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Authors

Pfefferbaum, Adolf
Sullivan, Edith V
Jernigan, Terry L
et al.

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A Quantitative Analysis of CT and Cognitive Measures in Normal Aging and Alzheimer's Disease

Adolf Pfefferbaum, Edith V. Sullivan, Terry L. Jernigan, Robert B. Zipursky, Margaret J. Rosenbloom, Jerome A. Yesavage, and Jared R. Tinklenberg

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Abstract. Patients with presumptive Alzheimer's disease (AD) and healthy community volunteers received computed tomographic (CT) brain scans and cognitive tests. The CT scans were quantitatively analyzed with a semiautomated thresholding technique to derive volumetric measures of cerebrospinal fluid (CSF)-to-tissue ratios in six regions of interest (ROIs): lateral ventricles, vertex sulci, frontal sulci, Sylvian fissures, parieto-occipital sulci, and third ventricle. Regression analysis was performed on CT data from 85 older volunteers (ages 51-82) to generate age norms for each ROI. Within this group, tissue loss, as measured by the % CSF in each ROI, was highly correlated with age, although each ROI showed different rates of change over age. For all ROIs, the AD group had significantly more tissue loss than expected in normal aging. In addition, AD patients with a presenescent onset (before age 65) tended to have greater vertex sulcal and frontal sulcal tissue reduction than AD patients with a senescent onset (age 65 or after). When regional tissue reduction, corrected for age, was correlated with cognitive test scores, two sets of double dissociations emerged within the AD group: large CT *z* scores (i.e., decreased tissue and increased CSF) of frontal sulci, but not of the third ventricle, correlated with low Comprehension and Boston Naming Test scores, whereas large CT *z* scores of the third ventricle, but not of the frontal sulci, correlated with low scores on Digit Symbol and Picture Arrangement. These results suggest that heterogeneity of structural and functional integrity exists among patients with AD.

Key Words. Brain imaging, aging, Alzheimer's disease, brain-behavior relationships.

The analysis of brain X-ray computed tomography (CT) has evolved from qualitative to quantitative approaches and from linear to volumetric measurement. A recently developed quantitative and volumetric method for analyzing brain CT was first used to describe brain changes associated with normal aging (Pfefferbaum et al.,

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Adolf Pfefferbaum, M.D., is Chief, Psychiatry Service, Palo Alto VA Medical Center, and Professor, Department of Psychiatry and Behavioral Sciences, Stanford University Medical School. Edith V. Sullivan, Ph.D., is Health Science Specialist, Psychiatry Service, Palo Alto VA Medical Center, and Senior Research Associate, Department of Psychiatry and Behavioral Sciences, Stanford University Medical School. Terry L. Jernigan, Ph.D., is Staff Psychologist, Psychology Service, San Diego VA Medical Center, and Assistant Professor of Psychiatry and Radiology, Department of Psychiatry, University of California School of Medicine at San Diego. Margaret J. Rosenbloom, M.A., is Health Science Specialist, Psychiatry Service, Palo Alto VA Medical Center. Robert B. Zipursky, M.D., Jerome A. Yesavage, M.D., and Jared Tinklenberg, M.D., are Staff Psychiatrists, Psychiatry Service, Palo Alto VA Medical Center, and Assistant Professor, Associate Professor, and Professor (respectively), Department of Psychiatry and Behavioral Sciences, Stanford University Medical School. (Reprint requests to Dr. A. Pfefferbaum, Psychiatry Service (116A3), Veterans Affairs Medical Center, 3801 Miranda Ave., Palo Alto, CA 94304, USA.)

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1986). This technique offers the opportunity to examine regional differences in brain morphology characteristic of neurological and neuropsychiatric disorders that do not present with specific space-occupying lesions. A further benefit derived from assessing specific neuroanatomical regions is the potential for determining whether differences in structural integrity can be related to normal or abnormal performance on cognitive tasks subserved by circumscribed brain regions.

The approach taken here has been to use interactive computer algorithms to make quantitative estimates of the proportion of cerebrospinal fluid (CSF) and brain tissue in a region of interest (ROI) (Pfefferbaum et al., 1986). First, the brain-skull margin is identified and the brain is isolated. Two-dimensional digital filtering is then used to reduce beam hardening artifact, which is responsible for the increase in signal intensity near the brain-skull interface (Jacobson et al., 1985). For each brain section, a threshold is found which separates CSF from brain tissue. These data can then be summed over contiguous sections and within specified ROIs to yield volumetric measures of CSF-tissue proportions within circumscribed cortical and subcortical regions of interest (Pfefferbaum et al., 1988). An additional advantage of this approach is that CSF-tissue differentiation is determined independently for individual scans, rather than relative to an absolute CT number (cf. Zatz et al., 1982) and thus is free of distortion due to day-to-day variability or drift in CT numbers.

Age not only exerts a strong effect on brain structure, but also interacts in a complex manner with the onset and progression of different diseases. The "age-matched" group design avoids rather than investigates the influence of age. These considerations are particularly relevant for studies of patients with age-related disease, such as Alzheimer's disease (AD), who develop the disease at a stage in their life when variability among healthy people increases (Pfefferbaum et al., 1986) and when changes in brain structure begin to accelerate (Zatz et al., 1982), and among whom there is heterogeneity in course of illness (Mayeux et al., 1985). Because of the detection of gradual and progressive brain changes throughout the adult age span in a healthy community volunteer control group, an age-regression model and computed *z* scores have been used to assess patients' deviations from age norms. The mean of such *z* scores from the control sample is, by definition, zero. An individual patient's *z* score provides an estimate of deviation from control age norms, and the mean of *z* scores from patient groups reflects the extent to which those patients, as a group, demonstrate pathology independent of their individual ages.

Part I of this article is a replication of a regional CT analysis using older community volunteers, age 60 to 79. Part II describes a quantitative analysis of the six ROIs, described in Part I from 41 AD patients and 1-year followup from 10 of them. Part III examines the influence of aging alone and aging combined with pathology on brain-behavioral relationships, using data from the patients and older community volunteers who also underwent neuropsychological testing within 1 month of the CT scan.

Part I

The acceleration and increased variability of structural brain changes among healthy community members over the age of 60 make it important to have specific and stable

age norms against which to detect abnormalities in patients with age-related diseases, such as AD. The original age norms were based on a sample of 57 community members, ranging in age from the 20's to the 80's. The subjects used in the original age-range norm construction were chosen randomly from a larger sample of controls to yield roughly an equal age distribution over the six decades of adulthood. The unused sample included 48 older community volunteers.

