MAJOR PAPER

Automatic Extraction of the Cingulum Bundle in Diffusion Tensor Tract-specific Analysis: Feasibility Study in Parkinson’s Disease with and without Dementia

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Purpose: Tract-specific analysis (TSA) measures diffusion parameters along a specific fiber that has been extracted by fiber tracking using manual regions of interest (ROIs), but TSA is limited by its requirement for manual operation, poor reproducibility, and high time consumption. We aimed to develop a fully automated extraction method for the cingulum bundle (CB) and to apply the method to TSA in neurobehavioral disorders such as Parkinson’s disease (PD).

Materials and Methods: We introduce the voxel classification (VC) and auto diffusion tensor fiber-tracking (AFT) methods of extraction. The VC method directly extracts the CB, skipping the fiber-tracking step, whereas the AFT method uses fiber tracking from automatically selected ROIs. We compared the results of VC and AFT to those obtained by manual diffusion tensor fiber tracking (MFT) performed by 3 operators. We quantified the Jaccard similarity index among the 3 methods in data from 20 subjects (10 normal controls [NC] and 10 patients with Parkinson’s disease dementia [PDD]). We used all 3 extraction methods (VC, AFT, and MFT) to calculate the fractional anisotropy (FA) values of the anterior and posterior CB for 15 NC subjects, 15 with PD, and 15 with PDD.

Results: The Jaccard index between results of AFT and MFT, 0.72, was similar to the inter-operator Jaccard index of MFT. However, the Jaccard indices between VC and MFT and between VC and AFT were lower. Consequently, the VC method classified among 3 different groups (NC, PD, and PDD), whereas the others classified only 2 different groups (NC, PD or PDD).

Conclusion: For TSA in Parkinson’s disease, the VC method can be more useful than the AFT and MFT methods for extracting the CB. In addition, the results of patient data analysis suggest that a reduction of FA in the posterior CB may represent a useful biological index for monitoring PD and PDD.

Keywords: automatic extraction, cingulum bundle, diffusion tensor imaging, Parkinson’s disease, tract-specific analysis

Introduction

The cingulum bundle (CB) connects the cortex with the prefrontal, temporal, and parietal lobes and is one of the prominent white matter fiber tracts in the limbic system. The CB runs anteriorly to the basal surface of the frontal lobe and then
ascends before running backwards through the parietal lobe, forming a ring-like belt around the corpus callosum (CC) and running anteriorly within the temporal lobe to its pole.\textsuperscript{1} Lesion studies have attributed a variety of neurobehavioral deficits to damage to the CB, including akinetic mutism, emotional disturbances, attentional deficits, motor activation, and memory impairment.\textsuperscript{2} Furthermore, the CB can be divided into an anterior and posterior CB on the basis of function. The anterior CB has been associated with executive function related to emotional control, and the posterior CB, with evaluative function, such as the monitoring of sensory events and the organism’s own behavior in the service of spatial orientation and memory.\textsuperscript{3}

Diffusion tensor imaging (DTI) is a noninvasive magnetic resonance (MR) imaging technique that is sensitive to the diffusion properties of water in brain tissue and provides information about the orientation of fiber pathways.\textsuperscript{4} DTI can provide quantitative information about water molecule diffusion in the brain, including the degree of anisotropy, such as fractional anisotropy (FA), and mean diffusivity (MD).\textsuperscript{5} Diffusion tensor tractography (DTT) is a post-processing technique for DTI that attempts to extract specific white matter fiber tracts from the tensor field. DTT is usually carried out by a fiber-tracking algorithm that traces the principle eigenvector of the diffusion tensor in small steps.\textsuperscript{6–9} Tract-specific analysis (TSA) is based on diffusion parameters along the specific fibers that have been identified by DTT.\textsuperscript{10} In the literature, TSA of the CB has been reported effective in Alzheimer disease (AD),\textsuperscript{11–15} schizophrenia,\textsuperscript{16–18} and Parkinson’s disease without (PD) and with dementia (PDD).\textsuperscript{19} It is therefore important to quantify water molecule diffusion of the CB accurately for the diagnosis of these pathological conditions.

