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Simple Neuropsychological Test Scores Associated with Rate of Cognitive Decline in Early Alzheimer Disease

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Abstract

Background—Alzheimer disease (AD) characteristically begins with episodic memory impairment followed by other cognitive deficits; however, the course of illness varies, with substantial differences in the *rate* of cognitive decline. For research and clinical purposes, it would be useful to distinguish between persons who will progress slowly from persons who will progress at an average or faster rate.

Objective—To use neurocognitive performance features and disease-specific and health information to determine a predictive model for the rate of cognitive decline in subjects with mild AD.

Method—We reviewed the records of a series of ninety-six consecutive subjects with mild AD from 1995 to 2011 who had been administered selected neurocognitive tests and clinical measures. Based on Clinical Dementia Rating (CDR) of functional and cognitive decline over two years, subjects were classified as Faster ($n = 45$) or Slower Progressors ($n = 51$). Stepwise logistic regression analyses using neurocognitive performance features, disease-specific, health, and demographic variables were performed.

Results—Neuropsychological scores that distinguished Faster from Slower Progressors included Trail Making Test - A, Digit Symbol, and California Verbal Learning Test (CVLT) Total Learned and Primacy Recall. No disease-specific, health, or demographic variable predicted rate of progression; however, history of heart disease showed a trend. Among the neuropsychological

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variables, Trail Making Test - A best distinguished Faster from Slower Progressors, with an overall accuracy of 68%. In an omnibus model including neuropsychological, disease-specific, health, and demographic variables, only Trail Making Test - A distinguished between groups.

Conclusion—Several neuropsychological performance features were associated with the rate of cognitive decline in mild AD, with baseline Trail Making Test - A performance best separating those who declined at an average or faster rate from those who showed slower progression.

Keywords

Alzheimer Disease; Progression; Cognitive Decline

Introduction

Alzheimer disease (AD) is a neurodegenerative disorder manifested by progressively worsening cognitive and functional ability. 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 ϵ 4) and neurocognitive (e.g., worse episodic memory) patient characteristics associated with the *risk* of developing AD have shown promise in predicting rate of cognitive decline, though results have been mixed (Adak et al., 2004; Cosentino et al., 2008).

Only a handful of studies have examined neuropsychological performance to predict rate of AD progression. Preliminary findings show promise (e.g., Atchison, Bradshaw, and Massman (2004), but there is no clear agreement on what measures are most sensitive or whether a particular pattern of scores aids in prediction of rate of decline (e.g., Beatty, Salmon, Troster, & Tivis, 2002).

The lack of consensus regarding neurocognitive predictors may relate to the types of neurocognitive variables utilized thus far, which may be insensitive to rates of progression (Storandt, Grant, Miller, & Morris, 2002). 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, and higher recall of the most recently presented stimuli (recency) have been suggested 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; Schmid, Taylor, Foldi, Berres, & Monsch, 2013). It follows that such variables may play a role in predicting the rate of cognitive decline from early to later stages of AD.

Markers for rate of decline in AD include demographic, disease-specific, biomedical, and neurocognitive domains, but integrated approaches that examine measures from multiple

domains may better predict rate of future decline than any of the markers alone. The purpose of this study was to determine if baseline neuropsychological variables could predict 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 neuropsychological variables with disease-specific and health features to determine the best predictive model.

Methods

Participants

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

1. Diagnosis of probable or possible AD at baseline using the National Institute of Neurological and Communication Disorders and Stroke/AD and Related Disorders Association (McKhann et al., 1984) criteria. Other competing diagnoses and those with major Axis I psychopathology were excluded.
2. Baseline Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) score of 2.5 to 9.0, reflecting mild dementia (O'Bryant et al., 2008).
3. Completion of neuropsychological assessment at initial presentation ("baseline") that included measures of episodic memory, attention/processing speed, executive function, and language.
4. Baseline plus at least one follow-up visit over 1 to 3 years including completion of the CDR-SOB at each study visit.
5. Stable clinical diagnosis of possible or probable AD over the 1 to 3 year follow-up period, with no intervening neurologic events that might complicate or change diagnosis.
6. Fluency in English.
7. A reliable study partner.
8. Complete physical examination.

