Modeling the Time-course of Alzheimer Dementia

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Alzheimer's disease (AD) progresses from a preclinical period, through a middle phase of cognitive deterioration, to a late, profound state. The temporal progression of disability can be modeled with a horologic (time-based) function using "time-index" (TI) intervals (day- or year-units) to quantify an individual's disability across multiple cognitive and functional domains relative to a reference AD population. Clinicians and researchers can use TI quantification to assess dementia severity and initial therapy benefits. Rate of progression and confidence intervals require at least two successive measurements. Rate of progression measures can be used to support diagnosis and to investigate disease-course–modifying therapies.

Introduction

Alzheimer's disease (AD) progresses relentlessly along a temporal continuum [1,2••]. The progression of dementia with respect to the time-course of AD has been described most clearly by the Global Deterioration Scale (GDS) and Functional Assessment Staging (FAST) system [3]. Based on clinical experience and analysis of cognitive testing, the progression of dementia can be divided into three parts or phases [4]. The first part is the early or prodromal phase, in which it is sometimes difficult to distinguish dementia-associated changes from memory loss that accompanies normal aging [2,5–7,8•]. This preclinical phase has recently taken on critical importance because of the potential to treat and stop the AD process at the point of its earliest manifestation (prevention). The second part of AD is the phase of obvious deterioration; cognitive, behavioral, and social functions are gradually and progressively lost over an interval of 2 to 15 years. During this second phase, the important clinical considerations are level of dementia severity and the rate of progression. The third part of AD is the late phase, in which progression is difficult to measure [9], and behavior and nursing management are the predominant concerns. During this late phase, the last remnants of the patient's personality are destroyed, but AD does not attack such vital functions as respiration and autonomic control. This is the phase when most AD patients die, but death comes from complications of cognitive dysfunction or nonspecific medical conditions.

This review addresses the issue of modeling dementia severity and progression with respect to the time-course of AD. The middle phase is the principle focus because it is the portion of AD progression that is most easily measured, and therefore, data are readily obtainable for developing models. The measurement of dementia severity is an important issue for clinical management. Measurement is also important for investigations of the etiology of AD and the efficacy of therapeutic interventions. Consequently, clinicians and researchers have developed a variety of approaches to measure dementia severity. Using these varied measures, information about the time-course of AD can therefore be applied to studying early symptoms and improving dementia screening. A major application of disease course modeling is for understanding the relationships between dementia symptoms and pathologic changes, particularly those obtained at autopsy. Such information will hopefully lead to more effective AD treatments and prevention.

The present discussion focuses on the development and application of the "time-index" (TI) model of dementia severity [1,10••]. The relationship of the course of AD to time (a horologic function) is the essential interaction to define dementia progression in this disease [11•,12,13]. The TI model provides definable interval units on which to assess the disability (as opposed to ability) continuum of the dementia caused by AD. The disability continuum must be specified to improve measurement. Disability measurement is assessed by tests that are composed of items. The relationship between the performance on the items and disability is properly defined using item response theory (IRT). IRT is a fundamental approach to developing tests of ability, behavior, and achievement, and is used for analysis of items on tests such as IQ and the Scholastic Aptitude Test (SAT). IRT requires that the ability (or disability) be unidimensional and this continuum is frequently referred to as the *latent trait*. Central issues in measuring dementia severity on the

disability continuum are improving tests' validity, reliability, and precision [14]. Classical test theory (CTT) only requires the addition of item responses and focuses on validity and reliability, but does not reference performance to the underlying ability (or disability). IRT transcends CTT by referring the measurement of both items and subjects to the hypothetical unidimensional continuum of ability.

For a background discussion of IRT, the reader is referred to introductory discussions [15,16] and an in-depth discussion [17]. There are several applications of IRT, the disability continuum, and modern psychologic measurement techniques for the evaluation of AD [1,18–20,21•,22,23•]. For further in-depth discussion of the modeling of AD processes, the reader should refer to the June, 2000 issue of *Statistics in Medicine*, which provides several manuscripts from a meeting on statistical applications in AD.

The Middle Phase of Alzheimer's Disease: Estimation of Dementia Disability with Respect to Disease Time-course

During the middle phase of AD there is a progressive deterioration of memory with interrelated losses of other cognitive faculties and social functions [3]. A horologic function to describe progression in AD can be expressed in terms of TI units for reference (*eg*, day- or year-units). Traditional scales that are used to assess symptoms of dementia give a rank-order to dementia severity, but they remain ordinal scales with inconsistent intervals between different values or stages [17,24,25]. The strength of a horologic model rests on the fact that scores from ordinal scales can be combined and translated into TI values, which lie on an interval scale (with units having equal values across the full range of AD severity). TI units offer potentially unlimited precision, and use of these units in a longitudinal analysis offers a method for assuring the validity and reliability of patient assessment on the disability continuum. With these units, individual and group rates of deterioration and the variability of the rate of progression can be accurately and meaningfully defined in a given patient or population.

The first theoretic concern in assessing the severity of the dementia associated with AD regards dimensionality, or the factor-structure of the impairment [26]. Many authors have emphasized the heterogeneity of AD [27]. There is considerable variation in the pattern of clinical symptoms associated with the progression of AD, and this heterogeneity has been the subject of extensive discussions [28]. The relation of the variations in the course of symptom progression to specific biologic factors is not clear [29]. The dementia of AD may be associated with conceptually separate cognitive domains including amnesia, aphasia, apraxia, and agnosia, although dysfunction in higher cognitive abilities may still relate indirectly to the underlying mnemonic factor that is affected by the AD process. Dissolution of these mental processes progresses during the course of AD, and there is considerable variability between patients. AD often causes psychologic and behavioral problems [30], which wax and wane during the course of the disease. This variability may be attributed to differences in genetic and environmental factors, which cause diversity in the pattern of brain impairment and the resulting clinical symptoms.

