Background: Positron emission tomographic studies of patients with Alzheimer disease (AD) suggest a loss of metabolic functional interactions between different cortical regions. Atrophy of the corpus callosum as the major tract of intracortical connective fibers may reflect decreased cortical functional integration in AD.

Objectives: To investigate whether regional atrophy of the corpus callosum is correlated with regional reductions of cortical glucose metabolism, as shown by positron emission tomography, and whether primary white matter degeneration is a possible cofactor of corpus callosum atrophy in AD.

Patients and Methods: We measured total and regional cross-sectional areas of the corpus callosum on mid-sagittal magnetic resonance imaging scans from 12 patients with AD and 15 age-matched control subjects. Regional cerebral metabolic rates for glucose in cortical lobes were measured by positron emission tomography using fludeoxyglucose F 18. White matter hyperintensities were rated in T2-weighted magnetic resonance imaging scans.

Results: The total cross-sectional area of corpus callosum was significantly reduced in patients with AD, with the most prominent changes in the rostrum and splenium and relative sparing of the body of the corpus callosum. Frontal and parietal lobe metabolism was correlated with the truncal area of the corpus callosum in AD. The ratios of frontal to parietal and of frontal to occipital metabolism were correlated with the ratio of anterior to posterior corpus callosum area in the group with AD. White matter hyperintensities did not correlate with corpus callosum atrophy in the patients with AD.

Conclusion: The regional pattern of corpus callosum atrophy correlated with reduced regional glucose metabolism independently of primary white matter degeneration in the patients with AD.

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THREE LINES of evidence support the notion of Alzheimer disease (AD) as a progressive neocortical disconnection syndrome.1-3 Neuropathological investigations4-6 find neurofibrillary tangles, a marker for cellular degeneration in AD, predominantly in large pyramidal neurons in cortical layers 3 and 5. These neurons give rise to long corticocortical connections within and between the hemispheres.7,8 They are detected in a clustered organization within the cortex of the primate brain.9 There is evidence1 for a similar clustered pattern of β-amyloid deposits in AD that would specifically connect these hallmarks of pathology with the corticocortical projecting neurons.

The corpus callosum is the major commissure connecting both cerebral hemispheres. Its fibers arise from a subset of the large pyramidal neurons in cortical layer 3.11,12 Several magnetic resonance imaging (MRI) studies13-18 report substantial atrophy of the midsagittal cross-sectional area of the corpus callosum in patients with AD. Primary white matter degeneration has been proposed13 to contribute to corpus callosum atrophy in subjects with AD who have a high prevalence of white matter hyperintensities on T2-weighted MRI scans.

Positron emission tomographic (PET) studies19-24 using fludeoxyglucose F 18 show reductions in the regional cerebral metabolic rates for glucose in AD in association neocortex, with a relative sparing of primary neocortex and subcortical areas. In addition, left-right asymmetries of regional cerebral metabolic rates for glucose and intrahemispheric metabolic uncoupling, evidenced by fewer statistically significant correlations between regional metabolic rates, have been reported in several studies.25-30 Haxby et al31 also demonstrate a significantly greater variance of anterior-
PATIENTS AND METHODS

PATIENT SELECTION

Twelve patients having clinically diagnosed AD (3 women and 9 men; mean ± SD age, 67.3 ± 8.2 years [range, 53-81 years]) were investigated. Nine patients were diagnosed as having probable and 2 patients as having possible AD, according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (now the National Institute of Neurological Disorders and Stroke) and the Alzheimer’s Disease and Related Disorders Association. One patient had biopsy-proven AD. Three patients exhibited predominantly visuospatial impairment. The degree of cognitive impairment was assessed using the Mini-Mental State Examination (MMSE). Four patients with an MMSE score of less than 10 were classified as having severe dementia, 5 patients with an MMSE score between 10 and 20 had moderate dementia, and 3 patients with a score of 20 or higher had mild dementia. The mean ± SD MMSE score was 12.5 ± 10.0. Eight patients had early-onset AD, and 4 patients had late-onset AD (cutoff, 65 years).

