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Does the Pattern of Atrophy of the Corpus callosum Differ between Patients with Frontotemporal Dementia and Patients with Alzheimer's Disease?

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Key Words
Corpus callosum · Frontotemporal dementia · Alzheimer's disease

Abstract
The pattern of callosal atrophy might be useful for the differentiation between frontotemporal dementia (FTD) and Alzheimer's disease (AD) in advanced cases. However, it is unclear whether the pattern of callosal atrophy differs between patients with FTD and patients with AD in mild to moderate stages. Volumetric MR images were recorded from 48 probands (12 with FTD, 12 with late-onset AD, and 24 controls). All patients were in a mild or in a moderate stage. The corpus callosum was divided into five segments. A repeated-measures analysis of variance showed that there was no difference in the pattern of callosal atrophy between the groups. We provide evidence that patients with FTD and patients with late-onset AD do not differ in the pattern of callosal atrophy on condition that: (1) FTD patients and AD patients are in a mild to moderate stage and (2) FTD patients and AD patients differ in age.

Introduction

Frontotemporal dementia (FTD) as well as Alzheimer's disease (AD) are neurodegenerative dementing disorders. FTD is one of three clinical syndromes described under the umbrella of frontotemporal lobar degeneration [1]. Clinically, FTD patients show profound alteration in personality and social conduct, with relative preservation of memory function. AD, the most common form of dementia, refers to patients with multiple cognitive deficits including progressive worsening of memory [2]. The clinical differentiation of the two dementing illnesses may be difficult in some cases [3, 4].

It has been suggested that FTD patients and AD patients differ in their patterns of callosal atrophy [5]. Callosal atrophy is supposed to occur as a consequence of the death of projecting pyramidal cells in layer III of the neocortex and to reflect the pattern of neocortical neurodegeneration [6, 7]. The degeneration predominantly involves the frontomedian, orbitofrontal and anterior temporal cortices in FTD, and the temporal and parietal lobes in AD [8, 9]. Accordingly, two previous studies showed that the midsagittal callosal area/intracranial area ratio was significantly smaller for the anterior parts of the cor-

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pus callosum in patients with FTD relative to patients with AD [5, 10]. FTD and AD patients had little overlap in the posterior callosal area/total callosal area ratio [5]. Callosal atrophy had some diagnostic validity: the anterior callosal area/pericallosal space area ratio correctly classified 85% of dementia patients [10].

However, it is unclear whether the pattern of callosal atrophy differs (1) between mild FTD and mild AD and (2) between FTD patients and AD patients who differ in age. Both previous studies included patients in advanced stages and thus participants varied greatly in the severity of the disease. Moreover, AD patients were relatively young on average: 61 years [5] and 68.4 years [10]. As in clinical practice early-onset AD is a rare condition, we focused on a more representative population of elderly AD patients. We included only patients within mild or moderate stages of the disease. Our hypothesis was that callosal atrophy is more pronounced in the anterior segments in FTD and in the posterior segments in AD.

Materials and Methods

Probands

This study was carried out in co-operation between the memory clinics of the Universities of Leipzig and Regensburg and the Max-Planck Institute (MPI) of cognitive neuroscience. Every FTD patient seen in the Leipzig or Regensburg memory clinic during the last 2 years was enrolled. Exclusion criteria were the presence of early memory deficits, lacking approval, contraindications for MRI scanning or major lesions of the periventricular white matter. This resulted in a consecutive sample of 12 FTD patients (8 men/4 women), who met the core diagnostic criteria of 'FTD' according to Neary et al. [1]. In 7 patients, the clinical presentation was dominated by disinhibition, irritability, aggressiveness, lack of social awareness or restlessness to variable degrees and 5 patients were mainly characterised by inertia, loss of volition or aspontaneity.

