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# Consecutive Brain SPECT Surface Three-Dimensional Displays Show Progression of Cerebral Cortical Abnormalities in Alzheimer's Disease

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## Abstract

Purpose: To monitor progression of cerebral blood flow deterioration, this study used consecutive surface SPECT to evaluate the feasibility of brain surface displays (BSD) to follow Alzheimer's disease (AD) to determine whether overtime is a consistent feature of the disease.

Methods: Eighteen men (mean age, 75.7 years) with probable Alzheimer's disease (AD), with moderate to profound dementia indicated by the Mini-Mental State Examination (MMSE; median score, 10; range, 0 to 19), underwent brain Tc-99m ethyl cysteinate dimer SPECT. Brain SPECTs were obtained using a three-head gamma camera. Brain surface displays (BSD) were reconstructed from transaxial data using a threshold of 55% of the maximum pixel count. A second series of SPECTs were obtained after 5 to 23 months (except for one, which was done after 60 months). Each BSD was graded semiquantitatively, by visual interpretation, from zero to 8 (normal = 0, mild = 2, moderate = 4, severe = 6, and profound = 8) depending on the extent of the perfusion defects in the frontal, temporal, or parietal (or all of these) pattern of AD. MMSE scores were used to calculate "time index" values for estimating severity at the time of the SPECTs.

Results: The initial BSD scores correlated significantly with dementia severity (r = 0.71, **P** < 0.001). All 18 patients had decreased blood flow on consecutive SPECTs. Scores for BSD progressed at a rate of 2.5 +/- 1.7 points per year and correlated significantly with the time interval between the scans (r = 0.71;**P** < 0.001).

Conclusions: The BSDs of SPECT scan data have considerable objective discriminatory power for assessing

the severity and progression of AD-related hypoperfusion, particularly in the moderate to profound dementia ranges, and is potentially more reliable than the MMSE. Consecutive BSDs simplify SPECT image interpretation for measuring loss of brain function over time and could be useful for assessing the efficacy of therapeutic interventions for AD patients such as vitamin E and cholinesterase inhibitors.

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Alzheimer's disease (ad), which accounts for approximately 70% of cases of dementia (1) is a progressive condition and preferentially affects the posterior temporal and inferior parietal lobes (2,3).

The tools available to measure the severity of AD include objective mental status tests, clinical ratings, and ratings of daily living skills (4); these methods, however, are relatively complicated procedures and difficult to integrate into a single dimension of disease severity. The "time index" (TI) model has been used to measure progression of AD dementia on a standard continuum and can be used to estimate the rate of change with respect to time (5).

Functional neuroimaging such as PET (6,7) or SPECT (8) is a powerful clinical tool for evaluating the presence and extent of dementia-related changes in the brain. Overall, the sensitivity and specificity of SPECT in AD diagnosis range from 86% to 88% and from 87% to 96%, respectively (9,10); the rate of diagnostic accuracy of SPECT for histologically verified cases of AD is 83% (11).

Brain surface displays (BSDs) have been used for diagnosis in patients with stroke (12), slowly progressive apraxia (13), and chronic hypnosedative abuse (14). The current study used consecutive surface SPECT BSDs to monitor progression of cerebral blood flow deterioration and shows the feasibility of using BSDs to follow AD to determine whether change over time is a consistent feature of AD.

## Materials and Methods

Eighteen men (mean age, 75.7+/-4.9 years at the time of the first SPECT scan; range, 66 to 87 years) with diagnoses of probable AD (15), with two confirmed at autopsy, had SPECT scan studies performed at least twice. Clinical dementia severity was assessed using the Mini-Mental State Examination (MMSE) (16). Fifteen patients had MMSEs an average of 11 days before the first scan (+/-51 days; range, 149 days before to 114 days after), whereas three patients were tested only near the time of the second SPECT. For the initial MMSE, the median score was 10 (range, 0 to 19; 6 patients with 0; 3 with 2 to 10; 9 with 11-19;Table 1; the MMSE is an ordinal scale, not an interval scale, making parametric statistics across a broad range inappropriate). Second MMSEs were obtained for the 10 patients with scores of 10 or more at least 292 days later, and 7 of these 10 showed deterioration on the second score (3 were unchanged from 10, 11, and 15 at 434, 647, and 579 days, respectively). The severity of the dementia was calculated by transforming the initial MMSE scores to TI values (5); TI = 0 years for MMSE scores of 23; TI = 6 years for MMSE scores of 0). TI values of dementia severity at the time of the first SPECT averaged 4.4 +/- 2 year units (range, 1.9 to 7.6). Fifteen patients had two consecutive SPECTs, and three patients had subsequent third SPECTs (Table 1).

