
MAJOR PAPER

The Optimal Trackability Threshold of Fractional Anisotropy for Diffusion Tensor Tractography of the Corticospinal Tract

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Purpose: In order to ensure that three-dimensional diffusion tensor tractography (3D-DTT) of the corticospinal tract (CST), is performed accurately and efficiently, we set out to find the optimal lower threshold of fractional anisotropy (FA) below which tract elongation is terminated (trackability threshold).

Methods: Thirteen patients with acute or early subacute ischemic stroke causing motor deficits were enrolled in this study. We performed 3D-DTT of the CST with diffusion tensor MR (magnetic resonance) imaging. We segmented the CST and established a cross-section of the CST in a transaxial plane as a region of interest. Thus, we selectively measured the FA values of the right and left corticospinal tracts at the level of the cerebral peduncle, the posterior limb of the internal capsule, and the centrum semiovale. The FA values of the CST were also measured on the affected side at the level where the clinically relevant infarction was present in isotropic diffusion-weighted imaging.

Results: 3D-DTT allowed us to selectively measure the FA values of the CST. Among the 267 regions of interest we measured, the minimum FA value was 0.22. The FA values of the CST were smaller and more variable in the centrum semiovale than in the other regions. The mean minus twice the standard deviation of the FA values of the CST in the centrum semiovale was calculated at 0.22 on the normal unaffected side and 0.16 on the affected side.

Conclusion: An FA value of about 0.20 was found to be the optimal trackability threshold.

Keywords: *MRI, diffusion tensor imaging, tractography, fractional anisotropy, corticospinal tract*

Introduction

Three-dimensional diffusion tensor tractography (3D-DTT) is a novel technique for non-invasive visualization of neuronal fiber tracts.¹ It has been used chiefly to depict the corticospinal tract (CST), an important projection fiber tract that controls motor functions, for the purpose of evaluating spatial relationships between the CST and cerebral lesions such as infarctions and tumors.²⁻⁵

3D-DTT is deduced from diffusion ellipsoids characterized by three eigenvectors and three eigenvalues. Fractional anisotropy (FA) is a rotationally invariant index of anisotropic diffusion

defined by three eigenvalues.⁶ High FA values indicate thick fiber bundles running in a uniform direction with preserved water diffusion along the axons. The principal eigenvector of an ellipsoid is considered parallel to the direction of the axons. In contrast, low FA values indicate a mixture of fibers in different directions—in other words, crossed fibers—or impaired water diffusion along the axons. In such an ellipsoid, the principal eigenvalue is close to the second eigenvalue and the principal eigenvector may not represent the direction of the axons. Since fibers are tracked along the principal eigenvectors, it should be understood that the accuracy of fiber tracking might be limited in regions with low FA values (Fig. 1).

Setting a lower limit on the FA values of diffusion ellipsoids and terminating tract elongation