Measures

The Washington University Clinical Dementia Rating scale (CDR; Morris, 1993) was developed to stage the severity of AD. The CDR is based upon ratings of global 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: 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 across six domains and ranges from 0 – 18. In AD, the CDR-SOB score increases by 1.5 points annually on

average (Aisen, Petersen, & Thal, 2008). Thus, as there is no consensus definition of faster versus slower 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 over two years, a rate considered to be *typical* or “Faster” and clinically significant, and an increase of less than three points defined as “Slower” progression.

At baseline, all subjects had been administered a battery of standard neuropsychological tests tapping multiple cognitive domains, in addition to provision of health history by subjects and study partner. Predictor variables from key cognitive domains as outlined below were chosen to determine which factors best accounted 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.

Neuropsychological 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 Tests A and B (Reitan & Wolfson, 1995). Executive Functioning was assessed with Phonemic Fluency (FAS Test) and Semantic Fluency (Animals) (Borokowski et al., 1967). Language was measured by the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) Neuropsychological Battery abbreviated Boston Naming subtest (Morris, 1988). Attention was assessed by the WAIS-R Digit Span subtest (Wechsler, 1981).

Clinical measures—Health history had been gathered for each subject from the National Alzheimer Coordinating Center Uniform Data Set which includes self- and study partner report of lifetime history of heart disease (heart attack/cardiac arrest, atrial fibrillation, angioplasty/endarterectomy/stent, cardiac bypass procedure, pacemaker, and/or congestive heart failure), cerebrovascular disease (stroke and/or transient ischemic attack), traumatic brain injury (TBI) with loss of consciousness over 20 minutes, diabetes, hypercholesterolemia, hypertension, and depression within the last two years. Duration of illness and age at diagnosis were collected through self- and study partner report.

Biomarker data (ApoE genotype, cerebrospinal fluid tau and AB₄₂, presence of brain amyloid, quantitative MRI, etc.) were unavailable for most subjects and were beyond the intended scope of this investigation.

Psychiatric Measures—Psychiatric symptoms were assessed with the Neuropsychiatric Inventory (Cummings et al., 1994) and The Geriatric Depression Scale (Yesavage et al., 1984). In addition, mental status examination was performed by an experienced geriatric psychiatrist.

Statistical Analyses

Differences between progressor groups (Slower versus Faster) on the categorical predictor variables (health history and disease specific characteristics) were analyzed using exact χ^2 or Fisher’s Exact test and continuous predictor variables (neuropsychological scores) were

analyzed using independent samples t-test. Percentages for the categorical measures and Mean (SD) for the continuous measures are reported. Associations between all continuous predictor variables were examined with Pearson product-moment correlations. Logistic regression was used to explore relationship between progression group and predictor variables. The different classes of models reflect our interest in understanding the prediction made by neuropsychological measures in addition to, or the absence of, demographic and clinical characteristic of patients. Three classes of stepwise logistic models were utilized, including 1) examination of select episodic memory detail scores from the CVLT, 2) other neuropsychological variables, and 3) clinical and demographic variables (see Table 1). For logistic regression model building, predictors entered the model if $\alpha < 0.05$ and were deleted if $\alpha > 0.10$. To include as many cases as possible, a final logistic regression model included all significant predictors ($p < 0.05$) based upon the results of the stepwise model. When available, demographically adjusted neuropsychological standard scores were utilized to control for the influence of demographic factors. The sensitivity and specificity for each final model in predicting the progression of AD were examined using receiver operating characteristic (ROC) analyses and area under the curve (AUC). A cut-score that optimized sensitivity and specificity was selected. Assumptions of all statistical analyses were reviewed for violations; graphs for all measures were examined for normality and symmetry, bivariate plots were examined for linearity and homoscedasticity, descriptive statistics for continuous measures were examined for skewness, and equality of variances was examined for independent samples t-tests. When there was concern about violations to the assumptions, non-parametric tests were performed where feasible; the non-parametric results, all similar to the parametric results, are not provided. All statistical analyses were performed using IBM® SPSS version 20 (2011 IBM® SPSS Statistics, Chicago, IL). The significance level was set at .05 with a 2 sided test; no corrections were made for multiple comparisons.

