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# Temporal Quantification of Alzheimer's Disease Severity: 'Time Index' Model

## Abstract

A fundamental issue in the clinical and neuropathological assessment of Alzheimer's disease patients is quantification of dementia severity progression. Several methods have been advanced for the purpose of staging dementia with various sensitivities at different phases of the disease, but no mathematical function has been developed to link these measures to a physical continuum. Using a dynamic method for quantifying illness severity, change in severity over time was referenced to a cumulative temporal index, a physical dimension. Data from 33 patients with probable Alzheimer's disease with at least 2 successive assessments on three 50-point scales measuring cognitive, behavioral, and daily living skills were used to determine rate of change. 'Fuzzy-logic' smoothing of the data, integration over time, and least-squares regression were used to derive a cubic polynomial function to calculate a severity measure in which 'days of illness' was estimated from the severity score. This method can be used to improve the comparability of performance across various mental status tests, and to link measures of very early phases of preclinical dementia and late profound dementia phases. This method also provides a description of an 'average' time course for any population from which the index is derived.

## Key Words

Alzheimer's disease  
Dementia  
Dementia progression  
Dementia severity  
Mini mental status examination

## Introduction

In his original article, Alzheimer [1] described a 5-year progression of clinical symptoms which was associated with neurofibrillary and plaque changes in the brain. Blessed et al. [2] drew a major new focus to Alzheimer's disease (AD) by defining the expression of this disease in the domains of cognitive function ('Information-Memory-Concentration Test'; IMC) and daily and personality function ('Blessed Dementia Rating Scale'; DRS) and

showing a clear association between the occurrence of symptoms in these domains and the presence of the brain pathology. Dementia of the Alzheimer type is now accepted as a syndrome which is associated with a progressive decline over time (DSM-III-R, APA [3]). However, the tools that are available for quantification of the severity of AD (clinical ratings, objective mental status tests, and ratings of daily living skills) have been difficult to integrate into a single dimension of disease severity.

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In individual patients, AD progresses over long pre-clinical and clinical periods. Therefore, measures of dementia severity associated with AD must be made with reference to this progression of clinical symptoms over the prolonged time course. Several studies have examined measures of dementia progression in Alzheimer patients over periods of time [4–22]. For example, Blessed IMC test scores change at a relatively consistent rate (4–4.5 points per year) across populations of AD patients [23–26], but the relations of value changes on this scale over time to patient age, severity, and other factors have been difficult to assess. Salmon et al. [16] have emphasized the examination of ‘annual rate of change’ (ARC). However, problems exist with the effort to define ARC since the numerical scales differ across various clinical tests, and different tests show marked variability in performance changes over time [27, 28]. Further, the number scales which have been developed are not consistent across different levels of severity within the same test, and change must tend toward zero at the most mild (ceiling effect) and severe (floor effect) phases of the illness [22].

Numerous efforts have been made to develop tests of dementia severity (for example: Blessed et al. [2]; Folstein et al., [29]; Mattis [30]). Several such tests have been designed specifically to quantify dementia severity with reference to specific cognitive symptoms associated with a diagnosis or progression of AD [31–33]. These assessments applied to AD severity have been compared and shown to reflect similar aspects of cognitive ability dimensions [5, 34]. However, when these tests have been evaluated longitudinally, most studies have emphasized the variability of progression in individual AD patients [8, 9, 14, 19, 22, 35–41] and hence the heterogeneity of AD [42]. There have been several efforts to standardize measures of dementia severity by geographic location, educational level [43–46], sex [47], and other demographic cross-sections [48–50], but without an absolute reference. There is, therefore, a clear need to develop improved standards by which patients with conservative diagnoses of AD [51] may be assessed more precisely for the severity of their dementia over the broad range of the disease.

To determine the underlying structure of the severity measures, efforts have been made to factor analyze the performance by AD patients [25, 52–55], but these factors cannot be referred back to any independent standard. No study has yet solved the problem of clinically quantitating dementia by mapping symptom severity in living patients to a universal underlying parameter using a mathematical function.

This study suggests that by using rate of change information, one obtains a measure which contains a physically quantifiable dimension: time. Time may be the most relevant dimension on which to base the development of more universal measures of dementia severity. Using rates of change, cognitive measures can be related directly to the dimension of time. This will improve the ability to relate rates of change on different scales, and to compare dementia severity and rates of change on different scales across studies. Further, this measure will allow the standardization of rate of change information, which may be a relevant parameter for classifying subtypes of AD [21].

