PAPER

Corpus callosum atrophy is associated with mental slowing and executive deficits in subjects with age-related white matter hyperintensities: the LADIS Study

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Background: Previous research has indicated that corpus callosum atrophy is associated with global cognitive decline in neurodegenerative diseases, but few studies have investigated specific cognitive functions.
Objective: To investigate the role of regional corpus callosum atrophy in mental speed, attention and executive functions in subjects with age-related white matter hyperintensities (WMH).
Methods: In the Leukoaraiosis and Disability Study, 567 subjects with age-related WMH were examined with a detailed neuropsychological assessment and quantitative magnetic resonance imaging. The relationships of the total corpus callosum area and its subregions with cognitive performance were analysed using multiple linear regression, controlling for volume of WMH and other confounding factors.
Results: Atrophy of the total corpus callosum area was associated with poor performance in tests assessing speed of mental processing—namely, trail making A and Stroop test parts I and II. Anterior, but not posterior, corpus callosum atrophy was associated with deficits of attention and executive functions as reflected by the symbol digit modalities and digit cancellation tests, as well as by the subtraction scores in the trail making and Stroop tests. Furthermore, semantic verbal fluency was related to the total corpus callosum area and the isthmus subregion.
Conclusions: Corpus callosum atrophy seems to contribute to cognitive decline independently of age, education, coexisting WMH and stroke. Anterior corpus callosum atrophy is related to the frontal-lobe-mediated executive functions and attention, whereas overall corpus callosum atrophy is associated with the slowing of processing speed.

Corpus callosum is the largest commissural structure consisting of white matter tracts that connect the cerebral hemispheres according to an anterior–posterior topographical organisation. Recent research using diffusion tensor magnetic resonance imaging (MRI) has augmented earlier postmortem findings of corpus callosum topography and has shown that the anterior parts of corpus callosum (rostrum and genu) connect the orbitofrontal, lateral and medial frontal cortices, whereas the body and splenium connect parietal, temporal and occipital homotopic regions.[1] In neurodegenerative diseases, the corpus callosum area is markedly reduced, indicating marked axonal loss.[2–5] In Alzheimer's disease, the severity and pattern of corpus callosum atrophy have been associated with cortical neuronal loss[6] independently of white matter hyperintensities (WMH).[7] In vascular dementia and other ischaemic conditions, however, corpus callosum atrophy is correlated with WMH and hence may result from subcortical ischaemic damage.[8 9]

Earlier studies have shown that corpus callosum atrophy is associated with global cognitive status,[5 6 10] but, to date, few studies have investigated the role of regional corpus callosum atrophy in specific cognitive processes. Based on the topographical organisation of corpus callosum, the integrity of its subregions may reflect distinct cognitive deficits. In particular, anterior corpus callosum atrophy may be related to the frontal-lobe-mediated executive deficits. Previous work of the Leukoaraiosis and Disability (LADIS) Study has shown that age-related WMH are associated with cognitive impairment in elderly subjects without dementia.[11] Moreover, in these subjects, the corpus callosum area has been found to be inversely related to motor deficits and global cognitive decline.[12] This study examined the independent contribution of regional corpus callosum atrophy to deficits in mental speed, attention and executive functions in a large sample of elderly subjects with WMH by using quantitative MRI analysis and targeted neuropsychological test methods. The demographic and medical background variables, and coexisting WMH were controlled by using multivariate analysis.

MATERIALS AND METHODS

Subjects and study design

The LADIS Study is a longitudinal European multicentre study aimed at investigating the importance of age-related WMH in transition to disability. Eleven centres in European countries participated in the study (see the appendix), collecting a sample of 639 elderly subjects with different degrees of WMH. Details of the study protocol have been published earlier.[13] The sample consisted of initially non-disabled subjects without dementia who had mild cognitive or motor disturbances, mood changes, other neurological problems, or in whom age-related WMH