Methods

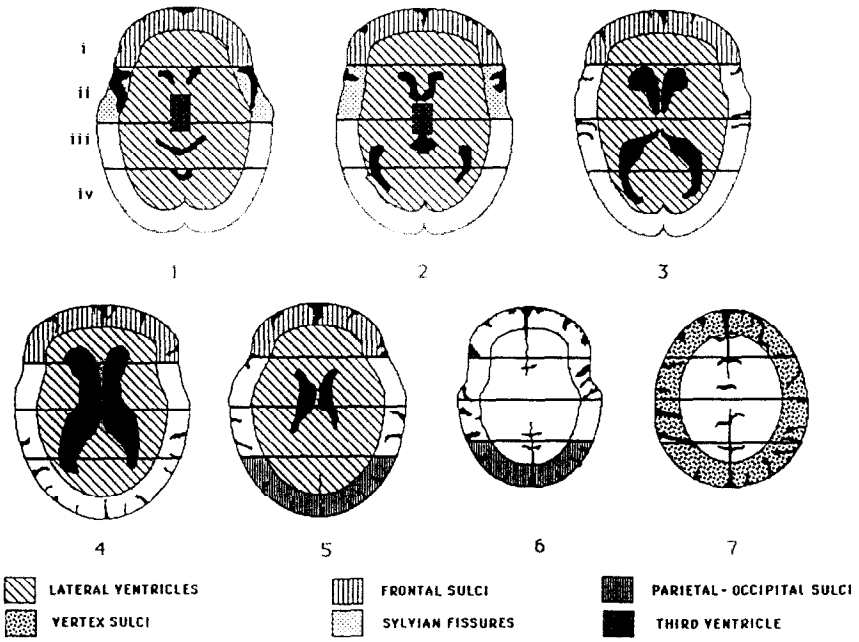
Subjects. Reference subjects were recruited from two sources: (1) a large pool of healthy ambulatory subjects recruited from veterans' and service organizations and from the local community through newspaper advertisements (Madvig et al., 1984), and (2) a group of older healthy volunteers recruited from a retired teachers' organization (Feinberg et al., 1980). The reference subjects were healthy and without major medical problems, but did not receive the same diagnostic workup received by the AD patients. The total original reference group, reported previously (27 men, 30 women), was selected randomly from the larger pool to span the adult age range (age: mean = 54.2, SD = 18.5, range = 20-82 years; education: mean = 15.1, SD = 2.8, range = 9-20 years). CT data of these 57 controls were used to generate age-regression curves for each of the six CT measures calculated (Pfefferbaum et al., 1986, 1988). The extended reference group (15 men, 33 women) included the older volunteers not chosen for the original 57-member reference group (age: mean = 71.7, SD = 5.5, range = 60-79 years; education: mean = 17.0, SD = 3.0, range = 9-24 years). Data from a subset of the reference subjects appear in Jernigan (1986).

Procedure.

CT scans. A thorough description of the CT scanning procedure, image analysis and its validation, filtering procedures, and quantification of ROIs was provided by Zatz et al. (1982), Pfefferbaum et al. (1986, 1988), and Zipursky et al. (1990). In summary, CT scans, obtained with an EMI-1010 scanner, consisted of 8-14 contiguous tomographic sections, 8-mm thick, obtained at +15° to the canthomeatal line. An index section was identified for each scan that included the anterior horns of the lateral ventricles, the third ventricle, and the quadrigeminal cistern and was usually below the posterior horns of the lateral ventricles. The index section and the next six sections superior to it were used for data analysis (Fig. 1). Sections were filtered to minimize spectral shift artifact and then windowed to allow each pixel to be classified as either CSF (fluid) or tissue.

ROIs. Six ROIs were derived for this study, two global (lateral ventricles and vertex sulci) and four neuroanatomically more circumscribed (frontal sulci, Sylvian fissures, parieto-occipital sulci, and third ventricle) (Fig. 1). Fluid pixels falling within specific ROIs were summed and expressed as a percentage of all fluid and tissue in defined brain areas. CSF volume of the lateral ventricles was operationally defined as the % fluid in the central 55% of CT sections 1-5, and that of the vertex sulci was defined as % fluid in a peripheral band consisting of the outer 45% of section 7. For the specific measures, total brain area on each section was divided into equal quarters, anterior to posterior. Three sulcal measures were derived from fluid pixels of the peripheral band. The specific sulcal measures were the frontal sulci, which included the outer segment of the anterior quadrant of CT sections 1-5 and most likely encompassed fluid spaces of the prefrontal cortex; the Sylvian fissures, which included the outer segment of the second quadrant of sections 1-2 and provided an estimate of the integrity of the posterior frontal and temporal lobes; and the parieto-occipital sulci, which included the outer segments of the most posterior quadrant of sections 5-6 only, in an effort to exclude the cerebellum. To generate the % fluid measures for these sulcal areas, the fluid pixels in the peripheral segment of these quadrants were divided by the sum of the areas of the quadrant for the sections included in each measure. To obtain a measure of the third ventricle, rectangular ROIs were drawn to enclose the boundaries of the third ventricle on each of the two most inferior CT sections, and all fluid pixels within the two ROI rectangles were summed

Fig. 1. Schematic representation of the 7 computed tomographic sections used for quantifying the 6 regions of interest



Fluid-tissue threshold was determined for each section, as described in the text. Each section was divided into central 55% area and peripheral 45% area to facilitate quantification of lateral ventricular and cortical sulcal volumes, respectively. In addition, the sections were divided into quarters of equal area (anterior to posterior) to provide regional measurements of cortical sulcal volume. The third ventricle was localized using rectangular regions of interest from sections 1 and 2.

and divided by the sum of the area of the two sections. All CT data were expressed as % fluid in the ROIs [i.e., fluid/(fluid + tissue)] (Pfefferbaum et al., 1988).

Statistical analysis. As described by Pfefferbaum et al. (1988), the % fluid CT measures from each ROI for the 57 community controls were plotted against age to form age-regression curves. To identify the best fit to the % fluid data, the age term was also squared and cubed, and the function with the highest correlation was used; this was age-squared for all but the third ventricle, for which simple age was best. In addition, the % fluid values were arcsin transformed to stabilize the variance with respect to age. To accommodate the increasing variance observed with increasing age in some CT measures, a variance-regression procedure, described by Jernigan et al. (1982), was applied where appropriate. This procedure first computed the regression of a CT variable on age. Then the absolute value of the residuals was again regressed on age to provide an estimate of the standard error of the regression at each age. Age-corrected z scores were calculated for each of the CT measures for each subject in the following way: the % fluid measure expected for a given subject (as derived from the appropriate regression curve) was subtracted from the subject's observed % fluid measure, and this difference was then divided by the standard deviation expected for the subject's age.

