

Callosal Atrophy Correlates with Temporal Lobe Volume and Mental Status in Alzheimer's Disease

Sandra E. Black, Scott D. Moffat, David C. Yu, Jayson Parker, Peter Stanchev, Michael Bronskill

ABSTRACT: Background: Recent studies have reported significant atrophy of the corpus callosum (CC) in Alzheimer's Disease (AD). However, it is currently unknown whether CC atrophy is associated with specific cortical volume changes in AD. Moreover, possible atrophy in extra-callosal commissures has not been examined to date. The purpose of the present study was to quantify atrophy in two cerebral commissures [the CC and the anterior commissure (AC)], to correlate this measure with cognitive status, and to relate commissural size to independent measures of temporal lobe volume in AD patients. **Methods:** A sample of AD patients and of age- and education-matched normal control subjects (NCs) underwent MRI and a cognitive test battery including the Dementia Rating Scale and Mini Mental State examination. Mid-sagittal regional areas within CC and AC were measured along with superior, middle and inferior temporal lobes volumes. **Results:** Alzheimer's Disease patients had significantly smaller callosa than did NCs. The callosal regions most affected in AD included the midbody, isthmus and genu. The isthmus and midbody areas of the CC were positively correlated with cognitive performance and with superior temporal lobe volume in AD patients. The mid-sagittal area of the AC and the superior temporal volumes did not differ between AD patients and NCs. **Conclusions:** The study demonstrated that the regional morphology of the CC correlates with current cognitive status and temporal lobe atrophy in AD. As well, the lack of difference for the AC suggests that commissural atrophy in AD is regionally specific.

RÉSUMÉ: Corrélation de la morphologie régionale du corps calleux au volume du lobe temporal et à la performance cognitive dans la maladie d'Alzheimer: Introduction: Des études récentes ont rapporté une atrophie significative du corps calleux (CC) dans la maladie d'Alzheimer (MA). Cependant, nous ne savons pas si l'atrophie du CC est associée à des changements spécifiques du volume cortical dans la MA. De plus, on n'a jamais examiné s'il existait une atrophie des commissures extra-calleuses. Le but de cette étude était de quantifier l'atrophie au niveau de deux commissures cérébrales {le CC et la commissure antérieure (CA)}, de corréler cette mesure à l'état cognitif et de relier la taille commissurale à des mesures indépendantes du volume du lobe temporal chez des patients atteints de MA. **Méthodes:** Un échantillon de patients atteints de la MA et de sujets contrôles appariés pour l'âge et le niveau d'éducation (CNs) ont subi une RMN et une évaluation de la fonction cognitive au moyen de l'échelle de la démence et du Mini-examen de l'état mental. Les zones sagittales médianes du CC et la CA ont été mesurées ainsi que le volume des lobes temporaux supérieurs, moyens et inférieurs. **Résultats:** Les patients atteints de la MA avaient une mesure du CC significativement plus petite que les CNs. Les régions du CC les plus atteintes dans la MA comprenaient la partie moyenne du corps, l'isthme et le genou. L'isthme et la région moyenne du CC étaient positivement corrélés à la performance cognitive et au volume du lobe temporal supérieur chez les patients atteints de la MA. La région sagittale moyenne de la CA et les volumes temporaux supérieurs n'étaient pas différents chez les patients atteints de la MA et les CNs. **Conclusions:** Cette étude démontre que la morphologie régionale du CC est corrélée à l'état cognitif et à l'atrophie du lobe temporal dans la MA. De plus, l'absence de différence au niveau de la CA suggère que l'atrophie commissurale dans la MA est spécifique à la région.

Can. J. Neurol. Sci. 2000; 27: 204-209

The corpus callosum (CC) is the largest interhemispheric commissure, containing some 200 million neurons¹ integrating widespread areas of the neocortex of the left and right cerebral hemispheres. Because the CC preserves the anterior-posterior distribution of cortical neurons,^{2,3,4} quantification of callosal morphology may provide insight into the regional cortical topographic changes associated with normal aging and Alzheimer's Disease (AD).