TABLE 1. Eighteen Patients' Age, Mini-Mental State Examination (MMSE) Score, Time Index (TI), Consecutive SPECT Grades, and Interval (by Day) Between the First and Second SPECT (Δ 1–2) and the Second and Third SPECT (Δ2–3).

| Patient | Age (yr) | MMS | TI | SP-1 | SP-2 | SP-3 | Δ1–2 | Δ2–3 |
|---|---|---|---|---|---|---|---|---|
| 1 | 75 | 0 | 7.57 | 4 | 8 | | 210 | |
| 2 | 73 | 0 | 7.52 | 6 | 8 | | 172 | |
| 3 | 72 | 0 | 7.34 | 6 | 7 | | 289 | |
| 4 | 73 | 0 | 7.18 | 8 | 8 | | 406 | |
| 5 | 76 | 0 | 6.09 | 4 | 5 | | 502 | |
| 6 | 67 | 0 | 2.89 | 1 | 8 | | 1706 | |
| 7 | 74 | 2 | 6.04 | 4 | 6 | | 193 | |
| 8 | 87 | 8 | 4.12 | 5 | 8 | | 331 | |
| 9* | 77 | 10 | 3.17 | 3 | 4 | | 253 | |
| 10* | 69 | 11 | 3.90 | 2 | 3 | 4 | 202 | 224 |
| 11 | 73 | 22 | 3.51 | 3 | 4 | | 360 | |
| 12 | 78 | 11 | 2.97 | 1 | 2 | 3 | 163 | 334 |
| 13 | 77 | 14 | 2.90 | 5 | 6 | | 261 | |
| 14 | 74 | 14 | 2.85 | 2 | 5 | | 566 | |
| 15* | 76 | 15 | 2.80 | 4 | 6 | | 384 | |
| 16 | 84 | 16 | 3.26 | 4 | 8 | | 294 | |
| 17 | 80 | 16 | 2.55 | 0 | 1 | 2 | 208 | 271 |
| 18 | 76 | 19 | 1.94 | 2 | 3 | 5 | 211 | 200 |
| Mean | 75.7 | 8.2 | 4.4 | 3.6 | 5.6 | 3.5 | 373 | 257 |
| STD | 4.9 | 6.9 | 2.0 | 2.0 | 2.3 | 1.3 | 351 | 59 |

*The MMSE score did not decrease on at least one subsequent-measure.
SP-1, the first SPECT; SP-3, the third SPECT.

Table 1. Eighteen Patients' Age, Mini-Mental State Examination (MMSE) Score, Time Index (TI), Consecutive SPECT Grades, and Interval (by Day) Between the First and Second SPECT ([DELTA] 1-2) and the Second and Third SPECT ([DELTA]2-3).*The MMSE score did not decrease on at least one subsequentmeasure.SP-1, the first SPECT; SP-3, the third SPECT.

Each patient received an intravenous injection of 20 to 30 mCi (925 MBq to 1.11 GBq) Tc-99m ethyl cysteinate dimer (DuPont-Merck Pharmaceutical, N. Billerica, MA) and routinely underwent a first-pass study (except for five patients who had hexamethylpropylene on the first SPECT). Thirty minutes after injection, SPECT was performed using a triple-head gamma camera (Prism, Picker, Cleveland, OH) fitted with an ultra-high-resolution collimator and interfaced with a 64-bit computer. The patient was placed in the triple-head gamma camera to acquire SPECT data from 120 projections over 360[degrees], with 30 seconds per projection. In the severely demented patients (MMSE score < 10), when there was mild or moderate agitation and restlessness, a dose of lorazepam (1 to 4 mg) was given intravenously 5 minutes after Tc-99m ethyl cysteinate dimer injection. The acquisition time of each brain SPECT was 22 minutes. The SPECT images (coronal, sagittal, and transaxial sections) were reconstructed using a Butterworth filter (order of 4, cutoff 0.3), and backprojected with no attenuation correction. BSDs were reconstructed from transaxial data, and the BSD threshold value was set at 55% of the maximum pixel count.

