Fiber Connections between the Cerebral Cortex and the Corpus Callosum in Alzheimer’s Disease: A Diffusion Tensor Imaging and Voxel-Based Morphometry Study

Regional cortical atrophy in Alzheimer’s disease (AD) most likely reflects the loss of cortical neurons. Several diffusion tensor imaging studies reported reduced fractional anisotropy (FA) in the corpus callosum in AD. The aim of this study was to investigate the association between reduced FA in the corpus callosum and gray matter atrophy in AD. Thirteen patients with AD with a mean (±standard deviation) age of 68.3 years (±11.5) and mean Mini Mental State Examination (MMSE) score of 21.8 (±4.8) were recruited. There were 13 control subjects with a mean age of 66.7 years (±6.4) and MMSE of 29.1 (±0.7). We used voxel-based morphometry of gray matter maps and region of interest-based analysis of FA in the corpus callosum. FA values of the anterior corpus callosum in AD patients were significantly correlated with gray matter volume in the prefrontal cortex and left parietal lobes. FA values of the posterior corpus callosum were significantly correlated with gray matter volume in the bilateral frontal, temporal, right parietal, and occipital lobes. In control subjects, no correlations were detected. Our findings suggest that decline of FA in the corpus callosum may be related to neuronal degeneration in corresponding cortical areas.

Keywords: Alzheimer’s disease, corpus callosum, cortical fibers diffusion tensor imaging, fractional diffusion anisotropy voxel-based morphometry

Introduction

Neuropathological studies in Alzheimer’s disease (AD) have shown neurofibrillary tangles, senile plaques, and neuronal and synaptic loss not only in areas of the mesial temporal lobe but also in a subset of intracortical projecting neurons in neocortical association areas that maintain interhemispheric connections through the corpus callosum (Ohm et al. 1995; Giannakopoulos et al. 1997). These changes involve not only the neuronal somata in the cortical gray matter but also the neuronal fibers in the subcortical white matter (Brun and Englund 1986). Neural degeneration in AD starts in the neural periphery with loss of synaptic functional and structural integrity, redistribution of cell organelles and elements of cytoskeleton from axons and dendrites to the neuronal soma, and axonal and dendritic degeneration (Brun and Englund 1986). Impaired integrity of nerve fibers leads to less constrained diffusive motion of water molecules. Diffusion tensor imaging is a novel technique that allows measurement of the subcortical fiber tract integrity in vivo (Le Bihan et al. 1991). From the diffusion tensor, the fractional anisotropy (FA), a quantitative measure describing the anisotropy of water diffusion, can be calculated at each voxel (Basser and Pierpaoli 1996). The FA reflects the integrity of neuronal fibers in the white matter and characterizes the microarchitecture of local brain tissue.

Consistent with the loss of interhemispherically projecting neurons, diffusion tensor–based studies have reported reduced FA in the anterior and posterior corpus callosum in patients with AD (Rose et al. 2000; Bozzali et al. 2002; Stahl et al. 2003; Head et al. 2004). However, it is still unknown whether the AD-related diffusion changes in the corpus callosum reflect regional loss of callosally projecting neurons in the cortical gray matter.

In the present study, we investigated correlations between FA in the corpus callosum and cortical gray matter volume using automated voxel-based morphometry (VBM) (Ashburner and Friston 2000) in AD patients and healthy elderly controls. A correlation between a decline in fiber tract integrity in the corpus callosum and gray matter atrophy in corresponding cortical areas would support the notion that a decline in FA reflects a loss of intracortical projecting neurons in AD.

