Pictorial Review Of Diffusion Tensor Imaging and Tractography

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Background

Diffusion tensor imaging (DTI) is an advanced form of diffusion weighted imaging in magnetic resonance imaging with useful clinical applications. However, understanding DTI can be challenging, since the technology is dependent on highly complex mathematics and physics. Learning the basic concepts of tensor analysis is key to interpreting DTI and tractography.

Diffusion imaging is based on the inherently random motion of water molecules known as Brownian motion. DTI exploits Brownian motion of water molecules in tissues allowing characterization of molecular diffusion in three dimensions of space.

Diffusion anisotropy effects can be fully characterized and utilized to provide exquisite detail on tissue microstructure. The two most common scalar metrics are fractional anisotropy (FA) and mean diffusivity (MD), which are used to generate images of the diffusion data.

Tractography can also be performed using data from diffusion tensor imaging to allow the mapping of the white matter fiber tracts in the brain.

Physics of Diffusion Tensor Imaging

By adding two magnetic field gradient pulses to a conventional spin echo pulse sequence, the signal of moving water molecules can be diminished, and the signal of stationary or "restricted" water molecules can be relatively increased. This method of imaging is known as Diffusion Weighted Imaging (DWI).

The two gradient pulses must be equal in magnitude and timing before and after the 180 degree refocusing pulse of the spin echo pulse sequence. The effects of the two gradient pulses on the phases of moving water molecules are cancelled out, permitting the remainder of the pulse sequence to elicit a strong signal from the stationary water molecules.

Moving water molecules on the other hand demonstrate loss of signal because they are only influenced by one of the gradient pulses without the phase reversal of the second. (Fig .1)

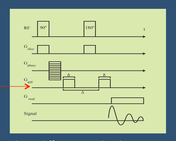

Fig.1 : basic diffusion weighted sequence

DTI compiles data from numerous DWI acquisitions, each with a different orientation of the diffusion sensitizing gradient pulses, generating voxels representing the rate and preferred direction of diffusion at various points in space.

Diffusion is predominantly anisotropic in the white matter fiber tracts. The direction of maximum diffusivity coincides with fiber tract orientation and is contained within a 3 x 3 matrix of diffusivity measurements known as a diffusion tensor, which can be graphically depicted as an a ellipsoid (Fig. 2). The ellipsoid is characterized by an eigenvector and its eigenvalues.

Eigenvectors (**v**)– direction of the ellipsoid (orientation)
Eigenvalues (**λ**) - shape of the ellipsoid (diffusivities)

Fig.2: Diffusion Ellipsoid

$$\mathbf{ADC} = \begin{bmatrix} ADC_{xx} & ADC_{xy} & ADC_{xz} \\ ADC_{yx} & ADC_{yy} & ADC_{yz} \\ ADC_{zx} & ADC_{zy} & ADC_{zz} \end{bmatrix}$$

Complex 9 non-zero element matrix with 6 distinct elements

Transformation

$$\lambda = v^{-1} ADC\ v$$

Changes frame of reference from the scanner to the local region of interest
v = the eigenvector matrix
v $^{-1}$ =the inverted eigenvector matrix

$$\begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix}$$

Resultant diffusion tensor after diagonalization, a simple matrix with 3 nonzero diagonal elements which represent the eigenvalues

The transformation is a change of frame of reference relative to MR scanner to the local of region of interest. The mathematical equivalence of the transformation is 'diagnonalization' of the diffusion tensor. This operation simplifies the matrix representation of diffusion tensor as shown above. Scalar (invariant) diffusion metrics can be calculated from the eigenvalues. Fractional Anisotropy (FA) reflects the anisotropic fraction of the magnitude of the diffusion tensor. FA varies between 0 (isotropic diffusion) and 1 (infinite anisotropy). The degree of brightness indicates the degree of anisotropy on a gray scale FA map. Alternatively, a color scale can be used to represent the degree of anisotropy

$$FA = \sqrt{\frac{3}{2}} \frac{\sqrt{(\lambda_1 - \hat{\lambda})^2 + (\lambda_2 - \hat{\lambda})^2 + (\lambda_3 - \hat{\lambda})^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

with the trace $\hat{\lambda} = (\lambda_1 + \lambda_2 + \lambda_3) / 3$

Mean Diffusivity $MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$

Relative Anisotropy $RA = \frac{\sqrt{(\lambda_1 - \hat{\lambda})^2 + (\lambda_2 - \hat{\lambda})^2 + (\lambda_3 - \hat{\lambda})^2}}{\sqrt{3}\hat{\lambda}}$

