MR Tractography: A Review of Its Clinical Applications

Kei Yamada1*, Koji Sakai2, Kentaro Akazawa1, Sachiko Yuen1, and Tsunehiko Nishimura1

1Department of Radiology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine
Kajii-Cyo, Kawaramachi Hirokoji Sagaru, Kamigyoku, Kyoto 602-8566, Japan
2Faculty of Human Health Sciences, Kyoto University Graduate School of Medicine
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Magnetic resonance tractography based on diffusion-tensor imaging was first introduced to the medical imaging community a decade ago. It has been successfully applied to a number of neurological conditions and most commonly used for preoperative planning for brain tumors and vascular malformations. Areas of active research include stroke, and dementia, where it provides valuable information not available through other imaging techniques. This technique was first introduced using the deterministic streamline algorithm and has evolved to use more sophisticated probabilistic approaches. We will review the past, present, and future of tractography, focusing primarily on its clinical applications.

Keywords: brain tumor, diffusion-tensor imaging, diffusion-weighted image, MRI, tractography

Introduction

Diffusion-tensor imaging (DTI)-based tractography is one of the most remarkable advances in the field of neuroimaging in the past decade. This method offers in vivo localization of neuronal fiber tracts, which was previously impossible. As a clinical tool, this technique primarily targets intracranial space-occupying lesions, i.e., brain tumors and vascular malformations.1–6 Although many scientific papers have shown it to be robust, its clinical application has some limitations, and these will be addressed latter in this article.

Basics of DTI and Tractography

Water-diffusion anisotropy (directionality) in the white matter of the brain is defined based on axonal alignment.3 Water diffuses preferentially in a direction parallel to the axon’s longitudinal axis, but diffusion is relatively restricted in the perpendicular axis. This phenomenon can be represented mathematically by the so-called diffusion ellipsoid or tensor (Fig. 1).

The tensor has 3 eigenvalues. The long one pointing along the axonal direction is λ1, and the 2 small axes are λ2 and λ3 (Fig. 2). The diffusivity along the principal axis, λ1, is also called the longitudinal, axial, or parallel diffusivity (Fig. 2). The diffusivities in the 2 minor axes (λ2 and λ3) are often averaged to produce a measure of the radial diffusivity (λ2 + λ3)/2, also called the perpendicular diffu-
Fig. 2. Diffusion constants of a given ellipsoid are shown. $\lambda_1$ represents diffusivity in the longest axis of this tensor. $\mathbf{v}_1$ represents the vector orientation of $\lambda_1$.

Fig. 3. Tracking starts at a pixel (or region of interest [ROI]). The fiber assignment by continuous tracking (FACT) program tracks the ellipsoids as long as the adjacent vectors are strongly aligned.

Evolution in Imaging Techniques

When the DTI-based tractography technique was first introduced, its major drawback was the duration of the examination, which was typically more than 30 min. Multi-shot (segmented) echo planar imaging (EPI) was an imaging method of choice in the early days. It requires cardiac gating, which limits the number of echoes acquired and thus extends imaging time; the technique was used primarily to reduce image distortion. Other techniques, including line-scan and PROPELLER (periodically rotated overlapping parallel lines with enhanced reconstruction), reduce susceptibility-induced distortion but are also time consuming. Later studies demonstrated single-shot EPI with parallel imaging technique as an alternative to multi-shot EPI. Because its use can shorten image acquisition to less than 5 min, with fair tractographic results, it has become the imaging method of choice for brain DTI.

For clinical scans, the signal-to-noise ratio (SNR) of the images must be balanced against scan time because motion artifact becomes overt when the scan time is too long. This can be accomplished using a scanner with a higher field or by averaging multiple DTI acquisitions. Combining data from several separate DTI examinations of approximately 5 to 10 min each effectively increases the SNR. Motion correction and image registration between techniques (Fig. 3). Neural connections are mapped by designating at least 2 arbitrary regions of interest (ROI) in 3D space. Tracking is terminated when a pixel with low fractional anisotropy (FA) or a predetermined trajectory curvature between 2 contiguous vectors is reached (Fig. 4). These are often called "stop criteria."

Whether this can be used to distinguish between different pathological substrates, e.g., demyelination versus neuronal loss, remains controversial.

