Longitudinal Volumetric Computed Tomographic Analysis of Regional Brain Changes in Normal Aging and Alzheimer's Disease

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Objective: This study used a semiautomated image analysis technique to quantify the rate and regional pattern of cerebrospinal fluid (CSF) volume changes in the computed tomographic brain examinations of healthy adults and patients with Alzheimer's disease (AD).

Design: Longitudinal, within-subject design, with statistical correction for longitudinal method error (eg, head repositioning effects).

Setting: Palo Alto (Calif) Department of Veterans Affairs Medical Center.

Patients and Other Participants: The 41 patients with AD were recruited from the Geriatric Psychiatry Research Unit and the National Institute of Mental Health Clinical Research Center of the Palo Alto Department of Veterans Affairs Medical Center. The 35 healthy control subjects were recruited from the local community.

Main Outcome Measures: Cerebrospinal fluid volumes estimated from computed tomographic scans.

Results: Even after accounting for an estimate of method error (eg, head positioning effects) across computed tomographic examinations, the patients with AD showed greater annual CSF volume increases than did the control group. This CSF volume enlargement was not uniform across brain regions of interest; rather, the patients with AD showed disproportionate volume increases in the ventricular system and the sylvian fissures. Greater CSF volume changes in the patients with AD were significantly associated with greater cognitive decline on the Mini-Mental State Examination. Furthermore, younger patients with AD showed more rapid progression on computed tomographic scans than did older patients.

Conclusions: The rate of CSF volume enlargement is region specific, with the most marked annual rate of change occurring in the ventricular system and the sylvian fissures. In addition, younger patients show more rapid progression in the ventricular and frontal sulcal brain regions of interest than do older patients.

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DIRECT STUDY of the neuropathologic abnormalities characteristic of Alzheimer's disease (AD) is dependent on counts of microscopic plaques and tangles that are available only at autopsy or brain biopsy.[1-4] Since such neuropathologic studies are necessarily cross-sectional in nature, they cannot address questions about the rate and regional pattern of brain morphologic change in AD or in normal aging. While in vivo structural brain imaging does not directly measure specific microscopic changes, the presence of diffuse brain atrophy on neuroimaging examination is viewed as corroborative evidence for the diagnosis of AD.[5] Furthermore, several reports suggest that groups of patients with AD differ from age-matched healthy control subjects on the basis of measures of hippocampal tissue integrity that are drawn from qualitative computed tomographic (CT) scan assessments,[6] quantitative magnetic resonance imaging (MRI) volumes,[7] or estimates of interuncal distance.[8] These studies suggest that structural imaging methods are sensitive to morphometric changes in AD that may be markers of the hallmark neuropathologic abnormalities in this disease.

The most marked morphologic abnormality observed in vivo on CT examination of patients with AD is enlargement of the cerebrospinal fluid (CSF) volume in the lateral ventricles and cortical sulci exceeding that which is seen in healthy control subjects (see De Carli et al[9] for re-

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SUBJECTS AND METHODS

HEALTHY CONTROL SUBJECTS

A total of 59 healthy elderly control subjects (ages, 55 to 82 years) participated in our previous cross-sectional CT study, using Picker Synerview scanners (Department of Veterans Affairs Medical Center, Palo Alto, Calif).[18] Of this group, 35 subjects (23 men and 12 women) completed a second CT examination (mean interscan interval, 2.6 years; SD=0.96) and are included in the present longitudinal analyses. All subjects completed a physical examination, blood panel screening, and psychiatric interview to ensure that, at the time of the follow-up assessment, they continued to be free of significant psychiatric, neurologic, or medical conditions (including alcohol and drug abuse) and were not prescribed psychoactive medications. All subjects gave informed consent for continued participation in the study. The demographic characteristics of both the control and the patient groups are presented in **Table 1**.

PATIENTS WITH AD

All patients with AD were being followed up regularly in an assessment program at the Geriatric Psychiatry Research Unit and the National Institute of Mental Health Aging Clinical Research Center of the Palo Alto (Calif) Department of Veterans Affairs Medical Center. The patients included 26 men and 15 women who met criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association for definite (n=3) or probable (n=38) AD and who had completed two examinations using Picker CT brain scans (mean interscan interval, 2.1 years; SD=1.0). These patients are a subgroup of the 117 patients with AD described by Sullivan et al.[18] Since the patients with AD were undergoing longitudinal assessment, they were classified for the present study according to their most recent diagnoses. The subjects with AD met the same exclusionary and inclusionary criteria described above for the control group. All subjects, or, when appropriate, their legal representatives, provided informed consent.

MENTAL STATUS TESTING

The control subjects and the patients with AD received the MMSE[28] as part of a larger assessment, and MMSE data were analyzed only if the test results were considered to be valid and only if the task was administered within 6 months of the CT scan for the control subjects (n=32; baseline mean, 20.1 days [range, 0 to 110 days]; follow-up mean, 6.6 days [range, 0 to 91 days]) or within 3 months of the CT scan for the patients with AD (n=34; baseline mean, 33.5 days [range, 0 to 84]; follow-up mean, 12.4 days [range, 0 to 62]).

COMPARISON WITH PREVIOUS STUDY

To assess whether the subset of patients with AD who received two CT examinations was representative of our total group studied cross-sectionally,[18] we compared those patients who completed both studies with those for whom only a single evaluation was available. These two subgroups of subjects did not differ significantly with regard to age at entry into the study, years of education, age of reported symptom onset, or duration of illness at baseline. Subjects who completed both evaluations did, however, have significantly higher MMSE scores at baseline than did those who had only a single examination (means, 17.5 and 14.5, respectively; $P<.02$).

CT SCANNING

Computed tomographic images were obtained without contrast using one of two identical Picker Synerview scanners (1200SX model) with 10 to 15 contiguous 10-mm-thick sections acquired at approximately $+10°$ relative to the cantomeatal line. Images were generated with a 512×512 matrix, which was later reduced to a 256×256 matrix and a pixel size of 0.94×0.94. Damage from the Loma Prieta, Calif, earthquake in October 1989 necessitated that scans after that date be collected on the second machine. Of the 41 subjects with AD, 28 received both of their brain scans on a single scanner; the remaining 13 subjects completed one protocol on each of the two scanners. For the normal control (NC) group, 12 subjects were scanned on a single machine and 23 changed scanners. This group difference in scanner assignment was statistically significant (χ^2 [1 *df*]=8.76, $P<.01$).