Subjects and Methods

Subjects

Thirteen patients with AD mean (±standard deviation [SD]) age 68.3 (±11.5) years (6 women and 7 men) were recruited from the Department of Psychiatry, Alzheimer Memorial Center, Ludwig-Maximilian University Munich, Germany. The mean Mini Mental State Examination (MMSE) score was 21.8 (±4.8). Patients fulfilled the criteria of the National Institute of Neurological and Communicative Disease and Stroke and the Alzheimer’s Disease and Related Disorders Association for the diagnosis of clinically probable AD (McKhann et al. 1984). The clinical assessment included detailed medical history, neurological and neuropsychological examinations, and laboratory tests (routine hematology and biochemistry screen, thyroid function tests). Major systemic, psychiatric, or neurological illnesses were carefully investigated and excluded in all subjects by clinical and neurological examinations, blood testing (complete blood count, sedimentation rate, electrolytes, glucose, blood urea nitrogen, creatinine, liver-associated enzymes, cholesterol, high-density lipoprotein, triglycerides, antinuclear antibodies, rheumatoid factor, HIV, serum B12, folate, thyroid function tests, and urine analysis), and psychiatric examination. Patients were particularly screened to exclude the presence of major cerebrovascular disease. Only subjects were included which had no more than 3 subcortical white matter hyperintensities as examined on $T_2$-weighted magnetic resonance imaging (MRI) scans exceeding 10 mm in diameter.

Thirteen healthy control subjects (7 women and 6 men, mean [±SD] age 66.7 [±6.1] years) with MMSE 29.1 (±0.7) were recruited. The controls did not complain about cognitive problems, and there was no evidence of cognitive deficits as measured by neuropsychological testing using the Consortium to establish a Registry for Alzheimer’s Disease battery.

Patient and control groups were matched for age (Student’s $T$-test, $t = 0.42$, degrees of freedom [df] = 24, $P = 0.68$) and gender (Pearson Chi-Quadrat test: $\chi^2 = 0.07$, df = 1, $P = 0.78$). As expected, there was a significant difference in MMSE scores between AD and control groups,
with 21.7 (SD = 4.8) in patients with AD and 29.0 (SD = 0.9) in the control group (Mann-Whitney U = 6.0, P = 0.001).

All patients and controls were only examined after they had given their written informed consent. The study was approved by the Ethical Committee of the Medical Faculty of the University Munich.

Magnetic Resonance Imaging (MRI)

We performed MRI examinations of the brain on a 1.5-T MRI scanner (Magnetom Sonata Maestro Class, Siemens Medical Solutions, Erlangen, Germany) using a new 8-channel phased-array head coil and integrated hardware and software solutions of parallel acquisition technique.

For the structural data, we applied a high-resolution T₁-weighted magnetization-prepared rapidly acquired gradient echo (MPRAGE) sequence with a spatial resolution of 1.1 mm³ and echo time/time to inversion/time repetition (TE/TI/TR) of 3.9/800/1570 ms. A total of 160 sagittal slices with a matrix size of 256 × 256 and a field of view of 270 × 270 mm² were measured. In order to identify white matter lesions, 56 T₂-weighted axial slices were acquired using a conventional sequence (TE/TR/TI: 60/8340/2500 ms) with a matrix size of 256 × 208 and a field of view of 230 × 187 mm², which resulted in a voxel size of 0.9 × 0.9 × 3.6 mm³. Prior to image registration, data were collected with a spin-echo single-shot sequence (TE/TR 71/6000 ms); diffusion gradients in 6 different spatial directions were applied as described by Bassler and Pierpaoli (1996). The b values were 0 and 1000 s/mm². The images had a matrix size of 128 × 128 with a field of view of 230 × 230 mm², the resulting voxel size was 1.8 × 1.8 × 3.6 mm³. Thirty-six axially orientated slices were acquired. Ten measurements were performed and averaged. During each course, each subject was scanned without changing their position in the scanner.

The diffusion-weighted MRI scans were performed with parallel imaging. Test measurements were performed in a single healthy control to visually assess image quality, signal-to-noise, and artifacts for the modified sensitive encoding (Pruessmann et al. 1999) and generalized autocalibrating partially parallel acquisition (GRAPPA) (Griswold et al. 2002) algorithm. The GRAPPA algorithm revealed fewer ghosting artifacts (N/2 artifacts) and a better signal-to-noise, which resulted in a better image quality. Using a parallel-imaging acceleration factor of 3, considerable ghosting artifacts degraded the image. Therefore, for all following examinations we used the GRAPPA reconstruction algorithm with an acceleration factor of 2 and 24 reference lines (autocalibration signals) in the k-space center.