From the Cognitive Neurology Unit, Department of Medicine and Research Program in Aging, Sunnybrook Women's College and Health Sciences Centre, University of Toronto, Toronto, Ontario (SEB, DCY), Gerontology Research Center, National Institute on Aging, Baltimore MD (SDM), Institute of Mathematics and Computer Science, Bulgarian Academy of Sciences (PS), Medical Imaging, SWCHSC and Department of Medical Biophysics, University of Toronto, Toronto, Ontario (MB).

RECEIVED SEPTEMBER 9, 1999. ACCEPTED IN FINAL FORM MAY 23, 2000.
Reprint requests to: Sandra E. Black, Head, Division of Neurology, Cognitive Neurology Unit, Sunnybrook Women's College and Health Sciences Centre, Room A421-2075, Bayview Avenue, North York, Ontario M4N 3M5 Canada

Alzheimer's disease is a dementia characterized pathologically by the presence of amyloid plaques, neurofibrillary tangles and neuronal loss. Histopathologic and functional neuroimaging studies have demonstrated that the regions most severely compromised in AD are the hippocampus, the posterior cingulate gyrus and the temporal, posterior parietal and prefrontal association cortices, with relative sparing of the occipital cortex, anterior temporal regions and primary sensory and motor cortices.^{5,6,7} The pyramidal cells in lamina III represent one of the principal cell layers affected in the neocortex.⁸ Because the axons of cortical pyramidal cells give rise to the corpus callosum,⁹ pyramidal degeneration would be expected to result in atrophy of the CC in a manner that corresponds to the regional pathophysiology of the disease process.

Recent studies have reported significant reductions in mid-sagittal CC size in AD.¹⁰⁻²⁰ For example, Biegon et al¹² found that AD was accompanied by a reduction in CC area in the genu and midbody regions, while Lyoo et al¹³ reported that, relative to age-matched controls, individuals with AD demonstrated significant atrophy of the midbody and posterior CC. Interestingly, Teipel et al¹⁷ reported significant rostral and splenial CC atrophy in AD patients and further noted that the degree of CC atrophy was correlated with cerebral glucose metabolism in the corresponding cortical regions (see also Yamauchi¹⁴). Janowsky et al¹⁵ found that the entire cross sectional area of the CC was significantly smaller in AD patients compared to samples of both healthy elderly and 'incipient dementia' control subjects. Moreover, they reported a positive correlation between CC area and cognitive status as assessed by the Mini Mental Status Examination (MMSE), suggesting that atrophy of the CC may be useful in tracking cognitive decline in AD.¹³⁻¹⁶

In the present study, AD patients and healthy elderly control subjects underwent magnetic resonance imaging (MRI). As well as investigating regional CC atrophy in AD, this study quantified temporal lobe volume and administered cognitive status and dementia screening tests to these subjects in order to examine correlations between CC atrophy, cortical degeneration and cognitive performance in AD. It was predicted that regional atrophy within the CC would reflect the known topographical selectivity of AD⁵⁻⁷ and that CC atrophy would correlate with cognitive measures. For example, atrophy of the isthmus should correlate with superior temporal lobe volumes, since it interconnects these regions as indicated in Figure 1. Moreover, because previous studies have not investigated the status of other commissural systems, the present study also examined the mid-sagittal area of the anterior commissure (AC) in AD patients and NCs. Because the AC houses fibres originating primarily in the most anterior portions of the temporal lobes,^{21,22} which are relatively spared in AD,^{5,23} it was predicted that there would be no difference between AD patients and controls in AC area.

METHOD

Subjects

Patients with probable AD were recruited from the Cognitive Neurology Clinic at Sunnybrook and Women's College Health Science Centre, University of Toronto (Toronto, Canada). The

group consisted of 23 patients (10 males, 13 females) who met the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association diagnostic criteria for probable AD.²⁴ The mean age of AD patients was 69.1 (\pm 1.9) years, and the mean years of education was 12.9 (\pm 0.6).

