Greater Abnormalities of Brain Cerebrospinal Fluid Volumes in Younger Than in Older Patients With Alzheimer's Disease

Edith V. Sullivan, PhD; Paula K. Shear, PhD; Daniel H. Mathalon, PhD; Kelvin O. Lim, MD; Jerome A. Yesavage, MD; Jared R. Tinklenberg, MD; Adolf Pfefferbaum, MD

• *Objective.*—This study used a semiautomated analysis technique to quantify differences in regional brain cerebrospinal fluid volumes observed with computed tomography between healthy adults and patients with Alzheimer's disease (AD).

Design.—Cross-sectional, between-subject design, using an age-regression model.

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

Patients and Other Participants.—The 117 patients with probable or definite AD were recruited from the Geriatric Psychiatry Research Unit and National Institute of Mental Health Clinical Research Center of the Palo Alto Department of Veterans Affairs Medical Center. The 114 healthy volunteers were recruited from the local community.

Main Outcome Measures.—Cerebrospinal fluid volumes estimated from computed tomographic scans and neuropsychological test scores.

Results.—The computed tomographic estimates of ventricular and sulcal cerebrospinal fluid volumes increased significantly in all sampled brain regions in normal aging and were vastly larger in AD than in normal aging. Furthermore, younger patients with AD had significantly greater cerebrospinal fluid volume enlargement than did older patients with AD compared with healthy controls of their age. When the AD group was divided on the basis of reported age at symptom onset, patients in the early-onset group (onset before age 65 years) were quantitatively more abnormal than and showed a different pattern of abnormality from the patients in the late-onset group. This onset difference was also evident in neuropsychological test performance.

Conclusions.—This cross-sectional study revealed a number of converging findings that suggested greater abnormality in the early-onset than in the late-onset group of patients with AD. The possibility remains, however, that the two onset groups represent different stages along a continuum of pathologic changes.

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Neurochemical, neuroanatomic, and functional heterogeneity of Alzheimer's disease (AD) is now widely accepted.[1-14] It has been suggested that a portion of this variability is explicable on the basis of age at symptom onset.[2,13-15] Early-onset, or presenile, AD is clinically detectable before age 65 years, whereas late-onset, or senile, AD occurs at age 65 years and later. Although not all studies have revealed differences between these onset groups, those reporting negative findings typically have not controlled for the effects of normal aging. The distinction between onset groups relies on an adequate description of normal, age-related changes, since these aging effects are inherently more pronounced in late- than early-onset AD. In the present study, we examined age-related brain morphologic characteristics with x-ray computed tomography (CT) in healthy adults and in patients with AD, with age at the time of scanning used as a continuous variable. In addition, we classified the patients with AD as having early-onset (before age 65 years) or late-onset (age 65 years or older) disease and examined differences between these two AD subgroups in CT measures that were adjusted for the effects of normal aging.

The cerebrospinal fluid (CSF)–filled spaces in the brain enlarge and tissue volume decreases throughout the life span of healthy adults. This process, detectable with in vivo neuroimaging techniques, accelerates and becomes more variable after the fifth decade of life.[16-21] The accelerating rate of change and increasing variability occurring after about the age of 60 years makes it particularly important to account for these normal aging effects when age-related degenerative disease, such as AD, is characterized. It is critical, therefore, for neuroimaging studies of degenerative diseases in the elderly to differentiate disease-related from normal age-related changes in brain morphologic characteristics.

The CT technology has been used extensively in research applications to document increases in the amount of CSF in the ventricular system[22-25] and cortical sulci.[26,27] Our laboratory has developed a semiautomated computerized quantification technique for CT data that yields volumetric measures of defined brain regions of interest (ROIs).[19,20,28] With the use of regression analysis, volumet-

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From the Department of Psychiatry and Behavioral Sciences, Stanford (Calif) University School of Medicine, and Psychiatry Service, Department of Veterans Affairs Medical Center, Palo Alto, Calif.

Reprint requests to Psychiatry Service (116A3), Department of Veterans Affairs Medical Center, 3801 Miranda Ave, Palo Alto, CA 94304 (Dr Sullivan).

Table 1.—Demographic Characteristics of the Control and Alzheimer's Disease (AD) Groups*

Group	Cases by Sex	Age, y	Education, y	Handedness	Mini-Mental Status Examination (Range, 0-30)	Age at AD Symptom Onset, y	Symptom Duration of AD, y
Total control (aged 21-82 y)	84 M, 30 F	52.1	15.6	101 R, 11 non-R	28.7	...	...
		17.73	2.4	...	1.18	...	...
		21-82	12-22	...	25-30	...	...
		114	114	112	79	...	..
Older control (aged ≥55 y)	34 M, 25 F	66.7	15.4	55 R, 4 non-R	28.7	...	...
		7.59	2.32	...	1.1	...	...
		55-82	12-22	...	26-30	...	...
		59	59	59	55	...	...
Total AD	63 M, 54 F	69.1	13.9	92 R, 4 non-R	15.4	64.3	5.3
		7.76	2.48	...	6.36	7.77	3.48
		550-84	8-19	...	0-29	50-83	0-21
		117	110	96	108	104	104
Early-onset AD	38 M, 20 F	64.1	14.3	42 R, 4 non-R	14.8	58.5	6.1
		5.07	2.49	...	5.95	3.64	3.79
		55-80	8-19	...	0-26	50-64	0-21
		58	52	46	51	58	58
Late-onset AD	20 M, 26 F	75.3	13.4	37 R, 0 non-R	16.2	71.7	4.2
		4.89	2.57	...	7.23	4.77	2.76
		66-84	8-18	...	0-29	65-83	1-18
		46	44	37	44	46	46

*Values are mean, SD, range, and number, given in that descending, vertical order.

ric neuroimaging data from healthy control subjects spanning the adult age range can be used to quantify the effects of normal aging and to estimate norms for each year in the adult lifespan. Separate age norms for each brain ROI can then be applied to the quantitative data obtained from pathologic groups, thus affording the opportunity to quantify pathologic brain changes independent of the significant and systematic effects of normal aging.[17,19,20] This approach is particularly important for evaluating neuroanatomic correlates of AD subtypes that are related to age at onset,[2-5,13,22,29,30] where the effects of disease and its onset would otherwise be confounded with the effects of normal aging.

This study provides CT data for a sample of 114 healthy control subjects, with ages evenly distributed from the second to the eighth decade of life. These normative data were used to examine CT measures obtained from a sample of 117 patients with a diagnosis of probable or definite AD to assess patterns of regional brain abnormalities as they relate to age at scanning, age at symptom onset, and cognitive test performance.

SUBJECTS AND METHODS

Healthy Control Subjects

The control subjects were recruited from the local community through advertisement and word of mouth and were paid for their participation. All controls were first screened by telephone, and potentially acceptable subjects were then invited to our laboratory for a psychiatric interview and medical examination. Prospective subjects between 20 and 85 years of age were enrolled in the study if they had no history of major psychiatric disorders (as assessed by a psychiatrist using the Schedule for Affective Disorders and Schizophrenia[31]), serious neurologic disease or injury, metabolic dysfunction, electroconvulsive shock treatment, abuse of alcohol or other drugs, or current treatment with psychoactive medications. Additionally, subjects were excluded if their CT scans were technically inadequate for the image analysis procedure. None of these control subjects had participated in our earlier CT imaging studies.[19,20,28,32] Informed consent was obtained from all subjects. The demographic characteristics of the control group (84 men and 30 women) are presented in Table 1.

For some comparisons, only the controls spanning the age range of the patients with AD (aged 55 years and older) were used. This older control group included 34 men and 25 women (Table 1). The men and women did not differ in age or Mini-Mental State Examination (MMSE) score,[33] but the women had fewer years of education than did the men ($F[1,57]=5.37$, $P<.025$).

Patients With AD

The participants included 117 patients (63 men and 54 women) with presumed AD; Table 1 presents their demographic data. The subjects with AD were drawn from a pool of patients examined at the Geriatric Psychiatry Research Unit and National Institute of Mental Health Dementia Clinical Research Center of the Palo Alto (Calif) Department of Veterans Affairs Medical Center. The patients included in this analysis met the National Institute of Neurologic and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association criteria for definite AD (confirmed by autopsy in 11 and by biopsy in one) or probable AD (N=105).[34,35] Since many of these patients had been followed up longitudinally, they were classified for the present study according to their most recent diagnoses. These updated diagnoses reflected changes in the classification of 12 patients from a diagnosis of probable to definite AD; 10 patients from possible to probable; and one patient from questionable

mixed vascular plus AD to probable AD. With the exception of their dementia, the subjects with AD met all of the inclusionary and exclusionary criteria described for the control subjects. All subjects or, when appropriate, their legal representatives signed informed consent forms.