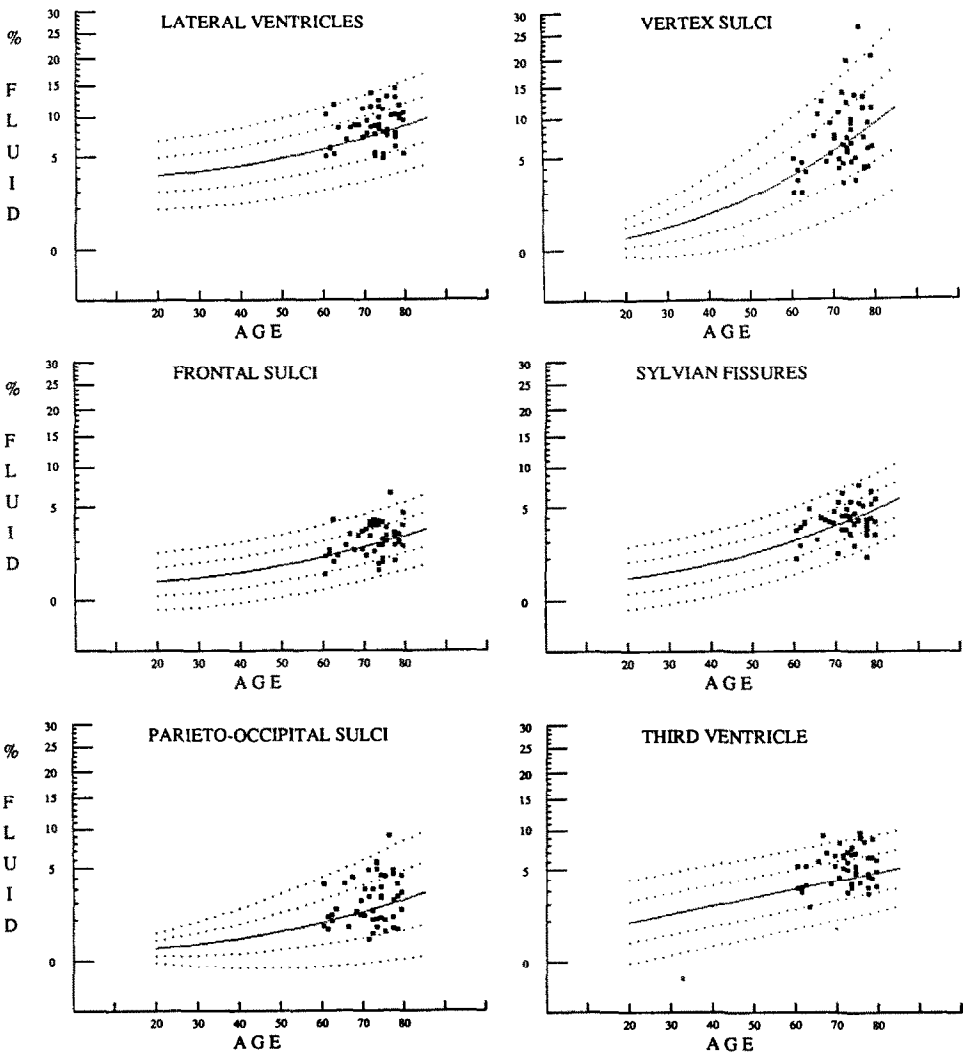
Results

Fig. 2 displays the % fluid values of the extended reference group superimposed on regression lines representing means and SDs for the original 57 subjects. The CT values of the individual subjects of the extended reference group fell within 2 SDs.

For no ROI did more than two subjects from the extended reference group fall outside the age norms, and thus values for the subject group were well within the maximum of four outliers that would be expected by chance.

To test whether the extended control group was different from the original one, the six ROI measures were tested with three analyses: *t* tests comparing mean *z* scores, *F* ratios comparing sample variances, and *t* tests comparing the slope of each

Fig. 2. Computed tomographic (CT) data for each region of interest of the individual subjects comprising the extended reference group ($n = 48$) plotted against the expected values (bold, center regression line) derived from the CT data of the original reference group ($n = 57$)



The dotted regression lines are 1 and 2 SDs above and below the expected mean. The data are plotted to reflect an arcsin square root transformation, with the ordinate displaying the % fluid measure on a transformed scale.

ROI measure as a function of age (i.e., the rate of change with age across subjects) (Table 1). The mean z scores of these ROIs ranged from 0 to 0.5 SD larger than those of the original group; only the lateral and third ventricular mean measures were significantly larger. Thus, the original control data may have slightly underestimated the effects of age on fluid/tissue ratios in later ages. Neither the variance nor the slope analyses yielded any significant differences.

Table 1. Computed tomographic (CT) z scores for 6 regions of interest (ROIs) of the original and extended reference groups: Means, SDs, and group comparisons (2-tailed tests)

	Original ($n = 57$)		Extended ($n = 48$)				
	Mean		Mean		Means	Variances	Slopes
CT ROI	Mean	SD	Mean	SD	t	F	t
Lateral ventricles	-0.001	1.013	0.384	0.88	-2.06[1]	1.340	0.704
Vertex sulci	0.001	1.06	0.23	0.935	-1.16	1.282	-0.055
Frontal sulci	0.0002	1.006	0.251	0.942	-1.31	1.137	0.124
Sylvian fissures	0.0003	0.962	0.001	0.94	-0.01	1.133	1.864
Parieto-occipital sulci	0.017	1.018	0.309	0.903	-1.54	1.264	0.040
Third ventricle	-0.0004	0.968	0.543	0.885	-2.98[2]	1.194	0.027

1. $p < 0.05$.
2. $p < 0.01$.

In an attempt to search for common factors in the CT data, principal component analyses (varimax orthogonal transformation solutions) performed on the two reference groups separately yielded two significant factors for each group (Table 2). For both groups, one factor was associated with the lateral and third ventricles and the other factor with the vertex and parieto-occipital sulci. An exception to this overlapping pattern of factors was that the frontal sulcal measure of the extended reference group was not strongly associated with either of the two significant factors.

Discussion

The age-regression curves of the six CT ROIs from the original reference group accommodated the CT values of the extended reference group well. As observed here, age-related increase in ventricular size appears to accelerate after age 60, as previously shown by Zatz et al. (1982) and by the original finding that the age-squared predicted ventricle size better than simple age.

The most prominent factor contributing to differences in brain morphology described by CT images is aging (reviewed by Freeman et al., 1984). In the present study, age-related changes, in general, were observed as continuous increases in CSF volume with aging. Age regressions for the specific ROIs showed different rates of change. The ventricular increase over the 60-year span was nearly three-fold, which is consistent with other findings based on CT (e.g., Barron et al., 1976; Schwartz et al., 1985; Takeda and Matsuzawa, 1985), whereas the sulcal increase was 10-fold.

Table 2. Principal component analyses for computed tomographic *z* scores of the 6 regions of interest for the 2 reference groups

Group	Original reference ($n = 57$)			Extended reference ($n = 48$)		
Factor:	1	2	3	1	2	3
Eigenvalues	2.464	1.627	0.645	2.178	1.675	0.900
Variance proportion	0.411	0.271	0.108	0.363	0.279	0.150
Orthogonal transformation solution (varimax)						
Lateral ventricles	0.881[1]	0.214	0.152	-0.003	0.903[1]	-0.013
Vertex sulci	0.189	0.89[1]	0.211	0.840[1]	-0.168	0.287
Frontal sulci	0.425	0.632[1]	0.259	0.176	0.053	0.903[1]
Sylvian fissures	0.295	0.117	0.844[1]	-0.410	0.532	0.519
Parieto-occipital sulci	0.213	0.772[1]	0.349	0.886[1]	0.172	-0.079
Third ventricle	0.698[1]	0.144	0.534	0.482	0.602[1]	0.368

1. Variables associated within a given factor.

Thus, for a 1,300-g brain that is 40% cortex, the change in sulcal volume from about 2% at age 60 to 10% at age 80 would be equivalent to a tissue loss of about 2 g/year. Accompanying the increase in mean sulcal volume was a greater increase in variability than was found for the ventricular measure. In a recent study with magnetic resonance imaging, Jernigan et al. (1990) found similar age-related changes over this age range. Post-mortem neuronal cell counts of cortical gyri reflect a dramatic, normal age-related change, similar to the CT sulcal volume increases described here. Depending upon the region studied, cell loss was upwards to 50% across the adult age range, with a comparable cell loss from the superior frontal gyrus from the 50's to the 90's (reviewed by Kemper, 1984).

The principal component analysis provides evidence to suggest that the ventricles and sulci enlarge independently, as observed in other CT studies of normal volunteers (Gyldensted, 1977; Jacoby et al., 1980; Ford and Winter, 1981; Zatz et al., 1982). Further support for independent atrophic processes for the ventricles and sulci is provided by post-mortem anatomical studies, in which gyral atrophy and ventricular dilation were poorly correlated (reviewed by Kemper, 1984).

Each of the four ROIs of more circumscribed brain regions was characterized by its own age-related mean and variance. Specifically, the third ventricle, similar to the lateral ventricles, had about a four-fold linear acceleration of the mean across all decades with a rather stable variance, whereas the increase in the Sylvian fissure volume showed a more accelerated function and an eight-fold mean increase. The frontal sulcal fluid measure increased by four-fold, whereas the parieto-occipital sulcal fluid measures only doubled over the six decades. Clearly, changes in fluid volume related to healthy aging vary from brain region to region. Consequently, these normal regional variations must be taken into consideration in attempts to characterize pathological changes of age-related diseases.