Less attention has been paid to assessing the rate of dementia progression. Some patients have a slower progression of their disease; others have a more steady deterioration of mental function. The progression rate varies depending on numerous factors, suggesting considerable heterogeneity in the disease, its manifestations, concomitant medical conditions, and day-to-day level of patient function [31,32]. Therefore, it is important to develop models of disease progression that allow for the prediction of variations in disease course and determine the sources of these variations as completely as possible.

Underlying the complexity of the clinical presentation and variation of the deterioration rate lies a force of relentless progression, which is presumably related to the attack of AD on the mnemonic, neuroplastic processes of brain function [33,34]. Although it is not clear if the pathologic progression of AD is a final common pathway representing a predetermined sequential cascade of loss of neuron function [34,35], or a combination of neuropathologic processes impacting on neuronal survival, the clinical progression of AD can be expressed as a unidimensional continuum.

Calculating the 'Alzheimer Standard Horologic Function of Relative Dementia' Scale

Using tests composed of items that reflect the progression of dementia (*eg*, the Mini-Mental State Exam, [MMSE]) [36,37], patients may be assessed on numeric scales that reflect progression along this continuum [38•]. By determining how scores from different scales (s) change (Δs) over time (t), during an observed time interval (Δt), the temporal rate of progression ($\Delta s/\Delta t$) can be modeled as a function of scale score [f(s)] [1,6,10••,11•,12,38•,39–41]. This relationship is algebraically modeled as:

$$\text{Rate of change (temporal progression)} = \frac{\Delta s}{\Delta t} \simeq f(s)$$

The measured rate of change will be equal to zero at the floor (0) and the ceiling (c) of the test. The function will be largest at the level of performance where the chosen measure most accurately measures patient functioning. (*eg*, the MMSE is less useful in tracking the earliest changes in AD [sensitivity] or the most advanced stages

[floor effect] where the function will be close to 0). Therefore, an appropriate monotonic function can be chosen to estimate the mean population rate of change at a given scale score. As the time interval (Dt) approaches zero, the population curve may be estimated as follows:

$$\frac{\Delta s}{\Delta t}\ \underset{(\text{limit as } \Delta t \to 0)}{=}\ \frac{ds}{dt} \simeq b \times (s\text{-}0)^M \times (c\text{-}s)^N$$

M and *N* are coefficients that reflect the shape of the curve, which approximates the mean, and *b* is a calibration factor to adjust for magnitude of change. This equation is efficient because it incorporates the ceiling and floor effects and uses a small number of variables. The proportion of the variation of dementia severity accounted for by the equation depends on the efficiency of the test. Many other equations, estimation models, or nonparametric approaches could fit the equation equally or better [42,43]. There must also be allowances for specific factors that may affect severity and cause variability [32].

Data for the MMSE from the CERAD data set (Consortium to Establish a Registry for Alzheimer's Disease [10]) is used for demonstration purposes. The CERAD data set consists of 981 AD patients from 21 clinical sites in the United States. The CERAD MMSE values are shown with an equation fitted so that M = 1, N = 2, c = 30, and b = 1/750 (Fig. 1). This equation can be transformed to:

$$dt = \frac{ds}{b \times s \times (c - s)^2} = \frac{750 \times ds}{s \times (30 - s)^2}$$

Integrating (dt) produces (TI):

$$TI = \frac{1}{b \times s \times (c - s)} - \frac{1}{b \times c^2} \times \ln \frac{(c - 1)}{(s)} + \text{constant}$$

$$= \frac{25}{(s - 30)} + 0.83 \times \ln \frac{(30 - 1)}{(s)} + 5.3$$

(5.3 sets TI = 0 for MMSE = 24)

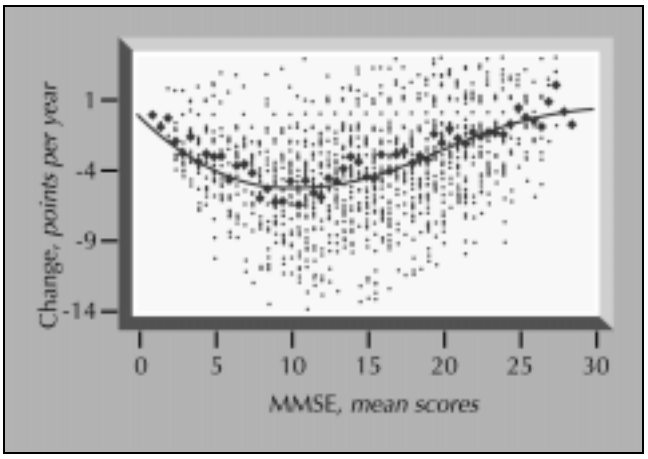

Figure 1. Consortium to Establish a Registry for Alzheimer's Disease (CERAD) data set, calculated annual rates of change plotted versus average Mini-Mental State Exam (MMSE) scores for individual AD patients (1490 transitions, *small dots*). *Large dots* show mean rates for each average MMSE score. The *thick line* represents the function described in the text, which closely fits the mean data.