For the analyses based on symptom onset, the subjects with AD were divided into groups with early (N=58) and late (N=46) onset. This classification was made on the basis of whether symptoms of dementia were apparent before the age of 65 years (as reported by the patient and/or an informant). Useful information about disease onset was not available for 13 subjects with AD. Descriptive information for these two onset groups is presented in Table 1. One-way analyses of variance (ANOVAs) revealed that the two onset groups were similar in terms of global cognitive status as assessed by the MMSE; however, at the time of CT scanning, the early-onset group was younger ($F[1,102]=131.0, P<.001$), had a longer duration of illness ($F[1,102]=7.39, P<.01$), and showed a trend toward having completed more education ($F[1,95]=2.99, P<.08$) than the late onset group. A χ^2 analysis indicated that the ratio of men to women was significantly higher in the early-onset than the late-onset group ($\chi^2=5.05, df=1, P<.03$).

CT Scanning

The CT scanning was conducted on two scanners (Picker Synerview model 1200SX, Picker International Inc, Highland Heights, Ohio), which generated images with a 512×512 matrix and a pixel size of 0.47×0.47 mm. Damage from an earthquake in October 1989 necessitated that scans after that date be collected on the second machine; 96 subjects underwent scanning on one scanner and 18 on the second scanner. For each subject, a series of 10 to 15 slices was collected. Each slice was 10 mm thick and was oriented at approximately +10° relative to the canthomeatal line.

Detailed information about the image analysis procedure has been provided previously, including descriptions of the filtering and quantitative data analysis.[19,20] A newly implemented refinement of this analysis was the application of a homomorphic spatial filter as is also used with MRI data.[36] In short, for each scan, an index slice, selected to include the first bilateral appearance of the anterior horns of the lateral ventricles, was identified. The volumetric quantitative data analysis included six slices: the index slice and the five slices rostral to it. Each slice was filtered to reduce spectral shift artifact, and pixels belonging in the skull were stripped from the image with an automated algorithm. After this procedure, trained operators employed a semiautomated, computer-interactive thresholding technique to classify each pixel in the image as representing CSF or tissue and to separate the left and right hemispheres with a midline. Reliability of the measurement was based on a sample of 20 scans from our laboratory's total collection of more than 600 CT scans obtained with the same type of scanner, which were performed on controls as well as patients from a number of different diagnostic groups. Intraclass correlation based on the ratings of three independent operators was .986 for the total CSF pixels in the six scored slices. For the difference in total pixels between the cerebral hemispheres, the intraclass correlation was .996, indicating highly reliable measurements for analyses of volume differences between the hemispheres.

The ROIs

Six ROIs were derived: two general indexes (ventricular system and vertex sulci) and four that were neuroanatomically more circumscribed (frontal sulci, Sylvian fissures, parieto-occipital sulci, and third ventricle). Within each CT slice, a central area was defined to include the inner 55% of the volume; the remaining 45% was defined as a peripheral region. The CSF volume of the *ventricular system* was calculated as the sum of the CSF pixels in central portions of the four lowest slices. Pixels classified as CSF in the peripheral area of the sixth (highest) slice were summed to create the volume of the *vertex sulci*. To calculate the specific regional measures, each slice 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 slices 1 to 4 (selected to encompass CSF-filled spaces in the prefrontal cortex); the *Sylvian fissures*, which included the outer segment of the second quadrant of slices 1 to 2 and provided an estimate of the integrity of the posterior frontal and the lateral temporal lobes; and the *parieto-occipital sulci*, which included the outer segments of the most posterior quadrant of slices 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. The *third ventricle* was measured differently from the ROIs defined above, in that operators drew rectangular boundaries encompassing the third ventricle on the one CT slice determined visually to contain the greatest volume of CSF in the third-ventricular area; this typically coincided with the index slice or the slice superior to it. All CSF pixels falling within the rectangle were included in this ROI. Since the pixels composing the third ventricle were also included in the ventricular system ROI and the same pixels composing the vertex sulcal ROI were included in the parieto-occipital sulcal ROI, all analyses testing differences across ROIs were based on the four nonoverlapping ROIs, ie, exclusive of the third ventricle and vertex sulci. Each ROI is illustrated in Fig 1.

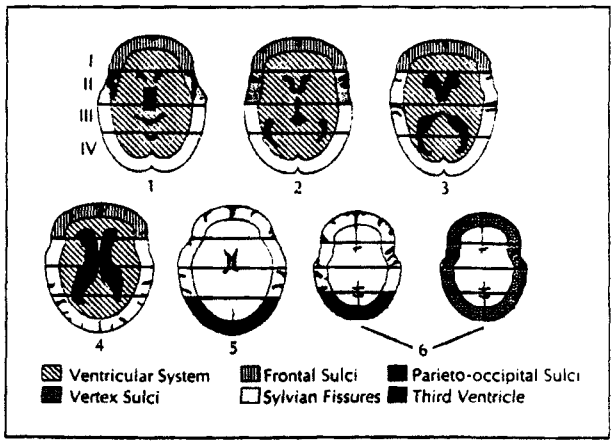

Fig 1.—*Schematic representation of the six regions of interest.*

Cognitive Tests

Both the control subjects and the patients with AD performed the MMSE and Trailmaking Tests A and B.[37] In addition, the control subjects performed seven subtests of the Wechsler Adult Intelligence Scale–Revised (WAIS-R),[38] whereas the patients with AD were administered the entire WAIS.[39] In addition to scoring the MMSE figure (the double pentagon) according to the conventional pass-fail criteria, we devised a novel, 14-point scale in an effort to formulate a more sensitive measure of constructional praxis. The scoring system for this figure took into account spatial orientation and scale of the drawings as well as line quality.

Cognitive data were analyzed only if the tests had been administered within 6 months of the CT scan for the controls and within 3 months of the CT scan for the patients with AD. For the controls, the mean interval between the MMSE and the scan was 19.2±16.7 days and the interval between the remaining tests and the scan was 11.1±17.7 days; for the patients with AD, the mean interval between the MMSE and the scan was 29.4±26.1 days and the interval between the remaining tests and the scan was 28.4±25.5 days. Not all patients could perform all tests; only valid scores are reported here.

Table 2.—Computed Tomographic Scores for Six Regions of Interest (ROI)*

ROI	CSF, Pixels: All Controls (n=114)	CSF, Pixels: Older Controls (n=59)	CSF, Pixels: All Patients With AD (n=117)	CSF, Pixels: Early-Onset AD (n=58)	CSF, Pixels: Late-Onset AD (n=46)	Head Size–Corrected Scores, Pixels: All Controls (n=114)	Head Size–Corrected Scores, Pixels: Older Controls (n=59)	Head Size–Corrected Scores, Pixels: All Patients With AD (n=117)	Head Size–Corrected Scores, Pixels: Early-Onset AD (n=58)	Head Size–Corrected Scores, Pixels: Late-Onset AD (n=46)
Ventricular system	3773.0 (179.46)	4642.8 (273.25)	8059.7 (225.97)	8286.0 (376.19)	7981.8 (297.98)	0 (174.12)	930.0 (257.24)	4355.1 (213.34)	4484.7 (350.64)	4371.7 (287.96)
Third ventricle	83.2 (4.07)	100.6 (6.15)	159.1 (4.83)	157.1 (7.22)	159.6 (7.57)	0 (4.07)	17.4 (6.15)	75.9 (4.83)	73.9 (7.21)	76.5 (7.56)
Vertex sulci	301.0 (21.72)	422.5 (30.66)	729.9 (29.99)	748.4 (44.4)	715.7 (43.35)	0 (21.69)	119.8 (30.86)	427.0 (30.09)	448.2 (44.63)	409.9 (43.08)
Frontal sulci	499.6 (33.53)	681.1 (51)	1180.9 (41.72)	1228.8 (63.09)	1124.7 (58.76)	0 (33.39)	185.8 (50.03)	686.1 (41.72)	727.7 (63.1)	636.6 (59.28)
Sylvian fissures	165.4 (13.82)	244.9 (20.92)	551.2 (22.06)	556.0 (35.14)	526.3 (29.79)	0 (13.75)	81.3 (20.56)	387.9 (21.76)	389.7 (34.69)	365.9 (29.4)
Parieto-occipital sulci	155.6 (12.08)	208.7 (18.22)	398.3 (20.53)	420.8 (31.6)	378.4 (29.96)	0 (11.86)	50.0 (18.14)	239.2 (20.57)	266.7 (31.8)	214.3 (29.43)

*Values are mean (SE). For all comparisons, both AD groups had significantly greater cerebrospinal fluid volumes than did the older control group (P=.0001). The computed tomographic z scores of the early-onset AD group were greater than those of the late-onset AD group.
†$P \leq .01$. ‡$P \leq .05$. §$P \leq .001$. ‖$P \leq .0001$.

Statistical Analysis

The raw CSF pixel counts in the six ROIs of each subject were converted to standardized scores by means of a two-step regression procedure designed to correct for individual variation in head size and to take into account the variations due to normal aging. First, the CSF volume in each ROI was regressed on the total intracranial volume of the six slices (ie, the sum of all CSF and tissue pixels in the full series of analyzed image slices) in the normal control group. The residuals from this series of linear regressions represented CSF volume for each ROI after correcting for normal variation in head size as estimated from the volume of the six slices. In the second step, a quadratic regression was applied to the head size–residualized scores across the adult age range of the normal control group, providing a model for age-related changes that are independent of head size. Age-related changes in the volume of the Sylvian fissure measure were found to be most accurately modeled with a cubic function, while effects of normal aging on the remaining five ROIs were represented well by quadratic functions.