The present study involves an analysis of longitudinal data from a population with a relatively homogeneous diagnosis of probable AD [56, 57]. Reisberg et al. [58] have suggested that ‘typical time course of Alzheimer’s disease’ can be estimated from staging. The present analysis demonstrates that the severity of dementia can be described as the position along an ‘average’ time course for probable AD patients. This temporal scale or ‘time index’ provides a basis for comparison of severities, rates of decline, or other heterogeneous factors among studies that use different instruments. This quantification can be extended from periods involving what is considered normal function to the extremes of the bedfast state. Measurements of the rate of progression can be validated by using the ‘time index’ as the comparison coordinate. Further, individual test items can be better assessed for sensitivity to the progressive development of AD symptoms by analyzing them against the ‘time index’ axis.

## Methods

### *Description of Scales*

Three 50-point scales were developed so that separate ratings, each addressing a different domain, could be independently applied to a patient, yet yield comparable results across a broad continuum of dementia severity (59). The Extended Mini-Mental Assessment (XMS) includes 30 points from the Mini-Mental State Exam (MMSE) [29], with an additional 5 points each from the number of animals named in a minute, personal orientation, general knowledge, and basic observable functions, designed to improve the performance of the MMSE at the least and most severe ends of its range. The Activities of Daily Living (ADL) measure includes 24 points from instrumental ADLs [60], 23 points from the basic ADLs [61], and a 3-point calibration question to extend the scale to 50 points. The Global Assessment of Dementia (GAD) was formulated around the Clinical Dementia Rating scale (CDR) [33] values of 0 (normal), 1 (mild), 2 (moderate), and 3 (severe) multiplied by 10. The number of items was expanded from 6 (from the CDR) to 10 by doubling the memory item and adding language, visuospatial and personality items. A 4 (profound) and 5 point (complete) value were added to

each item so that the maximum sum of the 10 items would be 50, with queries based partly on the Global Deterioration Scale [32]. In this population, correlations between the three scales exceeded 0.9 and relationships neared linear with intercepts close to zero. Accordingly, the sum of the three scales provided a range of 0-150 (dynamic range of 150 points). The average of the 3 scales (range 0-50) allows for the comparison of the scores in the same range as the values of the three individual scales, Average Global Clinical scale (AGC).

### Subjects

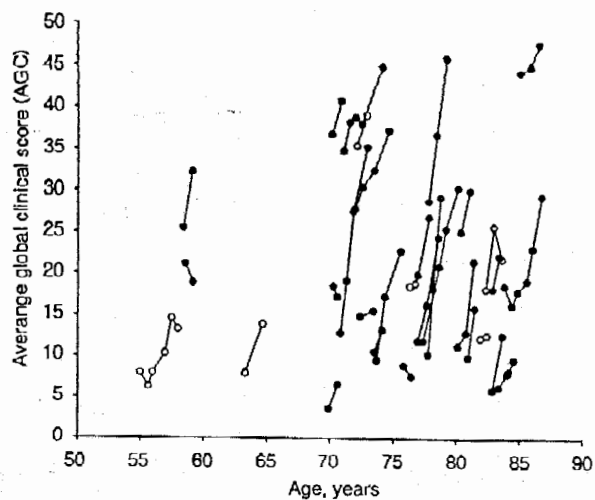
Patients who were included in this study had presented to the Southern Illinois University Alzheimer Clinic [59] with complaints of memory loss or related dysfunctions and were found to have primary degenerative dementia (by DSM-III-R criteria [3]) and probable AD (by NINCDS-ADRDA criteria [56]). Of patients meeting these criteria, 33 were evaluated using the three 50-point scales on at least two separate occasions; mean interval between evaluations was  $263 \pm 97$  (126-602) days. In this group, 27 were female: mean age:  $76.7 \pm 6.6$  years; education:  $11.5 \pm 3$  years; MMS:  $14.0 \pm 8$  (0-25); AGC:  $23 \pm 11$  (4-48); and 6 were males: mean age =  $69.3 \pm 11$ ; education =  $11.3 \pm 3$ ; MMS =  $16.7 \pm 7$  (1-25); AGC =  $17.9 \pm 9$  (6-39). The average values for all of the patients at the time of the first evaluation were: mean age:  $75 \pm 7.7$  (55-85); MMS:  $16 \pm 7.2$  (1-26); AGC:  $18 \pm 10.8$  (4-44).