Volume Ratio $VR = \frac{\lambda_1 \lambda_2 \lambda_3}{(\hat{\lambda})^3}$

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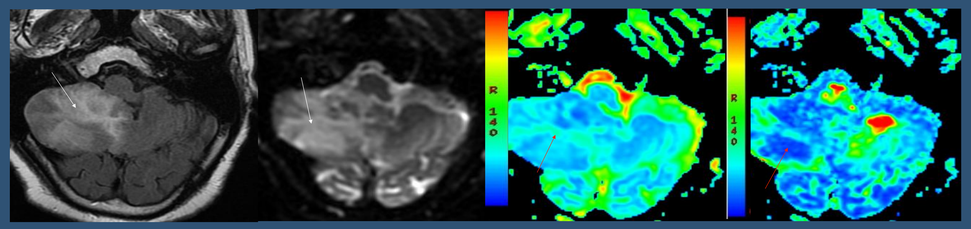
Case 1

82-year-old man with history prostate cancer who presented with a 1 week history of weakness, difficulty walking, and decreased appetite with persistent nausea and vomiting and 14 pound weight loss. Below: Axial MRI demonstrated a large T2 FLAIR hyperintense area in the right cerebellar hemisphere inferiorly with patchy restricted diffusion. A striated appearance on gradient imaging was consistent with hemorrhage (not shown). The mass was hypointense to isointense on T1 and hyperintense on T2. Mass effect on the fourth ventricle and lower mid brain with low-lying cerebellar tonsils was noted. DDX: Lhermitte-Duclos (dysplastic gangliocytoma) versus less likely a vascular insult involving the right PICA.

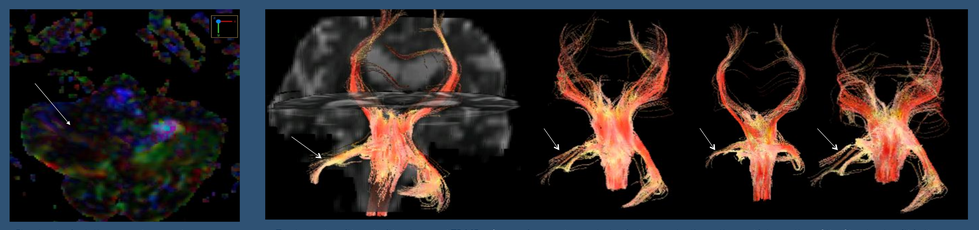


T2 FLAIR: hyperintense lesion (arrow) in right cerebellum with mass effect on 4th ventricle

Mean diffusivity: hyperintensity in right cerebellum with mass effect on 4th ventricle (white arrow)

Mean diffusivity color map: patchy areas of increased diffusivity in right cerebellum (red arrow)

FA map: decreased fractional anisotropy in the right cerebellum (red arrow).

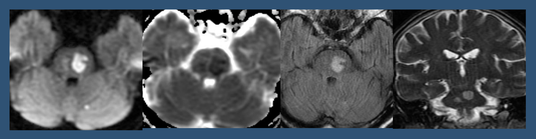


Structural orientation map: decreased orientation of the fiber tracts within the right cerebellum (white arrow).

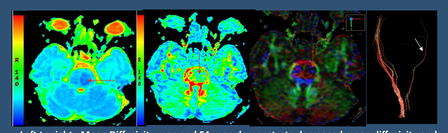
Tractography with and without coronal T2 MR reference images demonstrate displacement, attenuation and interruption of the fiber tracts within the right cerebellum (white arrows)

Case 4

52-year-old male with history of alcohol and cocaine abuse presenting with dysarthria and difficulty walking.



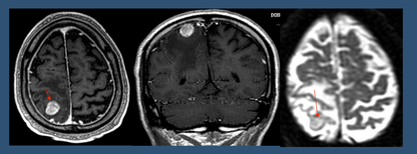
Left to right: Hyperintensity on DWI and hypointensity on ADC map consistent with area of restricted diffusion within the left less so right pons, representing acute ischemic stroke. Axial FLAIR and T2 coronal images demonstrate hyperintensity within the left less so right pons consistent with edema.



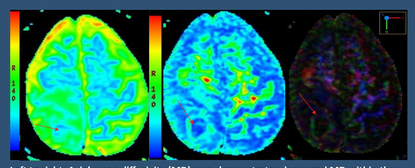
Left to right: Mean Diffusivity map and FA map demonstrate decreased mean diffusivity and decreased fractional anisotropy within the left pons. The structural map shows asymmetric orientation of the fiber tracts within the pons with splaying and disruption of the fiber tracts of the left pons (red arrows). Tractography demonstrates attenuation of the left corticospinal tracts (white arrow).

