4 is linked with slower progression. Martins, Oulhaj, de Jager, and Williams (2005) observed that faster decline was associated with both one and two copies of the ApoE ε4 allele in an investigation of 199 incident cases of AD, while slower decline was associated with the presence of ApoE ε2 allele. Hoyt, Massman, Schatschneider, Cooke, and Doody (2005) followed 189 patients with probable AD for two years and found that patients with 2 ApoE ε4 alleles exhibited a slower rate of decline on a global cognitive measure (MMSE) and a functional measure (Independent Activities of Daily Living, Lawton & Brody, 1969) than those with 1 or 0 alleles, but genotype did not affect performance on measures within specific cognitive domains.

Kleiman et al. (2006) genotyped 366 patients with AD and found that the presence of ApoE ε4 did not affect decline on cognitive or functional measures when duration of symptoms were controlled. Still other studies have found no association between ApoE ε4 genotype and rate of cognitive decline (Bracco et al., 2007; Dal Forno et al., 1995; Growdon, Locascio, Corkin, Gomez-Isla, & Hyman, 1996; Helzner et al., 2009).

One reason for the discordant results presented above may be that the ApoE ε4 is a risk factor for AD, but does not play a role in rate of cognitive decline. An alternative hypothesis for these outcomes may be that ApoE ε4 only impacts rate of cognitive decline early in the disease process. For example, Cosentino and colleagues (2008) found that the presence of at least one ApoE ε4 allele predicted faster progression, but ApoE ε4 was a sensitive predictor only in early stages of dementia severity, not in later stages. Lane & Farlow (2005) noted that ApoE ε4 carrier status was associated with faster decline in mild AD; however, it was associated with slower decline in patients with moderate AD. Consequently, the effect of ApoE ε4 on future rate of cognitive decline is still unclear as its reliability as a predictor may be moderated by disease severity.

Vascular/metabolic. Several studies have found that vascular and metabolic factors affect the rate of dementia progression after a diagnosis of AD (Mielke et al., 2007; Regan et al., 2006). MacDonald et al. (2011) studied cognitive decline in 306 incident dementia cases from the Kungsholmen Project and found history of cardiovascular disease to be the single predictor related to cognitive change on the MMSE after 3 years (demographic, genetic, overall health markers, disease comorbidity, depression, lifestyle, and sensory impairment factors were not significant). Helzner and colleagues (2009) observed that higher total cholesterol and low-density lipoprotein–C concentrations combined with history of diabetes was associated with

faster cognitive decline on a multidomain composite scale of cognitive functioning in patients with AD (N = 156). Baseline age, sex, race/ethnicity, education, stroke, hypertension, heart disease, triglyceride concentration, high-density lipoprotein concentration, and ApoE genotype were not associated with decline. Roselli et al. (2009) examined 162 patients with AD and found that male sex, arterial hypertension, type II diabetes, and lack of acetyl cholinesterase inhibitor therapy were associated with faster decline on the MMSE. In another study, Mielke et al. (2007) followed 135 individuals with AD for 3 years and concluded that some factors were associated with a faster rate of decline (atrial fibrillation, systolic hypertension, and angina), while others were associated with a slower rate of decline (history of coronary artery bypass graft surgery, diabetes, and anti-hypertension medications). In 2011, this group found that atrial fibrillation and systolic hypertension predicted faster cognitive decline while vascular index score (global vascular history), current atrial fibrillation, systolic blood pressure, current smoking, antihypertensive drugs, and history of stroke, diabetes, coronary artery bypass surgery, or myocardial infarction were not significant predictors of rate of decline in patients with AD (N = 216) (Mielke et al., 2011). These results provide some evidence that vascular and metabolic risk factors may affect future rate of cognitive decline, but a predictive profile has not been identified.

Despite some evidence supporting a relationship between vascular risk factors and increased rate of cognitive decline in AD, other investigations found no relationship (Abellan van Kan et al., 2009; Bhargava, Weiner, Hynan, Diaz-Arrastia, & Lipton, 2006). Regan et al. (2006) studied 224 patients with AD and commented that vascular risk factors alone did not significantly alter deterioration after 18 months, but the occurrence of cerebrovascular events within the time-period examined was associated with more rapid decline. These contradictory

results may be explained by an interaction between ApoE ε4, stroke, and time identified by Mielke et al. (2011). Specifically, the authors noted that a history of stroke and presence of ApoE ε4 might predict a different progression trajectory, with faster initial decline and a subsequent slow-down compared to patients with different combinations of risk factors. Given the presented findings, cerebrovascular disease burden appears to contribute to faster cognitive decline in AD, though the extent of this relationship is unclear.

Brain imaging. Features derived from structural brain imaging have been examined as predictors of the rate of cognitive decline. Low brain volume measured by MRI has been related to increased dementia severity, as well as to faster cognitive decline (Chan et al., 2001; Fox, Scahill, Crum, & Rossor, 1999; Murphy et al., 1993). Jack et al. (2011) analyzed volumetric changes in the hippocampus, entorhinal cortex, whole brain, and ventricles from serial MRI studies in 64 subjects with AD, and atrophy rates were greater in patients with CDR decline at follow-up than patients with stable CDR. Brickman and colleagues (2008) studied white matter hyperintensities in 84 patients with AD and found that severity of baseline atrophy and baseline white matter hyperintensities in patients with mild AD were associated with faster annual rate of cognitive decline on the modified MMSE. The interaction of these factors also predicted future cognitive decline across 8 years. However, white matter hyperintensities are common among healthy aging populations (i.e., occurring in up to 11-21% in middle-aged adults and up to 94% by age 82; Debette & Markus, 2010). In addition, the association of cerebral volumes and actual in vivo cognitive function is variable, which make these findings less reliable in predicting rate of decline.

In addition to MRI studies, other imaging-based investigations have been undertaken. In a study of regional cerebral blood flow, perfusion to the right posterodorsal, anterior and superior

prefrontal cortices and the inferior parietal cortex was found to be significantly lower in AD patients with rapid cognitive decline on the MMSE (Nagahama et al., 2003). Colloby et al. (2010) utilized positron emission tomography in 16 patients with AD and 15 with dementia with Lewy bodies and found that reduced normalized ^{123}I-5IA-85380 uptake in left superior, middle, and inferior frontal gyri and prepostcentral and anterior cingulate regions significantly correlated with decline in executive function after one year in patients with dementia. However, because of the small and diagnostically mixed sample, these findings require further investigation before reliable conclusions can be made. Overall, the results of these investigations provide some support for the use of brain-based biomarkers in predicting rate of future cognitive decline, but due to small sample sizes, further investigations are required before they can be validly and reliably used in clinical populations.

Cerebrospinal fluid markers. The relationship of cerebrospinal fluid biomarkers to rate of decline has also been investigated, though results have been mixed. Kester et al. (2009) examined cerebrospinal fluid biomarker levels of beta amyloid 1-42 (Aβ42, the main component of amyloid plaques found in AD), tau protein (the presence of which is suggested to reflect neuronal damage), phosphorylated-tau-181 (p-tau-181, which contributes to neurofibrillary tangles and reflects pathological tau), the ratio of tau to Aβ42, the ratio of p-tau-181 to Aβ42, and the ratio of p-tau-181 to tau in individuals with early AD and found that low p-tau-181:tau ratios predicted cognitive decline of 3 points on the MMSE (N = 151). These results were supported by Snider et al. (2009) who also found that faster rate of decline on CDR Sum of Boxes was predicted by low Aβ42, high tau or p-tau-181 levels, and high tau:Aβ42 ratio. However, Huey, Mirza, & Putnam (2006) and Stefani, Martorana, & Bernardini (2006) found no relationship between cerebrospinal fluid markers and degree of cognitive deterioration. Such

discordant findings suggest that though cerebrospinal fluid biomarkers may be associated with AD progression, further investigation is necessary in understanding their role in predicting rate of cognitive decline.

Neurocognitive

The nature of AD imparts significant cognitive deterioration over time. Some investigations have considered whether early patterns of cognitive deficit on neuropsychological measures predict future rate of decline in AD (Beatty & Salmon, 2002; Berg, Danziger, Storandt, & Coben, 1984; Coen et al., 1996; Mortimer et al., 1992; Rasmusson, Carson, Brookmeyer, Kawas, & Brandt, 1996). Though many findings show promise, a consistent neurocognitive prediction profile has not emerged.

Though many investigations use brief, global measures like the MMSE to quantify initial cognitive function, the use of more in-depth neurocognitive measures may be warranted. For example, Atchison, Bradshaw, and Massman (2004) examined 211 patients who were followed for 12 to 18 months after an initial neuropsychological evaluation that included a global measure of intelligence, a confrontation naming measure, and an attention screening measure [Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981); Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983), and Verbal Series Attention Test (Mahurin & Cooke, 1996)]. The groups were similar in education, gender, medication, ApoE genotype, history of stroke, and history of traumatic brain injury. Initial MMSE scores for all subjects were equal and they were split into slow, medium, and fast decliners, based on MMSE score change. Fast Decliners performed worse at baseline on WAIS-R Block Design, Digit Symbol, Arithmetic, Similarities, and Picture Completion, as well as the Verbal Series Attention Test. There were no

significant univariate differences for WAIS-R Information, Digit Span, Vocabulary, Comprehension, and Object Assembly, as well as BNT. Notably, though global screening scores were similar, in-depth neuropsychological assessment revealed discrepancies between groups. These results indicate that more sensitive measures of cognitive functioning may be better at predicting rate of decline than brief, global measures alone.

Several investigations have examined deficits in specific cognitive domains and found significant associations with faster decline in AD, but there is no clear agreement on the characteristics of a pattern for prediction of future rate of decline. In terms of language measures, Beatty and Salmon (2002) examined primary and supplementary measures of semantic memory and found that lower BNT and lower semantic fluency scores, but not letter fluency scores, were associated with more rapid decline on a global measure of cognitive impairment (The Dementia Rating Scale; Mattis, 1988). An earlier investigation also concluded that initial poor performance on BNT was associated with faster cognitive decline as measured by the MMSE (Boller & Becker, 1991). In contrast, Rasmusson et al. (1996) found that *better* BNT performance at baseline was associated with faster decline, while lower Token Test (a measure of auditory comprehension; Renzi & Vignolo, 1962) performance predicted faster decline on the MMSE. Beyond language performance, deficits in other areas of cognition have been associated with faster cognitive decline. In addition to higher levels of aphasia, Berg et al. (1984) found low WAIS-R Digit Symbol performance (a measure of graphomotor processing speed) was associated with more rapid cognitive decline as reflected by the MMSE and Blessed Dementia Scale in 43 subjects with mild AD.

Combinations of several cognitive domains have also been utilized to predict the rate of cognitive decline. For example, Marra et al. (2000) examined performance on multiple cognitive

domains, including verbal and visual memory, simple and demanding attention, working memory, constructional praxis, language, and visuospatial reasoning in 55 patients with early stage AD (defined as onset of symptoms within the past two years). Patients were considered to be "fast decliners" if they evidenced a decline of 25% on the MMSE after approximately 1 year. After performing a principle components analysis on all neuropsychological variables, reduced visuospatial attention, verbal learning and recall, a primacy effect in verbal memory (early list items recalled better than items from later serial positions), and impaired inductive reasoning were significant factors. Discriminant analysis on these factors indicated that they were significant in identifying fast decliners. In another multivariate investigation, Musicco et al. (2010) studied 154 newly diagnosed AD patients with mild, moderate, or severe impairment within the cognitive domains of memory, executive function, praxis, and language. The authors compared the number of patients with loss of at least 5 points on the MMSE within 2 years between impairment groups. Those with more severe memory and executive functioning impairments at baseline had worse prognoses over two years. However, in a multivariate analysis, only executive functioning predicted faster progression.

Overall, cognitive performance measures may play an important role in predicting future rate of cognitive decline in AD. Importantly, detailed assessment of performance in specific cognitive domains may provide more sensitive predictors of rate of cognitive decline than brief global measures, such as the MMSE alone. Many of these investigations focused on language measures, but visuospatial functioning, attention, processing speed, and executive functioning also appear to be significantly associated with rate of decline. Notably, few investigations included episodic memory performance as predictors. This may be related to decreased variability across this domain in patients with AD due to the inherent overlap between

performance in this area and diagnosis with AD (Fox et al., 1999). However, given that impaired episodic memory is hallmark feature of AD, further investigation of the predictive impact of episodic memory function in addition to other cognitive domains is warranted.

In addition, only Marra and colleagues, (2000) examined qualitative memory performance variables such as recency and primacy effects (better recall of late or early list items, respectively), increased intrusions (recalled items not on the list) and repetitions (repetition of items already recalled), and poor discriminability (ability to classify presented and non-presented stimuli). These features of neurocognitive functioning have been relevant in differentiating AD from healthy aging and other dementias, as well as predicting risk of developing AD (De Anna et al., 2008; Schmid et al., 2013; Thompson, Stopford, Snowden, & Neary, 2005). Further investigation into these more qualitative components of cognitive functioning might shed further light on the ability for cognitive measures to predict future rate of cognitive decline.

Integrated Investigations

Given the complex nature of the presented patient characteristics and mixed findings within each area, several studies have integrated predictive factors across demographic, disease-severity, biomedical, and neurocognitive domains to determine which factors best account for variance in predicting rate of cognitive decline.

Buccione et al. (2007) examined cognitive and behavioral markers of fast and slow cognitive and functional decline in 43 individuals with AD. Neuropsychological predictors were memory [Digit Span Forward, Corsi Block Tapping task, Immediate Visual Memory, Immediate Recall of a 15-word list, Prose Recall, recall of Rey's Complex Figure (Carlesimo & Buccione,

2002)], language [Phrase Construction, Battery for the Assessment of Aphasic Disorders Naming test (Carlesimo & Caltagirone, 1996; Miceli, Laudanna, Burani, & Capasso, 1994)], general intelligence [Ravens Coloured Progressive Matrices (Carlesimo & Caltagirone, 1996)], constructional praxis [copy of Rey's Complex figure, freehand copy of geometrical figures (Carlesimo & Caltagirone, 1996)], and executive functioning [Phonological word fluency, Modified Card Sorting Test (Nocentini & Vincenzo, 2002)]. Behavioral predictors based on caregiver report on the Neuropsychiatric Inventory (Cummings et al., 1994), were separated into four factors. Factor 1 included euphoria, disinhibition, and aberrant motor behavior; Factor 2 was irritability, anxiety, agitation; Factor 3 was defined as depression and apathy; and Factor 4 included hallucinations and delusions. Results indicated that cognitive decline was predicted by freehand copy of geometrical figures, Word Fluency, and Factor 4 (hallucinations and delusions). Functional decline was predicted by freehand copy of geometrical drawings and Factor 4. Overall, this investigation supported the hypothesis that psychiatric and neurocognitive factors may play a significant role in predicting rate of cognitive decline. An unexpected finding was the lack of difference between fast and slow decliners on delayed recall tests, which have been sensitive to decline in the early stages of dementia in other investigations (Arnaiz & Almkvist, 2003; Marra et al., 2000). The authors noted that this result could be explained as an early floor effect influencing performance on delayed recall tasks of patients with memory impairment. Though several psychiatric and cognitive factors were examined in this study, biomarker and demographic predictors were not considered in this investigation.

An investigation by Sona et al. (2011) aimed to identify factors associated with rapid cognitive decline, defined as a reduction of 6 or more points on the MMSE in 18 months. One hundred eighty individuals with probable AD met this criterion. The predictors investigated were

age, gender, family history of dementia, level of education, smoking habits, diabetes, hypertension, angina or heart attack, cholesterol levels, C-reactive protein, cerebrovascular disease, ApoE genotype, brain derived neurotrophic factor, treatment of cholinesterase inhibitors, and baseline cognitive functioning based on CDR and MMSE. In a multivariate regression, the authors found that CDR and CDR Sum of Boxes, and the use of cholinesterase inhibitors were significantly correlated with rapid cognitive decline. In a multivariate logistic regression analysis, younger age, male sex, and cholinesterase inhibitor treatment made a significant contribution in distinguishing rapid cognitive decliners from slow decliners. A major limitation to this study is cursory cognitive assessment. As discussed earlier, more sensitive and domain-specific measures of cognitive functioning may be better predictors of decline than brief global measures alone.

Rasmusson et al. (1996) studied 132 patients with probable AD and examined MMSE performance over an average of 2.5 years of disease progression. The predictors included patient characteristics (sex, race, education, age at study entry, estimated age at illness onset, estimated illness duration at entry, handedness, and history of dementia in a first degree relative), clinical variables (MMSE score, extrapyramidal symptoms, delusions, hallucinations, depression, and dependency), and cognitive performance (WAIS-R Block Design, Spatial Delayed Recognition Span Test, Benton Visual Retention Test, Responsive Naming Test, BNT, category fluency, Token Test, and Gollin's Incomplete Figures Test (Benton, 1963; Kertesz, 1982, Gollin, 1960). More rapid cognitive decline on the MMSE was predicted by higher levels of education, history of dementia in a first degree relative, non-right handedness, better performance on the BNT, Gollin's Incomplete Figures Test, and Benton Visual Retention Test-Delay, and worse performance on the Responsive Naming test, Block Design, and Benton Visual Retention Test-

Copy. Overall, the results from this investigation support previous findings of higher education predicting faster cognitive decline; however, findings on psychiatric measures (i.e., presence of hallucinations or delusions) were not consistent with results from Buccione et al. (2007). Results of cognitive measures were mixed and verbal episodic memory and biomarker factors were not included. However, these findings support further investigation of the impact of domain-specific neurocognitive measurement on the prediction of the rate of future cognitive decline.

In a large, multivariate investigation, Lopez et al. (2010) combined 14 randomized clinical trial placebo groups (a total of 3728 patients with probable AD) to predict fast versus slow decline on the MMSE and the ADAS-cog over 12 to 24 weeks. The predictors examined were age, gender, body mass index, age at diagnosis, total cholesterol, Hachinski Ischemia score (Hachinski, 1978), history of diabetes, extrapyramidal signs, history of hypertension, baseline cognitive status [MMSE Total, attention (MMSE "World" backward spelling score), baseline global status (CDR-Sum of Boxes score)], baseline functional status (CDR function domain score), and Neuropsychiatric Inventory score. In this investigation, fast decliners were younger with more severe disease at baseline. Fast decline on the MMSE (loss of 1.5 - 2 points) was independently associated with younger age, absence of diabetes, and relatively lower baseline "World" spelling score, higher Neuropsychiatric Inventory score, higher baseline CDR Sum of Boxes, higher baseline CDR function domain score, and lower baseline MMSE Score than the subjects that declined at a slower rate. Similar results were found when examining decline on the ADAS-cog. In a multivariate analysis of these factors, logistic regressions found younger age, baseline "World" score, Neuropsychiatric Inventory total, and CDR Sum of Boxes to be predictors of fast decline on the MMSE. Younger age and baseline MMSE score were also independent predictors of ADAS-cog decline. This study measured decline across a very short

period of time, which limits findings. However, it included factors from all major areas previously investigated to predict rate of future cognitive decline. Further, in this investigation, though baseline cognitive performance was only very cursorily measured by the MMSE, it appeared to better predict future rate of cognitive decline than biomedical variables, supporting the need for further investigation into these markers.

Section Summary

These investigations suggest that several demographic, disease-severity, psychiatric/behavioral, biomedical, and neurocognitive factors may be relevant in predicting the rate of cognitive decline in AD, though some appear to be more reliable than others. Methodological discrepancies likely contribute to the heterogeneity of findings. First, differing specificity and sensitivity of the prediction and outcome measures selected may affect the evaluation of decline. For example, the MMSE may be less sensitive to decline than the CDR resulting in studies with different outcomes based upon the measure utilized (Adak et al., 2004). In addition, brief measures such as the MMSE may be less sensitive to decline than more detailed neuropsychological measures (Atchison et al., 2004). Second, differences in the definition and time frame of decline could impact findings. The studies reviewed investigated decline from 6 months up to10 years, which could result in different predictors across the disease span. Third, specific measurement and definition of markers, particularly biological and neurocognitive, vary greatly between investigations, which could result in discrepant conclusions regarding the same global construct. Further, significant factors from some studies will interact and share variance with factors found to be significant in other investigations, adding to inconsistent findings. Finally, differences in data collection, the number of patients studied, and individual patient characteristics (education,

medical comorbidities, etc.), and patient care and treatment during investigation could impact results.

In addition to these methodological considerations, the disease process itself may diminish the impact of some potential predictors such as episodic memory, as more impaired patients may not be able to perform the task, resulting in floor effects for some variables. In several studies, the effect of predictive factors has been seen early in the disease process, but become nonexistent as severity increases (Cosentino et al., 2008; Storandt et al., 2002). MacDonald et al. (2011) attributed these findings to the possibility that predictors important early in the disease process may become less significant as the disease progresses and other factors may be more important later. Thus, focusing on early stages of the disease process may produce the most reliable results. Furthermore, prognosis from early disease stages would produce more practical and clinically relevant information in terms of financial and caretaking planning for patients and families, as well as tailoring treatment interventions that may have differential efficacy based upon rate of decline.

Despite the limitations of various prediction-of-progression schemes, some patterns have emerged that help inform this line of research. Overall, age at onset appears to be a significant independent predictor of future rate of decline, but becomes less dependable when other factors are considered. Level of education evidenced mixed results, which may be dependent on complex interactions of the dementing proves and availability of cognitive reserve. However, like age of onset, level of education may be less robust when biomarker and cognitive features are considered. The severity of cognitive impairment at baseline appears to be more reliably related to future rate of progression, but estimates of rate of decline prior to diagnosis have not necessarily correlated with future rates of decline. Hippocampal, entorhinal cortex, and total

brain volumes as well as CSF markers may be significant biomarker predictors of decline, but these markers require further investigation as many of these studies utilized small sample sizes, limiting generalizability. Finally, while vascular risk factors appear related to increased rates of future decline, clear cerebrovascular events appear to consistently increase rate of cognitive decline.

Examination of domain-specific deficits indicates that greater impairment in certain areas of cognitive functioning is associated with increased rate of cognitive decline. The cognitive domains most consistently associated with decline are executive functioning, attention, and visuospatial functioning. Few studies examined episodic memory performance as a predictor, and given the importance of this construct in diagnosis and staging of AD, further investigation is warranted. In studies integrating multiple domains of predictive factors, neurocognitive measures and global measures of functioning at baseline appear to be more robust predictors of decline than specific biomedical variables (Lopez et al., 2010; Sona et al., 2011). Thus, neurocognitive factors are an important component in developing a multivariate disease progression model. However, few investigations have been conducted and a specific pattern of neurocognitive deficits in relation to prediction of decline has not been identified.