Data Analysis

Anisotropy Measurement

From the diffusion-weighted sequence, the values for FA in each voxel were calculated with software developed in-house (Interactive Data Language, version 5.4, Research Systems Inc., Boulder, CO). The resulting maps as well as the T₂-weighted images (those of the diffusion tensor sequence with a b value of 0) and the MPRAGE images were converted separately into 3-dimensional volume data sets.

Regions of interest (ROIs) in the anterior and posterior corpus callosum with a pixel number 20 carefully placed bilaterally in 3 consecutive slices on which these structures were completely shown (Fig. 1) on the T₂-weighted images, as it was reported previously (Bozzali et al. 2002). The correct ROI position was visually compared with the corresponding layers of the MPRAGE data sets.

Cortical Gray Matter Measurement

The regional gray matter volume was determined using VBM with Matlab 6.5 (MathWorks, Natick, MA) through statistical parametrical mapping (SPM 2, Wellcome Department of Imaging Neuroscience, London, UK, see also http://www.fil.ion.ucl.ac.uk/spm). An optimized VBM protocol was followed for preprocessing and subsequent analysis of imaging data. This method has previously been described in detail (Ashburner and Friston 2000; Good et al. 2001).

Normalized Group-Specific Template and Priors

After manual realignment of the T₁-weighted scans, a group-specific template was created from the scans of the AD subjects. First, each structural MRI was normalized to the standard T₁-weighted MRI template (Ashburner et al. 1997; Ashburner and Friston 2000). Normalized scans were then smoothed (12-mm full width at half maximum isotropic Gaussian kernel) and averaged to obtain a group-specific T₁-weighted template. All structural MRI scans positioned in native space were then normalized to this template. Afterward, group-specific average maps were created for gray matter, white matter, and cerebrospinal fluid. These maps, called prior images, carry the a priori information on the tissue distribution for Bayesian segmentation of MRI scans. In addition, gray matter images were smoothed with a 12-mm kernel and averaged to obtain a group-specific gray matter template.

Optimized Normalization and Segmentation

The native MRI scans were segmented using the group-specific T₁-weighted template and gray matter, white matter, and cerebrospinal fluid priors. The original structural images were then normalized. The optimized normalization procedure involves an iterative normalization of gray matter maps from native to standard space and aims to reduce any contribution from nonbrain voxels and to afford optimal spatial normalization of gray matter. The normalized gray matter maps were resliced to a final voxel size of 1.0 mm³ and smoothed with a 12-mm full width at half maximum isotropic Gaussian kernel. Additionally, the partitioned gray matter images were modulated by the Jacobian determinants from spatial normalization to correct volume changes introduced during the nonlinear spatial transformations (Ashburner and Friston 2000). The modulated gray matter images were used afterward for further statistical analysis.

Statistical Analysis

For statistical analysis, we employed the general linear model on a voxel basis. The voxel-based analysis is a measurement of the gray matter density throughout the brain. The output of the method is a statistical parametrical map showing where gray matter density differs significantly among groups. Prior to regression analysis, scans were proportionally scaled to the global mean threshold at 40% of global intensity to reduce the influence of any remaining nonbrain tissue. Proportional scaling to the global mean allows detection of voxels with a relatively accelerated loss or a relative preservation of gray matter (i.e., more or less than the global loss). Results were thresholded at an uncorrected P value <0.001 and an extended threshold of 50 contiguous voxels was applied.
Independent regression models were calculated for FA in the anterior and posterior corpus callosum as independent predictor variables of gray matter density. The analyses were repeated using the MMSE score as the covariate to control for general cognitive function and age as the covariate to control for age effects on cognitive functions. In the AD group, we controlled the results for MMSE score and age and in the control group for age.

Results

For the AD group, the FA values in the anterior corpus callosum were significantly positively correlated with gray matter volume in the bilateral prefrontal cortex, superior temporal gyrus with left side predominance, left postcentral, and right lingual gyrus. After controlling for MMSE score and age, the FA values of the anterior corpus callosum showed significant correlations with gray matter volume in the bilateral prefrontal cortex and left parietal lobe (Table 1, Fig. 2).

