Diffusion Tensor Imaging

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Introduction

Diffusion-weighted imaging (DWI) provides a method of noninvasive tissue characterization that is unique and complementary to other imaging techniques. Diffusion tensor imaging (DTI) and DTI-based fiber tracking ("tractography") have enabled unprecedented, *in vivo* visualization of individual WM tracts and their relationships with cerebral pathology. DWI has already revolutionized the imaging of acute stroke and is now clinically routine; DTI and tractography are rapidly making their way into the clinical realm. The acquisition, post-processing and analysis of diffusion imaging data are technically complex with many steps, decisions and compromises to be made that affect the final result. Even if qualitative interpretation by a radiologist is the sole objective rather than quantitative analysis, a "black-box" approach to image production is ill-advised. As DTI and tractography make further inroads into clinical practice, an understanding of basic principles and applications is becoming increasingly important to neuroimaging specialists.

Principles of DWI, DTI and Tractography

MR images can be sensitized to the random, thermally-driven motion of water molecules in specific directions through the use of paired dephasing and rephasing magnetic field gradients (DWI). Diffusion in tissues is a function of direction in 3D space (i.e. anisotropic) and this profile can be approximated by a tensor "ellipsoid" model (DTI). The orientation of the diffusion tensor ellipsoid (specifically its primary axis or major eigenvector) is generally assumed to be parallel to the local white matter fascicles. These directional patterns may be visualized using color maps representing the major eigenvector direction, the most common example being the use of red, green, and blue (RGB) color channels to represent left-right, anterior-posterior, and superior-inferior directions, respectively [1]. Color intensity is often weighted by an index of diffusion anisotropy (most commonly the fractional anisotropy [FA]), yielding a convenient summary map from which the degree of anisotropy and the local fiber direction can be determined. Such maps are particularly appealing because anyone familiar with normal fiber tract anatomy can readily survey the organization of the major tracts by paging through directionally-encoded 2D sections just as standard clinical MR images are typically viewed. Moreover, the relationship of a lesion to specific tracts in the region is often readily assessed.

Another approach to depicting white matter connection patterns is to employ mathematical algorithms that attempt to follow the trajectories of individual fiber tracts in 3D. Such trajectories are estimated by starting at a specified location (known as the "seed" point), estimating the direction of propagation (often defined by the major eigenvector), and moving a small distance in that direction. The tract direction is then re-estimated and another small step is taken. This process is repeated until some predetermined criterion for terminating the tract has been met. The

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resulting “tractograms” may be displayed in a variety of ways using 3D computer-graphical techniques.

Most tractography algorithms estimate a single discrete trajectory for each seed point location. Many of these algorithms use the major eigenvector to estimate the tangent of the trajectory for a white matter fiber bundle [2-4] although tracking methods based upon the full diffusion tensor field have also been developed [5-7]. Seed locations are usually defined either globally over the entire brain or in a user-specified region. Tracts are typically propagated in both forward and reverse directions until some termination criterion is met; commonly employed criteria include: intersecting a voxel where the anisotropy is below a specified threshold or encountering an excessively sharp “bend” between steps along the putative tract. Tracts may be defined by constraining them to pass through one or more specified regions of interest [8,9].

Tractography algorithms are capable of generating anatomically plausible estimates of white matter trajectories in the brain and they have been used to depict major projection pathways (e.g. pyramidal tract, internal capsule, corona radiata), commissural pathways (e.g. corpus callosum, anterior commissure), and association pathways (e.g. arcuate, frontooccipital, and uncinate fasciculi) [8-12]. Of course, it must be remembered that a given DTI-based trajectory is an imperfect model-based construct and does not (indeed *cannot*) directly correspond to a physical axonal fiber, given the marked discrepancy of scale between the microstructural anatomy and the spatial resolution of clinical imaging. This point is easily forgotten when admiring the aesthetic depictions of WM anatomy that tractograms offer. It is also a misconception pervasive in lay media reports concerning tractography and in medicolegal contexts.