In sum, our ability to predict patient-specific rate of cognitive decline remains limited. This outcome is likely due to methodological discrepancies between studies. In addition, though some areas such as neurocognitive performance have shown inconsistent results, this may be due to insufficient depth in examination of this domain, and further investigation of this area may lead to better prediction models.

Qualitative Features of Verbal Episodic Memory Performance

Though some studies have investigated neurocognitive performance, results have been inconsistent. One possibility for the lack of an identified cognitive profile is an important aspect of the neurocognitive performance in AD has not been investigated. Much of the research in the previous studies has utilized a quantitative approach to operationalize cognitive variables and has largely ignored the potentially informative qualitative data present in the neurocognitive assessment. Edith Kaplan and colleagues proposed a qualitative approach to neurocognitive assessment as a method for evaluating an individual's behavioral approach to a task (Kaplan, 1988). Analyzing these qualitative factors may reveal the patient's *process*, which can provide a more elaborate picture of cognitive functioning. In addition, scrutiny of qualitative factors can provide more refined assessment than quantitative and standardized scores alone, and may provide information regarding underlying reasons for low quantitative scores (Lamar, Swenson, Kaplan, & Libon, 2004; Milberg, Hebben, & Kaplan, 2009). Such analysis of qualitative features of neurocognitive performance may provide a more sensitive approach to predicting future rate of cognitive decline in early AD than quantitative data alone.

Individuals with AD are likely to exhibit unique qualitative features in their performance on cognitive assessment, and analysis of these variables has been useful in developing patterns of cognitive functioning. For example, individuals with AD are more likely to make intrusion as well as repetition errors than healthy aging populations (Cahn & Salmon, 1997; De Anna et al., 2008). Patients with AD are also more likely to evidence worse word recognition discriminability and more liberal response bias than healthy aging individuals (Snodgrass & Corwin, 1988). Qualitative variables have also been useful in predicting the rate of conversion from mild to more pronounced deficits within the course of the AD disease-process itself,

specifically when examining conversion from MCI to AD. Chang et al., (2010) found that a qualitative marker of learning impairment (learning efficiency index) combined with decreased retention of information reliably predicted progression from MCI to AD in a sample of 607 patients. In a study of 44 amnestic type MCI patients, Lonie et al. (2010) observed that Hopkins Verbal Learning Test-Revised (Brandt & Benedict, 2001) discrimination index (total correct minus false positives on recognition), combined with a measure of global cognitive functioning (Addenbrooke's Cognitive Examination; Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000) differentiated individuals who converted to AD with 74% accuracy. In a PET study of 19 patients with AD, CVLT cued recall intrusions were associated with hippocampal formation dysfunction while free recall intrusions were associated with dysfunction in the prefrontal cortex (Desgranges et al., 2002). Thus, qualitative markers may be important markers for AD disease progression.

As described above, qualitative features of cognitive performance show promise in predicting course of decline from earlier in the disease process (i.e., development of AD and conversion to AD from MCI). The use of a process approach utilizing qualitative neurocognitive variables could likewise benefit prediction of future rate of cognitive decline. Verbal episodic memory is a very sensitive measure in the diagnosis of AD (Albert, Moss, Tanzi, & Jones, 2001; Tierney et al., 2005). Some investigations have examined this construct in the prediction of future rate of cognitive decline and found lower performance to be associated with worse prognosis (Musicco et al., 2010). Moreover, Marra et al. (2000) found that a primacy effect (i.e., recall of information presented earliest in a list) on a test of verbal episodic memory (Rey Auditory Verbal Learning Test; Schmidt, 1996) was related to faster cognitive decline. These results, taken together with similar findings from earlier in the disease process, lend support for

examining qualitative features of verbal memory performance as further analysis of could add valuable information to predictors of decline.

The lack of investigation into qualitative features of verbal episodic memory is likely because many of the measures utilized in previous investigations are brief in nature and may not record or provide sufficient variability in qualitative performance. The California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) is a measure of verbal learning and memory that allows for the examination of qualitative performance characteristics such as primacy and recency effects as well as approximation of the strategy utilized in learning (i.e., serial vs. semantic clustering). Schmid et al., (2013), compared 29 cases of incident dementia to 29 normal controls matched on age, education, demographic status, ApoE genotype, and found that qualitative neuropsychological factors including number of intrusions and response bias on the CVLT were significant predictors of diagnosis of dementia in combination with other cognitive, clinical, and demographic factors (delayed recall of figures, three WAIS-R Block Design subtest variables, number of errors and repetitions on letter fluency, self- report of memory problems, a feeling of sadness, and cardiac problems). Further, in a small study of 34 patients with possible AD, the recency index of the CVLT predicted conversion from MCI to AD with 86% accuracy, with a sensitivity of 93% and specificity of 81% (Lekeu et al., 2010). When this measure was combined with MMSE and short delay cued recall, accuracy, sensitivity, and specificity increased to 100%. Though these results are promising, due to the small sample size in this investigation, conclusions must be tempered. However, the findings from these investigations of qualitative performance characteristics of the CVLT prior to diagnosis with AD support the examination of qualitative features as potential predictors of future cognitive decline in AD.

Summary

Prediction of the rate of cognitive decline in AD has proven to be a difficult challenge. Though several investigations have been conducted, few reliable predictors have been identified. As several demographic, clinical, disease-specific, biological, and cognitive factors have been associated with future cognitive decline, further investigation utilizing a combination of these markers may be necessary to discern the most sensitive predictors. Further, the predictive efficacy of cognitive variables has been understudied and domain-specific measures should be included in integrated investigations. Examination of qualitative neurocognitive variables may reveal more specific features associated with progression of AD and inclusion of these factors may provide more a more sensitive approach to determine the rate of cognitive decline. The presented study is an attempt to evaluate the ability of qualitative verbal episodic memory performance characteristics to predict the rate of future cognitive decline in AD; and in addition, to discern the incremental efficacy of combining these markers with other important individual-specific variables, in predicting rate of future cognitive decline in AD.

CHAPTER TWO

Aims and Hypotheses

Overall Aim

To investigate the ability of neurocognitive, demographic, biomarker, and clinical factors to predict the future rate of cognitive decline in early AD and to develop a model to reliably distinguish fast from slow decliners.

Aim 1. To investigate the ability of verbal episodic memory performance characteristics at baseline to predict fast vs. slow cognitive decline in early stage AD.

Hypothesis 1. Verbal memory performance features from the California Verbal Learning Test (CVLT) will predict fast vs. slow cognitive decline in early stage AD.

Aim 2. To examine the efficacy of adding neurocognitive factors to the model developed in Aim 1.

***Hypothesis 2*.** Combining significant performance feature CVLT scores with additional indices of neurocognitive functioning and global cognitive functioning, will better predict fast vs. slow decline in early stage AD than the model developed in Aim 1.

Aim 3. To examine the efficacy of adding demographic and clinical features to the prediction model developed in Aim 2.

***Hypothesis 3*.** Demographic and clinical factors will be significant contributors to the model developed in Aim 2.

Exploratory Aim. To examine the efficacy of adding biomarker features to the prediction model developed in Aim 3.

CHAPTER THREE

Detailed Method

This project constitutes a retrospective analysis of data collected from 1995 to 2011 at the Alzheimer's Disease Center (ADC) at the University of Texas Southwestern Medical Center. The Clinical Core of the ADC collects neurocognitive and clinical data of individuals with AD and healthy aging persons at regular intervals. Since 1995, all participants have received a comprehensive neurocognitive and clinical assessment, while a subset has also undergone MRI and biomarker/serum analysis. The ADC thus provides a longitudinal sample of participants at all stages of the AD process in which to analyze factors related to rate of cognitive decline in early AD.

Participants

Data were derived from subjects enrolled in the ADC. The University of Texas Southwestern Medical Center institutional review board approved the study and all subjects provided informed consent for participation. Subjects for this investigation had English as a primary language. In addition to these criteria, male and female participants who met the following criteria were included in the current study:

1. *A priori* consensus diagnosis of probable or possible AD at baseline using the National Institute of Neurological and Communication Disorders and Stroke/AD and Related Disorders Association (NINCDS/ADRDA) criteria.
2. Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) score of 2.5 to 9.0 (O'Bryant et al., 2008) at baseline, indicating early very mild to mild AD.
3. Completion of neuropsychological assessment at baseline including the CVLT.

4. Follow-up evaluation within 2 years with CDR. Two-year follow-up was chosen to allow an adequate time for cognitive decline and to limit patient attrition. This timeframe is consistent with previous research in prognosis of AD.

Exclusion criteria were failure to meet one or more of the above listed requirements. In addition, any participants with symptoms that may confound diagnosis of AD (e.g., parkinsonism and Lewy body disease) were excluded. A sample of 96 subjects that meet these criteria was identified (See Appendix A for discussion of excluded participants).

Measures

Selected tests and test scores were chosen based on their demonstrated independent utility in predicting the rate of future cognitive decline in early AD and/or an identified risk factor for developing AD.

Overall Functioning

Clinical Dementia Rating Scale (CDR). The Washington University Clinical Dementia Rating Scale (Morris, 1988) was developed to clinically denote the presence of dementia of Alzheimer's type and stage its severity. The CDR utilizes a semistructured interview protocol with patient and informant. The CDR assesses cognitive functioning in six domains: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. Each domain is rated on a 5-point scale of functioning as follows: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment. The Global CDR is derived from these domains and is made up of five cognitive impairment staging groups: CDR-0 =

normal, CDR-0.5 = very mild dementia, CDR-1 = mild, CDR-2 = moderate, CDR-3 = severe.

CDR Sum of Boxes (CDR-SOB). The CDR-SOB is a summed total score of ratings within each of the six CDR domains and ranges from 0-18. The CDR-SOB has a greater range of demonstrated sensitivity to change in AD than the Global CDR score (O'Bryant et al., 2008). In AD, the CDR-SOB score increases by 1.5 points annually on average (Aisen et al., 2008), and two-year increase in the CDR-SOB has been significantly associated with functional decline as measured by loss of one or more points on the Independent Activities of Daily Living (Coley, Andrieu, & Jaros, 2011).

Neurocognitive Measures

Episodic Memory

California Verbal Learning Test (CVLT). The California Verbal Learning Test (Delis et al., 1987) is a widely utilized and well-validated measure of verbal learning and episodic memory. In addition to quantitative learning and recall scores, the measure provides scores that depict numerous qualitative indices of learning and recall. The CVLT and other measures of verbal episodic memory have been sensitive to diagnosis of AD as well as rate of cognitive decline (Cahn & Salmon, 1997; De Anna et al., 2008; Marra et al., 2000; Schmid, et al., 2013). The present study utilized the following scores: Total Learning T-score, Long-delay Free Recall z-score, Long Delay Cued Recall z-score, % Recall from Primacy Region z-score, % Recall from Recency Region z-score, Recall Consistency z-score,

Semantic Clustering z-score, Total Intrusions z-score, Recognition Discriminability z-score, Total Perseverations z-score, and Response Bias z-score.

Wechsler Memory Scale - Revised Visual Reproduction subtest. The Wechsler Memory Scale – Revised Visual Reproduction (Wechsler, 1987) subtest is a measure of visual learning and memory, which requires the immediate and delayed recall and recognition of simple visual figures. Impaired performance on nonverbal learning and memory tasks have been shown to be significant in predicting rate of cognitive decline in AD (Rasmusson et al., 1996). Visual Reproduction II Scaled score and Visual Reproduction Percent Loss scores were analyzed.

Executive Functioning

Trail Making Test. The Trail Making Test is a commonly used measure of processing speed, visual scanning, and mental flexibility (Lezak, Howieson, & Loring, 2004; Reitan & Wolfson, 1995). Part A of the test involves simple attention, visual scanning, and psychomotor speed. Part B additionally requires mental set shifting, is thought to be more of a measure of executive functioning than Trails A, and has been associated with rate of cognitive decline (Bowie & Harvey, 2006; Lopez et al., 2010). The present study utilized the Trail Making Test - B Time T-score.

FAS Test. The FAS Test is a verbal fluency test that involves the spontaneous production of words restricted to a specific letter within a time constraint of 60 seconds for each trial (Borokowski, Benton, & Spreen,1967). Several investigations have suggested that this search presents executive functioning demands (Henry, Crawford, & Phillips, 2004; Perret, 1974). Musicco et al. (2010) found executive

functioning as measured by letter fluency to significantly predict rate of cognitive decline in AD. FAS Total Words T-score were used for analysis.

Semantic Fluency. The semantic fluency test is a verbal fluency test that involves the spontaneous production of words restricted to a specific category (i.e., animals) within a time constraint of 60 seconds (Strauss, Sherman, & Spreen, 2006). Decreased semantic fluency score has been related to faster rate of cognitive decline, and this study used Category Total Words T-score (Beatty, et al., 2002).

Language

Boston Naming Test. The Boston Naming Test (Kaplan et al., 1983) is a 60-item visual confrontation naming test. It is widely used in the assessment of semantic memory (Ferraro & Lowell, 2010). Boston Naming Test has been variably associated with rate of future cognitive decline (Atchison et al., 2004; Rasmusson et al., 1996). The 30-item version of the Boston Naming Test was included and a prorated Boston Naming Test Total T-score was calculated and analyzed for this study. The CERAD neuropsychological battery (Morris et al., 1993) contains a short 10-item form of the BNT, which was also analyzed for this study.

Visuospatial

Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1981) Block Design. The WAIS-R Block Design subtest is a visuoconstruction task that involves physical manipulation of blocks to match a presented pattern within a specific time limit. It is considered to be sensitive to the ability to analyze and synthesize visual information (Strauss et al., 2006). The Block Design Scaled score has been

sensitive to predicting rate of cognitive decline in AD and was included in the analysis (Rasmusson et al., 1996).

Attention

WAIS-R Digit Span subtest. The Digit Span subtest of the WAIS-R is a measure of simple auditory attention and working memory. Digit Span Forward involves auditory presentation and recall of a sequence of numbers, and is a considered to be a measure of simple attention. Digit Span Backward additionally requires reverse report of presented numbers and is considered to be a measure of working memory (Lezak et al., 2004). This study utilized Digit Span Backward percentile scores as it was found to significantly predict rate of cognitive decline in a study by Musicco et al., (2010).

Processing Speed

WAIS-R Digit Symbol Coding subtest. The Digit Symbol Coding subtest of the WAIS-R is a time-restricted number/symbol substitution task that measures processing speed, attention, and visual scanning. Berg et al. (1984) found graphomotor processing speed to be significant in predicting future rate of cognitive decline (Digit Symbol Coding Scaled Score was used).

Global Cognitive Functioning

Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Neuropsychological Battery. The CERAD Neuropsychological Battery (Morris et al., 1993) is a set of assessments that are used to detect cognitive impairment in AD. The battery consists of Verbal Fluency, Boston Naming Test, Mini-Mental State Exam, Word List Memory, Constructional Praxis, Word List Recall, Word

List Recognition, and Recall of Constructional Praxis. A demographically corrected summed score of these subtests (CERAD Total Score) has been useful in rating global cognitive functioning and charting progression in AD (Chandler, Lacritz, & Hynan, 2005; Rossetti et al., 2010) and was used in this study.

Biomarker and Clinical Measures

Subject Health History. The National Alzheimer Coordinating Center Uniform Data Set Form A5 is a record of subject health history. It includes the presence or history of various medical and psychiatric conditions that may affect the development and/or rate of cognitive decline in AD (Buccione et al., 2007; MacDonald et al., 2011; Mielke et al., 2010). This study utilized history of cardiac disease (heart attack/cardiac arrest, atrial fibrillation, angioplasty/endarterectomy/stent, cardiac bypass procedure, pacemaker, and/or congestive heart failure), vascular disease (stroke and/or transient ischemic attack), traumatic brain injury, diabetes, hypercholesterolemia, hypertension, depression within the last 2 years, and history of psychiatric symptoms (i.e., presence of hallucinations or delusions).

MRI. Structural brain imaging was performed on a subset of subjects with a 1.5 or 3T Phillips MRI scanner and high-resolution T1-weighted structural images were acquired. The present study utilized total brain volume, and hippocampal volume as these have been associated with cognitive decline in AD (Jack et al., 2011).

Genotype. Apolipoprotein E genotyping involved DNA amplification and extraction from blood samples. Apolipoprotein E ε4 allele type has been significantly associated with risk of developing AD and the present study utilized presence of apolipoprotein E ε4 allele type (Adak et al., 2004).

Demographic

Several demographic variables that have been associated with future rate of cognitive decline, including age of onset, age at diagnosis, level of education, and gender were included (Jacobs et al., 1994; Scarmeas et al., 2006).

Dependent Variable

Cognitive decline was measured using the Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB; Morris, 1993) which increases by 1.5 points annually on average in AD (Aisen et al., 2008). As there is no clear consensus in the literature regarding a definition of "fast" versus "slow" cognitive decline, for the purpose of this study, "Faster" cognitive decline was defined as an increase of three or more points on the CDR-SOB approximately two years after baseline (i.e., faster than average), and an increase of less than three points was defined as Slower progression.

Independent Variables

See Table 1.

Primary Analyses

The relationships between predictor variables and rate of progression were investigated with stepwise logistic regression analyses. Descriptive results were produced for all variables, including means and standard deviations for continuous measures. Statistical assumptions were examined prior to analysis including checking data for normal distribution of predictors, equal variances between populations, independent random sampling, adequate sample size, and linear relationships between variables. In addition, standard errors were examined in regression

analyses to preserve goodness of fit. The level of significance was set at $p < 0.05$ for comparisons of means, correlations, and regression analyses. Relationships between predictor variables and the outcome were analyzed using T-tests (Mann-Whitney U tests for variables that are not normally distributed). Associations between all predictor variables were examined with Pearson product-moment correlations.

When performing logistic regression model building, several steps were performed. First, for each initial stepwise logistic regression, a predictor was added if alpha < 0.25 and deleted if alpha > 0.26. Variables entering into the equation were then backwards reduced according to Wald significance. In the final logistic regression model predictors were added if alpha < 0.05 and deleted if alpha > 0.10. Thus, the individual predictors that accounted for the most variance were included in the final logistic regression model. The impact of demographic factors was adjusted for by utilizing demographically adjusted standard scores and including the demographic variables of age, education, and gender into the original logistic regression models. Sensitivity and specificity of each model in predicting the progression of AD were displayed by plotting receiver operating characteristic curves. Finally, a cut-score that optimizes sensitivity and specificity was selected and accuracy of classification examined.

Aim 1. The CVLT variables (% Recall from Primacy Region z-score, % Recall from Recency Region z-score, Recall Consistency z-score, Semantic Clustering z-score, Total Intrusions z-score, Recognition Discriminability z-score, Total Perseverations z-score, and Response Bias z-score), and demographic variables of age, education, and gender were included as predictors in a stepwise logistic regression to predict Slower vs. Faster progression based upon 2-year follow up data.

Aim 2. Additional neurocognitive variables (CVLT Total Learning T-score, Long-delay Free Recall z-score, Visual Reproduction I Percentile, Visual Reproduction II Percentile, Trail Making Test - B Time T-score, FAS Total Words T-score, Boston Naming Test Total T-score, Category Total Words T-score, Block Design Scaled score, Digit Span Backward percentile, Digit Symbol Coding scaled score, CERAD Total Score), and demographic variables of age, education, and gender, and significant Aim 1 variables were used in stepwise logistic regression to predict Slower vs. Faster progression based upon 2-year follow up data.

Aim 3. The health variables of history of heart disease, vascular disease, traumatic brain injury, diabetes, hypercholesterolemia, hypertension, depression within the last 2 years, psychiatric disorders, duration of illness, age of onset, and demographic variables of age, education, and gender, and Aim 2 variables were used in stepwise logistic regression to predict Slower vs. Faster progression based upon 2-year follow up data.

Exploratory Aim. The variables left hippocampal volume, total brain volume, presence of ApoE ε4, and Aim 3 variables were used in stepwise logistic regression to predict Slower vs. Faster progression based upon 2-year follow up data.

Discussion of Methodological Alterations

Due to sampling limitations, some methodological alterations were made:

The rule of thumb for logistic regression suggests a minimum of 5 observations in the smallest group per predictor is required to adequately conduct logistic regression. A sample size of at least 30 observations in the smaller group was considered large enough for analysis of 5 predictor variables. Due to the small number of observations for Trail Making Test - B (N = 62), Boston Naming Test (N = 29), and Block Design (N = 48), these measures were excluded from the stepwise logistic regression analyses. Trail Making Test - A and the Boston Naming portion of the CERAD were substituted in these analyses. Similarly, MRI measures, ApoE ε4 genotype, and history of hypercholesterolemia, epilepsy, hallucinations, and delusions were excluded from stepwise logistic regression analyses due to low number of observations.

Most Pearson Product Moment correlations between predictor variables were below 0.70. However, as expected, Age of Disease Onset and Age at Visit were highly correlated ($r = 0.95$), and Age at Onset was excluded from analyses.

CHAPTER FOUR

Summary of Investigation

PREDICTING THE RATE OF DECLINE IN EARLY ALZHEIMER DISEASE: THE ROLE OF NEUROCOGNITIVE PERFORMANCE FEATURES

Abstract

Objective: Alzheimer disease (AD) is a neurodegenerative disorder that characteristically begins with episodic memory impairment followed by other cognitive deficits over time; however, the course of illness varies, with significant variability in terms of the *rate* of cognitive decline across affected individuals. Several studies have examined demographic, clinical, biological, and neurocognitive performance markers to predict rate of AD progression, but findings are mixed. The current study utilized neurocognitive performance features along with disease-specific and health features to determine the best prediction model for the rate of future cognitive decline in subjects with mild AD.

Method: Ninety-six subjects with mild AD at baseline were administered a comprehensive battery of neurocognitive tests and clinical measures. Based on Clinical Dementia Ratings (CDR) of functional and cognitive decline within two years, subjects were determined to be Faster (n = 45) or Slower Progressors (n = 51). Stepwise logistic regressions using neurocognitive performance features, disease-specific, health, and demographic variables were performed in a hierarchical fashion to determine optimal predictors of rate of progression.

Results: Several individual neurocognitive measures distinguished Faster from Slower Progressors at baseline, including Trail Making Test - A, Digit Symbol, California Verbal

Learning Test (CVLT) Total Learned, CVLT Primacy Recall, and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Neuropsychological Battery Total Score. No disease-specific, health, or demographic variables predicted rate of progression; however, history of cardiac illness showed a trend. In a stepwise logistic regression of neurocognitive performance features alone, a combination model of three measures (Trail Making Test - A, Semantic Fluency, and CERAD Total) distinguished Faster from Slower Progressors with 76% accuracy. In an omnibus model including neurocognitive, disease-specific, health, and demographic variables, only Trail Making Test - A distinguished groups (68% correct classification). **Conclusion:** Several neurocognitive performance features may play a role in predicting rate of decline in mild AD. Notably, three relatively brief and commonly used measures were found to predict differences in rate progression with good accuracy. Results from the current research provide important advances in understanding the role of neurocognitive measures in predicting rate of decline in AD.