Seventeen community-dwelling normal control subjects (NCs) (10 males, 7 females) were recruited from the Greater Toronto Area. They had no history of any neurologic or psychiatric disease and performed within normal limits on formal neuropsychological testing. Furthermore, MRI scans from all NCs were within normal limits for their age. Normal controls had an average of 13.2 (\pm 0.6) years of education and a mean age of 71.9 (\pm 1.0) years. NCs did not differ from AD patients in either age [$t(38) = 1.18$, $p = .25$] or years of education [$t(38) = 0.43$, $p = .67$] indicating that AD patients and controls were adequately matched on these variables.

Subjects underwent MRI and were administered the Mattis Dementia Rating Scale (DRS)²⁵ and the MMSE.²⁶ The mean delay between the date of MRI and the date of cognitive testing was 44.4 (\pm 52.8) days. MMSE data for one AD patient and DRS data for three AD patients were excluded from cognitive analyses because the date of cognitive testing deviated by more than six months from the date of MRI. All NCs scored above 129 on the DRS which is above the recommended cut-off for probable dementia.²⁵ The mean score on the DRS for AD patients ($X = 105.37 \pm 17.17$) was significantly lower [$T(34) = 8.09$, $p < .001$] than the mean score for NCs ($X = 139.76 \pm 3.58$). The mean score on the MMSE for AD patients ($X = 18.1$, ± 5.4) was significantly lower [$t(37) = 7.37$, $p < .001$] than the MMSE scores of the NCs ($X = 28.2$, ± 1.8).

Procedure

Magnetic resonance imaging

MRI scans were performed on a 1.5T General Electric Signa MR system. A T1-weighted 3-D volume technique (TR = 35 ms; TE = 5 ms; flip angle = 35 degrees; field of view = 22 cm; matrix size = 192 X 256) was used to obtain 124 contiguous sagittal slices (1.2 mm thickness). MR images were processed on a Sun microcomputer workstation using ANALYZE computer software (Biomedical Imaging Resource) for 3-D volume reconstruction and measurement. It is important to note with respect to white matter disease, that the subjects in the AD and NC samples had minimal white matter changes well within normal limits for age.

Corpus callosum and anterior commissure measurement

The CC was isolated based on intensity thresholds and automatically traced using an automated technique. This program divided the CC in mid-sagittal view into six subdivisions designed to maintain the anterior-posterior distribution of cortical neurons through the CC.^{2,3,4} The CC was segmented based on criteria devised by Witelson (1989).⁴ The rostrum of the CC was included as part of the genu (see Figure 1). All CC measures were obtained blind with respect to the disease status of subjects.

The anterior commissure in mid-sagittal section represents the convergence of axons from cell bodies which reside primarily in the anterior temporal lobe.^{21,22} The AC was traced in mid-sagittal section using a hand tracing technique (See Figure