Twelve patients with AD (late onset) were consecutively enrolled by the memory clinic of the University of Leipzig. They were matched to the FTD patients in gender and severity of cognitive impairment using two criteria: (1) maximum differences of two points in the total score of the Mini-Mental Status Examination (MMSE) [11] and (2) those FTD patients with a normal MMSE score were matched with an AD patient with a mild dementia syndrome. All met the ICD-10 diagnostic criteria for AD. According to ICD-10 research criteria, 9 AD patients had a mild dementia syndrome and 3 had a moderate dementia syndrome.

Two control groups with cognitively normal probands were formed: one for comparison with the FTD group (COFTD; n = 12) and one for comparison with the AD group (COAD; n = 12). Both control groups were matched for age and gender with the respective patient group. Probands of the COAD group were recruited by the Leipzig Longitudinal Study of the Aged (LEILA 75+) [12]. Probands of the COFTD group were part of the database of the MPI with one exception (1 woman) who was also recruited by the LEILA 75+. Written informed consent was obtained from all participants.

All probands of the FTD group, AD group and COAD group were interviewed and examined by a specialist in geriatric psychiatry. Cognitive skills were assessed using the MMSE. In all AD and FTD cases, a collateral source was interviewed. Using the Clinical Dementia Rating (CDR) scale [13], the clinician rated each participant in six areas of cognition and of function: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. A CDR global score was assigned according to published rules to indicate the presence or absence of dementia and, when present, its severity. A CDR global score of 0 indicates no dementia. CDR global scores of 0.5, 1, 2 and 3 indicate very mild, moderate and severe dementia.

Probands recruited by the MPI (COFTD group) were originally enrolled for functional MRI experiments. Before admission, a brief history and physical inspection was taken by a physician and a high-resolution T_1-weighted MRI scan of the head was acquired. Probands were included if they complied with the informed consent for conducting general functional MRI experiments, passed the examination and did not exhibit pathological or abnormal features in their MR tomograms.

Magnetic Resonance Imaging

All participants were investigated with a volumetric T_1-weighted imaging protocol. Participants of the memory clinics in Leipzig and Regensburg were investigated on a 1.5-tesla tomograph (Leipzig: Siemens Vision; Regensburg: Siemens Magnetom Symphony) and participants of the MPI were investigated on a 3-tesla tomograph (Bruker). The following parameters were used: (1) Leipzig: TR 11.4 ms, TE 4.4 ms, 128 slices, transverse orientation, matrix 256 × 256, voxel size 0.9 × 0.9 × 1.5 mm; (2) Regensburg: TR = 11.1 ms, TE = 4.3 ms, sagittal orientation, matrix 256 × 256, voxel size 0.9 × 0.9 × 1.0 mm, and (3) MPI: high-resolution whole-head 3-dimensional modified driven equilibrium Fourier transform protocol [14, 15], 128 sagittal slices, 1.5 mm thickness, FOV 25.0 × 25.0 × 19.2 cm, matrix 256 × 256. All datasets were analysed using the BRIAN system [16]. Datasets were transposed into transverse orientation and aligned with the stereotactical coordinate system [17], using the anterior and posterior commissure as reference points, and scaled to an isotropic voxel resolution of 1 mm. The sagittal slice best representing the midsagittal plane (few or absent grey matter and a visible septum pellucidum) was selected. The corpus callosum was divided into five subregions as suggested by Weis et al. [18] (fig. 1). Callosal subregions were manually outlined. Pixels of high signal intensity were assigned to the corpus callosum. Signal intensity was assessed visually without using an objective threshold. To evaluate the measurement reproducibility, 15 images were independently outlined by a second rater. The mean difference between the two measures was 8.3 mm^2 (± 34.1 mm^2) and did not differ significantly from zero. The correlation coefficient was 0.92 ($p < 0.001$, one-tailed). Additionally, the midsagittal intracranial area was manually outlined following the technique by Pantel et al. [7].