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view). These CT findings have been confirmed in an MRI study using global assessments of ventricular and sulcal CSF volumes.[10] Reports of specific regional brain changes on MRI suggest that AD is associated with volumetric gray matter decrements throughout the brain, possibly more pronounced in temporal regions[11-13]; these same regions are the locus of the reduced glucose metabolism reported in positron-emission tomographic studies[14,15] and the pathognomonic abnormalities found at autopsy.[16,17] In our own recent analysis,[18] we found that patients with AD showed disproportionate CSF volume abnormalities on CT in regions encompassing the sylvian fissures and frontal sulci, relative to the vertex and parieto-occipital sulci. Furthermore, younger patients with AD had greater abnormality than did older patients in comparison with their healthy age-mates. Thus, our volumetric CT measurements appear to be sensitive to the regional pattern of brain tissue abnormalities in AD that have been observed in vivo with MRI as well as post mortem.

Longitudinal AD studies of progression in morphologic abnormalities have relied on CT image acquisition protocols. Patients with AD as a group have been found to show significant brain CSF volume increases over time[19-21] that exceed the changes associated with healthy aging.[22-26] The existing literature has focused almost exclusively on measures of ventricular change in patients with AD,[19,21-25] despite the fact that cortical changes are the hallmark features of this disorder. Wippold and colleagues[26] reported that patients with AD showed greater progression than did control subjects on longitudinal measures of both cortical sulcal and ventricular volumes. These investigators did not, however, examine relative cortical and sulcal changes in their patients.

The existing literature is mixed with regard to the

For each subject's baseline CT series, the index section was defined as the first section with a bilateral appearance of the anterior horns of the lateral ventricles that was also superior to the temporal bones (to minimize bone hardening artifact). This index section and the five sections superior to it were used for the volumetric image analysis. (All six sections were available for all subjects.) Since the present study relies heavily on within-subject comparisons, particular care was taken to minimize indexing discrepancies within each individual's pair of scans. For consistency with previously published studies on these subjects' baseline data, the decision was made to retain our standard indexing criteria for the baseline scan and then to match the indexing of the follow-up scan to that baseline as closely as possible for all subjects in both groups. For nearly all images, this matching procedure conformed to our standard indexing criteria. In a few instances, however, the follow-up index section was shifted slightly in the interests of minimizing within-subject error (approximately 2% of the cases).

In the first step of the image analysis, all pixels belonging in the skull were stripped from each section using an automated algorithm. Each section was then filtered to reduce spectral shift and beam hardening artifact, using a homomorphic filtering approach originally developed for MRI.[29] This technique was modified for CT to add an internal smoothing procedure in addition to the peripheral smoothing procedure employed in MRI.[18,30] Internal smoothing is necessary for CT data because the sharp signal transitions between CSF-filled spaces, areas of calcification, and tissue introduce ringing artifacts when filtered. Each section was smoothed internally by replacing pixels of very high or low intensity, with values equivalent or close to the mean value of all tissue pixels. A nonparametric operator[31] was applied to a histogram of all brain tissue and CSF pixel values to identify the pixel value that maximally differentiated CSF from brain tissue on that section. The mean tissue pixel value for a given section was then estimated. Any pixel within a brain tissue region that had an attentuation value above an absolute threshold of approximately 65 Hounsfeld units (HU), which were typically areas of calcification, were replaced with the mean tissue value. Pixels with values less than 72% of the tissue mean (primarily the CSF-filled spaces) were replaced with a value equal to 85% of the tissue mean. Next, the abrupt signal transition marking the periphery of the brain was reduced by projecting the most peripheral pixel values radially to completely fill the 256×256 matrix. The resulting internally and peripherally smoothed image was submitted to a 15×15 convolution low-pass filter to characterize the distribution of low-frequency beam hardening and spectral shift artifact, mathematically inverted, and multiplied with the original image to create a filtered image substantially free of spectra shift and beam hardening artifact.[29]

Trained operators blind to subject diagnosis applied a semi-automated, computer-interactive thresholding technique to classify each pixel in the filtered image as most representing either CSF or tissue.[32] Reliability of the measurement was tested previously in a sample of 20 scans from our laboratory's total collection of over 600 Picker CT scans. The sample included control subjects as well as patients from a number of different diagnostic groups. The intraclass correlation based on the ratings of three independent operators was .986 for the total CSF pixels in the six scored sections.

REGIONS OF INTEREST

Within each CT section, a central area was defined to include the inner 55% of the volume; the remaining 45% was defined as a peripheral region. Four ROIs were then derived by summing peripheral or cortical CSF pixels across predesignated sections, ie, the ventricular system, frontal sulci, sylvian fissures, and parieto-occipital sulci. The CSF volume of the ventricular system was calculated as the sum of the CSF pixels in central portions of the four lowest sections. To calculate the cortical measures, each section was subdivided into four quadrants of equal volume in the anteroposterior direction. The three sulcal measures were all derived from CSF pixels in the peripheral band. The frontal sulci included the outer segment of the anterior quadrant of sections 1 through 4 (selected to encompass CSF-filled spaces in the prefrontal cortex); the sylvian fissures included the outer segment of the second quadrant of sections 1 and 2 and provided an estimate of the integrity of the posterior frontal and the lateral temporal lobes; and the parieto-occipital sulci included the outer segments of the most posterior quadrant of sections 5 and 6 only, in an effort to exclude the cerebellum. These ROIs were defined geometrically and thus did not coincide perfectly with traditional lobar anatomy based on sulcal infoldings. Nonetheless, they did substantially encompass the structures for which they were named and allowed for the systematic analysis of large data sets. All ROI pixel counts were converted to cubic centimeters (cc) prior to statistical analysis. Each ROI is illustrated in **Figure 1**.