DTT is associated with limitations according to the tracking algorithms, parameters, and regions of interest (ROI) within which we define points for tracking start and end. In particular, manual drawing of the ROI is a major problem because it is operator-dependent, has poor reproducibility, and is time-consuming when performed for many subjects. Tractography results are influenced by the number and location of ROIs, known as seed and target ROIs. Although well designed ROI placements for various white matter tracts have been suggested,\textsuperscript{20} such interactive manual ROI selection requires extensive anatomical knowledge of white matter tracts. To overcome this limitation, automated placement of ROIs has been designed,\textsuperscript{21–23} whereby an expert (such as a radiologist) with anatomical knowledge defines the ROIs in the standard brain atlas, and the ROIs are then linearly or nonlinearly transformed into individual data.\textsuperscript{21–23} Alternatively, an atlas-aligned tract probability map, which is created by averaging tractography results in each subject, can be applied to extract the tracts directly without fiber tracking.\textsuperscript{24} However, results by those methods are influenced by the quality of registration and atlas construction. In addition, the non-linear registration process takes a long time (approximately 30 to 180 min, depending on file size and extent of anatomical deformation).\textsuperscript{22} Although these atlas-based methods are useful for complex fiber tracts that are difficult to reconstruct manually, such as crossing fibers, the methods may not be required for simple fiber tracts that can be extracted easily, such as the CB, which has no crossing fibers. Therefore, it is not necessary to construct a probability map or atlas ROI to extract regions of the CB.

To tackle the manual ROI selection problem, we propose 2 fully automated methods to extract the CB–voxel classification (VC) and auto diffusion tensor fiber tracking (AFT). The VC method directly extracts regions of the CB from each voxel within box ROIs using thresholds of FA and crossing angle, skipping the fiber-tracking step. The box ROIs for extracting the CB are generated automatically using the location of the corpus callosum because the CB runs parallel to its dorsal portion. The AFT method uses fiber tracking from automatically selected seed and target ROIs to extract regions of the CB. The seed and target ROIs are automatically extracted using part of the VC method. For comparison, we also perform manual diffusion tensor fiber tracking (MFT) using manually drawn ROIs.

A fundamental problem for DTT is the lack of an appropriate gold standard for tractography, which makes it difficult to validate different methods. Therefore, we compared similarities among the results by the 3 approaches instead of defining the result of the manual fiber tracking as a gold standard. Between normal control (NC) subjects and patients with PD and PDD, we compared FA values within the CB extracted by all 3 methods as well as from another manual ROI-based method in which a small number of regions was manually defined.

Materials and Methods

Subjects

There were 45 subjects: 15 PD patients, 15 PDD patients and 15 NC subjects. The institutional review board of Juntendo University Hospital approved this study, and informed consent was ob-
Table 1. Demographic and clinical characteristics of all subjects

<table>
<thead>
<tr>
<th></th>
<th>NC (n = 15)</th>
<th>PD (n = 15)</th>
<th>PDD (n = 15)</th>
<th>P value (NC vs PD)</th>
<th>P value (NC vs PDD)</th>
<th>P value (PD vs PDD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male : female</td>
<td>6 : 9</td>
<td>9 : 6</td>
<td>8 : 7</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Age, years</td>
<td>69.5(7.1)</td>
<td>69.8(6.1)</td>
<td>71.3(5.6)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Disease duration, months</td>
<td>NA</td>
<td>70.6(60.1)</td>
<td>139.0(94.2)</td>
<td>NA</td>
<td>NA</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Hoehn and Yahr stage</td>
<td>0</td>
<td>2.3(1.3)</td>
<td>2.9(0.7)</td>
<td>NA</td>
<td>NA</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.4(1.2)</td>
<td>26.1(3.4)</td>
<td>20.2(4.0)</td>
<td>NS</td>
<td>NS</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>UPDRS-III score</td>
<td>NA</td>
<td>19.0(11.6)</td>
<td>26.9(9.5)</td>
<td>NA</td>
<td>NA</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Levodopa dosage (mg/day)</td>
<td>0</td>
<td>409.1(251)</td>
<td>687.0(126.0)</td>
<td>NA</td>
<td>NA</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Data indicate mean (standard deviation, SD); MMSE, mini-mental state examination; NA, not applicable; NS, not significant (P > .05); NC, normal control; PD, Parkinson disease; PDD, Parkinson disease with dementia; UPDRS, Unified Parkinson’s Disease Rating Scale.