For comparison, 15 healthy volunteers (7 women and 8 men; mean ± SD age, 70.0 ± 8.7 years [range, 53-84 years]) were studied. All control subjects scored 29 or above on the MMSE (mean ± SD score, 29.7 ± 0.5). Magnetic resonance imaging and neuropsychological data from a subset of 15 subjects, 7 patients with AD and 8 controls, had already been included in a previous study on corpus callosum atrophy in AD.

Substantial comorbidity in the patients with AD and in controls was excluded by history and the results of physical and neurological examinations, psychiatric evaluation, chest x-ray film, electrocardiography, electroencephalography; brain MRI scans, and laboratory tests (complete blood count; sedimentation rate, serum electrolytes, glucose, urea nitrogen, creatinine, liver-associated enzymes, cholesterol, high-density lipoprotein cholesterol, triglyceride, antinuclear antibody, rheumatoid factor, VDRL, human immunodeficiency virus, vitamin B12, folate, and thyroid function test levels and urinalysis). Intracerebral disease, such as cerebral infarction, neoplasms, and chronic cerebrovascular lesions, was excluded for all subjects by normal results on an MRI scan, except for overall brain atrophy in the patients with AD. No subject had a history of diabetes mellitus, stroke, or head trauma. Four subjects, however, 2 patients with AD and 2 controls, showed mild systolic hypertension with a systolic blood pressure not above 165 mm Hg and a diastolic blood pressure below 90 mm Hg during the clinical examination.

The maximum period between MRI and PET measurement was 4 months in the patients with AD and 38 months in the controls. After a complete description of the study to the subjects, written informed consent was obtained from all subjects or the holders of their durable power of attorney to undergo MRI and PET examinations and neuropsychological assessment for clinical investigation and research. The protocol was approved by the National Institute on Aging’s Institutional Review Board.

MAGNETIC RESONANCE IMAGING

Eighteen T1-weighted and 18 proton-weighted axial slices (slice thickness, 6 mm; repetition time [TR]/echo time [TE], 2000/80 milliseconds and 2000/20 milliseconds, respectively), 32 proton-weighted coronal slices (slice thickness, 6 mm, and TR/TE, 2000/20 milliseconds) were obtained on a 0.5-T tomograph (Picker Instruments, Cleveland, Ohio). Furthermore, 1 patient with AD was administered a 64-slice, T2-weighted, and sagittally oriented volumetric sequence (slice thickness, 2.50 mm in plane resolution 1 × 1 mm; TR/TE, 36/6 milliseconds; and flip angle, 30°). All remaining 25 subjects were investigated with a 90-slice, T1-weighted, and sagittally oriented volumetric sequence (slice thickness, 2 mm; TR/TE, 20/6 milliseconds; and flip angle, 45°).

POSITRON EMISSION TOMOGRAPHY

Fifteen images were obtained parallel to the inferior orbital line using a PET scanner (model PC2048-15B; Scanditronix, Uppsala, Sweden) with reconstructed transverse and axial resolutions of 6.5 mm each. Subjects were placed in the scanner under resting conditions with eyes covered, the ears occluded, and the head fixed in a thermoplastic mask to minimize movement. Further details of the procedure are described elsewhere.

PSYCHOMETRIC TESTING

Each subject was administered the Mattis Dementia Rating Scale by trained psychometricians to obtain an overall assessment of cognitive function.

DATA ANALYSIS

Callosal Areas

Areas of the total corpus callosum and 5 callosal subregions were measured by one investigator (S.J.T.) blind to the subject’s diagnosis in the sagittal T1-weighted MRI slice that best represented the midsagittal section according to a previously described method and using commercial software for measuring region of interest (Analyze; Biomedical Imaging Resource, Mayo Foundation, Rochester, Minn) on a Sun workstation (Sun Microsystems, Mountain View, Calif). Interrater and intrarater reliability of this method, assessed with the intraclass correlation coefficient, has been previously reported. The number of pixels within each region was added automatically and multiplied by the pixel area to obtain absolute values (square millimeters) for the healthy controls using a new MRI-based method to measure cross-sectional areas of corpus callosum, and we correlated the measures with regional patterns of cortical glucose metabolism obtained with PET studies using fludeoxyglucose F 18. We also evaluated the white matter hyperintensity load in patients with AD and controls to see if primary white matter degeneration might correlate with corpus callosum atrophy in AD. A correlation between the regional cortical meta-
areas of total corpus callosum and of 5 subregions (labeled C1 to C5 in the rostral-occipital direction) (Figure 1).

