Clinical MR tractography: past, present, and future

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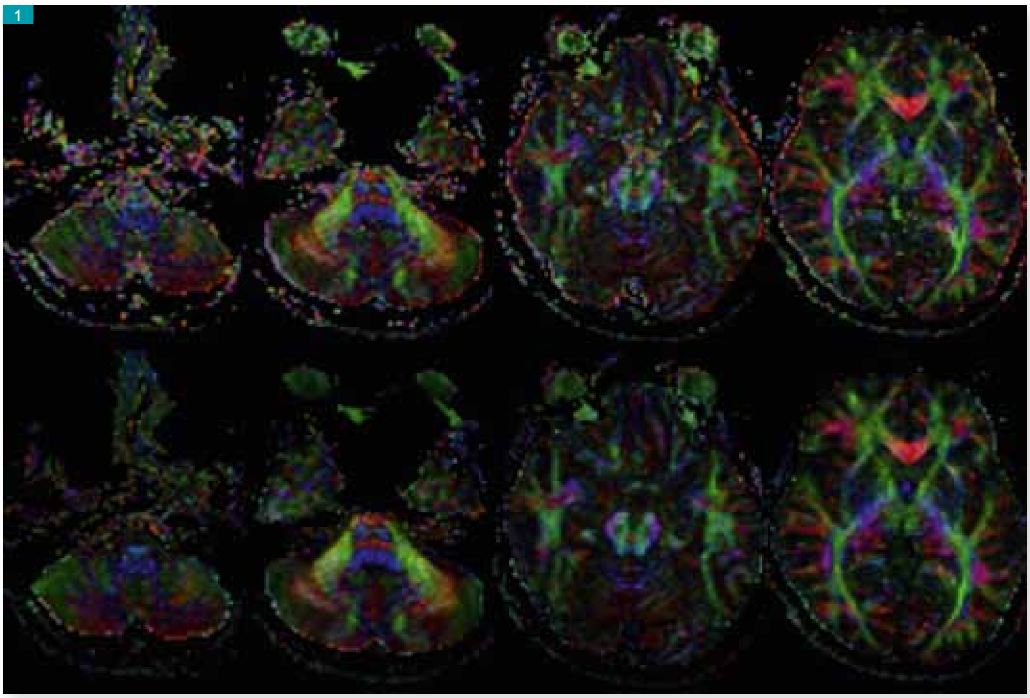


Figure 1. Effect of image registration. Color-coded vector maps of a DTI data set of a normal volunteer are shown (b = 1000, averaging = 1, and 32 motion probing gradient directions). The images of the upper row represent the calculated vector maps without image registration. The images of the lower row represent those with registration. Note that one can achieve higher image quality using this technique, especially at the boundaries between the CSF and the brain surface. 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 FA.

Diffusion-tensor tractography is one of the most remarkable advances in the field of neuroimaging in the past decade. This method offers *in vivo* visualization of water diffusion along neuronal fiber tracts, which previously was not possible. As a clinical tool, this technique primarily targets intracranial space-occupying lesions, that is, brain tumors and vascular malformations [1-6]. Surgical resection of brain masses involving the so-called eloquent areas remains a huge challenge.