Predicting The Rate Of Decline In Early Alzheimer Disease:

The Role of Neurocognitive Performance Features

Alzheimer disease (AD) is a neurodegenerative disorder manifested by worsening cognitive and functional ability over time. AD imparts multiple and complex effects on patients, caregivers, and society, including medical and specialized care costs, lost wages, nursing home placement, and significant emotional burden. Most of these effects are exhibited across multiple years, as the inexorable and progressive course of cognitive decline significantly impacts patients' ability to function in daily life and dictates their care needs.

The disease tends to follow a general pattern of early episodic memory impairment followed by other cognitive deficits over time, but significant variability is seen in terms of the *rate* of cognitive decline. If the trajectory of an individual's disease course could be predicted, it might enable patients and caregivers to optimize resources and adjust family and social activities in a timely fashion. Further, research and treatment protocols could be tailored to the progression trajectory for individual patients. Several demographic (e.g., age and level of education), clinical (e.g., history of traumatic brain injury), biomedical (e.g., presence of ApoE ε4) and neurocognitive (e.g., worse episodic memory) patient characteristics associated with *risk* of developing AD have shown promise in predicting *future* rate of cognitive decline, though results have been mixed (Adak et al., 2004; Cosentino et al., 2008).

Only a handful of studies have examined neurocognitive performance to predict rate of AD progression, but preliminary findings show promise. For example, Atchison, Bradshaw, and Massman (2004) examined 211 patients who were followed for 12 to 18 months after an initial neuropsychological evaluation that included all subtests from a global measure of intelligence [Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981)], a confrontation

naming measure [Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983)], and an attention screening measure [Verbal Series Attention Test (Mahurin & Cooke, 1996)]. Subjects that declined faster on the MMSE performed worse at baseline on the WAIS-R subtests of Block Design, Digit Symbol, Arithmetic, Similarities, and Picture Completion, as well as the Verbal Series Attention Test. Notably, though global cognitive screening scores (MMSE) were similar, in-depth neuropsychological assessment revealed baseline performance differences between groups. These results indicate that more sensitive measures of cognitive functioning may be better at predicting rate of decline than brief, global measures alone.

Other investigators have examined deficits in specific cognitive domains and found significant associations between performance on domain-specific measures and faster decline in AD, but there is no clear agreement on what measures are most sensitive or whether a particular pattern of scores aids in prediction of future rate of decline. In terms of language measures, Beatty and colleagues examined primary and supplementary measures of semantic memory in 152 subjects with probable AD and found that lower Boston Naming Test (BNT) and semantic fluency scores, but not letter fluency scores, were associated with more rapid decline on a global measure of cognitive impairment (Dementia Rating Scale; Mattis, 1988) (Beatty, Salmon, Troster, & Tivis, 2002). An earlier investigation also concluded that initial poor performance on BNT was associated with faster cognitive decline as measured by the MMSE (Boller & Becker, 1991). In contrast, Rasmusson et al. (1996) found that *better* BNT performance at baseline was associated with faster decline, while lower Token Test (a measure of auditory comprehension; Renzi & Vignolo, 1962) performance predicted faster decline on the MMSE in 132 patients with probable AD. Berg et al. (1984) found low WAIS-R Digit Symbol performance at baseline (a measure of graphomotor processing speed), in addition to higher levels of aphasia, was

associated with more rapid cognitive decline as reflected by the MMSE and Blessed Dementia Scale in 43 subjects with mild AD.

Combinations of neuropsychological measures have also been utilized to predict the rate of cognitive decline. For example, Marra et al. (2000) examined performance on multiple cognitive domains, including verbal and visual memory, simple and demanding attention, working memory, constructional praxis, language, and visuospatial reasoning in 55 patients with early stage AD (defined as onset of symptoms within the past two years). Patients were considered to be "fast decliners" if they evidenced a decline of 25% on the MMSE after approximately one year. After performing a principle components analysis on all neuropsychological variables, lower visuospatial attention, verbal learning and recall, a primacy effect in verbal recall (i.e., early list items being recalled better than items from later serial positions), and impaired inductive reasoning were components of the factor carrying the most variance. Discriminant function analysis on this factor indicated that these measures were significant in identifying fast decliners. In another multivariate investigation, Musicco et al. (2010) studied 154 newly diagnosed AD patients with mild, moderate, or severe impairment within the cognitive domains of memory, executive function, praxis, and language. The authors defined progression as the loss of at least five points on the MMSE within two years Those with more severe memory and executive function impairments at baseline had were more likely to progress over two years. However, in a multivariate analysis, only severely impaired executive functioning at baseline predicted faster progression. These investigations highlight that although neurocognitive measures may help predict rate of progression, there is a lack of consensus in identifying early cognitive markers for faster decline.

The lack of consensus regarding neurocognitive predictors may relate to the types of neurocognitive variables utilized thus far, which may be insensitive to distinguishing rates of progression (Storandt et al., 2002). For example, summation variables such as "total learned" are often used to assess memory performance, though such global or composite scores may mask distinguishing underlying performance characteristics. A *process approach* (e.g. see Kaplan, 1988) utilizing performance features of memory and cognition may enhance our ability to predict the rate of cognitive decline in AD. For example, several performance characteristics such as intrusion and recognition errors during word-list learning and recall, as well as higher recall of the most recently presented stimuli (recency) have been identified as valuable in predicting progression from healthy aging and mild cognitive impairment (MCI) to AD (Ahmed, Mitchell, Arnold, Nestor, & Hodges, 2008; Lekeu et al., 2010; Lonie et al., 2010; Myers, Kluger, Golomb, Gluck, & Ferris, 2008; Schimd, et al., 2013). It follows that such variables may play a role in predicting the rate of cognitive decline from early to later stages of AD, although the potential contribution of these factors has not been evaluated.

Markers for rate of decline in AD span across demographic, disease-specific, biomedical, and neurocognitive domains; however, no consensus has emerged. Integrated approaches that examine measures from these domains together, may better predict rate of future decline than any of the markers alone (Sona et al., 2011). The purpose of this study was to address these gaps in our understanding of predicting the rate of cognitive decline in early AD, by: 1) examining the role of verbal episodic memory performance characteristics, 2) evaluating the incremental contribution of additional neurocognitive performance features across different measures, and 3) integrating these variables with disease-specific and health features to determine the best prediction model for the rate of future cognitive decline in subjects with mild AD.

Methods

Participants

Data were derived from subjects enrolled longitudinally from 1995 to 2011 at the Alzheimer's Disease Center (ADC) at the University of Texas Southwestern Medical Center. All participants met the following criteria for inclusion:

1. *A priori* consensus diagnosis of probable or possible AD at baseline using the National Institute of Neurological and Communication Disorders and Stroke/AD and Related Disorders Association (NINCDS/ADRDA) criteria.
2. Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) score of 2.5 to 9.0 at baseline, indicating very mild to mild AD (O'Bryant et al., 2008).
3. Completion of neuropsychological assessment at baseline including the California Verbal Learning Test (CVLT; Delis et al., 1987).
4. Follow-up evaluation between 1 to 3 years with CDR data available. Two-year follow-up was chosen to allow an adequate time for cognitive decline and to maximize sample size.
5. Fluency in English.

In addition, any participants with symptoms that may confound diagnosis of AD (e.g., parkinsonism, Lewy body disease, etc.) were excluded. Ninety-six subjects met criteria for the study (See Appendix A).

Measures

Rate of progression. The Washington University Clinical Dementia Rating Scale (CDR; Morris, 1993) was developed to clinically denote the presence of AD and stage its severity. The CDR is based upon observer ratings of cognitive functioning in six domains: Memory, Orientation, Judgment and Problem Solving, Community Affairs,

Home and Hobbies, and Personal Care. Each domain is rated on a 5-point scale of functioning as follows: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment.

The CDR Sum of Boxes (CDR-SOB) is a summed total score of ratings within each domain and ranges from 0 -18. In AD, two-year increase in the CDR-SOB has been significantly associated with functional decline as measured by loss of one or more points on the Independent Activities of Daily Living (Coley et al., 2011). In AD, the CDR-SOB score increases by 1.5 points annually on average (Aisen et al., 2008). As there is no clear consensus in the literature regarding a definition of rapid versus slow cognitive decline, for the purpose of this study, "Faster" cognitive decline was defined as an increase of three or more points on the CDR-SOB approximately two years after baseline (i.e., faster than average), and an increase of less than three points was defined as "Slower" progression.

Predictors of rate of progression. At baseline, all patients were administered a battery of neuropsychological tests covering several cognitive domains including memory, speed of information processing, language, attention, visuospatial ability, and executive function in addition to providing health history and information specific to course of illness. Predictors from all of these areas were chosen to determine which factors best account for variance in predicting rate of cognitive decline. All variables were chosen based on their frequency in clinical use and demonstrated utility in identifying AD in its early stage and/or predicting the rate of cognitive decline. Independent Variables are summarized in Table 2 (see Chapter Three for description of measures).

Cognitive measures. Episodic Memory was assessed using the California Verbal Learning Test (Delis et al., 1987) and Wechsler Memory Scale - Revised Visual Reproduction subtest (Wechsler, 1987). Processing Speed was measured by the Wechsler Adult Intelligence Scale – Revised (WAIS-R) Digit Symbol subtest (Wechsler, 1981) and Trail Making Test- A (Reitan & Wolfson, 1995). Executive Functioning was assessed with Trail Making Test - B, Phonemic Fluency (FAS Test), and Semantic Fluency (Animals) (Borokowski, et al.,1967; Reitan & Wolfson, 1995). Language was measured by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Neuropsychological Battery Naming subtest (Morris, 1988). Visuospatial functioning was assessed using WAIS-R Block Design (Wechsler, 1981). Attention was measured using WAIS-R Digit Span subtest (Wechsler, 1981). Global Cognitive Functioning was assessed using the total score from the CERAD Neuropsychological Battery (Morris, 1988; Chandler, et al., 2005).

Clinical measures. Subject health history was gathered using the National Alzheimer Coordinating Center Uniform Data Set which collects self or informant report of history of heart disease (heart attack/cardiac arrest, atrial fibrillation, angioplasty/endarterectomy/stent, cardiac bypass procedure, pacemaker, and/or congestive heart failure), vascular disease (stroke and/or transient ischemic attack), traumatic brain injury with loss of consciousness over 20 minutes, diabetes, hypercholesterolemia, hypertension, depression within the last two years, and hallucinations and/or delusions. Disease-specific factors of duration of illness and age at diagnosis were collected through self or informant report.

Demographic variables. Subject age, level of education, and gender were collected via self or informant report.

Statistical Analyses

The relationships between predictor variables and rate of progression were investigated with stepwise logistic regression analyses. Relationships between predictor variables and Progressor group were analyzed using t-tests. Associations between all predictor variables were examined with Pearson product-moment correlations. When performing logistic regression model building, several steps were performed. First, for each preliminary stepwise logistic regression model, a predictor was added if alpha < 0.25 and deleted if alpha > 0.26. Variables entering into the equation were then backward eliminated according to predictor significance. The final model was entered into a logistic regression with predictors added if alpha < 0.05 and deleted if alpha > 0.10. Thus, the individual predictors that accounted for the most variance were included in the final logistic regression model. Models controlled for the impact of demographic factors by utilizing demographically adjusted standard scores. Sensitivity and specificity of each model in predicting the progression of AD were examined by plotting receiver operating characteristic curves. A cut-score that maximized sensitivity and specificity was selected.

Results

Demographic Characteristics

Of the 1,011 consecutive participants with a diagnosis of AD drawn from the ADC, 96 met criteria for inclusion (see Appendix A for discussion of excluded sample). Of these, 45 were identified as Faster Progressors (CDR-SOB decline of greater than or equal to 3 points) and 51 were identified as Slower Progressors (CDR-SOB decline of less than 3 points). Independent

samples t-tests revealed that the groups did not differ in terms of age at baseline, level of education, age of AD onset, or duration of illness (Table 3). A Chi-square test indicated that groups were similar in terms of gender (Table 4).

Dementia Severity and Progression

Both groups were similar in terms of dementia severity at baseline, with Faster and Slower Progressors having mean CDR-SOB scores ranging from 3.0 to 8.0, indicating very mild to mild dementia [$Mean(SD)_{Faster}$ = 5.04 (1.22); $Mean(SD)_{Slower}$ = 5.31 (1.17); O'Bryant et al., 2008]. Independent samples t-tests revealed that groups were similar on baseline CDR-SOB and MMSE scores (Table 5). Time to follow-up was also similar, ranging between 1 and 3 years. As expected, Faster Progressors declined approximately seven points on CDR-SOB [Mean (SD) = 12.03 (3.21); Range = 7.0 - 18.0], while Slower Progressors remained stable [Mean (SD) = 5.40 (1.92); Range = 0.5 - 9.0].

Descriptive Statistics

CVLT performance features, neurocognitive measures, and clinical data.

Aim 1: Predictors of disease progression – performance features of verbal episodic memory. Means, standard deviations, ranges, frequencies, and t-test results for all CVLT variables at baseline are presented in Table 6. The Faster Progressors group scored significantly lower on the Percent Recall from the Primacy Region of the word list than the Slower Progressors. Semantic Clustering of related words, Percent Recall from the Recency Region of the list, and Recognition Discriminability were also worse in Faster Progressors, though the differences were not significant. Recall Consistency, number of

Intrusions on Free Response trials, Response Bias, and number of Perseverations were not statistically different between groups.

Aim 2: Predictors of disease progression – neurocognitive assessment. Means, standard deviations, ranges, frequencies, and t-test results for all neurocognitive measures are presented in Table 7. The number of subjects who completed each test was variable due to alterations to the testing battery across the 15-year span of the data collection period. Faster Progressors performed at a lower level than Slower Progressors on all neurocognitive measures with the exception of CVLT Long Delay Free Recall. The Faster Progressors group performed significantly worse on Digit-Symbol, Trail Making Test - A, CVLT Total, and CERAD Total than the Slower Progressors. Boston Naming Test was also significantly worse in Fast Progressors; however, the number of observations was low for this measure. Differences in performance approached significance ($p < 0.1$) on several measures including Digit Backwards Longest Span, CERAD Boston Naming Total, and Trail Making Test - B. Performance on all other measures was not statistically different between groups.

Aim 3: Predictors of Disease Progression – Clinical Variables. Health history, variables were coded to reflect presence or absence of illness. Chi-square and Fisher's exact tests indicated that Faster Progressors and Slower Progressors did not significantly differ on any health or psychiatric variables (Table 8).

Research Hypotheses

Aim 1: Predictors of disease progression – performance features of verbal episodic memory. It was postulated in Hypothesis 1 that performance features of the CVLT would predict faster progression of mild AD.

Individual prediction analyses. Percent Recall from the Primacy Region (Primacy) significantly predicted progression (OR = 0.825, p = 0.04; Table 9). In contrast, Percent Recall from the Recency Region, Recall Consistency, Semantic Clustering, Free Recall Intrusions, Recognition Discriminability, Response Bias, and Free Recall Perseverations did not predict progression.

Backward elimination stepwise regression analysis. When all CVLT performance scores and demographic factors were entered into stepwise logistic regression and eliminated using a backward stepwise procedure, only Primacy significantly predicted progression ($\chi^2 = 4.668$, $p < .05$ with df = 1; Table 10). The Hosmer-Lemeshow goodness-of-fit test indicated that the model fit the data adequately (p = .329). Primacy significantly predicted prediction, with lower scores having increased odds of faster progression [Odds Ratio = 0.825, CI = .689 – .987]. The area under the receiver operator characteristic (ROC) curve was used to characterize the final adjusted model, which showed discrimination between Faster Progressors and Slower Progressors (AUC = .621, *p* = .04, CI = .509 - .733; see Figure 1). A Primacy z-score of -0.5 provides 75% sensitivity and 47% specificity with 60% correct classification.

Aim 2: Predictors of disease progression – neurocognitive assessment. It was postulated in Hypothesis 2 that additional neurocognitive assessment measures in

combination with significant performance features of the CVLT would be predictors of faster progression of mild AD.

Individual prediction analyses. Several individual neurocognitive measures predicted progression (Table 11). Digit Symbol (OR = .797; p < .01) predicted progression and the area under ROC curve was .676 ($p < .01$, CI = .556 - .796). Trail Making Test - A also predicted progression (OR = .944, p < .01, see below for further analyses). CVLT Total Learned predicted progression (OR = .950, p = .02) and the area under ROC curve was .628 (p = 0.03, CI = .515 - .741). CERAD Total predicted progression (OR = 0.926, p = 0.02) and the area under the ROC curve was .679 ($p < 0.01$, CI = .569 - .790). See Appendix C for corresponding ROC Figures.

The remaining neurocognitive variables were not systematically related to progression. Whereas the CERAD Boston Naming and Trail Making Test - B approached significance, Phonemic Fluency, Semantic Fluency, Longest Digit Span Backward, Visual Reproduction I, Visual Reproduction II, CVLT Long Delay Free Recall, Block Design, and full Boston Naming Test did not significantly predict progression.

Backward elimination stepwise regression analyses. When CVLT Primacy, additional neurocognitive measures and demographic factors were entered into stepwise logistic regression and eliminated through a backward stepwise procedure, a combination of CERAD Total Score, Semantic Fluency, and Trail Making Test - A significantly predicted progression (Table 12). The Hosmer-Lemeshow goodness-of-fit test indicated that the model fit the data adequately (p = .30). All three predictors made significant contributions to prediction of progression (p < .05). The area under receiver operator characteristic curve was used to characterize the final adjusted model, which showed

good discrimination between Faster Progressors and Slower Progressors (AUC = .769, p < .01, CI = .658 - .880; see Figure 2). A cutoff score of 0.56 determined membership in the Faster Progressors group with 67% sensitivity and 84% specificity (76% correct classification). This score was obtained by combination scores of TMT-A T = 34, CERAD Total = 64, and Semantic Fluency T = 33.

Aim 3: Predictors of disease progression – clinical variables. It was postulated in Hypothesis 3 that a model of health, psychiatric, and disease-specific variables combined with significant performance features from the CVLT (from Aim 1) and significant additional neurocognitive assessments (from Aim 2), and would be a significant predictor of faster progression of AD.

Individual prediction analyses. None of the health history variables were individual predictors of faster decline (Table 13). Cardiac history approached significance in predicting progression (OR = 0.381, p = 0.05) and the area under receiver operator characteristic curve was .587 (p = 0.15, CI = .471 - .702; see Appendix C). Cerebrovascular Event, TBI, Hypertension, Hypercholesterolemia, Diabetes, and Depression Within the Past Two Years did not significantly predict progression.

Backward elimination stepwise regression analysis. When Health Variables, Duration of Illness, Trail Making Test - A, CERAD Total, Semantic Fluency, and demographic factors were entered into stepwise logistic regression and reduced through a backward stepwise procedure, only Trail Making Test - A significantly predicted progression (Table 14; χ^2 = 11.106, p < .01). The Hosmer-Lemeshow goodness-of-fit test indicated that the model fit the data adequately (p = .96). The area under receiver operator characteristic curve was used to characterize the final adjusted model, which showed

good discrimination between Faster Progressors and Slower Progressors (AUC = .706, $p < .01$, CI = .590 - .821; see Figure 3). A predicted T-score of 39 or lower determined membership in the Faster Progressors group with 71% sensitivity and 66% specificity (68% correct classification).

Results Summary

Table 15 summarizes the significant prediction models. An integrated model including Trail Making Test - A, CERAD Total, and Semantic Fluency best predicted rate of progression, followed by individual neurocognitive measures, and a health marker.

Discussion

The rate of decline in AD has been difficult to predict, due to the multifactorial contributors to decline including neurocognitive, clinical, and biomarker features, in addition to various other individual differences. Neurocognitive measures have been investigated as possible predictors of rate of progression in few investigations. Findings from these studies, while somewhat variable, suggest that neurocognitive measures may be effective in predicting rate of decline, sometimes better than clinical, demographic, and biomarkers (Lopez et al., 2010; Sona et al., 2011). Whereas global cognitive test scores have generally been used as predictors, an important component of neurocognitive assessment (i.e., performance *features* of episodic memory) has been examined in rate of progression in a very limited fashion. The purpose of this study was to examine the ability of performance features of the CVLT to predict future rate of decline in subjects with mild AD. Additionally, the ability of these features to predict decline in

the context of comprehensive neurocognitive assessment in addition to clinical features was examined.

Aim 1: Predictors of Disease Progression - Performance Features of Verbal Episodic Memory

Hypothesis 1 postulated that performance features of verbal episodic memory performance would predict faster cognitive decline in individuals with mild AD. Percent Recall from the Primacy Region (Primacy) of the CVLT predicted faster progression. In an ROC analysis of Primacy, the area under the curve was 0.62 and the confidence interval did not cross the line of discrimination (0.50), indicating that this measure had acceptable, but not impressive discrimination ability.

Primacy was the only performance feature of the CVLT to significantly distinguish Faster from Slower Progressors at baseline and predict rate of progression. Reduced memory of items presented early in learning trials has been associated with impaired secondary memory or long-term memory, a hallmark feature of AD (Massman, Delis, & Butters, 1993; Simon, Leach, Winocur, & Moscovitch, 1994). These deficits in primacy encoding have been linked to lesions in brain structures related to AD including the medial temporal lobe (e.g., hippocampus, entorhinal cortex, parahippocampal gyrus) and have been shown to be present even in very mild AD (Bayley et al., 2000). In the present study, mean performance of Primacy in Faster Progressors ($z = -1.98$) was lower than Slow Progressors ($z = -0.94$) by approximately one full standard deviation at baseline. In contrast, secondary memory as measured by a gold standard test, CVLT Long Delay Free Recall, was similar between both groups; however, performance in both groups was moderately to severely impaired. This raises the possibility that hallmark

features of secondary memory may reach a floor effect in mild AD, but more subtle features such as primacy effect may continue to decline. This discrepancy may explain the ability of Primacy to differentiate Faster from Slower Progressors and predict rate of progression.