The values of the 2 most anterior regions of the corpus callosum (C1 and C2) were added to obtain the frontal callosal area, and the values of the areas C3 to C5 were added to obtain the posterior callosal area. The corpus callosum ratio was calculated as the frontal callosal area divided by the posterior callosal area. Each of the absolute values was divided by the total intracranial volume to normalize callosal measurements for head size.

**Total Intracranial Volume**

The total intracranial volume was measured on the proton-weighted coronal slices using locally developed software (Quantas; Laboratory of Neurosciences, National Institute on Aging, National Institutes of Health, Baltimore, Md) for manual tracing and volumetry of intracranial structures. The total intracranial volume was traced at the inner edge of the dura. Each pixel represents a volume element (voxel) of 1 × 1 mm in the coronal plane and 6 mm in the rostral-occipital axis. An approximation of the total intracranial volume can be obtained by automatically adding the voxels belonging to the traced regions of interest over all slices.

**PET Analysis**

A template of circular regions of interest, 8 mm in diameter and encompassing 12 pixels, was constructed for all 15 horizontal PET slices. The regions of interest were evenly spaced throughout the cortex and subcortical and thalamic nuclei according to anatomical sections, parallel to the inferior orbitomeatal line, of an atlas of the human brain. This template was adjusted to the individual brain. The template was selected that best corresponded to the individual PET slice by visual inspection. Regions of interest of the template then were manually adjusted to the individual slice.

Metabolic values of regions of interest in the frontal, temporal, parietal, and occipital lobes were averaged to obtain lobar mean values of regional cerebral metabolic rates for glucose. Regions of interest covering the precentral and postcentral areas and the primary visual cortex (Brodman area 17) were excluded. Values obtained for the regions of interest of both thalami were added separately to obtain mean metabolic rates for the left and right thalamus.

All lobar metabolic values were normalized to the metabolic rate of the thalamus as an internal reference region that is relatively preserved in AD. Because functional deactivation from the more severely affected hemisphere could decrease metabolic activity in the ipsilateral thalamus, the side with the higher mean metabolic value was used for normalization. Thalamic normalization was done by dividing each lobar metabolic value by this thalamic value.

The values for all regions of interest belonging to parietal, temporal, and occipital cortical areas were added to obtain a mean parietotemporo-occipital cortical metabolic rate, which then was normalized to the thalamic metabolism.

Metabolic ratios were defined as the frontal lobe metabolism divided by the temporal, parietal, and occipital metabolic rates.

**White Matter Hyperintensity Rating**

Periventricular and deep white matter hyperintensities were graded by one investigator (S.J.T.) on the T1- and proton-weighted axial MRI slices using a modification of a reported rating scale. Signal changes on the corpus callosum were added as an extra item to this scale. Regional periventricular and deep white matter hyperintensity sub-scores were added to obtain a total periventricular and total deep white matter hyperintensity score.

**Statistical Methods**

Patient and control groups were compared in age using the Student t test and for the extent of periventricular and deep white matter hyperintensity scores using the Mann-Whitney U test. The sex ratio was compared between groups using the χ2 test. Differences in absolute and normalized total callosal areas between patients with AD and controls were assessed with the Student t test. Group differences in the distribution of callosal areas were tested using repeated-measures analysis of variance with groups as the between-subjects factor and the 5 callosal subregions as the within-subject factor. A significant group-by-subregion interaction was followed up by pairwise single-effect analysis using the Student t test.