Case 2

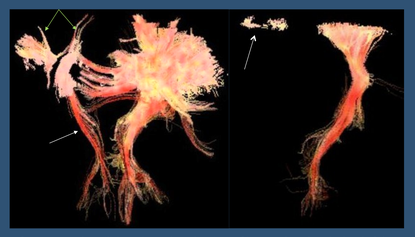
66-year-old male with history of high-grade neuroendocrine carcinoma of the stomach (T4b N2 M1) status post gastrectomy, right hemicolectomy, distal pancreatectomy, splenectomy and chemoradiation. The patient presented after two episodes of left-sided hemiparesis, spasm and weakness with a constant frontal headaches for 3-4 weeks.



Left to right: MRI T1 axial and coronal postcontrast images demonstrate a 2 cm enhancing high right parietal mass with frontoparietal vasogenic edema and sulcal effacement. Apparent diffusion coefficient (ADC) map demonstrates mixed restricted diffusion within the lesion and T2 shine through within the region of vasogenic edema.



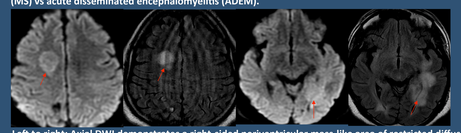
Left to right: Axial mean diffusivity (MD) map demonstrates decreased MD within the right parietal mass with moderately decreased MD within surrounding vasogenic edema. Fractional anisotropy and structural orientation maps demonstrates decreased fractional anisotropy and dominant fiber orientation within the mass and surrounding vasogenic edema.



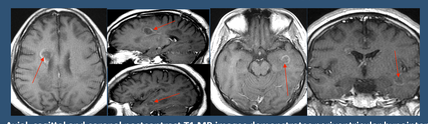
Left: Tractography utilizing mirrored seed regions of interest (ROIs) at the level of the mesencephalon demonstrates attenuated corticospinal tract on the right side (white arrow) with splaying and interruption of the fiber tracts within the right frontoparietal lobe (green arrows). Right: Tractography utilizing mirrored seed ROIs at the level of the mesencephalon and bilateral high parietal target ROIs demonstrates complete local disruption of the right corticospinal tract.

Case 3

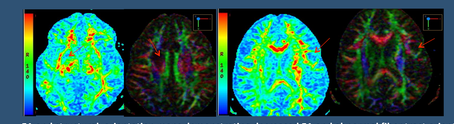
24 yo male with hypertension and complex partial seizures, blindness, and left extremity weakness. Brain biopsy demonstrated histopathological features of a demyelinating process, most likely multiple sclerosis (MS) vs acute disseminated encephalomyelitis (ADEM).



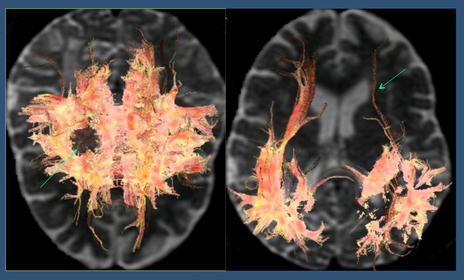
Left to right: Axial DWI demonstrates a right-sided periventricular mass-like area of restricted diffusion within the right centum semiovale that is hyperintense on FLAIR consistent with demyelinating process (red arrow). A second axial DWI demonstrates a left temporal periventricular area of restricted diffusion that is also hyperintense on FLAIR consistent with demyelinating process (red arrows).



Axial, sagittal and coronal postcontrast T1 MR images demonstrates periventricular hypointensities within the right centrum semiovale and left temporal lobe lesions with partial ring-like enhancement. Multiple sclerosis (MS) can have this appearance, particularly tumefactive MS (red arrows).



FA and structural orientation maps demonstrating decreased FA and abnormal fiber tract orientation in association with the right centrum semiovale and left temporal lobe lesions (red arrows).

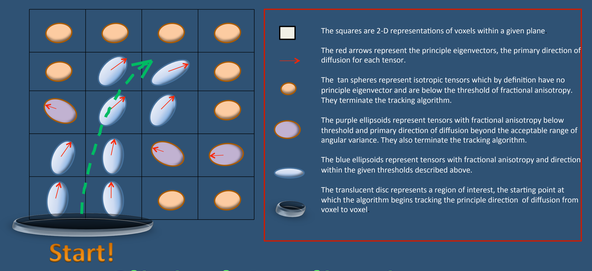


Tractography demonstrates interruption of the fiber tracts by the tumefactive MS lesions (green arrows)

Tractography

Tractography uses mathematical algorithms to bidirectionally track the course of white matter fiber tracts passing through a selected region of interest. The most commonly used tracking algorithm follows the principle directions of diffusion (the principle eigenvectors) of adjacent voxels (tensors) so long as the fractional anisotropy is above a set threshold and the principle direction of diffusion is within a given angular range (cone of probability).