Visual interpretation of Tc-99m SPECT surface BSD was performed independently by two board-certified nuclear medicine physicians experienced in SPECT (W.J.S., U.Y.R.). For these evaluations, the physicians were blinded to clinical history and the MMSE score of each patient. Visual findings of each BSD were graded semiquantitatively, from zero to 8 according to the readers' confidence in the severity and extent of the defects in the cerebral cortex: 0 = definite absence of defects; 2 = mild: a few small defects; 4 = moderate: some perfusion defects involving the temporal, parietal, and frontal lobes; 6 = severe: extensive perfusion defects in the temporal, parietal, and frontal lobes; 8 = profound: further extensive perfusion defects, preservation of perfusion only in the sensorimotor and occipital cortices and cerebellum.

## Results

SPECT showed that these patients all had patterns of decreased blood flow consistent with AD and no indications of significant stroke or other neurologic disorders. Table 1 summarizes the 18 patients' clinical data, including the MMSE and the graded consecutive BSD SPECT scores.

In seven cases (patients 11 to 14 and 16 to 18), the first and second SPECTs and the first and subsequent MMSE scores concurrently deteriorated:figures 1A to C illustrate worsening SPECT abnormalities. Patient 6 had a 2-year history of memory decline, when a minor auto accident occurred a week before the first brain SPECT, which was rated "near normal"; 6 months after the brain SPECT, he was disoriented to place and time, and his cognitive function declined progressively. His first MMSE was performed 4.5 years later (score 0), just before his second SPECT, which showed severe impairment.
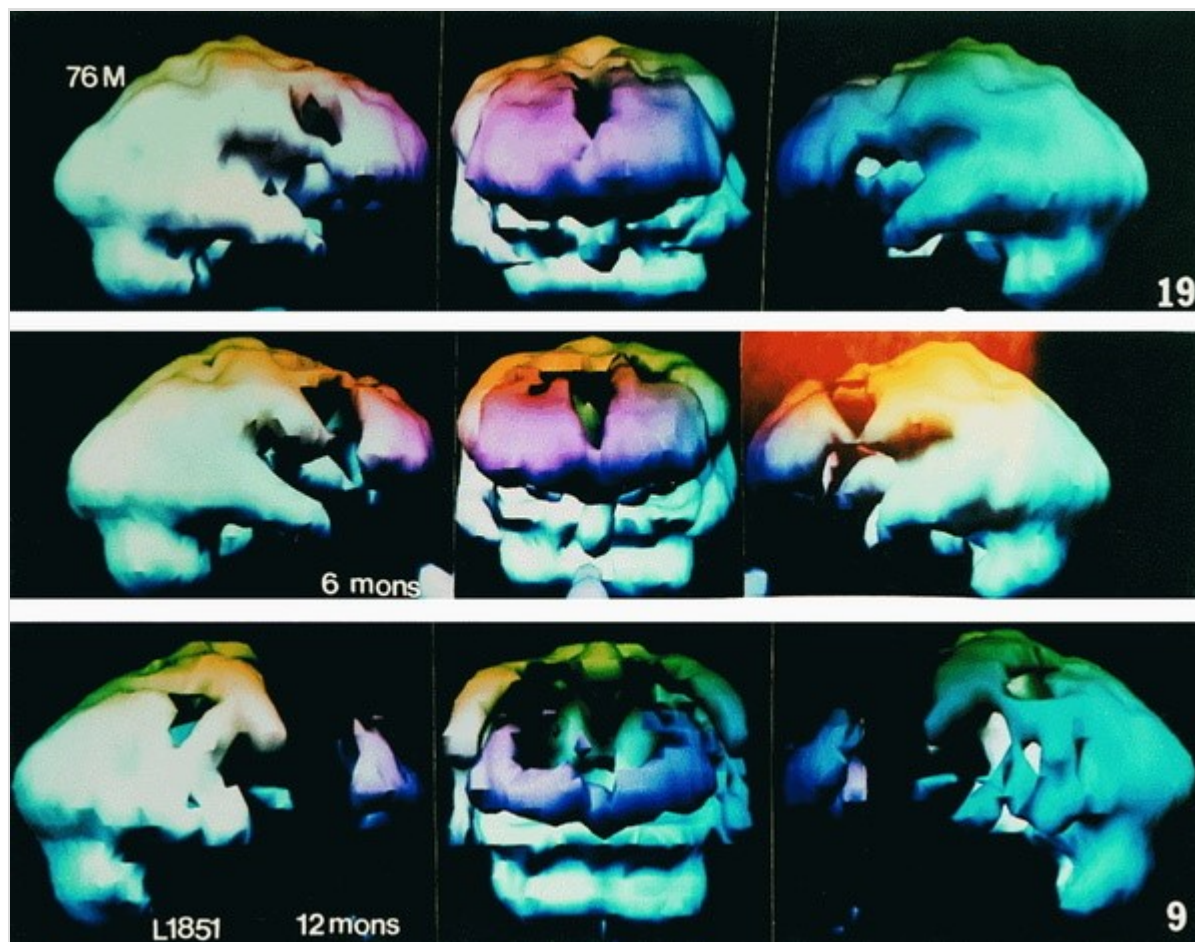
Fig. 1. (Case 17). Three consecutive SPECT BSDS are rated from mild(upper plane) to mild-moderate (middle plane), then to moderate to severe (lower plane); MMSE score declined from 19 to 9.