Further analyses were performed on the normalized corpus callosum areas. In a multiple regression model, we predicted the normalized total corpus callosum area as a dependent variable by periventricular and deep white matter hyperintensity scores, age, and in the group with AD, by the Mattis Dementia Rating Scale score as an overall assessment of dementia severity. Four stepwise multiple regression models were performed separately for patient and control groups using the 5 normalized callosal subregions as predictors for each normalized lobar regional cerebral metabolic rate for glucose.

Correlations between metabolic and corpus callosum ratios, between frontal corpus callosum and frontal lobe metabolism, and between posterior corpus callosum and posterior cortical metabolism were assessed using the Pearson product moment correlation. The homogeneity of variance of the metabolic ratios between groups was tested using the Fisher F test. A value of P < .05 was considered significant.
Table 1. White Matter Hyperintensity (WMH) Ratings in Patients With Alzheimer Disease (AD) and Controls

<table>
<thead>
<tr>
<th>Hyperintensity</th>
<th>Maximal Possible Score</th>
<th>Controls (n = 15)</th>
<th>Patients With AD (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periventricular (range)</td>
<td>6 (0-6)</td>
<td>1.8 ± 1.5 (0-5)</td>
<td>2.9 ± 1.7 (1-6)</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>2</td>
<td>0.07 ± 0.26</td>
<td>0.08 ± 0.29</td>
</tr>
<tr>
<td>Deep white matter</td>
<td>24 (0-24)</td>
<td>4.9 ± 3.9 (0-11)</td>
<td>5.9 ± 6.9 (0-20)</td>
</tr>
<tr>
<td>Total range</td>
<td>0-6</td>
<td>0-5</td>
<td>0-6</td>
</tr>
<tr>
<td>Range of regional WMH</td>
<td>30</td>
<td>0.53 ± 0.83</td>
<td>0.42 ± 0.90</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>24</td>
<td>0.27 ± 0.46</td>
<td>0.33 ± 0.78</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD except where noted.

Table 2. Cross-sectional Areas of Corpus Callosum and Its Subregions (in Square Millimeters)

<table>
<thead>
<tr>
<th>Region</th>
<th>Controls (n = 15)</th>
<th>Patients With AD (n = 12)</th>
<th>% Reduction Between Patients With AD and Controls†</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA</td>
<td>511.7 ± 86.4</td>
<td>434.0 ± 63.5‡</td>
<td>−15</td>
</tr>
<tr>
<td>C1</td>
<td>133.6 ± 29.6</td>
<td>112.8 ± 23.3</td>
<td>−16</td>
</tr>
<tr>
<td>C2</td>
<td>68.3 ± 15.0</td>
<td>60.7 ± 10.8</td>
<td>−12</td>
</tr>
<tr>
<td>C3</td>
<td>66.9 ± 14.8</td>
<td>60.7 ± 10.8</td>
<td>−9</td>
</tr>
<tr>
<td>C4</td>
<td>64.7 ± 16.3</td>
<td>61.2 ± 14.4</td>
<td>−5</td>
</tr>
<tr>
<td>C5</td>
<td>153.5 ± 29.6</td>
<td>117.9 ± 19.0§</td>
<td>−23</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD. TCA indicates total corpus callosum area; AD, Alzheimer disease.
†Determined as follows: square millimeters of areas in patients with AD minus square millimeters of areas in controls divided by square millimeters of areas in controls.
‡P < .05.
§P < .001.

Table 3. Normalized Cross-sectional Areas (in Square Millimeters) of Corpus Callosum and Its Subregions