For computational purposes, this equation is equivalent to:

$$= 8.26 - 1.05 \times s + 0.17 \times s^2 - 0.01535 \times s^3 + 0.000647 \times s^4 - 0.00001046 \times s^5$$

This function may then be plotted inversely to show the general relationship between MMSE score and time (Fig. 2a). However, this function is important because it may be applied to any test (or combination of tests or scales) for measuring dementia severity, to translate the scores on that test to a standard representation of dementia severity.

From the relationship between time and score, a "test information function" can be calculated (Fig. 2b). Tests whose items have better psychometric characteristics (that correspond more closely to the progression of AD) will provide a stronger test information function [15,17], which will be associated with a decrease of the variability of the estimate of severity on the disability continuum.

An important issue is the statistical relationship of the TI scale to the natural continuum of AD progression. The equations presented above show a convenient method to transform MMSE scores into TI values. However, Figure 1 shows how poorly this equation represents the actual MMSE change data. The inverse of the test information function shows the standard error of measurement (Fig. 2c). Figures 2b and 2c show that the MMSE provides a poor estimate of patient severity early in the AD time-course and late in the course due to ceiling and floor effects. A more precise analysis of the statistics involved can be obtained from examining the individual items of

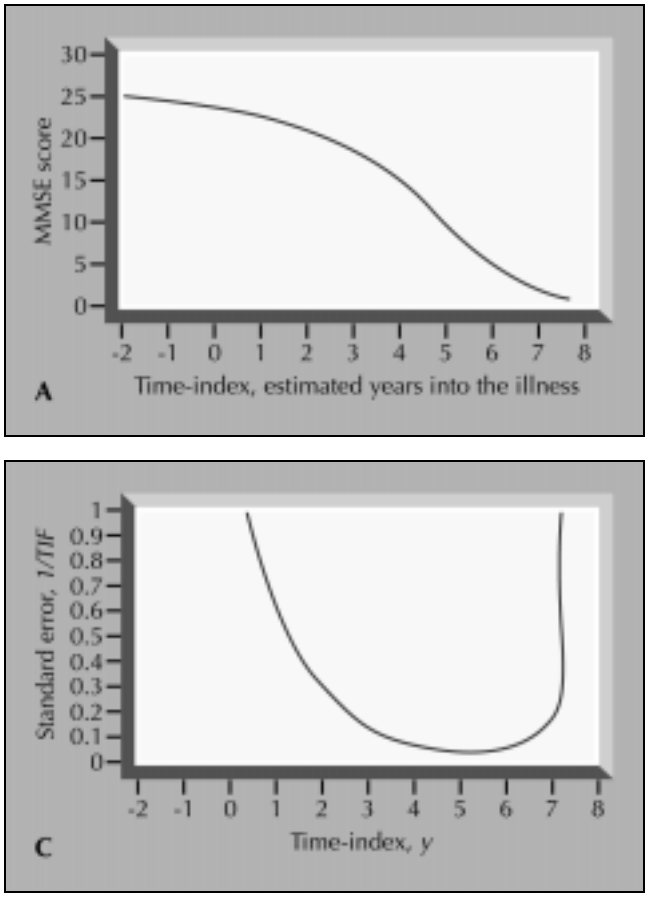

Figure 2. **A**, Calculated function estimates the relation between Mini-Mental State Exam (MMSE) scores and the time-course of AD (in time-index (TI) year units). **B**, Calculated test information function for MMSE. **C**, The calculated standard error of measurement for the MMSE with respect to dementia severity, as measured using TI units.

the MMSE, then using the characteristics of those items to calculate the standard error of measurement [17]. The analysis process can be repeated iteratively until stable item response functions are obtained [17].

Any test used to measure dementia severity can be referenced to the disability dimension. Test scores can be calibrated to TI units for any population of AD patients by analyzing data from an appropriate scale applied to that population over at least two time points. Adding items with strong discriminatory characteristics will improve the power and decrease the variability of the measurement. The horologic function can be affected by variables such as age, gender, and education [6,10••,44] and can be adjusted accordingly. Factors adjusting for other variables that influence the rate of progression will also decrease the disparity between the "true level of disability" and the data.

Estimation of Rate of Dementia Progression

The patient population on which the TI function was originally developed [1] included 33 patients (mean age 76.7 ± 6.6 years; range 54–87; 27 female) with probable AD, evaluated with the Global Clinical Scale (GCS [14]) on two to six occasions. The GCS includes brief cognitive testing (including the MMSE and animal naming in 1 minute), activities of daily living assessment, and structured clinical impression. By systematic combination, these multiple scales provide a 150-point dynamic range. GCS values were then translated into TI units [1]. Using TI units, the repeated measures over time clearly demonstrate the devastating progression of AD (Fig. 3a). Note that this pattern of rapid clinical deterioration relative to normal aging is consistent with the progressive atrophy reported in the medial temporal region of the brain of AD patients [45]. A similar rapid rate of dysfunction development occurs for perfusion in the cerebral cortex [46].