Results

Demographic Characteristics

Ninety-six subjects met criteria for inclusion. Of these, 45 were identified as Faster Progressors and 51 as Slower Progressors. The groups did not differ in age at baseline, level of education, age of AD onset, or duration of illness (Table 2). Faster versus Slower Progressors were also similar in gender distribution (Female: 56% versus 47%, $p = .42$) and ethnicity (white: 91% versus 94%, $p = .70$). A total of 46 subjects were taking one or more medications, with group differences being non-significant (26 Slower Progressors and 20 Faster Progressors; $X^2 = .41$, $df = 1$, $p = .52$). Depressive symptoms were assessed via psychiatric interview, Neuropsychiatric Symptom Inventory, and/or Geriatric Depression Scale. While no subjects were clinically diagnosed with major depression, the number of subjects in the Slower and Faster Progressor groups who obtained elevated depression (GDS) scores were similar (23 vs 16, $X^2 = .90$, $df = 1$, $p = .34$). Additionally, no between-group differences were seen for the number of subjects taking antidepressants ($n_{\text{Slower}} = 14$, $n_{\text{Faster}} = 10$), cholinesterase inhibitors ($n_{\text{Slower}} = 14$, $n_{\text{Faster}} = 9$), NMDA inhibitors ($n_{\text{Slower}} = 8$; $n_{\text{Faster}} = 5$), or other medications (Gabapentin, Tranquilizers, or Detrol/Toterdine, minimum $p > .390$).

Dementia Severity and Progression

Both groups were similar in dementia severity based on CDR-SOB ($p=0.28$) and MMSE scores at baseline ($p=.06$, See Table 2). Time to follow-up was also similar, ranging between 1 and 3 years ($p=0.71$). Faster Progressors declined approximately seven points on CDR-SOB [baseline 5.04 (1.22) versus follow-up 12.03 (3.21)], while Slower Progressors remained stable [baseline 5.31 (1.17) versus follow-up 5.40 (1.92)].

Neuropsychological characteristics

CVLT measures at baseline are presented in Table 3. The Faster Progressors scored significantly lower on the Percent Recall from the Primacy Region of the word list than the Slower Progressors. Means for Semantic Clustering of related words, Percent Recall from the Recency Region of the list, and Recognition Discriminability were also lower for the Faster Progressors, though the differences were not significant. Recall Consistency, number of Intrusions on Free Response trials, Response Bias, and number of Perseverations did not differ between groups.

Descriptive statistics from the remainder of the neuropsychological measures are presented in Table 3. The number of subjects who completed each test differed due to changes in the test battery across the 15-year span of the data collection, although groups were similar in terms of missing data. The Faster Progressors performed significantly lower than the Slower Progressors on Digit-Symbol, Trail Making Test - A, and CVLT Total. Differences on Digit Backwards Longest Span and CERAD Boston Naming Total were not significant ($p < 0.07$), as was the case with scores on all other measures. As reflected in Table 3, the largest effect sizes between groups were seen on Trails A (.76), CERAD Boston Naming (.76), Digit Symbol (.65), and CVLT Total (.50).

Lifetime health history variables were coded to reflect presence or absence of the condition at any time; Faster Progressors and Slower Progressors did not significantly differ on any health variable (Table 4).

