ASFNR Guidelines for Clinical Application of Diffusion Tensor Imaging

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1. <u>Definitions</u>:

a. *Diffusion Tensor Imaging (DTI)* refers to the acquisition and reconstruction of MR images with diffusion-encoding gradients applied in a minimum of 6 non-collinear directions, followed by voxel-wise calculation of the tensor representation of a 3D Gaussian model of the diffusion profile and subsequent mapping of any number of tensor parameters. Most commonly these would include the scalar parameters *mean diffusivity* (the trace of the diffusion tensor, equivalent to the directionally averaged *apparent diffusion coefficient [ADC]* common to conventional diffusion-weighted imaging) and *fractional anisotropy [FA]* (one of several available measures of the degree to which the diffusion tensor deviates from a spherical shape, i.e. the degree to which the diffusion profile is directionally dependent).

b. *Directional color mapping* refers to the additional DTI post-processing step in which a color scheme is used to encode the direction of the major eigenvector (i.e. the direction of maximum diffusivity). The most widely used color scheme assigns the colors red to left-right, green to anterior-posterior, and blue to superior-inferior directions with proportionate combinations of these colors assigned to directions in between these principal directions. The brightness or intensity of color is typically used to indicate the FA (ranging from 0 to 1); such maps are known as “Directional FA” or “Color FA” maps.

c. Diffusion tensor *tractography*, also known as *fiber tracking*, refers to the additional DTI post-processing step in which a predefined algorithm is used to generate computer graphical representations of anatomical fiber bundles as follows: Starting from selected *seed points*, multiple trajectories or *streamlines* are traced though the imaged volume by iteratively stepping in directions determined by the tensor shapes and orientations encountered as the algorithm proceeds. Tractography algorithms may be constrained by predetermined *stopping criteria* in order to terminate trajectories likely to be erroneous; such criteria typically include thresholds for minimum anisotropy and maximum turning angle.

2. **Indications**: The most common indications for DTI may be broadly categorized as either *tract / lesion localization* or *tissue characterization*. (Although these are distinct applications, each with its own approaches and potential pitfalls, they are not mutually exclusive).
    a. *Tract / lesion localization*: Mapping of specific white matter fiber tracts (by directional color mapping and/or tractography), most commonly to depict the locations and spatial relationships of lesions with respect to functionally critical tracts for purposes of surgical risk assessment and treatment planning.
    b. *Tissue characterization*: The use of any DTI metric to discriminate normal from abnormal tissue or to discriminate one abnormal tissue from another.
3. **Acquisition**: The specifics of DTI acquisition are naturally a function of scanner vendor, field strength, hardware / software configurations, and user preference. The following guidelines are offered as general "rules of thumb."
    a. An ongoing program of routine scanner maintenance and quality assurance (field homogeneity, gradient performance, etc.) is important for all clinical MRI but especially for quantitative methods like DTI.
    b. As a "signal-starved" technique, DTI benefits substantially from higher field strengths; while DTI may be obtained at 1.5T, higher field (e.g. 3T) is generally preferred if available. Additionally, parallel image acquisition using a multi-channel head coil is strongly recommended to mitigate the increased susceptibility effects typically present when performing DTI at higher field strengths.
    c. DTI is most commonly performed using single-shot, spin-echo, echoplanar image acquisition at b-values similar to those used for conventional DWI (typically b=1000s/mm^2).
    d. DTI acquisitions generally are prone to a host of artifacts related to susceptibility, eddy current, head motion, cardiac pulsatility, and partial volume effects. Methods are available to mitigate such artifacts, depending on the available hardware, software, time, and expertise. Radiologists using DTI should be aware of these artifacts and make informed decisions regarding how and when to correct for them, with the understanding that uncorrected DTI artifacts can lead to critical errors of interpretation (particularly for tractography).
    e. DTI acquisitions are most commonly 2D whereas tract localization is a 3D endeavor. Optimal use of directional color maps for treatment planning usually requires multiplanar (e.g. axial, coronal, sagittal) reformatting; this fact should be considered when selecting slice thickness and spacing so as to avoid a "venetian blind" appearance of reformats (e.g. zero slice gap is strongly recommended). Voxel dimensions approaching isotropic with no slice gap are generally preferred for fiber tracking.
    f. Increasing the number of diffusion-encoding directions acquired for DTI trades scan time for more robust fitting of the tensor model in the presence of noise. However, for most clinical applications, a point of diminishing returns is reached in the range of 25-30 directions, unless one is fitting a model more complex than the standard single-tensor model.
    g. The more directions one encodes, the more often the b=0 reference image is used in the tensor calculations, compounding the deleterious effects of a noisy b=0 image; therefore, as a rule of thumb, consider acquiring one additional b=0 reference image for (roughly) every 8-10 diffusion-encoding directions. (Note, this may cause problems for certain DTI reconstruction programs that expect a single b=0 reference image to be present in the data set.)

These examples (adapted from Mukherjee et al. 2008b) provide typical clinical DTI acquisition parameters:

Acquisition Parameter	3T	1.5T
Parallel factor	2	2
Slice thickness	2.0 mm	2.5 mm
Matrix	128 x 128 x 60	96 x 96 x 50
Field of view	256 mm	240 mm
# Diffusion-encoding directions	25	25
# b=0 image sets	3	3
# repetitions (NEX)	1	1
b-value	1000 s/mm^2	1000 s/mm^2
TE/TR	min/<12 s	min/<10 s
Total acquisition time	<7 min	<6 min