For individual patients, the rate of progression is determined by dividing the change in TI units from one time-point to another by the time-interval between those points.

$$\text{Rate of Progression} = \frac{TI2 - TI1}{t2 - t1} = \frac{\Delta TI}{\Delta t}$$

Day-units per day or year-units per year yield identical values. Because the TI units are calibrated to represent the representative population mean across the full span of the sample, the mean rate of progression for the population at any level equals 1. Thus, when the rate of progression for an individual patient is larger than 1, the patient's progression is faster than the reference population, and when

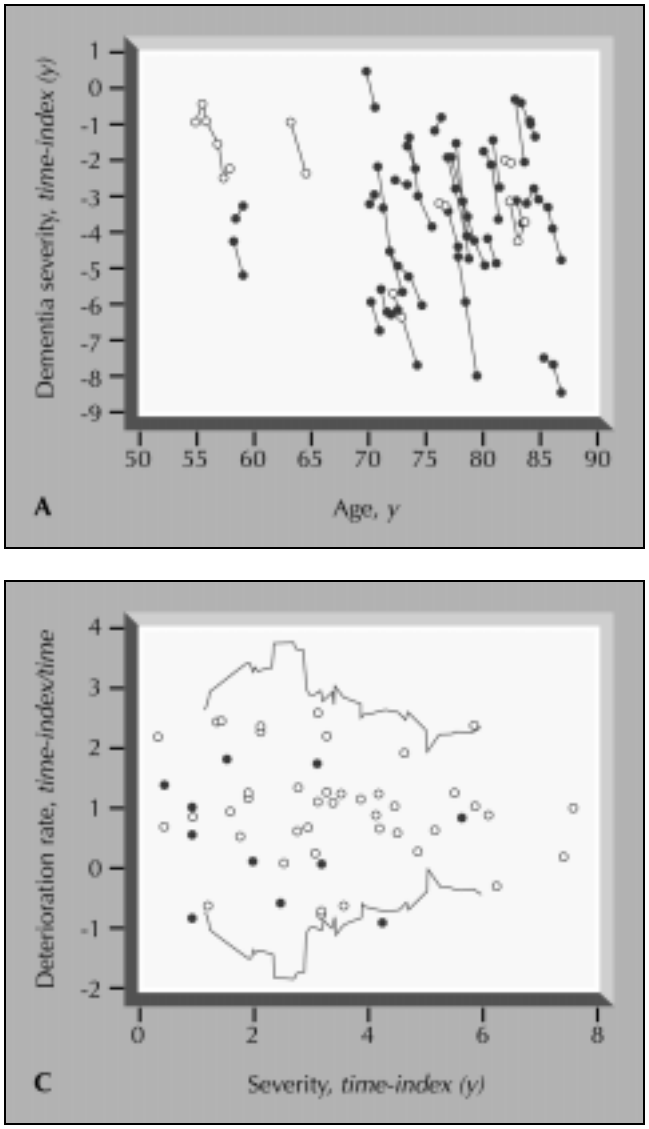

Figure 3. **A**, Severity of illness in 33 probable Alzheimer's disease (AD) patients measured over time, plotted in relation to age. *Open circles* represent men, *closed circles* represent women. *Connected points* represent sequential values for individual patients, 88 observations. A time-index (TI) score of 0 represents the onset of the illness, whereas a score of 6 year-units is associated with profound dementia (*see* Ashford *et al*. [1] for details). Note the devastating progression of AD. **B**, Rate of progression is plotted as a function of age. Data calculated from Figure 1. Correlation: r = 0.15; mean rate at 55 y = 0.63; mean rate at 90 y = 1.247. 55 observations, 20 independent; points are connected for individual patients with more than two measurements. These data suggest that the rate of progression increases with age; however, the correlation is low, and the variability is high. Rate at one interval seems to have no relationship to rate at another interval. **C**, Estimation of the variation in the rate of progression as a function of dementia severity. Correlation: r < 0.001. Data calculated from Figure 1. Smoothed two standard deviation lines of the local mean rates of progression are shown. The smoothing function used a window of ± 6 months. Relationships between variability and severity are likely to be related to characteristics of the assessment methods.

the rate is less than 1, there is slower progression. A zero change indicates no progression, and a negative value indicates improvement.

Variability in the Rate of Alzheimer's Disease Progression

A critical issue associated with the measurement of dementia severity is the quantification of variation. Heterogeneity of symptoms occurs across patients. A variety of biologic, psychiatric, and other factors can influence measurement. Variation in measurement of dementia severity in individual patients is related to such factors as measurement-related, illness-related, treatment-related, and chance fluctuations in performance, as well as short-term and long-term disease-associated changes. In the population examined using linear regression, age had no more than a small effect on rate (Fig. 3b). The standard deviation in the GCS also varies with respect to dementia severity (Fig. 3c). These analyses suggest that, by standardizing the measures of progression across the whole course of AD to TI units, insight is gained about observed variations in dementia severity. Using this approach, any factor that contributes to patient variability can be assessed for its influence on the horologic function.

The greatest factor affecting the variability of the rate measurement is the inter-test interval (Dt). When the duration of the intervals between tests is examined, the rates of change associated with short intervals are highly variable (Fig. 4a,b). Longer inter-test intervals show variations, which approach the actual variation of symptom progression across the whole disease course. Thus, the relation between the test-retest interval (Δt) and variability (confidence intervals around the regression line) has two asymptotes (infinity at $\Delta t = 0$; 1 at Δt = infinity; note that 1 is defined as the mean rate of progression). Accordingly, the standard deviation of

the rate variation can be fit by a hyperbolic function (H) that approximates the standard deviation of the mean (Hstd):

$$H = (X - \text{value}) \times (Y - \text{value})$$

Hstd = time interval (Δt) × [rate variation (std of DTI/Dt, at that Dt) – 1]