Part II

A new set of age regressions derived from all data of the older-age subjects was created in an effort to differentiate age-related from disease-related changes in patients with AD.

Methods

Subjects. The patients with AD (32 men, 9 women; age: mean = 64.3, SD = 8.3, range = 49-83 years; education: mean = 14.2, SD = 2.6, range = 9-21 years) were drawn from longitudinal studies in progress since 1982 at the Geriatric Psychiatric Rehabilitation Unit and the NIMH Dementia Clinical Research Center of the Palo Alto Veterans Affairs Medical Center. Followup diagnoses of AD were based on NINCDS/ADRDA criteria (McKhann et al., 1984; Khachaturian, 1985). Because of the longitudinal nature of the study, diagnoses were performed at least twice: at entry and at followup visits. The diagnoses at the time of the current data analysis of these patients included 23 with probable AD, 6 patients with possible AD, 6 patients with AD plus clinical evidence of multi-infarct dementia (MIX), and 6 cases with definite AD (confirmed by autopsy). Hachinski scores, which reflect degree of vascular involvement in the patient's condition (Hachinski et al., 1975), were available for four of the six definite cases and ranged from 1 to 3; for 15 of the 23 patients with probable AD and ranged from 0 to 4; for five of the six patients with MIX and ranged from 1 to 5; and for four of the six patients with possible AD and ranged from 0 to 3. There were no group differences in Hachinski scores (Kruskall-Wallis test: $H(3) = 3.95$). Two additional patients (not included in the 41) were retrospectively excluded from this analysis on the basis of autopsy evidence of Parkinson's disease alone or of multi-infarct dementia without AD. On average, the duration of disease, estimated retrospectively from descriptions of first symptoms, was 4.2 years (SD = 2.9, range = 1-16). The mean score on the Mini-Mental State Examination (MMSE; Folstein et al., 1975) was 20.1 (SD = 5.9, range = 9-30); in repeat testing 4 years later, the score of the patient with the earlier score of 30 had dropped to 23. With the exception of the MMSE, the cognitive test scores serving as dependent measures of behavior in Part III of this study were not used to establish the diagnoses. A preliminary report of a subset of these patients was presented by Jernigan (1986).

All subjects from the original and extended reference groups who were ≥ 50 years old were used to form an older reference group for the AD patients. These 85 subjects (age: mean = 69.5, SD = 7.7, range = 51-82 years; education: mean = 16.2, SD = 3.1, range = 9-20 years) formed the older reference group.

Procedure. The same scanner and procedure described in Part I were used in Part II.

Statistical Analysis. New age regressions, based on the CT scores of only the older reference group of 85 subjects, were computed, as described in Part I, for each of the six ROIs. The data from the restricted older age range control group (51-82 years) constructed for this analysis were well described by a linear regression on age with no acceleration of variance with age.

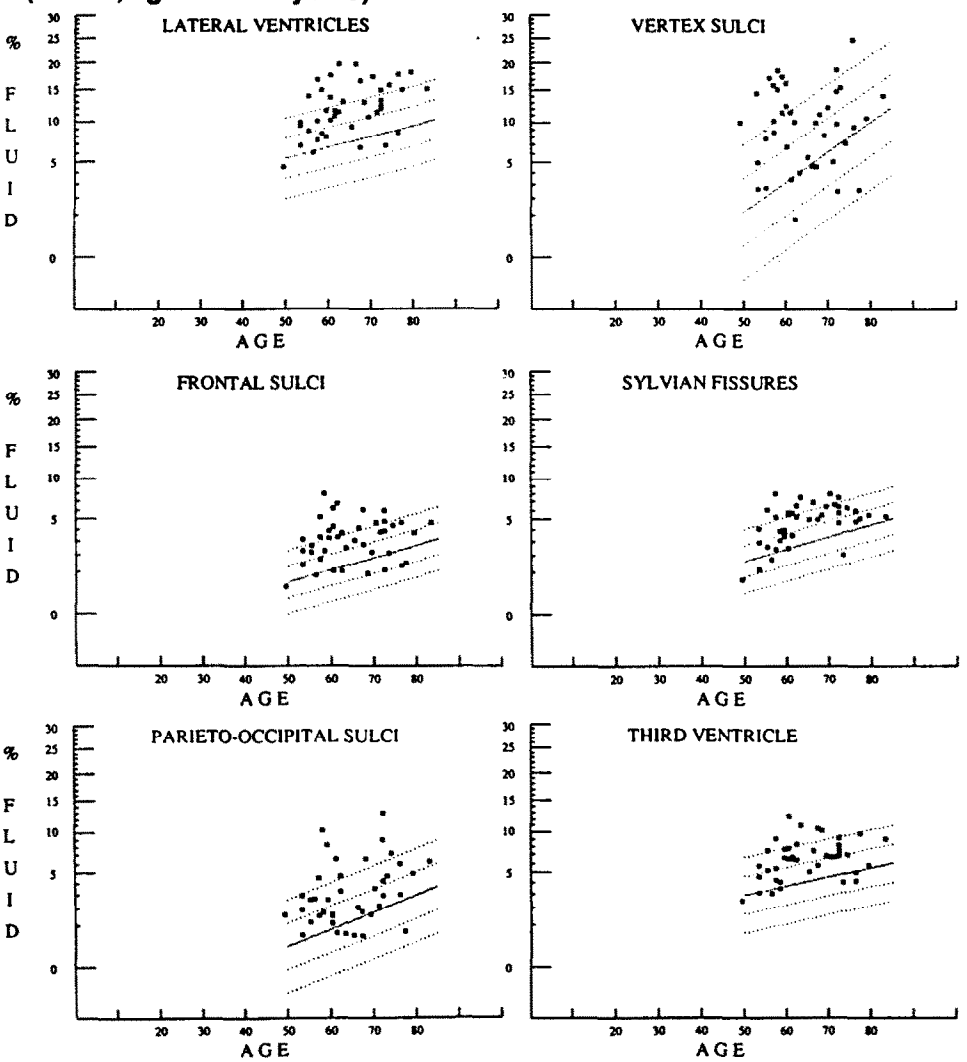
Results

CT Measures. Within the older reference group, age was significantly correlated with % fluid volume for each of the six ROIs (lateral ventricles = 0.36; vertex sulci = 0.56; frontal sulci = 0.49; Sylvian fissures = 0.49; parieto-occipital sulci = 0.47; and third ventricle = 0.34). The increase in mean % fluid volume of this older (51-82 years of age) reference group ranged from about two-fold (lateral ventricles) to about 10-fold (vertex sulci). Unlike the increasing ROI variance with age for the larger

20-82 age range, the variance within each ROI remained nearly constant when only the data from the restricted 51-82 age range years were analyzed. Within this group, however, variances differed from ROI to ROI.