To model normal aging 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 neuroanatomic correlates of normal aging (eg, *increases* in the predicted CSF volumes of young 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.[40] This cutoff was selected on the basis of pathologic evidence that adult brain weights are substantially achieved by approximately the age of 10 years.[41]

Second, the accurate calculation of predicted CSF volume at any given age is confounded by the considerable heteroscedasticity of obtained volumes across the lifespan (ie, there is greater variance in the obtained CSF volumes of older subjects relative to younger individuals[17-21]). With the use of a modification of Glejser's test for heteroscedasticity,[42] an age-specific estimate was made of the SD in the ROI CSF volume for all ages 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 five of the six 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 controls' data before the patients' data were examined.

Finally, for both patients and controls, each subject's CSF volumes on individual ROIs 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.

RESULTS

CT Findings in Healthy Control Subjects

The mean CSF volumes for the six ROIs in the normal control group are presented in Table 2, expressed both as raw pixel counts and as head size–residualized scores. By definition, the scores for the controls averaged approximately 0 on all of the CT indexes expressed as head size–residualized scores and age-corrected z scores. Figure 2 displays the head size–residualized scores of the 114 controls plotted against age. The most obvious feature of these non–age-corrected data is the highly significant increase in CSF-filled spaces with aging in all six ROIs. The correlations between age and the head size–residualized scores were as follows: for the vertex sulci, r=.58; for the frontal sulci, r=.64; for the Sylvian fissures, r=.69; for the parieto-occipital sulci, r=.43; for the ventricular system, r=.65; and for the third ventricle, r=.49 ($P \leq .0001$ in all cases).

For subjects in the older normal control group, a series of analyses was conducted to examine the relationship between the age-corrected z scores and demographic variables, including sex, years of education, and MMSE score. First, because the z scores were based on a single age regression for both men and women, a multivariate analysis of variances was computed with the four nonoverlapping ROI z scores as dependent measures and sex as a grouping variable. With the use of Wilks' criterion, this analysis did not identify a significant main effect for sex (F[4,54]=1.52, not significant), suggesting that sex was not an important mediating variable in the CT results for the

Age-Corrected z Scores		
All Patients With AD (n=117)	Early-Onset AD (n=58)	Late-Onset AD (n=46)
2.196 (0.16)	2.731 (0.257)	1.665† (0.1921)
1.262 (0.117)	1.487 (0.18)	0.95‡ (0.167)
1.353 (0.15)	1.766 (0.22)	0.888† (0.197)
1.443 (0.143)	1.937 (0.24)	0.845§ (0.182)
2.513 (0.232)	3.363 (0.347)	1.283‖ (0.238)
1.470 (0.174)	1.924 (0.267)	0.977† (0.227)

older normal control subjects on these four ROIs. Similarly, the vertex sulci did not show a significant effect of sex ($F[1,57]=0.19$, not significant). For the third ventricle, however, the women had significantly lower z scores than did the men ($F[1,57]=8.24$, $P=.006$). There were no significant correlations between any of the six ROI z scores and either years of education or total MMSE score in the control subjects.

CT Findings in Patients With AD

The raw CT data of each patient with AD were converted to head size– and age-corrected z scores derived from the CT values of the total control group to investigate disease-related changes independent of the normal age-related changes. In the following analyses, the presence, magnitude, and location of age-corrected brain volume abnormalities were investigated in the patients with AD through comparisons with the older control group. The raw pixel counts, head size–residualized scores, and age-corrected z scores are presented in Table 2 for the AD and older normal control groups for the six ROIs. The head size–residualized scores of the individual patients with AD are plotted against age in Fig 3 for the six ROIs.

To investigate differences between the AD and control groups, a 2×4 repeated-measures ANOVA was performed on the age-corrected CSF volume z scores across the four nonoverlapping ROIs (ventricular system, frontal sulci, Sylvian fissures, and parieto-occipital sulci). As anticipated, the subjects with AD had significantly greater CT z scores overall relative to the controls ($F[1,174]=102.7$, $P<.001$). The ROI effect was significant ($F[3,174]=5.14$, $P<.002$). Post hoc comparisons confirmed that the AD group had significantly greater CSF volumes in each ROI ($P<.0001$ for all four comparisons). In addition, the repeated-measures ANOVA revealed a significant group×ROI interaction ($F[3,174]=6.11$, $P<.001$), indicating that while the patients with AD demonstrated significant increases in CSF for all four ROIs, some ROIs showed more marked abnormality than others. Post hoc comparisons with paired *t* tests performed on the age-corrected z scores revealed that the Sylvian fissures and the ventricular system showed significantly greater abnormality than the frontal and the parieto-occipital sulci ($P=.0001$ for all comparisons except the ventricular system vs parieto-occipital sulci, where $P=.0009$) but did not differ from each other.

Table 3 presents the matrix of simple correlations for the CT indexes and demographic variables in the AD group. The MMSE scores were significantly and negatively correlated ($P\leq.0002$) with CT z scores of the ventricular system, Sylvian fissures, and frontal sulci. (Lower MMSE scores reflect greater impairment.) In contrast, neither reported duration of disease nor years of education correlated significantly with any CT z score. Even after accounting for the effects of normal aging, the CT z scores for all six ROIs were strongly and negatively correlated with age at scanning; that is, greater CSF volumes were associated with *younger* age (Fig 4).

Early-Onset vs Late-Onset AD

In keeping with the extensive existing literature that focuses on early-onset vs late-onset AD, we dichotomized our subjects for selected analyses into two groups based on reported age at symptom onset. In relating the present analyses of onset groups to those reported above for age at scanning, it is noteworthy that 26 of the 48 patients in the early-onset group underwent scanning at age 65 years or older (ie, when their age at scanning fell into the range most characteristic of the late-onset group). Thus, while the information provided by analysis of onset age overlaps considerably with that derived from data from age at scanning, the two classification schemes are not identical.

We examined potential differences in the pattern of CSF increases exhibited by patients with early compared with late disease onset by means of a repeated-measures ANOVA. Since the proportions of men and women were significantly different in the two onset groups, onset age and sex were both used as grouping factors; the four nonoverlapping ROIs served as the within-subject factor. Even when age-corrected z scores were used to take the effects of normal aging into account, there was a significant main effect for onset age, with the early-onset group demonstrating larger CSF volumes than the late-onset group ($F[1,100]=25.68$, $P<.0001$). Thus, this group effect reflected greater abnormality in the patients in the early-onset than the late-onset group relative to healthy controls of their age. In addition, the main effect for ROI ($F[3,100]=10.48$, $P<.0001$) and the ROI×onset group interaction ($F[3,100]=3.33$, $P=.02$) were significant. Post hoc paired *t* tests revealed that the CT volumes of the early-onset group were greater for the Sylvian fissures and the ventricular system than for the frontal or parieto-occipital sulci, whereas the increased CSF observed in the late-onset group was equivalent across all ROIs (Fig 5). Thus, the earlier finding in the total group of patients with AD of disproportionate enlargement of the Sylvian fissures and ventricular system is likely to be attributable to the patients with early onset.

Of the main effect of sex, the sex×onset group interaction, and the sex×ROI interaction, none was significant. However, the three-way interaction (ROI×sex×onset group) was statistically significant ($F[3,100]=3.02$, $P<.03$). Follow-up comparisons were performed to parse this three-way interaction. When the ROIs were considered individually, a significant main effect for onset group (with patients in the early-onset group more impaired than those

