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Automated Fiber Tracking of Human Brain White Matter Using Diffusion Tensor Imaging

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Abstract

Reconstruction of white matter tracts based on diffusion tensor imaging (DTI) is currently widely used in clinical research. This reconstruction allows us to identify coordinates of specific white matter tracts and to investigate their anatomy. Fiber reconstruction, however, relies on manual identification of anatomical landmarks of a tract of interest, which is based on subjective judgment and thus a potential source of experimental variability. Here, an automated tract reconstruction approach is introduced. A set of reference regions of interest (rROIs) known to select a tract of interest was marked in our DTI brain atlas. The atlas was then linearly transformed to each subject, and the rROI set was transferred to the subject for tract reconstruction. Agreement between the automated and manual approaches was measured for 11 tracts in 10 healthy volunteers and found to be excellent ($\kappa > 0.8$) and remained high up to 4–5 mm of the linear transformation errors. As a first example, the automated approach was applied to brain tumor patients and strategies to cope with severe anatomical abnormalities are discussed.

Introduction

Tractography based on diffusion tensor imaging (DTI) can reconstruct three-dimensional pathways of white matter tracts based on pixel-by-pixel fiber orientation information [1–8]. Although this method is an effective tool to evaluate the anatomy of white matter tracts, there are well-known limitations with regard to validity (accuracy) and reproducibility (precision). In terms of accuracy, it has been shown that tractography can reconstruct core regions of major white matter tracts fairly accurately, although there are known cases where tractography provides false negative or false positive results (see, e.g., (Pierpaoli et al., 2001)). For reproducibility, one of the major sources of variability is the dependency of tractography on the manual delineation (reference region of interest (rROI)) of anatomical landmarks specific to a tract of interest, which involves human subjective judgment. The rROI placement requires a skilled operator who is familiar with white matter structures and trained to read DTI-derived

images. As tractography software becomes widely available, the lack of a skilled operator could be a bottleneck with regard to both the accuracy and precision of the study.

In the past, it has been shown that well-designed ROI placement utilizing the anatomical features of the tracts can produce highly reproducible results (Huang et al., 2004). In this paper, we tested the feasibility of automated tract reconstruction for 11 prominent white matter tracts. This approach is based on our previous publications in which robust protocols for rROI placements were designed and tested for these 11 tracts (Wakana et al., 2007). Most of these protocols are relatively insensitive to the sizes and locations of the rROIs and, therefore, we hypothesized that the rROIs could be placed automatically by using simple linear registration. We tested this by storing these rROIs in a DTI atlas in MNI coordinates (ICBM-DTI-81), which (including rROIs) was then linearly transformed to individual data. Reliability was tested by intentionally mis-registering the rROIs.

Methods and Materials

Subjects

Institutional_[SM1] Review Board approval was obtained for the study and written, informed consent, including HIPAA compliance, were obtained from all subjects. Ten healthy adults (mean 30.7 ± 6.8 years old; male 6, female 4, all right-handed) participated in our study. Three brain tumor patients were scanned; Patient #1: 50 years old male with right parietal oligodendroglioma, Patient #2: 53 years old female with right multilobulated ganglioblastoma multiforme, and Patient #3: 39 years old male with left frontoparietal oligodendroglioma.

MRI studies

A 1.5T MR unit (Gyrosan NT, Philips Medical Systems) was used. DTI data were acquired with a single-shot, echo-planar imaging (EPI) sequence with sensitivity encoding (SENSE), using a parallel-imaging factor of 2.5 (Pruessmann et al., 1999). The imaging matrix was 96×96 with a field-of-view of 240×240 mm (nominal resolution, 2.5 mm), zero-filled to 256×256 pixels. Transverse sections of 2.5 mm thickness were acquired parallel to the anterior commissure-posterior commissure line. A total of 50–55 sections covered the entire hemisphere and brainstem without gaps. The_[SM2] TE and the TR were 80 ms and $>8,000$ ms, respectively. Diffusion weighting was encoded along 30 independent orientations (Jones et al., 1999), and the b-value was $700 \text{ s}_{[SM3]}/\text{mm}^2$. Five additional images with minimal diffusion weighting ($b \approx 33 \text{ s}_{[SM4]}/\text{mm}^2$) were also acquired. The scanning time per dataset was approximately 6 minutes. To enhance the signal-to-noise ratio, imaging was repeated three times.

