Diffusion Tensor Imaging at the Crossroads: Fiber Tracking Meets Tissue Characterization in Brain Tumors

If my cursory and unscientific search of Medline is any indication, the growth of interest in diffusion tensor imaging (DTI) is showing no signs of slowing: entering "diffusion tensor" in the search window yields 185 articles published in 2004 and >100 articles published so far this year (through early June). Does this represent an "irrational exuberance?" Is there a DTI "bubble?" Such questions inevitably arise sooner or later in the lives of most new imaging techniques—at least those that get noticed—and DTI is no exception. Radiologists have spent so many years staring at grayscale images that we might be forgiven our excitement about a technique that provides some color for a change, useful or not. Nevertheless, the skeptics are already demanding statistical and histopathologic validation of DTI results, correlations with "gold standards," and clinical applications with outcomes analyses. Of course, these demands are perfectly justified; the transition from bench to bedside cannot be properly made until they have been met, and it is now incumbent upon clinical DTI investigators to try to meet them.

Among the myriad approaches to the analysis of DTI data, the method of fiber tracking or "tractography" is probably met with the most skepticism by those seeking clinical utility and validation. Perhaps the many layers of behind-the-scenes, computational analysis necessary to generate tractograms make some uncomfortable. Perhaps the wide variety of fiber-tracking methods that exist, coupled with an extreme sensitivity of the results to the methods used, imply a technique impossible to standardize. Perhaps there is simply something about colorful, 3D computer graphics that suggests style over substance. Whatever the reason, researchers who perform fiber tracking know that many clinical neurologists, neurosurgeons, and radiologists will need more evidence of clinical utility and reproducibility before they embrace tractography with the enthusiasm of the cognitive neuroscientists, though the latter are calling for validation as well, judging from the panel discussions and breakout sessions of a DTI workshop held last summer at the New York Academy of Sciences (1).

Before becoming caught up in the debate about validating tractography, however, let us remember that, though fiber tracking represents the highest level of postprocessing available for DTI data, there are simpler ways to analyze DTI data. These include voxel-based measures of diffusivity (directionally averaged or in specific directions), anisotropy, tensor shape (prolateness, oblateness), and tensor orientation; region-based measures of intervoxel directional coherence and interhemispheric symmetry; and whole-brain (perhaps gray-white segmented) measures of DTI parameter distributions. The promise of these approaches and, in some cases, their proven utility is in solving problems of tissue characterization. The hope is that these DTI parameters, unique in their ability to probe tissue microstructure at length scales commensurate with cellular membranes and organelles, will provide greater degrees of sensitivity and/or specificity for pathologic tissue changes than conventional MRI is able to provide. This is a very different goal from that of fiber tracking, which seeks to map the brain's network of interconnections in vivo, typically for purposes of visualizing anatomy (eg, mapping the position of a tract displaced by tumor) or establishing connectivity patterns (eg, mapping the connections between functional cortical areas involved in a particular cognitive process).

Many studies have employed DTI to address problems in tissue characterization, with some success. For example, the evidence for an inverse relationship between tumor cellularity and mean diffusivity is quite strong (2–5). Several studies have revealed a trend toward lower anisotropy in the peritumoral tissues of infiltrating versus noninfiltrating neoplasms (6–8), though statistical significance has been difficult to achieve and this bodes poorly for clinical decision making in individual patients. Although some recent evidence suggests that intratumoral anisotropy may discriminate low- from high-grade gliomas (9), there is also recent evidence to the contrary (7).

The number of brain tumor studies in which tensor data have been analyzed beyond mean diffusivity and anisotropy (eg, individual eigenvalues, tensor shape metrics, directional information) are too few for any conclusions to be drawn and making sense of the published data is exceedingly difficult, in light of the heterogeneity of methods for DTI data acquisition and postprocessing. In particular, many discrepancies in the tumor-DTI literature could probably be explained on the basis of inconsistent region-of-interest placements (intratumoral vs peritumoral, enhancing vs nonenhancing, T2-hyperintense vs normal-appearing white matter, partial volume effects well controlled vs poorly controlled, and so forth).

In this issue of the *AJNR,* Roberts et al (10) bring the methods of fiber tracking to bear upon an important problem of tissue characterization: measuring the integrity of white matter fibers in the vicinity of high-grade gliomas. They define a "fiber density index" (FDi) by first tracking all possible fiber trajectories through all voxels having sufficiently high anisotropy, then counting the number of trajectories per voxel in a region of interest. Although this index is found to be highly correlated with fractional anisotropy (FA), the authors suggest that the FDi may, in some cases, provide information that is complementary to FA. Specifically, they remind us that reduc-

tions in FA have poor specificity, potentially resulting from fiber depletion (tumor destroys fibers, reducing their absolute numbers), fiber dilution (tumor or vasogenic edema spreads intact fibers apart, reducing their density), or fiber degradation (fibers themselves become intrinsically less anisotropic, retaining normal numbers and density). The authors argue that FDi would distinguish degradation, in which FDi would presumably remain normal (at least until anisotropy falls below threshold), from depletion and dilution, in which FDi would be reduced.

It was inevitable that fiber-tracking methods would eventually be studied for purposes of tissue characterization rather than tract mapping per se. It is tempting to take a more quantitative approach to fiber tracking—one with potentially more immediate clinical application than a 3D color-graphic depiction of fiber tracts inside a transparent head, spinning on a workstation monitor—and Roberts et al are to be congratulated for their efforts in this regard; however, their study has several limitations to consider. Specifics regarding region-of-interest placement are lacking. The behavior of the tractography algorithm in the face of decreased anisotropy is uncertain (fiber tracking becomes less reliable as anisotropy declines). The high correlation between FDi and FA implies that these parameters will be largely redundant in practice (unless further study reveals the FDi to provide important information independent of FA). Whether a decrease in FDi reflects depletion rather than dilution of fibers is unclear; therefore, the problem of discriminating tumor infiltration from bland edema, which has major implications for treatment planning, remains unsolved. It also is not clear how the FDi might contribute to the estimation of tumor histology or grade.

The specifics of this study aside, there are more general concerns with a fiber-tracking approach to tissue characterization that should engender lively debate. The sensitivity of fiber-tracking algorithms to many physical and computational variables is still poorly understood; their behavior in the face of pathologically altered tissue even less so. Correlations with voxel-specific histologic data are difficult to come by, severely limiting prospects for evaluating accuracy and pathologic specificity. I hope that investigators will carefully consider these limitations and proceed with caution in the direction to which Roberts et al have pointed the way. I look forward to that day when the neurosurgeons will ask me, "Does the paucity of DTI fiber trajectories in this patient's pyramidal tract mean that those fibers are destroyed?" and I will know what to tell them.

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