Fig. 3 presents the % fluid scores of AD patients superimposed on the older age regressions. Over the six ROIs, 63 scores fell at or beyond 2 SD from the mean (Fig. 3), 51 more than would be expected by chance. Group analyses using *z* scores

Fig. 3. Computed tomographic (CT) data of each patient with Alzheimer's disease (n = 41) plotted against the expected values (bold, center regression line) derived from the CT data of the older reference group (n = 85, age = 51-82 years)



The dotted regression lines are 1 and 2 SDs above and below the expected mean. The data are plotted to reflect an arcsin square root transformation, with the ordinate displaying the % fluid measure on a transformed scale. Note that this transformation stabilized the SDs, so that they appear linear and equally spaced across the 30-year age range.

revealed that the mean z scores were very significantly different, and, on average, were 1 to 1.5 SD larger in the AD group than in the reference group. Comparisons of sample variances yielded no significant differences. In comparisons of slope of each ROI over age, the AD and reference groups differed significantly only on the vertex sulcal measure, for which the slope for the AD group was significantly smaller than the slope for the reference group. A trend toward a difference in slopes was apparent for the frontal sulcal scores (Table 3). There were no differences in any measures on the basis of gender. Examples of processed and unprocessed images from a reference subject and an AD patient appear in Fig. 4.

Table 3. Computed (CT) *z* scores for 6 regions of interest (ROIs) for the Alzheimer's disease (AD) group ($n = 41$): Means and SDs of the AD group and comparisons of the AD group with the older reference group ($n = 85$)

			Means	Variances	Slopes
CT ROI	Mean	SD	*t*	*F*	*t*
Lateral ventricles	1.544	1.124	-7.80[2]	1.268	-0.558
Vertex sulci	1.199	1.359	-5.59[2]	1.452	3.019[1]
Frontal sulci	1.353	1.331	-6.37[2]	1.673	1.590
Sylvian fissures	1.165	1.064	-6.00[2]	1.147	-0.028
Parieto-occipital sulci	1.145	1.241	-5.56[2]	1.530	0.822
Third ventricle	1.108	0.952	-5.92[2]	1.091	0.223

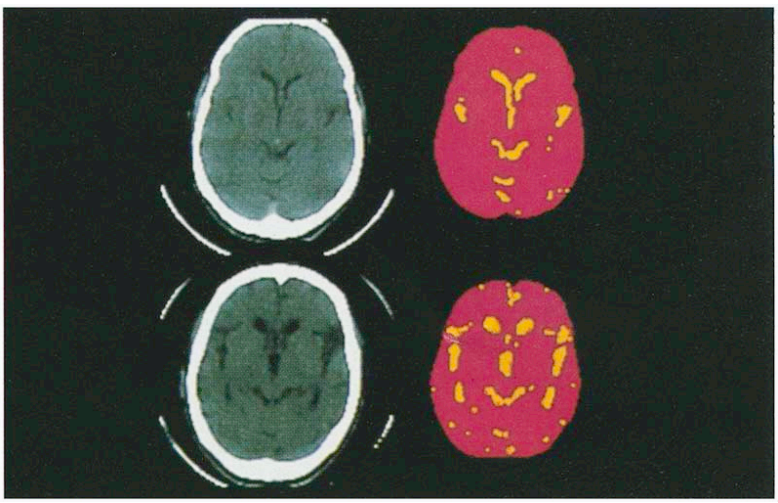
1. $p < 0.01$.
2. $p < 0.0001$.

Within the AD group, abnormally large CT z scores in one brain region were not necessarily associated with those in other regions. Correlation matrices for the six ROIs for the 85 reference subjects and the 41 AD patients showed similar patterns of associations. In particular, lateral ventricular CT z scores were significantly correlated with third ventricular, Sylvian fissure, and frontal CT z scores but not with vertex or parieto-occipital sulcal CT z scores; by contrast, the vertex sulcal CT z scores correlated with the frontal and parieto-occipital sulcal CT z scores. The only ROI that shared a relationship with both lateral ventricular and vertex sulcal measures was the frontal measure.

For the AD group, this pattern of results was also evident when the regression slopes of each ROI against age were compared with each other. In particular, the slopes based on the vertex sulcal and the frontal sulcal z scores differed from the slope of the lateral ventricles, whereas the slopes based on the third ventricles, Sylvian fissures, and parieto-occipital sulci differed from the vertex sulcal slope. That is, the slopes of the vertex sulcal and frontal sulcal z scores both showed a negative relationship with age, whereas the slopes based on the remaining ROI z scores were basically flat. No other comparison of slopes approached significant differences. All t values of slope comparisons within the reference group were about zero.

CT-Demographic Correlations. In an effort to test for relationships between CT

Fig. 4. Examples of processed and unprocessed images from a reference subject and an Alzheimer's disease (AD) patient



The black and white images are unprocessed films of section 7 in Fig. 1. The color images are filtered and thresholded versions of the adjacent black and white sections; cerebrospinal fluid is presented in yellow and tissue in red. The computed tomographic *z* scores of the reference subject (58-year-old woman) and the AD patient (58-year-old woman) were as follows: lateral ventricles (obtained from sections 1-5), 0.05 and 3.67; vertex sulci (section 7), -0.27, 3.89; third ventricle (sections 1-2), -0.27, 3.89; Sylvian fissure (sections 1-2), 0.22, 3.59; frontal sulci (sections 1-5), -0.91, 3.43; and parieto-occipital sulci (sections 5-6), -1.25, 2.91. The reference subject, who had 13 years of education, and the AD patient, who had 14 years of education, achieved the following Wechsler Adult Intelligence Scale scores: Verbal IQ, 120, 91; Performance IQ, 121, 54; and Full Scale IQ, 121, 74.

measures and demographic and dementia severity measures, Pearson product-moment correlation coefficients were calculated for each ROI *z* score with age, education, disease duration (established retrospectively from time of first symptom), and MMSE scores among the AD cases. Three correlations were significant (for all three, $p < 0.01$, two-tailed; nonparametric correlation analyses produced similar results) (Table 4), and the pattern of results was consistent with the concept of sulcal and ventricular independence. Larger volumes of the lateral ventricles and the Sylvian fissures were correlated with poorer scores on the MMSE, whereas the vertex sulcal measure was not. Because the expected changes due to normal aging have been removed in the process of creating the *z* scores, correlation between *z* scores and age suggests an interaction of age and the pathological condition being examined. The vertex sulcal measure, but not the ventricular or Sylvian fissure measures, correlated negatively with age; that is, younger patients had larger sulci for their age than did older patients. Furthermore, age was positively correlated with duration of illness ($r = 0.40$, $p < 0.03$); that is, younger AD patients had relatively larger vertex sulci than was expected for their age, even though they had been ill for a shorter time than the older patients.

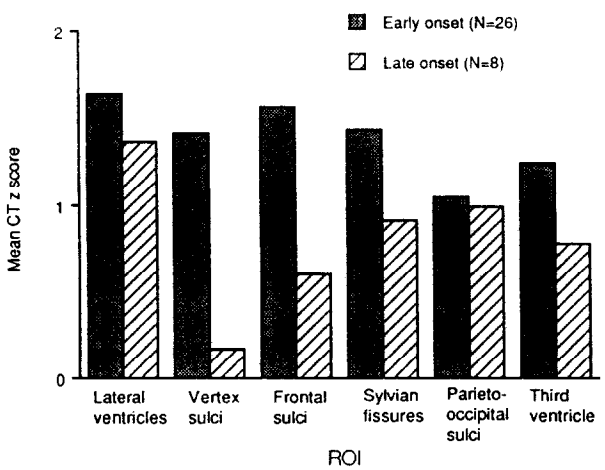
Table 4. Pearson correlation coefficients of each region of interest (ROI) with demographic measures for 41 patients with Alzheimer's disease

ROI	Age	Education	Duration of disease	Mini-Mental State Exam
Lateral ventricles	0.10	0.01	-0.06	-0.49[1]
Vertex sulci	-0.47[1]	0.14	-0.06	0.10
Frontal sulci	-0.26	0.00	-0.27	-0.02
Sylvian fissures	0.01	-0.01	0.08	-0.51[1]
Parieto-occipital sulci	-0.14	0.17	-0.25	-0.26
Third ventricle	-0.05	0.14	-0.18	-0.25

1. $p < 0.01$ (2-tailed tests).

