

Callosal tissue loss parallels subtle decline in psychomotor speed. A longitudinal quantitative MRI study. The LADIS Study

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ABSTRACT

Cross-sectional studies have suggested that corpus callosum (CC) atrophy is related to impairment in global cognitive function, mental speed, and executive functions in the elderly. Longitudinal studies confirming these findings have been lacking. We investigated whether CC tissue loss is associated with change in cognitive performance over time in subjects with age-related white matter lesions (WML). Two-hundred-fifty-three subjects, aged 65–84 years, were evaluated by using repeated MRI and neuropsychological evaluation at baseline and after 3 years. The effect of overall and regional CC tissue loss on cognitive decline was analyzed with hierarchical linear regression models. After controlling for age, sex, education, and baseline cognitive performance, the rates of tissue loss in the total CC area, and in rostrum/genu and midbody subregions were significantly associated with decline in a compound measure of cognitive speed and motor control, but not in those of executive functions, memory, or global cognitive function. Total CC area and midbody remained significant predictors of speed also after adjusting for baseline WML volume, WML progression, and global brain atrophy. However, the relationship between anterior CC and speed performance was mediated by WML volume. In conclusion, the overall and regional rate of CC tissue loss parallels longitudinal slowing of psychomotor performance. The adverse effect of CC tissue loss on psychomotor function may be driven by altered interhemispheric information transfer between homologous cortical areas.

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1. Introduction

The corpus callosum (CC) is a large bundle of commissural nerve fibers connecting the two cerebral hemispheres according to an anterior–posterior topographical organization. In neurodegenerative diseases, the size of the CC is significantly reduced reflecting axonal loss and atrophy (Black et al., 2000; Di Paola, Luders, et al., 2010; Hallam et al., 2008; Hampel et al., 2002; Meguro et al., 2003;

Pantel et al., 1999; Yamauchi, Fukuyama, Nagahama, et al., 2000). Microstructural abnormalities of CC are already present in patients with amnesic mild cognitive impairment and become more prominent in mild Alzheimer's disease suggesting that CC changes occur very early in the disease process (Di Paola, Di Iulio, et al., 2010). The proposed mechanisms for these changes are Wallerian degeneration resulting from atrophy of the corresponding cerebral cortex and retrogenesis due to myelin breakdown (Di Paola, Di Iulio, et al., 2010; Di Paola, Luders, et al., 2010). In cerebrovascular diseases however, the mechanisms may be different, as CC changes have been related to cerebral white matter lesion (WML) load (Lee et al., 2010; Ryberg et al., 2008; Tomimoto et al., 2004).

Cross-sectional studies have indicated that CC size is associated with global cognitive decline as evaluated with dementia screening methods (Black et al., 2000; Moretti et al., 2005; Pantel et al.,

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1999; Yamauchi, Fukuyama, & Shio, 2000). Only a few studies have evaluated cognitive functions in detail and have reported inconsistent results (Giubilei et al., 1997; Meguro et al., 2003). Our previous cross-sectional studies in subjects with age-related WML showed that reduced CC area was related to both global cognitive impairment (Ryberg et al., 2007) and specific cognitive deficits (Jokinen et al., 2007) independently of WML volume and other confounding factors. Total CC area was related to slowing in processing speed, whereas anterior CC area was specifically associated with impaired executive functions and attention (Jokinen et al., 2007).

The clinical importance and mechanisms behind CC atrophy and cognitive decline are still under scrutiny. Particularly longitudinal studies have been few. A recent study from our group has shown that regional CC tissue loss is associated with incident dementia during 3-year follow-up (Frederiksen et al., 2011). The purpose of the present study was to investigate whether longitudinal tissue loss in CC and its subregions differentially contribute to change in global and specific cognitive functions independently of coexisting WML and brain atrophy.