<table>
<thead>
<tr>
<th>Region</th>
<th>Controls (n = 15)</th>
<th>Patients With AD (n = 12)</th>
<th>% Reduction Between Patients With AD and Controls†</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA/TCV</td>
<td>34.3 ± 5.1</td>
<td>28.9 ± 3.7‡</td>
<td>−16</td>
</tr>
<tr>
<td>C1/TCV</td>
<td>8.9 ± 1.7</td>
<td>7.5 ± 1.5§</td>
<td>−16</td>
</tr>
<tr>
<td>C2/TCV</td>
<td>4.6 ± 1.0</td>
<td>4.0 ± 1.0</td>
<td>−13</td>
</tr>
<tr>
<td>C3/TCV</td>
<td>4.5 ± 0.8</td>
<td>4.0 ± 0.6</td>
<td>−11</td>
</tr>
<tr>
<td>C4/TCV</td>
<td>4.4 ± 1.1</td>
<td>4.1 ± 0.8</td>
<td>−7</td>
</tr>
<tr>
<td>C5/TCV</td>
<td>10.3 ± 1.9</td>
<td>7.9 ± 1.2</td>
<td></td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD. TCA indicates total corpus callosum area; TCV, total intracranial volume.
†See the second footnote to Table 2 for the formula used.
‡P < .005.
§P < .05.
||P < .001.

P < .03) with the frontal-to-parietal metabolic ratio and with the frontal-to-occipital metabolic ratio (r = 0.72; P < .01) (Figure 2 and Figure 3). The frontal-to-temporal metabolic ratio was not correlated with the corpus callosum ratio.

In controls, there was no significant correlation between any of the metabolic ratios and the corpus callosum ratio. The variance of all 3 metabolic ratios was significantly greater in subjects with AD than in controls (P < .01).

In the group with AD, a normalized area of callosal region C3 explained a significant (P < .03) proportion of variance of normalized frontal lobe and normalized parietal lobe metabolism (Figure 4 and Figure 5). No other corpus callosum subregion contributed to the predictive power of the multiple regression model. Neither normalized occipital lobe metabolism nor temporal lobe metabolism was correlated with the area of any corpus callosum region.

In controls, the multiple regression explained no significant proportion of variance of any normalized lobar metabolic value predicted by any corpus callosum subregion.

Figure 1. Corpus callosum measurements in the midsagittal slice showing the subregions. C1 indicates the rostrum; C2, the anterior truncus; C3, the middle truncus; C4, the posterior truncus; and C5, the splenium (from Hampel et al18).

Figure 2. The frontal-to-occipital metabolic ratio in the disconnection group with AD was correlated significantly (r = 0.72; P < .01) with the frontal-to-parietal metabolic ratio and with the frontal-to-occipital metabolic ratio (r = 0.72; P < .01).

Figure 3. The correlation between posterior corpus callosum and normalized posterior metabolism was not significant (r = 0.45; P > .05). On the other hand, areas of the 2 callosal subregions that represented the posterior part of the callosal body (C3 and C4) did not differ significantly between patients with AD and controls (Table 2 and Table 3). Normalized total callosal areas were not correlated with age, deep white matter and periventricular hyperintensity scores, and in the group with AD, the Mattis Dementia Rating Scale score.

In the group with AD, the correlation of the values between rostral corpus callosum and normalized frontal lobe metabolism was not significant (r = 0.45; P = .15); similarly, the correlation between posterior corpus callosum and normalized posterior metabolism was not significant (r = 0.52; P = .08). The corresponding correlations in the control group also did not reach significance.

The anterior-posterior corpus callosum ratio in the group with AD was correlated significantly (r = 0.64;
We investigated whether regional corpus callosum atrophy in AD was correlated with cortical glucose metabolism, to evaluate the use of corpus callosum area as an indirect marker of cortical disconnection in AD. We found atrophy of the corpus callosum, predominantly in the callosal rostrum and splenium, in patients with AD with a relatively wide range of white matter hyperintensities. This pattern remained stable after normalization to total intracranial volume to control for a possible effect of different sex ratios between groups. The frequency of white matter hyperintensities did not differ between patients with AD and controls, and white matter hyperintensities did not contribute to corpus callosum atrophy in patients with AD. This is generally consistent with our previously published report\(^1\) of corpus callosum atrophy in patients with AD with only minimal white matter changes. Because parietal and occipital cortical areas project mainly through the posterior corpus callosum,\(^{40,41}\) the inclusion of 3 patients with AD with Balint syndrome who exhibited predominantly occipitoparietal cortical disease\(^{42}\) may account for the predominance of posterior corpus callosum atrophy in our sample with AD. In contrast to our findings, Vermersch et al\(^{13}\) reported more white matter changes in their group with AD than in healthy controls and a significant correlation between corpus callosum atrophy and white matter hyperintensities. The mean ± SD age in their sample with AD, however, was higher than in ours (75.6 ± 9.5 years vs 67.3 ± 8.2 years) (P < .04). Because there is evidence\(^{43}\) of specific white matter changes in late-onset AD, a greater contribution of primary white matter degeneration to corpus callosum atrophy might occur in late-onset than in early-onset AD.