Terminology

As clinical tractography is still in its infancy, published reports frequently employ inconsistent terminology in describing pathologically altered tracts. Such descriptive terms as “disruption,” “displacement,” “deviation,” “deformation,” “destruction,” “degeneration,” “infiltration,” “interruption,” and “splaying” are frequently used in the context of DTI-tractography without precise definitions. For example, there are at least two dictionary definitions for “disrupt:” (1) “to break apart or interrupt the normal unity of,” or (2) “to throw into disorder." Thus, "disrupted" is an ambiguous term that can mean either "interrupted" (i.e. tract continuity has been broken) or "disorganized" (i.e. the tract has been infiltrated and is less ordered than normal but it is not broken). Adding to this ambiguity is the possibility of partial interruption, i.e., some of the fibers within a given tract may be broken while others remain intact. In the spirit of encouraging the use of consistent terminology by DTI-tractography investigators as well as radiologists reporting clinical DTI studies, the following definitions are suggested:

Deviation: Any portion of tract course is altered by bulk mass effect while maintaining tract coherence, with “coherence” implying that multiple adjacent fiber trajectories follow parallel pathways or they diverge/converge in an ordered fashion. "Deviation" is preferred over "displacement" because it is more specific and informative. (For example, road repairs may "displace" traffic without providing an alternate route; "deviated" implies that the flow of traffic is systematically routed around the repairs.

Infiltration: Any portion of a tract shows significantly reduced anisotropy while retaining sufficiently ordered structure to allow its identification on directional color maps and to allow fiber tracking to proceed. Note that infiltration by tumor is not discriminated from infiltration by edema as this cannot yet be reliably done.

Interruption: Any portion of a tract is visibly discontinuous on anisotropy-weighted directional color maps, and/or fiber tracking is discontinuous despite reasonable relaxation of termination criteria. ("Reasonable" termination criteria are those that impede the generation of recognizably spurious tracts but do not necessarily penalize fiber tracking for low anisotropy, provided excessively sharp turns are adequately avoided.) “Interruption” is preferred over the more ambiguous “disruption” and the more pathologically definitive “destruction.” Note also that a tract may be interrupted either partially or completely.

Degeneration: A tract characterized by significantly reduced size and/or anisotropy at a substantial distance from a lesion affecting the same neural pathway (either cortical or subcortical), such that secondary Wallerian degeneration rather than infiltration can reasonably be presumed. (Example: a chronically atrophic-appearing pyramidal tract in the brainstem, distal to a non-infiltrating lesion of the corona radiata).

Splaying: A tract separated by a lesion into distinct bundles deviated in different directions.

Although these definitions are not perfect (e.g. a severely deviated or infiltrated tract might be mistaken for an interrupted one), they represent a reasonable approach given the limitations inherent to DTI and tractography. Note also that these definitions are not mutually exclusive; e.g. a tract may be both deviated and infiltrated, deviated and interrupted, etc.

Clinical Applications

The clinical role of DTI/tractography is currently being defined. Unlike standard diffusion-weighted imaging (DWI), which quickly became indispensable based on its application to acute stroke, there is not yet a “killer app” for tractography. Broadly categorized, DTI-tractography applications include: *tissue characterization* (e.g., estimating the histology, grade or margins of a neoplasm), *lesion localization* (e.g., determining the specific anatomical fiber tract involved by a lesion) and *tract mapping* (e.g., preoperative mapping of a tract deviated by a tumor).

Problems of tissue characterization have typically been addressed using scalar DWI/DTI parameters, most commonly ADC and FA, on a voxel-wise basis. A large number of studies have shown these parameters to be more sensitive to pathology than standard clinical MRI, based on changes found in the so-called “normal-appearing” WM. Unfortunately, this high sensitivity is accompanied by low specificity, particularly in the case of FA. Thus, while the common DTI parameters might have appeal as imaging endpoints in clinical trials (based on their sensitivity to subclinical pathological changes), their day-to-day clinical utility is currently quite limited. Recent efforts to derive greater pathological specificity from DTI parameters have focused on directionally specific (e.g., longitudinal, transverse) diffusivities and other features of the diffusion tensor but the clinical role of these emerging techniques is not yet defined.

Lesion localization is a more straightforward application of DTI-tractography than tissue characterization, a few anatomical controversies notwithstanding [13,14]. The ability to localize lesions to specific tracts on imaging has obvious importance to the clinician attempting to correlate a patient's disease with his clinical presentation and findings on neurological examination. For example, the correlation between conventional imaging findings and clinical disability in multiple sclerosis is notoriously poor; this is due, at least in part, to the lack of functional specificity in standard imaging-based estimates of disease burden (e.g., the total number or volume of lesions on T1-/T2-weighted images). DTI-tractography enables more functionally specific estimates of disease burden ("importance sampling" [15]) which better correlate with clinical disability. This approach may be similarly applied in the setting of focal infarcts [16,17].