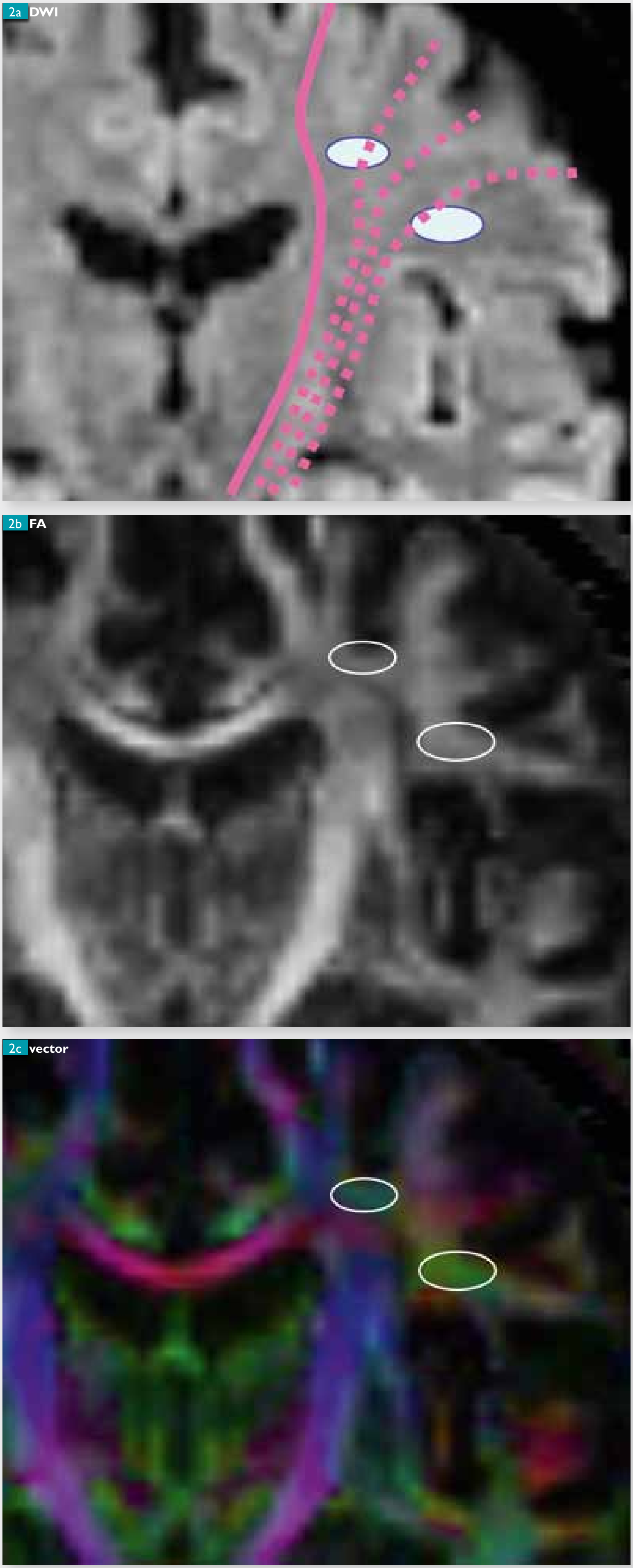
Various adjunct strategies have been employed to improve patient outcomes. These include awake surgery, intraoperative navigation systems, and intraoperative electrical stimulation. It has also been suggested that preservation of cortical, as well as subcortical, function is critical for improving outcomes; thus, the visualization of eloquent white matter tracts is an important issue. However, when using diffusion-tensor tractography clinically, some limitations need to be addressed. These will be discussed later in this article.

The basics of tractography

Water-diffusion anisotropy (directionality) in the white matter of the brain is defined on the basis of axonal alignment [3]. Water diffusion preferentially diffuses along the axon's longitudinal axis but is relatively restricted in the perpendicular axis. This phenomenon can be represented mathematically by the so-called diffusion ellipsoid, or tensor. These tensors can be reconstructed to track three-dimensional macroscopic fiber orientation in the brain.

The translation of the longest axis of the tensor (v1) into neural trajectories can be achieved by various algorithms. These algorithms can be broadly classified into two types; that is, deterministic and probabilistic. Deterministic algorithms were the first ones invented and remain the most commonly used clinically. One of the first deterministic methods invented was the Fiber Assignment by Continuous Tracking (FACT) algorithm [1, 7].

▶ **Diffusion-tensor tractography offers *in-vivo* visualization of the neuronal fiber tracts.**



Trajectories are mapped by designating two arbitrary regions of interest (ROI) in three-dimensional space. Tracking is terminated when a pixel with low fractional anisotropy (FA) or a predetermined trajectory curvature between two contiguous vectors is reached.

Evolution in imaging techniques

When the diffusion-tensor imaging (DTI)-based tractography technique was first introduced, its major drawback was the duration of the examination (typically more than 30 minutes) [8]. Multi-shot (segmented) echo planar imaging (EPI) was one of the imaging methods of choice in the early days. As it requires cardiac gating, this limits the number of echoes acquired and thus leads on to an extended imaging time.