Data acquisition

A 3.0-tesla MR unit (Achieva, Philips Medical Systems, Best, Netherlands) was used for all MR imaging. Diffusion data were acquired with a single shot echo-planar diffusion imaging sequence (repetition time [TR]/echo time [TE], 5443/70 ms; matrix size, 128 × 128; field of view (FOV), 224 × 224 mm²; slice thickness, 3 mm with no gap). A total of 50 axial images covered the whole cerebrum. Diffusion weighting was encoded along 32 motion-probing gradient (MPG) vectors, and the b-value was 1000 s/mm². One additional image with no diffusion weighting (b = 0 s/mm²) was also acquired. Interpolation along the z-axis was performed to obtain isotropic data (voxel size, 1.75 × 1.75 × 1.75 mm³).

Data preprocessing

To avoid the influence of head rotation in comparing automatic and manual methods for extracting the CB, we quantified brain rotation using the mid-sagittal plane and anterior commissure-posterior commissure (AC-PC) line. To extract the mid-sagittal plane, we implemented an algorithm based on Kullback-Leibler’s measure according to the method described by Nowinski and associates.28,29 The AC-PC line was approximated by the vector from the most inferior points of the genu to that of the splenium of the CC in the mid-sagittal plane. The CC in the mid-sagittal plane was extracted using a minimum FA threshold of 0.25 and a maximum crossing angle threshold of 45° between the normal vector of the mid-sagittal plane and the major eigenvector of the diffusion tensor. We utilized the normal vector of the mid-sagittal plane for axial and coronal rotations and the AC-PC line for sagittal rotation. With this brain rotation, the MPG vectors were also rotated.

Definition of the anterior and posterior CB

We divided the CB into 2 portions according to the position of the CC in the mid-sagittal plane as described in a previous report.19 We referred to the portion from the genu to the center of the CC as the anterior CB and the portion from the center to the splenium of the CC as the posterior CB (Fig. 1). We defined the level of the genu of the CC in the sagittal plane as the CCg, the center as the CCC, and the splenium as the CCs (Fig. 1). In our proposed automatic methods, these genu and splenium boundary lines, which are parallel to the coronal plane, were automatically detected with a contour trace of the CC. We used the most posterior point of the genu and the most anterior point of the splenium of the CC as detection conditions. The center of the CC was the middle of those lines.
Extraction of the CB

We utilized the shape of the corpus callosum in the mid-sagittal plane for extracting the CB because the CB runs sagittally under the cortical mantle of the medial surface of the hemisphere, maintaining an almost parallel position to the CC.\textsuperscript{1} We proposed 2 fully automatic extraction methods, VC and AFT, and performed MFT for comparison. Figure 2 shows a flowchart of the 3 methods used for extracting the region of the left anterior CB.

1. VC method

In this approach, we extracted the CB directly using thresholds of both the FA and crossing angle within automatically generated box ROIs, a method that did not require the fiber-tracking step. For the left anterior CB, we placed a box ROI at a tangent point of the CC located on the automatically detected CCg in the mid-sagittal plane (Fig. 3). The width of the box ROI was along the normal vector of the mid-sagittal plane, the height along the tangent vector of the CC, and the depth along the normal vector of the CC (Fig. 3). Candidate voxels were extracted by thresholds of the FA value and crossing angle between the tangent vector of the CC and the major eigenvector of the diffusion tensor within the box ROI. This process was repeated from the automatically detected CCg to the CCc for the left and right anterior CB and from the CCc to the CCs for the left and right posterior CB. The candidate regions were extracted by morphological closing operation and after removing small components. The VC algorithm was implemented in-house using C++.
2. AFT method
In this approach, we performed fiber tracking of the CB using automatically extracted seed and target ROIs. We used the VC method to extract these ROIs. Specifically, for the left anterior seed ROI (one candidate seed ROI) of the left anterior CB, we placed the left box ROI at a tangent point of the CC - 10 mm from the automatically detected CCg in the coronal direction. Similarly, for the left posterior seed ROI of the left posterior CB, we placed the left box ROI at a tangent point of the CC - 10 mm from the automatically detected CCc in the coronal direction. Candidate voxels were extracted by the threshold of the FA value and crossing angle within the left box ROI. This process repeated from the -10 mm to the +10 mm points of the automatically detected CCg and CCc in the coronal direction to avoid underextraction of candidate voxels due to noise. Candidate regions were extracted only in the coronal plane of the CCg and CCc by morphological closing operation and after removing small components. The extraction result from the CCg was defined as the left anterior seed ROI, and that from the CCc was defined as the left posterior seed ROI. In a similar way, the left anterior target ROI was extracted using the CCc, and the left posterior target ROI was extracted using the CCs. This was repeated to obtain seed and target ROIs for the right anterior CB and right posterior CB.