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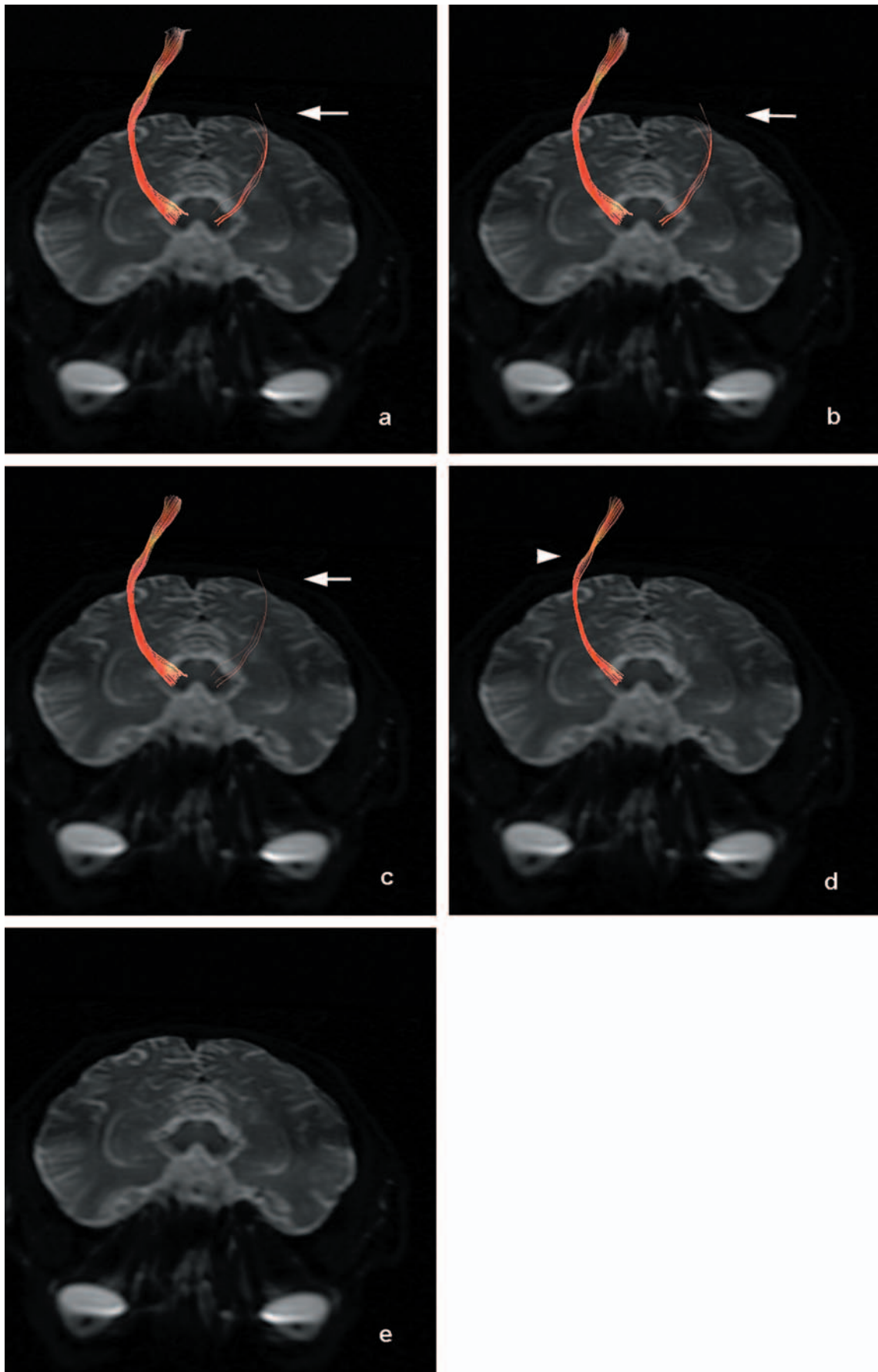


Fig. 1.

below the threshold is one way to avoid inaccurate fiber tracking. Such limits are called *trackability thresholds or stop criteria*.¹ To our knowledge, however, trackability thresholds for FA values have not yet been discussed. The higher the threshold, the higher is the possibility of termination of correct tract elongation that should, in actuality, be continued (Fig. 1). Our objective was to investigate the optimal trackability threshold for FA values to ensure accurate and efficient fiber tracking of the CST in cases of acute or subacute infarction.

Materials and Methods

Patient population

The eligibility of patients was as follows: 1) patients with acute or subacute ischemic stroke; 2) patients with motor deficits; 3) patients with no hemorrhage; 4) patients with clinically relevant infarction in the posterior limb of the internal capsule or in the centrum semiovale in isotropic diffusion-weighted images; and 5) patients who had undergone diffusion tensor MR (magnetic resonance) imaging. Thirteen eligible patients were enrolled in this retrospective study. They comprised eight men and five women, ranging in age from 51 to 75 years. The time intervals between onset and diffusion tensor MR imaging ranged between 2 hours and 12 days. Twelve patients had an infarction in either the right or left cerebral hemisphere, while the other patient had an infarction in both sides. Thus, 14 affected and 12 unaffected normal corticospinal tracts were evaluated.

We followed the informed consent guidelines of our hospital and this study was approved by our institutional review board.