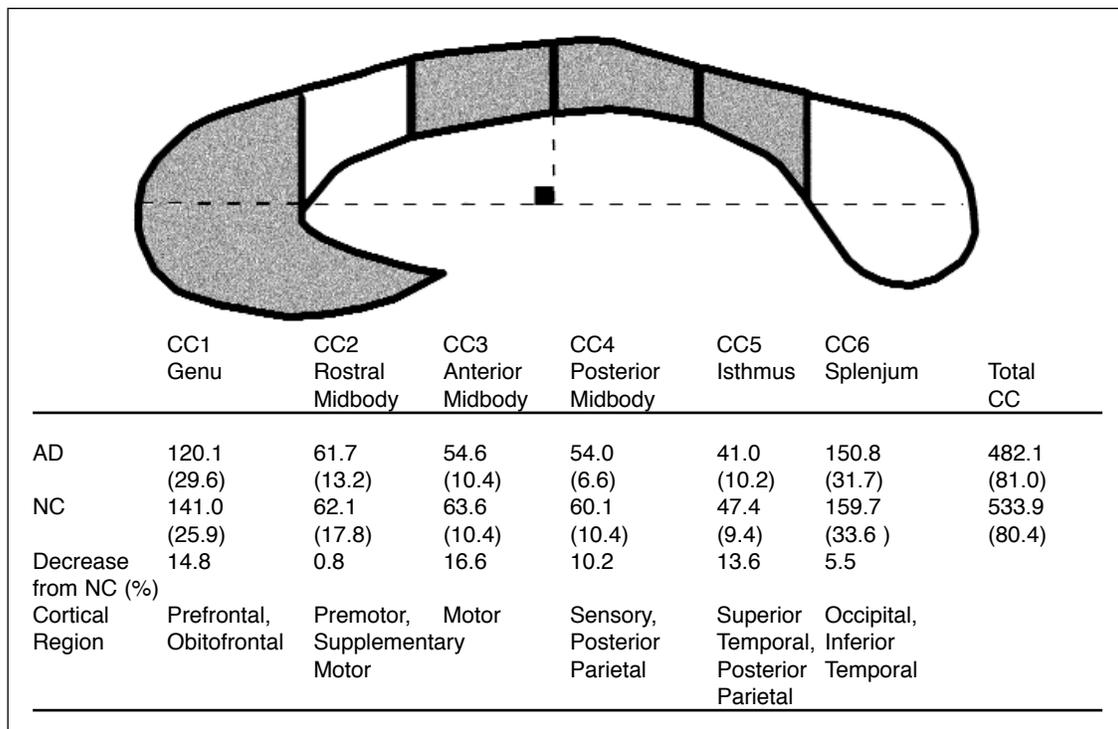


Figure 1: Regional callosal subdivisions and mean regional area measures (s.d.) in Alzheimer's Disease (AD) patients and normal control subjects (NCs). Stippled areas reflect CC regions which were significantly smaller in AD patients compared to those in NCs ($p < .05$).

2). Under 3X magnification, the experimenter traced the perimeter of the AC using a computer mouse, and the area of the AC was calculated by the ANALYZE software package. To establish that the area of this small structure could be traced reliably, the AC of each participant was traced at three separate times, twice by one of the experimenters (SM) and once by another independent rater (DY). All AC tracings were performed

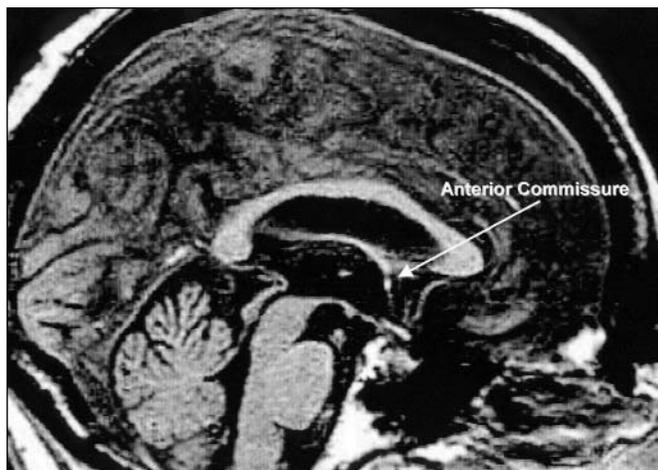


Figure 2: Mid-sagittal MRI showing the corpus callosum and anterior commissure (white arrow).