degree of overlap between patients with AD and control subjects in the rate of CSF volume enlargement in CSF-filled spaces of the brain. Luxenberg and colleagues[25] reported that the distributions of lateral ventricular change scores for patients and control subjects were completely nonoverlapping and, therefore, that this longitudinal CT measure was of possible diagnostic importance. In contrast, other researchers have identified subgroups of patients who do not show significant deterioration[19,20,23] or have reported that the rate of cortical sulcal and ventricular dilatation in AD groups overlaps considerably with that of normal aging.[22,26]

Several methodologic issues may contribute to discrepant estimates of rate of change across studies, including small sample sizes, the prevalent use of linear and area measurement rather than more sensitive volumetric techniques, and inclusion within single studies of images that were acquired using varied CT scanner models. Additionally, there are a number of factors inherent in longitudinal CT image acquisition that contribute to within-subject variability across scans. Scanner drift (incremental miscalibration of the scanner) can affect the estimated signal value of individual pixels as well as the accuracy of the selected field of view (the volume of actual tissue that is represented by each pixel in the image). Perhaps more importantly, even when careful guidelines are applied for head placement in the scanner, slight positioning discrepancies are inevitable across scans. This change in head positioning may distort longitudinal change estimates for focal brain regions[27] and can potentially affect the measured volumes of all brain regions of interest (ROIs).

While previous work has not explored methodologic error such as head positioning directly, several published articles present counter-intuitive findings that are

Table 1. Study Group Characteristics* Descriptive Information

Study Group	n	Age at Entry, y	Education, y	MMSE Score		Age at AD Symptom Onset, y	Disease Duration at Baseline, y
				Baseline	Follow-up		
NC	35; 23 M, 12 F	67.4±7.4	15.4±2.2	28.7±1.1	28.6±1.5	...	...
AD	41; 26 M, 15 F	70.7±7.6	13.3±2.5	17.5±5.5	11.5±7.3	65.9±8.2	5.2±4.4

*Data are mean±SD. NC indicates normal control; AD, Alzheimer's disease; and MMSE, Mini-Mental State Examination.

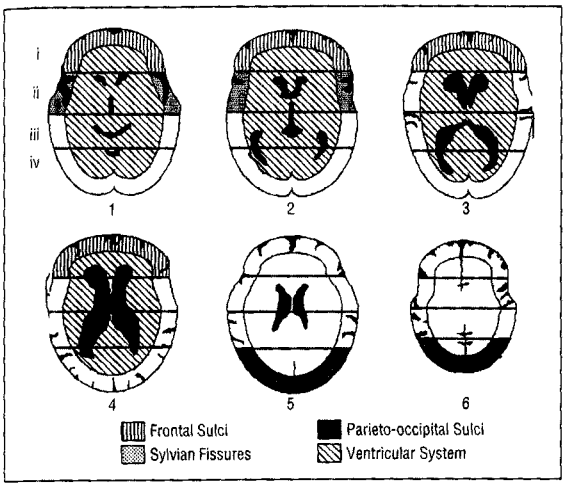

Figure 1. *Schematic representation of the four brain regions of interest.*

potentially reflective in part of such error. For example, Burns et al[20] excluded their sylvian fissure measurement from statistical analysis because it showed reduction (ie, improvement) over time in their AD sample. Similarly, in an article by Gado et al,[24] two of the three indexes on which AD and control subjects differed significantly in terms of rate of ventricular enlargement also showed unexpected, slight negative (ie, improved) mean change scores in the control subjects. Given the possibility that head positioning effects as well as other components of method error contaminate the measurement of rate of change, we have attempted to quantify the magnitude of identifiable longitudinal method error for each subject and have removed this error estimate statistically before examining rates of decline.

This study provides longitudinal follow-up data for a subset of the AD and healthy elderly control subjects described previously.[18] Our primary goals were (1) to characterize the pattern of change over time in the CSF volumes of specific brain regions in patients and in healthy control subjects; (2) to examine whether age is negatively associated with rate of decline, given our previous cross-sectional finding of a negative relationship between age and degree of brain abnormality; (3) to quantify identifiable within-subject method error; and (4) to explore the relationship between structural change and increasing severity of dementia, as estimated from the Mini-Mental State Examination (MMSE). We first present a cross-sectional analysis in which the AD and control groups are compared at entry into the study, to document the initial degree and regional pattern of CSF volume abnormality in this subgroup of patients. The analysis then turns to a longitudinal investigation of observed CSF volume change in these two groups and a consideration of factors that may be associated with rate of decline.

RESULTS

CROSS-SECTIONAL STUDY STATISTICAL PROCEDURES

Cross-sectional analyses explored the magnitude and regional pattern of CSF volume enlargement in the AD group at entry into the study. To examine disease-related changes that were independent of normal aging, we applied a normative two-step regression procedure developed in our laboratory[33] to convert the raw CSF pixel counts for each of the four ROIs into a standardized score designed to correct for normal aging and for individual variation in head size. First, the CSF volume in each ROI was regressed on the total intracranial volume of the six sections (ie, the sum of all CSF and tissue pixels in the full series of analyzed image sections) in a larger sample of 114 NC subjects spanning the adult age range[18,30]; the healthy elderly control subjects for the present study are a subset of this larger control sample. The residuals from this series of linear regressions represented the CSF volumes for each ROI after correcting for normal variation in head size, as estimated from the volume of the six sections. In the second step, a quadratic regression equation was applied to the head size–residualized scores across the age range of the NC group (second through eighth decade of life), providing a model for age-related changes that are independent of head size.