2. Methods

2.1. Subjects and design

Data was derived from the Leukoaraiosis and Disability (LADIS) study, a longitudinal multicenter study aiming at investigating the role of the age-related WML in transition to functional disability. The full details of the study protocol and cohort have been given in previous reports (Inzitari et al., 2009; Pantoni et al., 2005). In short, 639 subjects were enrolled at 11 European centers according to the following inclusion criteria: (a) age 65–84 years, (b) changes in cerebral white matter of any degree according to the revised version of the scale of Fazekas (Pantoni et al., 2005), (c) no or mild impairment in instrumental activities of daily living, IADL (none or only 1 domain compromised in the IADL scale (Lawton & Brody, 1969)), and (d) presence of a contactable informant. The exclusion criteria were: (a) presence of severe illness and therefore likely to drop out (cardiac, hepatic or renal failure, cancer, or other relevant systemic diseases), (b) severe unrelated neurological disease, (c) leukoencephalopathy of non-vascular origin (immunological, demyelinating, metabolic, toxic, infectious, other), (d) severe psychiatric disorders, (e) and inability or refusal to undergo brain MRI. The subjects were recruited from different settings (stroke unit/department or cerebrovascular disease clinic, memory or dementia clinic, neurological or geriatric wards/clinic, and population studies on aging) on the basis of the following referral reasons: cognitive or motor complaints, minor cerebrovascular events, mood alterations, other neurological problems, WML as an incidental finding on brain imaging, and volunteers and controls from other studies.

The assessment at study entry included structured medical evaluations, neuropsychological assessment, and brain MRI. The clinical evaluations were carried out annually and MRI was repeated after three years at the last follow-up visit. Arterial hypertension was determined as blood pressure $\geq 140/90$ mm Hg in subjects who were not taking antihypertensive medication. Diagnosis was based on multiple blood pressure measurements taken on several separate occasions. Diabetes mellitus was defined on the basis of previous diagnosis and/or current treatment with insulin or oral hypoglycemic medications, or at least 8-h fasting plasma glucose ≥ 7.0 mmol/l or 126 mg/dl. The study was approved by the ethics committees of each participating centre, and all subjects signed an informed written consent.

2.2. Neuropsychological assessment

The neuropsychological battery of the LADIS study covered tests evaluating both global cognitive function and specific cognitive domains. The methods were the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), the Vascular Dementia Assessment Scale-cognitive subscale (VADAS) (Ferris, 2003; Ylikoski et al., 2007), the Stroop test (MacLeod, 1991), and the Trail making test (Reitan, 1958). The VADAS scale has been developed on the basis of the widely known ADAS battery to assess vascular cognitive impairment and includes six additional subtasks: delayed word recall, symbol digit modalities test, digit span, maze, digit cancellation, and verbal fluency. To reduce the number of outcome variables, three compound scores were constituted to evaluate relevant cognitive domains (Madureira et al., 2006). *Speed and motor control* were evaluated with the Trail making test, part A (time), and the digit cancellation (number of correct responses) and maze (time) subtasks of the VADAS. *Executive functions* were evaluated by using the subtraction scores from the Trail making test (B-A) and the Stroop test (color incompatible – color neutral), and the VADAS verbal fluency (number of animal names generated in 60 s) and the symbol digit modalities tests (number of correct responses). *Memory functions* were assessed using the VADAS word recall, delayed recall, word recognition, and digit span subtasks. For the compound measures, the

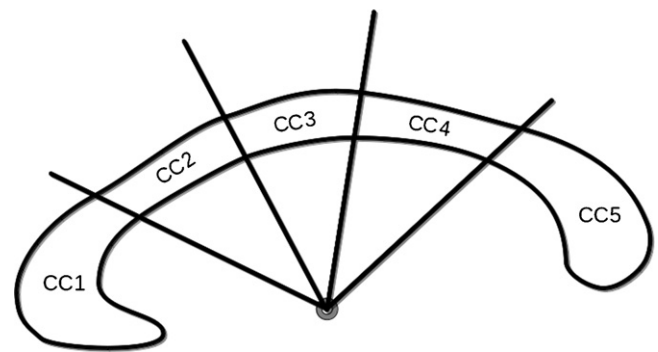


Fig. 1. Segmentation of the corpus callosum (CC) subregions obtained from the mid-sagittal MRI slice. CC1, rostrum/genu; CC2, rostral body; CC3, midbody; CC4, isthmus; CC5, splenium.

individual raw scores were first converted into standardized z scores, inverted if appropriate, and then combined by calculating the mean z score within a domain. High values indicated better performance. Additionally, *global cognitive function* was evaluated with the VADAS total score, in which high values indicate worse performance.