For the tumor patient studies, a 3.0T MR unit (Philips Medical System) was used. The DTI acquisition parameters were the same as those in the control studies except for the following parameters: imaging matrix was 112×112 with a field of view of 230×230 mm and slice thickness was 2.1 mm. Diffusion weighting was encoded along 32 independent orientations. The scanning time was approximately 4.5 min with no signal averaging.

Data processing

The DTI datasets were transferred to a personal computer running a Windows platform and were processed using DtiStudio (mri.kennedykrieger.org or www.MriStudio.org) (Jiang et al., 2006). Images were first realigned with Automatic Image Registration (Woods et al., 1998), using the first minimally diffusion-weighted image as a template, in order to remove any potential small bulk motion that may have occurred during the scans. The six elements of the diffusion tensor were calculated for each pixel using multivariate linear fitting. After diagonalization, three eigenvalues and eigenvectors were obtained. For the anisotropy map,

fractional anisotropy (FA) was used (Pierpaoli and Basser, 1996). The eigenvector associated with the largest eigenvalue was used as an indicator of the fiber orientation. We also created an averaged diffusion-weighted image (aDWI) by adding all of the diffusion-weighted images. This image was used for image registration.

Tractography methods

For the 3D tract reconstruction, the Fiber Assignment by Continuous Tractography (FACT) method (Mori et al., 1999; Xue et al., 1999) with_[SM5] the “brute-force” method (Huang et al., 2004) was used with a fractional anisotropy threshold of 0.2, and a principal eigenvector turning angle threshold of 40° between two connected pixels. The fiber tracking based on FACT was performed by DtiStudio (Jiang et al., 2006). A multi-ROI approach was used to reconstruct tracts of interest [2, 10], exploiting the existing anatomical knowledge of tract trajectories. Tracking was performed from all pixels inside the brain (the so-called brute-force approach), and fibers penetrating manually defined ROIs were assigned to the specific tracts associated with those ROIs. A description of the tracking protocol is provided in our previous papers (Stieltjes et al., 2001; Mori et al., 2002; Wakana et al., 2004; Wakana et al., 2007). In this study, we reconstructed the following 11 white matter tracts: forceps major (FMa); forceps minor (FMi); anterior thalamic radiation (ATR); cingulum of the cingulate cortex (CgC); cingulum of the hippocampal region (CgH); corticospinal tract (CST); inferior fronto-occipital fasciculus (IFO); inferior longitudinal fasciculus (ILF); superior longitudinal fasciculus (SLF); the temporal projection of the SLF (tSLF); and uncinate fasciculus (Unc). There were two protocols for the SLF reconstruction, one to reveal trajectories to the frontal, parietal, and temporal lobes, and the other to select only the projections to the temporal lobe (tSLF).

Automated tracking

The protocols described above have been confirmed for high intra- and inter-rater reproducibility (Wakana et al., 2007). These protocols were transferred to the ICBM-DTI-81 atlas manually. This anatomical template with knowledge-based rROIs for each tract will be referred to as a tract-specific rROI template (TRT) hereafter. Each protocol contains more than two rROIs and these ROIs were combined by an “AND” operation; tracts that penetrate all rROIs were selected for reconstruction. The TRT also contains rROIs for a “NOT” operation to remove commonly found contaminations. The TRT was then transferred to data from each subject using an affine transformation and tracking was performed automatically. For the linear transformation, our in-house software, Landmarker (www.mristudio.org or mri.kennedykrieger.org) was used, in which the transformation is based on an Automated Image Registration (AIR) algorithm (Woods et al., 1998). To drive the transformation, aDWI_[SM6] images from the ICBM-DTI-81atlas and each subject were used. After the TRT was transformed to the shape of each subject, it was read by DtiStudio to perform the automated reconstruction.

To evaluate the accuracy of the automated tracking results, the tracts were manually reconstructed by an experienced rater (WZ). The spatial matching was examined using a kappa analysis (Landis and Koch, 1977). The automated and manual tracking results were first converted to binary information of the same pixel dimension as the DTI data (256×256×50–55), in which pixels that were occupied by the tracts were assigned a value of 1, and other non-occupied pixels were assigned a value of 0. Two tracking results were then superimposed, which yielded four different pixel categories: (1) pixels did not contain the tract in either trial (nn); (2) pixels that contained the tract in only one of the two trials (pn, np); and (3) pixels that contained the tracts in both trials (pp). Expectation values (Enn, Enp, Epn, and Epp) for each class were then calculated using the equations:

$$\begin{aligned}
 \text{Expected nn (Enn)} &= (nn+np)(nn+pn)/N \\
 \text{Expected np(Enp) or Epn} &= (nn+np)(np+pp)/N \text{ or } (nn+pn)(pn+pp)/N \\
 \text{Expected pp(Epp)} &= (pn+pp)(np+pp)/N
 \end{aligned}$$

Where $N=nn+np+pn+pp$ is the total number of pixels_[SM7] of the white matter in each subject.