The tensors of cerebral white matter can be reconstructed to track 3-dimensional (3D) macroscopic fiber orientation in the brain. The translation of the longest axis of the tensor ($\mathbf{v}_1$) into neural trajectories can be achieved by various algorithms. These algorithms can be broadly classified into 2 types, deterministic and probabilistic. Deterministic algorithms were the first developed and remain the most commonly used clinically. One of the first was the FACT (fiber assignment by continuous tracking) algorithm, by Mori and colleagues. These are also called line propagation or streamline techniques (Fig. 3). Neural connections are mapped by designating at least 2 arbitrary regions of interest (ROI) in 3D space. Tracking is terminated when a pixel with low fractional anisotropy (FA) or a predetermined trajectory curvature between 2 contiguous vectors is reached (Fig. 4). These are often called "stop criteria."

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these datasets produces higher image quality.

Image resolution is another important factor that could affect the results of tractography. Especially important is the resolution in the z-axis, i.e., slice thickness, to obtain voxels that are near isotropic in shape.\textsuperscript{16,17} When a regular slice thickness of 5 to 8 mm is used, the effect of partial volume averaging degrades the dataset and leads to apparently inferior tracking results (Fig. 5).\textsuperscript{16} This adverse effect is most pronounced for fibers that run through the imaging planes, e.g., the arcuate fasciculus.\textsuperscript{16}

Advances in Imaging Techniques

Depiction of crossing fibers has always been the central problem for tractography. For instance, at the level of the centrum semiovale, the motor tracts of the brain should have a fan-shaped configuration, but the fiber-tracking technique can only depict the fibers traveling from the vertex of the brain. The multiple crossing fibers at this level lead to inaccurate estimation of the direction of anisotropy in these areas. The development of new models and methods seeks to provide solutions to these problems. Recent studies have shown successful reconstruction of multiple intravoxel fibers\textsuperscript{15,18–20} and improved reproducibility and reliability of tractography (Fig. 6).

These more advanced techniques require higher angle resolution and higher b-values, which prolong imaging time. The highest b-values that can be used on a regular clinical scanner are usually limited to approximately 3000 s/mm\textsuperscript{2}. Although a simulation study has shown that the benefit of increasing the b-value in this range would not enable robust depiction of the crossing fibers,\textsuperscript{21} clinical studies have shown that b-values below 3000 s/m\textsuperscript{2} can depict at least some of the crossing fibers (Fig. 7).\textsuperscript{15}

Advances in Postprocessing Techniques

The probabilistic approach is the alternative to the deterministic approach, e.g., FACT. By its nature, the deterministic approach can only produce one reconstructed trajectory per seed point and cannot therefore depict branching fibers. The applied arbitrary anisotropy threshold forces early termination of the reconstructed pathway. These issues have limited the usefulness of deterministic approaches in defining certain fiber tracts.

Probabilistic tractography algorithms aim to address these criticisms by considering multiple pathways emanating from the seed point and from each point along the reconstructed trajectories. Thus, the probabilistic method accounts for the uncertainty in the estimation of fiber direction. It also attempts to provide some estimate of confidence in the projected neural pathway. This method is also known to be resistant to noise, which would be a clear benefit for clinical scans that have limited SNR.

For neurosurgical planning, however, the probabilistic approach has some weaknesses.\textsuperscript{22} First, it is slower and so cannot be used interactively. Second, probabilistic methods may be harder to interpret visually. Instead of discrete geometric pathways, probabilistic methods generate a 3D volume of potential connectivities. The depicted connectivity maps tend to leak into unexpected regions of the brain. Thus, anatomical knowledge is required to judge which parts of the depicted fibers are relevant.

Limitations of Tractography

Perhaps the most important limitation of tractography is that it is not fully validated. Attempts to clinically validate this technique have been made in the past.\textsuperscript{23–27} Most of these efforts are based on comparisons of the tractographic images and known neuroanatomy. A study that evaluated deterministic tractography in patients who underwent intraoperative electrophysiological testing indicated that tractography may underestimate the fiber tracts.\textsuperscript{28} Thus, the tool has to be used with caution, knowing that we are observing only a fraction of reality. The probabilistic approach mentioned above would depict more fibers, thereby leading to less serious underestimation. However, because the relevant fibers have to be judged in each case based on anatomical knowledge, it remains to be proven whether the probabilistic approach is a better tool.