Two-ROI tractography was performed for each area (left anterior, right anterior, left posterior, right posterior) using the seed ROI and target ROI. The fiber-tracking algorithm was based on the principle direction of the diffusion tensor. The FA threshold of fiber tracking was the same as the value used for the ROI extraction. Two-ROI tractography analysis was repeated after the exchange of seed and target ROIs and the 2 fiber-tracking results were summed. The dTV software automatically extracted the tracking line using track-line voxelization, and voxelization along the tractography of the left or right anterior or posterior CB and closing operation function were performed between the seed ROI and target ROI. The result was defined as a region of the left or right anterior or posterior CB.

Comparison of extraction methods
Three operators (K.I., K.K., and H.Y.) independently selected the 3 boundary lines of the CCg, CCc, and CCs and performed MFT in MR images from 20 participants (10 NC, 10 PDD). We used inter-coronal slice distance to evaluate inter-operator variability in boundary line placement and compared the positions of the CCg, CCc, and CCs between the manual and automatic detection methods.

We used the Jaccard index to evaluate inter-operator variability in CB extraction by MFT (Equation [1]):

\[
\text{Jaccard index} = \frac{|X_{\text{ref}} \cap X|}{|X_{\text{ref}} \cup X|}, \tag{1}
\]

where \(X_{\text{ref}}\) is the voxel sets for reference, \(X\) is the voxel sets to be evaluated, and \(|\cdot|\) indicates the number of voxels. The Jaccard index represents the extent of overlap between the reference and target volumes. We compared the performance of the 3 extraction methods (VC, AFT, and MFT) using the Jaccard index (Equation [1]), the number of underestimated voxels (Equation [2]), and the number of overestimated voxels (Equation [3]):
Fig. 3. Schematic illustration of the left box region of interest (ROI). The left box ROI (blue) is placed on a tangent point (green) of the corpus callosum (red). The width direction is the normal vector of the mid-sagittal plane (u), the height direction is the tangent vector (v) at a contour point of the corpus callosum, and the depth direction is the normal vector (w) at a contour point of the corpus callosum.

Fig. 4. An example of manual region of interest (ROI) placement for fiber tracking of the left cingulum bundle. The mid-sagittal section of the color fractional anisotropy (FA) map was used to determine coronal plane at the levels of the genu (CCg), center (CCc), and splenium (CCs) of the corpus callosum (CC), indicated by the white vertical lines (A). The ROIs for tractography of the anterior and posterior cingulum bundle were placed manually on each coronal plane of the CCg (B), CCc (C), and CCs (D), as indicated in the white area.

Underestimated voxels = \(|X_{ref} \setminus X|\) \[2\]
and

Overestimated voxels = \(|X \setminus X_{ref}|\), \[3\]
where \(\setminus\) indicates set difference.

We used the region of overlap between the results of MFT by more than 2 operators to set the optimal parameters for the automatic VC and AFT methods including the size of the box ROI (search range: width, height, and depth of 1.75 to 8.75 mm at 1.75 mm intervals), the threshold of FA value (search range: 0.15 to 0.25 at 0.01 intervals) and the crossing angle (search range: 30° to 60° at 5° intervals). We used the leave-one-out method for quantitative comparison of the 3 extraction methods. Moreover, we evaluated correlation coefficients of FA values among 20 subjects along the CB extracted by each of the 3 extraction methods.

