Structural Changes of the Corpus Callosum in Mild Cognitive Impairment and Alzheimer’s Disease

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Key Words
Corpus callosum · Mild cognitive impairment · Alzheimer’s disease · Magnetic resonance imaging · Structural changes

Abstract

\textbf{Background:} Although previous studies demonstrate significant atrophy of the corpus callosum (CC) in patients with Alzheimer’s disease (AD), CC alterations in mild cognitive impairment have not been investigated yet.

\textbf{Methods:} 21 subjects with mild cognitive impairment, 10 with AD and 21 healthy controls were investigated using magnetic resonance imaging. In the midsagittal slice the CC was traced manually. Additionally, voxel-based morphometry (VBM) was performed.

\textbf{Results:} The CC was significantly smaller in patients with AD compared to healthy controls in both manual tracing and VBM. The atrophy was prominent in rostral parts of the CC. In subjects with mild cognitive impairment, the two rostral CC segments were smaller compared to controls when manually traced. In contrast, VBM revealed no significant difference between subjects with mild cognitive impairment and controls.

\textbf{Conclusion:} Manual tracing was more sensitive in detecting discrete structural CC changes than VBM. Alterations of the CC in mild cognitive impairment rank in between normal aging and AD, supporting the hypothesis that mild cognitive impairment most often represents a preclinical stage of AD.

Introduction

Alzheimer’s disease (AD) is the most frequent among the diversity of dementing disorders. It is generally accepted that most often mild cognitive impairment represents its preclinical stage, defined by slight but consistently verifiable deficits that do not (yet) allow diagnosis of dementia. According to larger representative studies, subjects with mild cognitive impairment are at a high risk of developing AD in the near future, with conversion rates of 15–53% over a 3-year time period [1, 2].

Pathological processes in different cortical areas may lead to regional alterations of the corpus callosum (CC), the main interhemispheric fiber connection. CC atrophy is assumed to be the anatomical correlate of Wallerian degeneration of commissural nerve fibers and thus represents an index of neocortical destruction. Previous studies reported atrophy of the CC in AD [3, 4]. As those...
studies focused on advanced stages of the disease, there is little knowledge on whether the CC is already involved in the transitional phase between health and the onset of dementia. Therefore we investigated the CC in subjects with mild cognitive impairment, patients with AD and healthy controls using magnetic resonance imaging. Two different approaches – manual tracing on a midsagittal slice and voxel-based morphometry (VBM) – were compared. While manual segmentation still represents the ‘gold standard’ in the detection of atrophic changes, VBM – although still an experimental tool – offers the advantage to be automated and rater independent. Accordingly, comparison of the two techniques appears reasonable, particularly since it has not yet been performed for mild cognitive impairment and AD.

**Patients and Methods**

In the current study, 21 subjects with mild cognitive impairment defined according to the concept of aging-associated cognitive decline (AACD) [5], were enrolled. The AACD concept not only uses age-adjusted norms to define a cognitive deficit, but also considers decline in a broader potential range of cognitive domains, namely memory and learning, attention and concentration, thinking, language, and visuospatial functioning. Subjects with mild cognitive impairment/AACD were identified according to the following criteria: (1) performance of at least 1 standard deviation below the age-adjusted norm on a standardized test of cognition, involving at least one of the aforementioned domains; (2) exclusion of any medical, neurological or psychiatric disorder that could produce cognitive deterioration as determined by history and/or clinical examination; (3) normal activities of daily living, and (4) exclusion of dementia.