### Results

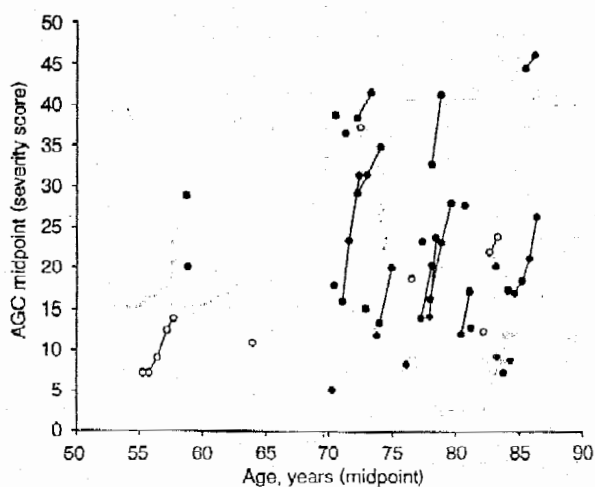
#### Time Index Calculation

For establishing the 'time index' line, AGC values were first plotted against age (fig. 1a). An AGC midpoint score was calculated as the mean of two successive AGCs for a particular patient to represent the average severity between test sessions (fig. 1b). Using the dates for each pair of sequential AGC test scores, the number of days between the two test sessions was calculated. The two test

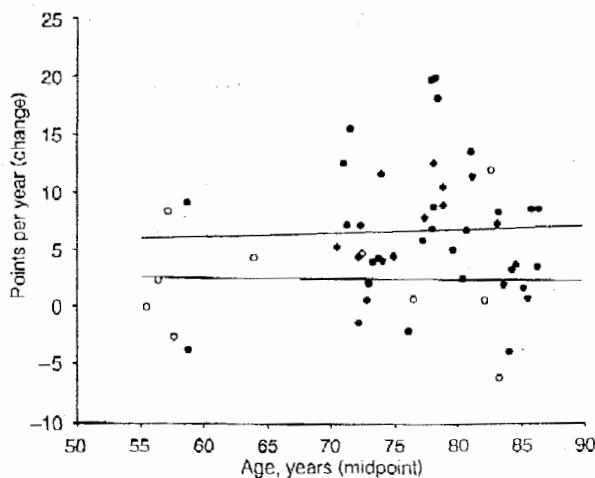
**Fig. 1. a** The AGC values (normal < 5; complete dementia = 50) for each patient are plotted against the patient's age at the time of the test. 27 = Females; 6 = males. Values for the same patient are connected. Note the dramatic deterioration for most individual patients over time. Three patients who were evaluated only twice showed slight improvement, and 3 other patients showed transient improvements. **b** The midpoint scores are shown for each patient according to the age midway between the 2 observations. **c** The rate of change values are shown for each midpoint score, plotted against the age at the midway point. The regression line for all points suggests that older patients deteriorate more rapidly than younger patients. However, when the values for men and women are regressed separately, the lines are flat with respect to age, and suggest that women, who as a group are older than men, deteriorate more rapidly than the men [26]. The population size is too small to statistically support this finding.