Canceling the (Dt) term simplifies to:

$$\text{Hstd} = \text{std of } (\Delta TI - \Delta t)$$

The 95% confidence limits for the rate of progression (CLR-95) for a specific testing interval are estimated as two-standard-deviations from the mean rate (two standard deviations from either side of the mean encompass 95.45% of the population within a normal distribution). Thus, the limits of the rate of progression for a particular time-interval of observation (Dt) are:

$$CLR - 95 = 1 \pm \frac{2 \times \text{Hstd}}{\Delta t}$$

For the data of the 33 patients evaluated with the GCS, Hstd = 0.72 (Fig. 4a). The variability in rate of deterioration reflects the test-retest interval-related variation and the short and long-term natural variation in AD progression between different patients during the different phases of the disease. The longer the time interval is between measurements for an individual patient, the more reliable the measure of deterioration [47]. The present analysis shows that short-term variations tend towards infinity (as would be the case for small variations occurring in a single day, when the denominator for the rate of change approaches 0). The calculation for the GCS suggests that a patient may go 1.5 years without deteriorating and still have a rate of change consistent with a diagnosis of AD (Fig. 4a, zero-crossing point). But a patient who showed no deterioration over a 2-year period would be unlikely to have AD. (*Note*, there are no data in this sample for intervals beyond 3 years). By contrast, the MMSE as an index of dysfunction due to AD (CERAD data set) contains considerable variability [48] and requires more than 4 years of lack of progression to suggest that the condition is not consistent with AD (Fig. 4b, zero-crossing point, Hstd = 2). Tests with better items, and more rigorous statistical techniques would improve the validity, reliability, and precision of the TI units for a target population. Such improvement would lead to a decrease in the time-interval required to support the AD diagnosis.

Heterogeneity of the Alzheimer's Disease Temporal Continuum and Pathology

As the progression of AD is measured progressively more accurately, variations in the progression can then be related to specific factors that affect the heterogeneity of the progression [12,32]. The course itself can be fast or slow and in different cases may manifest a wide variety of diverse medical, neurologic, and psychiatric symptomatology [30,31,49]. Further, patterns of impairment may differ between AD and multi-infarct dementia [50].

A watershed observation in the study of AD was the establishment of a link between dementia severity and AD pathology [51]. However, even clearly normal elderly individuals can have AD pathologic changes [8]. Further, there is considerable heterogeneity in the pathology of the disease [52]. Thus, the specification of the relationship between dementia severity and AD pathology, for example, Braak stage [53], is a critical step in the advancement of knowledge about AD. This knowledge can be expanded still further to understanding the full spectrum of the development of AD pathology over the lifetime of the individual patient [54].

Although histologic brain measures represent the extent of AD pathology, they cannot be assessed twice to reflect rate of change. However, available measures of brain pathology in the living patient may be used to assess the degree of severity of brain dysfunction and change over time. In practice, the TI units do correspond to changes in brain perfusion changes with correlations up to 0.8 [46,55]. However, single biologic measures, for example, of the cerebrospinal fluid (CSF), might reflect how rapidly the AD process is attacking the brain (unfortunately, CSF levels of the microtubule–associated protein tau have not been found to reflect rate of progression.) Ultimately, the goal of AD research is therapeutic intervention to arrest the development of factors related to AD progression at the earliest phase of the disease. These mathematic models provide the most efficient approach for assessing the effects of such factors.

Future Directions

There are several specific applications of the TI model for studying AD. For example, use of IRT applied to the TI continuum to find the best items for identification of early AD patients would allow the development of a probability function to determine the earliest signs that would indicate that AD should be suspected. From an initial age at shift from normal to dementia [56], the TI can give an estimation of how long the disease has been progressing,