The multi-shot technique was used primarily to reduce image distortion, but later studies demonstrated that single-shot EPI (ssEPI) with parallel imaging technique is an alternative to the multi-shot EPI. Using ssEPI, image acquisition can be shortened to less than five minutes while obtaining fair tractographic results [5]. Thus, the ssEPI technique is now considered the standard 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, since motion artifact becomes overt when the scan time is too long. Thus, it seems reasonable to combine data from several separate DTI examinations, each approximately five to ten minutes in length, to effectively increase the SNR [9]. Motion correction and image registration between these data sets would result in higher image quality (Figure 1).

Imaging resolution is another important factor that could affect the results of tractography. Especially important is the resolution in the z-axis (that is, slice thickness) to obtain voxels that are close to isotropic shape. When a regular slice thickness of 5 mm to 8 mm is used, the effect of partial volume averaging degrades the data set and leads to apparently inferior tracking results [10]. It has also been shown that this adverse effect is most pronounced at the areas with crossing fibers [10].

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Figure 2. Illustration of the pyramidal tract fibers descending from the primary motor cortex. The trunk and lower extremity fibers are drawn with purple lines. The fibers from the hand/face/tongue regions (dashed lines) are much more difficult to depict owing to the presence of crossing fibers, such as the superior longitudinal fasciculus and the arcuate fasciculus (circles).

More advanced imaging techniques

Depiction of crossing fibers has always been the central problem for tractography. For instance, the motor tracts of the brain should have a fan-shaped configuration at the level of the centrum semiovale. However, the fiber-tracking technique can only depict the fibers traveling from the vertex of the brain. This is attributable to the existence of multiple crossing fibers at the level of the centrum semiovale, which leads to inaccuracy in the estimation of the direction of anisotropy in these areas (Figure 2).

The development of new models and methods seeks to provide solutions for these problems. Recent studies have shown successful reconstruction of multiple intravoxel fibers [9, 11, 12]. These new techniques would improve the reproducibility and reliability of tractography (Figure 3, 4).

In order to carry out these more advanced techniques, one has to use higher angular resolution of the diffusion-sensitizing gradients, as well as higher b-values, which would prolong imaging time. The highest b-values that one can use on a regular clinical scanner are usually limited to approximately 3000 s/mm^2. However, 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 [13].

Probabilistic approach

The probabilistic approach is the alternative to the deterministic approach, (for example, FACT). By its nature, the deterministic approach is only able to produce one reconstructed trajectory per seed point and is therefore, not able to depict branching fibers. The applied arbitrary anisotropy threshold will force the 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

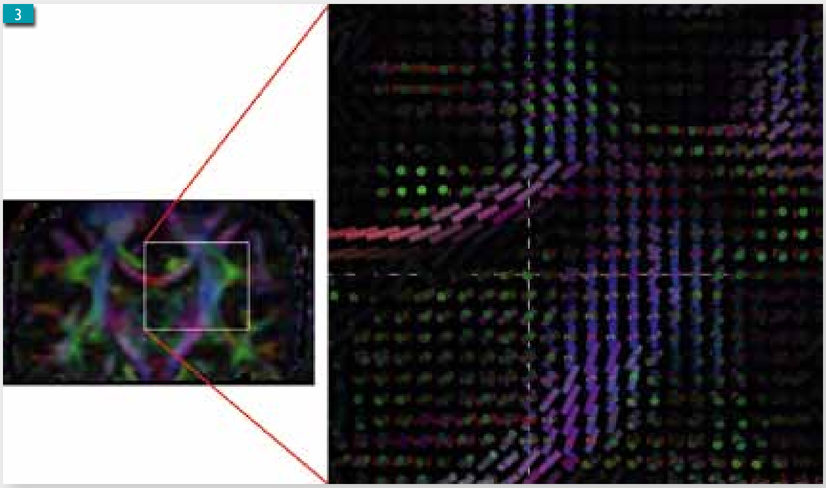

Figure 3. Areas with crossing fibers at the centrum semiovale. With multi-tensor analysis, one can now resolve the crossing fibers. A model-dependent approach (two tensor model) was used for this analysis.