For the calculation, pixels with an FA lower than the threshold ($FA > 0.2$) were not included.

Then κ (kappa) was calculated by

$$\kappa = (\text{observed agreement} - \text{expected agreement}) / (100 - \text{expected agreement}),$$

where

$$\begin{aligned}
 \text{observed agreement} &= (nn+pp)/N * 100 \\
 \text{expected agreement} &= (Enn+Epp)/N * 100
 \end{aligned}$$

This analysis was applied in a pair-wise manner; there are three combinations from the three trials. The κ values were determined for the three pair-wise combinations and an average κ was determined from_[SM8] the 10 normal subjects. According_[SM9] to criteria set by Landis and Koch (1977), the κ value of 0.11–0.2 is considered "slight," 0.21–0.4 is "fair," 0.41–0.60 is "moderate," 0.61–0.80 is "substantial," and 0.81–1.0 is "almost perfect" agreement.

To evaluate the effect of errors in the image registration, the transformed TRT was intentionally shifted along the X, Y, and Z axes for up to 10 mm and the automated reconstruction was performed. The matching of the manual results and the automated results with the registration errors were evaluated by the same kappa analysis described above.

Results

Agreement between automated and manual methods using normal

The ROI locations of the 11 tracts basically followed our previous protocols that were designed to minimize operator variability in ROI placement. Figs. 1 illustrates how ROI locations affected the tract reconstruction using the TRT of the CST. With one ROI, we usually obtain fibers with low specificity (Fig. 1A). In this case, our target was the corticospinal tract (CST) and the first ROI was placed on the cerebral peduncle, which led to reconstruction of the large portion of the corona radiata; the CST occupied a portion of the corona radiata. By adding the second ROI at the motor cortex (Fig. 1B), and retrieving only the fibers that penetrated both ROIs ("AND" operation), specificity for the CST increased substantially, although there were still many fibers that apparently did not belong to the CST (indicated by orange arrowheads). In Fig. 1C and 1D, two more ROIs with a "NOT" operation were added to remove commonly found contaminations that occur primarily outside the two initial "AND" ROIs.

In this paper, we implemented ROI protocols for 11 major tracts in the ICBM-DTI-81 atlas and tested whether these tracts could be reliably reconstructed. Table 1 summarizes agreement of the manual and automated methods for 10 normal subjects. Kappa values more than 0.80_[SM10] (almost perfect) were found for all 11 tracts, indicating a high level of matching. The lowest kappa of 0.81 ± 0.07 was found for the CST. The_[SM11] reconstructed tracts were superimposed on FA maps and tract-specific FA values were determined for each tract and the results were compared between the two approaches. Fig. 2 shows correlation plots of FA values of the reconstructed tracts. All 11 tracts show high correlation ($R^2 = 0.96 \pm 0.04$). Fig._[SM12] 3 shows actual reconstruction results of the CST, which has the poorest agreement ($\kappa = 0.81$). With_[SM13] the automated method, reconstruction results sometime include trajectories that reach postcentral sulcus, which is attributed to the relatively low κ value.

To evaluate the robustness of the automated method in terms of misregistration of the TRT for each subject, the transformed TRTs were intentionally shifted in the X, Y, and Z orientations

(Fig. 4). In this figure, the results of the CST, which is most sensitive to registration quality, and the IFO and ^[SM14] the FMa, which have higher kappa values and very different trajectories from the CST, are shown. Although the effect of misregistration errors varies depending on tract trajectories, the automated tracking method is reliable up to 4 – 5 mm of misregistration.