Logistic regression prediction models

In the logistic regression analyses for the CVLT measures, only Percent Recall from the Primacy Region (Primacy) significantly predicted progression (OR = 0.825, $p = 0.04$). In the ROC analyses, the AUC showed significant discrimination between Faster Progressors and Slower Progressors (AUC = .621, $p = .04$, 95% CI: .509 – .733). A Primacy z-score of -0.5 provided 75% sensitivity and 47% specificity with 60% correct classifications.

Several individual neuropsychological measures were associated with faster progression. Trail Making Test - A predicted progression (OR = .944, $p < .01$, 95% CI: .908 – .981), with an AUC of .701 ($p < .01$, 95% CI: .590 – .821). There were insufficient data for Trails B to make comparisons, as many subjects reached the time ceiling of five minutes (our standard time cutoff), made 5 errors necessitating discontinuation, or could not complete the task for another reason and were excluded from the sample. Digit Symbol (OR = .797; $p < .01$) predicted progression, with an AUC of .676 ($p < .01$, 95% CI: .556 – .796). CVLT Total Learned predicted progression (OR = .950, $p = .02$) and the AUC was .628 ($p = 0.03$, 95%

CI: .515 – .741). None of the remaining neuropsychological variables individually predicted progression.

When CVLT Primacy, other neurocognitive measures and demographic factors were entered into a stepwise logistic regression model, Trail Making Test - A significantly predicted Faster progression. Specifically, a Trail Making Test - A T-score of 39 or lower predicted membership in the Faster Progressors group with 71% sensitivity and 66% specificity (68% correct classification).

None of the health history measures was an individual predictor of faster decline (Table 4). Cardiac history showed a trend in predicting progression (OR = 0.381, $p = 0.06$), but lifetime history of stroke, TBI, hypertension, hypercholesterolemia, diabetes, and recent or current depression did not predict progression. When health history measures, Duration of Illness, Trail Making Test - A, and demographic factors were included as predictors in a stepwise logistic regression model, only Trail Making Test - A significantly identified Fast Progressors (OR = 0.944, 95% CI: 0.908 to 0.981).

Discussion

The rate of decline in AD has been difficult to predict, and the use of neuropsychological measures has been examined as possible predictors in few investigations. Findings from these studies, while somewhat variable, suggest that neurocognitive measures may be useful in predicting rate of decline, sometimes performing 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 rarely examined in terms of rate of progression.

Although Percent Recall from the Primacy Region (Primacy) of the CVLT predicted faster progression, ROC analysis revealed the area under the curve was 0.62 and the confidence interval did not cross the line of discrimination (0.50), suggesting a limited association. Reduced memory of items presented early in learning trials has been associated with impaired secondary memory or long-term memory in AD (Massman, Delis, & Butters, 1993). These deficits in primacy encoding have been linked to lesions in brain structures including the medial temporal lobe 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 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 even in mild AD, but more subtle features such as Primacy Effect may continue to decline. Along these lines, it has been reported that primacy-recency patterns change with severity of memory impairment in AD, with primacy showing the earliest change (Pepin & Eslinger, 1989).

Contrary to expectation, most episodic memory performance features did not predict rate of progression in our study, though these features have predicted cognitive decline in *preclinical* stages of AD (Schmid et al., 2013). We found response bias, number of intrusions, and recognition discrimination were worse in Faster Progressors at baseline, but the magnitude of the differences was not significant, and none ended up in the final prediction models. 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 *detection* of AD, but they may not distinguish rate of *progression* in AD. Once these measures reach a threshold of reduced performance, they may no longer reliably be associated progression. This notion of a threshold of impairment is supported by studies of some episodic memory performance features in AD, which find that although intrusion errors, discrimination, and response bias were significantly different between subjects with AD and controls, they did not differ by disease severity (Bartok et al., 1997; Schram, Rubert, & Loewenstein, 1995). It is also possible that certain episodic memory characteristics that typify the early development of clinical symptoms in AD may parallel the buildup of underlying neuropathological processes such as amyloid deposition (Sperling et al., 2011) and, like amyloid, may serve as a marker of disease rather than a marker of progression. Exploration of various neuropsychological measures and qualitative performance features merit further study along these lines.