To estimate normal aging effects more accurately, two mathematical considerations were incorporated into the final polynomial functions. First, an unconstrained quadratic solution has the disadvantage of generating inflection points at the extreme age ranges that are inconsistent with the known neuroanatomical correlates of normal aging (eg, increases in the predicted CSF volumes of the youngest subjects relative to older subjects). To eliminate these inflections, the quadratic models were constrained to allow only increases in CSF volume after the age of 10 years.[33] This cutoff was selected on the basis of postmortem evidence that adult brain weights (and, presumably, intracranial volumes) are substantially achieved by approximately age 10 years.[34]

Second, the precise calculation of predicted CSF volume at any given age is reduced by the considerable heteroscedasticity of obtained volumes across the lifespan (ie, there is often greater variance in the obtained CSF

Table 2. Cerebrospinal Fluid (CSF) Volumes for Four Regions of Interest (ROI) in 41 Patients With Alzheimer's Disease (AD) and 35 Normal Control (NC) Subjects*

ROI	CSF, cc		Head Size Corrected Score, cc		z Scores	
	NCE	AD	NC	AD	NC	AD
Frontal sulci	6.59 (±0.60)	9.66 (±0.45)	2.17 (±0.59)	5.29 (±0.44)	0.13 (±0.17)	1.08 (±0.18)
Sylvian fissures	2.48 (±0.26)	4.80 (±0.27)	1.01 (±0.26)	3.36 (±0.27)	0.20 (±0.18)	2.17 (±0.29)
Parieto-occipital sulci	1.90 (±0.24)	3.12 (±0.25)	0.56 (±0.24)	1.74 (±0.24)	0.12 (±0.21)	1.06 (±0.22)
Ventricular system	45.98 (±3.17)	70.26 (±3.65)	12.39 (±2.91)	37.39 (±3.48)	0.24 (±0.19)	1.99 (±0.28)

*Data are mean (±SE).

volumes of older subjects relative to younger individuals).[32,35-38] Using a modification of Glejser's test for heteroscedasticity,[39] an age-specific estimate was made of the SD in the ROI CSF volumes across the age range represented in the control sample. These age- and ROI-specific SDs were then entered as weights in the regression model used to generate predicted CSF volumes. The final regression model, then, was a weighted least squares constrained quadratic function for three of the four ROIs; age-related changes in the sylvian fissure were best modeled with a weighted least squares unconstrained cubic function. All age modeling was performed on the control data before the patient data were examined.

Finally, for all patients and control subjects, CSF volumes were converted to head size–corrected and age-corrected z scores, based on the regression analyses conducted in the control group. These age-corrected z scores were calculated from the head size–residualized scores by subtracting the predicted CSF volume for a given age from the observed volume and then dividing this difference score by the age-specific SDs derived above. By definition, these z scores have a mean of zero and an SD of one in the full control group. Positive values reflect higher (more abnormal) CSF volumes than are expected given the subject's age and head size; negative scores reflect lower volumes than are expected. Since z scores were calculated on the basis of cross-sectional data from healthy control subjects, these scores were used only in the cross-sectional (and not in the longitudinal) component of the present study.

ESTIMATES OF CSF VOLUME AT ENTRY INTO THE STUDY

The raw CSF volumes for each of the four ROIs are provided in **Table 2**. A multivariate analysis of variance that compared the AD and healthy elderly control groups on these baseline values in the four ROIs (frontal sulci, sylvian fissures, occipital sulci, and ventricular system) confirmed that the AD group had significantly greater CSF volumes overall than did the control group (using Wilks' criterion, $F[4,71]=11.25$; $P<.001$).

Previous cross-sectional work in our laboratory has demonstrated the importance of parsing the CSF volume increase associated with normal aging from that specific to disease states.[18,33,37] To provide information about the magnitude of the pathologic brain changes in the patients above and beyond the effects of normal aging, we performed a second MANOVA on the age- and head size–corrected z scores. This analysis was consistent with the results previously observed in our larger sample and showed that, relative to their age-mates, the patients with AD had significantly higher CSF volumes overall than did the NC group ($F[4,71]=10.01$, $P<.001$). A multivariate test of parallelism revealed that, independent of this group effect, the profile of impairment across ROIs differed significantly between the diagnostic groups ($F[3,72]=3.36$, $P<.03$). As was expected in the NC group, there were no significant differences among ROI z scores. In contrast, the AD group demonstrated significantly greater CSF volume abnormalities in the ventricular system and sylvian fissures than in the frontal and occipital sulci ($P<.001$ for all significant comparisons). This analysis was repeated using both diagnostic group and sex as grouping factors; neither a significant main effect of sex nor significant sex interactions were identified.

Correlational analyses revealed that, within the AD group, frontal and sylvian ROI z scores at baseline were significantly and negatively associated with age at scan. In other words, younger patients with AD were more impaired for their ages than were older patients (frontal sulci, $r=-.55$, $P<.001$; sylvian fissures, $r=-.48$, $P<.01$; parieto-occipital, $r=-.20$, NS; and ventricular system, $r=-.28$, $P<.09$). By definition, z scores in the NC group were not correlated with age. In the AD group, greater CSF abnormality (higher z scores) in each ROI at baseline was significantly associated with greater cognitive dysfunction (lower MMSE score) (frontal sulci, $r=-.38$, $P<.02$; sylvian fissures, $r=-.38$, $P<.021$; parieto-occipital sulci, $r=-.36$, $P<.02$; and ventricular system, $r=-.48$, $P<.01$). We were unable to identify a significant relationship between reported duration of illness at baseline scan and CSF volume in any of the four ROIs. All of these cross-sectional results are consistent with the reported findings from the larger AD subject pool.[18]

LONGITUDINAL ANALYSES STATISTICAL PROCEDURES

While method error such as head positioning variability is present in both cross-sectional and longitudinal samples, this error is difficult to quantify cross-sectionally because it is confounded with normal variation across individuals. In a longitudinal design, such error may contribute to an apparent change in brain morphology across time. A portion of this longitudinal method error, however, is manifested as change in volumes that should theoretically remain constant across scans, such