The FA values in the posterior corpus callosum in patients with AD were significantly positively correlated with reduced gray matter volume in the bilateral frontal, bilateral temporal lobes, right hippocampus, right parietal lobe, and insula. After controlling for MMSE and age as covariates, the FA of the posterior corpus callosum was significantly correlated with gray matter volume in the bilateral frontal and temporal lobes and right parietal and occipital cortices (Table 2, Fig. 2).

In control subjects, significant positive correlations were detected between the FA values in the anterior corpus callosum and the cortical gray matter volume in the left superior temporal gyrus, bilateral parietal lobe, and right posterior cingulate gyrus. Controlling for age as a covariate in control subjects changed the results. We found no significant positive correlations between FA in the anterior corpus callosum and cortical gray matter volume.

FA values in the posterior corpus callosum in control subjects were significantly positively correlated with gray matter density in the frontal lobe, predominantly in the left hemisphere, left temporal, and left parietal lobes. Controlling for age as a covariate in control subjects changed the results. We found no significant positive correlations between FA in the posterior corpus callosum and cortical gray matter volume.

Table 1

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>BA</th>
<th>Coordinates (mm)</th>
<th>$T_9$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$x$</td>
<td>$y$</td>
</tr>
<tr>
<td>FrONTAL Lobe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>Left</td>
<td>8</td>
<td>-43</td>
<td>17</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>Left</td>
<td>6</td>
<td>-20</td>
<td>24</td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>Right</td>
<td>6</td>
<td>31</td>
<td>-14</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>Left</td>
<td>8</td>
<td>-35</td>
<td>25</td>
</tr>
<tr>
<td>PARIETAL LOBE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior parietal lobule</td>
<td>Left</td>
<td>7</td>
<td>-13</td>
<td>-72</td>
</tr>
<tr>
<td>Inferior parietal lobule</td>
<td>Left</td>
<td>39</td>
<td>-40</td>
<td>-65</td>
</tr>
<tr>
<td>Precuneus</td>
<td>Left</td>
<td>7</td>
<td>-12</td>
<td>-50</td>
</tr>
<tr>
<td>Precuneus</td>
<td>Left</td>
<td>7</td>
<td>-14</td>
<td>-69</td>
</tr>
<tr>
<td>Precuneus</td>
<td>Left</td>
<td>19</td>
<td>-40</td>
<td>-75</td>
</tr>
</tbody>
</table>

Note: The threshold value was set at $P < 0.001$, uncorrected. The cluster extension, representing the number of contiguous voxels passing the height threshold, was set at $>50$. Brain regions are indicated by Talairach and Tournoux coordinates $x$, $y$, and $z$ (Talairach and Tournoux 1988): $x$, the medial to lateral distance relative to midline (positive = right hemisphere); $y$, the anterior to posterior distance relative to the anterior commissure (positive = anterior); $z$, superior to inferior distance relative to the anterior-posterior commissure line (positive = superior). $T_9$, $T$ value with 9 degrees of freedom; BA, Brodmann area.

Discussion

In this study, we report correlations between FA in the corpus callosum and cortical gray matter volume in AD patients and healthy elderly subjects.

Several studies have shown a notable decrease of corpus callosum area in patients with AD, consistent with the loss of intracortical projecting fibers (Friedland et al. 1985; Minoshima et al. 1997; Hampel et al. 1998; Ishii et al. 1998; Demetriades 2002; Teipel et al. 2005). Diffusion tensor imaging studies have reported significantly reduced FA values in the anterior (Head et al. 2004) and posterior corpus callosum in AD (Rose et al. 2000; Bozzali et al. 2002; Takahashi et al. 2002; Stahl et al. 2003; Fellgiebel et al. 2004; Sugihara et al. 2004; Choi et al. 2005).