2.3. Magnetic resonance imaging

The baseline and follow-up MRI scans were performed using the same protocol at each centre (Gouw et al., 2008; Ryberg et al., 2007; van Straaten et al., 2006). This standard protocol included T1-weighted magnetization prepared rapid-acquisition gradient-echo (MPRAGE; scan parameters: coronal or sagittal plane, TE: 2–7 ms, TR: 9–26 ms, flip angle: 15–30, voxel size $1 \times 1 \times 1$ to 1.5 mm^3), T2-weighted fast spin echo (scan parameters: axial plane, TE: 100–130 ms, TR: 4000–6600 ms, voxel size $1 \times 1 \times 5 \text{ mm}^3$, 19–31 slices), and fluid-attenuated inversion recovery (FLAIR; scan parameters: axial plane, TE: 100–160 ms, TR: 6000–10,000 ms, TI: 2000–2400, voxel size $1 \times 1 \times 5 \text{ mm}^3$, 19–31 slices) sequences.

2.3.1. Corpus callosum area measurement

The CC analysis was conducted in the Danish Research Center for Magnetic Resonance, Copenhagen, Denmark as detailed earlier (Frederiksen et al., 2011). MPRAGE images were reoriented to standard Montreal Neurological Institute (MNI) template orientation, using a 6-parameter rigid transformation SPM5 software package (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>). Follow-up MPRAGE images were co-registered to baseline MPRAGE images. CC was located automatically on the midsagittal section of the MPRAGE data set using the learning-based active appearance models (AAMs). AAMs parameterize object variability from a training set of manually annotated CCs, from which a constrained deformation basis is achieved for localization of objects similar to the training set based on a computational framework. The resulting AAMs localized the CCs in the entire data set. Any inaccuracies were corrected by a trained reviewer unaware of the clinical status. Finally, the CC was automatically divided into five subregions using radial dividers emanating from the origin with equal angular spacing: rostrum/genu (CC1), rostral body (CC2), midbody (CC3), isthmus (CC4) and splenium (CC5) as illustrated in Fig. 1. The area of each segment was calculated automatically. CC area was adjusted for head size by multiplying with the y and z scaling parameters derived from a 12-parameter affine registration of the MPRAGE to the MNI template. The annual percent of change was calculated in total CC area and each subregion using the following formula: $[(CC_{fu}) - (CC_b)] / (CC_b \times (ISI)) \times 100\%$, where CC_{fu} = CC area at follow-up, CC_b = CC area at baseline, and ISI = interscan interval.

2.3.2. Evaluation of white matter lesions

WML volume was analyzed at baseline on the axial FLAIR images by a single rater using a semi-automated method (van Straaten et al., 2006). The lesions were marked and borders were set by using local thresholding on each slice. No distinction was made between subcortical and periventricular hyperintensities. Areas of hyperintensity on T2-weighted images around infarctions and lacunes were disregarded. After all lesions were delineated the total volume of WML was calculated automatically. Progression of WML was evaluated by comparing the baseline and follow-up scans in a side-by-side manner using the modified Rotterdam progression scale, in which absence or presence (0 vs. 1) of progression is rated separately in three periventricular and four subcortical white matter regions, basal ganglia, and infratentorial regions (range 0–9). Intra-rater reliability of the ratings of 20 randomly selected scans scored twice was 0.81 (weighted Cohen's kappa) (Gouw et al., 2008).

2.3.3. Evaluation of brain atrophy

Brain atrophy was assessed at baseline with a template-based visual rating scale ranging from 1 (no atrophy) to 8 (severe atrophy) separately on ventricular and

Table 1
Characteristics of the sample ($n = 253$).

	Mean (SD)/ n (%) ^a	Range
Demographic factors		
Age	73.7 (5.0)	
Sex, male ^a	123 (48.6)	
Education	10.3 (3.8)	
Clinical findings		
History of clinical stroke ^a	77 (30.4)	
Hypertension ^a	168 (66.4)	
Diabetes ^a	31 (12.3)	
MRI findings		
Brain atrophy score, baseline	7.95 (2.3)	2–14
WML volume, ml, baseline	21.4 (21.9)	1.1–129.1
WML progression score	2.1 (1.8)	0–7

WML, white matter lesion.

^a Indicates values in n (%).

sulcal areas as validated before in the LADIS study (Ryberg et al., 2008; Schmidt et al., 2010). The sum of the two ratings was used as a global measure of atrophy.