We hypothesized that performance features of verbal episodic memory combined with additional neurocognitive measures would better predict faster vs. slower progression. This hypothesis was partially supported, as several individual neuropsychological measures of verbal learning and processing speed were significantly associated with faster decline (CVLT Primacy and Total Learning, Digit Symbol, and Trail Making Test - A). However, Trail Making Test - A time was found to be the best predictor of decline, as other neuropsychological scores including CVLT accounted for less variability and fell out of the final model. ROC analysis revealed that the area under the curve for the final model was 0.701, indicating that this model had good discriminative ability, even though it was based only upon Trail Making Test - A performance.

It is interesting to note 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; Bhargava et al., 2006). While it is possible that Faster Progressors in this sample had somewhat more severe disease at baseline than Slower Progressors, differences on a more general measure, the MMSE, were much more subtle and nonsignificant. In addition, overall rated functioning, as measured by the CDR-SOB was 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 seem to suggest that despite similarities in global baseline ratings and level of gross cognitive impairment, Faster Progressors may demonstrate subtle evidence of greater neuropsychological impairment at baseline.

Two separate measures of processing speed were identified as individual predictors of faster vs slower decline (Trail Making Test - A and Digit Symbol) and showed the largest effect

sizes. Lower processing speed at baseline has been identified as an independent predictor of rate of progression in several studies of patients with more advanced cognitive impairment (Atchison et al., 2004; Saxton et al., 2009), even though processing speed is typically not one of the earliest or specific deficits demonstrated in AD. Nevertheless, there is evidence that processing speed continues to demonstrably decline as AD severity increases (Martelli, Barban, Zoccolotti, & Silveri, 2012). Why processing speed served as a predictor rate of cognitive decline in subjects with mild AD, while other cognitive domains such as memory, executive functioning, and language were less sensitive is not entirely clear. Processing speed is a fundamental cognitive construct that is involved in many higher order processes and generally shows significant correlations with an array of neuropsychological domains, however. Furthermore, tests of processing speed tend to reflect general cognitive integrity and may have lower specificity for particular disorders such as AD.

In contrast to another report (Bruno et al., 2013), we found that CVLT Primacy was less sensitive to progression than other neurocognitive predictors when considered together. Verbal learning, as 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, our study sample was selected specifically to fall within a constrained range of “mild” AD. It is possible that due to the constrained range, the observed performance on learning and memory did not provide enough variability to distinguish between groups. Although the mean performance of Faster Progressors was lower on memory measures, the range of performance completely overlapped between groups. 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.

Although lifetime biological comorbidities with the exception of depression were more strongly associated with more rapid rate of cognitive decline (see Table 4), they did not differ significantly between Faster and Slower progressors. The failure of comorbidities to significantly predict decline was surprising, in that a number of studies have suggested that such factors affect cognitive and functional decline. For example, Mielke et al. (2007), who followed 135 individuals with AD for 3 years, concluded that some cardiac-related 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 antihypertensive medications). In 2011, this group found that atrial fibrillation and systolic hypertension predicted faster cognitive decline, while a 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 history of cardiovascular disease at baseline (which was assessed in this study) were significantly related to faster cognitive decline in subjects with AD. Overall, these findings

indicate that although vascular and metabolic risk factors may affect rate of cognitive/functional decline in AD, their contribution may be relatively small and inconsistent.

Like health factors, duration and age at onset of illness 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, O'Hara et al., (2002), but others found that rate of decline was unrelated to age of onset (Huff et al., 1987; Stern et al., 1994). In regard 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.