The ability of Primacy to distinguish faster from slower rates of decline in mild AD is also supported by a previous investigation of neurocognitive predictors. Marra and colleagues (2000) examined lower primacy recall on the Rey Auditory Verbal Learning Test (RAVLT), a list-learning measure of verbal episodic memory similar to the CVLT. Primacy recall, together with reduced visuospatial processing speed and attention, verbal learning and recall, and impaired inductive reasoning, was associated with a 25% decline on the MMSE in one year in 55 patients with early AD. However, in that study, primacy was examined as a factor in combination with the other neurocognitive variables, and the ability of primacy per se to predict progression was not examined. The current study is, to our knowledge, the first one to demonstrate the ability of primacy to independently predict decline in AD. This finding, taken together with the results from the Marra, et al. study suggests that primacy is a reasonable neurocognitive marker for rate of decline in mild AD.

Contrary to expectation, several episodic memory performance features did not predict rate of progression in the present study, though these features have predicted cognitive decline in preclinical stages of AD. For example, Schmid et al. (2013) found response bias and number of intrusions on the CVLT predicted a future diagnosis of AD in 29 cognitively normal subjects in combination with other cognitive, clinical and demographic factors (e.g., delayed recall of figures, three WAIS-R Block Design subtest qualitative variables, number of errors and repetitions on letter fluency, self- report of memory problems, a feeling of sadness, and cardiac problems). Similarly, in a study of 44 subjects with amnestic type MCI, recognition

discrimination on the Hopkins Verbal Learning Test – Revised (Brandt, 1991), combined with a brief measure of global cognitive functioning (Addenbrooke's Cognitive Examination; Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) significantly predicted of conversion to AD (Lonie et al., 2010). In the present study, although response bias, number of intrusions, and recognition discrimination were worse in Faster Progressors, the magnitude of the difference was less than 0.5 standard deviation and not significant.

One explanation for this discrepancy in indicators for progression between preclinical and clinical stages is that these measures may be markers for early decline and *diagnosis* of AD, but they may not distinguish rate of *progression* in AD. In other words, once these measures reach a threshold of reduced performance, they may no longer reliably predict prognosis. This notion of a threshold of impairment is supported by studies of episodic memory performance features in AD, which have found that though intrusion errors, discrimination, and response bias were significantly different between subjects with AD and controls, they did not differ by disease severity in the patient population (Bartok et al., 1997; Schram, Rubert, & Loewenstein, 1995). Taken together, these findings may indicate that even though performance features of verbal episodic memory are sensitive preclinical markers of decline and indicators of disease, they may have limited sensitivity in accurately predicting *progression* once cognitive decline has manifested.

Aim 2: Predictors of Disease Progression – Neurocognitive Assessment

Hypothesis two postulated that performance features of verbal episodic memory combined with additional neurocognitive assessment measures would better predict faster vs. slower progression. This hypothesis was partially supported, and a combination model of Trail

Making Test - A, CERAD Total, and Semantic Fluency was a significant predictor of decline. However, the significant predictor from Aim 1 (CVLT Primacy) accounted for less variability and fell out of the final model. In an ROC, the area under the curve for the final model was 0.769, indicating that this model had good discrimination ability.

Several individual neurocognitive measures significantly predicted decline (Trails A, Digit Symbol, CVLT Total and CERAD Total), although the individual measures did not predict as strongly as the combination model (see Table 15). These measures comprise a range of cognitive domains including processing speed, verbal learning, and global cognitive functioning. In addition, it is worth noting that Faster Progressors performed worse (though not significantly so) on all neurocognitive measures at baseline. This is consistent with previous investigations indicating that greater neurocognitive impairment at baseline seems to be associated with more rapid progression (Atchison et al., 2004; Rasmusson et al., 1996). Whereas it is possible that Faster Progressors in this sample had somewhat more severe dementia than Slower Progressors at baseline, differences on a more omnibus measure, the MMSE, were much more subtle and nonsignificant. In addition, overall functioning, as measured by the CDR-SOB was highly similar between groups. Further, demographic factors that are known to affect neurocognitive performance such as age, level of education, and gender were similar between groups. Taken together, these results indicate that despite similarities in global baseline ratings and level of gross cognitive impairment, Faster Progressors may be more cognitively impaired than Slower Progressors on certain measures, and this discrepancy may only be realized through more detailed neuropsychological assessment.

Beyond individual neurocognitive measures, a combination of neurocognitive measures showed better ability to predict decline than any one measure alone. This is not surprising, as

combination models include complementary performance features that account for more variance than individual measures alone. This is also consistent with the literature, as several investigations have found combinations of neurocognitive measures to be predictive of rate of progression at early stages of AD. For example, Musicco et al. (2010) studied 154 newly diagnosed AD patients and found that impairment on a combination score comprised of performance on a modified version of the Wisconsin Card Sorting Test, a Verbal Fluency Test, and the Digit and Corsi Block Span Tests Backward predicted a one- to four-fold increase in progression (with worse prognosis associated with severe executive dysfunction) on the MMSE within 2 years. In the study by Marra and colleagues described above, a combination factor made up of executive functioning, processing speed, attention, learning, and memory was associated with faster decline in mild AD, with 80% correct classification overall. Although only a limited number of investigations have used combination models, the model derived in the present study was able distinguish faster from slower decliners in mild AD with similar accuracy. Unfortunately, both of the investigations described above utilized procedures that concatenated a number of measures into a single construct and did not further reduce these models, which limits the ability to analyze the efficacy of these models to predict progression in comparison to their component neurocognitive measures.

Despite the use of different models, the combination model and individual neurocognitive predictors of decline derived in the present study are composed of aspects of the cognitive domains found to be significant predictors in other investigations of progression in mild AD. For example, Trail Making Test - A and Digit Symbol are measures of visual scanning and graphomotor processing speed. Lower processing speed has been identified as an independent predictor of rate of progression in several studies (Atchison et al., 2004; Berg et al.,

1984; Saxton et al., 2009). In addition, there is evidence that processing speed continues to demonstrably decline as AD severity increases (Martelli, Barban, Zoccolotti, & Silveri, 2012; Nebes & Brady, 1992). Further, semantic fluency can be considered a measure of executive functioning and is also mediated by speed of information processing due to its timed component (Balota & Ferraro, 1996; Bryan, Luszcz, & Crawford, 1997). This measure has also been shown to predict progression in mild AD (Beatty et al., 2002; Coen et al., 1996). In contrast, other measures of executive functioning such as Phonemic Fluency and Trail Making Test - B did not distinguish faster from slower progressors in the present study. Finally, the CERAD Total score, a global cognitive composite measure, also independently predicted decline. This is not surprising given that the CERAD total score is comprised of verbal fluency, confrontation naming, verbal and visual memory, and a cognitive screening test (MMSE), which have all shown promise in predicting rate of progression in previous investigations. In sum, the domain of processing speed appears to reliably predict rate of cognitive decline, while executive functioning and global measures may be less sensitive.

In addition to being less sensitive to the rate of progression than the combination model, CVLT Primacy was less sensitive than other neurocognitive predictors. This stood in contrast to the previous literature that indicated primacy is an early cognitive marker for onset of AD. For example, Bruno and colleagues (2013) found recall of primacy region words on the RAVLT after a delay was a predictor of future AD diagnosis in a non-demented elderly sample (n = 204; Bruno, Reiss, Petkova, Sidtis, & Pomara, 2013). However, in the present study, Primacy was not as sensitive to decline as other neurocognitive measures like Trail Making Test - A. It is possible that whereas Primacy is a marker of impairment or decline in the early stages of AD, it may become a less sensitive marker for rate of decline as the disease progresses, as is the case for

CVLT Recall and Visual Reproduction II (discussed below). Another hypothesis is that Primacy is susceptible to greater interindividual variability as the disease progresses, because performance is largely dependent upon global cognitive functioning as well as relative preservation of other cognitive domains (e.g., attention and executive functioning). This is supported by the large standard deviations in Primacy and other CVLT features at baseline in the present study. In contrast, domains such as processing speed are relatively preserved in earlier stages of AD, which may increase the sensitivity of measures like Trail Making Test - A to more subtle changes in dementia severity. In sum, though Primacy was a significant predictor of rate of decline, other neurocognitive measures appear more sensitive independently and in combination.

Verbal learning, measured by the CVLT, was another independent predictor of progression that did not remain in the stepwise model once other variables were included. In addition, episodic memory as measured by the CVLT and Visual Reproduction were not independent predictors of progression. Given that rapid forgetting and reduced learning are salient to the diagnosis and rating of severity of AD, these results are somewhat surprising. However, in this case the study sample was selected specifically to fall within a constrained range of "mild AD," indicating a similar level of learning and memory impairment between groups. It is likely that due to the constrained range, the observed performance on learning and memory did not provide enough variability to be sensitive in distinguishing groups. In fact, in the present study, though the mean performance of Faster Progressors was lower on memory measures, the range of performance essentially completely overlapped between groups (see Table 7). Alternatively, as performance on this measure was in the moderately to severely impaired range in both groups, a floor effect may have been realized, reducing the variability

between groups. Thus, similar to the CVLT performance features discussed earlier, all neurocognitive markers that indicate presence of disease may not be reliable markers of disease progression.

Aim 3: Predictors of Disease Progression – Clinical Variables

Hypothesis 3 postulated that health, psychiatric, and disease-specific variables would be significant contributors to the prediction model when combined with neurocognitive assessment features. This hypothesis was not supported, as there was no significant contribution of health or disease-specific variables; however, a history of cardiac illness approached significance in an independent regression.

The inability of health markers to predict decline was foreseeable given mixed findings from previous investigations of prognosis in AD. For example, Mielke et al. (2007) followed 135 individuals with AD for 3 years and concluded that some factors were associated with a faster rate of decline (atrial fibrillation, systolic hypertension, and angina), while others were associated with a slower rate of decline (history of coronary artery bypass graft surgery, diabetes, and anti-hypertension medications). In 2011, this group found that atrial fibrillation and systolic hypertension predicted faster cognitive decline while vascular index score (global vascular history), current atrial fibrillation, systolic blood pressure, current smoking, antihypertensive drugs, and history of stroke, diabetes, coronary artery bypass surgery, or myocardial infarction were not significant predictors of rate of decline in patients with AD (N = 216; Mielke et al., 2011). Finally, Regan et al., (2006) found that only cerebrovascular accidents within the 18 month follow-up period, but not simply history of cardiovascular disease at baseline (which was assessed in this study) were significantly related to faster cognitive decline in a sample of 224

subjects with AD. Overall, these findings indicate that although vascular and metabolic risk factors may affect rate of cognitive decline in AD, a consistent pattern of predictors remains elusive.

Regarding psychiatric variables, findings from a limited number of investigations have indicated that the presence of hallucinations and delusions may predict faster rate of decline. For example, Doody and colleagues (2010) found hallucinations and delusions were significant predictors of decline on the CDR Sum of Boxes in 597 patients with AD who were followed for 15 years. In addition, Buccione found delusions and hallucinations to predict faster decline in 47 subjects with AD. Notably, the samples in these studies were mixed in dementia severity, and these psychiatric symptoms more often appear later in the disease process (Lyketsos et al., 2011), which may account for their low incidence in mild AD and reduced sensitivity in predicting rate of progression as seen in the present study.

Like health and psychiatric factors, disease-specific features of duration of illness and age at onset did not significantly predict rate of progression in this study. This outcome was not surprising as some investigations have found younger age of onset related to faster cognitive decline, but overall results are mixed. For example, in a large study of 1,062 patients, O'Hara et al., (2002) found that age below 75 at the time of initial visit (in conjunction with moderate to severe aphasia and initial MMSE score greater than 7) was associated with faster decline (>3 points/year) on the MMSE. In contrast, some investigations found that rate of decline was unrelated to age of onset (Huff et al., 1987; Stern et al., 1994). In regards to other disease-specific factors, Faster and Slower Progressors were by virtue of sample selection of mild AD, similar in duration of illness and degree of dementia severity at baseline. In sum, the findings

from the present study lend support to the notion that disease-specific markers of duration of illness and age at onset do not predict rate of progression in mild AD.

Limitations

Though a sample size of 96 is larger than most studies in this area, changes to the test battery over 15 years of the study and missing data resulted in the exclusion of approximately 100 subjects with mild AD. However, given the similarities between the included and excluded sample, it is unlikely that inclusion of these subjects would have greatly altered the results (see Appendix A). Of perhaps greater concern is that a low number of observations for some neurocognitive and clinical measures limited appropriate statistical analysis. For example, observations of Block Design, Boston Naming Test, and Trail Making Test- B were insufficient for inclusion in a stepwise logistic regression in the present study. In previous investigations, the cognitive domains of visuospatial construction, language, and executive functioning have had some evidence of predicting progression in AD, but findings were mixed. Analyzing these measures in a stepwise fashion may have further elucidated the role of these domains in predicting progression. However, given that none of these measures significantly predicted progression alone, it is unlikely that they would have made a significant contribution to the overall regression model.

Beyond scarcity of data, the relatively low incidence of health and psychiatric abnormalities in the present sample limits the ability to generalize findings to populations with significant medical comorbidities. As discussed earlier, it is unlikely that these factors would have been sensitive predictors given the variable findings from previous investigations; however, further investigation is necessary to determine if the results from this study would apply to less

medically and psychiatrically healthy individuals. In addition, the sample in this study was composed of primarily well-educated, White individuals, and previous investigations have found that rates of incidence and prognosis of AD vary by cultural group, which may limit the generalizability of these findings (Bachman et al., 1993; Bachman, Green, Benke, Cupples, & Farrer, 2003; Miles, Froehlich, Bogardus, & Inouye, 2001).

A general limitation of research in this area is the lack of consensus definitions of fast and slow progression. Many investigations use decline in MMSE scores or other screening measures to determine decline. In contrast, the present study utilized CDR-SOB to prevent circularity of using cognitive measures to predict cognitive outcome, but this operationalization makes it difficult to compare the findings from this investigation to others. Additionally, the duration of time between baseline and follow-up varies between investigations. Some studies measure the course of disease progression over a period of two years, which may not directly scale to the course of progression over five years, given the non-linear trajectory of decline in AD (Ito et al., 2011; Stern et al., 1994). Nonetheless, operationalizing rate of decline on a global functioning measure like the CDR-SOB over two years may increase the ecological validity of these findings.

Research Implications and Future Directions

Several promising findings from this investigation may aid future research in predicting prognosis in AD. It will be important to cross-validate and replicate these results in larger samples, as regression analyses are dependent upon sample characteristics. In addition, investigation of the reliability of these predictors in a demographically heterogeneous sample should be conducted to ensure generalizability. This investigation only considered one point of

follow-up, due to limitations in sample size, thus the current design only allowed for examination of linear change between two time points. However, rate of decline in AD is often not linear and decline may be faster in earlier and severe stages, while plateauing in moderate stages (Ito et al., 2011; Stern et al., 1994). Thus, future investigations should conduct analyses of predictors of progression across multiple time points, which may provide a more accurate trajectory of decline.

Notably, performance on many domain-specific and comprehensive neurocognitive measures (Trail Making Test - A, Digit Symbol, CVLT Total, CVLT Primacy, and CERAD Total) predicted faster decline in this study despite similar baseline CDR and MMSE scores across groups. Further, performance on the MMSE did not predict rate of progression. These findings support conclusions from previous investigations that suggest that omnibus brief cognitive screening measures like the MMSE are not sufficient to reliably predict rate of progression of AD (Atchison et al., 2004; Rasmusson et al., 1996). Therefore, future investigations should use detailed measures of neurocognitive function to predict rate of future decline.

Several demographic, health, and neurocognitive performance features associated with the identification of AD did not predict more rapid progression in this study. Age, educational attainment, immediate and delayed episodic memory, language performance, cardiac illness, and traumatic brain injury have all been associated with increased risk of developing AD and conversion from MCI to AD. In addition, performance features of verbal episodic memory including response bias, intrusion errors, and discrimination did not predict rate of decline, though they have identified conversion from preclinical to clinical stages in AD in previous work (Lonie et al., 2010; Schmid et al., 2013). As described earlier, these markers may serve an

important role in identifying presence of disease process, but may not be useful in predicting prognosis. A similar phenomenon is potentially seen with regards to biomarkers of ApoE ε4 and beta-amyloid accumulation in AD. These markers have been shown to be risk factors of AD, but once they reach a certain threshold (or in the case of genetic factors, absence or presence), they are not useful in predicting rate of progression (Bracco et al., 2007; Dal Forno et al., 1995; Growdon et al., 1996; Helzner et al., 2009; Huey et al., 2006; Stefani et al., 2006). Some aspects of neurocognitive performance may function similarly in that once early markers of disease (such as reduced episodic memory performance) reach a certain threshold, the ability for these markers to reliably distinguish between Faster and Slower Progressors is diminished.

The strongest independent predictor of Faster vs. Slower decline was Trail Making Test - A. In previous investigations, perceptual speed did not reliably distinguish individuals who will eventually be diagnosed with AD from normal aging in a preclinical elderly population (Bäckman, Jones, Small, Aguero-Torres, & Fratiglioni, 2003; Schmid et al., 2013). However, in a meta-analysis of 47 studies of prognosis in MCI, perceptual speed showed the largest effect size in predicting conversion even though episodic memory and global cognitive function showed greater degrees of impairment in this preclinical-to-clinical stage of AD (Bäckman et al., 2005). This indicates that individuals early in the disease course (premorbid and preclinical) may evidence distinguishable performance features on some measures like episodic memory, but as severity increases, other domains like processing speed become more sensitive predictors of decline. This hypothesis is supported by the presence of preclinical to clinical neuropathological changes in the brain from transentorhinal regions (affecting episodic memory) to limbic regions (affecting perceptual speed, attention, executive functions, verbal abilities, and visuospatial functions; Almkvist, 1996). Thus, it may be that these biological changes manifest themselves in

measurements of behavioral changes. Further investigation should focus on the relationship between neuropathological and neurocognitive predictors of cognitive decline to better elucidate biological and behavioral basis of change and better predict rate of decline.

Of all the performance features of the CVLT, Primacy Recall was the only significant predictor of rate of cognitive decline. Although primacy did not predict faster decline better than other neurocognitive test results, the role of primacy across the preclinical through clinical stages should be explored further. Primacy has been indicative of worse outcomes in studies predicting future diagnosis of dementia (Bruno et al., 2013), and supported by the results of the present study, may continue to be an important factor in prognosis through clinical AD. Future studies should investigate longitudinal performance on this measure from preclinical through later stages of AD, to examine the course of this marker in the same individuals over time. For example, low primacy may simultaneously increase likelihood of future dementia, conversion from MCI to AD, and faster rate of decline. Much like the theory of episodic memory described above, it may also reach a threshold of insensitivity in predicting future course. Another hypothesis would be that some neurocognitive performance attributes (e.g., Primacy) are sensitive to decline at different times in the disease course based on individual characteristics and disease severity. Further investigation of such markers could lead to more sensitive predictors of prognosis from normal aging through severe dementia.

Clinical Implications

Several neurocognitive measures were found to be significant predictors of future rate of cognitive decline in subjects with mild AD. Notably, a model utilizing three relatively brief, commonly used measures (Trail Making Test - A, Semantic Fluency, and CERAD Total)

showed good ability to discriminate between fast and slow progressors. These findings indicate that using a test battery that includes these three measures could provide useful information regarding prognosis to patients, caregivers, and clinicians. Further, by using cut points that maximize differences between Faster and Slower Progressors, a reliable formula for prognosis may be developed. For example, in this investigation, Faster Progressors were more likely to perform at a Trail Making Test - A T-score < 30 and a CERAD Total score < 60 than Slower Progressors. Taken together, a formula based on these cutoffs could improve upon the sensitivity derived in the model to identify patients likely to decline rapidly. This could provide forewarning to patients and caregivers in order to plan for decline and related costs.

This model could also help identify and target particular individuals for treatment intervention and to optimize resources. For example, numerous attempts at effective pharmacological treatment for AD have failed. However, due to the lack of consensus, most clinical trials cannot reliably separate subjects based upon rate of progression. If Faster and Slower Progressors could be identified, pharmacological trials could target a specific group, which may improve trial efficacy overall. In terms of behavioral interventions, caregiver and patient therapy could focus on issues most salient for each group. For example, families of a Faster Progressor may more likely benefit from family and individual psychotherapy to provide support in adjusting to their rapidly declining loved one. On the other hand, a Slower Progressor may benefit from training in compensatory techniques. Thus, this relatively brief and cost-effective protocol for predicting progression in individuals in early stages of a difficult disease could improve the care and quality of life of those affected.

Conclusion

Alzheimer disease is a complex disorder, and as with most chronic illnesses, understanding and predicting prognosis is a difficult task. The results of this study, combined with findings from the literature, suggest that neurocognitive performance features that may predict development or onset of the disease, namely episodic memory impairment, may not necessarily predict rate of progression. Instead, processing speed appears to be an important marker in differentiating faster from slower progressors in the early stages of illness. Further, three relatively brief and commonly used measures were found to predict differences in rate of progression with high accuracy. Although further investigation is necessary, results from the current research provide important advances in understanding the role of neurocognitive measures in predicting rate of decline in AD.

REFERENCES

Abellan van Kan, G., Rolland, Y., Nourhashémi, F., Coley, N., Andrieu, S., & Vellas, B. (2009). Cardiovascular disease risk factors and progression of Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *27*(3), 240–6. doi:10.1159/000203365

Adak, S., Illouz, K., Gorman, W., Tandon, R., Zimmerman, E. A., Guariglia, R., Moore, M. M., et al. (2004). Predicting the rate of cognitive decline in aging and early Alzheimer disease. *Neurology*, *63*(1), 108–114. Retrieved from http://www.neurology.org/content/63/1/108.short

Ahmed, S., Mitchell, J., Arnold, R., Nestor, P. J., & Hodges, J. R. (2008). Predicting rapid clinical progression in amnestic mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders*, *25*, 170–177. doi:10.1159/000113014

Aisen, P., Petersen, R., & Thal, L. (2008). ADNI Clinical Core. *ADNI Steering Committee*.