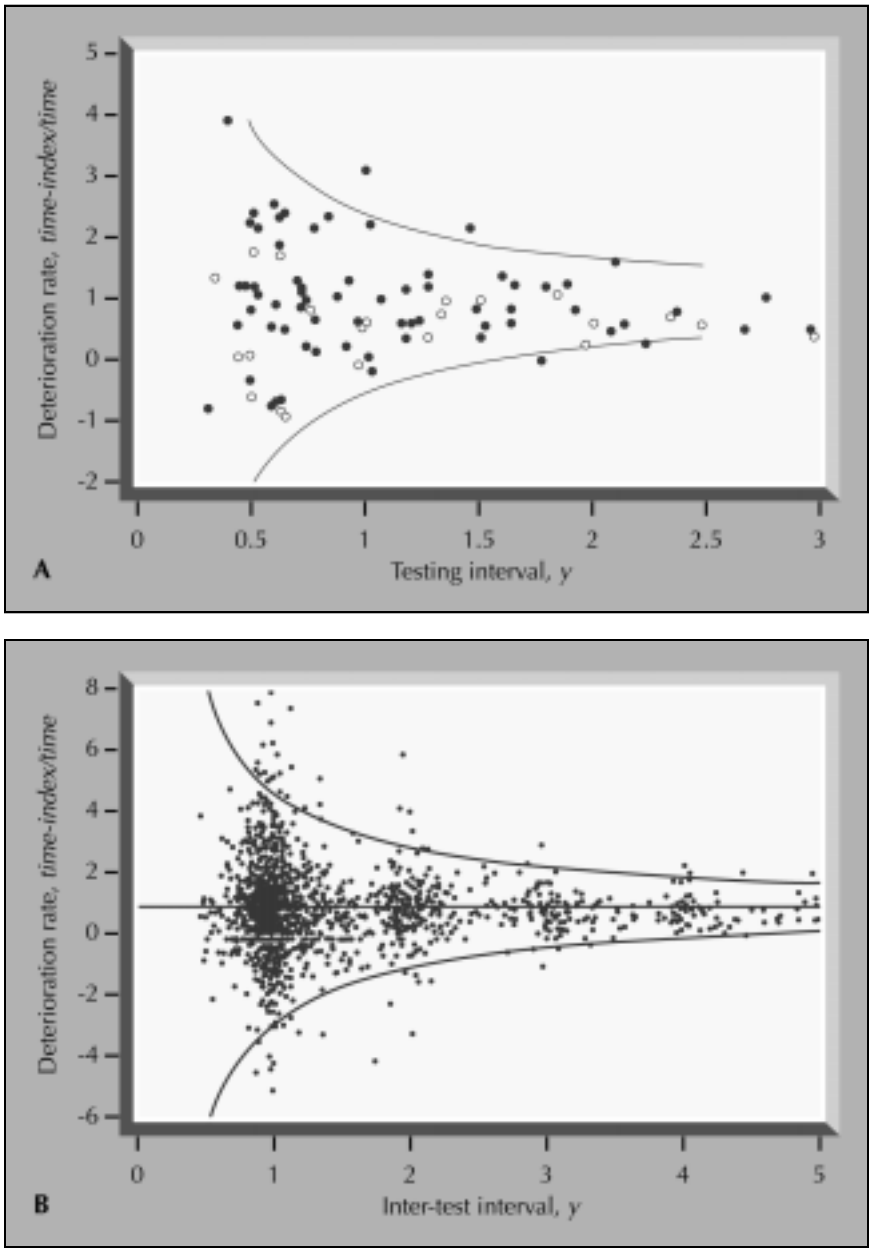

Figure 4. **A**, Rate of deterioration in relation to testing interval for Global Clinical Scale (GCS) data. The GCS data were transformed into time-index (TI) units, then the changes across the test-retest intervals were divided by the testing intervals to provide rate data (*open circles* = men; *closed circles* = women). The TI function defines the mean rate of progression as 1, but it was 0.95 for this sample. The mean rate for men was 0.57 and for women was 1.07, though the data could not support this difference statistically. There were no correlations between rate and age ($r < 0.1$), severity ($r < 0.05$), or interval ($r = 0.1$). The *solid lines* show the hyperbolic estimate of two standard deviations from the mean. **B**, Consortium to Establish a Registry for Alzheimer's Disease (CERAD) data for the mini-mental state exam, transformed into TI values, then changes were divided by the time-interval to yield rate (1700 intervals). Test-retest intervals were approximately 1 year. The *solid line* is the hyperbolic estimation of the two-standard deviation line.

an estimate that can be compared with the available clinical history.

For late-stage patients, test items must be used that are appropriate for assessing severe levels of impairment. One test composed of items for this purpose is the Severe Impairment Battery [9]. Applying the IRT analysis to these items, using the TI units, will enhance the capacity to assess severely impaired patients. References of the TI units to underlying AD pathology, either by in vivo brain scan measurement or autopsy analysis, could provide information about the validity of the observations about AD patients with respect to the AD progression.

The Alzheimer disability continuum has no absolute beginning or end. A patient's performance can be analyzed to determine his or her location on this continuum. Items can also be studied to determine those that most efficiently predict a certain point on the continuum. Analyses can be made to determine mean survival from any chosen beginning-point to any chosen end-point. Evaluations can be obtained to make initial estimates of degrees of response to therapeutic interventions, measure longitudinal therapy-related changes in disease progression rates, or determine at what level of dementia severity that optimal benefit is obtained [57].

Conclusions

In sum, the horologic method offers a promising, flexible approach for improving the measurement of AD severity. Any currently available severity assessment tool that produces an ordinal scale can be calibrated to the dementia disability continuum using this method. However, individual questionnaire items should be tested for their characteristics [18,20,21•,22,23•,58] to create more efficient scales. Substantive cognitive factors can also be resolved [26], which can be associated with biologic factors. With items that have better test stability, investigational studies can use fewer patients and shorter periods of time. Algorithms can be developed for efficient and precise assessment of dementia without the need to complete long tests in which many of the items are not relevant to a particular patient's evaluation [17,59]. This "Alzheimer standard horologic function of relative dementia," using TI units, provides a framework for refining methods for the representation of dementia severity and neuropathology across the full range of AD.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Ashford JW, Shan M, Butler S, *et al.*: **Temporal quantification of Alzheimer's disease severity: 'time index' model.** *Dementia* 1995, **6:**269–280.
2. •• Ashford JW, Schmitt F, Kumar V: **Diagnosis of Alzheimer's disease.** In *Advances in the Diagnosis and Treatment of Alzheimer's Disease.* Edited by Kumar V, Eisdorfer C. New York: Springer Publishing; 1998.

This chapter gives an in-depth description of the diagnosis of AD, including early detection, and a full description of the average time-course of the disease.

3. Reisberg B, Sclan SG, Franssen E, *et al.*: **Commentary: Dementia staging in chronic care populations.** *Alz Dis Assoc Dis* 1994, **8:**S188–S205.
4. Brooks JO, Kraemer HC, Tanke ED, Yesavage JA: **The methodology of studying decline in Alzheimer's disease.** *J Am Ger Soc* 1993, **41:**623–628.
5. Larrabee GJ, Crook TH: **Estimated prevalence of age-associated memory impairment derived from standardized tests of memory function.** *Int Psychogeriatr* 1994, **6:**95–104.
6. Butler M, Ashford JW, Snowdon DA: **Age, education, and changes in the mini-mental state exam scores of elderly women.** *J Am Ger Soc* 1996, **44:**675–681.
7. Unger JM, van Belle G, Heyman A: **Cross-sectional versus longitudinal estimates of cognitive change in nondemented older people: a CERAD study.** *J Am Geriatr Soc* 1999, **47:**559–563.
8. • Schmitt FA, Davis DG, Wekstein DR, *et al.*: **"Preclinical" AD revisited: neuropathology of cognitively normal older adults.** *Neurology* 2000, **55:**370–376.