We found a significant correlation between the anterior-posterior corpus callosum ratio in patients with AD and the frontal-to-occipital and frontal-to-parietal metabolic ratios but not the frontal-to-temporal metabolic ratio. Reduced metabolism in occipital relative to frontal association cortical areas was accompanied by an analogous pattern of reduced posterior corpus callosum relative to frontal corpus callosum area. The anterior-posterior metabolic pattern has previously been established\(^{31}\) as a sensitive marker of cortical disconnection in AD. Thus, the significant correlation between the corpus callosum and metabolic ratios supports our notion that corpus callosum atrophy in AD may indicate a loss of intracortical connective neurons due to primary cortical disease rather than primary subcortical fiber loss. The anterior two thirds of the temporal lobe, including

\[ r = 0.64 \]

\[ r = 0.72 \]

\[ r = 0.63 \]

\[ r = 0.62 \]
the allocortical areas of its mesial aspect, have no direct contralateral projections through the corpus callosum, which may account for the lack of a significant correlation between the temporal metabolic and corpus callosum ratio. The inclusion of 3 subjects with AD who had undergone primary visuospatial impairment who were diagnosed as having the Balint syndrome increased the variance of the data, without introducing a statistically distinct subgroup (Figures 1 and 2). By visual inspection, the subjects with the Balint syndrome exhibited both parieto-occipital hypometabolism and posterior corpus callosum atrophy. The sample, however, was too small to allow for statistical testing of this pattern.

In controls, we did not find any correlation between metabolic and corpus callosum ratios. This likely reflects the narrow range of the metabolic ratio data in the control group.

The normalized frontal callosal cross-sectional area in our group with AD was not correlated significantly with normalized frontal metabolism, and the normalized posterior corpus callosum area did not correlate with normalized parietotemporo-occipital cortical metabolism. In contrast, Yamauchi et al. reported a correlation between frontal and parietotemporo-occipital cortical metabolism and frontal and posterior corpus callosum areas in AD. Significant correlations, however, between 2 large regions in PET studies and the corpus callosum may reflect a global reduction of cortical glucose metabolism parallel to overall brain atrophy, rather than a specific correlation between a regional pattern of cortical hypometabolism and corpus callosum atrophy. Looking at smaller cortical and corpus callosum regions, we did find a significant correlation of the frontal and parietal lobes cortical metabolic rates with region C3, representing the middle truncus of the corpus callosum. This finding is surprising. Both cortical regions may send a small proportion of their interhemispheric fibers through this callosal region, but the major part of projections runs through callosal areas whose atrophy was not related to metabolism in both lobes

CONCLUSIONS

A significant correlation between metabolic and corpus callosum ratios suggests a region-specific loss of interhemispheric projecting neurons in neocortex as the main cause of corpus callosum atrophy in AD, independent of primary white matter pathology. Metabolic impairment in PET cannot be explained only by damage to callosally projecting neurons. However, because these neurons form a subgroup of the intracortical projecting large pyramidal neurons in cortical layers 3 and 5, the correlation between corpus callosum atrophy and the anterior-posterior metabolic pattern in PET studies may be representative for the temporal course and regional distribution of AD pathology to corticocortical projecting neurons.

To establish the corpus callosum as a possible in vivo marker for the progress and regional distribution of neocortical degeneration in AD, future studies on a larger AD sample are warranted to allow the further investigation of the strength of correlations between corpus callosum atrophy and the pattern of cortical metabolic impairment in the dependency of disease progression.

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REFERENCES