Albert, M. S. (2011). Changes in cognition. *Neurobiology of Aging*, *32*(Suppl 1), S58–63. doi:10.1016/j.neurobiolaging.2011.09.010

Albert, M. S., Moss, M. B., Tanzi, R., & Jones, K. (2001). Preclinical prediction of AD using neuropsychological tests. *Journal of the International Neuropsychological Society*, *7*(5), 631–639. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11459114

Almkvist, O. (1996). Neuropsychological features of early Alzheimer's disease: preclinical and clinical stages. *Acta Neurologica Scandinavica*, *94*(S165), 63–71. doi:10.1111/j.1600-0404.1996.tb05874.x

Arnaiz, E., & Almkvist, O. (2003). Neuropsychological features of mild cognitive impairment and preclinical Alzheimer's disease. *Acta Neurologica Scandinavica*. Retrieved from http://onlinelibrary.wiley.com/doi/10.1034/j.1600-0404.107.s179.7.x/full

Atchison, T. B., Bradshaw, M., & Massman, P. J. (2004). Investigation of profile difference between Alzheimer's disease patients declining at different rates: examination of baseline neuropsychological data. *Archives of Clinical Neuropsychology*, *19*(8), 1007–1015. doi:10.1016/j.acn.2003.12.011

Atchison, T. B., Massman, P. J., & Doody, R. S. (2007). Baseline cognitive function predicts rate of decline in basic-care abilities of individuals with dementia of the Alzheimer's type. *Archives of Clinical Neuropsychology*, *22*, 99–107. doi:10.1016/j.acn.2006.11.006

Bachman, D. L., Green, R. C., Benke, K. S., Cupples, L. A., & Farrer, L. A. (2003). Comparison of Alzheimer's disease risk factors in white and African American families. *Neurology*, *60*(8), 1372–1374. doi:10.1212/01.WNL.0000058751.43033.4D

Bachman, D. L., Wolf, P. A., Linn, R. T., Knoefel, J. E., Cobb, J. L., Belanger, A. J., White, L. R., et al. (1993). Incidence of dementia and probable Alzheimer's disease in a general population: The Framingham Study. *Neurology*, *43*(3, Part 1), 515–515. doi:10.1212/WNL.43.3_Part_1.515

Bäckman, L, Jones, S., Small, B. J., Aguero-Torres, H., & Fratiglioni, L. (2003). Rate of cognitive decline in preclinical Alzheimer's disease: the role of comorbidity. *The Journal of Gerontology: Psychological Sciences*, *58B*(4), 228–236. Retrieved from http://psychsocgerontology.oxfordjournals.org/content/58/4/P228.short

Bäckman, L., Jones, S., Berger, A.-K., Laukka, E. J., & Small, B. J. (2005). Cognitive impairment in preclinical Alzheimer's disease: a meta-analysis. *Neuropsychology*, *19*(4), 520–531. doi:10.1037/0894-4105.19.4.520

Balota, D. A., & Ferraro, F. R. (1996). Lexical, sublexical, and implicit memory processes in healthy young and healthy older adults and in individuals with dementia of the Alzheimer type. *Neuropsychology*, *10*(1), 82–95. doi:10.1037//0894-4105.10.1.82

Barnes, D. E., & Yaffe, K. (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Neurology*, *10*(9), 819–828. doi:10.1016/S1474-4422(11)70072-2

Bartok, J. A., Wilson, C. S., Giordani, B., Keys, B. A., Persad, C. C., Foster, N. L., & Berent, S. (1997). Varying patterns of verbal recall, recognition, and response bias with progression of alzheimer's disease. *Aging, Neuropsychology, and Cognition*, *4*(4), 266–272. doi:10.1080/13825589708256651

Bayley, P. J., Salmon, D. P., Bondi, M. W., Bui, B. K., Olichney, J., Delis, D., Thomas, R., et al. (2000). Comparison of the serial position effect in very mild Alzheimer's disease, mild Alzheimer's disease, and amnesia associated with electroconvulsive therapy. *Journal of the International Neuropsychological Society*, *6*(3), 290–298. Retrieved from http://journals.cambridge.org/production/action/cjoGetFulltext?fulltextid=49066

Beatty, W., Salmon, D. P., Troster, A. I., & Tivis, R. D. (2002). Do primary and supplementary measures of semantic memory predict cognitive decline by patients with Alzheimer's disease? *Aging, Neuropsychology, and Cognition*, *9*(1), 1–10. doi:10.1076/anec.9.1.1.838

Becker, J. T., Huff, F. J., Nebes, R. D., Holland, A., & Boller, F. (1988). Neuropsychological function in Alzheimer's disease: Pattern of impairment and rates of progression. *Archives of Neurology*, *45*(3), 263–268.

Borkowski, J. G., Benton A. L., Spreen, O. (1967). Word fluency and brain damage. *Neuropsychologia.* 5(2) p. 135-140

Benton, A. L. (1963). *The revised visual retention test: clinical and experimental applications*. State University of Iowa; Distributor for the USA, Psychological Corporation, New York.

Berg, L., Danziger, W., Storandt, M., & Coben, L. (1984). Predictive features in mild senile dementia of the Alzheimer type. *Neurology*. Retrieved from http://www.neurology.org/content/34/5/563.short

Bertram, L., & Tanzi, R. (2008). Thirty years of Alzheimer's disease genetics: the implications of systematic meta-analyses. *Nature Reviews Neuroscience*, *9*(10), 768–778.

Bhargava, D., Weiner, M. F., Hynan, L. S., Diaz-Arrastia, R., & Lipton, A. M. (2006). Vascular disease and risk factors, rate of progression, and survival in Alzheimer's disease. *Journal of Geriatric Psychiatry*, *19*(2), 78–82. doi:10.1177/0891988706286505

Blessed, G., Tomlinson, B., & Roth, M. (1968). The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *British Journal of Psychiatry*, *114*(512), 797–811.

Boller, F., & Becker, J. (1991). Predictors of decline in Alzheimer's disease. *Cortex, 27*(1), 9-17.

Bondi, M. W., Houston, W. E. S. S., Salmon, D. P., Corey-bloom, J., Katzman, R., Thal, L. J., & Delis, D. C. (2006). Neuropsychological deficits associated with Alzheimer's disease in the very-old: Discrepancies in raw vs. standardized scores. *Journal of the International Neuropsychological Society*, *9*(5), 783–795.

Bowie, C. R., & Harvey, P. D. (2006). Administration and interpretation of the Trail Making Test. *Nature protocols*, *1*(5), 2277–81. doi:10.1038/nprot.2006.390

Bracco, L., Piccini, C., Baccini, M., Bessi, V., Biancucci, F., Nacmias, B., Bagnoli, S., et al. (2007). Pattern and progression of cognitive decline in Alzheimer's disease: role of premorbid intelligence and ApoE genotype. *Dementia and Geriatric Cognitive Disorders*, *24*(6), 483–491. doi:10.1159/000111081

Brandt, J. (1991). The Hopkins Verbal Learning Test: development of a new memory test with six equivalent forms. *The Clinical Neuropsychologist*, *5*(2), 125-142.

Brandt, J., & Benedict, R. H. (2001). *Hopkins Verbal Learning Test, Revised: Professional Manual*. Psychological Assessment Resources.

Brickman, A. M., Honig, L. S., Scarmeas, N., Tatarina, O., Sanders, L., Albert, M. S., Brandt, J., et al. (2008). Measuring cerebral atrophy and white matter hyperintensity burden to predict the rate of cognitive decline in Alzheimer disease. *Archives of Neurology*, *65*(9), 1202–1208. doi:10.1001/archneur.65.9.1202

Brooks, J. O., & Yesavage, J. A. (1995). Identification of fast and slow decliners in Alzheimer disease: A different approach. *Alzheimer Disease and Associated Disorders*, *9*(Supplement 1), S19–25.

Bruno, D., Reiss, P. T., Petkova, E., Sidtis, J. J., & Pomara, N. (2013). Decreased recall of primacy words predicts cognitive decline. *Archives of Clinical Neuropsychology*, *28*(2), 95–103. doi:10.1093/arclin/acs116

Bryan, J., Luszcz, M. A., & Crawford, J. R. (1997). Verbal knowledge and speed of information processing as mediators of age differences in verbal fluency performance among older adults. *Psychology and Aging*, *12*(3), 473–478.

Buccione, I., Perri, R., Carlesimo, G. A., Fadda, L., Serra, L., Scalmana, S., & Calagirone, C. (2007). Cognitive and behavioural predictors of progression rates in Alzheimer's disease. *European Journal of Neurology*, *14*, 440–446. doi:10.1111/j.1468-1331.2006.01693.x

Butters, N., Granholm, E., Salmon, D., Grant, I., & Wolf, J. (1987). Episodic and semantic memory: A comparison of amnesic and demented Patients. *Journal of Clinical and Experimental Neuropsychology*, *9*(5), 479–497.

Cahn, D. A., Salmon, D. P., Bondi, M. W., Butters, N., Johnson, S. A., Wiederholt, W. C., & Barrett-Connor, E. (1997). A population-based analysis of qualitative features of the neuropsychological test performance of individuals with dementia of the Alzheimer type: implications for individuals with questionable dementia. *Journal of the International Neuropsychological Society*, *3*(4), 387–93. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9260448

Carlesimo, G., & Caltagirone, C. (1996). The Mental Deterioration Battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. *European Neurology,* Retrieved from http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowAbstractBuch&ArtikelNr=117297&ProduktNr=234264

Carlesimo, G., Buccione, I., Fadda, L., Graceffa, A., Mauri, M., Lorusso, S., Bevilacqua, G., et al. (2002). Normative data of two memory tasks: Short-Story recall and Rey's Figure. *Nuova Rivista di Neurologia*, *12*(1), 1–13. Retrieved from http://cat.inist.fr/?aModele=afficheN&cpsidt=13544940

Cervilla, J., Prince, M., Joels, S., Lovestone, S., & Mann, A. (2004). Premorbid cognitive testing predicts the onset of dementia and Alzheimer's disease better than and independently of APOE genotype. *Journal of Neurology, Neurosurgery, and Psychiatry*, *75*(8), 1100–1106. doi:10.1136/jnnp.2003.028076

Chan, D., Fox, N. C., Scahill, R. I., Crum, W. R., Whitwell, J. L., Leschziner, G., Rossor, A. M., et al. (2001). Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. *Annals of Neurology*, *49*(4), 433–42. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11310620

Chandler, M. J., Lacritz, L. H., Hynan, L. S., Barnard, H. D., Allen, G., Deschner, M., Weiner, M. F., et al. (2005). A total score for the CERAD neuropsychological battery. *Neurology*, *65*(1), 102–6. doi:10.1212/01.wnl.0000167607.63000.38

Chang, Y.-L., Bondi, M. W., Fennema-Notestine, C., McEvoy, L. K., Hagler, D. J., Jacobson, M. W., & Dale, A. M. (2010). Brain substrates of learning and retention in mild cognitive impairment diagnosis and progression to Alzheimer's disease. *Neuropsychologia*, *48*(5), 1–26. doi:10.1016/j.neuropsychologia.2009.12.024.Brain

Chui, H., & Gatz, M. (2005). Cultural diversity in Alzheimer disease: the interface between biology, belief, and behavior. *Alzheimer Disease & Associated Disorders*, *19*(4), 250–255.

Coen, R. F., Maguire, C., Swanwick, G. R., Kirby, M., Burke, T., Lawlor, B. A., Walsh, J. B., et al. (1996). Letter and category fluency in Alzheimer's disease: a prognostic indicator of progression? *Dementia (Basel, Switzerland)*, *7*(5), 246–50. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8872414

Coley, N., Andrieu, S., Jaros, M., Weiner, M., Cedarbaum, J., & Vellas, B. (2011). Suitability of the Clinical Dementia Rating-Sum of Boxes as a single primary endpoint for Alzheimer's disease trials. *Alzheimer's & Dementia*, *7*(6), 602–610. doi:10.1016/j.jalz.2011.01.005

Colloby, S. J., Perry, E. K., Ph, D., Pakrasi, S., Pimlott, S. L., Wyper, D. J., Mckeith, I. G., et al. (2010). Nicotinic 123I-5IA-85380 single photon emission computed tomography as a predictor of cognitive progression in Alzheimer's disease and dementia with Lewy bodies. *American Journal of Geriatric Psychiatry*, *18*(1), 86–90. Retrieved from http://journals.lww.com/ajgponline/Abstract/2010/01000/Nicotinic_123I_5IA_85380_Single_Photon_Emission.12.aspx

Cosentino, S., Scarmeas, N., Helzner, E. P., Glymour, M. M., Brandt, J., Albert, M., Blacker, D., et al. (2008). APOE E4 allele predicts faster cognitive decline in mild Alzheimer's disease. *Neurology*, *70*(19), 1842–1849. doi:10.1212/01.wnl.0000304038.37421.cc.APOE

Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*, *44*(12), 2308–14. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7991117

Dal Forno, G., Rasmusson, D., Brandt, J., Carson, K., Brookmeyer, R., Troncoso, J., & Kawas, C. (1995). Apolipoprotein E genotype and rate of decline in probable Alzheimer's disease. *Archives of Neurology*, *53*(4), 345–350.

De Anna, F., Attali, E., Freynet, L., Foubert, L., Laurent, A., Dubois, B., & Dalla Barba, G. (2008). Intrusions in story recall: when over-learned information interferes with episodic memory recall. Evidence from Alzheimer's disease. *Cortex*, *44*(3), 305–11. doi:10.1016/j.cortex.2006.08.001

Debette, S., & Markus, H. S. (2010). The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ*, *341*, c3666–c3666. doi:10.1136/bmj.c3666

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1987). California Verbal Learning Test: Adult Version. The Psychological Corporation. *San Antonio, TX*.

Desgranges, B., Baron, J.-C., Giffard, B., Chételat, G., Lalevée, C., Viader, F., De la Sayette, V., et al. (2002). The neural basis of intrusions in free recall and cued recall: A PET study in Alzheimer's disease. *NeuroImage*, *17*(3), 1658–1664. doi:10.1006/nimg.2002.1289

Devanand, D., Pelton, G., Zamora, D., Liu, X., Tabert, M., Goodkind, M., Scarmeas, N., et al. (2005). Predictive utility of apolipoprotein E genotype for Alzheimer disease in outpatients with mild cognitive impairment. *Archives of Neurology*, *62*(6), 975–80. doi:10.1001/archneur.62.6.975

Doody, R. S., Massman, P., & Dunn, J. K. (2001). A method for estimating progression rates in Alzheimer disease. *Archives of Neurology*, *58*(3), 449–454. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11255449

Doody, R. S., Pavlik, V., Massman, P., Rountree, S., Darby, E., & Chan, W. (2010). Predicting progression of Alzheimer's disease. *Alzheimers Research and Therapy*, *2*(2), 1–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9200630

Drachman, D. A., O'Donnell, B. F., Lew, R. A., & Swearer, J. M. (1990). The prognosis in Alzheimer's disease: "how far" rather than "how fast" best predicts the course. *Archives of Neurology*, *47*(8), 851–856. doi:10.1001/archneur.1990.00530080033007

Farrer, L., Cupples, L., Haines, J., Hyman, B., Kukull, W., Mayeux, R., Myers, R., et al. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *Journal of the American Medical Association*, *228*(16), 1349–1356.

Ferraro, F., & Lowell, K. (2010). Boston Naming Test. *Corsini Encyclopedia of Psychology*. Retrieved from http://onlinelibrary.wiley.com/doi/10.1002/9780470479216.corpsy0139/full

Folstein, M. F., Robins, L. N., & Helzer, J. E. (1983). The Mini-Mental State Examination. *Archives of General Psychiatry*, *40*(7).

Forlenza, O. V, Diniz, B. S., Talib, L. L., Radanovic, M., Yassuda, M. S., Ojopi, E. B., & Gattaz, W. F. (2010). Clinical and biological predictors of Alzheimer's disease in patients with amnestic mild cognitive impairment. *Revista Brasileria de Psiquiatria*, *32*(3), 216–222.

Fox, N. C., Scahill, R. I., Crum, W. R., & Rossor, M. N. (1999). Correlation between rates of brain atrophy and cognitive decline in AD. *Neurology*, *52*(8), 1687–1689. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10331700

Gatz, J. L., Tyas, S. L., John, P. S., & Montgomery, P. (2005). Do depressive symptoms predict Alzheimer's disease and dementia? *Journal of Gerontology*, *60*(6), 744–747.

Gómez-Tortosa, E., Mahillo-Fernández, I., Guerrero, R., Montoya, J., Alonso, A., & Sainz, M. J. (2011). Outcome of mild cognitive impairment comparing early memory profiles. *The American Journal of Geriatric Psychiatry*, 1–9. doi:10.1097/JGP.0b013e31823038c6

Goodglass, H., Kaplan, E., & Weintraub, S. (1983). The revised Boston naming test. *Lea & Febiger, Philadelphia*.

Growdon, J., Locascio, J., Corkin, S., Gomez-Isla, T., & Hyman, B. (1996). Apolipoprotein E genotype does not influence rates of cognitive decline in Alzheimer's disease. *Neurology*, *47*(2), 444–448.

Guarch, J., Marcos, T., Salamero, M., & Blesa, R. (2004). Neuropsychological markers of dementia in patients with memory complaints. *International Journal of Geriatric Psychiatry*, *19*(4), 352–358. doi:10.1002/gps.1074

Guarch, J., Marcos, T., Salamero, M., Gasto, C., & Blesa, R. (2008). Mild cognitive impairment: a risk indicator of later dementia, or a preclinical phase of the disease? *International Journal of Geriatric Psychiatry*, *23*, 257–265. doi:10.1002/gps

Hachinski, V. (1978). Cerebral blood flow differentiation of Alzheimer's disease from multi-infarct dementia. *JAMA Neurology*, *32*(9). Retrieved from http://scholar.google.com/scholar?hl=en&as_sdt=0,44&q=Hachinski+Ischemic+score#7

Hall, C. B., Derby, C., LeValley, A., Katz, M. J., Verghese, J., & Lipton, R. B. (2007). Education delays accelerated decline on a memory test in persons who develop dementia. *Neurology*, *69*(17), 1657–1664. doi:10.1212/01.wnl.0000278163.82636.30

Haxby, J. V., Raffaele, K., Gillette, J., Schapiro, M. B., & Rapoport, S. I. (1992). Individual trajectories of cognitive decline in patients with dementia of the Alzheimer type. *Journal of Clinical and Experimental Neuropsychology*, *14*(4), 575–592.

Helzner, E. P., Luchsinger, A., Scarmeas, N., Cosentino, S., Brickman, A. M., Glymour, M. M., & Stern, Y. (2009). Contribution of vascular risk factors to the progression in Alzheimer disease. *Archives of Neurology*, *66*(3), 343–348.

Hendrie, H. C., Hall, K. S., Pillay, N., Rodgers, D., Prince, C., Norton, J., Brittain, H., et al. (1993). Alzheimer's disease is rare in Cree. *International Psychogeriatrics*, *5*(1), 5–14. doi:10.1017/S1041610293001358

Hendrie, H., Osuntokun, B., Hall, K., Ogunniyi, A., Hui, S., Unverzagt, F., Gureje, O., et al. (1995). Prevalence of Alzheimer's disease and dementia in two communities: Nigerian Africans and African Americans. *American Journal of Psychiatry*, *152*(10), 1485–1492.

Henry, J., Crawford, J., & Phillips, L. (2004). Verbal fluency performance in dementia of the Alzheimer's type: a meta-analysis. *Neuropsychologia*. Retrieved from http://lewybodies.com/goto/http://www.abdn.ac.uk/~psy086/dept/pdfs/Neuropsychologia_2004_DAT_VF_meta.pdf

Holmes, C., & Lovestone, S. (2003). Long-term cognitive and functional decline in late onset Alzheimer's disease: therapeutic implications. *Age and Ageing*, *32*(2), 200–204. Retrieved from http://ageing.oxfordjournals.org/content/32/2/200.short

Hoyt, B. D., Massman, P. J., Schatschneider, C., Cooke, N., & Doody, R. S. (2005). Individual growth curve analysis of APOE epsilon 4-associated cognitive decline in Alzheimer disease. *Archives of Neurology*, *62*(3), 454–459. doi:10.1001/archneur.62.3.454

Huey, E. D., Mirza, N., Putnam, K. T., Soares, H., Csako, G., Levy, J. A., Copenhaver, B., et al. (2006). Stability of CSF beta-amyloid(1-42) and tau levels by APOE genotype in Alzheimer patients. *Dementia and Geriatric Cognitive Disorders*, *22*(1), 48–53. doi:10.1159/000093261

Huff, F., Growdon, G., Corkin, S., & Rosen, T. (1987). Age at onset and rate of progression of Alzheimer's disease. *Journal of the American Geriatric Society*, *35*(1), 27–30.

Ito, K., Corrigan, B., Zhao, Q., French, J., Miller, R., Soares, H., Katz, E., et al. (2011). Disease progression model for cognitive deterioration from Alzheimer's Disease Neuroimaging Initiative database. *Alzheimer's & Dementia*, *7*(2), 151–160. doi:10.1016/j.jalz.2010.03.018

Jack, C. R., Shiung, M. M., Gunter, J. L., O'Brien, P. C., Weigand, S. D., Knopman, D. S., Boeve, B. F., et al. (2011). Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. *Neurology*, *67*(4), 591–600. doi:10.1212/01.WNL.0000162054.15428.E9.Motor

Jack, C. R., Knopman, D. S., Jagust, W. J., Shaw, L. M., Aisen, P. S., Weiner, W., Petersen, R. C., et al. (2010). Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurology*, *9*(1), 1–20. doi:10.1016/S1474-4422(09)70299-6.Hypothetical

Jacobs, D., Sano, M., Marder, K., Bell, K., Bylsma, F., Lafleche, G., Albert, M., et al. (1994). Age at onset of Alzheimer's disease: Relation to pattern of cognitive dysfunction and rate of declin. *Neurology*, *44*(7).

Jonker, C., Geerlings, M. I., & Schmand, B. (2000). Are memory complaints predictive for dementia? A review of clinical and population-based studies. *International Journal of Geriatric Psychiatry*, *15*(11), 983–991. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11113976

Jorm, A. F., Masaki, K. H., Davis, D. G., Hardman, J., Nelson, J., Markesbery, W. R., Petrovitch, H., et al. (2004). Memory complaints in nondemented men predict future pathologic diagnosis of Alzheimer disease. *Neurology*, *63*(10), 1960–1961. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15557525

Kaplan, Edith. (1988). The process approach to neuropsychological assessment. *Aphasiology*, *2*(3-4), 309–311. doi:10.1080/02687038808248930

Kawas, C. H., Corrada, M. M., Brookmeyer, R., Morrison, A., Resnick, S. M., Zonderman, A. B., et al. (2003). Visual memory predicts Alzheimer's disease more than a decade before diagnosis. *Neurology*, *60*, 1089–1093.