In five cases (patients 1-5), patients had scores of 0 on the MMSEs done near the time of their first scans, but their BSD grades showed progressive deterioration, as seen in figures 2 and 3. One patient (number 4) with a score of 0 on the MMSE at the time of the first scan, whose initial SPECT was already graded as profound, showed the same profound grading 13 months later, but there was slight deterioration noted near the posterior temporal and occipital regions. Another patient's (number 9) MMSE scores were not changed (scores of 10) in a 14-month interval, but the SPECT scans showed deterioration from mild-moderate to moderate. Another patient (number 10) had no significant interval changes on the MMSE over 26 months (scores of 11, 12, and 11), but his corresponding three consecutive SPECTs evolved from mild through mild-moderate to moderate. Similarly, another patient (number 15) with moderate dementia severity showed no MMSE change over 19 months, but the BSD score changed from moderate to severe during this time. These findings indicate that SPECT appears to have discriminatory power even in severe AD and beyond the cognitive changes measured by the MMSE.
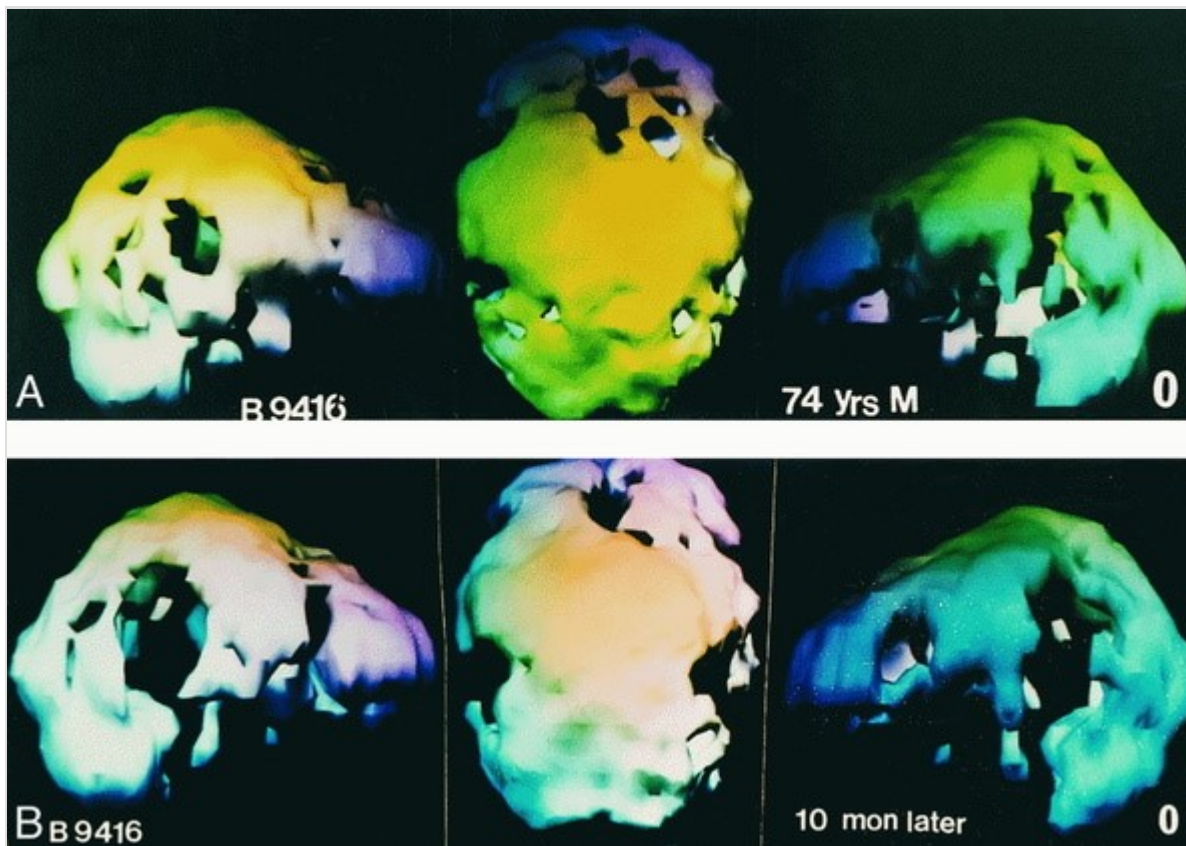
Fig. 2. (Case 3). Although a 74-year-old man's initial MMSE score was 0 and he deteriorated during the next 10-month interval, his SPECT deteriorated from (A) severe to (B) severe-profound.
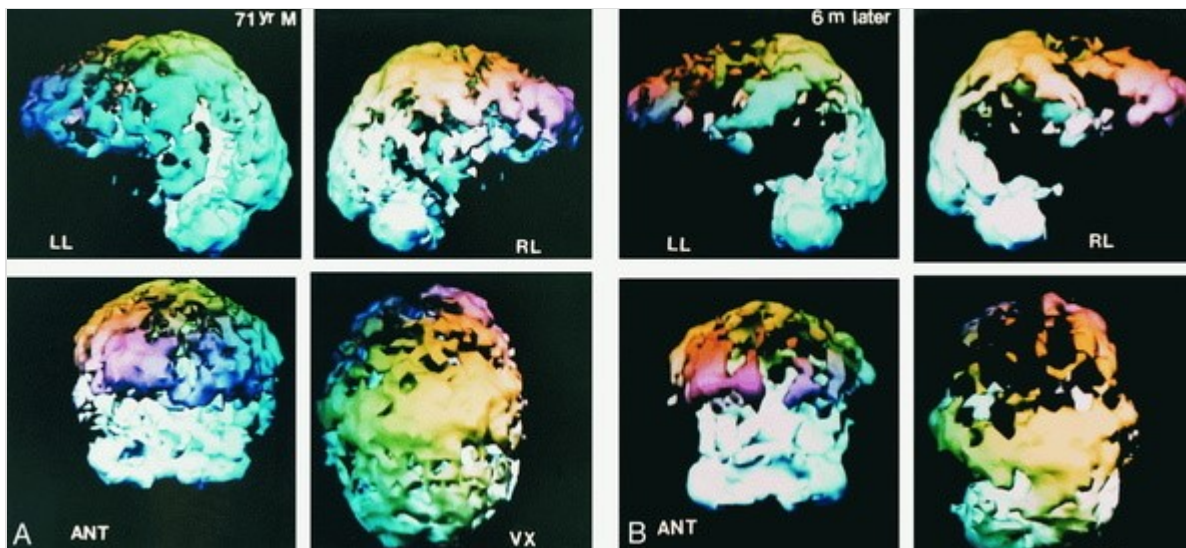