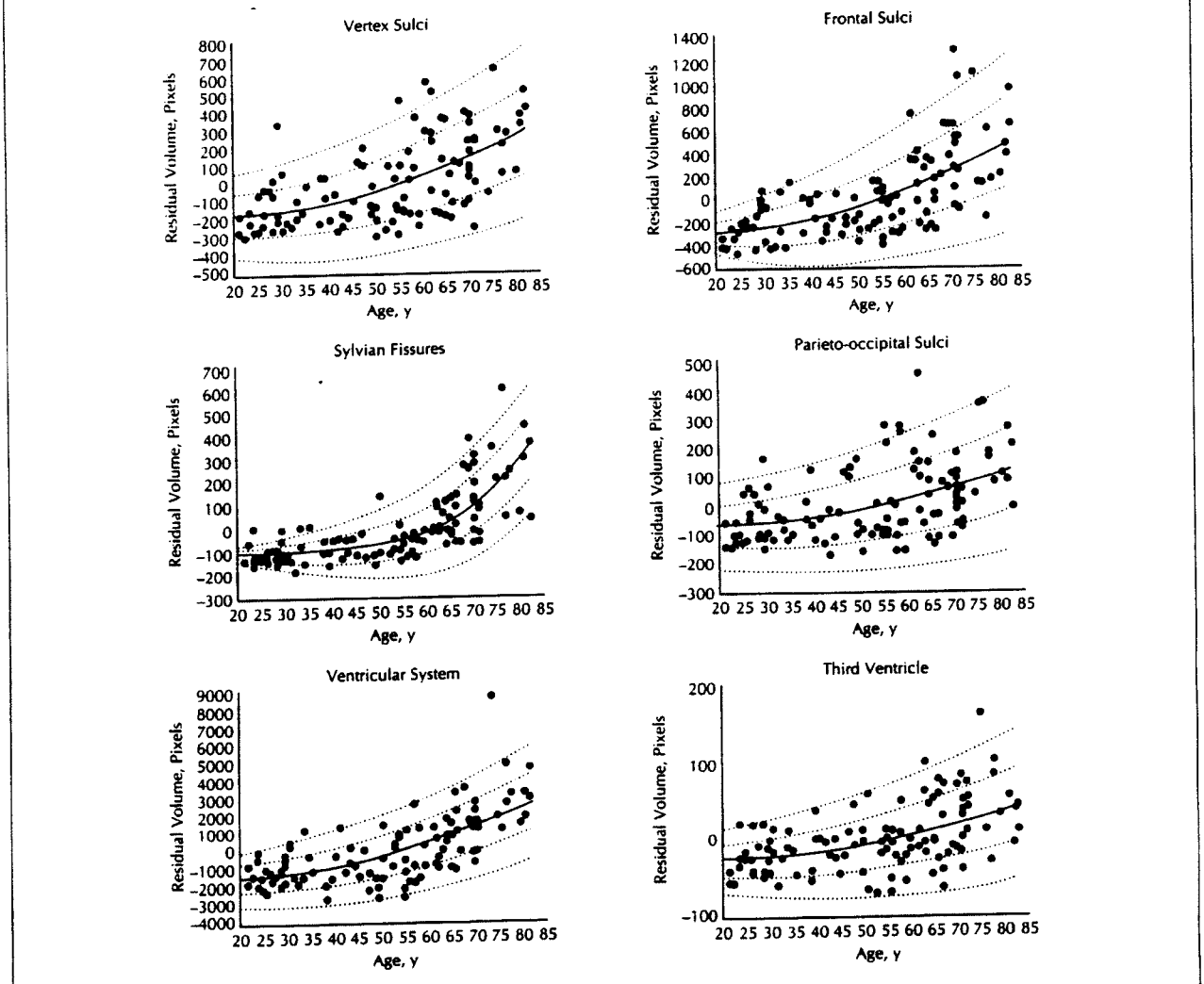

Fig 2.—*Head size–residualized scores of the 114 normal control subjects plotted against age (solid lines, expected mean; dotted lines, 1 and 2 SDs of the normal control subjects). Cerebrospinal fluid volume increased significantly with age in all six regions of interest.*

in the late-onset group) was present in the frontal sulci ($P<.001$), Sylvian fissures ($P<.001$), parieto-occipital sulci ($P<.04$), and ventricular system ($P<.01$). For three of the four ROIs, there was no significant interaction between sex and onset group, reflecting the fact that both men and women showed the expected onset-group differences (ie, women in the early-onset group were relatively more impaired than those in the late-onset group and men in the early-onset group were relatively more impaired than those in the late-onset group). On the parieto-occipital measure, however, this pattern occurred only in the men, which was reflected in a significant sex×onset group interaction for this ROI ($P<.01$). This sex interaction, however, was not present in the ROIs showing the most prominent elevations in the ROI profile in the early-onset group, namely the Sylvian fissure and the ventricular system. For the third ventricle, an ANOVA revealed that the early-onset group tended have larger CSF z scores than the late-onset group ($F[1,100]=3.14$, $P<.08$), but neither sex ($F[1,100]=1.69$, not significant) nor the sex×onset group interaction ($F[1,100]=.04$, not significant) was significant. The ANOVA for the vertex sulci showed the expected onset-group difference ($F[1,100]=5.99$, $P<.02$) as well as a sex×onset group interaction ($F[1,100]=4.20$, $P<.05$).

For each ROI, an analysis of covariance was used to test whether the onset-group differences would endure once disease duration and severity (as reflected by the MMSE scores) were taken into account. In each case, the relatively greater impairment in the early-onset group persisted (for frontal sulci and Sylvian fissures, $P<.001$; for the ventricular system, $P<.002$; for the vertex sulci, $P<.003$; for the parieto-occipital sulci, $P<.01$; and for the third ventricle, $P<.03$).

Differences in the onset of AD have traditionally been examined by means of non–age-corrected brain data. When we conducted a repeated-measures ANOVA on our non–age-corrected brain data (ie, raw pixel counts and head size–corrected pixel counts), no significant effects for group, sex, or their interaction emerged. These results underscore the importance of taking the effects of normal ag-

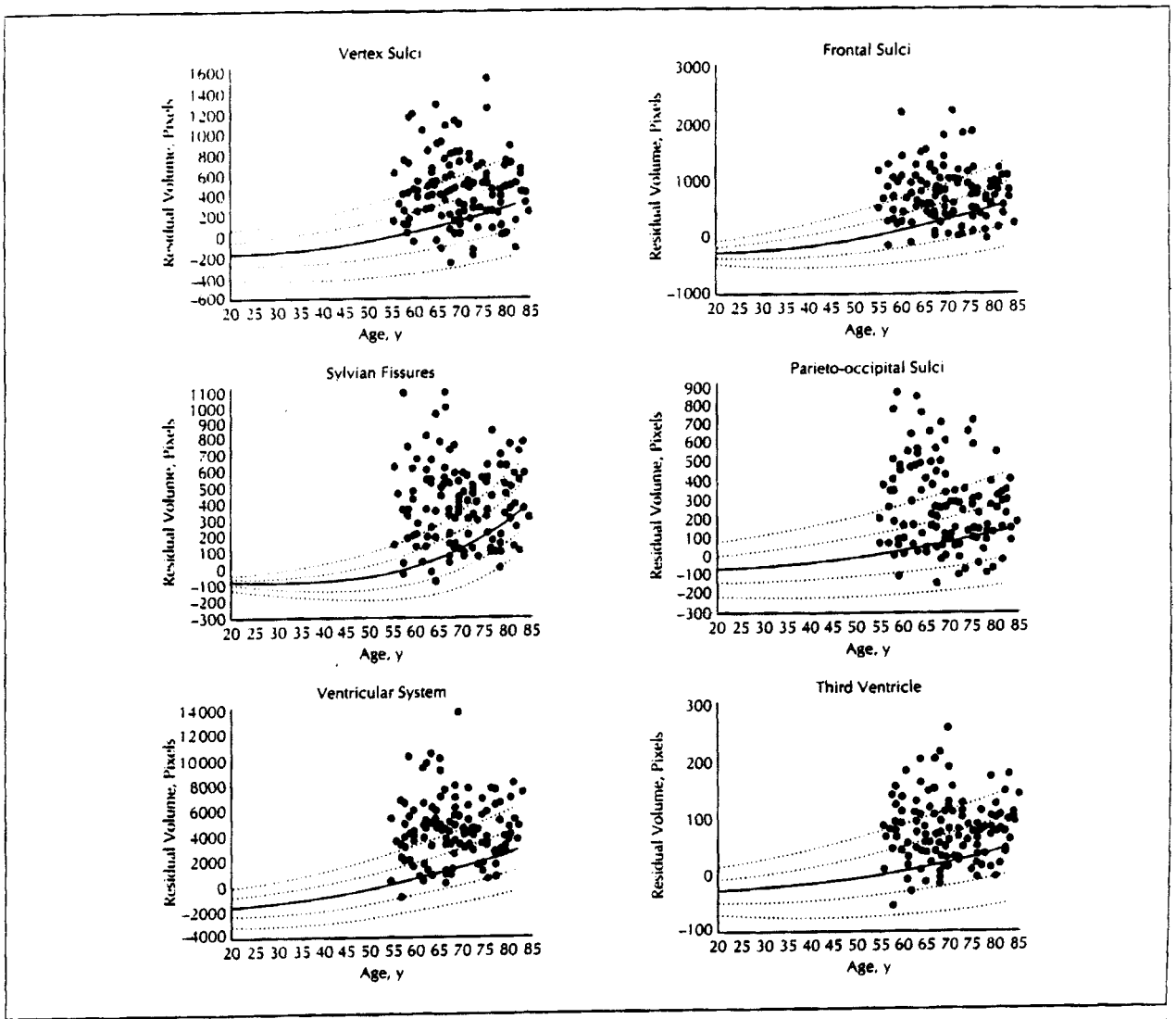

Fig 3.—*Head size–residualized scores of the 117 patients with Alzheimer's disease plotted against age at computed tomographic scanning (solid lines, expected mean; dotted lines, 1 and 2 SDs of the normal control subjects). The entire scatter of cerebrospinal fluid volume estimates in the patients with Alzheimer's disease was raised significantly above the expected values of the controls in each region of interest.*

Table 3.—Correlations (*r* and *P* Values) of Demographics Variables With Computed Tomographic (CT) *z* Scores for Each Region of Interest for the Patients With Alzheimer's Disease (AD)*

	Ventricular System	Vertex Sulci	Frontal Sulci	Sylvian Fissures	Parieto-occipital Sulci	Third Ventricle
Age at CT scan	−.36 .0001	−.39 .0001	−.44 .0001	−.52 .0001	−.35 .0001	−.31 .0006
Age at AD symptom onset	−.30 .003	−.35 .0002	−.39 .0001	−.44 .0001	−.29 .003	−.29 .004
Symptom duration	−.10 NS	−.07 NS	−.10 NS	−.09 NS	−.05 NS	−.03 NS
MMSE	−.35 .0002	−.01 NS	−.37 .0001	−.37 .0001	−.03 NS	−.07 NS
Education	.11 NS	.13 NS	−.03 NS	.05 NS	.10 NS	.16 NS

*MMSE indicates Mini-Mental State examination; NS, not significant.