Brain Tumors

Surgical resection of brain tumors involving the so-called eloquent areas remains a huge challenge. Various adjunct strategies, including awake surgery, intraoperative navigation systems, and intraoperative electrical stimulation, have been employed to improve patient outcomes. It has also been suggested that improved outcomes require preservation of cortical as well as subcortical function, so visualization of eloquent white matter tracts is critical.

Tractography has been shown to be a promising tool for assessing the eloquent white matter tracts. The most common target has been the pyramidal tract\textsuperscript{26–33} because of the relative importance of this
Fig. 5. Fiber tracts of the corticospinal tract (CST, green) and superior longitudinal fasciculus (SLF, yellow) are superimposed on the color-coded vector maps. Note that the SLFs obtained from images of 2-mm sections are more robust than those of 6-mm sections. Depiction of the CST did not substantially differ between the images of 2- and 6-mm sections. The vector elements of the color maps are assigned to red (x element, left to right), green (y element, anteroposterior), and blue (z element, superoinferior). The intensities of the color map are scaled in proportion to the fractional anisotropy (FA).

Fig. 6. Areas with crossing fibers at the centrum semiovale. With multi-tensor analysis, one can now resolve the crossing fibers. A model-dependent approach (2-tensor model) was used for this analysis.

Fig. 7. A 58-year-old woman with glioblastoma. A large right parietal lobe tumor is noted, with surrounding vasogenic edema. Note that the pyramidal fibers of the lesional side (right hemisphere) are not depicted using single-tensor tractography, whereas they are shown well using multi-tensor tractography.
fiber bundle for activity in daily life. Because the centrum semiovale is one of the most difficult areas for which to obtain a reliable landmark to locate the pyramidal tract during surgery, this technique would be particularly helpful.

Another important fiber pathway is the optic radiation (OR). Damage to the OR results in visual field defects, so preoperative knowledge about its location is important. However, areas such as the anterior part of Meyer’s loop are difficult to depict with this technique.34 This underestimation of the OR probably occurs due to the presence of adjacent fibers such as the inferior longitudinal fasciculus, inferior occipitofrontal fasciculus, and thalamic radiation from the medial geniculate body.35 A recent study has shown this problem can be overcome by depicting the uncinate fasciculus (UF), which represents the anterior limits of the optic radiation (Fig. 8).36

Ischemic Stroke

DTI has also been used in the field of stroke imaging to assess the relationship between the eloquent fiber tracts and small brain infarcts (Fig. 9).37,38 These clinicoradiological correlation studies have indicated that tractographic results have a fair correlation with clinical symptoms. More recent

Fig. 8. The tractography of the left uncinate fasciculus (UF) and optic radiation (OR) is shown. Frontal and lateral views are provided. The UF is demonstrated as a bright yellow bundle and the OR as a blue bundle. The anterior part of Meyer’s loop is anatomically expected to exist adjacent to the posterior border of UF, but this part of the OR is not depicted using tractography. R, right; L, left; A, anterior; Post, posterior; S, superior.

Fig. 9. A 52-year-old patient with right hemiparesis. A: T2-weighted image shows a small hyperintense lesion located at the left thalamus/internal capsule. From this T2-weighted image alone, it is difficult to discern whether the internal capsule or thalamus is involved. B: Diffusion-weighted imaging (DWI) with superimposed sensory and motor tracts reveals that the lesion directly involves the left motor fibers, a finding that was well correlated with the patient’s motor symptoms.
studies have shown that it may also be used to measure patient outcomes after stroke.39–41

Attempts have also been made to assess the language circuits,42–44 including the arcuate fasciculus, a fiber tract that connects the temporal lobe (primary auditory cortex), Wernicke’s area, and Broca’s area (frontal lobe). This fiber bundle is considered to be eloquent when the left hemisphere is considered, and vascular insult to this circuit can result in conduction aphasia.43 Studies have shown that the degree of damage to this circuit can predict the patient’s language function in the chronic stage following the vascular event.44

Tractography has also been used in the field of pediatric ischemic brain insult.45–47 One study has measured the FA of the pyramidal and sensory tracts and shown that one can predict the occurrence of cerebral palsy using this information.47 This study also indicated that tract-based analysis (TBA) is superior to manual ROI measurements. The classical ROI method relies on a priori hypotheses about the lesion location. Tract-based analysis is conceptually similar to ROI analysis in that it also uses a priori knowledge about the tract location, but the slight difference lies in the fact that TBA determines the measurement points by automatically defined fiber tracts extending into the 3D space. This makes the measurements slightly more objective and somewhat more specific than ROI analysis, but one must keep in mind that the results differ depending on the arbitrarily chosen stop criteria.48 This issue will be addressed again later.