Methods for 3D-DTT of the CST

Diffusion tensor MR imaging was performed with a 1.5T scanner with echo planar capability (Signa Horizon, GE Yokogawa Medical Systems, Tokyo, Japan). For diffusion tensor MR imaging,

we used a single-shot spin-echo echo planar sequence with TE at 67–96 ms and TR at 5000–6000 ms. Thirty interleaved, gapless, 5-mm-thick axial images were acquired in order to cover the entire brain. A field of view of 24 × 24 cm and a matrix of 128 × 128 interpolated to 256 × 256 were used. Diffusion gradients were applied in 13 non-collinear directions with a b-value of 1000 s/mm² as the peak diffusion gradient. Non-diffusion-weighted images (T₂-weighed images) were also obtained.

After realignment of these fourteen sets of images for eddy-current induced morphing on a workstation (Advantage Workstation 4.0, GE Yokogawa Medical Systems),⁷ 3D-DTT was undertaken on another workstation (Precision, Dell Inc., Kawasaki, Japan) with freely distributed software (VOLUME-ONE and its plug-in software).^{8,9} Interpolation along the z-axis was also applied to obtain isotropic data (with a voxel size of 0.9 × 0.9 × 0.9 mm). Diffusion tensor elements at each voxel were determined by least-square fitting and diagonalized to obtain three eigenvalues and three eigenvectors.

We used a knowledge-based, two-region-of-interest method for 3D-DTT of the CST.¹ We drew the first region of interest, or “seed,” on the cerebral peduncle in the midbrain so as to encircle the peduncle. Similarly, the second region of interest, or “target,” was drawn on the ipsilateral precentral gyrus so as to encircle the gyrus. Tracking started with a number of points scattered within the seed. Lines were drawn sequentially along the principal eigenvector of each diffusion ellipsoid. As a result, only those lines that reached the target were displayed. Methods of detecting the precentral gyrus in MR images were determined from published data.¹⁰ Since our objective was to find the optimal trackability threshold of FA values, we placed no limits on FA values for fiber tracking in this study. From our knowledge of neuroanatomy of the CST, we excluded from the following FA analysis the fiber lines we considered to be incorrectly tracked. We tracked both right and left

Fig. 1. Three-dimensional diffusion tensor tractography of the corticospinal tract (CST) with different trackability thresholds of fractional anisotropy (FA). Examples are shown of axial T₂-weighted images obtained with three-dimensional diffusion tensor tractography of the right CST performed at various FA trackability thresholds: (a) FA = 0, (b) FA = 0.10, (c) FA = 0.20, (d) FA = 0.30 and (e) FA = 0.40. All images are taken from above the patient from the anterosuperior location. (a) and (b) With little or no threshold, the right CST is tracked fully but some fiber lines are incorrectly tracked into the left, contralateral cerebral hemisphere (arrows) by way of the pons or the medulla. (c) With the FA threshold of 0.20, the right CST is tracked fully with few incorrectly tracked lines (arrow). (d) and (e) With a large FA threshold, no fiber lines are tracked into the left, but some or all of the right CST cannot be tracked (d, arrowhead). An FA value of between 0.20 and 0.30 seems optimal for the threshold in this case.