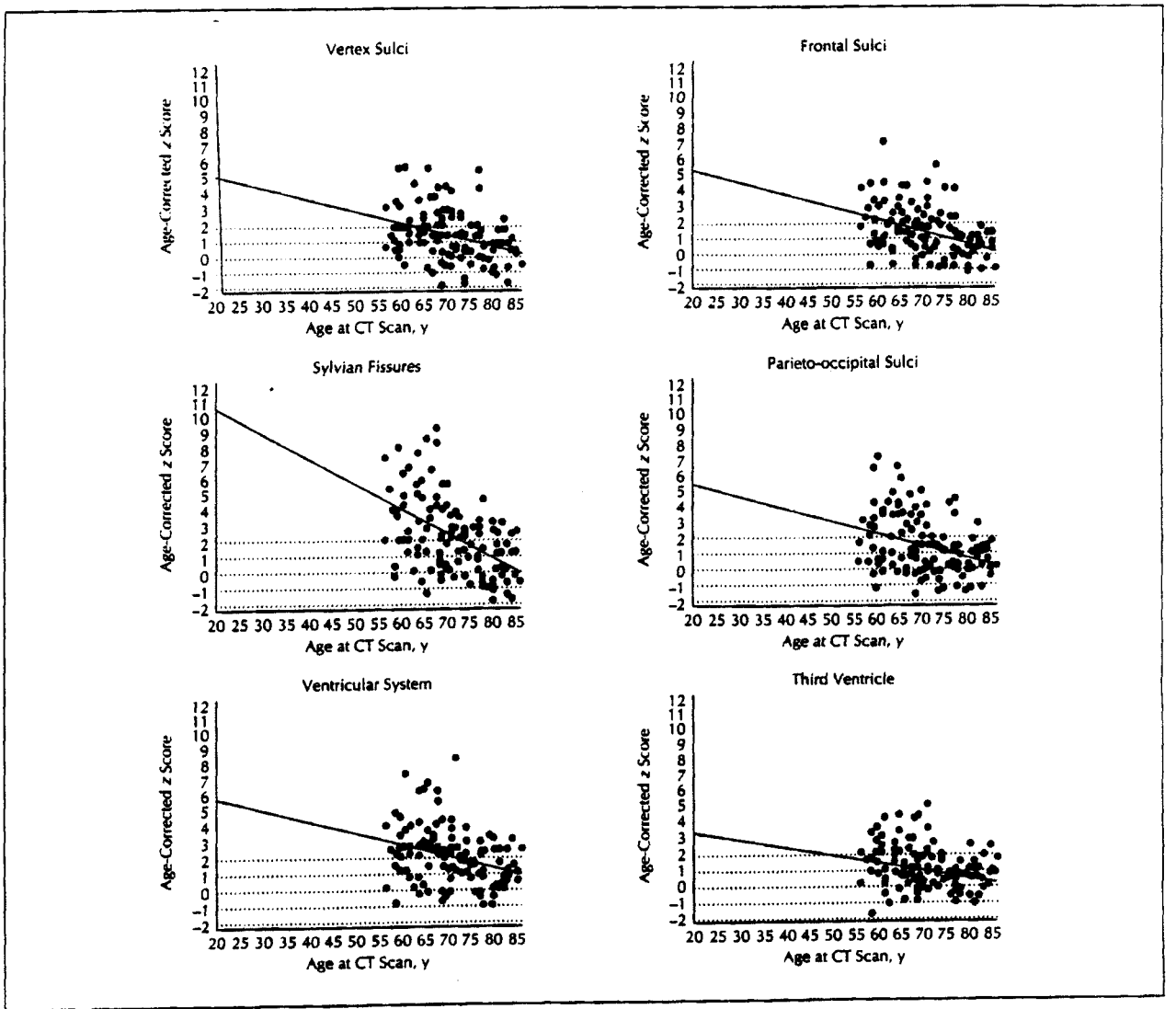

Fig 4.—*Age-corrected computed tomographic (CT) z scores of the 117 patients with Alzheimer's disease plotted against age at CT scanning (solid lines, expected mean; dotted lines, 1 and 2 SDs of the normal control subjects). Despite the age correction, age correlated significantly with CT z scores for each region of interest, indicating that the younger patients with Alzheimer's disease had greater cerebrospinal fluid increases for their age than did the older patients with Alzheimer's disease.*

ing into account when assessing differences in early-onset vs late-onset AD.

Other studies have suggested that the two cerebral hemispheres may be compromised differentially in presenile dementia (reviewed by Jagust et al[8]). To investigate this possibility, we asked whether the early-onset or late-onset AD groups showed disproportionate lateral asymmetry relative to the older control group. A repeated-measures ANOVA was calculated for each lateralized ROI (all ROIs except the third ventricle). The raw pixel counts for total CSF in each hemisphere served as the within-subjects measures; the between-subjects factor included three groups, namely, the older controls and the two AD-onset groups. We hypothesized that disproportionate asymmetries in the AD groups as compared with the control group would be reflected in significant group×hemisphere interactions. However, no significant group×hemisphere interactions were obtained in this analysis, suggesting that increased CSF in the patients with AD did not systematically affect one cerebral hemisphere disproportionately relative to the controls. In addition, these data did not provide evidence for differential lateral asymmetry between the two AD-onset groups.

The above analyses established that when the traditional cutoff age of 65 years is used to dichotomize the continuous measure of age at symptom onset, significant differences are apparent between the early- and late-onset groups in terms of the severity and regional pattern of CSF volume abnormalities. This result would be expected given the negative correlations of the brain measures with age at scanning. When age at onset is treated as a continuous variable in correlational analyses with the CT z scores, the same early- vs late-onset differences emerged as significant negative correlations, with earlier onset associated with greater age-corrected CSF volumes (Table 3 and Fig 5). Thus, it is not clear whether the age of 65 years simply

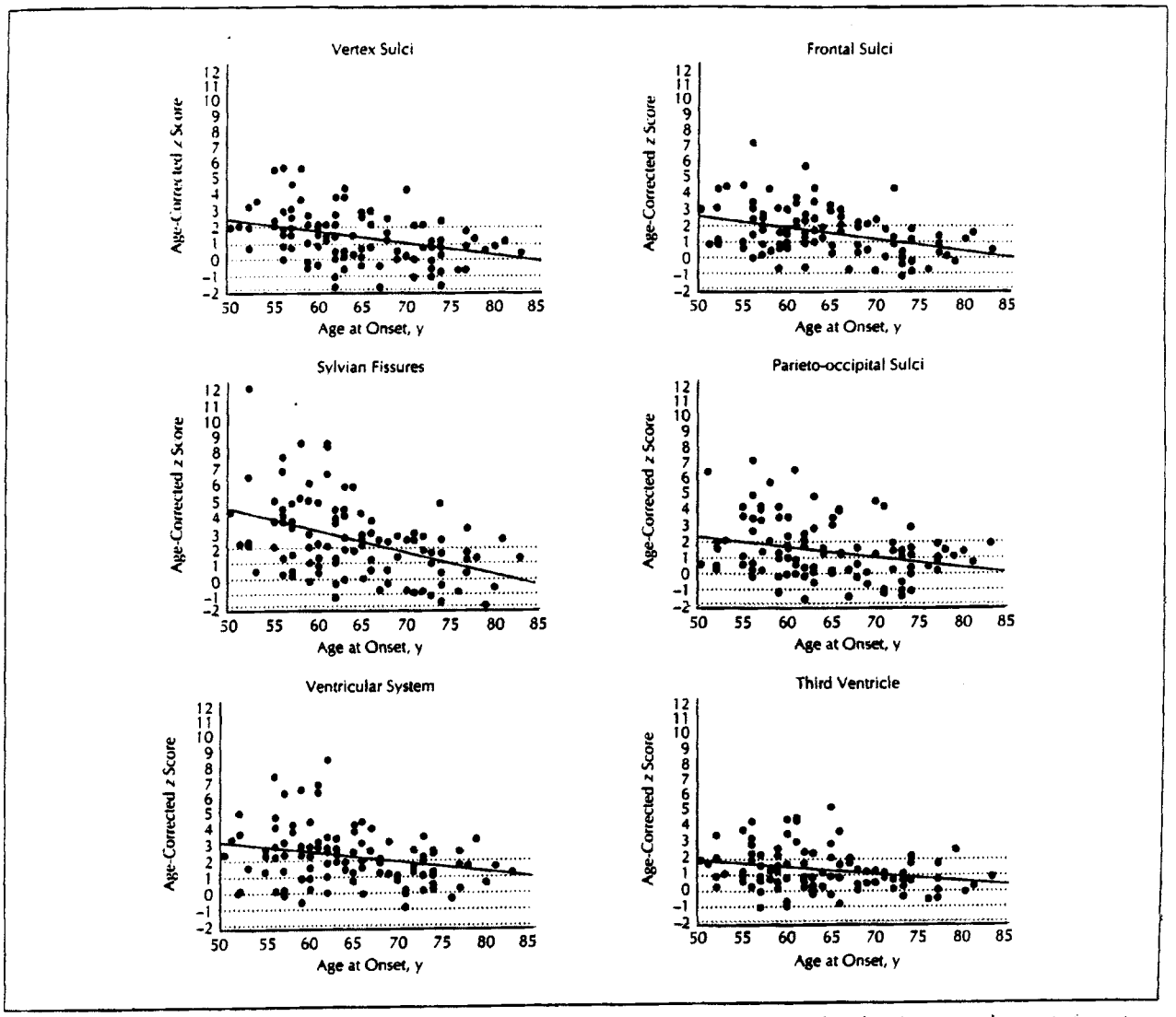

Fig 5.—*Age-corrected computed tomographic z scores of the 104 patients with Alzheimer's disease plotted against age at the onset of symptoms of Alzheimer's disease (solid lines, expected mean; dotted lines, 1 and 2 SDs of the normal control subjects). Despite the age correction, age at symptom onset correlated significantly with computed tomographic z scores for each region of interest, indicating that the patients with early onset of Alzheimer's disease had greater cerebrospinal fluid increases for their age than did the patients with later onset.*