2.4. Study sample

Of the baseline sample ($n = 639$), 43 subjects died during follow-up, 73 subjects dropped out from the study, and 43 subjects were assessed in follow-up only by telephone interview. Repeat MRI was not performed to 30 subjects because of refusal and to 47 subjects due to insufficient funding (one centre). The CC measurements were available for 328 subjects, whose baseline and follow-up scans were of sufficient quality for automated analysis. From the present study, we further excluded 75 cases with incomplete data set for evaluation of WML volume, WML progression, and/or brain atrophy. The final sample for the present analyses included 253 cases accordingly. The mean interval between MRI scans was 3.1 (SD 0.3) years. As it has been reported before, subjects with both MRI scans were younger, had more years of education, and had higher MMSE scores at baseline as compared to those who only participated in the baseline scanning (Gouw et al., 2008). However, of the subjects participating in both scans, those with and without CC evaluation did not differ from each other in terms of these variables ($p > 0.05$). Of the subjects that had complete MRI data set, baseline and 3-year follow-up data was available in 218 subjects in VADAS total score and 231 subjects for speed and motor control, 207 for executive functions, and 231 for memory functions compound scores.

2.5. Statistical analysis

Association of the CC annual percent change with other MRI findings was evaluated with Pearson and Spearman rank correlation. Relationships of CC change to change in cognitive performance was analyzed with hierarchical linear regression models, in which the four cognitive scores from the last follow-up assessment (speed and motor control, executive functions, memory functions, VADAS) were used as outcome variables separately. The predictors were entered in three steps. The first step included demographic factors (age, sex, years of education) and the baseline cognitive compound score corresponding to the outcome variable. The second step entered CC change percents one at the time (separate analyses for each CC area). The third step added other MRI predictors, i.e., baseline WML volume, WML progression score, and baseline brain atrophy score, in order to evaluate the independent predictive value of the CC change measures to cognitive change. Missing data in cognitive scores was not replaced, and therefore, different numbers of subjects were included in the analyses. Alpha level below 0.05 was considered significant.

3. Results

Demographic, clinical, and MRI characteristics of the sample are summarized in Table 1. At baseline, the mean MMSE score was 27.9 (SD 2.3). The scores ranged between 16 and 30 with quartile distribution 27, 29, and 30. At follow-up evaluation, the mean MMSE score was 26.9 (SD 3.7), range 8–30, and quartile distribution 26, 28, and 29. As evaluated with the modified Fazekas scale (Pantoni et al., 2005), 112 (44%) subjects had mild, 84 (33%) moderate, and 57 (22%) severe WML. CC measurements at baseline and follow-up, and annual percent changes in total CC area and in the five subregions are shown in Table 2. The average annual tissue loss was the highest in CC1 and CC5 subregions. Baseline and follow-up total CC area correlated significantly with baseline WML volume (ml) and brain atrophy score (Pearson correlations between -0.23 and -0.27 , $p < 0.001$), but not with WML progression score

Table 2
Corpus callosum measures adjusted for head size.

CC area	CC measures		
	Baseline scan, mm ²	Follow-up scan, mm ²	Annual change %
CC total	676.4 (90.6)	661.1 (88.1)	−0.66 (1.74)
CC1	191.0 (32.3)	184.5 (31.6)	−1.02 (2.25)
CC2	95.8 (17.9)	94.1 (16.4)	−0.34 (3.19)
CC3	89.6 (18.6)	88.2 (17.6)	−0.25 (3.54)
CC4	94.1 (18.5)	93.9 (18.6)	0.03 (2.90)
CC5	205.8 (35.1)	200.5 (34.7)	−0.76 (1.88)

CC, corpus callosum; CC1, rostrum/genu; CC2, rostral body; CC3, midbody; CC4, isthmus; CC5, splenium.

(Spearman rank correlation 0.02, $p = 0.708$). Correlations of the annual percent change of total CC area with baseline brain atrophy, WML volume, and WML progression were non-significant. Age correlated negatively with baseline total CC area (Pearson correlation -0.14 , $p < 0.024$), non-significantly with follow-up CC area (-0.82 , $p = 0.194$), and positively with annual percent change (0.14 , $p < 0.024$). Presence of hypertension, diabetes, or history of clinical stroke were not significantly associated with any of these CC measures (independent samples t -test $p > 0.05$).