Statistical Analysis

All statistical computations were performed using SPSS for Windows (version 8.0.0). The significance level was set to be 0.05 for all analyses. Baseline characteristics were compared using the Kruskal-Wallis H test. The relation between age and callosal size was tested by two correlation analyses (one-tailed significance): (1) with both control groups and (2) with both patient groups. As data were acquired using three different tomographs, the statistical analysis relied only

Table 1. Demographic characteristics

	COFTD	FTD	AD	COAD
Total	12	12	12	12
Female	4	4	4	4
Age, years				
Mean (SD)	60.4 (6.9)	60.5 (7.0)	77.9 (4.2)	78.4 (3.6)
Range	49–74	51–73	69–84	70–84
MMSE				
Mean (SD)		26.2 (3.1)	23 (2.1)	28.5 (1.3)
Range		19–29	20–26	25–30
CDR global score				
1		11	12	0
2		1	0	0
Duration				
Mean (SD)		4 (4)	2 (1)	
Range		1–10	1–3	

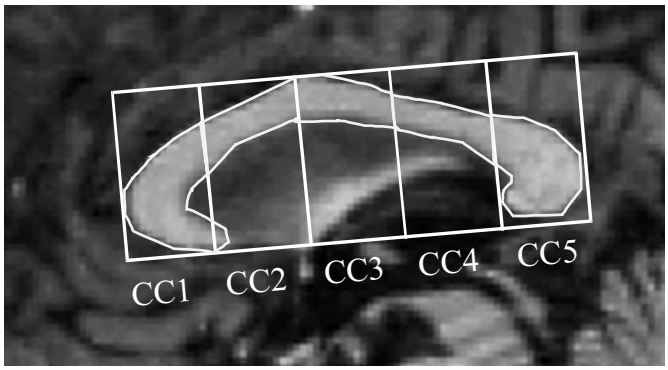

Fig. 1. The manual outlining of callosal segments is demonstrated. A rectangle was constructed round the corpus callosum and divided into five parts of the same size (CC1–CC5). CC1 amounts to the rostrum and genu and CC5 to the splenium.

Table 2. Callosal segment area/ICA ratios in patients with AD, in patients with FTD and in the two control groups (n = 48)

	COFTD mean ± SD (n = 12)	FTD mean ± SD (n = 12)	AD mean ± SD (n = 12)	COAD mean ± SD (n = 12)	COFTD-FTD % diff. (n = 24)	COAD-AD % diff. (n = 24)	FTD-AD % diff. (n = 24)	COFTD-COAD % diff. (n = 24)
CC1/ICA*100	1.26 ± 0.13	1.17 ± 0.18	1.06 ± 0.21	1.10 ± 0.15	7.1	3.6	9.4	12.7[a]
CC2/ICA*100	0.65 ± 0.09	0.55 ± 0.11	0.52 ± 0.08	0.56 ± 0.07	15.4[a]	7.1	5.5	13.9[a]
CC3/ICA*100	0.59 ± 0.09	0.57 ± 0.08	0.49 ± 0.06	0.54 ± 0.05	3.4	9.3	14.0[a]	8.5
CC4/ICA*100	0.59 ± 0.10	0.56 ± 0.09	0.50 ± 0.05	0.52 ± 0.06	5.1	3.9	10.7[a]	11.9[a]
CC5/ICA*100	1.34 ± 0.13	1.32 ± 0.26	1.21 ± 0.24	1.19 ± 0.19	1.5	–1.7	8.3	11.2
Total CC/ICA*100	4.44 ± 0.38	4.18 ± 0.54	3.78 ± 0.53	3.91 ± 0.39	5.9	3.3	9.6[a]	11.9[a]

CC = Corpus callosum; % diff. = proportional difference of the mean callosal segment/ICA ratios.
[a] Post hoc analysis (least significant difference) revealed a significant difference.