represents an arbitrary cutoff on an underlying continuum of disease across all levels of onset age or whether the obtained differences between early- and late-onset groups reflects an underlying discontinuity in the distribution of onset age–related pathologic CT changes. Since no single statistical criterion exists that would definitively establish the presence of such a discontinuity, we explored the data distribution from several perspectives.

A discriminant function analysis was used to generate a weighted linear composite of the four nonoverlapping ROI z scores (frontal and parieto-occipital sulci, ventricular system, and Sylvian fissures) that maximally discriminated the two onset groups. The resulting discriminant function (ie, the composite measure) reflected a continuous dimension of age-corrected CSF volume abnormality, with the patients in the early-onset group showing greater CSF volume for their age than those in the late-onset group. The discriminant function scores were saved and used as the dependent measure in the analyses that follow. The frequency distributions of the discriminant function scores are presented separately for the early- and late-onset groups in Fig 6.

We speculated that bimodality in the CT results for the two onset groups would potentially be reflected in a bimodal distribution of the discriminant function scores.[43] Visual inspection of the frequency histograms of these scores suggested no obvious bimodality or point of rarity. The late-onset group did show a modal value, with some tapering of frequency near the zero point of the discriminant function. However, the early-onset group was evenly spread over a wide range of values, with no obvious tapering of frequency in the range of scores characterizing the late-onset groups. Reflecting this overlap of the distributions, the discriminant function analysis correctly classified 78.3% of the late-onset cases but only 67.2% of the early-onset cases.

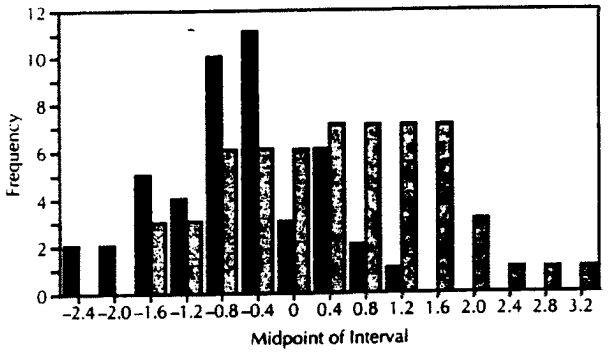

Fig 6.—*Frequency histogram of discriminant function scores for the early-onset (solid bars) and late-onset (shaded bars) Alzheimer's disease groups.*

The difficulty in correctly classifying a number of early-onset cases led us to assess the possibility that the variances of the CSF volumes decreased systematically as age at onset increased. This approach is consistent with the suggestion that age-related variability is an important consideration in geriatric research.[44] Accordingly, for each ROI z score, we looked for changes in variance at different ages at symptom onset by means of Glesjer's test of heteroscedasticity.[42] For each ROI, this test involved regressing the ROI z score on the continuous age at onset variable, saving the absolute value of the residuals, and then correlating these absolute residuals with age at onset. Systematic changes in the variance across onset levels would be reflected in significant correlations. These analyses revealed that for all ROIs except the vertex sulci, a younger age at onset was associated with greater variability in the ROI scores than was an older age at onset (for the Sylvian fissures and parieto-occipital sulci, $P<.02$; for the frontal sulci and third ventricle, $P<.02$; for the ventricular system, $P<.04$).

The analysis of the linear relationship between age at onset and ROI variances does not address the question of whether the variance changed in a discontinuous fashion around the onset group cutoff of 65 years of age. We believed that such a discontinuity would be reflected in a significant nonlinear relationship between the ROI variances and onset age. Therefore, we used hierarchic polynomial analyses to test for the presence of quadratic trends in the data. No significant higher-order effects were identified for any of the six ROIs. Overall, these analyses provided little support for the notion that the early-late dichotomy reflected an underlying discontinuity, or that these groups represented discrete entities.

Cognitive Test Performance of Healthy Control Subjects and Patients With AD

The cognitive test scores of the control and AD groups are presented in Table 4. Because the two groups received different forms of the WAIS, their scores were not directly comparable. On the seven WAIS-R subtests given, the age-corrected scaled scores of the control group were well above average. By contrast, in five of the 11 WAIS subtests, the total AD group achieved age-scaled scores that, by convention, would be considered in the impaired range (ie, below 8). Most of the subtests showing relative sparing were from the Verbal Scale. The AD performance on Trail-Making Tests A and B and on the MMSE figure could be directly compared with that of the older controls, who also performed these tests. The scores of the AD group (Table 4) were significantly poorer than those of the control group for these three measures ($P=.0001$).

When the AD group was divided on the basis of age at disease onset, the early-onset group performed significantly worse than did the late-onset group on seven WAIS subtests based on age-scaled scores, the three IQ summary scales, and Trail Making Test B (Table 4). In no case was the score of the late-onset group significantly worse than that of the early-onset group.

CT-Behavior Relationships in Healthy Control Subjects and Patients With AD

Brain-behavior relationships were examined by correlating the cognitive test scores with the CT z scores from the four anatomically circumscribed ROIs (frontal sulci, Sylvian fissures, parieto-occipital sulci, and third ventricle). We expected that greater CSF volumes would be related to poorer cognitive test scores. Thus, we predicted negative correlations for all relationships except Trail Making Test A and B, for which low scores reflect good performance and positive correlations were expected. These correlations were based on age-scaled WAIS or WAIS-R subtest scores. Age-corrected scores were used to minimize the influence of age on performance, which would otherwise act as a suppressor variable with the result of attenuating the brain-behavior correlations.

The controls showed only two CT–cognitive test score correlations among 40 (Table 5) that approached significance: frontal sulcal and third-ventricular z scores with Digit Symbol age-scaled scores. Standard multiple regression analyses were used to test the specificity of these two relationships. When the contribution of the remaining three nonoverlapping ROIs was partialed out, neither the semipartial correlation for the frontal ROI nor that for the third-ventricular ROI was significant; that is, neither ROI had a significant unique association with the Digit Symbol score.

Of the 56 correlations, 53 were in the expected directions. Of these bivariate correlations, 16 were significant at the .01 level (Table 6). To test the specificity of each significant correlation, the contribution of the remaining three ROIs was partialed out with standard multiple regression analyses. This procedure revealed seven specific CT-cognitive semipartial correlations significant at the .05 level. In particular, frontal sulcal z scores correlated uniquely with Picture Arrangement and Trail Making Test A; Sylvian fissure z scores correlated uniquely with Digit Symbol, Block Design, Object Assembly, and the MMSE figure; and parieto-occipital sulci correlated uniquely with Object Assembly.

Age at Scanning vs Age at Onset

Our analyses revealed significant associations between brain CSF values and both onset age and age at scanning. Although these two age variables were highly related ($r=.89$, $P<.001$), they were not identical. Therefore, we performed a series of calculations to determine the relative predictive importance of these two measures.