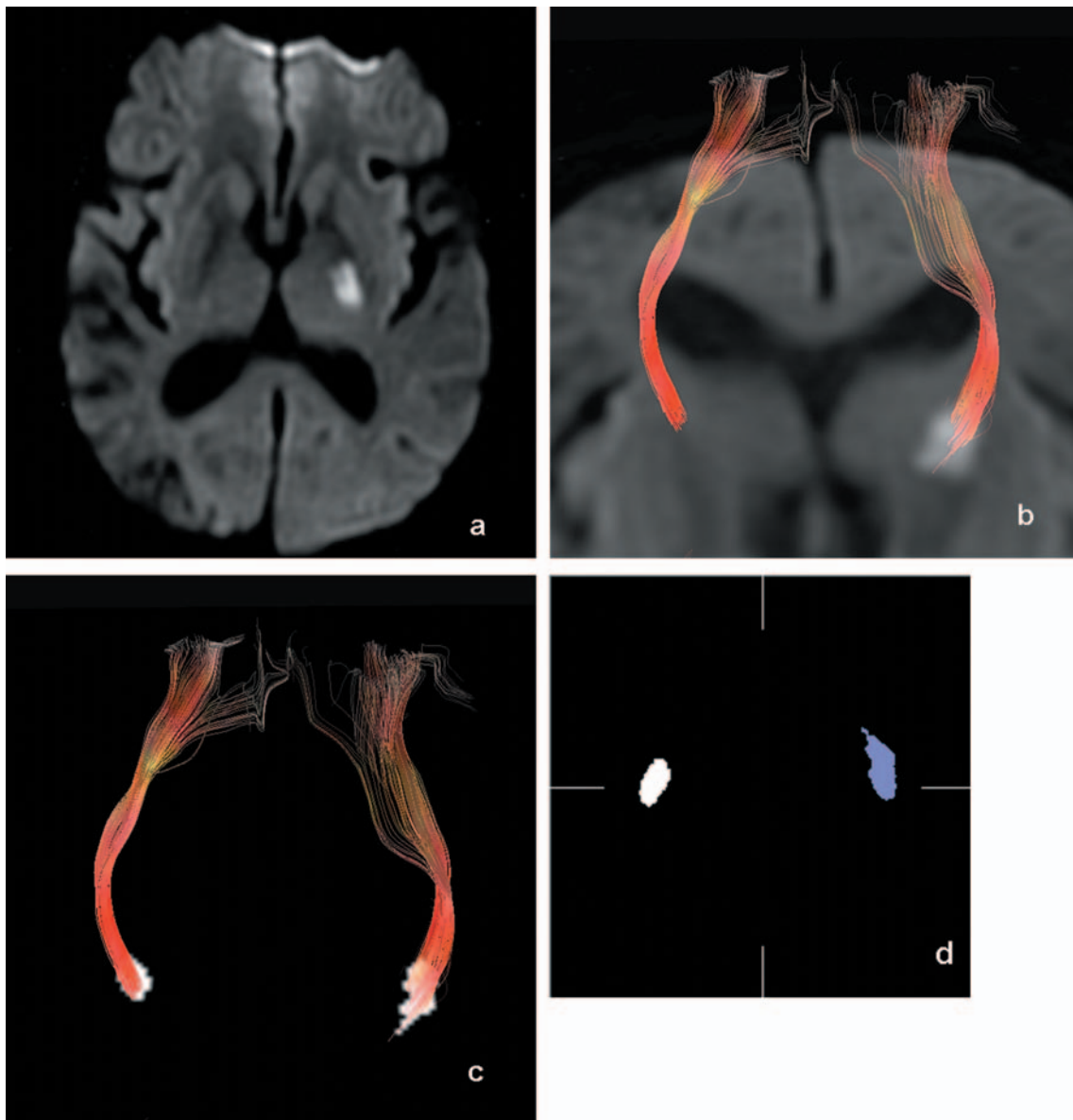


Fig. 2. Segmentation and selective fractional anisotropy measurement of the CST
(a) An acute infarct is visible in the left posterior limb of the internal capsule in this isotropic diffusion-weighted image. **(b)** Three-dimensional diffusion tensor tractography of the right and left CSTs (orange lines) is superimposed on the axial isotropic diffusion-weighted image. The CST of the affected cerebral hemisphere appears to run through the infarct. **(c)** CSTs are segmented through voxelization, the extraction of voxels penetrated by the CST. Cross-sections of the right and left segmented CSTs are colored white and shown on the same axial image. **(d)** Each of the cross-sections is established as a region of interest (colored light blue) for selective measurement of the fractional anisotropy of the right or left CST.
(a) and **(d)**: Viewed from below the patient from the caudal location
(b) and **(c)**: Viewed from above the patient from the anterosuperior location to show the right and left CSTs

corticospinal tracts and superimposed the 3D-DTT of these tracts on two-dimensional isotropic diffusion-weighted images.

Selective FA measurement of the CST with 3D-DTT

With the workstation, we extracted voxels that the CST penetrated and thus segmented the CST

(voxelization). These processes allowed us to deal with the CST as an image object. The voxels contained information on diffusion ellipsoids that enabled us to define a cross-section of the CST as a region of interest in order to selectively calculate the FA values of the CST at any level desired (Fig. 2).

The FA values of the right and left corticospinal tracts were measured on transaxial sections at the level of the cerebral peduncle, the posterior limb of the internal capsule, and the centrum semiovale, where the clinically relevant infarction was not present. We also measured the FA values of the CST on the affected side at the level where the clinically relevant infarction was shown engulfing the CST or adjacent to the CST. The right and left CSTs were evaluated in the same axial sections. Measurements were repeated three times at slightly different sections for each level.