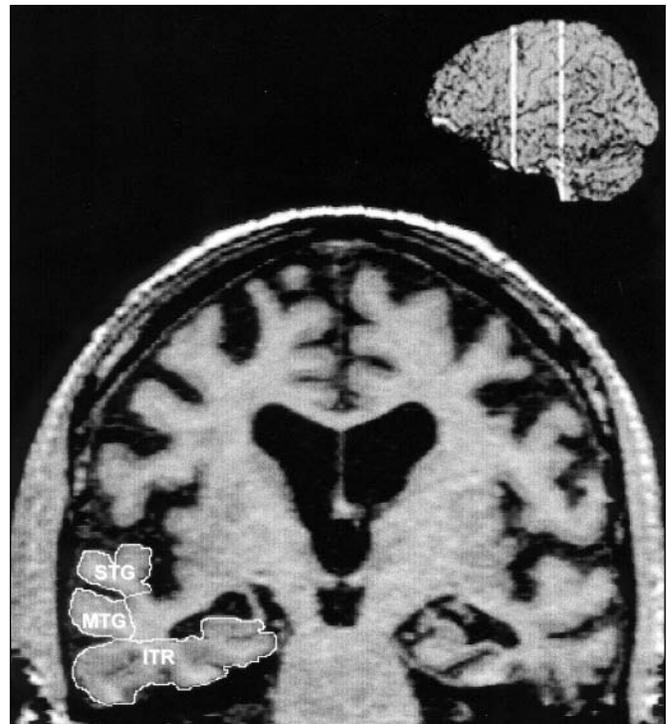


Figure 3: Coronal MRI depicting the regional demarcation of the superior temporal gyrus (STG), middle temporal gyrus (MTG) and inferior temporal region (ITR) in a representative AD patient.

Table 1. Correlations of Region Callosal and Anterior Commissure Areas with Cognitive Test Performance in AD patients.

	CC1	CC2	CC3	CC4	CC5	CC6	CC Total	AC
DRS	.44	.29	.54*	.43	.52*	.12	.39	.31
MMSE	.37	-.07	.31	.31	.57**	.06	.27	.30

* $p < .05$.** $p < .01$.

blind with respect to subject disease status and blind to the measurements obtained by other raters. Intraclass correlations revealed an intrarater reliability of $r = .87$ and an interrater reliability of $r = .77$. Anterior commissure data from one subject was excluded due to movement artifact which obscured the structure in mid-sagittal section.

Temporal lobe measures

Portions of the superior temporal gyrus (STG), middle temporal gyrus (MTG) and inferior temporal region (ITR) (comprising inferior temporal gyrus, occipitotemporal gyrus, parahippocampal gyrus and hippocampus) were manually traced bilaterally over a series of six coronal slices. The coronal slices were perpendicular to the anterior commissure-posterior commissure axis from a sagittal point of view and perpendicular to the interhemispheric fissure from an axial view. Anatomical delineation of the STG, MTG and ITR was based on the neuroanatomic atlas of Talairach and Tournoux²⁷ (see Figure 3). The first slice began at the AC and subsequent slices were posterior at 5.2 mm increments, thereby sampling the mid-temporal region from the AC posteriorly for approximately 31 mm. Following manual tracing of each of the six slices of each temporal region, the volume of each region was calculated according to Simpson's Law.²⁸ The volume of the individual temporal lobe regions was based on the computation of the mean of the corresponding volumes for both the left and right hemispheres. A subset of 20 temporal lobe regions was measured twice by the same rater (DY) and once by a second blind rater (JP) to establish reliability of volume calculations. Intraclass correlations revealed that the intrarater reliability for all temporal lobe volumes was greater than $r = .93$. Interrater agreement for the STG was $r = .85$, for the MTG $r = .83$ and for the ITR $r = .76$.

Intracranial capacity

The total intracranial capacity was derived using a tissue

Table 2. Correlations of Regional Callosal and Anterior Commissure Areas with Temporal Lobe Volumes in AD patients.

	CC1	CC2	CC3	CC4	CC5	CC6	AC
STG	.35	-.07	.43*	.37	.61**	.13	.39
MTG	.34	-.17	.36	.20	.41	.13	.35
ITR	.23	-.37	.45*	.18	.37	-.06	.17

* $p < .05$.** $p < .01$.

classification technique to strip away nonbrain tissues as described previously.²⁹ This gives an estimate of premorbid brain volume prior to any atrophic process, and allows any differences in head size to be taken into account in the group comparisons.

RESULTS

The results of the area measurements for each subregion and overall areas are shown in Figure 1. To investigate the hypothesis that AD patients had smaller CC regions than NCs, analysis of variance (ANOVA) was performed comparing the two groups with respect to the regional subdivisions of the CC. There was a main effect of disease status in which AD patients had significantly smaller callosal subregions in CC1 [$F(1,38) = 5.39$, $p = .03$], CC3 [$F(1,38) = 7.44$, $p = .01$], CC4 [$F(1,38) = 5.20$, $p = .03$] and CC5 [$F(1,38) = 4.19$, $p = .05$]. Overall, the total area of the CC was significantly smaller in AD patients than in NCs [$F(1,38) = 4.02$, $p = .05$]. AD patients and NCs did not differ significantly in the area of regions CC2 [$F(1,38) = 0.01$, $p = .92$] or CC6 [$F(1,38) = 0.72$, $p = .40$] (see Figure 1).