Comparison of FA values between groups

TSA is useful as a means of detecting subtle abnormal diffusion in the fiber tracts of patients.\textsuperscript{11–19} We compared FA values of the extracted anterior and posterior CBs made by each of the 3 extraction methods across 15 NC, 15 patients with PD, and 15
patients with PDD. One operator (K.I.) performed MFT for this analysis. We then evaluated the classifying capacity of each method for the 3 different groups of subjects (NC, PD, and PDD). In addition, the same operator (K.I.) performed another manual ROI-based method, manually selecting a small number of regions using a color FA map of the axial slice that included a fully volume lateral ventricle in a manner similar to the previous method described by Matsui’s group\(^3\) and measured the FA values among the 3 different groups.

**Statistical analysis**

Statistical analyses were performed using JMP 9.0.2 software (SAS Institute, Cary, NC, USA). We analyzed demographic and clinical data using analysis of variance (ANOVA) with the Tukey honestly significant difference (HSD) test for continuous variables and a chi-square test for categorical variables. We used one-way ANOVA followed by Tukey HSD post hoc test to compare the averaged FA among NC subjects, patients with PD, and patients with PDD. \(P < 0.05\) was considered to indicate statistical significance.

**Results**

Table 1 lists the demographic and clinical features of patients with PD or PDD and NC subjects. The 3 groups did not differ significantly with respect to age or gender distribution. As expected, patients with PDD scored significantly lower on the MMSE than patients with PD and NC subjects \((P < 0.01, P < 0.01)\), but there was no significant difference on the MMSE between patients with PD and NC subjects. There were significant differences in disease duration, Hoehn and Yahr stage, Unified Parkinson’s Disease Rating Scale (UPDRS)-III score, and levodopa dosage between patients with PD and those with PDD.

The mean inter-operator discrepancy in the CCg was 1.15 voxels, in the CCc, 0.45 voxels, and in the CCS, 0.76 voxels (Table 2). The mean discrepancy between automatic and manual detection of the CCg was 0.80 voxels, of the CCc, 0.39 voxels, and of the CCS, 0.71 voxels (Table 2).

Figure 5 shows the CB extraction results obtained from MFT, which was performed by 3 operators, and the results of VC, AFT, and the overlap regions of MFT. There were differences in the extracted CB regions obtained from the 3 extraction methods. The Jaccard index for each of the 3 MFT operators was 0.68, 0.70, and 0.72 (Fig. 6) and for each of the 3 extraction methods, 0.60, 0.72, and 0.59 (Fig. 6). The Jaccard index between AFT and MFT indicated a higher value than between VC and AFT and between VC and MFT because of the low number of underestimated and overestimated voxels (Fig. 6). However, the fiber-tracking methods, such as AFT and MFT, partially underestimated tracts of interest compared with VC (Fig. 7). Table 3 shows the optimal parameter values of the VC and AFT methods for extracting the anterior and posterior CB. Running on a laptop computer equipped with 2.0 GHz Intel Core 2 Duo processor and 2 GB RAM, the VC method takes about one second, AFT, about 10 s, and MFT, about 10 min to extract both the left/right anterior and posterior CB. Computation time for the VC method is very fast because it does not require the fiber-tracking step.

The correlation of FA values between MFT operators ranged from 0.93 to 0.96 (Fig. 8), and that between extraction methods ranged from 0.88 to 0.94 (Fig. 8).

There was no significant difference in FA of the left and right anterior or left and right posterior CB by any method. The FA of the left and right side was averaged for all subsequent statistical analyses. The FA value of the anterior CB obtained by VC, AFT, MFT, and manual ROI-based methods was significantly lower in patients with PD and PDD than in NC subjects (Table 4). The FA value of the posterior CB obtained by VC, AFT, MFT, and manual ROI-based methods was significantly lower in patients with PDD than in NC subjects (Table 4). However, although the FA value of the posterior CB obtained by the VC and manual ROI-based methods was significantly lower in patients with PDD than in patients with PD, this was not

Table 2. Distance between region of interest placements of 3 operators performing manual diffusion tensor fiber-tracking method and between manual and automatic extraction methods