Degenerative Diseases

Tractography has also been used extensively in patients with neurodegenerative diseases, especially in assessing those with dementia. The targets of these investigations include Alzheimer’s disease (AD),49–53 frontotemporal lobar degeneration (FTLD),54,55 and dementia with Lewy bodies (DLB).56 These studies typically measure the mean diffusivity (MD = 1/3 of the trace of the tensor) and FA of various regions using manual ROI placement; more recent studies often use tract-based analysis.

In patients with AD and FTLD, various areas of the brain, including the posterior cingulate, arcuate fasciculus, inferior occipitofrontal fascicles, and UF, have been shown to be involved. Of these areas, the UF is one of the most commonly investigated.51,52,54 The UF is the largest connection between the temporal and frontal lobes, and its traumatic disruption is known to result in severe memory impairment. In patients with AD and FTLD, the degree of damage to this fiber tract, as estimated by DTI, is known to correlate with the severity of the disease process.51,54

MD and FA measurements alone, however, do not provide specific information in discriminating the different pathological substrates, e.g., demyelination versus axonal loss versus neuronal dysfunction.56 For example, AD and DLB are characterized by different pathophysiological processes, at least in their pure forms. More specifically, AD is characterized by neuronal loss, whereas DLB is characterized by neuronal dysfunction. In their study of patients with AD52 and DLB,57 Bozzali and associates found very similar patterns of MD and FA changes in certain regions, such as the corpus callosum and pericallosal areas. Thus, any definitive interpretation of these MD/FA changes in terms of different pathological substrates seems difficult. Lesion distribution, on the other hand, was much more disease specific53,57 and may therefore be clinically useful in discriminating the 2 conditions.

One of the recent AD investigations was carried out using not only the MD/FA but also the radial diffusivity, based on the assumption that radial diffusivity would reflect myelin integrity.7 Although their study has successfully shown increased radial diffusivity at the frontal lobes, the assumption about the pathological substrate is purely speculative because there is no pathological proof. In addition, a recent study has discouraged these interpretations of axial/radial diffusivity because these can be easily affected by the presence of crossing fiber within the voxels.58 One must thoroughly check the alignment of the eigenvectors (v1) with the underlying tissue structures to interpret these parameters meaningfully.

Other Areas of Clinical Research

DTI has been applied to other fields, including vascular dementia,59 spinocerebellar atrophy,60,61 amyotrophic lateral sclerosis (ALS),62,63 developmental central nervous system (CNS) disease,64,65 multiple sclerosis,66,67 Parkinson’s disease,68,69 diffuse axonal injury (DAI),70 spinal cord lesions,71,72 and nerve roots.73 Most of these studies have attempted to predict patient prognosis, and the results appear promising.

Future Research

The imaging and post-processing aspects of tractography have evolved remarkably in the past decade. It is apparent that the environment for using
MR Tractography

this technique clinically is improving each year. However, performing the advanced techniques that are robust with respect to crossing fibers remains very time consuming,18–20 and imaging time for these techniques must be further shortened for clinical use.

A more objective way of analyzing tractographic results may be needed. Current analysis is limited to qualitative intrasubject comparisons, such as the contralateral ratio of the number of fibers depicted.44,74 Because these factors can be easily affected by image quality, it is often difficult to use the information for direct comparison between subjects. A recent study by Taoka’s group has shown that the selection of the FA threshold influences the measurement of diffusion tensor parameters when tract-based analysis is performed.48 It becomes apparent from this study that the operator-defined threshold of FA acts as a filter, below which all voxels are omitted from the final analysis. Whether such arbitrary selection of threshold is clinically relevant remains unknown and warrants future research.

Standardization of the technique may be necessary to allow for clinical studies of a larger scale. Given the rapid advances in the technical aspects of DTI and tractography, standardization may be a challenge.

Conclusions

Tractography has been shown to be a promising tool for assessing the white matter of the brain, and its clinical applications are expanding. The results derived from this technique need to be interpreted with caution to avoid over/underestimation of the fiber tracts.28,75 The pathological substrates underlying the changes we observe with this technique still await validation.

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