Two larger prospective studies demonstrated that the AACD criteria were a stable and broad concept that was instrumental in the prediction of the future development of dementia [2, 6]. Two additional groups comprised 21 cognitively unimpaired subjects and 10 patients with mild to moderate AD (according to the NINCDS-ADRDA criteria) [7], with all patients fulfilling the criteria of probable AD. The subjects with AACD and the healthy controls were recruited among participants of a population-based, interdisciplinary, longitudinal study of aging in the Heidelberg area (n = 252 born between 1930 and 1932) which has been described in detail elsewhere [8]. Those fulfilling the criteria for AACD as well as a comparable number of cognitively unimpaired subjects, a total of 71, participated in the MRI investigation. Subjects showing significant indications of cerebrovascular disease revealed by MRI or inappropriate/incomplete datasets due to motion artifacts or withdrawal in case of claustrophobia were excluded. Cerebrovascular disease was defined as changes suspicious for macro- or microangiopathic changes on the standard T2 or FLAIR MRI sequences. Hyperintensities in vessel territories or lacunar changes were considered to represent macroangiopathy, while multiple small hyperintensities or confluent lesions in the periventricular area were considered to represent microangiopathy. There were no significant differences in sociodemographic and neuropsychological characteristics between those who were excluded from the analysis and those who remained (n = 42). Additionally, MRI was performed in 10 age-matched patients with mild to moderate AD (MMSE [9] 19.2 ± 3.85), who were recruited from the section for geriatric psychiatry at the University of Heidelberg.

The clinical evaluation of all subjects included ascertainment of personal and family history as well as physical, neurological and neuropsychological examination. History of ischemic heart disease, cancer and cerebrovascular risk factors (hypertension and diabetes) were carefully evaluated. Global cognitive deficits were assessed using the Global Deterioration Scale (GDS) [10]. Cognitive performance was investigated with an extensive neuropsychological test battery of which a detailed description has been published previously [8]. All investigations were approved by the ethics committee of the Medical Faculty in Heidelberg. Written informed consent was obtained from all participating subjects after the procedures of the study had been fully explained.

The MRI data were obtained at the German Cancer Research Center with a 1.5-tesla Magnetom Symphony MR scanner (Siemens Medical Solutions, Erlangen, Germany) by using a T1-weighted three-dimensional magnetization prepared rapid gradient echo sequence (MP-RAGE, 126 coronar slices, image matrix = 256 × 256, voxel size = 0.98 mm × 0.98 mm × 1.8 mm, TR = 10 ms, TE = 4 ms).

Manual CC measurement was performed on a Silicon Graphics (SGI) workstation using the manual segmentation function of BRAINS software [11]. Ascertainment of the callosal area followed an established protocol [12]. After drawing a horizontal line in the mid-sagittal T1-weighted slice from the most anterior to the most posterior point of the CC, the CC was divided into five parts by constructing vertical lines of equal distance perpendicular to the horizontal line. The five subsections called CC1-CC5 correspond approximately to the five anatomical subdivisions of the CC (CC1 = rostrum and genu; CC2 = rostral body; CC3 = midbody; CC4 = isthmus; CC5 = splenium). Each subsection was then traced manually and the total callosal area was calculated by adding up the single values. The rater was blinded to the diagnosis. Twenty randomly selected scans were retraced twice by the same as well as by a second rater to achieve a measure of inter- and intrarater reliability. Both yielded an intra-/interclass correlation between r = 0.96 (CC2) and r = 0.99 (CC1, CC5).

To address inter-individual differences in head size, the manually traced CC areas were corrected by dividing them by each subject’s intracranial volume. Analyses of variance with post hoc Duncan’s tests were calculated to compare the data between the diagnostic groups.

In VBM analysis, the anatomical datasets were segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF), applying the iterative a-priori-knowledge-based algorithm implemented in SPM99 software (http://www.fil.ion.ucl.ac.uk/ spm). The intracranial volume was estimated by the sum of the three tissue types. VBM was used to perform statistical inferences about differences in white matter tissue distribution in space. Therefore brain segments were normalized (1 mm × 1 mm × 1 mm) into standard stereotactic space (T1 template provided by the Montreal Neurological Institute) and smoothed using a 10-mm full-width at a half-maximum Gaussian kernel. Two-sample t tests were calculated for each group comparison. Only significant results (p < 0.05, corrected for multiple comparisons as defined in SPM) and a cluster size equal or greater than 200 voxel are reported.
Results