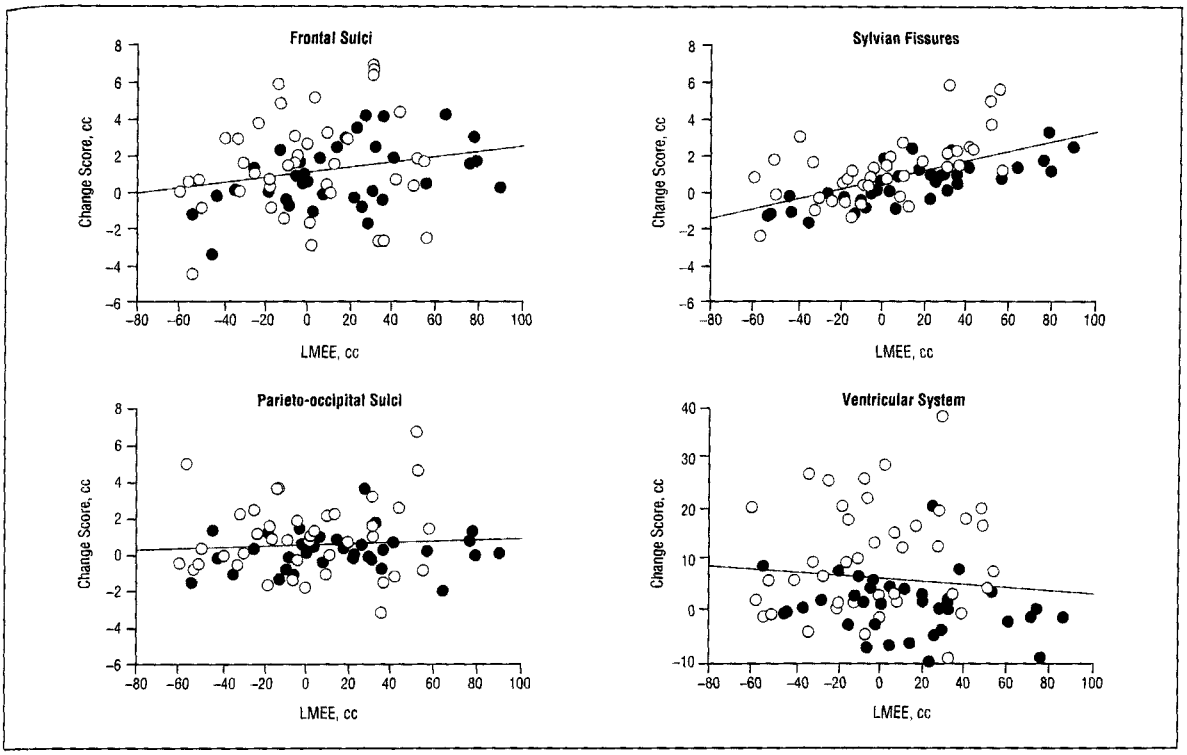

Figure 2. *Cerebrospinal fluid volume change (cc) for each of the four regions of interest, plotted over the longitudinal method error estimate (LMEE). The data for patients with Alzheimer's disease appear as open circles and for the normal controls as closed dots. The regression line is based on both groups combined.*

Table 3. Region of Interest (ROI) Change Scores in Normal Control (NC) Subjects and Patients With Alzheimer's Disease (AD) Groups*

	ROI			
Study Group/Change	Frontal Sulci	Sylvian Fissures	Parieto-occipital Sulci	Ventricular System
NC				
Raw change score, cc	1.06 (±1.82)	0.64 (±1.22)	0.24 (±1.07)	1.08 (±5.92)
Corrected change score, cc	0.80 (±1.62)	0.19 (±0.77)	0.13 (±1.05)	0.96 (±5.98)
Corrected rate of change, cc/y	0.31 (±0.68)	0.58 (±0.30)	0.05 (±0.47)	0.61 (±2.55)
AD				
Raw change score, cc	1.53 (±2.76)	1.19 (±1.82)	0.95 (±2.05)	10.55 (±10.83)
Corrected change score, cc	1.56 (±2.72)	1.24 (±1.40)	0.96 (±2.03)	10.57 (±10.79)
Corrected rate of change, cc/y	0.81 (±1.81)	0.62 (±0.87)	0.50 (±1.42)	5.28 (±5.89)

**Data are mean (± SE).*

as total measured cranial volume (CSF plus tissue). We reason that any observed change in intracranial volume is reflective of longitudinal method error and provides an estimate of the extent of this error.

Inspection of our longitudinal data revealed that the total volume of the six analyzed sections (ie, estimated intracranial volume) varied considerably within individuals across the two image acquisitions. This difference in measured intracranial volume across scans (follow-up minus baseline) ranged for all subjects from –60.5 to 89.5 cc and followed an approximately normal distribution. Furthermore, as seen in **Figure 2**, this difference score was correlated differentially with the apparent CSF volume changes (follow-up minus baseline CSF volumes) in the various ROIs (frontal sulci, r=.24, P<.04; sylvian fissure, r=.61, P<.001; parieto-occipital sulci, r=.093, NS; and ventricular system, r=–.082, NS). Thus, it was important to control for this longitudinal method error, so as not to confound true change with spurious change due to method error.

For each ROI, we used a two-step statistical procedure to correct ROI change scores for the longitudinal method error estimate (LMEE) (ie, the observed change in intracranial volume from the baseline to the follow-up scan). In the first step, the ROI change score for all subjects was regressed on diagnostic group and LMEE.

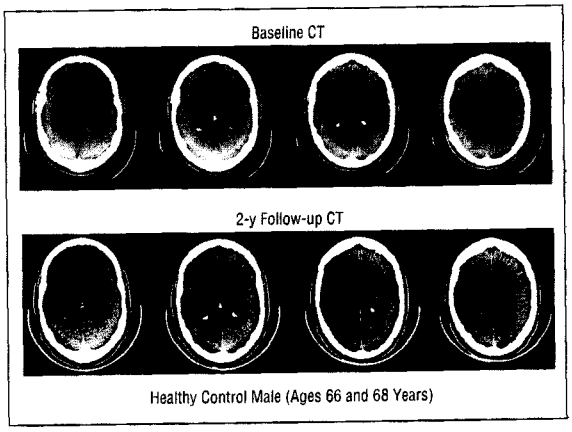

Figure 3. *Baseline and 2-year follow-up computed tomographic images for a man in the healthy control group.*

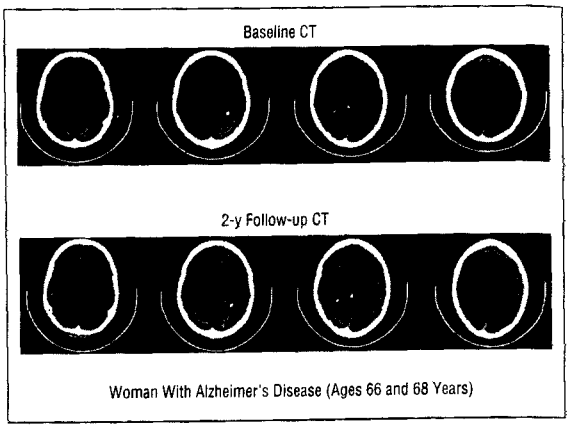

Figure 4. *Baseline and 2-year follow-up computed tomographic images for a woman in the Alzheimer's disease group.*