on ratios: (1) callosal measures were divided by the intracranial area (ICA) and multiplied by 100, and (2) callosal measures were divided by the total callosal area. Univariate analysis of variance (ANOVA) with group as factor was carried out to test group differences in the total callosal area/ICA ratio. Two repeated-measures ANOVA with group as between-subject factor were performed to assess group differences and interaction effects: (1) with the five callosal segments/ICA ratios as within-subject factor and (2) with the five callosal segments/total callosal area ratios as within-subject factor. Post hoc analyses were performed using least significant difference. This 'parametric' strategy was chosen for better comparability with other studies. However, our sample is small for this strategy with 48 probands in four groups and the corpus callosum being divided into five segments. Therefore, we checked the plausibility of our results with nonparametric tests (Kruskal-Wallis H test, U test). Finally, we tested the relation between the total callosal area/ICA ratio and MMSE using correlation analysis (one-tailed significance): we included COAD, FTD and AD (n = 36).

Results

Demographic characteristics are summarised in table 1. Kruskal-Wallis H testing revealed that groups differed significantly in age ($\chi^2 = 34.4$, d.f. = 3, $p < 0.001$). AD patients were older than FTD patients and COAD probands were older than COFTD probands. Groups differed significantly in MMSE score ($\chi^2 = 20.5$, d.f. = 2, $p <$

0.001). The COAD group had higher MMSE scores than the FTD group and the FTD group had higher MMSE scores than the AD group. The duration of the disease was longer in the FTD group than in the AD group ($U = 37$, $n = 24$, $p < 0.05$).

Age correlated significantly with the total callosal area/ICA ratios in the combined control groups ($r = -0.5$, $n = 24$, $p < 0.01$), but not in the combined patient groups ($r = -0.2$, $n = 24$, $p = 0.2$). As slopes differed between the groups, we did not include age as a covariate in the proceeding analyses as homogeneity of slopes is a prerequisite for ANCOVA.

Univariate ANOVA with post hoc least significant difference test showed that groups differed significantly in the total callosal area/ICA ratios ($F_{3, 44} = 4.6$, $p < 0.01$). The AD group had significantly smaller total callosal area/ICA ratios than the FTD group (–9.6%). Also, the COAD group had significantly smaller total callosal area/ICA ratios than the COFTD group, indicating the influence of age (–11.9%). Both clinical groups differed to almost the same degree from their control group, while the atrophy was slightly more pronounced in the FTD group: COAD versus AD (–3.3%, non-significant), COFTD versus FTD (–5.9 %, non-significant).

Looking at the five callosal segment/ICA ratios (table 2), differences in the pattern of callosal atrophy were noticeable, but small: in FTD as well as in COAD, callosal atrophy was most pronounced in the anterior two segments; in AD, callosal atrophy was most pronounced in the middle segment. However, all callosal segment/ICA ratios were smaller in AD relative to FTD, in FTD relative to COFTD, in COAD relative to COFTD and in all segments except the most posterior in AD relative to COAD. Accordingly, repeated-measures ANOVA for the five callosal segment/ICA ratios showed that there was no significant interaction between group and callosal segment/ICA ratios. We found some significant differences in single segment/ICA ratios between the groups, but this does not indicate that groups differed in their pattern of callosal atrophy.

Correspondingly, differences between the groups in the proportional size of callosal segments to total callosal area were very small (fig. 2). Repeated-measures ANOVA for the five callosal area/total callosal area ratios showed no significant interaction between group and segment. When using non-parametric tests, the results were essentially the same.

There was a significant correlation between the total callosal area/ICA ratio and MMSE ($r = 0.32$, $n = 36$, $p < 0.05$).