This recent paper describes the relation of subclinical memory impairment to Alzheimer pathologic changes. It also reviews this important issue.

9. Schmitt FA, Ashford JW, Ernesto C, *et al.*: **The Severe Impairment Battery: concurrent validity and the assessment of longitudinal change in Alzheimer's disease.** *Alz Dis Assoc Dis* 1997, **11:**S51–S56.
10. •• Mediondo MS, Ashford JW, Kryscio RJ, Schmitt FA: **Modeling mini-mental state exam changes in Alzheimer's disease.** *Statist Med* 2000, **19:**1607–1616.

This is a recent analysis by the authors, showing mathematic variations and the influence of age, gender, and education on the temporal progression of AD.

11. • Liu X, Teresi JA, Waternaux C: **Modelling the decline pattern in functional measures from a prevalent cohort study.** *Statist Med* 2000, **19:**1593–1606.

This rigorous mathematic paper discusses alternative approaches to model the nonlinear progression of dementia in AD. However, these approaches are essentially the inverse of the one described in the current paper.

12. Liu X, Tsai W-Y, Stern Y: **A functional decline model for prevalent cohort data.** *Statist Med* 1996, **15:**1023–1032.
13. Stern Y, Liu X, Albert M, *et al.*: **Application of a growth curve approach to modeling the progression of Alzheimer's disease.** *J Gerontol Med Sci* 1996, **51:**M179–M184.
14. Ashford JW, Kumar V, Barringer M, *et al.*: **Assessing Alzheimer severity with a global clinical scale.** *Int Psychogeriatr* 1992, **4:**55–74.
15. Weiss DJ, Yoes ME: **Item response theory.** In *Advances in Educational and Psychological Testing: Theory and Applications.* Edited by Hambleton RK, Zaal JN. Boston: Kluwer Academic Publishers; 1991:69–95.
16. Yen M, Edwardson SR: **Item-response theory approach in scale development.** *Nurs Res* 1999, **48:**234–238.
17. Hambleton RK, Swaminathan H, Rogers HJ: *Fundamentals of Item Response Theory.* New Bury Park, CA: Sage Publications; 1991.
18. Ashford JW, Kolm P, Colliver JA, *et al.*: **Alzheimer patient evaluation and the mini-mental state: item characteristic curve analysis.** *J Gerontol* 1989, **44:**P139–P146.
19. Teresi JA, Cross PS, Golden RR: **Some applications of latent trait analysis to the measurement of ADL.** *J Gerontol* 1989, **44:**S196–S204.
20. Teresi JA, Golden RR, Cross P, *et al.*: **Item bias in cognitive screening measures: comparisons of elderly white, Afro-American, Hispanic and high and low education sub-groups.** *J Clin Epidemiol* 1995, **48:**473–483.
21. • Teresi JA, Kleinman M, Welikson-Ocepek K: **Modern psychometric methods for detection of differential item functioning: application to cognitive assessment measures.** *Statist Med* 2000, **19:**1651–1683.

This application of IRT to the study of AD contains an in-depth discussion of methods for detecting differential item functioning in AD. However, the reference scale is not related to the time-base of AD progression.

22. Woodard JL, Auchus AP, Godsall RE, Green RC: **An analysis of test bias and differential item functioning due to race on the Mattis Dementia Rating Scale.** *J Gerontol* 1999, **53:**P370–P374.
23. • Mungas D, Reed BR: **Application of item response theory for development of a global functioning measure of dementia with linear measurement properties.** *Statist Med* 2000, **19:**1631–1644.

This is a recent, fundamental application of IRT to dementia assessment in AD.

24. Stevens SS: **On the theory of scales of measurement.** *Science* 1946, **103:**677–680.
25. Wang S-T, Yu M-L, Wang C-J, Huang C-C: **Bridging the gap between the pros and cons in treating ordinal scales as interval scales from an analysis point of view.** *Nurs Res* 1999, **28:**226–229.
26. Brooks JO, Yesavage JA, Taylor J, *et al.*: **Cognitive decline in Alzheimer's disease: elaborating on the nature of the longitudinal factor structure of the mini-mental state examination.** *Inter Psychoger* 1993, **5:**135–146.
27. Roses AD: **The Alzheimer diseases.** *Cur Neurol* 1994, **14:**111–141.
28. Eisdorfer C, Cohen D, Paveza GJ, *et al.*: **An empirical evaluation of the global deterioration scale for staging Alzheimer's disease.** *Am J Psychiatry* 1992, **149:**190–194.