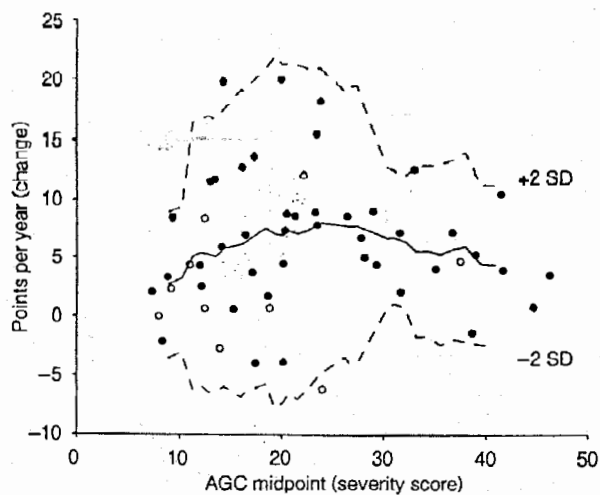
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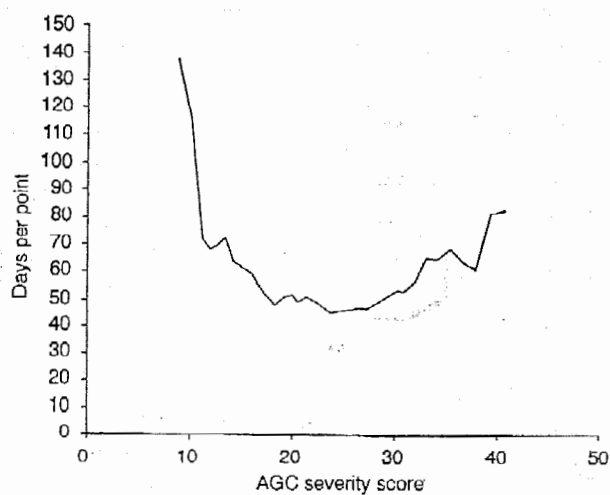
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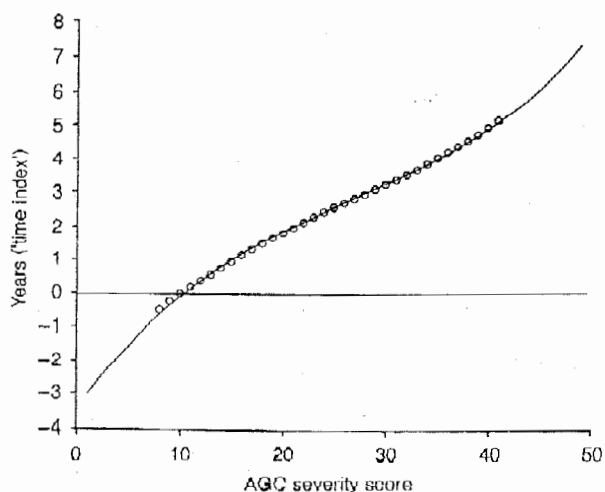
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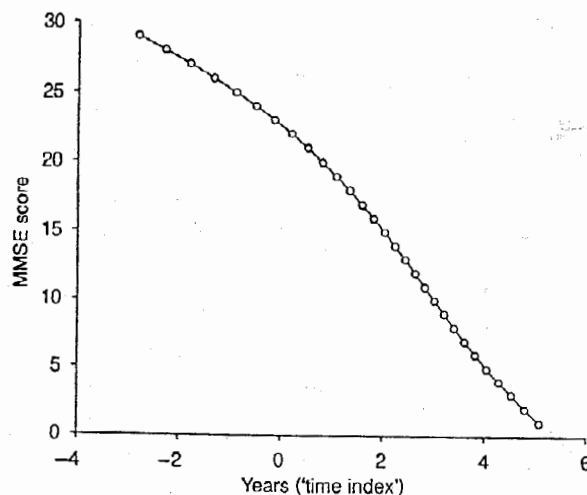
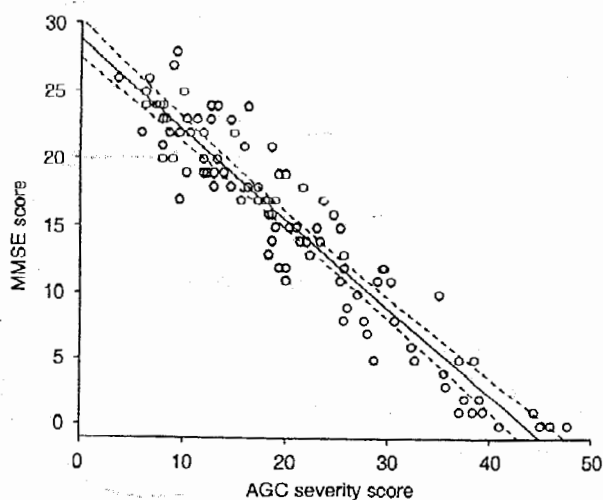
scores were subtracted to determine their difference. The rate of change (points per day) was calculated by dividing the AGC difference by the number of days between test sessions. (Directly calculating the inverse, days per point, would result in a division by zero if the score had not changed.)

$$\text{Rate of change} = \frac{(\text{AGC score 2} - \text{AGC score 1})}{(\text{time 2} - \text{time 1})} \text{ (in points per day)}$$

Rates of change (in points per year) were then plotted against age (fig. 1c).

These rates of change for individual patients were then used to establish average rates of deterioration for each possible AGC ordinal severity score (the data were sufficient to make this calculation only for scores between 8 and 41). For each possible rate value, the average rate of change was calculated using all pairs of severity values with midpoint scores within 5 points of the AGC severity value whose rate of change was being calculated. This technique is considered a 'fuzzy-logic analysis' [62] (see 'Appendix'), or more colloquially, a 'sliding average'. Standard deviations were calculated for the same points to indicate the variation in the population and are plotted with the averages (fig. 2a). The resultant averaged rates (points per year) at each severity score were inverted to obtain days per point (fig. 2b). This result was then integrated over the number of severity points to obtain ordinal estimates of time against the number of severity points (fig. 2c). An AGC score of 10 (a score of 9 approximately corresponds to an MMSE score of 23) was used as a reference point for onset of dementia (equates to year 0). In this analysis, inversion of the standard deviations

**Fig. 2.** a The same 'points per year' data from figure 1c are plotted against the midpoint scores from figure 1b. The middle line is the fuzzy logic calculation (sliding average) of the mean, and the upper and lower lines represent 2 SD above and below the mean line. b The fuzzy logic mean line was inverted, and units changed from years per point to days per point. Note that inversion of a zero value would have an infinite result, and inversion of negative values would be meaningless. Therefore, a different technique is required to estimate the standard deviation of the inverted line. c The days per point line in fig. 4 was integrated with respect to the AGC severity score (this calculus operation involves the generation of a running summation). The zero value was set at a severity score of 10, and the values for each integer point were plotted. The least-squares regression line is displayed, including its projections out to scores of 1 and 49. For example, it would take an estimated 5 years to progress from a score of 10 (mild) to a score of 40 (profound).