Abbreviations: CC1, rostrum and genu; CC2, rostral body; CC3, midbody; CC4, isthmus; CC5, splenium; LADIS, Leukoaraiosis and Disability; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; VADAS-cog, Vascular Dementia Assessment Scale—Cognitive; WMH, white matter hyperintensities

were found incidentally in brain imaging. Controls and volunteers from other study projects were also included. The inclusion criteria were as follows: age 65–84 years, changes in cerebral subcortical white matter (from mild to severe according to a revised version of the scale of Fazekas *et al*[13]), no or mild impairment in instrumental activities of daily living (none or one item compromised in this scale[13a]) and presence of a contactable informant. The exclusion criteria were: presence of severe illness likely leading to drop-out, severe unrelated neurological disease, leucoencephalopathy of non-vascular origin (immunological-demyelinating, metabolic, toxic, infectious or other), severe psychiatric disorders, and inability or refusal to undergo brain MRI. The study was approved by the local ethics committees of each participating centre. Informed written consent was received from all subjects. In all, 72 subjects were excluded from this study because MRI data of WMH or corpus callosum were incomplete (the dataset was not completed or the scans were of insufficient quality for quantitative analysis). The total sample in this study was therefore 567 subjects. The included and excluded subjects did not differ from each other in age, sex, education, history of stroke, the visual WMH rating or the Mini-Mental State Examination score.[14]

The baseline assessment on study entry included brain MRI and a comprehensive examination of social background and medical history by using a structured questionnaire and interview, and a collection of all available medical records. Functional and clinical assessment included a standard cardiovascular and neurological examination, functional status measures and a detailed neuropsychological examination. In the 3-year follow-up, the functional and clinical assessments will be repeated yearly for all the subjects. This study focused on the baseline data.

Neuropsychological examination

The neuropsychological test battery of the LADIS Study included global cognitive tests, the Mini-Mental State Examination[14] and the modified version of the Vascular Dementia Assessment Scale-cognitive (VADAS-cog),[15] with executive tests, the Stroop test[16] and the trail making test.[17] The methods were carefully selected and instructed to be suited for multicentre use.[18] In this study, we focused mainly on measures of mental speed, attention and executive functions. Specifically, mental speed was assessed with the trail making A test and the reading and coloured dots sections of the Stroop test (Stroop parts I and II). Attention and executive functions, encompassing mental flexibility, set-shifting and response inhibition, were assessed with the symbol digit modalities and the digit cancellation subtests of the VADAS-cog, and with the subtraction scores of the trail making and Stroop tests. These scores were calculated by subtracting the time taken in trail making A from the time taken in trail making B (trail making B−A) and similarly for the Stroop coloured colour-names and dots (Stroop III−II). Of the VADAS-cog subtests, the verbal fluency test with animal category was used to assess executive flexibility and semantic oral skills, and the digit span backwards test to assess the working memory capacity. Additionally, the object naming and constructional praxis (copying geometric forms) subtests from VADAS-cog were used.

Magnetic resonance imaging

All subjects underwent brain MRI locally at the centre where they were recruited according to a standard protocol.[13 19] The MRI was performed with a 1.5-T scanner in 10 centres and with a 0.5-T scanner in one centre. The protocol comprised three-dimensional high-resolution coronal or sagittal T1-weighted magnetisation prepared rapid acquisition gradient echo images (echo time 4–7 ms, repetition time 10–25 ms, field angle 15–30°, voxel size $1\times1\times1$ mm^3, field of view 250 mm), axial T2-weighted images (echo time 100–120 ms, repetition time 4000–6000 ms) and fluid-attenuated inversion recovery images (echo time 100–140 ms, repetition time 6000–10 000 ms, inversion time 2000–2400 ms). The images were collected centrally at the Image Analysis Centre of the Vrije Universiteit Medical Centre (Amsterdam, The Netherlands). The volume of WMH was assessed on the fluid-attenuated inversion recovery images by a single rater using a semiautomated method as detailed earlier.[19] The lesions were marked using a seed technique, and local thresholding was performed on each slice. The total volume of WMH was calculated automatically after all lesions were delineated.