<table>
<thead>
<tr>
<th></th>
<th>Inter-operator variability (voxels)</th>
<th>Manual-automatic variability (voxels)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CCg</td>
<td>CCc</td>
</tr>
<tr>
<td>Minimum</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Maximum</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Mean</td>
<td>1.15</td>
<td>0.45</td>
</tr>
<tr>
<td>SD</td>
<td>0.83</td>
<td>0.53</td>
</tr>
</tbody>
</table>

CCc, coronal plane at the level of center of the corpus callosum; CCg, coronal plane at the level of genu of the corpus callosum; CCS, coronal plane at the level of splenium of the corpus callosum; SD, standard deviation.
Fig. 5. Extracted cingulum bundle in data of one subject. The upper row shows the cingulum bundle extracted by each of 3 operators (A, B, and C) performing manual diffusion tensor fiber tracking (MFT). The lower row shows the cingulum bundle extracted by each of the 3 extraction methods—voxel classification (VC) (D), auto diffusion tensor fiber tracking (AFT) (E), and MFT (F). The cingulum bundle extracted by MFT is the region of overlap between results of MFT by more than 2 operators (F).

Fig. 6. The Jaccard index between sets of the cingulum bundle extracted by operators performing manual diffusion tensor fiber tracking (A) and between sets of the cingulum bundle extracted by the voxel classification (VC), auto diffusion tensor fiber tracking (AFT), and manual diffusion tensor fiber tracking (MFT) extraction methods (B). The number of overestimated and underestimated voxels between the VC, AFT, and MFT extraction methods (C–E). The average number of voxels in the cingulum bundle extracted by VC was 834, by AFT, 819, and by MFT, 849.
Table 3. Optimal parameter values of voxel classification (VC) and auto diffusion tensor fiber-tracking (AFT) methods for extracting the anterior and posterior cingulum bundle (CB)

<table>
<thead>
<tr>
<th>Extraction method</th>
<th>Structure</th>
<th>Box region of interest size (mm)</th>
<th>Threshold of fractional anisotropy</th>
<th>Threshold of crossing angle (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>width</td>
<td>height</td>
<td>depth</td>
</tr>
<tr>
<td>VC</td>
<td>anterior CB</td>
<td>10.5</td>
<td>3.5</td>
<td>8.75</td>
</tr>
<tr>
<td></td>
<td>posterior CB</td>
<td>12.25</td>
<td>8.75</td>
<td>8.75</td>
</tr>
<tr>
<td>AFT</td>
<td>anterior CB</td>
<td>12.25</td>
<td>3.5</td>
<td>12.25</td>
</tr>
<tr>
<td></td>
<td>posterior CB</td>
<td>15.75</td>
<td>3.5</td>
<td>10.5</td>
</tr>
</tbody>
</table>

The inter-operator variability for manual ROI placement in the MFT method was about one voxel in volume. Manual ROI placement is influenced primarily by environmental factors, such as the user-interface and the partial volume effect. The mean distance between ROI placements from manual and automatic methods was also about one voxel, which demonstrates the similar variability between the manual and automatic methods.

The inter-operator Jaccard index for MFT was about 0.70, indicating that it is difficult to suppress inter-operator variability with manual delineation of ROIs. Although the Jaccard index between AFT and MFT was similar to the inter-operator variability of MFT, the Jaccard indices between VC and MFT and between VC and AFT were lower. This indicates that the result of the proposed AFT extraction method is close to that of the MFT method. It is natural that the results of AFT and MFT were similar because both methods use the same fiber-tracking algorithm. However, the lower Jaccard index between the VC and AFT (MFT) results does not necessarily mean that the VC method is inaccurate because we did not use the gold standard of the extracted tract region, which is difficult to obtain for in vivo tractography.

The optimal parameter values of the FA and crossing angle differed among the VC and AFT methods. The crossing angle of AFT was weaker and the FA thresholds stronger than those of VC, possibly due to the curved shapes of CB. The seed and target ROIs extracted by AFT were located at the end of the anterior and posterior CB corresponding to the strongly curved shapes at the level of the CCg and CCs. Therefore, to avoid underextraction of candidate voxels for ROIs, the crossing angle threshold of AFT became weak. In contrast, the FA threshold of AFT became strong because of the weight of the crossing angle threshold.