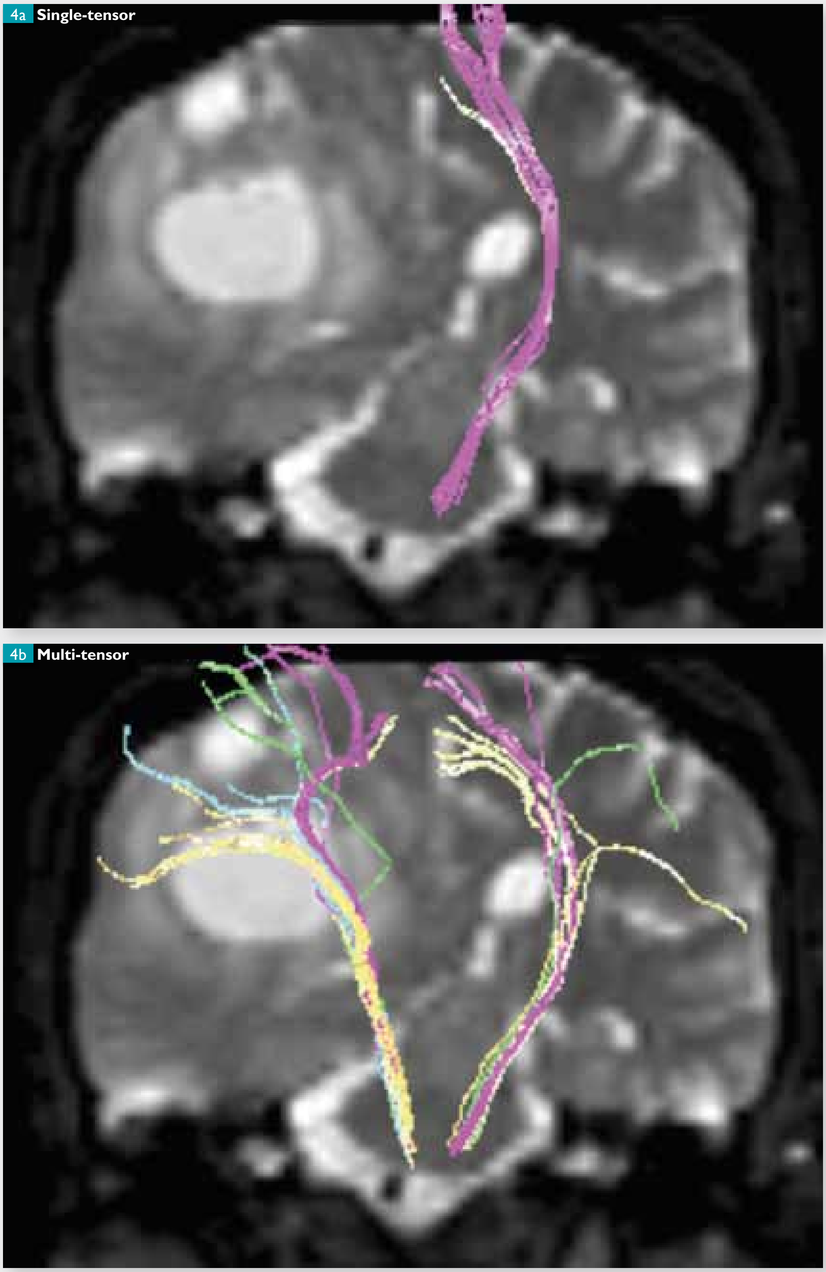

Figure 4. A 58-year-old woman with glioblastoma is shown. A large right parietal lobe tumor is noted with surrounding vasogenic edema. Note that the pyramidal fibers of the lesional side (right hemisphere) are not depicted using single-tensor tractography, whereas they are well shown using multitensor tractography.

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 SNRs.

For neurosurgical planning, however, the probabilistic approach has some weaknesses [15]. First, the probabilistic approach is slower and, therefore, 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, one has to use anatomical knowledge to judge which parts of the depicted fibers are relevant.

▶ **Tractography has been used for pre-operative assessment of eloquent white matter tracts.**

Limitations of tractography

Perhaps the most important limitation of tractography is that it has not yet been fully validated. Attempts to validate this technique have been made in the past [16-18]. 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 tests indicated that tractography appears to underestimate fiber tracts [19].