The assessment of corpus callosum atrophy was performed in the Danish Research Center for Magnetic Resonance (Copenhagen, Denmark), and the procedure has been described elsewhere.[12] In short, the magnetisation prepared rapid acquisition gradient echo images were stereotactically normalised to a reference T1-weighted image positioned in Talairach orientation (using SPM2 with a 12-parameter linear affine transformation) to correct for interindividual variability in brain size and orientation. For each subject, the results of the normalisation to parenchymal brain volume were checked manually by comparing the location of six marker points on the surface of the brain in relation to the template. By using a learning-based active appearance model,[20] the corpus callosum was automatically located and segmented on the midsagittal slice. The total cross-sectional corpus callosum area was automatically divided into five subregions by rotating and translating the corpus callosum into a coordinate system in which the x axis is parallel to the longest axis of the structure and the y axis passes through the centre of gravity. Radial dividers from the origo with equal angular spacing were used to subdivide the corpus callosum into rostrum and genu (CC1), rostral body (CC2), midbody (CC3), isthmus (CC4) and splenium (CC5), as shown in fig 1. Finally, the normalised area of the total corpus callosum and each subregion was calculated automatically.

Statistical analysis

The relationships between the neuropsychological test performance and the MRI predictors were analysed mainly using multiple linear regression in two sets of models. The

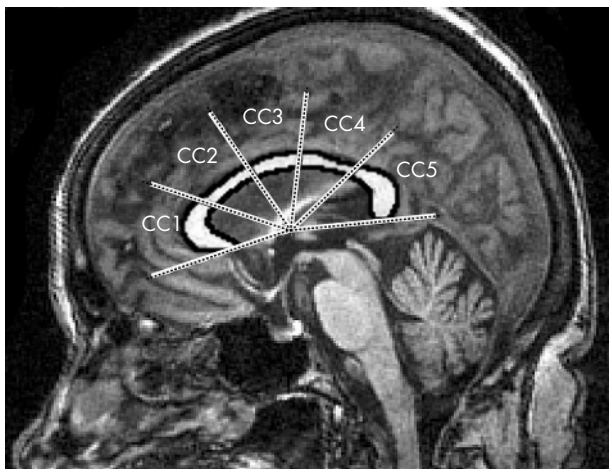

Figure 1 Segmentation of the corpus callosum (CC) subregions from the mid-sagittal magnetic resonance imaging slice. CC1, rostrum and genu; CC2, rostral body; CC3, midbody; CC4, isthmus; and CC5, splenium.

Table 1 Relationship of corpus callosum atrophy to cognitive functioning

	Corpus callosum area					
	Model I	Model II				
	CC total	CC1	CC2	CC3	CC4	CC5
Trail making A, time	–0.13*	–0.16	–0.01	0.00	0.12	–0.10
Trail making B–A, time	–0.03	–0.31**	–0.08	0.17	0.02	0.18
Stroop part I, time	–0.13*	0.06	0.07	–0.10	0.03	–0.22
Stroop part II, time	–0.13*	–0.01	–0.02	–0.01	–0.02	–0.10
Stroop part III–II, time	–0.03	–0.22*	0.12	0.05	0.00	0.03
Symbol digit modalities, correct	0.09	0.20*	0.04	–0.07	–0.03	–0.06
Digit cancellation, correct	0.05	0.21*	0.08	–0.12	–0.02	–0.10
Digit span backwards	0.07	0.19	0.12	–0.15	–0.01	–0.08
Verbal fluency	0.14**	0.12	–0.06	–0.09	0.18*	0.01

CC, corpus callosum; CC1, rostrum and genu; CC2, rostral body; CC3, midbody; CC4, isthmus; CC5, splenium.
Values are standardised β coefficients of linear regression models expressing the independent predictive values of CC measures to neuropsychological test performance, when controlling for age, education, history of stroke and volume of white matter hyperintensities. Model I includes total CC area, whereas model II includes the five CC subregions.
*$p<0.01$.
**$p<0.001$.

neuropsychological variables were set as outcome variables one by one. The explanatory variables included age, education, history of stroke (no *v* yes), and WMH volume as covariates in each model. In the first model set, the total corpus callosum area was added in the explanatory variables to assess the effect of overall corpus callosum atrophy. Instead, in the second set, the five regional corpus callosum measures were included to examine the independent contributions of the corpus callosum subregions to cognitive performance. All explanatory variables were entered simultaneously. The total number of linear regression analyses was 18 (model sets I and II; table 1).