Table 3 presents the results of the relationship between CC change and longitudinal cognitive performance. Decline in the speed and motor control compound score was significantly associated with annual tissue loss in total CC area, CC1, and CC3 after controlling for age, education, sex, and baseline speed performance. After controlling also for baseline WML volume, brain atrophy, and WML progression, total CC and CC3 remained significant, whereas CC1 was no longer significant (standardized beta 0.08, $p = 0.081$). The effect of CC1 annual tissue loss on decline in speed was weakened by baseline WML volume (standardized beta -0.16 , $p = 0.001$), but not baseline atrophy or WML progression ($p > 0.05$). The association between CC measures and change in executive functions and memory functions compound scores, and VADAS total score were non-significant. The demographic factors were not significantly associated with decline in speed independently of the MRI predictors and baseline cognitive performance. Since hypertension is one of the most important risk factors for white matter disease, we additionally controlled for hypertension status in the first step of the regression models. The results did not change. After additional controlling for baseline MMSE score, the results also remained unchanged, except for CC3 area, of which predictive power declined below the significance level in the fully adjusted models (standardized beta 0.08, $p = 0.085$).

Table 3
Corpus callosum (CC) tissue loss and change in cognitive performance over 3-year follow-up.

CC area	Cognitive compound scores			
	Speed	Executive	Memory	VADAS
CC total	0.12 (0.008) [§]	ns	ns	ns
CC1	0.10 (0.027)	ns	ns	ns
CC2	ns	ns	ns	ns
CC3	0.11 (0.016) [§]	ns	ns	ns
CC4	ns	ns	ns	ns
CC5	ns	ns	ns	ns

Hierarchical linear regression models predicting change in cognitive compound scores. Three-year follow-up scores were used as outcome variables and annual percent change of CC areas as predictor variables after controlling for age, education, sex, and the baseline cognitive score corresponding to the outcome variable. Values are standardized beta coefficients (p values). Associations denoted with [§] remained significant also after controlling for baseline WML volume, baseline brain atrophy score and WML progression.

CC, corpus callosum; CC1, rostrum/genu; CC2, rostral body; CC3, midbody; CC4, isthmus; CC5, splenium; ns, non-significant; VADAS, Vascular Dementia Assessment Scale-cognitive subscale (total score); WML, white matter lesion.

4. Discussion

We investigated whether CC tissue loss is related to parallel decline in cognitive performance in 3-year follow-up in subjects with age-related WML. The key finding of the study was that higher rate of CC tissue loss was related to subtle longitudinal decline in psychomotor speed, but not in executive functions, memory, or global cognitive function.

The present study is one of the first longitudinal studies exploring the role of CC tissue loss in age-related cognitive decline using a detailed neuropsychological evaluation encompassing both global and specific cognitive functions. Sullivan et al. have earlier investigated the cognitive correlates of callosal thinning in a 4-year follow-up study among elderly community-dwelling men using the MMSE, Stroop, and Trail making tests (Sullivan, Pfefferbaum, Adalsteinsson, Swan, & Carmelli, 2002). Paralleling our results they found a significant correlation between thinning of the CC body and the Stroop word reading task reflecting simple speeded processing, but no correlations were evident with the Stroop interference or the Trail making test, which are used in evaluating executive processes such as inhibition and set shifting.

In a cross-sectional study, we have previously demonstrated that overall CC atrophy (baseline total CC area) is associated with slowing of mental speed, and that anterior CC atrophy (rostrum and genu) is specifically related to impairment in attention and executive abilities (Jokinen et al., 2007). The present findings are in line with these results regarding psychomotor speed and suggest that mental slowing is associated not only with cross-sectional CC size, but also parallels CC area reduction over time. However, we were not able to demonstrate a longitudinal association between change in executive functions and CC tissue loss either in anterior or in total CC area.

The importance of the structural changes of CC in slowing of information processing has been suggested also in other cross-sectional studies within different populations. Smaller CC area, particularly in the anterior region, has been related to slower processing speed in healthy elderly (Fling, Chapekis, et al., 2011) and in subjects with mild cognitive disorders (Anstey et al., 2007). Diffusion tensor imaging studies of normal aging have reported slowed processing speed to be associated with indices of white matter integrity both in the anterior CC (Kennedy & Raz, 2009; Sullivan, Rohlfing, & Pfefferbaum, 2010) and in the middle sectors that project fibers to the premotor, postcentral, temporal, and parietal areas (Sullivan, Adalsteinsson, & Pfefferbaum, 2006; Sullivan et al., 2010). Moreover, speeded performance and CC diffusion measures have been associated most prominently in the CC genu and body in patients with multiple sclerosis (Hecke et al., 2010; Mesaros et al., 2009; Roosendaal et al., 2009) and chronic alcoholism (Rosenbloom, Sassoon, Fama, Sullivan, & Pfefferbaum, 2008). The relationship between anterior CC integrity and perceptual speed has been suggested to explain in part also the age-related changes in memory retrieval (Bucur et al., 2008).