The corpus callosum represents specific projections from cortical areas in an anterior-posterior topology. In the rhesus monkey, prefrontal cortical fibers were mapped in the genu and anterior third of the body of the corpus callosum (Sunderland 1940). Data from the human brain suggest a similar organization (Schaltenbrand et al. 1972; de Lacoste et al. 1985; Tan et al. 1991). There is a slight difference in the anterior topology of the corpus callosum between the human and the monkey brain. This can be explained by a rostral displacement of the prefrontal fibers during evolution. In the human brain, fibers stemming from frontal cortical areas project through the rostrum and genu, whereas primary sensorimotor, postero-temporal, parietal, and occipital cortical areas are represented in the body and the splenium of the corpus callosum (de Lacoste et al. 1985).

In agreement with these observations (Sunderland 1940; de Lacoste et al. 1985; de Lacoste and Woodward 1988), we found correlations between FA values in the anterior corpus callosum and gray matter volume in the bilateral frontal cortex in AD patients. Additionally, FA values of the anterior corpus callosum were significantly correlated with the left parietal lobe gray matter volume. This correlation probably reflects a simultaneous neurodegeneration along functional systems in AD patients. Several studies have reported functional connections between frontal and parietal lobes that play an important role in the control of spatially guided behavior (Cavada and Goldman-Rakic 1989; Andersen et al. 1990; Corbetta 1998; Petrides and Pandya 1999; Collette et al. 2005; Schumacher et al. 2005). Previous studies have shown that AD pathology progresses along such intracortical networks, for example, along the dorsal visual stream (Friston et al. 1993; McIntosh et al. 1994; Horwitz et al. 1995).

These studies were based on the assumption that memory and other cognitive abilities are the result of integrated activity of networks including multiple brain regions, rather than activity in an isolated brain region, and the interactions within these networks are disrupted by the neurodegeneration of AD (Friston et al. 1993; McIntosh et al. 1994; Horwitz et al. 1995; Grady et al. 2001). Hence, direct fiber connections between the anterior corpus callosum and the frontal lobe and functional network connectivity between the frontal and parietal cortices could explain the correlation between the anterior corpus callosum and the parietal lobe revealed in this study.

Fiber tracts of the posterior corpus callosum in patients with AD after controlling for age and for MMSE score correlated with the volume in the bilateral frontal, temporal, right parietal, and bilateral occipital lobes. Fiber connectivity between the splenium and the temporo-parieto-occipital cortex detected in our study agrees with previous findings from electrophysiological
stimulation and postmortem examinations (Sunderland 1940; de Lacoste et al. 1985). The significant correlation between the decline in the posterior corpus callosum fiber integrity and volume of the right parietal lobe gray matter may underlie the impaired ability of spatial and object attention in AD that have been reported in previous studies (Awad, Johnson, et al. 1986; Cronin-Golomb et al. 1991; Mendez et al. 1997). The correlations between the posterior corpus callosum and the frontal lobe may again reflect a simultaneous neurodegeneration of the frontal and parietal lobes in AD. The correlation between posterior corpus callosum may reproduce direct fiber connections between 1) posterior corpus callosum and the parietal lobe and 2) the frontal and parietal cortices.

When controlling for dementia severity as measured by MMSE, the result pattern was changed. The FA values of the anterior corpus callosum were correlated with gray matter density of the temporal lobes in addition to the gray matter density of the frontal and parietal lobes. The FA values of the posterior corpus callosum were only significantly correlated with the gray matter density of the temporal lobes on both sides and left parietal lobe but not with the gray matter density of the frontal and the occipital lobes (Fig. 2). Therefore, the correlations that were not detected after controlling for dementia severity may reflect the effect of the dementia severity in healthy elderly subjects.