**Fig. 3. a** MMSE scores are plotted versus AGC scores for 88 points from the 33 patients in the study and an additional group of 15 patients who were seen only once. The regression line is:  $1.45 \cdot (29 - \text{MMSE})$ ,  $r^2 = 0.90$ . The dashed lines represent the 95% confidence interval for the mean MMSE score given each AGC severity score. **b** The calculated relationship between MMSE scores and their 'time index' line is shown. However, the model is weak at the extremes where the line would be expected to slowly approach the limits.

would not clearly represent the data, and are therefore disregarded in the present analysis.

The 'time-index' data points (integrated days per point with respect to AGC severity score) derived from the fuzzy-logic analysis were approximated closely by a cubic polynomial function (fig. 2c). Using least-squares regression, the fitted equation was:

$$\text{Time index} = 156.61 \cdot X - 3.9928 \cdot X^2 + 0.049654 \cdot X^3,$$

where  $X$  is the AGC, scored on a 50-point scale, which explained 99.92% of the variance of the 'time index' curve. The fitted line was plotted beyond the data range to estimate 'time index' values before disease onset and in the terminal phase of the disease, though this estimation cannot be considered reliable outside the data range. Thus, the fuzzy-logic approach, a nonparametric method of smoothing, has resulted in a simple and stable relationship that can be used to reasonably translate a severity score to the 'time index' axis. The time plot (fig. 2c) shows that the scale has a curvilinear relationship with time, with query power weak in the early (including preclinical) phases of the illness and as well as the late phases (severe, profound). (Note: this same procedure was used with the three individual scales and the MMSE, with generally similar-shaped curves resulting, but a great deal more

irregularity occurred due to the relative instability of the individual scales for patients from time point to time point.)

#### 'Time Index' Relation to MMS Score

Since the MMS is a commonly used scale, a calculation was made to estimate time from the MMS score. MMS scores were plotted against the AGC score for each patient (fig. 3a) revealing an approximately linear function:

$$\text{AGC} = 1.45 \cdot (29 - \text{MMSE score})$$

(for AGC range 5–42: SE = 3.5;  $r^2 = 0.90$ ).

The estimated AGC may be used in the prior equation to estimate a 'time index', but with about 10% less accuracy than the actual global average (fig. 3b). Note that a MMSE score of 23 would equal an AGC score of 9; hence, a score of 9 or above on the AGC could be considered consistent with this commonly used diagnostic cut-off for dementia [29], and a score below 9 would be considered questionable according to CDR criteria [33].

The MMS scale with 30 units has more variability than the AGC score, which has a dynamic range of 150 units and gives a more stable estimate of disease severity. However, the shapes of the relationships of both scales with time were roughly similar. Further, the AGC was devel-