The obtained regression coefficient for LMEE was then used to correct each individual subject's ROI change score for the error estimate, using the following formula: Corrected Change Score = $(ROI_2\text{-}ROI_1)\text{-}b(LMEE)$ where ROI_2 is the CSF pixel count at follow-up for a given ROI, ROI_1 is the pixel count at baseline, and b is the regression coefficient for LMEE from the first step of the analysis. The corrected change score represents the measured change (in cc of CSF) that is independent of LMEE. An advantage of this correction procedure is that each ROI difference score was adjusted only to the degree that it correlated with LMEE; thus, no corrections were imposed artificially on values that were actually unrelated to the method error estimate. Age corrections were not considered to be necessary in the within-subject longitudinal analyses.

Rate of Change in CT ROIs

The raw and corrected difference scores (follow-up minus baseline volumes in cc, adjusted for method error) are presented in **Table 3** for each of the CT ROIs. No significant differences were present between difference scores for subjects assessed twice on our original CT scanner and those studied once on each of the two scanners. In the AD group, the corrected difference scores for two of the four ROIs correlated significantly and positively with the interscan interval, suggesting that greater CSF volume enlargement was associated with a longer interval between scans (frontal sulci, r=.26, NS; sylvian fissures, r=.48, P<.01; parieto-occipital sulci, r=.064, NS; and ventricular system, r=.42, P<.01). The control group showed a trend toward a significant relationship between interval and change in the sylvian fissures (r=.32, P<.06). These reduced correlations are likely reflective of the restricted range of CT difference scores within this group. Given the significant relationship of interscan interval to degree of change in the AD group, as well as the significant difference between diagnostic groups in terms of interscan interval, corrected difference scores for each subject were divided by that individual's interval to form an index of the corrected annual rate of change (cc/year). **Figure 3** and **Figure 4** illustrate the baseline and follow-up CT images for representative subjects from the NC and AD groups.

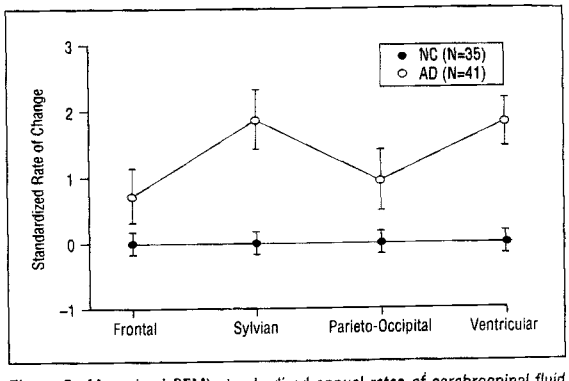

Figure 5. *Mean (and SEM) standardized annual rates of cerebrospinal fluid (CSF) volume change in the four regions of interest in the Alzheimer's disease (AD) group and normal control (NC) group.*

The corrected annual rates of change for the patients with AD and control subjects in the four ROIs were contrasted with a MANOVA. For this MANOVA, the corrected annual rates of change were standardized to the control group mean and SD for each region to remove regional differences in scale arising from differences in ROI size (ie, larger structures may change more per day than smaller structures, but not necessarily at a faster rate when structure size is considered). The means of the standardized rates of change for the four ROIs are shown in **Figure 5.** The results of the MANOVA showed that the AD subjects had significantly greater annual increases in brain CSF volume overall than did the control subjects (using Wilks' criterion, $F[4,71]=8.61$, P<.001). Within individual ROIs, the univariate differences were statistically significant for the sylvian fissures and the ventricular system (P<.001 for both comparisons) and approached significance for the parieto-occipital sulci (P<.08). A multivariate test of parallelism was also significant ($F[3,72]=2.88$, P<.05), suggesting that, independent of the group effect, the AD and NC groups differed in the configural pattern of their annual rates of change across the four ROIs. Within the AD group, follow-up paired t tests revealed that the rate of CSF vol-

Table 4. Correlations Between Corrected Annual Rates of Change and Baseline Demographic and CT Measures in 41 AD Patients*

Characteristics	Corrected Annual Rates of Change, cc/y			
	Frontal Sulci	Sylvian Fissures	Parieto-occipital Sulci	Ventricular System
Demographics at baseline				
Age, y	−0.39†	0.09	−0.14	−0.51§
Symptom duration, y	−0.14	0.15	0.20	−0.07
MMSE	−0.13	−0.33‡	0.07	−0.19
Raw CT volumes (cc) at baseline				
Frontal sulci	−0.11	0.11	−0.11	−0.24
Sylvian fissures	−0.09	0.13	−0.03	−0.07
Parieto-occipital sulci	−0.26	0.27	−0.38‡	−0.22
Ventricular system	−0.04	0.13	−0.24	0.04
CT *z* scores at baseline				
Frontal sulci	0.12	0.07	−0.02	0.04
Sylvian fissures	0.18	0.06	0.09	0.28
Parieto-occipital sulci	−0.16	0.23	−0.36‡	−0.07
Ventricular system	0.10	0.12	−0.18	0.21

**CT indicates computed tomography; MMSE, Mini-Mental State Examination.*
†P≤.01.
‡P≤.05
§P≤.001.

ume increase in the ventricular system was not significantly different from the rate of increase in the sylvian fissures (P=.932), and both the ventricular system and the sylvian fissures increased at a significantly faster rate than did the frontal sulci (P=.001 and P=.056, respectively). There was a trend for the ventricular system (P=.065) but not the sylvian fissures (P=.207) to increase in volume at a faster rate than the parieto-occipital sulci. The parieto-occipital sulci and frontal sulci did not significantly differ in their rates of volume increase (P=.590). Again, a MANOVA, which included sex as a factor, failed to identify significant main effects or interactions for sex.