The three groups did not differ in intracranial volume (F = 0.2, d.f. = 2, 49, p = 0.825). Total callosal area was significantly reduced in patients with AD when compared both with controls and subjects with mild cognitive impairment/AACD (F = 11.6, d.f. = 2, 49, p < 0.001). On the other hand, there was no significant difference in total callosal size between controls and AACD subjects. Comparison of the subdivisions of the CC showed significantly smaller CC1, CC2 and CC3 in patients with AD relative to controls and subjects with AACD (4.5 ≤ F ≤ 21.8, d.f. = 2, 49, 0.001 ≤ p ≤ 0.016). Furthermore, the two rostral segments of the CC were significantly smaller in

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (1) (n = 21)</th>
<th>MCI (2) (n = 21)</th>
<th>AD (3) (n = 10)</th>
<th>F value</th>
<th>d.f.</th>
<th>p value</th>
<th>Duncan test (5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>11 F/10 M</td>
<td>10 F/11 M</td>
<td>4 F/6 M</td>
<td></td>
<td></td>
<td></td>
<td>1 = 2 = 3</td>
</tr>
<tr>
<td>Age, years</td>
<td>66.2 ± 0.8</td>
<td>66.6 ± 0.6</td>
<td>66 ± 7.7</td>
<td>0.12</td>
<td>2.49</td>
<td>0.88</td>
<td>1 = 2 = 3</td>
</tr>
<tr>
<td>GDS</td>
<td>1.29 ± 0.46</td>
<td>1.71 ± 0.46</td>
<td>3.90 ± 0.88</td>
<td>76.73</td>
<td>2.49</td>
<td>&lt;0.001</td>
<td>1 &lt; 2 &lt; 3</td>
</tr>
<tr>
<td>ICV, dm³</td>
<td>1.38 ± 0.17</td>
<td>1.35 ± 0.13</td>
<td>1.37 ± 0.21</td>
<td>0.19</td>
<td>2.49</td>
<td>0.825</td>
<td>1 = 2 = 3</td>
</tr>
<tr>
<td>CC1</td>
<td>138.2 ± 19.2</td>
<td>125.3 ± 10.5</td>
<td>98.2 ± 17.0</td>
<td>21.80</td>
<td>2.49</td>
<td>&lt;0.001</td>
<td>1 &gt; 2 &gt; 3</td>
</tr>
<tr>
<td>CC2</td>
<td>62.9 ± 11.0</td>
<td>54.9 ± 6.9</td>
<td>47.0 ± 8.0</td>
<td>11.40</td>
<td>2.49</td>
<td>&lt;0.001</td>
<td>1 &gt; 2 &gt; 3</td>
</tr>
<tr>
<td>CC3</td>
<td>59.8 ± 10.7</td>
<td>59.9 ± 7.5</td>
<td>50.7 ± 6.0</td>
<td>4.48</td>
<td>2.49</td>
<td>0.016</td>
<td>1, 2 &gt; 3</td>
</tr>
<tr>
<td>CC4</td>
<td>59.1 ± 9.7</td>
<td>58.0 ± 6.7</td>
<td>54.1 ± 7.8</td>
<td>1.27</td>
<td>2.49</td>
<td>0.291</td>
<td>1 = 2 = 3</td>
</tr>
<tr>
<td>CC5</td>
<td>127.6 ± 28.4</td>
<td>128.5 ± 19.7</td>
<td>114.3 ± 19.1</td>
<td>1.39</td>
<td>2.49</td>
<td>0.260</td>
<td>1 = 2 = 3</td>
</tr>
<tr>
<td>CC total</td>
<td>447.6 ± 63.2</td>
<td>429.0 ± 37.3</td>
<td>356.5 ± 39.3</td>
<td>11.60</td>
<td>2.49</td>
<td>&lt;0.001</td>
<td>1, 2 &gt; 3</td>
</tr>
</tbody>
</table>

Means ± SD; ICV = intracranial volume; d.f. = degrees of freedom.
AACD subjects than in controls (CC1: 9.3% lower; CC2: 12.7% lower). The manual tracing is illustrated in figure 1. Callosal measures are summarized in table 1.