Although DTI-based, 3D fiber tracking can yield such quantitative measures as "connectivity" (the strength and/or likelihood of any functional connection between multiple cortical/subcortical areas) [18] or "fiber density" (the number of fiber trajectories identified per voxel in a region of interest) [19], in the clinical setting the technique is used primarily as a visualization tool. For example, DTI-tractography is uniquely suited to depict the aberrant fiber connections of various congenital/developmental anomalies [20,21] or the deviation of a fiber tract by a space-occupying mass [12,22,23]. Some investigators have integrated DTI-based tractography with cortical mapping using fMRI [24-27] or intraoperative electrocortical stimulation [28,29], in some cases using the results of cortical mapping to provide seed locations to the tractography algorithm. Preoperative tractography can provide confirmation that a tumor-deviated tract remains intact and potentially facilitate preservation of the tract during resection. This application is probably the best known to date although studies proving clinical utility are still relatively few. In one of the largest published series to date, patients whose high-grade gliomas were resected survived an average of 7 months longer, and were more functional, when DTI was added to neurosurgical navigation procedures [30].

Limitations and Pitfalls

There are several limitations of DTI that should be considered. Estimates of the eigenvector directions, and hence the local tract directions, are sensitive to image noise and assorted artifacts (ghosting, misregistration, motion) that can reduce the accuracy of the DTI data and ultimately the tracts derived from these data. Even relatively straightforward ADC calculations in routine DWI applications can be erroneous when "black-box" software is used carelessly, such as in a lesion having very low T2-weighted signal [31]. Crossing pathways are particularly problematic for DTI-based tractography as most algorithms (particularly those based upon the major eigenvector) are unable to resolve them. For example, the many intersecting pathways in the centrum semiovale, including corpus callosum, superior longitudinal fasciculus and corona radiata, create problems for the mapping of trajectories through this region. As a result, most reconstructions of the corpus callosum and corticospinal tract show connections only to medial cortical areas, whereas lateral connections are known to exist. New diffusion imaging methods, such as HARDI (High Angular Diffusion Imaging) [32,33], QBI (Q-Ball Imaging) [34], CHARMED (Composite Hindered and Restricted Model of Diffusion) [35], and DSI (Diffusion Spectrum Imaging) [34,36], promise more accurate depictions of intersecting tracts; investigators have just begun to perform tractography using diffusion image data obtained with these

advanced methods, with promising results [37]. Note, however, that these methods require much higher diffusion-weighting (typically 3,000-15,000 s/mm^2) and take much more time to acquire.

Other technical problems remain to be solved before tractography can be considered a reliable technique in the setting of clinical pathology. Consider, for example, one of the best known and most promising clinical applications of DTI-tractography—the preoperative assessment of brain tumors. A fiber tract that is deviated by a non-infiltrating tumor with no associated edema presents the most straightforward case for DTI-based tract mapping; high anisotropy is generally preserved in such a tract, allowing it to be readily identified on directional color maps and traced around the tumor with fiber tracking techniques. Such examples are becoming commonplace in the literature and at scientific meetings but intraoperative correlations and outcomes analyses are not so common and the published experience of some investigators raises some serious concerns. For instance, intraoperative tract mapping by evoked potentials analysis has revealed errors in preoperative, DTI-based assessments of tract size and proximity to tumors [38]. There are several potential sources of such error, including misregistration of multi-modality images and shifting of the brain during craniotomy and tumor resection [39].

Cases involving infiltrative tumors with associated edema can be even more problematic. Either edema or tumor infiltration may reduce the anisotropy of involved tracts without destroying them, posing a problem for tractography algorithms designed to terminate when the anisotropy falls below a designated threshold. It is difficult to know, in this setting, how to interpret an apparent loss of fiber trajectories. Relaxing the termination criteria may allow an algorithm to proceed through low-anisotropy regions but this increases the risk of generating spurious tracts because estimates of major eigenvector direction become less reliable for low-anisotropy tensors [40]. Moreover, tumor infiltration may cause tensor directional alterations that are more complex and less predictable than the bulk mass displacements of non-infiltrating tumors [41,42]. Finally, several materials commonly encountered in this clinical population, including hemorrhage, calcification, surgical hardware, and postoperative pneumocephalus, may cause susceptibility artifacts that are especially problematic for echoplanar imaging (EPI), the acquisition method used most commonly for DTI. Such cases would likely benefit from non-EPI acquisition schemes, such as diffusion-weighted fast spin-echo [43].

Conclusion

Further validation of DTI-tractography as a clinically relevant technique is still needed. Studies will have to become more quantitative, include greater numbers of patients, and employ statistical validation. For applications in tissue characterization, correlations with voxel-specific histological data will be critically important (but difficult to obtain). For applications in preoperative planning, correlations with intraoperative findings and postoperative outcomes will be necessary. Further study along these lines is surely forthcoming and more widespread clinical application of DTI-tractography is likely to follow.

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