Several diffusion MRI studies (Hanyu et al. 1999; Sandson et al. 1999; Kantarci et al. 2001; Stahl et al. 2003) have demonstrated that in addition to cortical gray matter changes, microscopic white matter changes occur in patients with AD, which cannot be detected by using conventional MRI. These findings agree with neuropathological studies reporting partial loss of myelin and axons together with hyaline fibrosis of arterioles and

Figure 2. Correlation between gray matter volume intensity and FA value in the anterior and posterior corpus callosum in patients with AD. Reduced gray matter volume intensity with decreased FA in the corpus callosum (red: anterior and green: posterior corpus callosum), controlling for MMSE score and age, in patients with AD. Color-coded SPM (T) map projected on the normalized rendered brain surface from the MRI scan of a healthy subject. Cluster extension set at ≥50 contiguous voxels passing the significance threshold of $P < 0.001$. 
Brain regions are indicated by Talairach and Tournoux coordinates representing the number of contiguous voxels passing the height threshold, was set at $T = 5$. A sensitive measurement of lesion size but is used as surrogate measure of final infarct size (Verheul et al. 1992; Lu et al. 2005). It can, however, not be excluded that the size of smaller vessels in the absence of focal lacunes or infarcts in about 60% of pure AD cases (Brun and Englund 1986). White matter changes were not directly related to the severity and localization of cortical pathology (Brun and Englund 1986; Sjobeck et al. 2006), but preferentially involved the frontal white matter, whereas AD pathology was concentrated in the left frontal, left temporal, and left parietal cortices and FA values in the posterior corpus callosum. These results are in agreement with previous studies that have reported reduction of the gray matter volume in the prefrontal and temporal gray matter (Raz et al. 1998), parietal (Resnick et al. 2000; Good et al. 2001) and occipital lobes (Polidori et al. 1993), cingulate gyrus (Good et al. 2001), as well as the anterior and posterior corpus callosum (Teipel et al. 1998; Sullivan et al. 2001; Pfefferbaum and Sullivan 2003) in healthy subjects. When controlling for age, we did not detect any correlation between gray matter volume and FA in the corpus callosum. These findings suggest that these correlations detected before controlling for aging indeed reflect an age-associated effect in elderly healthy subjects.

The lack of an effect in the healthy subjects after controlling for age and the presence of an effect after controlling for age and dementia severity in AD supports the notion that, analogous to the study of experimentally induced brain lesions in animals, the system-specific neuropathology of AD can serve as a lesion model to track the morphological substrate of connectivity within cortical networks (Brodal 1981).

In conclusion, this is the first study on correlations between FA values in the corpus callosum and cortical gray matter volume in AD patients and healthy control subjects. Results from our study support the notion that decline of FA in the corpus callosum may be related to neuronal degeneration in corresponding cortical areas.

Notes
The authors thank Felician Jancu (Ludwig-Maximilian University, Munich, Germany) for his technical assistance. All authors had full

### Table 2

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>BA</th>
<th>Coordinates (mm)</th>
<th>$T_9$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$x$</td>
<td>$y$</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>Right</td>
<td>6</td>
<td>30</td>
<td>-7</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>Left</td>
<td>6</td>
<td>-15</td>
<td>1</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>Left</td>
<td>9</td>
<td>-43</td>
<td>11</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>Right</td>
<td>6</td>
<td>15</td>
<td>-3</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>Right</td>
<td>9</td>
<td>33</td>
<td>18</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>Left</td>
<td>22</td>
<td>-56</td>
<td>-26</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>Left</td>
<td>22</td>
<td>-57</td>
<td>-40</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>Right</td>
<td>22</td>
<td>59</td>
<td>-22</td>
</tr>
<tr>
<td>Inferior temporal gyrus</td>
<td>Right</td>
<td>20</td>
<td>55</td>
<td>-29</td>
</tr>
<tr>
<td>Inferior temporal gyrus</td>
<td>Right</td>
<td>19</td>
<td>46</td>
<td>-53</td>
</tr>
<tr>
<td>Inferior temporal gyrus</td>
<td>Right</td>
<td>37</td>
<td>47</td>
<td>-48</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>Right</td>
<td>43</td>
<td>51</td>
<td>-17</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>Right</td>
<td>3</td>
<td>33</td>
<td>-35</td>
</tr>
<tr>
<td>Inferior parietal lobule</td>
<td>Right</td>
<td>40</td>
<td>55</td>
<td>-25</td>
</tr>
<tr>
<td>Subgyrus</td>
<td>Right</td>
<td>40</td>
<td>27</td>
<td>-38</td>
</tr>
<tr>
<td>Precuneus</td>
<td>Right</td>
<td>7</td>
<td>10</td>
<td>-65</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precuneus</td>
<td>Right</td>
<td>31</td>
<td>4</td>
<td>-68</td>
</tr>
<tr>
<td>Cuneus</td>
<td>Right</td>
<td>23</td>
<td>6</td>
<td>-75</td>
</tr>
</tbody>
</table>