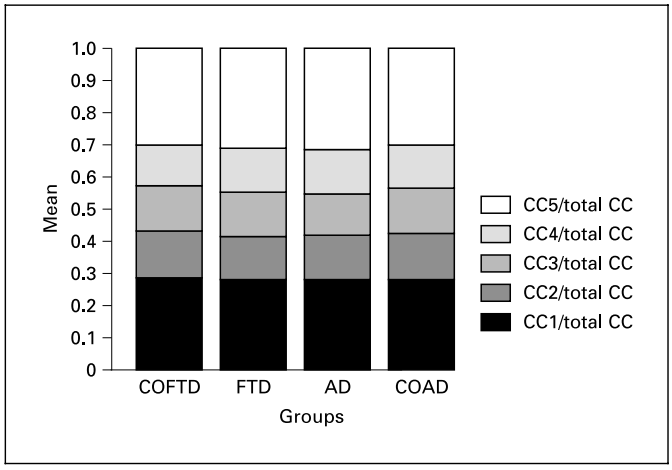

Fig. 2. The size of the five callosal segments relative to the total callosal area. There was no difference in the pattern of callosal atrophy between the four groups. CC = Corpus callosum.

Discussion

In contrast to previous reports, this study found no different patterns of callosal atrophy when comparing patients with FTD and patients with AD in mild to moderate stages. In both patient groups, the corpus callosum appeared to be atrophic relative to controls and the degree of atrophy was comparable, but small and not significant.

There are three main differences between our study and the previous studies [5, 10]. (1) We only included patients with mild to moderate disease severity. (2) As a consequence, the corpus callosum of the FTD group was on average less severely atrophied relative to the study of Yamauchi et al. [5]. Kaufer et al. [10] did not report absolute values, but a figure with error bars: the degree of callosal atrophy seems similar to our study. (3) In our study, the patient groups differed significantly in age in contrast to the other two studies, in which they did not differ.

In our study, the effect of age on the degree of callosal atrophy was larger than the effect related to FTD and to AD. The patient groups differed by 3–6% from their age-matched control groups in total callosal area/ICA ratios. The control groups differed by 12% from each other in total callosal area/ICA ratios; almost the same difference (10%) was found between the older AD group and the younger FTD group. As both clinical groups differed to almost the same degree from their respective control group and the atrophy was slightly more pronounced in

FTD patients, the difference between FTD and AD has to be attributed to the effect of age.

Looking at the pattern of age-related changes, the COFTD group and the COAD group differed significantly in four callosal segment/ICA ratios, most pronounced in the anterior two segments. These are the same segments which differed mostly between FTD and COFTD. Thus, it seems a consequence of age that there is no difference between the AD group and the FTD group in the anterior two segments. Moreover, in AD, callosal atrophy was most pronounced in the middle segment relative to COAD. The same segment was only weakly influenced by age, as seen by a comparison between COAD and COFTD. We conclude that age may 'cover' the pattern of AD-related callosal atrophy.

However, we found no difference in the pattern of callosal atrophy even between the age-matched groups. The main reason might be that the degree of callosal atrophy related to FTD and to AD was small. This corresponds to our sample characteristics, i.e. we only included mild and moderate stages. Already Yamauchi et al. [5] supposed that the variations in shape and size of the corpus callosum seen in the normal population may mask the characteristic pattern in early stages of FTD and AD.

Limitations of this study: the data were acquired using three different tomographs. We tried to handle this problem by using only ratios instead of raw data. However, contrasts within the images were different, which could have influenced the manual outlining.

Another problem is the assessment of disease severity. AD patients and FTD patients were matched in cognitive impairment using MMSE. However, this does not exactly ensure equivalent disease severity in all cases. Cognitive deficits are considered as early signs of AD, but not of FTD. As a consequence of the MMSE-based matching, the disease severity was slightly more pronounced in 1 FTD patient as measured by the CDR global score (table 1). FTD patients received higher ratings in the functional CDR scales judgement and problem solving, community affairs, home and hobbies. AD patients scored higher in the cognitive CDR scales memory and orientation. However, none of the FTD patients and none of the AD patients was severely impaired in any functional domain.

Conclusion

There seems to be no difference in the pattern of callosal atrophy between patients with FTD and patients with late-onset AD on condition that (1) FTD and AD patients are in a mild to moderate stage and (2) patient groups have a clearly different age. Not only the degree, but also the pattern of callosal atrophy may depend on the disease stage and on age.

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