Table 7 presents the correlations of age at scanning and age at onset with those cognitive variables that had previously revealed onset-group differences significant at the $P<.01$ level; in other words, these variables were observed to be important to the traditional subgrouping of patients with AD on the basis of onset. A comparison of correlations

Table 4.—Cognitive Test Scores for the Control (≥55 Years Old) and Alzheimer's Disease (AD) Groups*

Test	Older Controls	Total AD	Early-Onset AD	Late-Onset AD	Early<Late P≤
WAIS Age-Scaled Scores†					
Information	13.4	8.4	8.9	8.7	NS
	(0.33)	(0.48)	(0.51)	(0.85)	
	54	46	20	18	
Comprehension	. . .	10.3	9.8	11.5	NS
		(0.67)	(0.90)	(0.94)	
		50	22	19	
Arithmetic	. . .	7.0	5.6	8.7	.002
	. . .	(0.47)	(0.58)	(0.75)	
		50	22	19	
Similarities	. . .	9.5	9.9	10.4	NS
		(0.60)	(0.72)	(1.04)	
		50	22	19	
Digit Span	11.6	8.9	7.5	10.3	.015
	(0.40)	(0.55)	(0.73)	(0.79)	
	54	50	22	19	
Vocabulary	13.2	11.7	11.7	12.3	NS
	(0.26)	(0.48)	(0.59)	(0.77)	
	55	47	21	19	
Digit Symbol	12.7	6.7	4.8	9.0	.0025
	(0.29)	(0.65)	(0.84)	(1.05)	
	54	65	31	25	
Picture Completion	12.1	8.3	6.9	10.3	.02
	(0.30)	(0.62)	(0.84)	(1.04)	
	55	50	22	19	
Block Design	13.4	5.9	4.4	8.0	.007
	(0.36)	(0.61)	(0.83)	(0.95)	
	54	56	27	22	
Picture Arrangement	. . .	6.6	4.8	9.2	.0004
		(0.60)	(0.81)	(0.79)	
		47	21	18	
Object Assembly	12.4	7.8	6.5	9.9	.015
	(0.40)	(0.61)	(1.09)	(0.63)	
	54	46	21	18	
Verbal IQ	. . .	95.9	91.0	104.9	.04
		(3.06)	(4.72)	(4.29)	
		49	22	18	
Performance IQ	. . .	83.9	77.1	98.4	.0012
		(3.00)	(3.95)	(4.4)	
		44	22	15	
Full Scale IQ	. . .	93.3	89.0	102.3	.05
		(3.14)	(4.68)	(4.23)	
		44	21	16	
Trail Making A, s	38.4	109.7	119.0	105.7	NS
	(2.21)	(8.73)	(12.52)	(13.82)	
	55	51	22	24	
Trail Making B, s	89.9	245.7	272.8	220.6	.05
	(7.45)	(12.54)	(14.32)	(20.1)	
	55	39	18	19	
MMSE figure (maximum score, 14)	12.2	7.5	6.7	8.3	NS
	(0.22)	(0.52)	(0.77)	(0.84)	
	55	79	37	32	

*Values are mean (SE), number in descending vertical order. NS indicates not significant; MMSE, Mini-Mental State examination.
†Controls received the Wechsler Adult Intelligence Scale–Revised (WAIS-R), and the patients with AD received the WAIS; thus, the scores were not directly comparable.

between ages at scanning and onset with CT appears in Table 3. The correlations with age at scanning were relatively larger than those with age at disease onset for every variable.

To examine the unique contributions of the two age variables to the prediction of this subset of brain and cognitive variables, a series of standard multiple regressions was performed. On each dependent measure, we examined the significance of the semipartial correlations for the two age variables (ie, the unique predictive significance of one variable after partialing out variance shared with the other age measure). The results of these analyses (summarized in Table 8) revealed that on every CT and cognitive measure selected for multiple regression analysis, age at scanning contributed significantly to the prediction of the dependent measure, above and beyond the variance predicted by onset age. In contrast, once age at scanning was accounted for, age at disease onset did not significantly contribute to the prediction of any of the dependent measures other than Block Design ($P<.06$). Together, these findings suggest that despite the high correlation between the two age measures, age at scanning was a stronger predictor of both brain and behavioral data than was age at disease onset.

Table 5.—Correlations of Computed Tomographic *z* Scores With Behavioral Tests in the Patients With Alzheimer's Disease*

	Frontal Sulci	Sylvian Fissure	Parieto-occipital Sulci	Third Ventricle
Information† (n=46)	−.29 NS	−.33 .03	−.08 NS	−.07 NS
Comprehension (n=50)	−.32 .03	−.25 NS	−.10 NS	−.04 NS
Arithmetic (n=50)	−.43 .002	−.37 .008	−.29 .04	−.03 NS
Similarities (n=50)	−.19 NS	−.26 NS	−.08 NS	−.12 NS
Digit Span (n=50)	−.33 .025	−.24 NS	−.29 .04	−.04 NS
Vocabulary (n=47)	−.22 NS	−.30 .05	−.09 NS	−.16 NS
Digit Symbol (n=65)	−.40 .001	**−.43** **.0003**	−.27 .03	−.02 NS
Picture Completion (n=50)	−.25 NS	−.40 .005	−.32 .025	−.10 NS
Block Design (n=56)	−.49 .0001	**−.48** **.0002**	−.40 .003	−.01 NS
Picture Arrangement (n=47)	**−.48** **.0007**	−.40 .006	−.30 .04	.00 NS
Object Assembly (n=47)	−.35 .02	**−.51** **.0003**	**−.55** **.0001**	−.07 NS
Trails Making A (n=51)	**.50** **.0002**	.28 .05	.35 .015	−.04 NS
Trail Making B (n=39)	.42 .008	.41 .009	.27 NS	.13 NS
MMSE Figure (n=79)	−.25 .025	**−.35** **.002**	−.19 NS	−.12 NS

*Values are *r* and *P* values. NS indicates not significant; MMSE, Mini-Mental State examination. Boldface type indicates that the partial correlation coefficient is significant ($P<.05$), after removing the variance shared with the remaining three regions of interest.

†Wechsler Adult Intelligence Scale age-scaled scores were used in these correlations.

Table 6.—Correlations of Computed Tomographic *z* Scores With Behavioral Tests in the Control Subjects*

	Frontal Sulci	Sylvian Fissure	Parieto-occipital Sulci	Third Ventricle
Information† (n=54)	.12 NS	.01 .NS	.13 NS	.17 NS
Digit Span (n=54)	−.09 NS	.25 NS	.08 .NS	.05 NS
Vocabulary (n=55)	.13 NS	.07 .NS	.12 NS	.08 NS
Digit Symbol (n=54)	−.28 .04	−.18 NS	−.05 NS	−.30 .03
Picture Completion (n=55)	−.19 NS	−.04 NS	−.03 NS	−.05 NS
Block Design (n=54)	−.13 NS	.03 NS	.09 NS	.03 NS
Object Assembly (n=54)	−.18 NS	−.10 NS	.05 NS	.21 NS
Trail Making A (n=55)	.16 NS	−.11 NS	−.01 NS	.08 NS
Trail Making B (n=55)	.07 NS	−.14 NS	−.02 NS	−.10 NS
MMSE Figure (n=55)	−.13 NS	−.15 NS	.05 NS	−.23 NS

*Values are *r* and *P* values. NS indicates not significant; MMSE, Mini-Mental State examination.

†Wechsler Adult Intelligence Scale Revised age-scaled scores were used in these correlations. Bonferroni correction for 40 correlations (with $\alpha=.05$), $P=.001$.

Table 7.—Pearson Product-Moment Correlations

WAIS Age-Scaled Scores*	Scan Age		Onset Age	
	r	*P*	*r*	*P*
Arithmetic	.59	.0001	.47	.0020
Digit Symbol	.52	.0001	.44	.0006
Block Design	.55	.0001	.39	.0052
Picture Arrangement	.54	.0001	.45	.0041

*WAIS indicates Wechsler Adult Intelligence Scale.

COMMENT

This study replicates, with a new control sample and with a different CT scanner model and acquisition protocol (10-mm- rather than 8-mm-thick slices), our earlier reports of significant enlargement of brain CSF-filled spaces with normal aging.[19,20] As before, the variance also increased with age in the control group. The overall degree of change across the sampled age range was estimated by comparing the predicted CSF values for a 20-year-old of average head size with the predicted values for an 80-year-old. The increase in CSF volume with age in this cross-sectional analysis differed markedly from region to region and ranged from a twofold enlargement in the third ventricle to a ninefold enlargement in the Sylvian fissures. The remaining increases were approximately three times for the parieto-occipital sulci and the ventricular system and five times for the frontal and vertex sulci. These increases in CSF volume over this 60-year age span are largely in keeping with findings of our previous CT study.[20] The CT results were not related to sex differences, although other studies have reported sex differences in age-related brain changes (eg, Gur et al[45]); the discrepancy in the findings may well be attributable to sampling differences.

This quantitative CT analysis also showed that the patients with AD had profoundly abnormal enlargement of CSF-filled spaces in all ROIs, and there was no evidence of laterally asymmetric abnormality. On average, the estimated CSF volumes of the total AD group were 1.7 SDs greater than the expected mean of the control subjects, ranging from 1.3 SDs for the third ventricle to 2.5 SDs for the Sylvian fissures. Not only were the mean CT scores of the patients distinctly higher than the control expected mean but, also, a large number of patients had z scores above 2 SDs, ranging from 27 (23%) for the third ventricle to 66 (56%) for the Sylvian fissures.

We observed striking negative correlations between the age-corrected z scores and age in each ROI. Younger patients with AD had far greater brain tissue volume loss for their age than did older patients with AD, which confirms our previous findings based on a smaller sample of patients.[20] This relationship was evident only when the effects of normal aging on the brain were taken into account.

Table 8.—Multiple Regression Analyses With Age at Scanning and Age-at Symptom Onset as Predictors*

Dependent Variables	Predictor Variables: Scan Age F	Scan Age P	Onset Age F	Onset Age P
Age-corrected CT measures				
Sylvian fissures	5.96	.016	0.01	.940
Frontal	6.95	.010	0.14	.707
Ventricular system	4.95	.028	.30	.583
WAIS age-scaled scores				
Arithmetic	10.81	.002	1.04	.314
Digit Symbol	9.16	.004	0.96	.333
Block Design	15.72.	.000	3.99	.052
Picture Arrangement	4.67	.037	0.07	.798

*CT indicates computed tomographic; WAIS, Wechsler Adult Intelligence Scale.