Limitations

Although a sample size of 96 is larger than most studies in this area, changes to the test battery over 15 years and missing or limited data resulted in a lower number of observations for some neurocognitive and clinical measures, which limited appropriate statistical analysis. For example, observations of Trail Making Test- B were unfortunately insufficient for inclusion. In previous investigations, the cognitive domains of visuospatial construction and executive functioning appeared to predict progression in AD, but findings have been mixed (Musicco et al., 2010; Rasmusson et al., 1996). Analyzing these measures in a stepwise fashion may have further elucidated the role of these domains in predicting progression. For example, Ewers et al. (2012) found that Trail Making Test - B and right entorhinal cortex volume were the best single predictors of conversion from MCI to AD from among a variety of biomarkers and neuropsychological test scores.

Beyond scarcity of data, the relatively low incidence of health abnormalities in the present sample limits the ability to generalize findings to populations with medical comorbidities of greater number and severity. In addition, we utilized self- and informant-based report of health and symptom history, which may be somewhat imprecise and may limit the reliability of these findings. We also elected not to examine baseline biomarkers as predictors of progression, as the focus of this study was on neuropsychological variables. Inclusion of such measures (e.g. MRI volumetrics) may augment prediction equations, since they have shown independent predictive value in other investigations (e.g. Jack et al., 2011). Another study limitation is the relatively short follow-up period of 1–3 years, which may limit generalizability and may not provide predictive power beyond this time frame. Future investigations should expand this window and explore the added predictive value of various biomarkers.

Conclusion

In a group of subjects with AD studied over an average of two years, examination of neuropsychological measures, independently and in conjunction with sociodemographic and biological factors, showed that performance on Trail Making Test - A at initial visit was significantly associated with individuals who showed average or faster (CDR change ≥ 3 points) versus slower (CDR change <3 points) clinical disease progression. This finding, along with other neuropsychological features at baseline, may aid clinicians in providing prognostic information to patients and families.

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Table 1

Predictor Variables

<i>Model 1. CVLT¹ Performance Features (z-scores)</i>	<i>Model 2. General Neuropsychological Variables</i>	<i>Model 3. Clinical and Demographic Variables</i>
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. Hypercholesterolemia History
4. Semantic Clustering	4. Visual Reproduction I Percentile	4. Traumatic brain injury History
5. Total Intrusions	5. Visual Reproduction II Percentile	5. Diabetes History
6. Recognition Discriminability	6. Trail Making Test -A Time T-score	6. Hypertension History
7. Total Perseverations	7. Phonemic Fluency Total Words T-score	7. Cerebrovascular Event
8. Response Bias	8. Semantic Fluency Total Words T-score	8. Depression within the last 2 years
	9. CERAD ² Naming subtest Total *	9. Duration of illness
	10. Digit Span Backward Longest Span *	10. Age at diagnosis
	11. Digit Symbol Coding Scaled score	

Note.

Demographically adjusted scores were used, except where the use of raw scores* is indicated

¹CVLT = California Verbal Learning Test

²CERAD = Consortium to Establish a Registry for Alzheimer's Disease

Table 2
Demographic Characteristics and Indices of Dementia Severity by Progression Group

Measure	Progression Group			Independent	
	Slower	Faster	Range	Samples t-test	Effect Size
	Mean (SD)	Mean (SD)	Range	p-value	
Age at baseline (years)	71.57 (7.79)	71.95 (8.11)	54 to 85	0.818	-0.05
Education (years)	14.24 (3.40)	14.89 (2.90)	6 to 20	0.317	0.10
Age of AD Onset (years)	68.45 (8.39)	69.07 (7.69)	45 to 83	0.711	-0.08
Duration of Illness (years)	3.13 (2.65)	2.89 (2.38)	0 to 12.12	0.642	0.08
Time between baseline and follow-up (years)	1.79 (0.48)	1.82 (0.48)	1.02 to 2.82	0.706	-0.08
MMSE ¹ score at baseline	23.92 (3.06)	22.64 (3.58)	16 to 30	0.063	0.39
CDR-SOB ² at baseline	5.31 (1.17)	5.04 (1.22)	3.0 to 8.0	0.275	0.23
CDR-SOB at follow-up	5.40 (1.92)	12.03 (3.21)	0.5 to 9.0	<0.001	-2.48