Fig. 3. (Case 2). MMSE scores were 0 during a 7-month interval; however, SPECT worsened from (A) severe to (B) severe-profound, with virtually absent cerebral flow in temporal and parietal lobes.

BSD scores were examined with respect to the patient's age at the time of the SPECT. The SPECT severity was not associated with patients' age. Analysis of rates of change showed no significant relation with age ($r$ =0.26, $P$ > 0.05).

The TI values were calculated form the MMSE scores using an approximation of the equation in Ashford et al. (5):MATH

$$TI = LN(MMSE) - 2 \cdot LN(30 - MMSE)(\text{in year units})$$

Equation U1

The initial BSD scores correlated significantly with the TI values ($r = 0.71$, $P < 0.001$[ see the initial values in Fig. 4). These values were projected to the dates of the subsequent scans using the exact number of days between the SPECT scans (Fig. 4). Using the time interval between scans, the average rate of deterioration from the first to the last scan (not including the patient who began with a score of 8) was 2.5 +/- 1.7 points per year. The change in BSD score correlated significantly with the time interval ($r = 0.71$, $P < 0.001$), although the relation varied considerably when the patient with the longest interval or the most severe patients were removed from the calculations. Nonetheless, Figure 4 shows the relentless progression of decline in cerebral blood flow over time in these patients. Although this method of grading the SPECTs has a floor effect, it shows progression in most of the severely demented patients. Thus, except in the most severe case, all patients showed BSD deterioration over time.
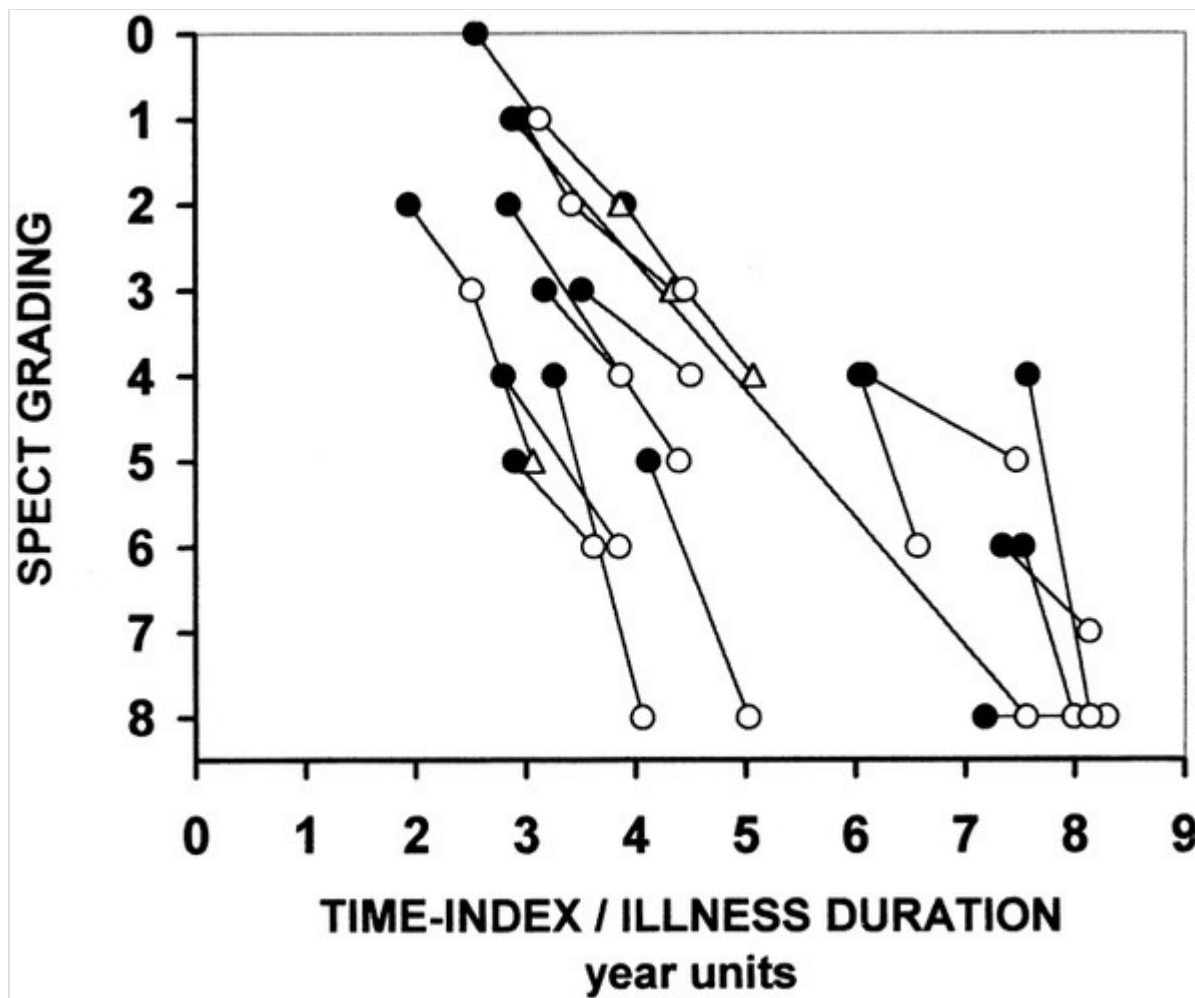


Fig. 4. SPECT BSD ordinary and dementia severity using time index (year units and time interval between SPECTs). Conversion of MMSE to time index severity allows the SPECT grades to be plotted against the estimated duration and severity of dementia from the first SPECT (solid circles) while showing the precise intervals between the SPECTs. The open circles represent the second SPECT performed, and the open triangles represent the third SPECT performed.