**Table 1.** MMSE items ordered according to difficulty on the MMSE

	MMSE				AGC				
	T	R2	MMSE	Year	T	R2	AGC	Year	R <sup>2</sup> Dif
Flag-M	0.41	0.14	37.6	-4.37	0.22	0.01	-31.8	-9.51	0.13
Ball-M	0.31	0.21	37.7	-3.91	0.26	0.04	-17.4	-5.14	0.17
Tree-M	0.55	0.19	32.8	-2.76	0.34	0.03	-15.2	-5.23	0.16
Sub-65	0.92	0.16	30.0	-2.67	0.36	0.01	-21.5	-7.81	0.15
Sub-72	0.99	0.25	26.6	-1.45	0.93	0.19	2.9	-1.70	0.05
Sub-79	1.30	0.50	25.2	-0.91	0.97	0.18	4.0	-1.43	0.32
Date	1.11	0.69	25.2	-0.81	1.00	0.29	5.6	-1.07	0.40
Sub-86	1.24	0.66	24.8	-0.69	1.24	0.30	6.7	-0.83	0.36
Clinic	0.59	0.47	24.5	-0.42	0.49	0.12	5.2	-0.92	0.35
Pentagon	0.70	0.65	22.5	0.14	0.53	0.16	8.3	-0.36	0.49
Floor	0.86	0.54	21.2	0.52	0.88	0.35	12.0	0.40	0.18
County	0.85	0.55	20.5	0.70	0.93	0.40	13.0	0.61	0.15
Day	1.07	0.75	19.6	0.96	1.02	0.42	14.1	0.81	0.32
Sub-93	2.04	0.95	19.8	0.97	1.87	0.64	13.9	0.82	0.31
Month	1.18	0.70	19.6	1.00	1.43	0.55	14.4	0.91	0.15
Year	1.92	0.83	19.4	1.10	1.58	0.58	14.5	0.93	0.25
Season	1.45	0.84	17.8	1.52	1.54	0.62	17.0	1.39	0.22
Sentence	1.29	0.77	12.6	2.77	1.23	0.61	24.7	2.65	0.16
Repeat	1.27	0.71	10.7	3.17	1.12	0.48	27.7	3.08	0.22
On floor	1.22	0.78	10.8	3.19	1.05	0.55	27.6	3.11	0.24
State	2.48	0.89	10.2	3.29	2.06	0.72	28.5	3.20	0.17
City	0.86	0.64	10.0	3.37	0.82	0.40	28.6	3.26	0.25
Fold half	0.92	0.69	8.9	3.61	0.85	0.41	30.1	3.52	0.28
Close i's	1.68	0.85	8.0	3.78	1.54	0.67	31.3	3.65	0.18
Watch	2.01	0.87	7.8	3.83	2.56	0.85	31.2	3.60	0.02
Take paper	0.82	0.54	6.8	4.12	0.67	0.36	34.1	4.19	0.18
Flag-R	1.54	0.75	6.5	4.14	1.29	0.62	33.7	4.04	0.13
Pencil	1.65	0.84	5.1	4.47	1.77	0.70	35.0	4.22	0.14
Tree-R	1.51	0.68	5.0	4.50	1.23	0.61	35.9	4.41	0.07
Ball-R	1.28	0.76	1.8	5.25	1.04	0.51	40.7	5.29	0.25
Average		0.63				0.41			0.22
SD		0.23				0.23			

Data is shown for logistic regression analyses of the individual items versus the MMSE and the AGC. T represents the slope of the logistic regression. R<sup>2</sup> represents the goodness of fit, the square of the correlation coefficient, estimating the proportion of the variation in the data accounted for by the regression. The columns headed by MMSE and AGC indicate the scores at which a patient has a 50% likelihood of getting the item correct. Year is the calculated estimation of when that time occurs. The R<sup>2</sup>Dif indicates that the MMSE explained a higher proportion of the variation in all cases, presumably because the AGC includes a broader range of items.

oped around the MMSE and the AGC embodies similar time course scales (linear regression explains 89–92% of the variance between the subcomponents of the AGC scale) [59]. However, regardless of scale range, the 'time index' provides a nonparametric means of comparing scales and offers a means to translate scale values to an absolute quantity, time.

#### *MMSE: Item Characteristic Curve Analysis*

A test of the utility of the 'time index' dimension was to examine individual items from the MMSE. In the past, items were analyzed against the MMSE score [63]. Using the 'time index' calculated from the AGC, the individual items of the MMSE were analyzed with a logistic regression analysis (SAS), to obtain item characteristic values (table 1). This analysis against the time line derived from the MMSE improves the analysis, though only to a small degree. The 'time index' explained a larger percentage of the variance than the MMSE score in 16/30 items (average  $r^2 = 62.8$  vs. 62.7%). These differences were not significant and did not follow any apparent pattern. When the MMSE items were regressed against the 'time index' derived from the global average, only 41.3% of the variance for the individual items was explained, presumably because the inclusion of ADLs, global estimation, and other scores distances the measure from the individual and similar item contributions. However, the global score is likely to give an estimation with a much broader application in spite of the less powerful results of this analysis. The MMSE item characteristics were similar to those of a prior analysis [63], as they have been in other studies [13, 14, 64].

The 'time index' analysis predicts that the memory items will be lost at least 2 years before a MMSE score is considered diagnostic of dementia (score of 23 or less), a similar time estimated by patient's caregivers [65; but note 66]. The 'time index' estimate suggests that the ability to repeat the 3 words is lost 10 years later than the first loss of the ability to recall the words after distraction. However, the reliability of these estimates is weak, as is shown by the individual item  $r^2$  values versus the 'time index'. Further, there are an inadequate number of patients or items testing for dementia severity in this early phase of the illness for reliable assessment in this range. The low  $r^2$ s for the items assessing severity in the early phase may indicate either that the shape of the progression line at this phase is poorly known or that the course of the illness at this phase is very variable [23, 67].

#### **Discussion**

This study is an initial demonstration of the utility of a basic quantity, 'time' in the assessment of dementia severity. The 'time index' concept provides a metric to estimate the global rate of progression in AD.