Thus, the tool has to be used with caution, knowing that observations are on only a fraction of the reality. The probabilistic approach mentioned above would depict more fibers, thus leading to less serious underestimation. The relevant fibers, however, have to be judged in each case based on anatomical knowledge, and thus it remains to be proven whether the probabilistic approach is a better tool.

Clinical application: brain tumors

Tractography has been used for preoperative assessment of eloquent white matter tracts. The most common target thus far has been the pyramidal tract [20-22], because of the relative importance of this fiber bundle for activity in daily life. The centrum semiovale is one of the most difficult areas from which to obtain a reliable landmark to locate the pyramidal tract during surgery, therefore, this technique would be particularly helpful.

▶ **Tractography is not only a clinical tool. It is also widely used in neuroscience.**

Another important fiber pathway is the optic radiation. Damage to the optic radiation results in a visual field defect. Therefore, preoperative knowledge about the location of the optic radiation is important. There are areas that are difficult to depict with this technique, which is the anterior part of Myer's loop [23].

Underestimation probably occurs due to the presence of a crossing fiber from the medial geniculate body to the superior temporal gyrus (that is, the primary auditory cortex) [24]. A recent study has shown that this problem can be overcome by depicting the uncinate fasciculus, which represents the anterior limits of the optic radiation [25].

Clinical application: stroke and beyond

DTI has also been used in the field of stroke imaging. The technique has been used to assess the relationship between the eloquent fiber tracts and small brain infarcts [26, 27]. These clinicoradiological correlation studies have indicated that tractographic results have a fair correlation with clinical symptoms. Later studies have shown that it may also be used to measure a patient's outcome after stroke [28-30].

Assessment of the language circuits, one of which is known as the arcuate fasciculus, has also been attempted [31-33]. This fiber tract connects the temporal lobe (primary auditory cortex), Wernicke's area, and Broca's area (frontal lobe). This fiber bundle is considered an eloquent one when the left hemisphere is considered. Vascular insult to this circuit can result in conduction aphasia [32]. 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 [33].

DTI can be applied to fields other than neuro-oncology and stroke. In fact, DTI has been used to characterize amyotrophic lateral sclerosis (ALS) [34, 35], pediatric ischemic brain insult [36-38], developmental CNS disease [39], multiple sclerosis [40], diffuse axonal injury (DAI) [41], and spinal cord lesions [42]. Most of these studies have attempted to predict the patients' outcome/prognosis, and the results appear promising.

Application to neuroscience

Tractography is not only a clinical tool; it is also widely used in the field of neuroscience. Many researchers, including the present authors, expect this field to be fruitful. At the same time, it is believed that the interpretation of the results should be done with caution, as there is not yet an effective reality check on this technique [43].

One should still rely on the classical neuroanatomy description at the histological level when looking at the results. It is apparent that all medical imaging has limitations, and this is true for DTI. Especially important will be the spatial resolution of this technique. With tractography, one is limited to looking at the system at a completely different scale from the histology.

The future

As illustrated in this article, there have been remarkable evolutions in both the imaging and post-processing aspects of this technique in the past decade. It is apparent that the environment for using this technique clinically is improving each year. However, performing the advanced techniques that are robust with respect to crossing fibers is still time consuming [11, 12]. The imaging time for these advanced techniques must become even shorter for clinical use.

A more objective way of analyzing tractographic results may be needed in the future. Current analysis is limited to qualitative intra-subject comparisons, such as the contralateral ratio of the number of fibers depicted or the anisotropy index. These factors can be easily affected by image quality, and, thus, it is often difficult to use the information for direct inter-subject comparisons.

A better way of representing the pathological processes of fibers is necessary. For instance, the anisotropy reduction can be driven by increased radial diffusivity (that is, increased diffusion perpendicular to the principal diffusion direction) or reduced axial diffusion. Both of these conditions would represent different pathological processes. It would be ideal if we would be able to handle these separately and attribute them to specific pathological processes. This would potentially expand the quality of the information obtained.

▶ The environment for clinical application of tractography is improving each year.

Standardization of the technique may be necessary in the future to allow for clinical studies of a larger scale. When this happens, it could be the sign that the technique has matured and truly established itself in this field ■

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