Application to tumor patients and multi-level approach—The ^[SM15] results shown in Fig. 4 indicate that this automated approach becomes unreliable if patients have severe anatomical deformation beyond 5 mm, which is typical in brain tumor patients. In Fig. 5, a modified approach for the CST is demonstrated. In this approach, two more ROIs are added in the TRT at the posterior limb of the internal capsule (IC) and corona radiata (CR) level (Fig. 5A). With normal anatomy, addition of these two ROIs does not have any impact (Fig. 5B) because the anatomical constraint by the two original ROIs (ROI #1 and #2 in Fig. 1) is more stringent. By removing the ROI placed at the motor cortex (Fig. 5C) or at the corona radiata (Fig. 5D), the specificity of the reconstruction to the CST gradually decreases. By switching on & off these ROIs, the altered neuroanatomy can be explored in a systematic manner. In Fig. 6, this approach is applied to three tumor patients. These three cases were selected because the tumorous tissues were located in the vicinity of the two functionally important tracts, the CST (motor) and the SLF (language), but their anatomical status is very different. Patient #1 showed moderate anatomical deformation, Patient #2 showed severe anatomical deformation, and Patient #3 had an invasive type of tumor with loss of tissue anisotropy but relatively little deformation. In all cases, the automated SLF reconstruction succeeded. In Patients #1 and #2, the SLFs were dislocated to the opposite orientations; inferior to the tumor in Patient #1 and superior in Patient #2. In Patient #3, the SLF was inside the T2 hyperintensity regions and the reconstructed SLF was much smaller than normal size due to the loss of anisotropy. The CST was automatically reconstructed only in Patient #1 by using the all four ROIs in the modified TRT. The CST was located medially to the tumor and its trajectory was slightly moved medially. For Patients #2 and #3, no tracts were reconstructed that penetrated the ROI at the motor cortex level. Similar results were obtained with manual reconstruction; we could not identify trajectories that reached the motor cortex in these patients. By ^[SM16] removing the ROI at the motor cortex, the specificity to the CST decrease and the reconstructed trajectory labels the corona radiata projecting to the cortex around the central sulcus (Fig. 5C). The equivalent procedure to the ipsilateral hemisphere of the tumor patients shows the relationship between the trajectories and the tumor locations (Fig. 5E and Fig. 6). Namely, they are severely dislocated medially in Patient #2 and embedded in the tumor and terminated due to the low anisotropy in Patient #3.

Discussion

In this paper, we tested automated tract reconstruction. In this approach, our experiences in ROI placement were stored in the TRT, which was then transferred to individual subject data. This ^[SM17] is similar to the approach Toosy et al. adopted to guide ROI placement to minimize interrater variability (Toosy et al., 2004). The success of this approach relies on three factors: 1) the trajectory of the tract of interest; 2) the efficacy of the ROI design; and 3) the quality of registration accuracy between the TRT and each subject's data. Some white matter tracts, such as the IFO and the SLF, do not have other tracts that share similar pathways. As a result, rather large ROIs can be defined without the risk of false positives. The matching between the manual and automated approaches is quite high (> 0.85), which is similar to the inter-rater variability of the manual approach (Wakana et al., 2007). On the other hand, the CST is a part of larger axonal bundles at the level of the internal capsule and the corona radiata. To delineate the CST specifically, precise identification of the motor cortex is required. Consequently, the reliability of the CST is the poorest among the tested tracts, although the average kappa for agreement with manual is more than 0.8, indicating a high level of agreement.

The intentional mis-registration test shows that the automated method is reliable up to 4 – 5 mm of mis-registration. In past studies, the registration accuracy of white matter structures by linear transformation was measured and the results indicated that most structures should be registered within 3 mm (Grachev et al., 1999; Ardekani et al., 2005). This gives a good estimate of the reliability of the automated approach for a normal subject. However, this reliability estimate is not applicable to patients with significant anatomical deformation. We therefore tested this approach in one of the most challenging areas, brain tumor patients.

As expected, the automated approach does not always work for patients with severe pathological conditions. There are two major reasons for this failure: 1) severe anatomical deformation that dislocates tracts of interest (Patient #2); and 2) loss of anisotropy that causes termination of fiber tracking (Patient #3). Identification of tracts of interest in this kind of situation would be difficult even with manual approaches. In this paper, we demonstrated using additional^[SM18] sets of ROIs with varying levels of specificity. For example, the ROI combination shown in Fig. 5D provides a more robust way to reconstruct fibers, with albeit lower specificity for the CST. Indeed, the fibers reconstructed in these images should be considered as a “corona radiata protocol” rather than a CST protocol. Apparently, the level of the specificity the tractography can provide varies, depending on the amount of anatomical deformation or anisotropy loss. Therefore,^[SM19] it is difficult to conclude the level of accuracy that the automated method (or even the manual approach for that matter) can offer for tumor patients. Unlike normal brain anatomy, agreement between manual and automated approach can not be used as a measurement of “success”, because we can not use a priori anatomical knowledge, on which the manual approach relies. Macroscopic anatomical distortion or invasion of tumor to specific white matter tracts can be evaluated to a large extent by inspecting DTI-based tract orientation images (color maps) by experienced researchers. The tracking based method (both manual and automated approaches) should be used as 3D guidance for such macroscopic evaluation of tract anatomy when there is a large amount of anatomical distortion. Whether the automated reconstruction with varying specificity is a useful tool for neurosurgical planning remains an unanswered question and requires further efficacy studies. However, the availability of automated results could be beneficial for the initial evaluation of white matter anatomy.