Note: The threshold value was set at $P \leq 0.001$, uncorrected. The cluster extension, representing the number of contiguous voxels passing the height threshold, was set at $v \geq 50$. Brain regions are indicated by Talairach and Tournoux coordinates $x$, $y$, and $z$ (Talairach and Tournoux 1988). $x$, the medial to lateral distance relative to midline (positive = right hemisphere); $y$, the anterior to posterior distance relative to the anterior commissure (positive = anterior); $z$, superior to inferior distance relative to the anterior-posterior commissure line (positive = superior). $T_9$ $T$ value with 9 degrees of freedom; BA, Brodmann area.

In the control group, we observed correlations between gray matter volume in the superior temporal gyrus, the parietal and occipital lobes, and the posterior cingulate gyrus and FA values in the anterior corpus callosum and between gray matter volume in the left frontal, left temporal, and left parietal cortices and FA values in the posterior corpus callosum. These correlations were entirely explained by the effect of age: after controlling for age there were no significant correlations between FAs in the corpus callosum and cortical gray matter in healthy elderly controls. Aging is associated with complex patterns of cognitive decline and alterations of brain structure (Good et al. 2001; Head et al. 2004). Many neuropathological and in vivo neuroimaging studies showed that normal aging is characterized by a substantial and extensive vulnerability of the cerebral cortex (West 1996; Raz et al. 1998; Good et al. 2001; Head et al. 2004). Previous MRI studies have examined an effect of aging in healthy adults (Raz et al. 1998; Good et al. 2001; Pfefferbaum and Sullivan 2003). In our study, we controlled the aging effect in healthy subjects. Without controlling for age in healthy subjects, we found significant correlations between gray matter volume in the superior temporal gyrus, parietal and occipital lobes, and posterior cingulate gyrus and FA values in the anterior corpus callosum and between gray matter volume in the left frontal, left temporal, and left parietal cortices with FA values in the posterior corpus callosum. These results are in agreement with previous studies that have reported reduction of the gray matter volume in the prefrontal and temporal gray matter (Raz et al. 1998), parietal (Resnick et al. 2000; Good et al. 2001) and occipital lobes (Polidori et al. 1993), cingulate gyrus (Good et al. 2001), as well as the anterior and posterior corpus callosum (Teipel et al. 1998; Sullivan et al. 2001; Pfefferbaum and Sullivan 2003) in healthy subjects. When controlling for age, we did not detect any correlation between gray matter volume and FA in the corpus callosum. These findings suggest that these correlations detected before controlling for aging indeed reflect an age-associated effect in elderly healthy subjects.
access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Part of this work was supported by grants from the Medical Faculty of the Ludwig-Maximilian University (Munich, Germany) to SJT, from the Hirnliga e. V. (Nürnberg, Germany) to DS and SJT, from the German Competency Network on Dementias (Kompetenznetz Demenzen) funded by the Bundesministerium für Bildung und Forschung, Germany, and by an unrestricted grant from Jannssen-Cilag GmbH (Neuss, Germany).

Conflict of Interest: None declared.

Address correspondence to Stefan J. Teipel, MD, Alzheimer Memorial Center, Dementia and Neuroimaging Section, Department of Psychiatry, Ludwig-Maximilian University, Nussbaumstrasse 7, D-80336 Munich, Germany. Email: stefan.teipel@med.uni-muenchen.de.

References


Awad IA, Johnson PC, Spetzler RF, Hodak JA. 1986. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. II. Postmortem pathological correlations. Stroke. 17:1090-1097.


West RL. 1996. An application of prefrontal cortex function theory to cognitive aging. Psychol Bull. 120:272–292.