Kertesz, A. (1982). *Western aphasia battery test manual*. Grune & Stratton. Retrieved from http://scholar.google.com/scholar?q=Responsive+Naming+Test&btnG=&hl=en&as_sdt=0,44#3

Kester, M. I., Van der Vlies, A. E., Blankenstein, M. A., Pijnenburg, Y. A. L., Van Elk, E. J., Scheltens, P., & Van der Flier, W. M. (2009). CSF biomarkers predict rate of cognitive decline in Alzheimer disease. *Neurology*, *73*, 1353–1358. Retrieved from http://www.neurology.org/content/73/17/1353.short

Kleiman, T., Zdanys, K., Black, B., Rightmer, T., Grey, M., Garman, K., Macavoy, M., et al. (2006). Apolipoprotein E epsilon4 allele is unrelated to cognitive or functional decline in Alzheimer's disease: retrospective and prospective analysis. *Dementia and Geriatric Cognitive Disorders*, *22*(1), 73–82. doi:10.1159/000093316

Kraemer, H. C., Tinklenberg, J., & Yesavage, J. A. (1994). “How far” vs “how fast” in Alzheimer’s disease the question revisited. *Archives of Neurology*, *51*(3), 275–279.

Kraybill, M. L., Larson, E. B., Tsuang, D. W., Teri, L., McCormick, W. C., Bowen, J. D., Kukull, W., et al. (2005). Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both. *Neurology*, *64*(12), 2069–2073. doi:10.1212/01.WNL.0000165987.89198.65

Lamar, M., Swenson, R., Kaplan, E., & Libon, D. J. (2004). Characterizing alterations in executive functioning across distinct subtypes of cortical and subcortical dementia. *The Clinical Neuropsychologist*, *18*(1), 22–31. doi:10.1080/13854040490507127

Lane, R. M., & Farlow, M. R. (2005). Lipid homeostasis and apolipoprotein E in the development and progression of Alzheimer’s disease. *Journal of Lipid Research*, *46*(5), 949–68. doi:10.1194/jlr.M400486-JLR200

Lawton, M. P., & Brody, E. M. (1969). Assessment of older people: self-maintaining and instrumental activities of daily living. *The Gerontologist*, *9*(3), 179–86. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/5349366

Lee, D. Y., Youn, J. C., Choo, I. H., Kim, K. W., Jhoo, J. H., Pak, Y. S., Suh, K. W., et al. (2006). Combination of clinical and neuropsychologic information as a better predictor of the progression to Alzheimer disease in questionable dementia individuals. *The American Journal of Geriatric Psychiatry*, *14*(2), 130–138. doi:10.1097/01.JGP.0000192487.58426.d2

Lekeu, F., Magis, D., Marique, P., Delbeuck, X., Bechet, S., Guillaume, B., Adam, S., et al. (2010). The California Verbal Learning Test and other standard clinical neuropsychological tests to predict conversion from mild memory impairment to dementia. *Journal of Clinical and Experimental Neuropsychology*, *32*(2), 164–173. doi:10.1080/13803390902889606

Lezak, M. D. (Ed.). (2004). *Neuropsychological Assessment 4th Edition* (p. 1016). Oxford University Press. Retrieved from http://books.google.com/books?hl=en&lr=&id=FroDVkVKA2EC&pgis=1

Lonie, J., Parra-Rodriguez, M., Tierney, K. M., Herrmann, L. L., Donaghey, C., O'Carroll, R. E., & Ebmeier, K. P. (2010). Predicting outcome in mild cognitive impairment: 4-year follow-up study. *The British Journal of Psychiatry*, *197*(2), 135–140. doi:10.1192/bjp.bp.110.077958

Lopez, O. L., Schwam, E., Cummings, J., Gauthier, S., Jones, R., Wilkinson, D., Waldemar, G., et al. (2010). Predicting cognitive decline in Alzheimer's disease: an integrated analysis. *Alzheimer's & Dementia*, *6*, 431–439. doi:10.1016/j.jalz.2010.04.003

Lucotte, G., Turpin, J., & Landais, P. (1994). Apolipoprotein E-epsilon 4 allele doses in late-onset Alzheimer's disease. *Annals of Neurology*, *36*(4), 681–682.

Lye, T., & Shores, E. (2000). Traumatic brain injury as a risk factor for Alzheimer's disease: a review. *Neuropsychology Review*, *10*(2), 115–129.

Lyketsos, C. G., Carrillob, M. C., Ryan, J. M., Khachaturiand, A. S., Trzepacze, P., Amatniekf, J., Cedarbaumg, J., et al. (2011). Neuropsychiatric symptoms in Alzheimer's disease. *Alzheimer's & Dementia*, *7*(5), 532–539. doi:10.1016/j.jalz.2011.05.2410.

MacDonald, S. W. S., Karlsson, S., Fratiglioni, L., & Bäckman, L. (2011). Trajectories of cognitive decline following dementia onset: what accounts for variation in progression? *Dementia and Geriatric Cognitive Disorders*, *31*(3), 202–209. doi:10.1159/000325666

Mahurin, R. K., & Cooke, N. (1996). Verbal series attention test: Clinical utility in the assessment of dementia. *The Clinical Neuropsychologist*, *10*(1), 43–53. doi:10.1080/13854049608406662

Marra, C., Silveri, M. C., & Gainotti, G. (2000). Predictors of cognitive decline in the early stage of probable Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *11*, 212–218. Retrieved from http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowAbstractBuch&ArtikelNr=17239&ProduktNr=225530

Martelli, M., Barban, F., Zoccolotti, P., & Silveri, M. C. (2012). Slowing of information processing in Alzheimer disease: Motor as well as cognitive factors. *Cognitive and Behavioral Neurology*, *25*(4), 175–185.

Martins, C. R., Oulhaj, A., De Jager, C., & Williams, J. H. (2005). APOE alleles predict the rate of cognitive decline in Alzheimer disease: a nonlinear model. *Neurology*, *65*(12), 1888–1893. doi:10.1212/01.wnl.0000188871.74093.12

Massman, P. J., Delis, D. C., & Butters, N. (1993). Does impaired primacy recall equal impaired long-term storage? Serial position effects in Huntington's disease and Alzheimer's disease. *Developmental Neuropsychology*, *9*(1), 1–15. doi:10.1080/87565649309540540

Mathuranath, P. S., Nestor, P. J., Berrios, G. E., Rakowicz, W., & Hodges, J. R. (2000). A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology*, *55*, 1613–1620. Retrieved from http://www.ftdrg.org/wp-content/uploads/mathuranath-et-al-2000.pdf

Mattis, S. (1988). Dementia rating scale (DRS). Odessa, FL: Psychological Assessment Resources. Retrieved from http://scholar.google.com/scholar?q=Dementia+Rating+Scale+(DRS)&btnG=&hl=en&as_sdt=0,44#0

McDowell, I., Xi, G., Lindsay, J., & Tierney, M. (2007). Mapping the connections between education and dementia. *Journal of Clinical and Experimental Neuropsychology*, *29*(2), 127–141. doi:10.1080/13803390600582420

Miceli, G., Laudanna, A., Burani, C., & Capasso, R. (1994). Batteria per l'Analisi dei Deficit Afasici BADA: Università Cattolica del Sacro Cuore. *Servizio di Neuropsicologia, Consiglio.* Retrieved from http://scholar.google.com/scholar?q=Batteria+per+l'Analisi+dei+Deficit+Afasici+BADA&btnG=&hl=en&as_sdt=0,44#1

Mielke, M. M., Rosenberg, P. B., Tschanz, J., Cook, L., Corcoran, C., Hayden, K. M., Norton, M., et al. (2007). Vascular factors predict rate of progression in Alzheimer disease. *Neurology*, *69*(19), 1850–1858. doi:10.1212/01.wnl.0000279520.59792.fe

Mielke, M. M., Zandi, P. P., Shao, H., Waern, M., Östling, S., Guo, X., Björkelund, C., et al. (2010). The 32-year relationship between cholesterol and dementia from midlife to late life. *Neurology*, *75*(21), 1888–1895. doi:10.1212/WNL.0b013e3181feb2bf

Mielke, M. M., Leoutsakos, J.-M., Tschanz, J. T., Green, R., Tripodis, Y., Corcoran, C., Norton, M. C., et al. (2011). Interaction between vascular factors and the APOE E4 allele in predicting rate of progression in Alzheimer's dementia. *Journal of Alzheimer's Disease*, *26*(1), 127–134. doi:10.3233/JAD-2011-110086.Interaction

Milberg, W., Hebben, N., & Kaplan, E. (2009). The Boston process approach to neuropsychological assessment. In I. Grant & K. M. Adams (Eds.), *Neuropsychological Assessment of Neuropsychiatric and Neuromedical Disorders* (3rd ed., pp. 42–65). Oxford University Press. Retrieved from http://scholar.google.com/scholar?q=milberg,+grant+and+adams&btnG=&hl=en&as_sdt=0,44#3

Miles, T. P., Froehlich, T. E., Bogardus, S. T., & Inouye, S. K. (2001). Dementia and race: Are there differences between African Americans and Caucasians? *Journal of the American Geriatrics Society*, *49*(4), 477–484. doi:10.1046/j.1532-5415.2001.49096.x

Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., & Hodges, J. R. (2006). The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia

screening. *International Journal of Geriatric Psychiatry*, *21*(11), 1078–85. doi:10.1002/gps.1610

Mitchell, A. J., & Shiri-Feshki, M. (2009). Rate of progression of mild cognitive impairment to dementia - meta-analysis of 41 robust inception cohort studies. *Acta Psychiatrica Scandinavica*, *119*(4), 252–265. doi:10.1111/j.1600-0447.2008.01326.x

Mormino, E. C., Kluth, J. T., Madison, C. M., Rabinovici, G. D., Baker, S. L., Miller, B. L., Koeppe, R. a, et al. (2009). Episodic memory loss is related to hippocampal-mediated beta-amyloid deposition in elderly subjects. *Brain*, *132*(5), 1310–1323. doi:10.1093/brain/awn320

Morris, J. C., Edland, S., Clark, C., Galasko, D., Koss, E., Mohs, R., Van Belle, G., et al. (1993). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD): Part IV. Rates of cognitive change in the longitudinal assessment of probable Alzheimer's disease. *Neurology*, *43*(12), 2457–65. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8255439

Morris, J. (2003). Dementia Update 2003. *Alzheimer Disease and Associated Disorders*, *17*(4), 245–258.

Morris, J. C. (1988). Consortium to establish a registry for Alzheimer's disease (CERAD) clinical and neuropsychological assessment of Alzheimer's disease. *Psychopharacological Bulletin*, *24*(4), 641–652.

Morris, J. C. (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*, *43*(11), 2412–2414.

Mortimer, J. A., Ebbitt, B., Jun, S.-P., & Finch, M. D. (1992). Predictors of cognitive and functional progression in patients with probable Alzheimer's disease. *Neurology*, *42*(9), 1689–96.

Mortimer, J., Snowdon, D., & Markesbery, W. (2003). Head circumference, education and risk of dementia: findings from the Nun Study. *Journal of Clinical and Experimental Neuropsychology*, *25*(5), 671–679.

Murphy, D. G., DeCarli, C. D., Daly, E., Gillette, J. A., McIntosh, A. R., Haxby, J. V, Teichberg, D., et al. (1993). Volumetric magnetic resonance imaging in men with dementia of the Alzheimer type: correlations with disease severity. *Biological psychiatry*, *34*(9), 612–21. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8292690

Musicco, M., Palmer, K., Salamone, G., Lupo, F., Perri, R., Mosti, S., Spalletta, G., et al. (2009). Predictors of progression of cognitive decline in Alzheimer's disease: the role of vascular and sociodemographic factors. *Journal of Neurology*, *256*, 1288–1295. doi:10.1007/s00415-009-5116-4

Musicco, M., Salamone, G., Caltagirone, C., Cravello, L., Fadda, L., Lupo, F., Mosti, S., et al. (2010). Neuropsychological predictors of rapidly progressing patients with Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *30*, 219–228. doi:10.1159/000319533

Myers, C. E., Kluger, A., Golomb, J., Gluck, M. a, & Ferris, S. (2008). Learning and generalization tasks predict short-term cognitive outcome in nondemented elderly. *Journal of Geriatric Psychiatry and Neurology*, *21*(2), 93–103. doi:10.1177/0891988708316858

Nagahama, Y., Nabatame, H., Okina, T., Yamauchi, H., Narita, M., Fujimoto, N., Murakami, M., et al. (2003). Cerebral correlates of the progression rate of the cognitive decline in probable Alzheimer's disease. *European Journal of Neurology*, *50*(1), 1–9. Retrieved from http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowAbstractBuch&ArtikelNr=70851&ProduktNr=229214

Nebes, R. D., & Brady, C. B. (1992). Generalized cognitive slowing and severity of dementia in Alzheimer's disease: implications for the interpretation of response-time data. *Journal of Clinical and Experimental Neuropsychology*, *14*(2), 317–26. doi:10.1080/01688639208402831

Nocentini, U., & Vincenzo, S. D. (2002). Executive functions assessment in neuropsychological practice: from Modified Card Sorting Test to Modified Card Sorting Test-roma Version. Normative values. Nuova rivista di Neurologia Retrieved from http://cat.inist.fr/?aModele=afficheN&cpsidt=13544941

O'Bryant, S., Waring, S. C., Cullum, C. M., Hall, J., Lacritz, L., Massman, P. J., Lupo, P. J., et al. (2008). Staging dementia using clinical dementia rating scale sum of boxes scores. *Archives of Neurology*, *65*(8), 1091–1095.

O'Hara, R., Thompson, J. M., Kraemer, H. C., Catherine, F., Taylor, J. L., Ross, L., Yesavage, J. A., et al. (2002). Which Alzheimer patients are at risk for rapid cognitive decline? *Journal of Geriatric Psychiatry and Neurology*, *15*, 233–238.

Ott, A., Van Rossum, C., Van Harskamp, F., Van de Mheen, H., Hofman, A., & Breteler, M. (1999). Education and the incidence of dementia in a large population-based study: The Rotterdam Study. *Neurology*, *52*(3), 2–7. Retrieved from http://www.neurology.org/content/52/3/663.short

Palmer, K., Berger, A. K., Monastero, R., Winbald, B., Backman, L., & Fratiglioni, L. (2007). Predictors of progression from mild cognitive impairment to Alzheimer disease. *Neurology*, *68*, 1596–1602.

Perret, E. (1974). The left frontal lobe of man and the suppression of habitual responses in verbal categorical behaviour. *Neuropsychologia*, *12*(3), 323–30. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/4421777

Petersen, R. C. (2009). Early diagnosis of Alzheimer's disease: Is MCI too late? *Current Alzheimer Research*, *6*(4), 324–330.

Pike, K. E., Savage, G., Villemagne, V. L., Ng, S., Moss, S., Maruff, P., Mathis, C., et al. (2007). Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. *Brain*, *130*(11), 2837–2844. doi:10.1093/brain/awm238

Poirier, J., & Davignon, J. (1993). Apolipoprotein E polymorphism and Alzheimer disease. *Lancet*, *342*(8873), 697. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21617520

Raber, J., Huang, Y., & Ashford, J. W. (2004). ApoE genotype accounts for the vast majority of AD risk and AD pathology. *Neurobiology of Aging*, *25*(5), 641–50. doi:10.1016/j.neurobiolaging.2003.12.023

Rasmusson, D. X., Carson, K. A., Brookmeyer, R., Kawas, C., & Brandt, J. (1996). Predicting rate of cognitive decline in probable Alzheimer's disease. *Brain and Cognition*, *147*(31), 133–147. Retrieved from http://psycnet.apa.org/psycinfo/1996-05395-003

Regan, C., Katona, C., Walker, Z., Hooper, J., Donovan, J., & Livingston, G. (2006). Relationship of vascular risk to the progression of Alzheimer disease. *Neurology*, *67*(8), 1357–62. doi:10.1212/01.wnl.0000240129.46080.53

Reitan, R., & Wolfson, D. (1995). Category Test and Trail Making Test as measures of frontal lobe functions. *The Clinical Neuropsychologist*. Retrieved from http://www.tandfonline.com/doi/abs/10.1080/13854049508402057

Renzi, A. De, & Vignolo, L. (1962). Token test: A sensitive test to detect receptive disturbances in aphasics. *Brain*, *85*. Retrieved from http://psycnet.apa.org/psycinfo/1964-06354-001

Roselli, F., Tartaglione, B., Federico, F., Lepore, V., Defazio, G., & Livrea, P. (2009). Rate of MMSE score change in Alzheimer's disease: influence of education and vascular risk factors. *Clinical Neurology and Neurosurgery*, *111*(4), 327–30. doi:10.1016/j.clineuro.2008.10.006

Rosen, W., Mohs, R., & Davis, K. (1984). A new rating scale for Alzheimer's disease. *The American Journal of Psychiatry*, *141*, 1356–1364. Retrieved from http://psycnet.apa.org/psycinfo/1985-08430-001

Rosenberg, R., Richter, R., Risser, R., Taubman, K., Prado-Farmer, I., Ebalo, E., Posey, J., et al. (1996). Genetic factors for the development of Alzheimer disease in the Cherokee Indian. *Archives of Neurology*, *53*(10), 997–1000.

Rossetti, H., Cullum, C., Hynan, L., & Lacritz, L. (2010). The CERAD Neuropsychological Battery Total Score and the progression of Alzheimer's disease. *Alzheimer Disease and Associated Disorders*, *24*(2), 138–142. doi:10.1097/WAD.0b013e3181b76415.The

Saxton, J., Snitz, B. E., Lopez, O. L., Ives, D. G., Dunn, L. O., Fitzpatrick, A., Carlson, M. C., et al. (2009). Functional and cognitive criteria produce different rates of mild cognitive impairment and conversion to dementia. *Journal of Neurology, Neurosurgery, and Psychiatry*, *80*(7), 737–43. doi:10.1136/jnnp.2008.160705

Scarmeas, N, Albert, S. M., Manly, J. J., & Stern, Y. (2006). Education and rates of cognitive decline in incident Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *77*(3), 308–316. doi:10.1136/jnnp.2005.072306

Scarmeas, Nikolaos, Brandt, J., Blacker, D., Albert, M., Hadjigeorgiou, G. M., Dubois, B., Devanand, D., et al. (2007). Disruptive behavior as a predictor in Alzheimer disease. *Archives of Neurology*, *64*(12), 1755–1761. doi:10.1001/archneur.64.12.1755.Disruptive

Schmid, N. S., Taylor, K. I., Foldi, N. S., Berres, M., & Monsch, A. U. (2013). Neuropsychological signs of Alzheimer's disease 8 years prior to diagnosis. *Journal of Alzheimer's Disease*, *34*(2), 537–46. doi:10.3233/JAD-121234

Schmidt, M. (1996). *Rey auditory verbal learning test: a handbook*. Los Angeles: Western Psychological Services.

Schram, L. L., Rubert, M., & Loewenstein, D. (1995). A qualitative analysis of semantic intrusive errors in Alzheimer's disease. *Archives of Clinical Neuropsychology*, *10*(3), 255–263. doi:10.1093/arclin/10.3.255

Silbert, L. C., Quinn, J. F., Moore, M. M., Corbridge, E., Ball, M. J., Murdoch, G., Sexton, G., et al. (2003). Changes in premorbid brain volume predict Alzheimer's disease pathology. *Neurology*, *61*, 487–492.

Simon, E., Leach, L., Winocur, G., & Moscovitch, M. (1994). Intact primary memory in mild to moderate Alzheimer disease: indices from the California Verbal Learning Test. *Journal of Clinical and Experimental Neuropsychology*, *16*(3), 414–22. doi:10.1080/01688639408402652

Small, B. J., Herlitz, A., Fratiglioni, L., Almkvist, O., & Backman, L. (1997). Cognitive predictors of incident Alzheimer's disease: A prospective longitudinal study. *Neuropsychology*, *11*(3), 413–420.

Snider, B. J., Fagan, A. M., Roe, C., Shah, A. R., Grant, E., Xiong, C., Morris, J. C., et al. (2009). Cerebrospinal fluid biomarkers and rate of cognitive decline in very mild dementia

of the Alzheimer type. *Archives of Neurology*, *66*(5), 638–645. doi:10.1001/archneurol.2009.55

Snodgrass, J. G., & Corwin, J. (1988). Pragmatics of measuring recognition memory: applications to dementia and amnesia. *Journal of Experimental Psychology*, *117*(1), 34–50. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2966230

Sona, A., Zhang, P., Ames, D., Bush, A. I., Lautenschlager, N. T., Martins, R. N., Masters, C. L., et al. (2011). Predictors of rapid cognitive decline in Alzheimer's disease: results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing. *International Psychogeriatrics*, 1–8. doi:10.1017/S1041610211001335

Song, X., Mitnitski, A., & Rockwood, K. (2011). Nontraditional risk factors combine to predict Alzheimer disease and dementia. *Neurology*, *77*(3), 227–234. doi:10.1212/WNL.0b013e318225c6bc

Soto, M., Andrieu, S., Arbus, C., Ceccaldi, M., Couratier, P., Dantoine, T., Datrigues, J., et al. (2008). Rapid cognitive decline in Alzheimer's disease. A concensus paper. *The Journal of Nutrition, Health and Aging*, *12*(10), 703–713. Retrieved from http://www.springerlink.com/index/RT97135N84752534.pdf

Sperling, R., Aisen, P. S., Beckett, L., Bennett, D., Craft, S., Fagan, A. M., Iwatsubo, T., et al. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, *7*(3), 280–292. doi:10.1016/j.jalz.2011.03.003

Stefani, A., Martorana, A., Bernardini, S., Panella, M., Mercati, F., Orlacchio, A., & Pierantozzi, M. (2006). CSF markers in Alzheimer disease patients are not related to the different degree of cognitive impairment. *Journal of the Neurological Sciences*, *251*(1-2), 124–8. doi:10.1016/j.jns.2006.09.014

Stern, R. G., Mohs, R. C., Davidson, M., Silverman, J., Kramer-Ginsberg, E., Searcey, T., Bierer, L., et al. (1994). A longitudnal study of Alzheimer's disease: Measurement, rate, and predictors of cognitive detioration. *American Journal of Psychiatry*, *151*(March), 390–396.

Stern, Y., Albert, S., Tang, M.-X., & Tsai, W.-Y. (1999). Rate of memory decline in AD is related to education and occupation. *Neurology*, *53*(9), 1–11. Retrieved from http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Rate+of+memory+decline+in+AD+is+related+to+education+and+occupation#5

Storandt, M., Grant, E. A., Miller, J. P., & Morris, J. C. (2002). Rates of progression in mild cognitive impairment and early Alzheimer's disease. *Neurology*, *59*, 1034–1041.

Stoub, T. R., Bulgakova, M., Leurgans, S., Bennett, D. A., Fleischman, D., Turner, D. A., & DeToledo-Morrell, L. (2005). MRI predictors of risk of incident Alzheimer disease A longitudinal study. *Neurology*, *64*, 1520–1524.

Strauss, E. H. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary*. Oxford University Press.