4. **Post-Processing**: As for DTI acquisition, the specifics of DTI post-processing largely depend on the hardware / software configuration available for image processing and the preferences and experience of the user. Some general guidelines:
    a. Source images should be inspected for quality assurance as the accuracy of all parameter maps and tractograms ultimately depends on the source images ("garbage in, garbage out"). Corrections of source images for head motion, susceptibility and eddy current artifacts are recommended if available.
    b. At a minimum, parametric maps should be generated for the fundamental tensor features of mean diffusivity (unless an ADC map is available from a separate DWI acquisition, which would be redundant) and anisotropy (most commonly fractional anisotropy). For indications requiring localization / mapping of specific tracts, directional color maps are the most reproducible format for viewing tensor orientations; if these maps are to be described and interpreted in the radiologist's report, it is recommended that they be generated in at least two planes (e.g. axial and coronal).
    c. In performing tractography, many choices must be made (algorithm, seed number / locations, step size, stopping criteria, etc.) that can profoundly influence the end results, limiting reproducibility. For example, diseased white matter often has abnormally low anisotropy even when the nerve fascicles remain intact; in this context, a lower setting of the anisotropy threshold may reveal the presence of fiber tracts thought to be absent at a higher threshold. No widely accepted guidelines for making these choices currently exist. Therefore, an open dialog and understanding of these uncertainties between the radiologist and the referring clinician is considered an essential prerequisite to appropriate clinical use of tractography.
    d. The same caveat applies to statistical image analysis methods (especially voxel-based analyses, including tract-based spatial statistics), some of which are designed for group analyses and may yield erroneous results in the assessment of individual patients. Great care must be taken in translating voxel-based analysis from its origins as a research tool into the clinical arena.
    e. Caution is advised when using region-of-interest (ROI) analysis as regional variations in tensor parameters are normally substantial. This is especially true for FA, which commonly approaches zero in white matter regions where multiple fiber populations occupying the same imaging voxel cross one another at near-perpendicular angles. (This occurs as a partial volume effect at virtually any interface between orthogonally oriented tracts.) The result of this regional variation is that even

small changes in ROI definition can yield substantial changes in mean FA over the ROI. Therefore, controlled and reproducible ROI definitions are critical for making any inter-scan comparisons; this is true whether the ROI's are 2D (e.g. placed on individual images) or 3D (e.g. tractography-based).

f. Some tractography processing packages are capable of exporting tractograms to neurosurgical navigation systems. Clinical use of this capability must be done with the understanding that the accuracy and precision of tract localization are limited by many technical factors including image coregistration errors and shifting of the brain during surgery.

5. <u>Reporting</u>:

a. *Technique*: It is not necessary to include technical details of acquisition or post-processing but the types of images generated and evaluated should be stated. (Example: "DTI acquisition was used to generate mean diffusivity and fractional anisotropy maps, as well as directional color maps reformatted in three planes; 3D tractograms of selected fiber tracts were generated from manually placed seed locations.")

b. *Findings and impression*:

i. *Scalar parametric maps*: Although these maps are inherently quantitative, they should be described qualitatively (Example: "The peritumoral white matter demonstrates decreased anisotropy, which may be the result of vasogenic edema and/or tumor infiltration"); quantitative reporting (e.g. FA values in a region of interest) is discouraged unless also provided is an estimate of the normal range to be expected for the reported parameter (e.g. +/- 2 standard deviations from the mean in an appropriate control population). Note that tensor features widely vary with anatomical location and with demographics (e.g. age, gender, handedness, etc.); this variance must be accounted for when determining normal ranges. Also note that despite a host of reports suggesting otherwise, *no tensor parameter has conclusively been proven to reflect any specific tissue microstructural feature*; reduction of anisotropy in particular is an especially non-specific finding. Therefore, characterizing tissue with such specific descriptors as, "tumor-infiltrated," "edematous," "gliotic," "demyelinated," "degenerated," or "less connected" solely on the basis of tensor parameters is to be avoided. If such descriptors are to be used, they should be based on preponderance of all available evidence and accompanied by appropriate differential considerations and estimated levels of confidence.

ii. *Directional color maps*: These maps are useful to depict the locations and spatial relationships of lesions in relation to specific white matter tracts. However, in the presence of pathology, the technical limitations of DTI may prevent some tracts, or portions thereof, from being visualized; therefore, spatial relationships should be described qualitatively, avoiding specific measurements of physical distance between lesion and tract margins. (Example: "The mass in the left superior frontal gyrus deviates the left superior longitudinal fasciculus [SLF] inferolaterally, placing the SLF at increased risk for injury during resection at the inferolateral tumor margin." Counterexample [to be avoided]: "The left SLF is located 5mm from the inferolateral tumor margin.") Also to be avoided is the assumption that non-visualized tracts are truly absent; such is often not the case. Tracts retaining sufficient organization to be visualized on these maps can be presumed intact and most likely functional, though not necessarily uninvolved by disease.

iii. *Tractograms*: The caveat provided above for directional color maps is even more relevant for fiber tracking; specific measurements of physical distance between lesion and tract margins should be avoided. Also to be avoided is the use of tractograms for purposes of tissue characterization rather than tract localization; specifically, the number or density of streamlines in a tractogram is highly dependent on many technical factors and has not been proven to accurately predict the number or density of intact nerve fibers or fiber bundles. (Specifically, there currently is no predictive value in failing to visualize a particular tract.) "Fiber counting" has not been sufficiently validated as a reliable method of tissue characterization for clinical applications.

c. *Disclaimer*: It is critical that physicians basing clinical decisions on DTI be familiar with the limitations and potential pitfalls inherent to the technique. As it is impossible to discuss in the radiologist's report all of the technical issues, a general disclaimer along the following lines is suggested: "Please note that DTI and tractography are based on certain biophysical assumptions and mathematical approximations; their results should be interpreted in conjunction with conventional anatomical imaging as well as other clinical data including physical examination and, if clinically indicated, intraoperative subcortical stimulation."

References and Recommended Reading:

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