Measurement of severity and the corollary measurement of rate of change have been fundamental concerns in the study of Alzheimer's disease. Neuropathological studies have generally sought to establish orders of severity [68] by demonstrating variations in senile plaque [2, 69] or neurofibrillary pathology [70] or loss of synapses [71–74]. However, neuropathology cannot address variations in rate of progression. Alternatively, several studies in living patients have pointed to heterogeneity in the clinical presentation of cognitive abnormalities in AD patients [42, 75–78]. The cognitive variations between patients are particularly prominent in mild stages of the illness [79], when clinical symptoms are the manifestation of disease affecting the relatively intact, complex nervous system [80] with sociocultural overlays. Further, AD may be caused by a variety of different etiological agents which can increase the potential variation of the presentation. Longitudinal factors associated with such heterogeneity are important to correlate with neuropathologic findings, since disease progression rates show marked variability [13, 14, 22], probably to some extent as a function of this disease heterogeneity [42, 81]. Disease progression eventually and relentlessly affects all higher-brain functions, perhaps resulting in a final homogeneous degenerative process later in the disease. This overall progression of symptoms must be considered as the primary issue when trying to assess biological factors affecting disease progression [59, 82, 83], and, in this circumstance, severity would be best assessed with this 'time index' approach.

Fuzzy-logic analysis, in the effort to define a global deterioration factor, allows for the spread of scale score information across intervals and individuals to determine smooth functions. It is a nonparametric approach that can produce a curve that is closer to the actual data than would be obtained from parametric techniques. The current method is a specific approach to standardize any scale (applied in any locale) to a time-based scale, taking a step away from arbitrary test scores. This study demonstrates the implementation of this method to translate severity measures to an estimation of duration of illness.

For any particular test, translating to a 'time index' in this way provides a potentially universal scale, depending, of course, on the study population. Also, a method is established that estimates rates of change across time,

independent of severity. Assessments of severity of disease may also be extended using this approach. Severity levels during mild phases of the disease, when patients score above the ceiling on most cognitive tests, can be incorporated by analyzing test measures that are more sensitive to changes in a higher functioning population. Similarly, phases of severe disease, which are below the floor of most tests, can be assessed by using lower ranging items. Many different studies have employed a wide range of test items to patients at different times of their illness. The analysis described in this paper can be used to define the relationships between the different tests of AD severity and to standardize assessment of patient severity, their rates of change over time, and the variability in those rates of change.

While many measures are available to assess function in patients who meet diagnostic criteria for dementia, more sensitive measures of memory must be developed to assess the earliest phases of AD [4, 84, 85]. Measures of memory in normal individuals have suggested that memory function can progressively decline with age, beginning in the 20s, particularly in the component involving acquisition of new information [86], and this is the same aspect of cognitive function which is predicted by this study to be disrupted earliest in the course of AD [85].

Assessments of AD pathology have shown that mild amounts of the AD neuropathology are found frequently in normal individuals in their 50s [87] or before [88], particularly in the brain regions responsible for storing new information. A possible relationship between these pre-clinical findings is that the hippocampal formation deteriorates over a subclinical period, memory difficulties only becoming clinically significant when a critical minimal amount of hippocampal function remains [89]. The 'time index' measure provides a framework by which individuals may be followed over time until they are diagnosed as having AD, and then the preclinical measures may be retrospectively estimated to determine rates of progression in the preclinical state. Longitudinal tests of complex memory processes in population-based studies, designed to track the longitudinal development of dementia, would be a practical approach for extending the 'time index' back into the preclinical population. By referring different measures to scores obtained from preclinical normals who have come to autopsy for other reasons, a relationship between AD pathology and preclinical cognitive dysfunction could be established.

It has been proposed that AD progression may be most accurately assessed in the middle phase of the disease [15], a time when individual patients are found to have a

relatively consistent rate of decline [9]. However, no method has surfaced to accurately characterize this rate of decline between different patients who may actually be at slightly different levels of severity though this is an important goal [23]. The 'time index' model provides a meaningful and constant dimension to make such between-patient comparisons whether for purposes of tracking disease progression or assessing the effects of therapeutic interventions. The 'time index' model also provides a basis for analyzing minimal disease progression. Using this standard, the variations of progression can also be quantified. Further, the rate of progression and variation in the rate can be established for different factors, and then the relationship between the factor indices can be compared, again with reference to the absolute unit of time. However, a statement that the disease is not progressing at any phase should only be made in the context of demonstrating no accumulation of pathology over time in any region of the brain. This concept of relating severity to pathology is particularly important because of questions regarding disease subtypes and variations in possible brain compensations for disease-related injury [80].