29. Murphy GM, Taylor J, Kraemer HC, *et al.*: **No association between apolipoprotein E e4 allele and rate of decline in Alzheimer's disease.** *Am J Psychiatry* 1997, **154:**603–608.
30. Cohen D, Eisdorfer C, Gorelick P, *et al.*: **Psychopathology associated with Alzheimer's disease and related disorders.** *J Gerontol* 1993, **48:**M255–M260.
31. Teri L, McCurry SM, Edland SD, *et al.*: **Cognitive decline in Alzheimer's disease: A longitudinal investigation of risk factors for accelerated decline.** *J Gerontol* 1995, **50:**M49–M55.
32. Milliken JK, Edland SD: **Mixed effect models of longitudinal Alzheimer's disease data: a cautionary note.** *Statist Med* 2000, **19:**1617–29.
33. Ashford JW, Jarvik L: **Alzheimer's disease: does neuron plasticity predispose to axonal neurofibrillary degeneration?** *N Engl J Med* 1985, **5:**388–389.
34. Ashford JW, Mattson M, Kumar V: **Neurobiological Systems Disrupted.** In *Advances in the Diagnosis and Treatment of Alzheimer's Disease.* Edited by Kumar V, Eisdorfer C. New York: Springer Publishing; 1998.
35. Ashford JW, Soultanian NS, Zhang S-X, Geddes JW: **Neuropil threads are colinear with MAP2 immunostaining in neuronal dendrites of Alzheimer brain.** *J Neuropath Exp Neurol* 1998, **57:**972–978.
36. Folstein MF, Folstein SE, McHugh PR: **"Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician.** *J Psychiatr Res* 1975, **12:**189–198.
37. Tombaugh T, McIntyre NJ: **The mini-mental state examination: a comprehensive review.** *J Am Geriatr Soc* 1992, **40:**922–935.
38. • Kraemer HC, Taylor JL, Tinklenberg JR, Yesavage JA: **The stages of Alzheimer's disease: a reappraisal.** *Dement Geriatr Cogn Disord* 1998, **9:**299–308.

This review of the approaches to staging AD provides a relevant discussion of the strengths and weakness of the MMSE and GCS. It suggests under what circumstances various approaches should be considered.

39. Morris JC, Edland S, Clark C, *et al.*: **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* 1993, **43:**2457–2465.
40. Galasko DR, Gould RL, Abramson IS, Salmon DP: **Measuring cognitive change in a cohort of patients with Alzheimer's disease.** *Statist Med* 2000,**19:**1421–1432.
41. Stern RG, Mohs RC, Davidson, *et al.*: **A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration.** *Am J Psychiatry* 1994, **151:**390–396.
42. Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K: **The rate of decline in function in Alzheimer's disease and other dementias.** *J Gerontol* 1999, **54:**M65–M69.
43. van Belle G, Arnold A: **Reliability of cognitive tests used in Alzheimer's disease.** *Statist Med* 2000, **19:**1411–1420.
44. Stern Y, Albert S, Tang M-X, Tsai W-Y: **Rate of memory decline in AD is related to education and occupation: Cognitive reserve?** *Neurology* 1999, **53:**1942–1947.
45. Jobst KA, Hindley NJ, King E, Smith AD: **The diagnosis of Alzheimer's disease: A question of image?** *J Clin Psychi* 1994, **55[suppl 11]:**22–31.
46. Shih W-J, Ashford JW, Stipp V, *et al.*: **Consecutive brain SPECT surface three-dimensional displays show progression of cerebral cortical abnormalities in Alzheimer's disease.** *Clin Nuc Med* 1999, **24:**773–777.
47. van Belle G, Uhlmann RF, Hughes JP, Larson EB: **Reliability of estimates of changes in mental status test performance in senile dementia of the Alzheimer type.** *J Clin Epidemiol* 1990, **43:**589–595.
48. Clark CM, Sheppard L, Fillenbaum GG, *et al.*: **Variability in annual mini-mental state examination score in patients with probable Alzheimer's disease.** *Arch Neurol* 1999, **56:**857–862.
49. Teri L, Hughes JP, Larson EB: **Cognitive deterioration in Alzheimer's disease: behavioral and health factors.** *J Gerontol* 1990, **45:**P58–P63.
50. Magni E, Binetti G, Padovani A, *et al.*: **The mini-mental state examination in Alzheimer's disease and multi-infarct dementia.** *Int Psychoger* 1996, **8:**127–134.
51. Blessed G, Tomlinson BE, Roth M: **The association between quantitative measures of dementia and of senile change in the cerebral gray matter in elderly subjects.** *Br J Psychiatry* 1968, **114:**797–811.
52. Geddes JW, Tekirian TL, Soultanian NS, *et al.*: **Comparison of neuropathologic criteria for the diagnosis of Alzheimer's disease.** *Neurobiol Aging* 1997, **18:**S99–S105.
53. Braak H, Braak E: **Staging of Alzheimer's disease-related neurofibrillary changes.** *Neurobiol Aging* 1995, **16:**271–284.
54. Ohm TG, Scharnagl H, Marz W, Bohl J: **Apolipoprotein E isoforms and the development of low and high Braak stages of Alzheimer's disease-related lesions.** *Acta Neuropathol (Berl)* 1999, **98:**273–80.
55. Ashford JW, Shih W-J, Coupal J, *et al.*: **Single SPECT measures of cerebral cortical perfusion reflect "time-index" estimation of dementia severity in Alzheimer's disease.** *J Nuc Med* 2000, **41:**57–64.
56. Small GW, Kuhl DE, Fujikawa DG, Ashford JW: **Clinical characterization of Alzheimer's disease: reliability of 'age at onset' and a new descriptor, 'age at shift.'** *J Ger Psychiatr Neurol* 1988, **1:**207–211.
57. Ashford JW, Schmitt FA, Wermeling D, *et al.*: **Advantages of the "time-index" method for measurement of Alzheimer dementia: assessment of metrifonate benefit.** In *Alzheimer Disease: From Molecular Biology to Therapy.* Edited by Becker R, Giacobini E. Boston: Birkhauser; 1996.
58. Helmes E, Merskey H, Hachinski VC, Wands K: **An examination of psychometric properties of the extended scale for dementia in three different populations.** *Alz Dis Assoc Disord* 1993, **6:**236-246.
59. Fillenbaum GG, Wilkinson WE, Welsh KA, Mohs RC: **Discrimination between stages of Alzheimer's disease with subsets of mini-mental state examination items.** *Arch Neurol* 1994, **51:**916–921.