Measurements were expressed with a box plot. The minimum and mean FA values with standard deviations were also obtained.

Results

Figure 3 shows the results of the FA measurements. Among the 267 regions of interest we measured, the minimum FA value was 0.22 as measured in the centrum semiovale of an affected cerebral hemisphere. The mean FA value of all regions of interest was 0.51 and its standard deviation was 0.11. The FA values of the CST (mean \pm standard deviation) on the unaffected side were 0.50 ± 0.04 at the level of the cerebral peduncle; 0.62 ± 0.05 at the posterior limb of the internal capsule; and 0.40 ± 0.09 at the centrum semiovale. The values on the affected side were 0.52 ± 0.06 , 0.60 ± 0.05 , and 0.40 ± 0.12 , respectively. At the level where the clinically relevant infarction was present, the FA value of the CST on the affected side was 0.52 ± 0.12 .

The FA values of the CST were smaller and more variable at the level of the centrum semiovale than at the level of the cerebral peduncle or the posterior limb of the internal capsule. No obvious differences were observed in the FA values of the CST between the affected and unaffected sides. The FA values of the CST also exhibited high variability at the level where the clinically relevant infarction was present, but the mean FA value was larger than that of the centrum semiovale.

Discussion

Setting a trackability threshold for FA values of diffusion ellipsoids reduces inaccurate fiber tracking and appears useful. However, the thresholds have not yet been discussed. Our results indicate that the optimal threshold of FA for 3D-DTT of the CST is around 0.20. The reason is as follows: Figure 3 demonstrates that the CST in the centrum semiovale has smaller FA values with greater

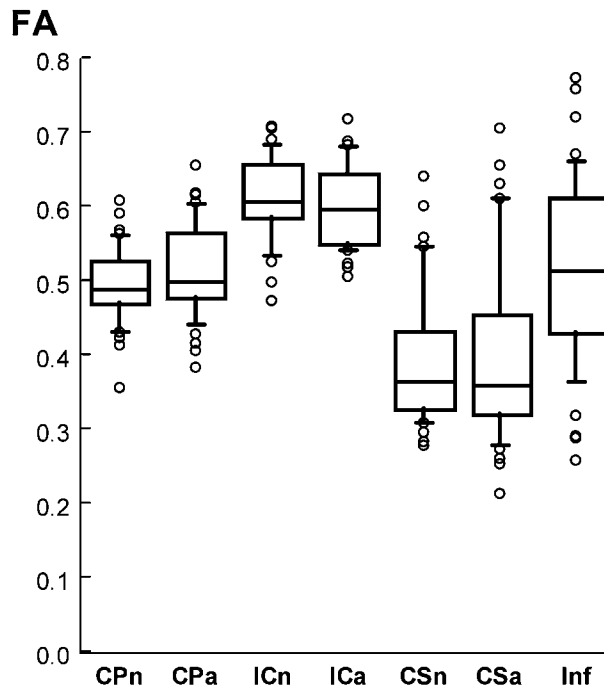


Fig. 3. Results of fractional anisotropy measurement of the CST

The fractional anisotropy measurements of the segmented CSTs are shown as a box plot for each location.

Abbreviations: CPn: cerebral peduncle on the normal unaffected side, CPa: cerebral peduncle on the affected side, ICn: posterior limb of the internal capsule on the normal unaffected side, ICa: posterior limb of the internal capsule on the affected side, CSn: centrum semiovale on the normal unaffected side, CSa: centrum semiovale on the affected side, Inf: at the level of the infarction on the affected side, and FA: fractional anisotropy

variability than that in the cerebral peduncle or the posterior limb of the internal capsule. Divergence of fibers to the cortex and fiber crossing are responsible for the low anisotropic diffusion of the centrum semiovale.¹¹ In contrast, the FA values of the CST are relatively high and stable in the cerebral peduncle and the posterior limb of the internal capsule (Fig. 3), indicating that axonal fibers converge tightly there and form a thick bundle in a uniform direction. These results suggest that, with too high an FA threshold, fiber tracking of the CST that should in fact be continued would be terminated in the centrum semiovale. Therefore, we must set the threshold based on the FA values of the CST in the centrum semiovale. Since many measurements of the human body, such as height and blood pressure, closely follow a normal distribution, the probability that an FA value lies between the mean plus and minus twice the stand-