The 3 methods often yielded different results in the CB extraction, depending on the algorithm. The fiber-tracking methods of AFT and MFT face serious problems from noise and partial volume

Discussion

We presented 2 automated approaches (VC and AFT) to extract the regions of the anterior and posterior CB and quantify FA values in these regions. The VC method extracts the CB directly without the fiber-tracking step, whereas the AFT method performs fiber tracking using automatically defined seed and target ROIs. We compared these automated methods to a manual method (MFT) and assessed the ability of each method to distinguish the NC subjects, patients with PD, and patients with PDD.
Fig. 8. The relations between fractional anisotropy (FA) measurements of the anterior and posterior cingulum bundle extracted by each of 3 operators performing manual diffusion tensor fiber tracking (MFT, top row) and FA measurements of the anterior and posterior cingulum bundle extracted by voxel classification (VC), auto diffusion tensor fiber tracking (AFT), and MFT extraction methods (bottom row).

Table 4. Fractional anisotropy values of the anterior and posterior cingulum bundle extracted by voxel classification (VC), auto diffusion tensor fiber-tracking (AFT), manual diffusion tensor fiber-tracking (MFT), and manual region-of-interest (ROI) methods in patients and control subjects

<table>
<thead>
<tr>
<th>Structure</th>
<th>Extraction method</th>
<th>Fractional anisotropy</th>
<th>P value</th>
<th>NC &gt; PD</th>
<th>NC &gt; PDD</th>
<th>PD &gt; PDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cingulum bundle</td>
<td>VC</td>
<td>0.366 ± 0.019</td>
<td>0.352 ± 0.016</td>
<td>0.344 ± 0.019</td>
<td>0.031*</td>
<td>0.020*</td>
</tr>
<tr>
<td></td>
<td>AFT</td>
<td>0.360 ± 0.015</td>
<td>0.343 ± 0.020</td>
<td>0.338 ± 0.021</td>
<td>0.007*</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td>MFT</td>
<td>0.364 ± 0.013</td>
<td>0.344 ± 0.020</td>
<td>0.344 ± 0.017</td>
<td>0.008*</td>
<td>0.007*</td>
</tr>
<tr>
<td></td>
<td>ROI</td>
<td>0.360 ± 0.018</td>
<td>0.338 ± 0.018</td>
<td>0.328 ± 0.021</td>
<td>0.006*</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Posterior cingulum bundle</td>
<td>VC</td>
<td>0.406 ± 0.019</td>
<td>0.393 ± 0.018</td>
<td>0.379 ± 0.014</td>
<td>0.071</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td></td>
<td>AFT</td>
<td>0.399 ± 0.016</td>
<td>0.391 ± 0.022</td>
<td>0.379 ± 0.018</td>
<td>0.322</td>
<td>0.006*</td>
</tr>
<tr>
<td></td>
<td>MFT</td>
<td>0.403 ± 0.015</td>
<td>0.393 ± 0.023</td>
<td>0.378 ± 0.018</td>
<td>0.346</td>
<td>0.004*</td>
</tr>
<tr>
<td></td>
<td>ROI</td>
<td>0.410 ± 0.024</td>
<td>0.399 ± 0.020</td>
<td>0.380 ± 0.020</td>
<td>0.321</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

* Indicates statistical significance (P < .05); NC, normal control; PD, Parkinson disease; PDD, Parkinson disease with dementia

Effects. For these reasons, fiber tracking from a seed ROI is often terminated early or traced in another direction before reaching the target. As a result, the fiber-tracking methods partially fail to extract tracts of interest. This problem may be reduced by probabilistic tractography, which estimates uncertainty in fiber direction caused both by noise and partial volume effects.32 However, probabilistic tractography is time-consuming. On the other hand, the VC method partially fails to extract the CB when the parameter threshold value is not appropriate. We observed that optimal parameter values differ between the parts of the CB. This problem may be solved by dividing the anterior and
posterior CB regions into more than 2 regions and individually adjusting parameters in each region.