Age of Onset. The observation of a negative correlation of age with vertex sulcal z score raised the question of whether a presenescent (before age 65), as contrasted with a senescent (at or after age 65), onset of disease could provide a viable basis for subtyping the AD group in this sample. Accordingly, the AD group was divided into patients with a disease onset before age 65 ($n = 26$; mean = 56.4 years; SD = 4.64) and at 65 years or older ($n = 8$; mean = 69.6 years; SD = 1.82); onset was poorly defined for seven patients, and they were therefore excluded from this analysis. The groups did not differ in severity of dementia as measured by the MMSE (mean for presenescent onset = 20.4; for senescent onset = 19.2; $t = 0.62$, $df = 26$). The younger onset subgroup had larger CT z scores for vertex sulci ($t = 2.436$, $df = 32$, $p = 0.02$) and a trend for the frontal sulci ($t = 1.778$, $df = 32$, $p = 0.085$) compared with the older onset subgroup. No such tendency was apparent in the remaining four CT-ROI/subgroup comparisons (lateral ventricles: $t = 0.596$; Sylvian fissures: $t = 1.235$; parieto-occipital sulci: $t = 0.137$; third ventricles: $t = 1.249$) (Fig. 5).

Fig. 5. Mean computed tomographic (CT) z scores of the early vs. late onset Alzheimer's disease subgroups for the 6 regions of interest (ROIs)



Repeat CT Scans. Of the 41 AD patients, 10 had repeat CT scans on the EMI-1010 scanner an average of 16 months later. This subgroup comprised eight men and two women, with a mean age of 61.1 years (7 with presenile and 3 with senile onset); seven had a diagnosis of probable AD, one with possible AD, and two with MIX. Because of the small sample size, paired comparisons of z scores were based on Wilcoxon tests, which showed significant increases (one-tailed) in size of the lateral ventricles ($p < 0.01$) and frontal ($p < 0.05$) sulci, but not of the other four regions, at the second scan.

Discussion

CSF volumes of all six ROIs were significantly larger in the AD group than in the reference group. Further analysis of this observation suggests (1) that not all brain regions were equally involved within individual patients and (2) that, as seen in repeat scanning, the lateral ventricles and frontal sulci may be particularly susceptible to AD-associated changes beyond those expected with normal aging.

The variability within the AD group suggests the presence of heterogeneity and thus subtypes (cf. Martin et al., 1986; Chui, 1987; Friedland et al., 1988). In addition to differences in regional anatomical pathology, AD may be subtyped by age of onset (e.g., Heston et al., 1981; Bondareff, 1983; Rossor et al., 1984; Mayeux et al., 1985; Albert et al., 1986; Brandt et al., 1989). That younger AD patients had relatively larger vertex and frontal sulci than were expected for their age supports other findings of inverse relationships between degree of neuroanatomical, neurochemical, and neuropsychological pathology and age (Chui, 1987; Hansen et al., 1988). In the present study, the two age subgroups did not differ in severity of dementia. In particular, the present study suggests a special vulnerability of the vertex and frontal sulci in AD with a presenescent onset. Thus, younger AD patients seem not to be protected by a youthful "margin of safety," but rather they may be selectively more severely affected by the disease than are older patients. If accurate, this observation may suggest a neuroanatomical substrate for the language impairment that often marks early-onset AD (for reviews, see Mayeux et al., 1985; Chui, 1989).

Severity of dementia, as measured by the MMSE, was related to only two CT measures. Its association with size of the lateral ventricles may reflect nonspecific deterioration (e.g., Luxenberg et al., 1987) and its association with size of the Sylvian fissures may reflect memory impairment (cf. Shimamura et al., 1988), common to all AD patients diagnosed by *DSM-III-R* (American Psychiatric Association, 1987) and NINCDS/ADRDA (McKhann et al., 1984; Khachaturian, 1985) criteria. A primary goal of Part III was to investigate further whether the observed abnormalities in CT-imaged brain structures were functionally significant—that is, whether they showed specific associations with poor cognitive test scores.

Part III

This study sought the separate effects of age and disease on brain-behavior relationships by correlating the results of the CT analyses with scores on traditional tests of cognitive function. Two types of brain and behavioral measures were used: global and specific. Global measures of brain integrity were the size of lateral ventricular

and vertex sulcal CT scores; global measures of demographic and cognitive status were age, education, duration of illness, and overall cognitive status.

Specific measures of brain integrity were frontal sulcal, third ventricular, Sylvian fissure, and parieto-occipital sulcal CT scores; measures of cognitive function comprised tests thought to depend upon the integrity of brain regions included in our CT ROIs. These measures permitted the use of a version of the double-dissociation model (Teuber, 1957; Jernigan, 1986) for specifying brain-behavior relationships. We hypothesized that diminished cognitive function would be associated with increased CSF and decreased brain tissue. Furthermore, if these relationships were specific, then specific cognitive deficits should be associated with CSF reduction in only one brain region. A partial report of these data was presented by Sullivan et al. (1990).

Methods

Subjects. The data reported here represent a post hoc analysis of data from AD patients and reference subjects, selected from the larger subject groups of Part II because they had cognitive evaluations around the time of their CT scans. Included were 19 patients with AD drawn from the sample of 41 patients and 35 of the 85 reference subjects. On average, the 19 AD patients were 66.2 years old (SD = 7.2, range = 57-83), had 14.7 years of education (SD = 2.8, range = 11-21), had been ill for 4.1 years (SD = 2.2, range = 2-12), and had an MMSE score of 21.4 (SD = 6.0, range = 11-30). The mean age of the 35 reference subjects was 66.1 years (SD = 9.0, range = 51-82) and their mean years of education was 15.0 (SD = 2.8, range = 9-20).

Procedure. On average, testing was completed within 3 days of scanning (for the AD group, absolute mean = 2.1 days; range = -21 to +1 days; for the older reference group, absolute mean = 0.9 days; range = -11 to +2 days).

Tests of cognitive function included the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1957), Trail Making (Parts A and B) (Army Individual Test, 1944), Boston Naming Test (Kaplan et al., 1978), and FAS letter fluency test (Benton and Hamsher, 1976).

Statistical Analysis. Differences in z scores among different areas of the brain were assessed by one-factor, repeated measures analyses of variance (ANOVAs) and Fisher Tests ($\alpha = 0.05$). Two-tailed tests of significance were used unless otherwise specified. Correlations between CT scores and demographic characteristics or cognitive test scores were derived from Pearson product-moment correlation tests. Values from parametric tests are reported here; nonparametric tests of significance yielded essentially the same results.

Results

Both the 35 reference subjects and the 19 AD patients with cognitive data were representative of the total groups from which they were drawn. Their mean CT z scores did not significantly differ from those of the remaining 50 reference subjects or 22 AD patients, respectively.

Cognitive Test Performance. Analyses of Wechsler subtests were based on scaled scores, which were not age-corrected. Compared with the reference group, the AD group was impaired on all of the cognitive measures (for most comparisons, $p < 0.0001$) (Table 5).