Two sets of longitudinal analyses in the healthy control subjects assessed regional differences in the rates of CSF volumes increase. To control for regional differences in the rates of change arising from differences in ROI size, the rate of change for each region was expressed as a percentage of the baseline ROI volume (ie, the percent change from baseline per year). First, a one-group MANOVA within the NC group showed no significant differences in the rates of CSF change among the four ROIs (using Wilks' criterion, $F[3,32]=1.11$, P=.36). Second, univariate analyses were undertaken to address the hypothesis in prior neuropsychological studies[40,41] that the frontal lobes are particularly vulnerable to normal aging. Paired t tests within the controls showed that the annual rate of change in the frontal sulci was not significantly different from the rates of change in the other ROIs.

Change in the MMSE

The MMSE scores at baseline and at follow-up for the two groups are presented in Table 1. A repeated-measures ANOVA confirmed that the AD group demonstrated greater impairment on this cognitive index overall than did the NC group ($F[1,64]=210.8$, $P<.001$) and showed greater decline in their scores across the two testing sessions than the NC group ($F[1,64]=37.0$, $P<.001$). Within the AD group, a longer interval between testing sessions was associated with greater decline in the MMSE score ($r=-.52$, $P<.01$). This relationship was not significant in the NC group ($r=.11$). The annual rate of change on the MMSE (calculated as the MMSE difference score divided by the interval between assessments) also differed significantly between the groups, with the AD group showing greater annual decline than did the NC group ($P<.001$).

Comparison of CT and MMSE Findings

The relationship between CT and MMSE changes in the AD group was examined using both difference scores (follow-up minus baseline value) and rates of change (difference score divided by interval). The correlations between MMSE difference scores and corrected ROI difference scores were significant or near significant for three of the four sampled brain regions (frontal sulci, $r=-.32$, $P<.07$; sylvian fissures, $r=-.56$, $P<.001$; parieto-occipital sulci, $r=.083$, NS; and ventricular system, $r=-.47$, $P<.01$), with greater CSF volume enlargement accompanying more marked cognitive decline. While individual differences in the interscan interval undoubtedly increased the variability among subjects in this analysis, the within-subjects effects were preserved since intervals between scans and between testing sessions were similar (although not necessarily identical) for any given subject.

When the MMSE and CT changes were compared in terms of annual rate of change, reduced correlation coefficients were obtained. The calculation of annual rate of MMSE change yielded a mean loss of 3.2 points per year in the subjects with AD (SD=2.7) and −0.09 points per year in the NC group (SD=0.73), which is consis-

tent with other published data on rate of decline on this test from other centers,[42] as well as our own.[43] None of the correlations between annual rate of change in the MMSE and CT ROIs reached statistical significance (frontal sulci, r=–.26; sylvian fissures, r=–.24; parieto-occipital sulci, r=–.09; and ventricular system, r=–.24).

Predictors of Annual Rate of Change

Correlational analyses were conducted to examine whether the measured annual rate of CSF volume increase in the subjects with AD was associated with the baseline demographic, cognitive, or neuroimaging indexes (**Table 4**). There was a significant relationship between age at baseline scan and annual rate of change in the frontal sulci (r=–.39, P<.02) and the ventricular system (r=–.51, P<.001), with younger patients with AD exhibiting more rapid progression than older patients. Slope tests confirmed that these negative correlations in the AD group differed significantly from the (nonsignificant) relationship between age at first scan and rate of change in the control group (P<.02 for the frontal sulci and P<.001 for the ventricular system). These age relationships are illustrated in **Figure 6**. Annual rates of change did *not* covary significantly with the reported duration of illness at entry into the study, cognitive status as assessed by the MMSE, or CSF volume at baseline (raw volume or age- and head size–corrected z scores) for any ROIs other than the parieto-occipital sulci.

Finally, we performed two discriminant function analyses to determine the accuracy with which patients with AD could be differentiated from control subjects on the basis of their baseline z scores and their annual rates of change. In the first analysis, group membership was predicted from the two ROI z scores that best characterized the cross-sectional abnormalities of the AD group, ie, the sylvian fissures and ventricular system. This model correctly classified 31 (75.6%) of the 41 patients with AD and 32 (91.0%) of the 35 NC subjects. Next, the corrected annual rate of change score for the ventricular system was added into the model to determine whether this longitudinal measure would improve the classification accuracy. Once again, 31 of the patients with AD and 32 of the NC subjects were correctly classified, an accuracy rate identical to that obtained from the cross-sectional data alone (although three subjects were classified differently by the two models).

COMMENT

The results of this study show that the abnormally rapid CSF volume enlargement that has been well documented in the ventricular system of patients with AD[19-26] is present also in the sylvian fissures and frontal sulci. Furthermore, this study provides the first evidence that the CSF volume progression is not uniform across all brain regions; rather, the patients with AD showed disproportionate volume increases in the ventricular system and sylvian fissures, relative to the other regions. Using the longitudinal change data in the NC group, we were unable to support the hypothesis that frontal lobe functioning may be disproportionately affected by normal aging.[41]