Suh, G., Ju, Y., Yeon, B. K., & Shah, A. (2004). A longitudinal study of Alzheimer's disease: rates of cognitive and functional decline. *International Journal of Geriatric Psychiatry*, *19*, 817–824. doi:10.1002/gps.1168

Swanwick, G. R., Coen, R. F., Coakley, D., & Lawlor, B. A. (1998). Assessment of progression and prognosis in "possible" and "probable" Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *13*, 331–335.

Talbot, C., Lendon, C., Craddock, N., Shears, S., Morris, J., & Goate, A. (1994). Protection against Alzheimer's disease with apoE epsilon 2. *Lancet*, *343*(8910), 1432–1433.

Tang, M.-X., Cross, P., Andrews, H., Jacobs, D. M., Small, S., Bell, K., Merchant, C., et al. (2001). Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in northern Manhattan. *Neurology*, *56*(1), 49–56. doi:10.1212/WNL.56.1.49

Teri, L., McCurry, S. M., Edland, S. D., Kukull, W. A., & Larson, E. B. (1995). Cognitive decline in Alzheimer's disease: a longitudinal investigation of risk factors for accelerated decline. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *50*(1), M49–55.

Thompson, J. C., Stopford, C. L., Snowden, J. S., & Neary, D. (2005). Qualitative neuropsychological performance characteristics in frontotemporal dementia and Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *76*(7), 920–7. doi:10.1136/jnnp.2003.033779

Tierney, M. C., Yao, C., Kiss, A., & McDowell, I. (2005). Neuropsychological tests accurately predict incident Alzheimer disease after 5 and 10 years. *Neurology*, *64*(11), 1853–1859. doi:10.1212/01.WNL.0000163773.21794.0B

Tyas, S. L., Salazar, J. C., Snowdon, D. A., Desrosiers, M. F., Riley, K. P., Mendiondo, M. S., & Kryscio, R. J. (2007). Transitions to mild cognitive impairments, dementia, and death: Findings from the Nun Study. *American Journal of Epidemiology*, *165*(11), 1231–1238.

Viatonou, S., Drame, M., Jolly, D., Morrone, I., Lang, P.-O., Viosin, T., Boyer, F. C., et al. (2009). Predictors of rapid cognitive decline among demented subjects aged 75 or more. *International Journal of Geriatric Psychiatry*, *24*, 709–715. doi:10.1002/gps

Villemagne, V. L., Pike, K. E., Darby, D., Maruff, P., Savage, G., Ng, S., Ackermann, U., et al. (2008). Abeta deposits in older non-demented individuals with cognitive decline are indicative of preclinical Alzheimer's disease. *Neuropsychologia*, *46*(6), 1688–1697. doi:10.1016/j.neuropsychologia.2008.02.008

Wechsler , D. (1981). Wechsler Adult Intelligence Scale-Revised. New York: Psychological Corporation, 1981.

Wechsler, D. (1987). Wechsler Memory Scale—Revised manual. San Antonio, TX: Psychological Corporation

Weiner, M. F., Rosenberg, R. N., Svetlik, D., Hynan, L. S., Womack, K. B., White, C., Good, S., et al. (2003). Comparison of Alzheimers disease in Native Americans and Whites. *International Psychogeriatrics*, *15*(4), 367–375. doi:10.1017/S104161020300961X

Williams, J. W., Plassman, B. L., Burke, J., Holsinger, T., & Benjamin, S. (2010). Preventing Alzheimer disease and cognitive decline. *Evidence Report / Technology Assessment*, *193*. doi:10.1059/0003-4819-154-3-201102010-00014

Williams, M. M., Storandt, M., Roe, C. M., & Morris, J. C. (2012). Progression of Alzheimer's disease as measured by Clinical Dementia Rating Sum of Boxes scores. *Alzheimer's & Dementia*. doi:10.1016/j.jalz.2012.01.005

Wilson, R S, Hebert, L. E., Scherr, P. A., Barnes, L. L., Mendes de Leon, C. F., & Evans, D. A. (2009). Educational attainment and cognitive decline in old age. *Neurology*, *72*(5), 460–465. doi:10.1212/01.wnl.0000341782.71418.6c

Wilson, R. S., Li, Y., Aggarwal, N. T., Barnes, L. L., McCann, J. J., Gilley, D. W., & Evans, D. A. (2004). Education and the course of cognitive decline in Alzheimer disease. *Neurology*, *63*(7), 1198–1202. doi:10.1212/01.WNL.0000140488.65299.53

Wilson, R., Schneider, J., Barnes, L., Beckett, L., Aggarwal, N., Cochran, E., Berry-Kravis, E., et al. (2002). The apolipoprotein E epsilon 4 allele and decline in different cognitive systems during a 6-year period. *Archives of Neurology*, *59*(7), 1154–1160.

Wilson, Robert S, Gilley, D. W., Bennet, D. A., Beckett, L. A., & Evans, D. (2000). Hallucinations, delusions, and cognitive decline in Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *69*, 172–177. Retrieved from http://jnnp.bmj.com/content/69/2/172.abstract

Zhang, M., Katzman, R., Salmon, D., Jin, H., Cai, G., Wang, Z., Qu, G., et al. (1990). The prevalence of dementia and Alzheimer's disease in Shanghai, China: impact of age, gender, and education. *Annals of Neurology*, *27*(4), 428–437.

TABLES

Table 1
List of Independent Variables by Aim

Aim 1. CVLT Features of Performance (z-scores)	*Aim 2.* Neurocognitive Variables	*Aim 3.* Clinical and Demographic Variables	*Exploratory Aim.* Biomarker Variables
1. % Recall from Primacy Region	1. Significant variables from Aim 1 analysis	1. Significant variables from Aim 2 analysis	1. Significant variables from Aim 3 analysis
2. % Recall from Recency Region	2. CVLT Total Learning T-score	2. Heart disease	2. Hippocampal volume
3. Recall Consistency	3. CVLT Long-delay Free Recall z-score	3. Vascular disease	3. Total brain volume
4. Semantic Clustering	4. Visual Reproduction I Percentile	4. Traumatic brain injury	4. Presence of ApoE ε4
5. Total Intrusions	5. Visual Reproduction II Percentile	5. Diabetes	
6. Recognition Discriminability	6. Trail Making Test - B Time T-score	6. Hypercholesterol-emia	
7. Total Perseverations	7. Phonemic Fluency Total Words T-score	7. Hypertension	
8. Response Bias	8. Semantic Fluency Total Words T-score	8. Depression within the last 2 years	
	9. Boston Naming Test Total T-score	9. History of psychiatric disorders	
	10. Block Design Scaled score	10. Age at diagnosis	
	11. Digit Span Backward Longest Span	11. Duration of illness	
	12. Digit Symbol Coding Scaled score		
	13. Demographically-corrected CERAD Total Score (Chandler, et al., 2005)		

Table 2
Predictor Variables

Model 1. CVLT Performance Features (z-scores)	*Model 2*. Neurocognitive Variables	*Model 3*. Clinical and Demographic Variables
1. % Recall from Primacy Region*	1. Significant variables from Model 1	1. Significant variables from Model 2
2. % Recall from Recency Region*	2. CVLT Total Learning T-score*	2. Cardiac History
3. Recall Consistency*	3. CVLT Long-delay Free Recall z-score*	3. Cerebrovascular Event History
4. Semantic Clustering*	4. Visual Reproduction I Percentile*	4. Traumatic brain injury (TBI) History
5. Total Intrusions*	5. Visual Reproduction II Percentile*	5. Diabetes History
6. Recognition Discriminability*	6. Trail A Time T-score*	6. Hypercholesterolemia History
7. Total Perseverations*	7. Trail B Time T-score*	7. Hypertension History
8. Response Bias*	8. Phonemic Fluency Total Words T-score*	8. Depression within the last 2 years
	9. Semantic Fluency Total Words T-score*	9. History of Delusions
	10. CERAD Naming subtest Total	10. History of Hallucinations
	11. CERAD Total Score*	11. Duration of illness
	12. Block Design Scaled score*	12. Age at diagnosis
	13. Digit Span Backward Longest Span	
	14. Digit Symbol Coding Scaled score*	

Note. *Demographically corrected (i.e., age and education) scores were used.

Table 3
Sample Demographics t-test Comparisons

Measure	Group	Mean (SD)	Range	t	p-value
Age at baseline				-0.231	0.818
	Slower	71.57 (7.79)	54 - 85		
	Faster	71.95 (8.11)	54 - 84		
Education				0.466	0.317
	Slower	14.24 (3.40)	6 - 20		
	Faster	14.89 (2.90)	9 - 20		
Age of AD Onset				-0.372	0.711
	Slower	68.45 (8.39)	45 - 83		
	Faster	69.07 (7.69)	51 - 83		
Duration of Illness (years)				0.372	0.642
	Slower	3.13 (2.65)	0 - 12.12		
	Faster	2.89 (2.38)	0 - 9.58		

Table 4
Sample Demographics chi-square tests

Measure	Group	Percent	χ^2	p-value
Sex (Female)			0.69	0.422
	Slower	47%		
	Faster	56%		
Race (White)*			0.16	0.592
	Slower	94%		
	Faster	91%		

Note.*Fisher's exact is presented for all cell with expected frequencies less than 5.

Table 5
Characterization of Dementia Severity at Baseline and Follow-up

Measure	Group	Mean (SD)	Range	*t*	p- value
Time between baseline and follow-up (years)				- 0.38	0.706
	Slower	1.79 (0.48)	1.02 - 2.82		
	Faster	1.82 (0.48)	1.01 - 2.50		
CDR-SOB at baseline				1.10	0.275
	Slower	5.31 (1.17)	3.0 - 8.0		
	Faster	5.04 (1.22)	3.0 - 8.0		
CDR-SOB at follow-up				-12.08	<0.001
	Slower	5.40 (1.92)	0.5 - 9.0		
	Faster	12.03 (3.21)	7.0 - 18.0		
MMSE score at baseline				1.88	0.063
	Slower	23.92 (3.06)	16 - 30		
	Faster	22.64 (3.58)	14 - 30		

Table 6
CVLT Performance Features by Progression Group

CVLT Variable	Group	N	Mean (SD)	Range	*t*	p-value
Semantic Clustering					1.55	0.124
	Slower	51	-0.90 (0.88)	-3.0 - 1.0		
	Faster	44	-1.23 (1.16)	-4.0 - 1.0		
Primacy					2.17	0.033
	Slower	51	-0.94 (2.49)	-5.0 - 4.0		
	Faster	45	-1.98 (2.16)	-5.0 - 3.0		
Recency					1.43	0.156
	Slower	51	0.71 (2.95)	-5.0 - 5.0		
	Faster	45	-0.27 (3.61)	-5.0 - 5.0		
Consistency					0.31	0.760
	Slower	51	-1.59 (1.56)	-5.0 - 2.0		
	Faster	45	-1.71 (2.25)	-1.0 - 5.0		
Intrusions					0.83	0.409
	Slower	51	1.28 (1.90)	-1.0 - 5.0		
	Faster	44	0.98 (1.59)	-1.0 - 5.0		
Discriminability					1.42	0.158
	Slower	50	-2.92 (1.50)	-5.0 - 0.0		
	Faster	45	-3.36 (1.48)	-5.0 - 1.0		
Response Bias					0.84	0.402
	Slower	50	1.24 (1.27)	-2.0 - 3.0		
	Faster	45	1.00 (1.51)	-2.0 - 3.0		
Perseverations					0.91	0.365
	Slower	50	-0.18 (0.87)	-1.0 - 3.0		
	Faster	44	-0.34 (0.83)	-1.0 - 3.0		

Note. Z-scores derived from CVLT normative data are presented for all variables. Primacy: percent recall from the Primacy region, Recency: percent recall from the Recency region, Discriminability: recognition discriminability, Consistency: recall consistency, Intrusions: number of intrusions on free response trials, Perseverations: number of perseverations on free response trials. Lower scores indicate worse performance on all measures except Intrusions, which is reverse-scored.

Table 7
Neurocognitive Test Scores by Progression Group

Measure	Group	N	Mean (SD)	Range	*t*	p-value
Digit-Symbol Scaled Score					2.84	0.006
	Slower	43	8.95 (2.72)	2 - 14		
	Faster	36	7.11 (3.05)	1 - 13		
Trail Making Test - A T-score					3.29	0.002
	Slower	44	41.84 (12.52)	11 - 63		
	Faster	34	32.18 (13.29)	7 - 57		
Phonemic Fluency T-score					1.53	0.128
	Slower	50	36.84 (10.13)	14 - 58		
	Faster	42	33.55 (10.36)	16 - 61		
Semantic Fluency T-score					1.02	0.310
	Slower	48	34.92 (11.15)	15 - 60		
	Faster	42	32.55 (10.80)	11 - 58		
Digit Backwards - Longest Span					1.87	0.065
	Slower	42	4.19 (0.97)	3 - 7		
	Faster	37	3.76 (1.09)	2 - 6		
Visual Reproduction I Percentile					1.46	0.166
	Slower	43	12.70 (16.39)	1 - 63		
	Faster	35	8.17 (10.91)	1 - 50		
Visual Reproduction II Percentile					1.43	0.157
	Slower	43	11.21 (15.85)	1 - 84		
	Faster	35	6.83 (9.70)	1 - 50		
CVLT Total T-score					2.40	0.018
	Slower	51	24.65 (9.64)	5 - 50		
	Faster	45	19.80 (10.13)	5 - 51		
Long Delay Free Recall Z-score					1.92	0.869
	Slower	49	-2.65 (1.16)	-5 - 1		
	Faster	45	-2.69 (0.90)	-5 - 0		
CERAD Boston Naming Total					3.57	0.058
	Slower	50	13.60 (1.67)	9 - 15		
	Faster	42	12.71 (2.71)	2 - 15		
CERAD Total					3.57	0.001
	Slower	48	69.48 (9.51)	48 - 88		
	Faster	42	62.00 (10.39)	36 - 82		

Block Design Scaled Score					1.13	0.265
	Slower	23	8.87 (3.51)	3 - 17		
	Faster	25	7.76 (3.31)	2 - 15		
Trail Making Test - B T-score					1.97	0.053
	Slower	35	35.37 (13.49)	11 - 59		
	Faster	27	28.30 (14.62)	6 - 60		
Boston Naming Test T-score					2.12	0.043
	Slower	13	42.46 (15.45)	20 - 66		
	Faster	16	30.25 (15.31)	9 - 57		

Table 8
Health History by Progression Group

Measure	Group	Absent	Present	p-value
Cardiac				0.058
	Slower (n = 50)	42	8	
	Faster (n = 45)	30	15	
Cerebrovascular Event*				0.462
	Slower (n = 50)	47	3	
	Faster (n = 42)	37	5	
TBI*				0.214
	Slower (n = 49)	45	4	
	Faster (n = 43)	35	8	
Hypertension				0.640
	Slower (n = 50)	24	26	
	Faster (n = 44)	19	25	
Hypercholesterolemia				0.159
	Slower (n = 50)	24	26	
	Faster (n = 44)	19	25	
Diabetes				0.538
	Slower (n = 50)	45	5	
	Faster (n = 44)	37	7	
Depression Within Past 2 Years*				>0.999
	Slower (n = 28)	20	8	
	Faster (n = 16)	12	4	
Delusions				0.315
	Slower (n = 48)	40	8	
	Faster (n = 43)	32	11	
Hallucinations*				0.244
	Slower (n = 51)	49	2	
	Faster (n = 44)	39	5	

Note. *Fisher's exact is presented for all cells with expected frequencies less than 5.

Table 9
Performance Features of Verbal Episodic Memory: Individual Logistic Regression

CVLT Variable	Wald χ^2	p-value
Primacy*	4.400	.036
Recency	2.073	.150
Consistency	0.100	.752
Semantic Clustering	2.328	.127
Intrusions	0.677	.411
Discriminability	1.991	.158
Response Bias	0.714	.398
Perseverations	0.825	.364

Note. * $p < 0.05$

Table 10
Performance Features of CVLT: Reduced Model

	Wald χ^2	p-value	Odds Ratio	95% C.I. for OR	
				Lower	Upper
Primacy	4.400	.036	.825	.689	.987

Table 11
Neurocognitive Measures: Individual Logistic Regression

Neurocognitive Variables	Wald χ^2	p-value
CVLT Total Learning T-score*	5.242	.022
Trail Making Test - A T-score*	9.210	.002
Digit Symbol Coding Scaled score*	6.751	.009
CERAD Total Score*	9.993	.002
Trail Making Test - B T-score**	3.606	.058
CERAD Boston Naming Total**	3.260	.071
CVLT Long-delay Free Recall z-score	0.028	.867
Visual Reproduction I Percentile	1.864	.172
Visual Reproduction II Percentile	1.818	.178
Phonemic Fluency T-score	2.303	.129
Semantic Fluency T-score	1.043	.307
Block Design Scaled score	1.258	.262
Digit Span Backward - Longest Span**	3.308	.069
Boston Naming Test T-score**	3.660	.056

Note. *$p < 0.05$, **$p < 0.1$

Table 12
All Neurocognitive Measures: Reduced Model

	Wald χ^2	p-value	Odds Ratio	95% C.I. for OR	
				Lower	Upper
Trail Making Test - A	6.508	.011	.943	.901	.986
Semantic Fluency	5.039	.025	1.086	1.011	1.167
CERAD Total	6.291	.012	.906	.839	.979

Table 13
Clinical Variables: Individual Prediction Analyses

Clinical Variables by History	Wald χ^2	p-value
Cardiac**	3.743	.053
Cerebrovascular Event	0.967	.325
TBI	2.095	.148
Diabetes	0.722	.392
Hypertension	.219	.640
Hypercholesterolemia	1.898	.168
Depression within the last 2 years	0.065	.798
Duration of illness	0.221	.638
Age at onset	0.141	.708

Note. **$p < 0.1$

Table 14
Model 3: Reduced Model

	Wald	p-value	Odds Ratio	95% C.I. for OR	
				Lower	Upper
Trail Making Test - A	9.210	.002	.944	.910	.980
Constant	6.308	.012	6.385		

Table 15
Area Under the Curve: Predictors of Progression

Model	AUC
Trail Making Test - A + CERAD Total + Semantic Fluency	0.769
Trail Making Test - A	0.706
CERAD Total	0.679
Digit Symbol	0.676
CVLT Total	0.628
Primacy	0.621
Cardiac History	0.587

FIGURES

Figure 1
ROC: CVLT Primacy

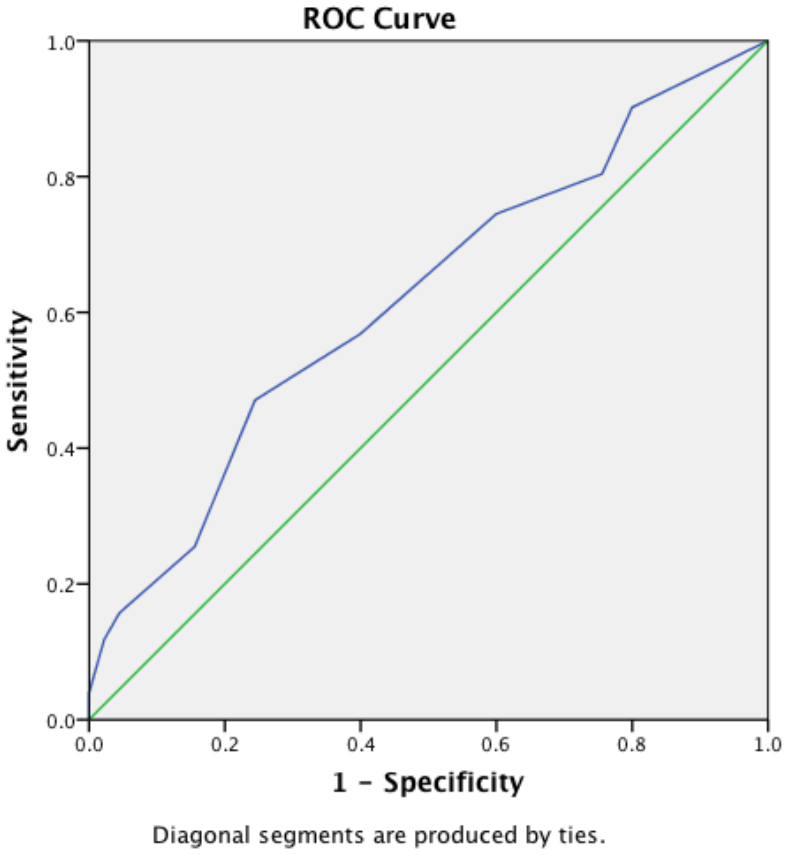


Figure 2
ROC: All Neurocognitive Measures: Reduced Model

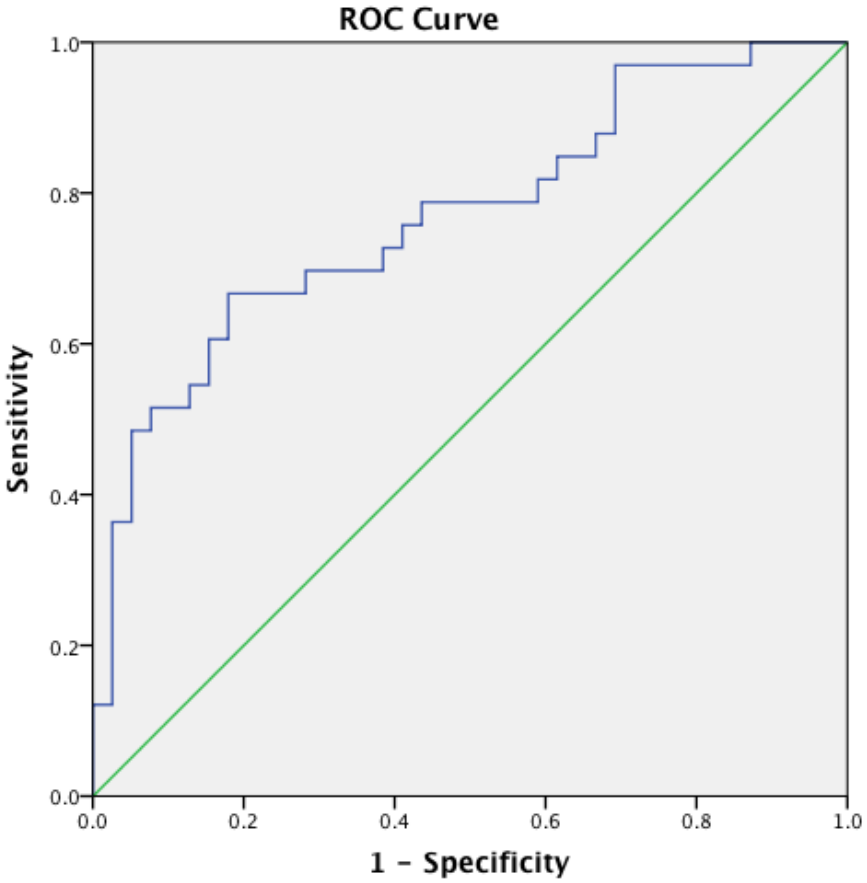
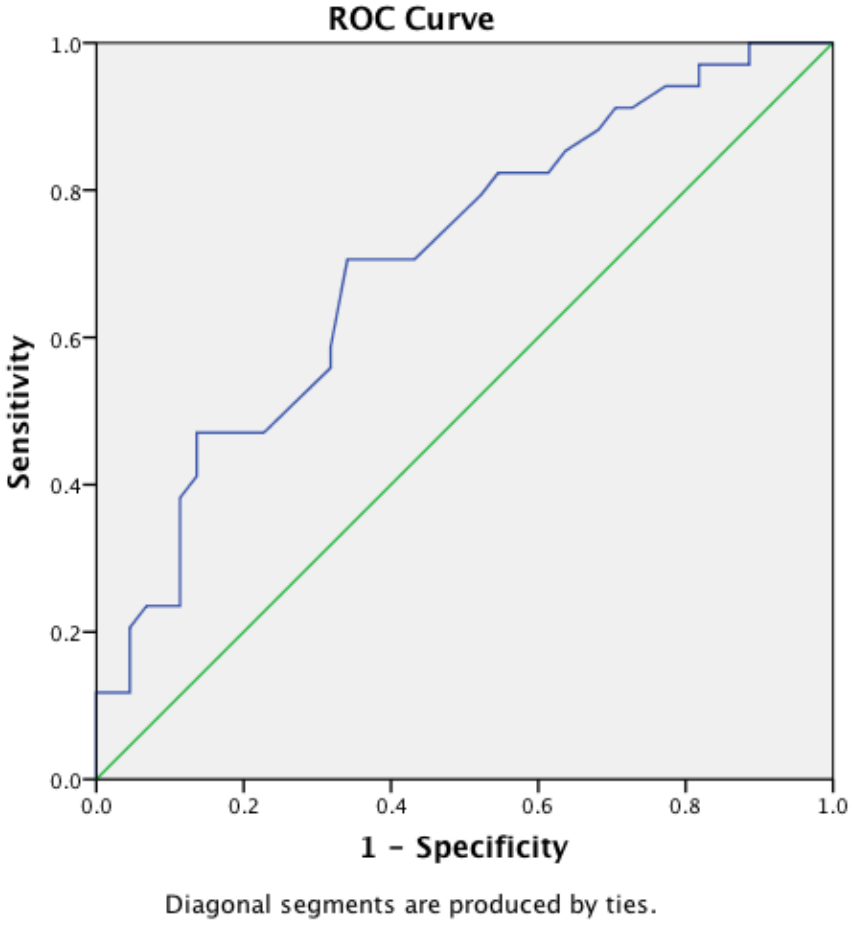


Figure 3
ROC: Model 3 (Trail Making Test - A)



APPENDIX A

Study Sample and Excluded Subjects

The number of subjects was reduced from the original dataset to comply with inclusion criteria (Figure 4). Demographic characteristics of the overall study sample and the excluded AD sample are described in Table 16. Independent samples t-tests between included and excluded groups revealed that the groups did not differ significantly by age or education. Fischer's exact tests indicated that groups were also similar across gender and race.