Table 5. Cognitive test performance: Mean and SDs

	Older reference ($n = 35$)		Alzheimer's disease ($n = 19$)	
Test	**Mean**	**SD**	**Mean**	**SD**
WAIS-R scaled scores				
Information	13.4	2.27	9.1[3]	3.4
Comprehension	14.7	2.67	10.1[3]	4.38
Arithmetic	12.1	2.53	6.5[3]	4.59
Similarities	12.2	2.87	9.4[1]	3.73
Digit Span	11.4	2.35	8.7[2]	3.4
Vocabulary	14.1	2.51	11.6[1]	4.02
Verbal raw score	77.9	10.81	55.4[3]	18.35
Digit Symbol	9.34	1.81	4.5[3]	3.94
Picture Completion	10.9	2.01	7.2[3]	3.31
Block Design	10.1	2.59	4.5[3]	3.96
Picture Arrangement	9.1	2.46	4.4[3]	3.51
Object Assembly	9.7	2.9	5.5[3]	3.85
Performance raw score	49.2	8.81	26.1[3]	16.64
Verbal IQ	125.9	12.05	103.3[3]	17.41
Performance IQ	120.7	9.76	90.4[3]	22.93
Full Scale IQ	125.7	10.81	97.5[3]	19.15
Trails A (sec)	42.7	16.51	107.4[3]	89.9
Trails B (sec)	98.0	55.1	240.5[3]	159.26
Boston Naming Test	55.3	3.31	42.5[3]	16.73
FAS total	43.5	10.3	28.3[3]	14.81

1. $p < 0.01$ (2-tailed test).
2. $p < 0.001$ (2-tailed test).
3. $p < 0.0001$ (2-tailed test).

Correlations Between CT Measures and Cognitive Test Scores. Negative correlations indicate that poor cognitive test scores were associated with large fluid-filled spaces for all tests except Trails A and B on which high scores reflect poor performance. The 0.01 level of significance (two-tailed) was used to test all specific brain-behavior correlation coefficients.

Reference group. In the analyses using % fluid CT scores (i.e., not age-corrected), no distinction was made between global and specific measures; thus, all possible correlations were performed. As already established, increasing age was highly correlated with greater % fluid in all ROIs. Poor scores on the cognitive tests were significantly correlated with large % fluid measures in six instances: five correlations involved vertex sulcal and Sylvian fissure scores and performance measures, and one involved Sylvian fissure and Boston Naming Test scores. In contrast, when CT z scores (i.e., age-corrected) were used, no significant CT-behavior correlations were observed (Tables 6 and 7); nor were there any correlations when both CT and behavior were corrected for age. Thus, the few observed correlations were age-mediated associations.

Table 6. Pearson correlation coefficients of global CT *z* scores with demographic and behavioral measures

	Older reference ($n = 35$)		Alzheimer ($n = 19$)	
Demographic or global behavioral measure	**Lateral ventricles**	**Vertex sulci**	**Lateral ventricles**	**Vertex sulci**
Age	-0.03	0.03	0.03	-0.49[1]
Education	0.19	-0.15	0.04	0.27
Duration of illness	—	—	0.31	-0.15
Mini-Mental State Exam score	—	—	-0.59[1]	-0.36
Verbal total raw score	0.30	-0.11	-0.58[2]	-0.12
Performance total raw score	-0.04	-0.22	-0.61[2]	-0.26

1. $p < 0.05$.
2. $p < 0.01$.

AD group. To observe the effect of disease with the effect of age removed, the correlations for the AD group used age-corrected CT *z* scores. CT *z* scores reflecting large ventricles were significantly correlated with low test scores of global cognitive function, including the MMSE and the Verbal and Performance total raw scores of the WAIS (Table 6). Vertex sulcal *z* scores were negatively correlated with age, indicating that younger patients with AD had larger vertex sulci than did older patients. In this subgroup of 19 patients, duration of AD did not significantly correlate with age ($r = 0.26, p < 0.3$), which contrasts with the significant relationship present in the larger group of 41 patients.

Six correlations for specific measures were significant at the 0.01 level (two-tailed): Comprehension and Boston Naming scores with frontal CT *z* scores; Arithmetic and Object Assembly with the Sylvian fissure CT *z* scores; and Digit Symbol and Picture Arrangement with third ventricular CT *z* scores (Table 7). These correlations were essentially unchanged or stronger when the behavioral tests, as well as the CT scores, were corrected for age (see Fig. 6, where CT *z* scores are plotted against cognitive *z* scores). Two sets of double dissociations emerged from these significant correlations: large third ventricular *z* scores, but not large frontal sulcal *z* scores, were associated with low scores on Digit Symbol and Picture Arrangement; and large frontal sulcal *z* scores, but not large third ventricular *z* scores, were associated with low scores on Comprehension and the Boston Naming Test (Table 7). It is noteworthy that the differences between the pairs of correlations were significant ($p < 0.05$) for all pairs except the last one ($p < 0.10$) (Walker and Lev, 1953).

Discussion

Within the AD group, double dissociations were clearly established with pairs of ROIs and cognitive tests. Specifically, performance on the Boston Naming and Comprehension tests was related to fluid volume in a region that included the prefrontal cortex but was not significantly related to the fluid volume of the third ventricle, whereas performance on the Digit Symbol and Picture Arrangement tests

was related to measures of the third ventricle but not of the prefrontal cortex. This set of results demonstrates that CT measures of circumscribed brain regions can be quantitated and applied successfully in identifying neuroanatomical substrates of specific cognitive function when this approach is coupled with the method of double-dissociation. Moreover, these results show that specific brain-behavior relationships can be established even within a diagnosis. This capability may be useful in characterizing patterns of deterioration in AD and thus may also provide further functional and anatomical clues to the heterogeneity of AD (cf. Martin et al., 1986; Friedland et al., 1988; Grady et al., 1988).

Table 7. Pearson correlation coefficients of specific CT *z* scores with cognitive measures