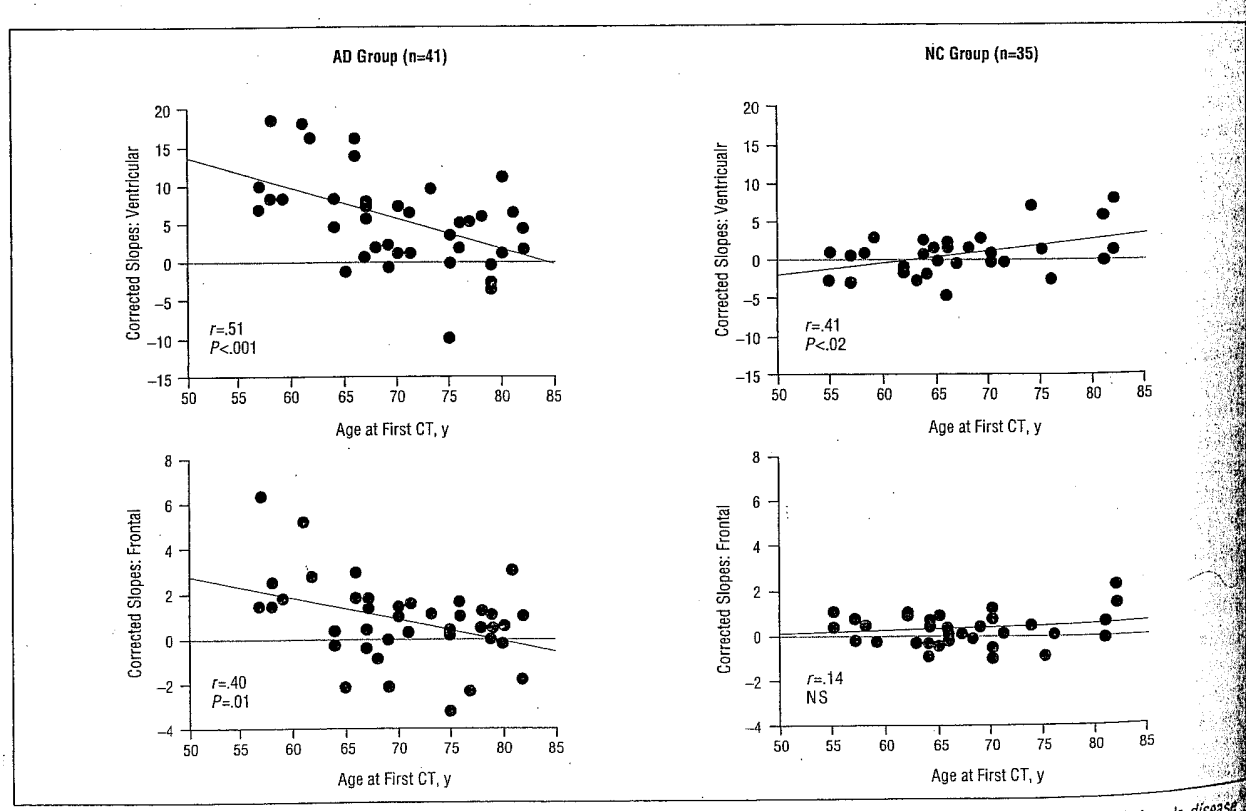

Figure 6. *Corrected annual rates of change (cc/y) for the ventricular system and frontal sulcal regions of interest plotted over age in the Alzheimer's disease (AD) group (left) and normal control (NC) group (right). CT indicates computed tomography; NS, not significant.*

Our earlier cross-sectional work sugggested[18,37] that younger patients with AD have greater CSF volume abnormalities for their ages than do older patients. The present results extend this finding by showing that younger patients may also demonstrate more rapid deterioration in regions encompassing the sylvian fissures and ventricular system than do older patients. This age relationship may reflect a more virulent disease form in younger individuals and is consistent with neuropathologic evidence that younger patients with AD have lower brain weights and greater ventricular dilatation post mortem than do older patients.[44]

A significant association between CSF volume increase and cognitive deterioration has been reported in previous studies.[20] In the present data, this relationship between ventricular change and MMSE change reached statistical significance when absolute difference scores were correlated, but the magnitude of the association was attenuated when rates of change in the two measures were correlated. It is possible that this pattern reflects, in part, an asynchronous decline, with measurable cognitive deterioration preceding frank structural change on neuroimaging.[45] It will be important for future work to examine the relationship between regional structural change and deterioration on tests of specific, localizable cognitive abilities.

While the patients with AD differed significantly from the NC subjects as a group, there was a considerable amount of overlap between the groups in terms of annual rate of change. In fact, group classification accuracy was not improved by adding information about rate of change to that available from cross-sectional measurements alone. It is quite likely that this linear estimate of change across only two time points may not accurately model disease progression across a longer time period. Cognitive studies,[42,46] for example, have shown that change scores on mental status examinations are poorly correlated across multiple time points. Although there was no evidence in these data to suggest that patients who entered the study with higher CSF volumes differed in their rate of progression from those who entered with less abnormality, it is possible that such a relationship would be present over a larger number of serial assessments.

A methodologic goal of this study was to examine the rate of change independent of identifiable method error. Longitudinal method error was estimated from observed change in intracranial volume, which theoretically should remain constant across scans. It is noteworthy that the LMEE was correlated significantly with several of the observed ROI change scores and, furthermore, that it was differentially correlated with the various ROIs. Goodkin et al[27] have presented a conceptual argument about the effect of positioning differences on measured change in small, focal areas of demyelination. Our findings demonstrate that head positioning and other methodologic factors are, in fact, a source of error that may distort measured rates of change even across large, geometrically defined brain ROIs and that may also confound within-subject analyses of configural brain changes across multiple measured regions. Indeed, using the LMEE correction enhanced the magnitude of the group effect in all four of the ROIs. While the LMEE is in no way a comprehensive estimate of all longitudinal error present in the data, this correction approach was successful in removing at least a portion of this error variation.

These results have several implications for other studies that have not corrected for longitudinal method error. To the extent that the method error is random with respect to the change being measured, controlling for this method error would be expected to enhance obtained differences between patients with AD and control subjects. Thus, negative findings from previous studies in the literature may be attributable to uncontrolled random method error attenuating the observed effects. However, as was the case in the present study, longitudinal method error may covary sytematically with observed within-subject ROI changes, thereby confounding true change with spurious change. Consequently, when longitudinal imaging studies fail to control for longitudinal method error, positive findings, as well as negative findings, are potentially attributable to spurious method changes across repeated scans. It is noteworthy that the correction factor had little impact on the ventricular system ROI, a region that has been the common focus of previous studies. This degree of error in the remaining ROIs may, however, account, in part, for some of the counterintuitive findings in the existing longitudinal CT literature, such as the report that sylvian fissure measurements decreased over time in patients with ADs[20] or that control subjects showed modest improvement longitudinally.[24]

To summarize, these data demonstrate that disease progression is apparent in subjects with AD even after correcting for longitudinal method error. Also, the degree of CSF volume increase is significantly associated with the magnitude of cognitive decline on the MMSE. The rate of CSF volume enlargement is region specific, with the most marked annual rate of change occurring in the ventricular system and sylvian fissures. In addition, younger patients appear to show more rapid change than do older patients, which is consistent with the cross-sectional finding that younger patients have greater CSF volume abnormalities for their ages than do older patients.[18]

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