Figure 4
Flowchart of Included Subjects

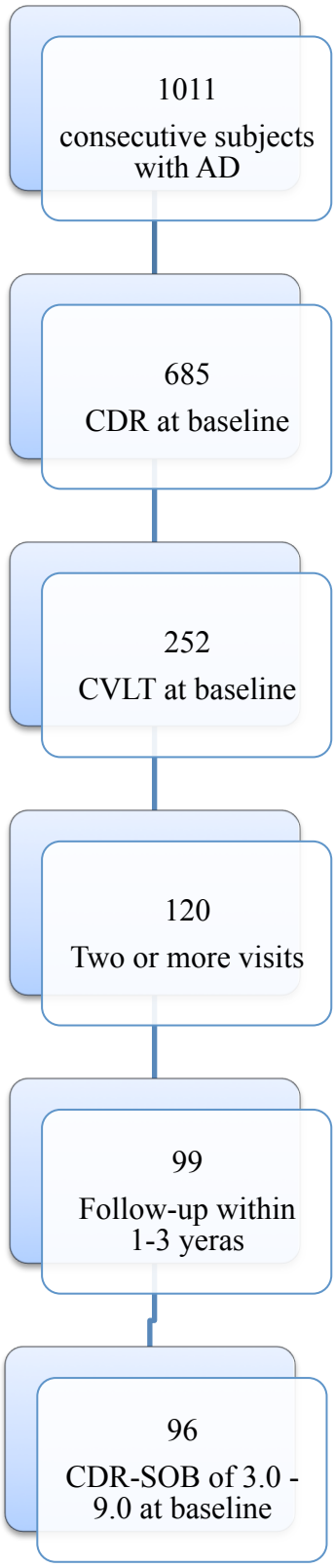


Table 16
Demographic Comparison of Included and Excluded Subjects

	Study Sample (N = 96)	Excluded Subjects (N = 915)	p - value
Age (years)			
Mean (SD)	71.75 (7.90)	70.4 (7.70)	0.35
Range	53.91 - 85.06	50.23 - 87.88	
Age of AD Onset (years)			0.58
Mean (SD)	68.74 (8.03)	68.21 (9.10)	
Range	45.00 - 83.32	33.89 - 92.0	
Education			0.20
Mean (SD)	14.54 (3.18)	13.75 (3.27)	
Range	6.0 - 20.0	1.0 - 22.0	
Sex			0.97
% Female	51%	57%	
Race			0.05
% White	93%	83%	

Note. Independent t-tests were performed for Age, Age of AD Onset, and Education. Chi-square was performed for Sex and Race.

APPENDIX B

Additional Analyses

In order to further explore prediction of progression, additional logistic regression analyses were conducted using different combinations of predictors.

Significant Neurocognitive Measures

In an additional analysis, only measures with significant differences in performance at baseline (based on t-tests described above) were entered into stepwise logistic regression. After backwards stepwise elimination, the only predictor significant in the final model was Trail Making Test - A (Table 17).

Domain-Specific Predictors

Neurocognitive measures were separated into specific cognitive domains. For domains that included more than one neurocognitive measure, a stepwise logistic regression was performed to determine the measure that accounted for the largest variance in predicting progression (See Table 18). The resulting single measure from each domain was entered into a logistic regression. Following a backwards stepwise elimination, Trail Making Test - A was the only significant predictor of progression (Table 19).

Table 17
Significant Neurocognitive Measures: Reduced Model

	Wald χ^2	p – value	Odds Ratio	95% C.I. for OR	
				Lower	Upper
Trail Making Test - A	9.210	.002	.944	.910	.980
Constant	6.308	.012	6.385		

Table 18
Neurocognitive Measures by Cognitive Domain

Cognitive Domain	Measure	Wald χ^2	p - value	Odds Ratio	95% C.I. for OR	
					Lower	Upper
Processing Speed						
	Digit Symbol	0.019	0.892	0.984	0.784	1.235
	Trail Making Test - A	5.784	0.016	0.940	0.893	0.989
Executive Functioning/Fluency						
	Phonemic Fluency	1.346	0.246	0.975	0.933	1.018
	Semantic Fluency	0.259	0.611	0.989	0.948	1.032
Working Memory						
	Digit Backward Span	3.308	0.069	0.656	0.416	1.033
Learning						
	Visual Reproduction I	1.311	0.252	0.980	0.947	1.015
	CVLT Total	3.495	0.062	0.954	0.909	1.002
Memory						
	Visual Reproduction II	1.656	0.198	0.967	0.918	1.018
	CVLT Long Delay Free Recall	0.011	0.917	1.031	0.578	1.841
Language						
	CERAD Boston	3.260	0.071	0.822	0.664	1.017
Global						
	CERAD Total	9.993	0.002	0.926	0.882	0.971

Table 19
Domain Specific Measures: Reduced Model

	Wald χ^2	p-value	Odds Ratio	95% C.I. for OR	
				Lower	Upper
Trail Making Test - A	9.210	.002	.944	.910	.980
Constant	6.308	.012	6.385		

APPENDIX C

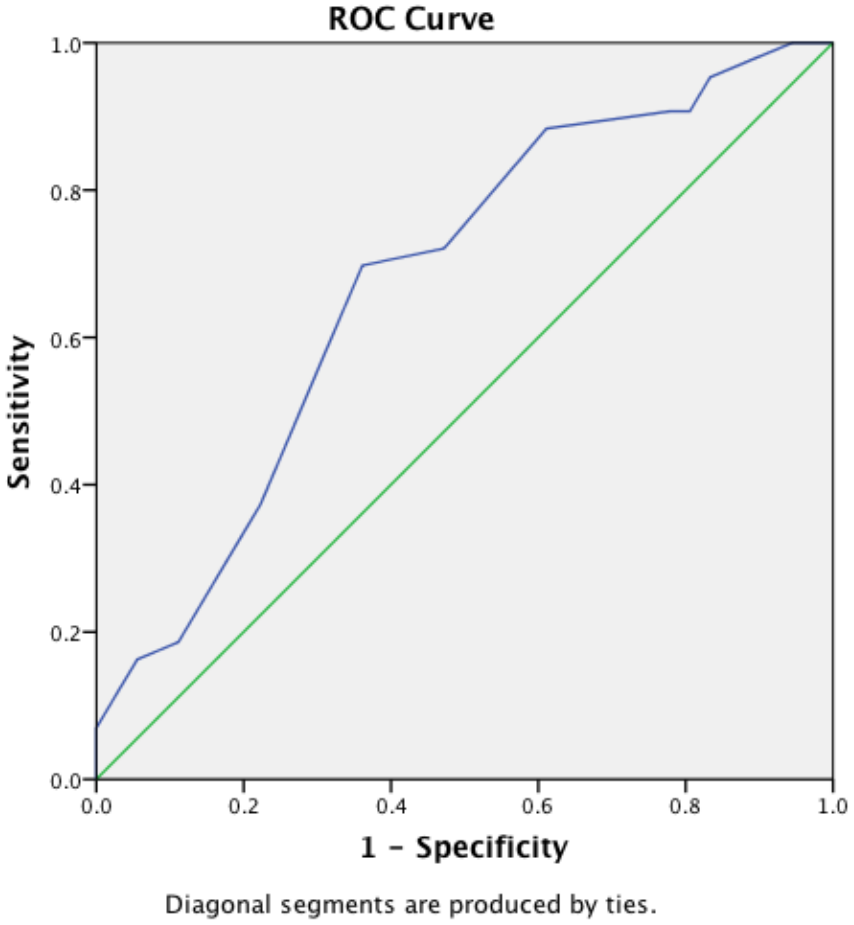
ROC Curves

Digit Symbol

Table 20
Digit Symbol Area Under the Curve

Area	Standard Error	p -value	95% CI	
			Lower Bound	Upper Bound
0.676	0.061	0.007	0.556	0.796

Figure 5
Digit Symbol Area Under the Curve

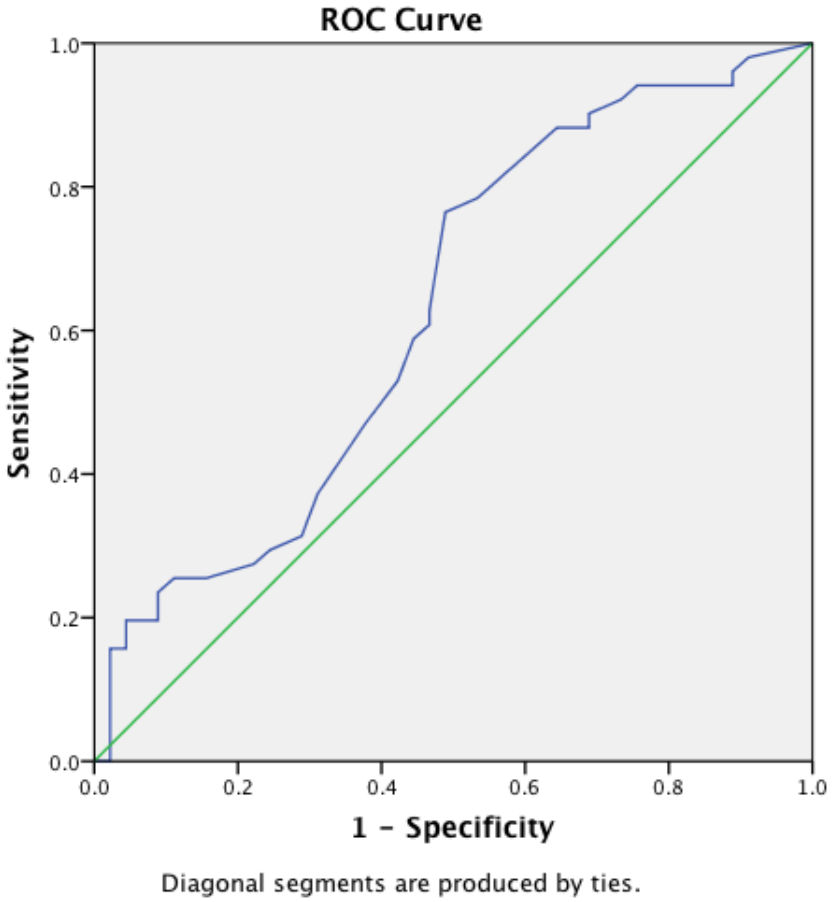


CVLT Total

Table 21
CVLT Total Area Under the Curve

Area	Standard Error	p - value	95% CI	
			Lower Bound	Upper Bound
0.628	0.058	0.031	0.515	0.741

Figure 6
CVLT Total Area Under the Curve

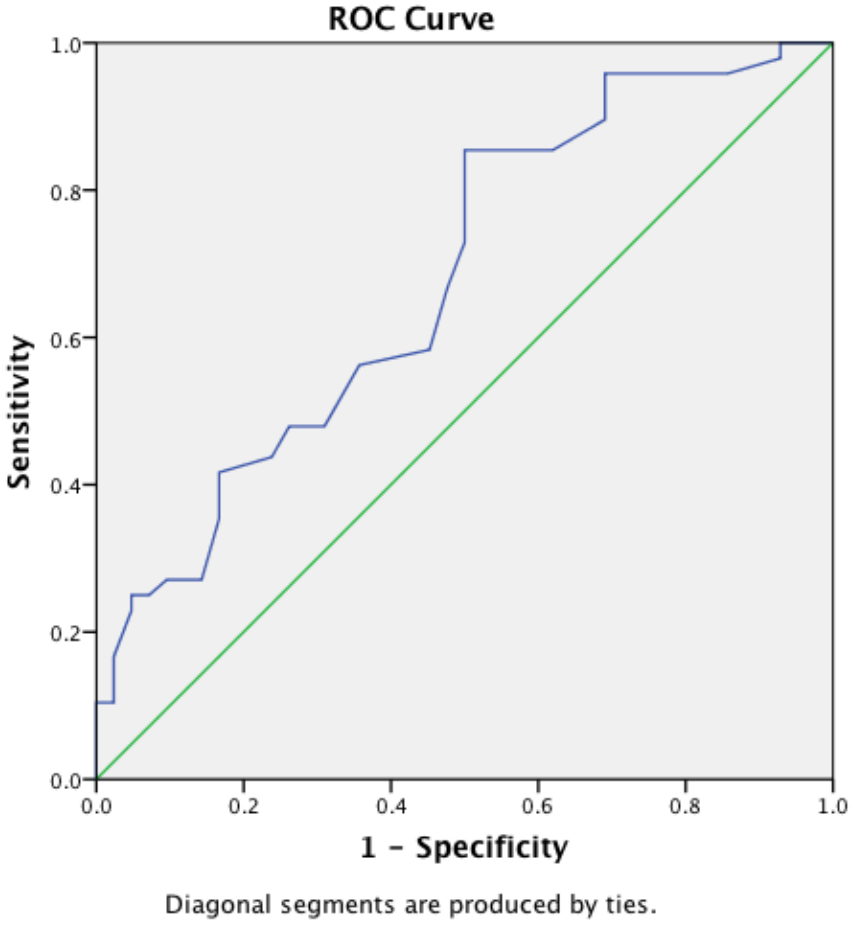


CERAD Total

Table 22
CERAD Total Area Under the Curve

Area	Standard Error	p - value	95% CI	
			Lower Bound	Upper Bound
0.679	0.056	0.003	0.569	0.790

Figure 7
CERAD Total Area Under the Curve

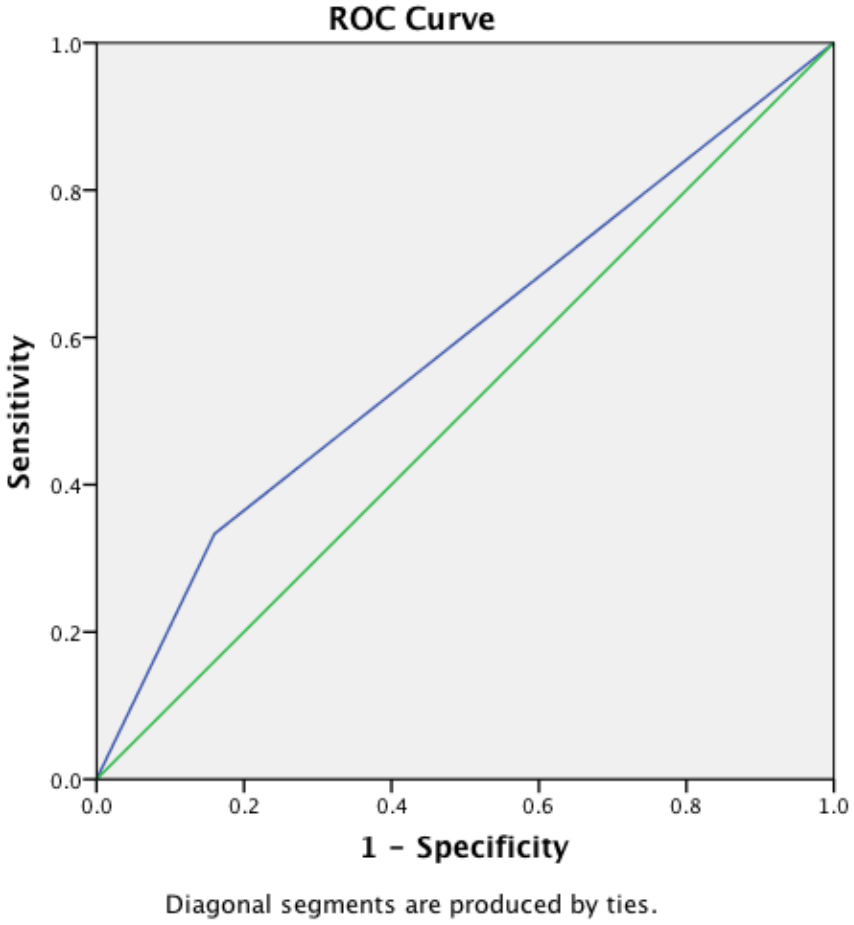


Cardiac History

Table 23
Cardiac History Area Under the Curve

Area	Standard Error	p-value	95% CI	
			Lower Bound	Upper Bound
0.587	0.059	0.146	0.471	0.702

Figure 8
Cardiac History Area Under the Curve



APPENDIX D

Exploratory Aim

Results

A very limited number of subjects had MRI morphometric data available (Table 24). In terms of MRI measures, Total Brain Volume [χ^2 (1, 19) = 0.905], Left Hippocampal Volume [χ^2 (1, 12) = 13.496], and Right Hippocampal Volume [χ^2 (1, 12) = 0.646], were not significant predictors of progression. Nonetheless, left hippocampus volume was significantly lower in Faster Progressors than Slower Progressors ($p < 0.01$).

ApoE ε4 genotype was available for 48 subjects. Distributions of ApoE ε4 allele types were not equal and had a low number of observations, which limited analyses (Table 25).

Discussion

It was hypothesized that MRI features would predict faster decline. Most analyses could not be completed due to a low number of observations available; however, there were some trends to consider. Left hippocampal volume was significantly lower in Faster than Slower Progressors, though the sample sizes were quite small. Despite this limitation, the findings from the present study are supported by an investigation by Jack et al. (2011) who analyzed volumetric changes in the hippocampus from serial MRI studies in 64 subjects with AD, and found atrophy rates were greater in patients with CDR decline at follow-up than patients with stable CDR. There are only few studies that examine the ability of hippocampal volume to predict prognosis in AD as many studies have focused on preclinical samples. The findings from the present and previous investigations indicate that hippocampal volume may play a role in

predicting rate of future decline in AD, but further investigation with larger sample size is necessary.

ApoE allele type was also hypothesized to predict progression, but this information was only available for approximately half of the sample, with very few ApoE ε4's, which limited the investigation of this marker. Overall, previous investigations have found ApoE allele type to have variable reliability in predicting rate of future cognitive decline. For example, Martins, et al., (2005) observed that faster decline was associated with both one and two copies of the ApoE ε4 allele in an investigation of 199 incident cases of AD, while Hoyt, et al.,(2005) paradoxically found that patients with 2 ApoE ε4 alleles exhibited a slower rate of decline than those with 1 or 0 alleles. In addition, several other studies have mixed association between ApoE ε4 genotype and rate of cognitive decline (Bracco et al., 2007; Dal Forno et al., 1995; Growdon et al., 1996; Helzner et al., 2009). In sum, the question regarding the role of ApoE ε4 genotype and rate of progression remains unanswered.

Table 24
MRI Measurements by Progression Group

MRI Measure	Group	Mean (SD)	Range	p-value
Total Brain Volume (cm^3)				0.521
	Slower (n = 13)	1174.00 (122.97)	981.90 - 1378.37	
	Faster (n = 6)	1126.60 (57.19)	1069.62 - 1219.08	
Left Hippocampal Volume (cm^3)				0.009
	Slower (n = 9)	3.49 (0.27)	3.06 - 3.81	
	Faster (n = 3)	2.61 (0.45)	2.14 - 3.03	
Right Hippocampal Volume (cm^3)				0.482
	Slower (n = 9)	3.43 (0.50)	2.72 - 4.22	
	Faster (n = 3)	3.18 (0.52)	2.84 - 3.78	

Note. Mann-Whitney U Tests are presented.

Table 25
ApoE Genotype Distribution by Progression Group

Group	ApoE 2, 3	ApoE 3, 3	ApoE 3, 4	ApoE 4, 4
Slower (n = 32)	1	12	10	9
Faster (n = 16)	0	6	8	2
Total (N = 48)	1	18	18	11