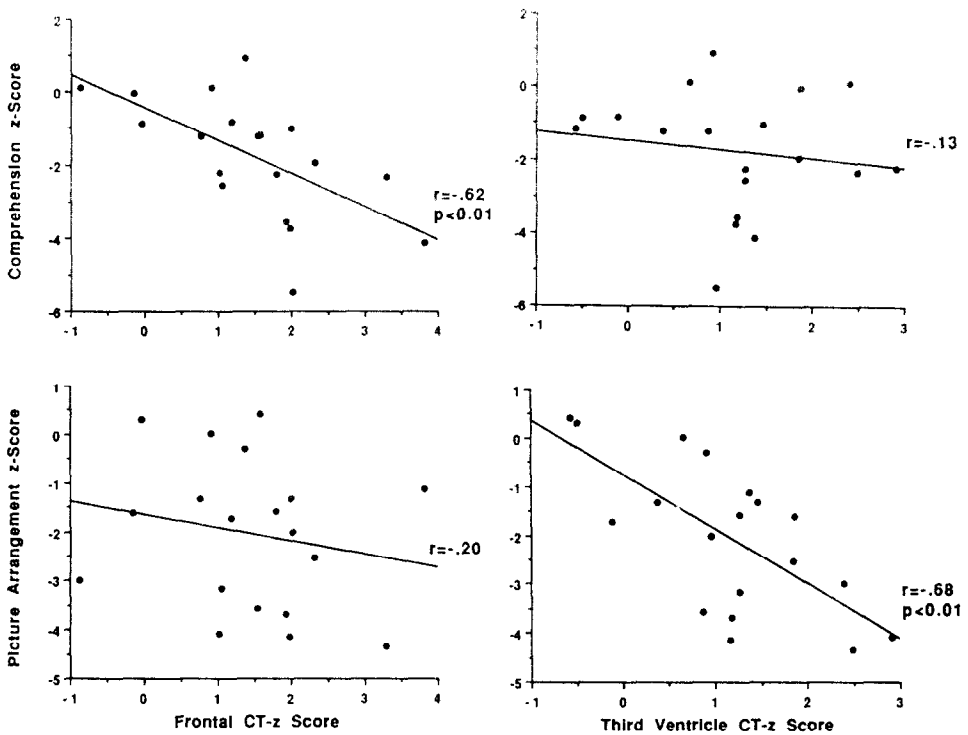
	Older reference group ($n = 35$)				Alzheimer's disease group ($n = 19$)			
Test	Frontal sulci	Sylvian fissures	Parieto-occipital sulci	Third ventricle	Frontal sulci	Sylvian fissures	Parieto-occipital sulci	Third ventricle
WAIS-R scaled scores								
Information	0.12	-0.22	-0.18	0.22	-0.46	-0.35	-0.14	-0.09
Comprehension	0.20	-0.22	-0.03	-0.04	-0.59[1]	-0.30	-0.26	-0.10
Arithmetic	-0.04	-0.20	-0.22	-0.17	-0.25	-0.57[1]	-0.23	-0.49
Similarities	0.08	-0.14	-0.27	0.05	-0.25	-0.04	-0.18	0.20
Digit Span	0.32	0.12	0.29	-0.12	0.11	-0.42	0.05	-0.21
Vocabulary	0.16	-0.22	-0.01	0.09	-0.50	-0.31	-0.12	-0.10
Digit Symbol	-0.11	-0.13	0.13	-0.05	-0.15	-0.51	-0.32	-0.62[1]
Picture Completion	-0.07	-0.28	-0.01	-0.05	-0.53	-0.49	-0.49	-0.34
Block Design	-0.15	-0.22	-0.10	-0.09	-0.14	-0.39	-0.35	-0.45
Picture Arrangement	-0.29	-0.04	0.02	0.18	-0.15	-0.49	-0.29	-0.62[1]
Object Assembly	-0.01	-0.13	-0.11	-0.08	-0.31	-0.60[1]	-0.27	-0.42
Trails A (sec)	0.14	0.41	0.00	0.17	0.03	0.52	0.00	0.54
Trails B (sec)	0.20	0.27	0.03	0.13	-0.05	0.46	-0.10	0.56
Boston Naming Test	0.16	-0.31	-0.01	0.13	-0.58[1]	-0.29	-0.30	-0.12
FAS total	0.04	0.03	0.08	0.05	-0.37	-0.42	-0.32	-0.44

Note. For Trails A, Trails B, and FAS, *n* of the Alzheimer's disease group = 17, 14, and 18, respectively; for FAS, *n* of the reference group = 33.

1. $p < 0.01$ (2-tailed test).

The double dissociations observed here are compatible with structure-function relationships reported elsewhere. Language function is traditionally recognized as a left para-Sylvian or a left frontal-lobe (Broca's area) function (for reviews, see Kolb and Whishaw, 1985; Ellis and Young, 1988). In this sample of AD patients, abnormality of the frontal language system was the primary source of the deficit and is suggestive of a precursor of speechlessness, which can occur in AD as well as with lesions of the anterior speech zone (Mazzocchi and Vignolo, 1979). Naming tests, which were developed to detect anomia often occurring with inferior frontal-lobe lesions (for review, see Benson, 1979), are especially sensitive to detecting AD-related

Fig. 6. Computed tomographic (CT) *z* scores of each of the 19 Alzheimer's disease patients with cognitive testing plotted against the cognitive test *z* scores



Taken together, the 4 plots show a double dissociation of brain-behavior relationships when the factor of age is removed from both scores.

language impairment (Huff et al., 1986). Picture Arrangement and Digit Symbol performance has been related to the function or integrity of the left and right posterior parietal lobes in studies of cortical glucose metabolism (Chase et al., 1984) and cortical lesions (Warrington et al., 1986). By contrast, in studies of alcoholism, deficits on these tests have been attributed to subcortical abnormalities, arising from diencephalic structures surrounding the third ventricle, or to frontal-lobe atrophy (for review, see Ryan and Butters, 1983). In studies of basal ganglia disease, including Parkinson's disease and progressive supranuclear palsy, Picture Arrangement performance is especially compromised (Pillon et al., 1986; Sullivan et al., 1989). Because of the absence of association with frontal sulcal atrophy, the Digit Symbol and Picture Arrangement deficits observed in the present study appear to have a subcortical basis. Taken together, these studies indicate that cortical as well as subcortical substrates exist for these two complex cognitive and motor functions and thus suggest that thorough studies of brain-behavior relationships cannot be restricted to cortical sites.

The brain-behavior correlations based on the WAIS subtests must be interpreted with caution. The WAIS was devised to assess normal intelligence and not to localize

brain lesions. Because of widespread use of the WAIS in neuropsychological settings, however, numerous investigators have tried to establish selectivity for subtests in reflecting function of different brain regions (e.g., Chase et al., 1984; Warrington et al., 1986). Such attempts have been made despite the fact that normal performance of each subtest (as well as most other established neuropsychological tests) probably requires multiple components of motor and cognitive skills. Each component itself may be subserved by different brain regions. Within the context of the present study, the multi-component nature of the tests must be considered. Accordingly, one interpretation of CT-cognitive test correlations stipulates that for a given subtest, a deficit reflects a subset of components compromised in AD and likely to be subserved by the associated brain region and likely not to be subserved by the dissociated brain region. Thus, some combination of the linguistic, problem solving, judgmental, and semantic memory components of the Comprehension subtest may be compromised and dependent upon the integrity of the frontal lobe, but not of the structures surrounding the third ventricle. Similar scenarios of component processes can be developed for the remaining subtests: Arithmetic involves calculation skills, working memory, and semantic memory; Object Assembly invokes knowledge of allocentric visual space, visual perception, and praxis; Digit Symbol invokes working memory, writing skills, and motor speed; and Picture Arrangement invokes cognitive sequencing, set formation and shifting, and working memory. Disruption of a brain region serving any one or a combination of these component processes may result in impaired performance.

Conclusion

Aging may exert the single most prevalent and prominent influence on brain structure and function. In accounting for this source of normal and expected variation in cross-sectional studies, the age-regression model provides a powerful method to control for age-related changes. The resulting distributions are continuous and thus free of artifact that may arise from arbitrary division of ages. The age-regression model also provides a means of comparing CT variables of subjects of different ages.

The cognitive data, as well as the CT data, suggest that heterogeneity exists within AD on the bases of age at onset and patterns of sparing and loss. Specific brain-behavior relationships can be established through quantitative and selective neuroradiological and neuropsychological measurements, even within a diagnostic category. Traditionally, the behavioral measures were of a continuous nature whereas brain status was simply categorical. The method of the present study allows for the brain measure to be continuous as well, thus permitting brain-behavior correlations to be calculated.

Demonstrating the co-occurrence of the presence of a brain lesion with sensory, motor, or cognitive impairment does not necessarily imply a specific association (Teuber, 1957; Jernigan, 1986). Only by establishing multiple dissociations can statements of specific association be made with confidence. Of particular relevance to this issue is that in the case of AD, only selective correlations were significant despite pervasive group abnormalities on brain and behavior measures. Whether enlargement of the brain's fluid-filled spaces observed in this study is attributable to gray

matter or white matter shrinkage is unknown and is largely unascertainable with CT technology. An answer to this question awaits study with magnetic resonance imaging, which supports reliable techniques for differentiating CSF, gray matter, and white matter tissue (e.g., Lim and Pfefferbaum, 1989).

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