To investigate whether AD patients and NCs differed in AC area, an independent samples t-test was performed with disease status as independent variable and AC area as dependent measure. AD patients ($X = 6.84 \text{ mm}^2$, ± 3.24) and NCs ($X = 7.34 \text{ mm}^2$, ± 2.29) did not differ significantly in the size of the AC [$t(37) = 0.54$, $p = .59$], suggesting some specificity of the group differences in the callosal subregions.

AD patients ($X = 1400.90$, ± 144.08) and controls ($X = 1399.20$, ± 134.28) did not differ in intracranial capacity which was used as an estimate of premorbid brain volume [$t(38) = 0.38$, $p = .80$].

To examine the degree to which regional callosal size indexed degree of cognitive decline in AD, partial correlations were performed between regional CC area and performance on the DRS and MMSE within the AD patients. Age and years of education were incorporated as covariates to control for the possible confounding influence of these variables on cognitive performance. Scores on the DRS were significantly positively correlated with the area of region CC3 [$r(15) = .54$, $p = .03$] and region CC5 [$r(15) = .52$, $p = .03$]. Scores on the MMSE were significantly positively correlated with the area of region CC5 [$r(18) = .57$, $p < .01$]. In contrast, the area of the AC was uncorrelated with performance on either the MMSE [$r(17) = .30$, $p = .21$] or the DRS [$r(14) = .31$, $p = .24$] (see Table 1).

To compare AD patients and NCs in their temporal lobe volumes, ANOVA's were performed with disease status as independent variable and temporal lobe volumes as dependent variables. Because we did not observe significant temporal lobe asymmetries in this sample (all p 's $> .05$), the mean of the left

and right side were used as dependent variable for temporal lobe volume measures. Consistent with the pathophysiology of AD, there was a main effect of disease status in which NCs had larger temporal lobe volumes for the ITR [$F(1,38) = 16.02, p < .001$] and MTG [$F(1,38) = 5.17, p = .03$]. AD patients and NCs did not differ in the volume of the STG [$F(1,38) = 2.49, p = .12$].

To examine the degree to which regional callosal size indexed temporal lobe atrophy in AD, correlations were performed examining the relationship between regional CC area and the volume of the STG, MTG and ITR within the AD patients (see Table 2). Given that the neurons of the STG are believed to pass through the isthmus of the CC,^{3,4} we predicted that the size of these structures would be correlated. Consistent with this topographical distribution of cortical projections through the CC, significant correlations between STG volume and the isthmus (CC5) were observed [$r(21) = .61, p < .01$]. In addition, STG volume also correlated with the area of the anterior midbody [$r(21) = .43, p = .04$] of the CC. No other significant correlations were observed and volumetric measures of this mid-temporal sample did not correlate significantly with AC area (see Table 2).

DISCUSSION

These results provide further evidence of significant CC atrophy in AD patients compared to healthy elderly control subjects. The mean total CC area in our AD sample (482.1 mm²) was similar to that reported in AD subjects by Biegon et al (480mm²)¹² and by Yamauchi et al (469mm²).¹⁴ Our CC sub-divisional areas also correspond closely to those reported by Lyoo et al¹³ who used the identical demarcation technique.⁴

Our data revealed significant atrophy throughout the midbody and isthmus of the CC, callosal regions which interconnect central, posterior parietal and temporal cortices.^{2,4,30} Significant atrophy was also noted in genu of the CC which houses fibres originating primarily in prefrontal cortex.^{2,3,4} Although CC atrophy is known to occur as a function of normal aging,^{31,32} the significant differences between AD patients and NCs reported here and by others¹⁰⁻²⁰ clearly demonstrate that the shrinkage in CC size in AD is out of proportion with that expected in normal aging. Moreover, our data demonstrated that AC area did not differ between AD patients and controls. As far as we are aware, this is the first study to investigate the effects of AD on a noncallosal commissural system. The lack of difference between AD and NC subjects in AC area supports the specificity of the atrophic changes to the cortical fibres which give rise to the CC, and provides additional evidence that the CC shrinkage in AD has some cortical specificity and does not represent generalized commissural or white matter damage.