In the present study, CC was divided into five subsections according to a radial partitioning scheme (Fig. 1), which roughly corresponds to the anterior–posterior topographical organization of the CC interhemispheric connections (Abe et al., 2004; Ryberg et al., 2007). However, diffusion tensor imaging studies have suggested fiber connections that do not completely follow the geometric classification schemes of CC (Hofer & Frahm, 2006). Specifically, CC1 (rostrum/genu) corresponds to the region responsible for the prefrontal connections, CC2 (rostral body) for the premotor and supplementary motor connections, CC3 (midbody) primary motor connections, CC4 (isthmus) primary sensory and parietal connections, and finally, CC5 (splenium) for the temporal and occipital connections. According to the study of Hofer and Frahm (2006), there may be overlap particularly

in CC3 projecting fibers to both primary motor and premotor regions.

The mechanisms behind CC tissue loss and consequential psychomotor slowing are most likely multifaceted. Shrinkage of CC may accelerate the decline in processing speed and accuracy by altering the interhemispheric transfer of information between cortical areas. CC can regulate this transfer either through excitation by sharing information between the two hemispheres or through inhibition by maintaining independent processing between the hemispheres (van der Knaap & van der Ham, 2011). Older adults have been observed to demonstrate enhanced bilateral cortical activation in cognitive tasks suggesting a compensatory mechanism or a reduction of functional differentiation during aging (Cabeza, 2002; Davis, Kragel, Madden, & Cabeza, 2012). Recent evidence suggests that aging is accompanied by decreased interhemispheric inhibition and increased excitation, and that these physiological changes correlate with callosal size and integrity (Fling, Peltier, Bo, Welsh, & Seidler, 2011).

When interpreting the results, it is important to bear in mind that the subjects were stratified into different degrees of white matter disease at study entry. All cases had mild to severe WML suggesting ischemic changes in the brain, and therefore, the global cognitive status of the subjects may be more variable as compared to healthy elderly population. Even so, all cases were functionally independent and free from dementia at study entry. After controlling for baseline MMSE score, the main results remained largely unchanged. Nor did baseline hypertension affect the results.

The present study has some limitations. A substantial number of subjects had died or refused to participate at follow-up. In addition, some subjects were unable to complete the entire neuropsychological evaluation. As has been reported before, the cases with missing data in follow-up evaluation were older, had lower education, and lower MMSE scores at baseline (Gouw et al., 2008; Jokinen et al., 2009). Therefore, the present sample represents a selected population possibly biased to some extent toward the well-functioning subjects within the original sample. Furthermore, not all MRI scans could be evaluated in terms of automated CC measurement due to insufficient image quality. It should also be noted that in this exploratory study, we did not correct for multiple comparisons.

Despite some loss of data during follow-up described above, an advantage of the study is nevertheless a large and well-defined study sample providing a unique opportunity to explore the longitudinal consequences of CC atrophy. We applied an extensive neuropsychological evaluation yielding robust summary measures for relevant cognitive domains and used automated quantitative image analysis for CC normalized according to head size. We were able to control for multiple confounding factors including demographic variables, WML volume, WML progression as well as ventricular and sulcal atrophy, and thus, the relative contribution of CC tissue loss to cognition could be proportioned. As progression of brain atrophy was not controlled for, its concomitant evolution with CC tissue loss cannot be ruled out. However, baseline and follow-up CC measures correlated significantly with baseline WML volume and atrophy, but not with WML progression. Nor did any longitudinal CC change measure correlate with other MRI findings suggesting that CC tissue loss does not occur only as a secondary consequence of WML or brain atrophy. It is notable, that higher age was associated with smaller total baseline CC area but lesser incremental tissue loss in 3-year follow-up. Nevertheless, age was not significantly related to decline in psychomotor speed independently of the MRI predictors and baseline cognitive performance.

To conclude, longitudinal callosal tissue loss was related to subtle reduction in psychomotor speed, but not in memory, executive functions, or global cognitive function independently of multiple confounding factors. This relationship was evident in total CC area as well as in anterior and midbody subregions. WML volume

contributed to the relation between anterior CC and speed performance suggesting that it has a mediating role between these changes. However, the effects of the overall and midbody CC tissue loss were independent of WML volume, WML progression, and brain atrophy.

Competing interests

None declared.

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