VBM revealed significant differences only for comparison between healthy controls and patients with AD. In the AD group, a significant loss of callosal volume was localized in the posterior part of CC1 and the anterior part of CC2 (peak coordinates = 2(x) 29(y) 10(z), cluster size = 606 voxels, T value = 4.06; fig. 2).

**Discussion**

To our knowledge, this is the first study showing significant atrophy of the CC in mild cognitive impairment as defined by the AACD criteria. Following neuropathological findings in preclinical stages of AD [13], MRI studies on subjects with mild cognitive impairment mainly focused the substructures of the medial temporal lobe [14–16]. In this regard, significant structural changes have been reported concordantly. It has been assumed that alteration of the CC might be restricted to manifest AD [17], representing the destruction of the then affected large pyramidal neurons in temporoparietal neocortical regions [13].

Recent findings in both structural and functional neuroimaging demonstrate that these areas are involved already before the clinical manifestation of dementia [18–20]. In this context, our result of significant CC atrophy in subjects with mild cognitive impairment seems plausible in that CC atrophy reflects early neocortical damage.

Our results demonstrate that CC atrophy in AACD subjects ranks in between healthy controls and patients with AD. Moreover, the structural alterations of the CC in the AACD group follow the same regional pattern as in AD, supporting the hypothesis that mild cognitive impairment indeed represents the preclinical stage of AD. It is remarkable that in our sample atrophy is restricted to the rostral parts of the CC. As revealed by recent diffusion tensor imaging (DTI) studies [21, 22], this region most likely contains commissural nerve fibers deriving from the frontal cortical fields. Following the mentioned DTI studies, commissural fibers from the temporo-parietal cortical regions, which are mainly involved in AD, project to the posterior part of the CC. Nonetheless, the majority of studies investigating structural changes of the CC in AD found its anterior part to undergo atrophic processes [3, 4, 23–28]. These findings might be explained by atrophic processes in the frontal cortex, specifically the anterior cingulate and middle frontal gyri in AD [29–33]. A recent MRI study demonstrated that patients with mild cognitive impairment who progressed to AD during follow-up (mean interval 2 years, maximum 4.5 years) showed greater atrophy not only in the left entorhinal cortex but also in the right inferior frontal gyrus compared with those who did not progress [34]. Thus we assume that our result of rostral CC atrophy in both AACD and AD subjects rather represents neurodegenerative processes in the frontal cortical regions.

As pointed out above, commissural fibers from the temporal regions cross through the splenium. This part of the CC also connects the cortical areas from the occipital lobe. This may mask the atrophy of the splenium caused by temporal lobe degeneration, as the occipital lobe is known to remain relatively spared even in advanced stages of AD [13]. Furthermore, it has to be taken into account that atrophy of the predominantly affected substructures of the medial temporal lobe (hippocampus, parahippocampal gyrus) does not lead to structural alterations of the CC because they have their own anatomical pathways: fibers arising from the hippocampus and

![Fig. 2. Distribution of significant white matter loss in patients with AD compared to healthy controls revealed by voxel-based morphometry (height threshold = 0.05 (corrected), cluster size ≥ 200 voxels).](image)
parahippocampal gyrus of each side run through the "umbria of fornix and join beneath the CC to form the body of the fornix" [35, 36].

We present the first study evaluating structural changes of the CC in AD using VBM. It seems that the approach of manual tracing is more sensitive to early structural changes of the CC, as this method could, in contrast to VBM, discriminate between healthy controls and subjects with AADC. The sensitivity of the VBM algorithm may be affected by segmentation inaccuracy, normalization errors and smoothing effects. Especially the spatial normalization process using the MNI template – which is based on MRI scans of healthy young volunteers – may have impaired the normalization of the CC as it might be assumed that those subjects have smaller ventricles than the patients/probands included in our analysis. These methodological limitations need to be addressed in future studies. Nevertheless, VBM, as a fully automatic and therefore observer-independent method could successfully be used to reveal morphological CC differences between patients with AD and healthy individuals.

References