¹ MMSE = Mini Mental State Exam

² CDR-SOB = Clinical Dementia Rating Scale Sum of Boxes

Table 3

Baseline Test Scores by Progression Group

Measure	Progression Group						Independent Samples t-test	Effect Size
	Slower			Faster				
	N	Mean (SD)	Range	N	Mean (SD)	Range	p-value	
CVLT ¹ Qualitative Variables	Semantic Clustering	51	-0.90 (0.88)	-3 to 1	44	-1.23 (1.16)	-4 to 1	0.124
	Primacy	51	-0.94 (2.49)	-5 to 4	45	-1.98 (2.16)	-5 to 3	0.033
	Recency	51	0.71 (2.95)	-5 to 5	45	-0.27 (3.61)	-5 to 5	0.156
	Consistency	51	-1.59 (1.56)	-5 to 2	45	-1.71 (2.25)	-1 to 5	0.760
	Intrusion Errors	51	1.28 (1.90)	-1 to 5	44	0.98 (1.59)	-1 to 5	0.409
	Discriminability	50	-2.92 (1.50)	-5 to 0	45	-3.36 (1.48)	-5 to 1	0.158
	Response Bias	50	1.24 (1.27)	-2 to 3	45	1.00 (1.51)	-2 to 3	0.402
	Perseverations	50	-0.18 (0.87)	-1 to 3	44	-0.34 (0.83)	-1 to 3	0.365
	Digit-Symbol Scaled Score	43	8.95 (2.72)	2 to 14	36	7.11 (3.05)	1 to 13	0.006
	Trail Making Test - A T-score	44	41.84 (12.52)	11 to 63	34	32.18 (13.29)	7 to 57	0.002
Neuropsychological Tests	Phonemic Fluency T-score	50	36.84 (10.13)	14 to 58	42	33.55 (10.36)	16 to 61	0.128
	Semantic Fluency T-score	48	34.92 (11.15)	15 to 60	42	32.55 (10.80)	11 to 58	0.310
	Digit Backwards - Longest Span	42	4.19 (0.97)	3 to 7	37	3.76 (1.09)	2 to 6	0.065
	Visual Reproduction I Percentile	43	12.70 (16.39)	1 to 63	35	8.17 (10.91)	1 to 50	0.166
	Visual Reproduction II Percentile	43	11.21 (15.85)	1 to 84	35	6.83 (9.70)	1 to 50	0.157
	CVLT Total T-score	51	24.65 (9.64)	5 to 50	45	19.80 (10.13)	5 to 51	0.018
	Long Delay Free Recall Z-score	49	-2.65 (1.16)	-5 to 1	45	-2.69 (0.90)	-5 to 0	0.869
	CERAD ² Boston Naming Total	50	13.60 (1.67)	9 to 15	42	12.71 (2.71)	2 to 15	0.058
								0.76

Note. Z-scores derived from CVLT normative data are presented for all CVLT 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.

¹ CVLT = California Verbal Learning Test

² CERAD = Consortium to Establish a Registry for Alzheimer's Disease

Table 4

Health History at Baseline by Progression Group

Measure	Progression Group		Two-sided p-value*
	Slower Present/Total (%)	Faster Present/Total (%)	
Cardiac	8/50 (16%)	15/45 (33%)	0.058
Cerebrovascular Event	3/50 (6%)	5/42 (12%)	0.462**
Traumatic Brain Injury	4/49 (8%)	8/43 (19%)	0.214
Hypertension	26/50 (52%)	25/44 (57%)	0.682
Hypercholesterolemia	17/28 (61%)	13/16 (81%)	0.195
Diabetes	5/50 (10%)	7/44 (16%)	0.538
Depression within past 2 Years	8/28 (29%)	4/16 (25%)	>0.999**

* χ^2 test p-value, except where noted

** Fisher's Exact p-value