## Discussion

Examination of the brains of AD patients with anatomic imaging techniques shows progressive deterioration (17). This study demonstrates that the pattern of AD neuropathologic progression is reflected in a consistent loss of cerebral blood flow using SPECT, across the full spectrum of the illness. SPECTs and MMSEs had concurrent progression of SPECT and MMSEs, and SPECT grading change and MMSE score deterioration showed substantial correspondence; although in three patients, the SPECT showed deterioration but the MMSE did not. In patients with severe AD, brain SPECT appears to have discriminatory power even when the MMSE has reached its floor effect. In addition, surface BSDs simplify SPECT interpretation for objective documentation of AD progression. These changes may provide more stable assessments of brain disease in living patients than do neuropsychologic tests, and thus they could be used for diagnostic confirmation and to study the efficacy of therapeutic interventions.

The magnitude of changes of BSD scores correlated significantly with the time intervals between the SPECT scans ($r = 0.71$, $P < 0.001$). MMSE scores, using the TI calculation, showed a similar correspondence to the SPECT changes ($r = 0.71$, $P < 0.001$), although they cover a considerably broader dynamic range of illness severity. Furthermore, MMSE scores tend to vary more because of changes in patients' psychological factors, including performance variability and test-retest effects. For the most severe case (4), the SPECTs had shown preservation of cerebral perfusion only in sensorimotor and occipital lobes, there being little remaining cerebral cortex to deteriorate, although careful comparison revealed that the one initially profound case also showed further deterioration of the remaining regions over time. Thus, BSDs appear to objectively document the location of AD-related pathology and the extent of involvement of the cortex across the full spectrum of the disease. These findings indicate that SPECT has discriminatory power for changes in the severity of AD over periods of time exceeding 6 months, at least in the moderate and severe dementia ranges.

It is interesting to note that preservation of perfusion in the sensorimotor cortex and cerebellum in severe cases of AD is similar to the pattern seen in healthy neonates, with relative preservation of Tc-99m ethyl cysteinate dimer or hexamethylpropylene activity concentrated in thalamic, basal ganglia, sensorimotor, and cerebellar regions (18,19). The primary sensorimotor areas and occipital visual are specifically spared in our patients with profound disease, and these are the regions where the earliest appearance of blood flow occurs in neonates.

In conclusion, surface BSDs simplify SPECT interpretation for objective documentation of AD progression. In patients with severe AD, BSDs appear to have discriminatory power even when the MMSE has reached its floor effect. Thus, consecutive BSDs simplify SPECT image interpretation for measuring loss of brain function over time, and they could be useful for assessing the efficacy of therapeutic interventions for AD patients, such as vitamin E and cholinesterase inhibitors.

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Key Words: Alzheimer's Disease; Brain SPECT; Mini-Mental State Examination; Tc-99m Ethyl Cysteinate Dimer; Surface Three-Dimensional Displays; Time Index.

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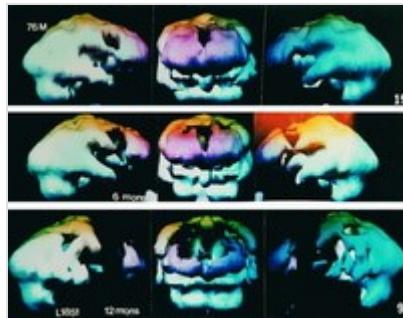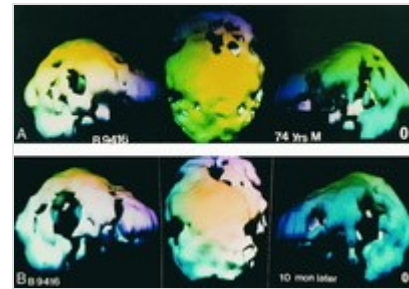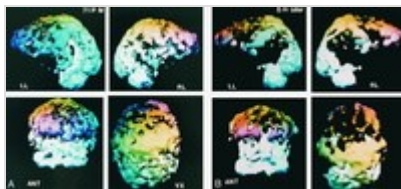

☐ Table 1


☐ Fig. 1


☐ Fig. 2


☐ Fig. 3

$$TI = LN(MMSE) - 2 \cdot LN(30 - MMSE)(\text{in year units})$$
☐ Equation U1


☐ Fig. 4

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