Thus, it is not surprising that studies that have not corrected for normal aging often have found no correlation between CT scores and age in patients with AD. It must be recognized that correcting for the significant enlargement of CSF-filled spaces in normal brain diminishes the chances of finding significant differences in diseases that are not characterized by exacerbated abnormalities with advancing age. This situation is depicted in Fig 4, which shows that while the youngest patients with AD are severely abnormal for their age, many of the oldest patients have CSF volumes that fall within normal limits for their age. This difference in detection of abnormality when the effects of normal aging are taken into account highlights the difficulty in clinically distinguishing AD from normal aging in the very old.

The obtained negative relationship between brain integrity and age in the AD group is neither an artifact of the age-regression model nor a necessary relationship in brain disease. Our studies of chronic alcoholism illustrate that the opposite result can occur with the use of the age-regression model. Specifically, CT and magnetic resonance imaging studies from our laboratory have revealed that age-related brain changes in chronic alcoholism were positively correlated with age. This finding suggests that in contrast with our AD results, age exacerbates the adverse effects of alcohol abuse on the brain.[32,40] Thus, the age-regression method has demonstrated sensitivity to both positive and negative relationships between age and disease severity.

When the patients with AD were classified into groups based on age at symptom onset, the patients in the early-onset group were more impaired for their age on the CT z scores than were the patients in the late-onset group. This onset-group difference persisted even after dementia duration and severity were accounted for statistically. Despite the pervasive abnormalities in all ROIs for both onset groups, their relative patterns of abnormalities differed: the age-corrected CSF volume enlargement of the early-onset group was especially prominent in the Sylvian fissures and ventricular system, whereas the late-onset group had more uniform CSF volume abnormalities across all regions. Indeed, 67% of the scores of the patients in the early-onset group were above 2 SDs for each of these two ROIs, whereas only 29% to 43% of the scores of these patients were this deviant in the remaining four ROIs. Sandor et al[46] reported an analogous result, in that prominent Sylvian fissure, temporal horn, and supracellar enlargement, as measured on CT scans, successfully classified 94% of patients with AD when only the early-onset cases were considered. Inclusion of late-onset cases reduced this correct classification rate to about 87%. Differences related to age in AD cases are further supported by postmortem studies. Mann[10] reported lower brain weights and greater ventricular dilatation in younger than in older patients with AD. In addition, younger patients with AD had more severe loss of temporal cortical pyramidal cells,[10] which may underlie widespread loss of cortical connectivity.[47,48] It is interesting in this context to emphasize observations made by Roth[14] and Iversen[15] that the syndrome originally described by Alzheimer[49] referred solely to the early-onset form of the disease.

The value of the Sylvian fissure enlargement in neuroimaging studies as a potential marker for AD[46,50] is not surprising in light of the devastation of the hippocampus and temporal neocortex in this disease.[51-53] Neuroimaging studies using qualitative ratings of these regions rather than volumetric assessment of the Sylvian-temporal system have been successful in distinguishing patients with AD from healthy elderly subjects.[50,54,55] At this juncture, it may be appropriate to acknowledge that the current trend in research has been to supplant CT with magnetic resonance imaging because of its finer resolution of tissue types and small structures (see also Johnson et al[56]). As seen in the present study, however, quantitative assessment of CT data remains a viable means for systematically studying morphologic changes associated with normal aging as well as disease, particularly in that CT is still more widely available than magnetic resonance imaging both in the clinic and in research settings and in that many research centers had started longitudinal studies of brain morphologic characteristics with the older technology.

The cognitive test results provided another source of support for early-onset vs late-onset group differences. Although both groups were impaired on most tests, the early-onset group was significantly more impaired than the late-onset group on seven of the 11 WAIS subtests (based on age-scaled scores), the three IQ scales, and Trail Making Test B. The WAIS deficits were preponderant for the Performance rather than the Verbal scales. This finding does not conform with one prevailing hypothesis contending that language difficulties are prevalent in patients with early-onset AD, whereas visuospatial deficits mark late-onset disease.[30,57,58] The cognitive tests used in the present study, however, were not ideally suited to examine specific cognitive processes and thus may have been insensitive to detecting such deficit patterns.

We identified several brain-behavior correlations that were statistically significant and provided evidence of several specific relationships in the AD group but not in the control group. The integrity of the frontal cortex, as reflected in the CSF volume estimates, was uniquely correlated with performance on Picture Arrangement and Trail Making Test A. While the frontal association with Picture Arrangement contradicts our previous CT finding of an association of Picture Arrangement with third-ventricular size,[20] a frontal basis for this test as assessing sequencing and problem solving was suggested by McFie and Thompson[59]; yet other studies have shown this test to

be sensitive to lesions in other areas as well (reviewed by Lezak[37]). Trail Making Test A relies on visual search capacity, which is at least in part likely to be subserved by the frontal eye fields.[60-62] Impairment in Object Assembly has been associated with posterior cortical lesions (reviewed by Lezak[37]). The correlations between Sylvian fissure size and Digit Symbol, Block Design, Object Assembly, and the MMSE figure are more difficult to interpret. It must be acknowledged that neither the WAIS subtests nor the Trailmaking Test were designed to localize brain pathology (see also Warrington et al[63]). Thus, it may be of little surprise that none of the brain-behavior correlations reported in our earlier study was replicated.[20] As previously argued, each of these tests probably invokes multiple cognitive processes and multiple brain regions, as exemplified by the Object Assembly result in the present study. Nonetheless, although cognitive deficits and brain abnormalities were pervasive among patients with AD, they did not produce significant correlations for all possible brain-behavior pairings. Rather, the relationships implied that the extent of a particular cognitive deficit was directly related to the amount of tissue replaced by CSF in a specific brain region, ie, lesion size. Thus, the potential is present for finding brain-behavior relationships in future studies in which tests of specific cognitive functions are used in conjunction with more circumscribed measures of brain regions (see also Eslinger et al[64]).

There are a number of ways in which the present findings lend support to the traditional early-onset–late-onset group dichotomy. The patients in the early-onset group were shown to be more impaired than their late-onset counterparts across all CT ROIs, and the two groups also demonstrated differences in the regional distribution of CSF accumulation in the brain. Patients with early onset were more variable in their CT values than were those in the late-onset group, a phenomenon that may be consistent with the idea of more advanced pathologic changes in these patients in the early-onset group. The cognitive data were consistent with the imaging findings in suggesting that the early-onset group was more impaired on age-corrected scores than was the late-onset group. While these converging results reflect greater abnormality and possibly more virulent disease in early-onset cases, it is also important to emphasize the limitations of these cross-sectional data. In particular, we cannot discount the possibility that the patterns of results in the two onset groups may represent different stages along a continuum of pathologic changes. We must also recognize that by dividing the AD group into early-onset and late-onset subgroups, we have actually taken the two ends of a distribution whose relationship with the defining variable (age) is significant and linear. We would expect, then, that differences tested on these two spectrum ends would be significant. Indeed, when we attempted to detect an obvious discontinuity or bimodality in the distributions of the patients in the early-onset and late-onset groups, none was found.

The onset group differences obtained in the present study are in keeping with the existing literature showing onset to be an important classification variable (eg, Kumar et al[9]). However, the predictive utility of age at symptom onset was less than that of age at scanning. Specifically, age at scanning was more highly associated with the CT and cognitive measures than was age at onset (as reflected in larger simple correlation coefficients). Furthermore, age at scanning was a significant and unique predictor of both brain CSF and cognitive status, above and beyond the contribution of age at onset. In contrast, with the exception of a single WAIS variable, age at onset did not contribute significantly to the prediction of the selected imaging or cognitive measures once age at scanning was taken into account. The predictive advantage of the scanning-age variable may be due, at least in part, to the precision of the measure. The estimation of age at symptom onset is an inherently unreliable measure, in that it is strongly dependent on the observational and mnemonic skills of friends and family members. Additionally, awareness of the initial symptoms of a disease with insidious onset may be biased because cognitive dysfunction may be more easily identified in younger individuals, particularly if they are still employed. Such lack of precision in the onset measure may also partially account for the counterintuitive finding that disease duration, which is completely dependent on the accuracy of the estimation of symptom onset, is not significantly associated with CSF volume abnormalities in this progressive disease.

We would like to emphasize that age at scanning is both conceptually and empirically related to age at symptom onset. Our results suggest that future cross-sectional studies consider using the continuous variable of age at entry into the study as a relatively reliable index that may have greater predictive utility than does the traditional estimation of age at symptom onset. Ultimately, however, statements about decline in AD can be made only from longitudinal data, particularly since younger patients are more impaired than are older individuals and since estimates of disease duration may be biased by the subject's age. We are presently examining follow-up CT scans for subjects whose baseline data are reported herein.[65] These measures will allow investigation of the rate of cognitive decline and brain tissue volume loss (with concomitant enlargement of CSF space) among individual patients who entered the study at different ages.

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