The distributions of the neuropsychological variables were checked for outliers and non-normality, and, if necessary, logarithmic transformation was used. Logarithmic transformation was applied also for WMH volume. Because of substantial skewness, the two additional tests, object naming and constructional praxis, were analysed by using logistic regression after these variables were turned into dichotomous variables (errors *v* no errors). These logistic regression analyses were otherwise identical with the above-mentioned linear regression models with the same explanatory variables and simultaneous entry method.

The results were also calculated by controlling for sex, handedness, number of lacunar infarcts, and presence of hypertension and diabetes, but these factors were not included in the final analysis, because the significant results remained unchanged. The proportion of missing values in the neuropsychological variables varied from 0.7% to 5.3%, and no replacement was used. Because of multiple analyses, the criterion for significance was set as $p<0.01$.

RESULTS

Table 2 gives the characteristics of the study sample. According to the visual rating scale,[13] 254 (45%) of the subjects had mild, 177 (31%) moderate and 136 (24%) severe WMH. The Pearson's correlation between total corpus callosum area and WMH volume was −0.33, $p<0.001$, and that between the corpus callosum subregions 0.51–0.83, $p<0.001$. Descriptive figures and correlations of the WMH volume and corpus callosum area in the LADIS subjects have been reported in more detail elsewhere.[12 19] Of the 163 subjects who had a history of stroke, 131 (82%) had one stroke event, 25 (16%) had two and 4 (3%) had >2 stroke events (disregarding three cases with missing data). The severity of stroke was minor in 146 (90%) subjects and major in 16 (10%). Furthermore, according to the trial of ORG 10172 in acute stroke treatment criteria,[21] 70 (44%) of the subjects with stroke history had lacunar infarcts, 38 (24%) had large-artery atherosclerosis, 14 (9%) had cardioembolism, and 36 (23%) had other or undetermined causes.

The linear regression analyses adjusted for age, education, history of stroke and WMH volume showed that the total corpus callosum area significantly predicted performance in the trail making A test, the Stroop test parts I and II, and in the verbal fluency test (model I in table 1). Furthermore, otherwise identical analyses but with the corpus callosum subregions as explanatory variables showed that CC1 (rostrum and genu) was the only subregion to independently predict the subtraction scores in the trail making test (B−A) and the Stroop test (III−II), as well as the number of correct responses in the symbol digit modalities and digit cancellation tests (model II in table 1). In addition, verbal fluency was predicted by CC4 (isthmus) area. All the significant results were in the expected direction—that is, a small corpus callosum area predicted poor cognitive performance.

The total explanatory power (R^2) in model I ranged from 0.13 to 0.33 and that in model II from 0.14 to 0.34. Of the covariates, age and education were significantly associated with cognitive performance in both models: age predicted trail making A, B−A, Stroop III–II, symbol digit modalities, digit cancellation and verbal fluency (standardised β coefficients 0.10–0.17, $p<0.01$), and education predicted all cognitive variables (0.22–0.47, $p<0.001$). History of stroke had no significant incremental contribution to cognitive performance. WMH volume significantly predicted trail making A (0.16, $p<0.001$), B−A (0.16, $p<0.001$), Stroop I (0.15, $p<0.001$), Stroop II (0.20, $p<0.001$), symbol digit modalities (–0.20, $p<0.001$), digit cancellation (–0.26, $p<0.001$) and verbal fluency (–0.16, $p<0.001$), when controlling for the other covariates and the total corpus callosum area. Despite fairly strong correlations between the explanatory MRI variables (see above), no excessive multicollinearity in the regression models was found.