Note that tractography based on DTI data has limited angular resolution and difficultly accurately representing crossing fiber tracts



The squares are 2-D representations of voxels within a given plane

The red arrows represent the principle eigenvectors, the primary direction of diffusion for each tensor.

The tan spheres represent isotropic tensors which by definition have no principle eigenvector and are below the threshold of fractional anisotropy. They terminate the tracking algorithm.

The purple ellipsoids represent tensors with fractional anisotropy below threshold and primary direction of diffusion beyond the acceptable range of angular variance. They also terminate the tracking algorithm.

The blue ellipsoids represent tensors with fractional anisotropy and direction within the given thresholds described above.

The translucent disc represents a region of interest, the starting point at which the algorithm begins tracking the principle direction of diffusion from voxel to voxel

Clinical Applications

Stroke

- DWI is used to detect ischemic changes in the setting of acute stroke.
- DTI demonstrates increased fractional anisotropy in regions of reversible ischemia in the setting of acute stroke and can also help characterize the chronicity of ischemia.
- Tractography can demonstrate Wallerian degeneration, in some cases more precisely than conventional MR techniques.
- Tractography can be used to monitor post treatment white matter tract reorganization.

Neoplasm

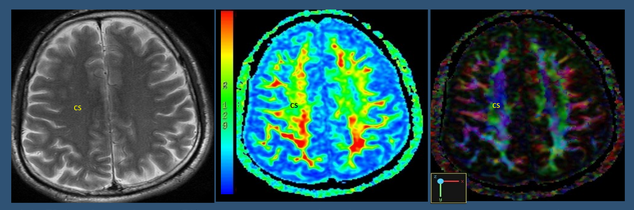
- DTI and tractography can demonstrate the involvement of white matter tracts by tumor, whether infiltrated, disrupted or displaced.
- DTI can better delineate the actual extent of certain tumors such as gliomas that may be underestimated with conventional MR.
- Increases in diffusivity surrounding tumors may help differentiate between peritumoral infiltration from peritumoral edema, for instance, vasogenic edema surrounding metastases.
- Tractography in conjunction with functional MRI (fMRI) is useful in determining the involvement and/or spatial relationship of tumor with respect to the white matter tracts and eloquent areas of the brain.
- DTI and tractography with or without fMRI can aid in preoperative planning and help predict postsurgical outcomes and potential morbidity, allowing for more informed decisions in patient management.

Demyelinating Disease (i.e. Multiple Sclerosis)

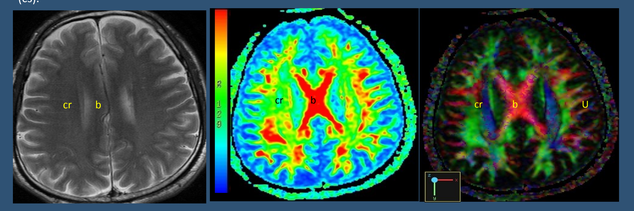
- Fractional anisotropy is more sensitive than mean diffusivity for detection of demyelinating lesions such as those of Multiple Sclerosis (MS).
- Abnormal diffusion in the corpus callosum may be the earliest imaging finding of MS, leading to early detection.
- DTI demonstrates findings that help characterize different types of MS, such as Relapsing-Remitting, Secondary-Progressive , and Primary-Progressive.
- Normal DTI does not exclude patients with early relapsing-remitting MS as they can demonstrate normal diffusivity.
- Mean diffusivity is higher in secondary-progressive MS than relapsing-remitting MS.
- While primary-progressive MS can demonstrate relatively few lesions on conventional MR sequences considering the severity of clinical symptoms, widespread albeit small diffusion and anisotropy abnormalities of the normal appearing white matter have been reported.
- Tractography has demonstrated that MS lesions can interrupt white matter fibers similarly to tumors.
- DTI and tractography may potentially differentiate between lesions which involve only myelin destruction or axonal injury and quantify the degree of axonal loss and/or demyelination.
- The correlation between the degree of corticospinal fiber tract loss and a supratentorial MS lesion load may permit quantification of axonal transection and Wallerian degeneration from MS lesions.

DTI and tractography can be used to more precisely to characterize normal development and aging, congenital anomalies, postsurgical/posttraumatic changes, psychiatric and neurodegenerative disorders as well.