At the far end of the disease spectrum, AD patients who come to autopsy have frequently been unassessable with cognitive tests for years, often after a prolonged period of time spent lying in a bed, occasionally with tube feeding. The 'time index' model provides a framework in which to develop tests which can measure the profound levels of severity and then link the new tests to tests more commonly used earlier in AD. In this range, more accurate measurement of severity can help to determine factors which predict institutionalization and death [90, 91]. Further, this approach provides a means to estimate dementia severity at the time of death, with an accuracy depending on the period of time that has elapsed since the last evaluation.

Measures of severity should be compared with assays of brain change. Anatomical changes can help to determine the underlying cognitive subfactors. For example, left brain deterioration may progress somewhat independently of right brain deterioration, and this discrepancy may be reflected by different test items [10]. Therefore, careful attention must be paid to subfactor scores on cognitive tests [14], and every possible attempt should be made to adequately assay each subfactor across the full duration of the illness. Such investigations will be most useful if each subfactor can be related to a specific aspect of the neuropathology in a particular region of the brain [72, 77, 92, 93], either as assessed in the living patient by



brain scan or in the deceased patient by various neuropathological indices of brain change. There is less usefulness in the analysis of clusters of functionally similar test items whose neuropsychological relationship is trivial (e.g. orientation). When cognitive sub-factors are analyzed for their temporal progression, it is expected that variations in rate of neuropathological progression will relate to the mnemonic load carried by individual regions of the brain [94, 95], and global deterioration of mnemonic function over the full course of the illness will be the dominant factor associated with disease progression [63, 81, 96-98].

The present study is a demonstration of the use of a new approach to quantitating the severity of dementia in Alzheimer patients. The sample size is small and not drawn methodically from a defined larger population, limiting generalizability. Also, the number of evaluations and intervals varied considerably between patients, bringing other statistical questions regarding the results. Larger intervals between evaluations may prolong the time estimation while shorter intervals will show more variability. However, this study demonstrates a temporal course of progression of dementia in patients with probable AD that is consistent with the literature. Making this estimation in such a small sample was feasible because of the stability of the AGC measurement. However, this sample was too small to provide a meaningful estimation of the variation in the rate of progression of individuals at different levels of severity, an important consideration for assessing disease heterogeneity.

The critical issue in measuring severity is relating changes in dementia status to etiological factors. Using a reliable standard such as 'time index,' any factor can be tested more sensitively than using the present assortment of rough scales used to determine dementia severity. There is clearly a need to examine more accurately all phases of the disease to establish a relationship between disease progression and etiological factors.

### Appendix: Fuzzy Logic

Fuzzy sets allow a type of categorization for grouping elements into classes that do not have sharply defined boundaries [99, 100]. Rather than restricting an element to a single class, an element can be assigned to a range of classes with graded membership. In this fashion, the tendency which drives element membership can be viewed as a smoothing function, as nearby elements may share some of the same and some different classes. Fuzzy logic deals with issues similar to those treated by probability theory, but focuses on ambiguities in describing events [101].

The 10% (5 points above and below a given midpoint) value of 'fuzzification' used in this calculation was originally chosen because a change of 5 points is considered a minimum clinically significant change. This value provided a good balance between accuracy and smoothness in estimating clinical progression. In our example, a patient with a score of 22 contributes to a range of classes from scores of 17 to 27. In our analysis, we made a contribution to each class equivalent (rectangular smoothing), but the contribution could be graded, for example, using a bell-shaped function. This approach captures the fuzzy relationship between actual test scores and the estimation of the rate of change of test scores at particular test scores. The extension of the rate of change on either side of the scores provides overlaps and gradation of values for the rate of change at the overlaps. Hence, at any point, the rate of change is affected by the values at the neighboring points, giving a boundary that is less sharp than given by the data. Other methods of smoothing may more closely fit the actual decline of Alzheimer patients.

The main concept behind fuzzy representation is in defining the relationship between individual objects and classes of objects (Average Global Clinical scores relate to a range of classes of dementia severity). Accordingly, a score for a particular element is operated upon by a mapping function:

$$\mu_A: X \rightarrow [X - 5, \dots, X + 5]$$

to each class (say element  $A = 22$ ; then it contributes to the set of classes [17... 27]) in the domain of  $X$  values (e.g. the range of ordinal numbers in Average Global Clinical score). The shape of the curve provided by each  $\mu_A$  (the shape can be different for each of them, if needed), gives a grade in the range of classes:  $X - 5$  to  $X + 5$ , for a value of element  $A$ . The shape of the curve (bell-shaped, triangular, rectangular, trapezoidal, etc.) captures the fuzziness of the degree of membership. In most cases, the  $\mu$  function is based on empirical values or expert opinion. Mathematical operations on fuzzy sets and their use in several applications can be found elsewhere [102].

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