The VADAS-cog naming objects and constructional praxis subtests reflecting primarily posterior cognitive functions were analysed with logistic regression analysis by using the same explanatory variables and covariates and identical model sets. Neither the total corpus callosum area nor any of the corpus callosum subregions significantly predicted performance in these tasks. The odds ratios varied between 0.990 and 1.009.

DISCUSSION

We investigated the role of regional and overall corpus callosum atrophy in cognitive deficits in a large sample of subjects with

Table 2 Characteristics of the subjects (n = 567)

Age (years)	74 (5)
Sex, women*	312 (55)
Education (years)	9.7 (3.8)
MMSE	27.4 (2.4)
Stroke present*	163 (29)
WMH volume (cm^3)	21.2 (22.8)
Total CC area (mm^2)	642 (134)
CC1	180 (40)
CC2	94 (25)
CC3	91 (24)
CC4	92 (27)
CC5	185 (40)

Values are means (SD) or n (%)*
CC, corpus callosum; CC1, rostrum and genu; CC2, rostral body; CC3, midbody; CC4, isthmus; CC5, splenium; MMSE, Mini-Mental State Examination; WMH, white matter hyperintensities.

age-related WMH. The results point out several novel findings. Atrophy in the most anterior parts of the corpus callosum (rostrum and genu) was independently associated with poor performance in neuropsychological tests assessing attention and executive functions and covering mental flexibility and response inhibition. These deficits possibly reflect a relatively focal dysfunction of the prefrontal cortices and their related subcortical circuits. Moreover, atrophy of the total corpus callosum area was associated with poor performance in tests of mental processing speed. This in turn could indicate a diffuse effect possibly reflecting overall subcortical damage and disconnection between the cerebral cortices.

Previous studies have shown that executive deficits and attention are related to the degree of WMH[22] and frontal cortical atrophy,[23] but to date, the role of corpus callosum atrophy in these deficits has been poorly understood. One of the few studies investigating specific executive functions in the elderly found that subjects with a higher corpus callosum atrophy rating had lower scores in trail making B, digit symbol and a letter-based fluency test.[2] The role of corpus callosum atrophy in executive functions is of particular interest, as it has been postulated that complex tasks require more efficient interhemispheric cooperation than simpler tasks.[24] The anterior region of the corpus callosum is believed to be involved in the transfer of attentional resources and higher cognitive information, and posterior regions in transfer of basic sensory information.[24] Further, functional imaging studies provide evidence for bilateral frontal lobe involvement in executive processing.[25]

In this study, performance in a category-based verbal fluency task was not predicted by the anterior corpus callosum area, as was expected, but by the total corpus callosum and the CC4 (isthmus) subregion. This was the only cognitive measure that was significantly related to any region other than the most anterior subregion in multivariate analysis. Although the category fluency task assesses flexible searching strategies—that is, executive control—it also requires semantic knowledge,[26] possibly mediated by the posterior cerebral cortices. Previous studies investigating the association between corpus callosum atrophy and verbal fluency performance in various patient groups have provided diverse results. Some studies have found a relationship between corpus callosum atrophy and verbal fluency,[2] whereas others have not.[10 27]

Executive functions, as an umbrella term, can be defined as "a set of cognitive skills that are responsible for the planning, initiation, sequencing, and monitoring of complex goal-directed behaviour".[28] The methods of assessing executive functions are generally highly multifactorial, and therefore, although they are sensitive to frontal lobe damage, performance in these can be impaired also for other (non-frontal) reasons.[28 29] In this study, attention and executive functions were evaluated by using widely studied and established tests, the Stroop, trail making, symbol digit modalities, digit cancellation and verbal fluency tests. It was found that most of the complex attentional and executive tasks were related to anterior, but not overall corpus callosum atrophy. Instead, the speed measures were related to overall, but not regional corpus callosum atrophy. Notably, task difficulty can be one factor explaining the observed dissociation between executive deficits and mental slowing.