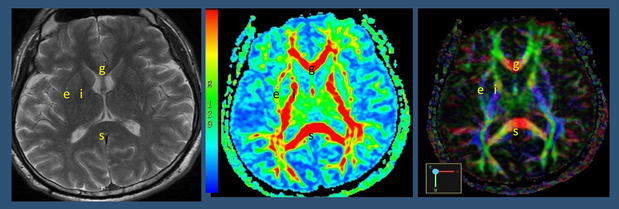
Normal anatomy and connectivity



Axial T2, functional anisotropy (FA) map, and structural orientation map at the level of the centrum semiovale (cs).



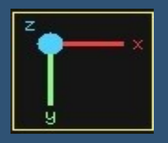
Axial T2, FA map, and structural orientation map at the level of the body of the corpus callosum (b), corona radiata (cr). and subcortical U fibers (U).



Axial T2, FA map, and structural orientation map at the level of the caudate and lentiform nuclei and the thalami. Note the internal and external capsules, denoted (i) and (e), respectively. Note the genu (g) and splenium (s) of the corpus callosum.

The fiber tracts have been classified into 3 groups based on their general course:

- **Commissural pathways** course horizontally and connect the two cerebral hemispheres.
- **Projection pathways** predominantly course dorsoventrally (descending pathways) or ventrodorsally (ascending pathways)
- **Association tracts** course longitudinally (anteroposteriorly or posteroanteriorly), connecting ipsilateral cortical gyri.



Limitations

- Diffusion tensor imaging characterizes the principal Eigenvector but lacks the angular resolution to characterize crossing fiber tracts well.
  - Imaging methods have been developed to overcome this limitation, such as diffusion spectrum imaging (DSI) and q ball imaging, but they take longer to acquire.
- Current DTI tractography algorithms can only estimate an approximation of the true course of the fiber tracts by interpolating the most probable course between adjacent voxels utilizing the directions of maximum diffusivity (maximum diffusion coherence).
- Current quantitative limitations of DTI tractography preclude accurate and precise measurement of the number of fibers within a given region of interest or tract.
- The lower fractional anisotropy within edematous brain parenchyma can prematurely interrupt the DTI tractography tracking algorithm, interrupting the fiber tract and overestimating the true margin of a pathological process, such as a tumor.
  - Lowering the threshold of fractional anisotropy can result in increased noise and erroneous tract elongation.
- User defined tract prolongation thresholds can limit reproducibility

Conclusion

DTI is a relatively new and exciting advanced magnetic resonance imaging technique that makes possible exquisite characterization of the white matter tracts of the brain as well as a broad spectrum of neuropathological processes. DTI and tractography are currently not broadly utilized, and there are technical limitations to overcome. However, this rapidly evolving technology is becoming more readily available, and its many adjunctive clinical imaging applications provide the radiologist and clinician with more precise insight into various neuropathophysiologic processes which may help better guide patient management.

References

- Hagmann P, Jonasson L, Maeder P, Thiran JP, Wedeen VJ, Meuli R. Understanding diffusion MR imaging techniques: from scalar diffusion-weighted imaging to diffusion tensor imaging and beyond. *Radiographics.* 2006 Oct;26 Suppl 1:S205-23.
- Nucifora PG, Verma R, Lee SK, Melhem ER. Diffusion-tensor MR imaging and tractography: exploring brain microstructure and connectivity. *Radiology.* 2007 Nov;245(2):367-84.
- Melhem ER, Mori S, Mukundan G, Kraut MA, Pomper MG, van Zijl PC. Diffusion tensor MR imaging of the brain and white matter tractography. *AJR Am J Roentgenol.* 2002 Jan;178(1):3-16.
- Huston JM, Field AS. Clinical applications of diffusion tensor imaging. *Magn Reson Imaging Clin N Am.* 2013 May;21(2):279-98.
- Stephen M. Hesseltine, MD; Yulin Ge, MD; Meng Law, MD, FRACR. Applications of diffusion tensor imaging and fiber tractography. *Applied Radiology.* 2007 May; Vol 36 Number 5. Retrieved from www.appliedradiology.com
- Schmahmann JD, Pandya DN. *Fiber Pathways of the Brain.* 2006. New York, NY: Oxford University Press.
- Catani M, Thiebaut de Schotten. *Atlas of Human Brain Connections.* 2012. New York, NY: Oxford University Press.
- Stieltjes B, Brunner RM, Fritzsche KH, and Frederik BL. *Diffusion Tensor Imaging and Atlas.* 2013. Berlin, Germany: Springer.

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