In conclusion, we introduced an automated approach for DTI-based tract reconstruction. Knowledge-based ROIs are stored in the ICBM-DTI-81 atlas, which are linearly transformed to each subject. For the normal population, a high level of agreement was found between the manual and automated approaches. The automated approach is robust up to 4–5 mm of mis-registration (or anatomical deformation). By employing multiple ROI sets with varying specificity, the automated approach has the potential to cope with pathological conditions that are associated with significant anatomical and anisotropy changes. This automated method is expected to provide an initial estimation of tract anatomy in an efficient manner.

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Fig. 1.

Locations_[SM20] of ROIs for reconstruction of the corticospinal tract (CST) and demonstration of anatomical constraints posed by each ROI. (A): One ROI defining the entire left midbrain leads to extraction of a large amount of projection fibers that connect the cortex and the brainstem. (B): Second ROI that defines the pre-central white matter region drastically increases the specificity of the reconstruction results for the CST. Note that each ROI is large and its placement is not necessarily precisely targeted to the CST. However, the anatomical constraints posed by multiple ROIs are strong enough to select only a small number of tracts. (C) and (D): ROIs can also be placed to remove all tracts that penetrate them (called a "NOT" ROI). The ROI in (C) removes tracts that penetrate the midline and the ROI in (D) removes projections to the cerebellum (indicated by orange arrows). A_[SM21], P, R, and L in the figure indicate anterior, posterior, right, and left orientations.

Fig. 2. Correlation_[SM22] plots of FA values of 11 tracts measured by the manual and automated approaches. The FA value for each tract was calculated by averaging FA values of pixels labeled by the reconstructed tract.

Fig. 3. Comparison of manual and automated reconstruction methods of the CST. The occasional inclusion of fibers projecting to the postcentral sulcus can be seen. The asterisks indicate the locations of the central sulcus.

Fig. 4. Sensitivity of the automated method to mis-registration. The TRT (tract-specific ROI template) transferred to each subject is intentionally shifted along the X, Y, and Z axes and the matching (kappa value) between the automated and manual methods is measured. The results are for the CST (A), IFO (B), and FMa (C). The error bars represent standard deviations from 10_[SM23] healthy volunteers. X_[SM24], Y, and Z axes correspond to the right-left, anterior-posterior, and superior-inferior orientations, respectively.

Fig. 5. Addition^[SM25] of two ROIs to the TRT of the CST and effects of ROI removal. (A) In addition to the original two “AND” ROIs at the cerebral peduncle (CP, ROI #1 in Fig. 1) and the motor cortex (MC, ROI #2 in Fig. 1), two new ROIs are added at the level of the posterior limb of the internal capsule (IC) and the superior corona radiata (CR). (B–C) Effects of removing the ROIs are demonstrated using the contralateral hemisphere of a brain tumor patient (Patient^[SM26] #2). (D) Tract reconstruction result of the ipsilateral hemisphere using CP + IC + CR ROIs.

Fig. 6.

Application_[SM27] of the modified TRT approach in brain tumor patients. (A) ROI locations in the TRT were used for the CST and the SLF. (B) Automated reconstruction results for Patients #1, #2, and #3. Yellow lines represent the CST and red the SLF. The purple objects are tumor locations defined by T2 hyperintensity. For Patient #1, the CST ROI with the CP+IC+CR+MC combination was used, while only the CP+IC combination was used for Patient #2 and the CP+IC+CR combination was used for Patient #3. For the SLF, no ROI modification was used for all patients.

Table 1
Agreement between manual and automated methods measured in 10 healthy volunteers

Tract Name	ATR	CG_C	CG_H	CST	FORCEPS_Major	FORCEPS_Minor
Average	0.89 ± 0.05 [*]	0.87 ± 0.07	0.92 ± 0.05	0.81 ± 0.07	0.91 ± 0.07	0.93 ± 0.06
Tract Name	IFO	ILF	SLF	SLF_temporal	UNC	
Average [*]	0.90 ± 0.06	0.89 ± 0.08	0.87 ± 0.08	0.95 ± 0.06	0.96 ± 0.03	

^{*} Average of kappa values and standard deviations