The FA in the anterior CB extracted by all 4 approaches was lower in patients with PD and PDD than in NC subjects, and the FA in the posterior CB extracted by all 4 methods was significantly lower in patients with PDD than in NC subjects. These results are consistent with those of a previous study by Kamagata and associates that used the MFT method; their measurements of FA value were higher than ours because they measured only the core of the CB using the erosion method.19 Our results show that only the FA in the posterior CB extracted by VC and manual ROI-based methods was lower in patients with PDD than in patients with PD, findings consistent with those of a previous study using the manual ROI-based method.31 Although the results using the VC method were consistent with those of the manual ROI-based method, the VC method is superior to the manual ROI-based method in automatically extracting the anterior and posterior CB without dependence on the operator. There was no difference between FA values in the posterior CB of the PD and PDD groups when extracted by the AFT and MFT methods because the fiber-tracking partially failed to extract the CB due to both noise and partial volume effects. This is consistent with findings of a previous study using the MFT method.19 Taoka and colleagues reported the tendency of TSA such as MFT to show statistically significant difference more clearly than manual-ROI method.33 However, TSA may underestimate FA value when fiber tracking partially fails to extract the tract.

DTI is a sensitive tool for assessing microstructural alterations of the white matter via water diffusion.34 The FA value describes the degree of anisotropy in the diffusion of water molecules. Decreased FA values are interpreted pathologically as being caused by neuronal loss, gliosis, or demyelination of white matter tracts.35 The decreased FA of the anterior CB in the PD and PDD groups may be related to the pathologic process of PD. Patients with PD have Lewy bodies in various areas of the brain, including the cingulate cortex.36–39 Because Lewy bodies appear in the anterior cingulate gyrus,36–39 neurodegeneration processes may occur in the anterior CB adjacent to the anterior cingulate cortex. The decreased FA of the posterior CB in the PDD group may be associated with the pathologic process responsible for dementia in PD. Metabolic abnormalities in the posterior cingulate regions40,41 and cerebral blood flow reduction in the posterior cingulate cortex42 have been reported in patients with PDD. Therefore, FA abnormalities in the posterior CB may reflect microstructural changes underlying the particular pathophysiology of PDD.

The pathologic processes underlying dementia in PD are still controversial. Cortical Lewy bodies, striatal and extrastriatal dopamine deficiencies, loss of ascending noradrenergic, cholinergic, and serotonergic projection to the cortex, distribution of corticostriatal connections, coexistence of Alzheimer disease pathology, and frontal dysfunction have all been considered responsible for dementia in PD.43–45 Nakata’s group reported lower FA values in the posterior CB extracted by MFT in patients with AD than healthy individuals.12 Although the dementia processes of PDD and AD may have different pathologic mechanisms, the posterior CB appears to be important in the dementing process in both PDD and AD.

Our results show that although the proposed VC method classified among the 3 different groups (NC, PD, and PDD) using FA values in the CBs, the AFT method classified only 2 different groups (NC, PD or PDD). Therefore, we believe that the proposed VC method could be more useful than the AFT method for TSA at the CB. Our results for the VC method suggest that a reduction of FA in the posterior CB may represent a useful biological index for monitoring PD and PDD.

Some limitations of the present study should be considered. The diagnoses of PD and PDD were not histopathologically confirmed. However, the validity of the diagnoses is supported by the fact that 18 months or more after being scanned, all patients remained free of symptoms of atypical parkinsonism and continued to respond satisfactorily to antiparkinsonian therapy. In addition, the number of participants was relatively smaller than those of previous study in Alzheimer disease.23 However, our results are supported by those of the previous study.19,31 Another limitation of our study is that we did not examine other diffusion indices, such as mean, radial, and axial diffusivity. Investigation to address this limitation is under way.

Conclusions

We developed 2 fully automated CB extraction methods for tract-specific analysis and compared the methods with a manual method. In our results, the FA values extracted by the proposed VC method differed between NC subjects and patients with PD and PDD, whereas FA values extracted by the AFT method were similar in patients with PD and PDD. This result indicates that the VC extraction method may be more useful than the AFT extraction method for tract-specific analysis of the
CB. Furthermore, the results from the VC extraction method suggest that a reduction of FA in the posterior CB may represent a useful biological index for monitoring PD and PDD.

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