ard deviation is considered to be nearly 0.95.¹² Consequently, it seems reasonable that we adopt FA values above the mean minus twice the standard deviation for fiber tracking. The results of FA measurements in the centrum semiovale therefore provide an FA threshold of 0.22 on the unaffected normal side and 0.16 on the affected side. Moreover, we found that the minimum of all of our FA measurements was a mere 0.22. This supports the position that an FA threshold of around 0.20 is optimal for both the affected and unaffected sides.

Trackability thresholds impose a general restriction on diffusion ellipsoids in order to ensure accurate fiber tracking. Accurate fiber tracking is often difficult in the brain stem where innumerable neuronal fibers gather, terminate at nerve cell bodies or cross to the contralateral side in a small area. Partial volume averaging is inevitable in MR imaging with several-millimeter-thick slices for minute brain structures, and it may lead to anatomically incorrect tracking. Inaccurate tracking can be avoided with tracking methods based on multiple regions of interest and grounded in knowledge of neuroanatomy. This approach is robust and effective, but is available only for neuronal fiber tracts whose anatomy has been well studied, such as the CST. In contrast, the restricting of FA values is available to neuronal fiber tracts whose anatomy is not yet understood. Moreover, a study of normative FA values of the human brain has demonstrated that FA values change little with age or sex, so the trackability threshold of FA is considered widely applicable.¹³

FA seems suitable for a trackability threshold, as it represents the magnitude of anisotropic diffusion. High FA values represent thick fiber bundles running in a uniform direction with preserved water diffusion along the axons, while low FA values represent a mixture of crossed fibers or impaired water diffusion. Decreased FA in acute white matter ischemia has been reported and FA is now in common use.¹⁴ Apart from FA, inner products of principal eigenvectors of consecutive diffusion ellipsoids are sometimes used as a stop criterion. This is based on the assumption that consecutive principal eigenvectors along a fiber tract should meet at small acute angles. However, we cannot verify the assumption, nor are values of the inner products as relevant to the pathophysiology of disease as is FA.

Our segmentation method for the CST consists of automated and computer-assisted processes that are considered highly reproducible. Furthermore, voxel-based segmentation allows us to measure the FA values of the CST selectively. The automated

segmentation renders FA measurements free from human error caused by the manual drawing of regions of interest. It is also an advantage in our study.

Some limitations exist in interpreting our results. First, we analyzed stroke patients to determine the optimal trackability threshold for 3D-DTT of the CST. We did so because FA frequently decreases in ischemic stroke and because ischemic stroke is one of the prime triggers of investigations of diffusion abnormalities.¹⁴ Moreover, ischemic stroke has priority as an important cause of death and disability. It has not been shown in this study, however, that the threshold can be applied to other brain diseases. Different MR imagers or different diffusion tensor imaging sequences may provide somewhat different FA values for the same subject. Therefore, setting the threshold for FA remains a practical and technical issue. For this reason we provide an approximate, rule-of-thumb value for the threshold. The threshold may need to be more finely adjusted depending on imaging parameters or the specifics of particular cases. Second, our results were obtained from analysis of the CST, which has a thick fiber bundle that accommodates 3D-DTT. In addition, its anatomical characteristics have been well investigated and described. Knowledge-based validation is available for the CST and is an established approach for 3D-DTT. We must be careful when applying the threshold to neuronal fiber tracts other than the CST. We infer that most tracts are similar to the CST in their FA characteristics in that they comprise myelinated fibers, but we may need to investigate the FA values for each tract. Although anatomical knowledge-based tracking is being established for some neuronal fiber tracts, the detailed anatomy of many other tracts is not yet sufficiently understood. During estimation of the FA threshold of such a tract, it may be practical to adjust the trackability threshold by referring to the FA values of a white matter region that includes the tract.

Conclusion

3D-DTT allowed us to selectively measure the FA values of the CST. An FA value of around 0.20 was found to be the optimal trackability threshold of FA for accurate and efficient 3D-DTT of the CST. We expect that this threshold will be widely applicable to 3D-DTT of other tracts.

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