Two additional tests assessing ability to name objects and copy geometrical figures were also analysed to cover functions that are assumed to rely mainly on the integrity of the more posterior brain areas. It was found that, after controlling for age, education, history of stroke and WMH volume, none of the corpus callosum measures was significantly associated with performance in these tasks. However, because of skewed distributions, the analyses may have been less sensitive than the previous ones.

In this study, the role of corpus callosum atrophy was examined in multivariate analysis by adjusting for demographic factors, and coexisting WMH and stroke. Still, a relatively large proportion of variance in cognitive performance remained unexplained by the models. In general, education had the strongest predictive value for cognitive performance above all explanatory variables, followed by WMH, corpus callosum measures and age. History of stroke had no independent predictive value for cognitive functions, incrementally to the other explanatory variables, which could be explained by the low frequency of major strokes in the sample. It should be noted that all corpus callosum subregions were entered simultaneously into the multivariate models as explanatory variables, which could lead to underestimation of their individual contributions owing to substantial mutual correlations. On the other hand, the possibility of a false positive error was minimised and robust independent contributions were identified.

One of the strengths of the present study is the large sample size that represents a mixed population of elderly subjects with a broad range of WMH (from mild to severe). The subjects were enrolled in the study on the basis of various referral reasons reflecting the diversity of clinical manifestations related to vascular brain pathology. Previous studies have investigated the relationship of corpus callosum atrophy to cognition, mainly in small patient samples, and have largely concentrated on Alzheimer's disease. As the sample extensively covered all degrees of WMH, the cases with severe WMH may have driven the results more than expected in a population-based sample.

Another advantage of the study is the sophisticated quantitative MRI analysis that provides accurate measures of corpus callosum morphology and WMH load. Volumetric analysis of WMH has proved to be more sensitive than the visual rating scales, with a potential ceiling effect.[19] WMH volume was not corrected for overall intracranial volume. However, controlling for sex, which could be expected to account for much of the interindividual variability in brain size, did not have any effect on the results. A previous study found no relationship between WMH volume and brain size independently of sex.[30]

We did not analyse the topography of the coexisting brain lesion, such as WMH, stroke or brain atrophy. Importantly, regional cortical atrophy was not controlled for in our analyses, and thus, it is conceivable that the corpus callosum measures reflect cortical atrophy, explaining part of the observed cognitive deficits. Earlier studies have suggested that, in Alzheimer's disease, the pattern of corpus callosum atrophy reflects the corresponding regional cortical neuronal loss, possibly resulting from a degeneration of axons of pyramidal

neurones in cortical layer III.[6 7] However, in the present study, the corpus callosum measures were corrected for parenchymal volume by means of a spatial normalisation procedure, which adjusts for brain size and thereby for major global atrophy. In the elderly, there are probably several mechanisms behind corpus callosum atrophy. Besides cortical atrophy, other possible factors could be axonal disruption due to vascular lesions such as stroke, WMH or changes in the normal-appearing white matter.

In conclusion, in cross-sectional analysis, corpus callosum atrophy seems to contribute to cognitive decline in the elderly, not only as an indirect manifestation of subcortical white matter lesions but possibly also as an indicator of reduced functional connectivity between cortical areas. It may also serve as a surrogate marker for regional cortical neuronal loss. Anterior corpus callosum atrophy seems to have a role in the frontal-lobe-mediated executive functions and attention, whereas overall corpus callosum atrophy is associated with the slowing of processing speed. Further studies are required to establish the clinical significance of corpus callosum atrophy longitudinally. Moreover, regional analysis of concomitant brain pathology will give further insight into the pathophysiological mechanisms leading to corpus callosum atrophy.

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*A list of collaborators of the LADIS Study is presented in the appendix.

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APPENDIX

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The LADIS Steering Committee is formed by Domenico Inzitari, MD, Timo Erkinjuntti, MD, PhD, Philip Scheltens, MD, PhD, Marieke Visser, MD, PhD, and Peter Langhorne, PhD.