Although there are some reports of white matter abnormalities in AD,³³ microscopic studies⁵ and gross anatomical investigations²⁹ reveal that grey matter structures are most affected. Moreover, Teipel et al¹⁸ and Hampel et al¹⁹ quantified regional callosal area and obtained measures of white matter hyperintensity load in AD patients and controls and reported that CC atrophy was independent of white matter hyperintensity ratings. The fact AD does not result in marked white matter damage, combined with the demonstrated independence of CC atrophy and ratings of MRI-determined white matter hyperintensities strongly suggests the CC atrophy

reflects cortical neuronal degeneration rather than primary white matter pathology.

An interesting question regarding CC atrophy in AD is whether the examination of *regional* CC morphology may reflect specific topographic changes in the neocortex. In the present study, the most dramatic differences were observed in the midbody, isthmus and genu of the CC. These findings mirror those obtained by Biegon et al¹² who also reported significant genu and midbody shrinkage in AD. Some studies, however, have observed reduction in CC size which is restricted to more posterior regions with a relative sparing of the anterior CC,¹⁴ while other studies have reported that the anterior CC may be primarily affected.¹⁵ Although the precise reason for disagreement between studies in the anatomical specificity of CC atrophy is not clear, marked differences in the operational divisions of the CC may play a prominent role.¹⁵ Disease heterogeneity and variations in the severity of the sample populations are also likely to be important factors. In particular, degenerative changes in the neocortex in AD are known to follow a temporal as well as topographic pattern, with posterior parietal, cingulate and temporal lobe damage preceding prefrontal involvement.³⁴ It is possible that differences between studies in the regional specificity of the CC findings are related to differences in the temporal window through which individual studies have viewed the disease process. It will be important for future investigations to examine the possibility that regional atrophy of the CC is time-dependent, with some CC regions being more affected than others at different stages of the illness.

As well as reporting reduced regional callosal size in AD, this study demonstrated that regional CC morphology correlates with cognitive status. In particular, the area of the isthmus of the CC was positively correlated with two independent measures of cognitive functioning in these patients. The present data suggest that regional CC morphology may reflect the severity of cognitive decline in AD.

Importantly, the identical callosal subregions which correlated with cognitive performance in AD also correlated with temporal lobe volume in our sample. This is precisely the callosal region identified by Thompson et al²⁰ as demonstrating the most substantial areal loss in AD. These findings are consistent with the observation that parietal and temporal lobe regions, whose neurons give rise to the isthmus and posterior midbody of the CC, are vulnerable in AD. However, it should be acknowledged, that significant correlations were also observed in CC3 (see Table 2). Although temporal lobe neurons are thought to project primarily through the posterior portion of the body of the CC in nonhuman primates,² deLacoste et al³ have reported that in humans, some temporal lobe fibres may pass through the callosal midbody. Moreover, significant correlations with other callosal regions would not be unexpected if decreases in temporal lobe volume are indirectly indicative of degenerative changes in other cortical zones.

In summary, the present data provide additional support for the notion that AD is accompanied by regionally specific callosal atrophy which is out of proportion with that expected in normal aging. Moreover, this degeneration does not generalize to the AC, a fibre tract which houses axons emanating from brain regions which are relatively spared in AD. Our findings combined with those of previous investigations suggest that AD

may be associated with progressive hemispheric disconnection and demonstrate the utility of quantifying CC atrophy as a marker of regional neuronal degeneration and cognitive decline. Future studies which examine lobar/gyral volumes in a variety of cortical regions will elucidate the degree to which callosal measurement may chart the cortical topography and cognitive decline in AD.

ACKNOWLEDGEMENTS

Research reported in this article was supported by grants to Dr. S.E. Black by the Ontario Mental Health Foundation and the Medical Research Council of Canada.

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