

Diffusion Tensor Imaging: A Step-by-Step Guide for Radiology and Neurology Clerkship Students, Residents, and Graduate Students Using Clinical Research Examples

Max J. Goodman^{1*}, Wesley T. Richerson², Dawn F. Wolfgram¹

¹Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

²Department of Biomedical Engineering, Marquette University and Medical College of Wisconsin, Milwaukee, WI, USA

*Corresponding Author: Max J. Goodman; mgoodman@mcw.edu

Diffusion-tensor imaging has become common practice in radiology and imaging research due to its many applications in brain connectivity and neurodevelopment as well as for pathologies including tumors, ischemia, trauma, and neurodegeneration. However, its novelty compared to other neuroimaging techniques has meant that graduate programs, particularly medical schools, have not included opportunities to learn how diffusion tensor imaging can visualize the brain and interpretation of the data clinically and in research. Diffusion tensor imaging can be a challenging utility to understand for newcomers and is subject to wide interpretation. We offer for medical and graduate students as well as residents a step-by-step guide in interpreting diffusion tensor imaging results for clinical analysis using simple explanations of physics and neuroscience and its application in clinical and translational research.

Keywords: magnetic resonance imaging; radial diffusivity; axial diffusivity; mean diffusivity; fractional anisotropy; radiology

INTRODUCTION

Diffusion-tensor imaging (DTI) is a non-invasive method that utilizes magnetic resonance imaging (MRI) technology to measure tissue water diffusion rates *in vivo* with high sensitivity and has useful neuroimaging applicability particularly in tumors, ischemia, trauma, neurodevelopment, and neurodegeneration. However, DTI can be challenging to understand for newcomers and is subject to wide interpretation. This paper will serve as a step-by-step way for medical and graduate students as well as residents to interpret DTI results for clinical analysis using simple explanations of physics and neuroscience as well as its application in clinical and translational research. However, note that DTI and MRI are utilized beyond neuroimaging and are applied to every subfield of radiology.

To understand DTI, it is important to first discuss what MRI is. MRI is a diagnostic tool used to noninvasively visualize soft tissue structures through their protonic orientation. Ordinarily in tissue, protons are spinning in a random orientation, but in an MRI the external magnetic field causes them to become parallel or antiparallel to each other.¹ Radiofrequency pulses are then applied which flip the protons and generate an image from the

energy it takes for protons to fall out of parallelism with each other and reach equilibrium. It is the variation of molecules that different tissues have which allow for MRI to distinguish anatomical and pathological features.

There are different sequences or types of MRI beyond DTI. The most common are T1-weighted, T2-weighted, fluid attenuated inversion recovery (Flair), proton density-weighted (PD), and diffusion-weighted (DWI). T1 is based on the rate it takes for protons to return to equilibrium, and T2 is based on the rate for protons to fall out of parallelism with each other.^{1,2} A short T1 means a fast recovery to equilibrium which produces a strong or bright signal whereas a short T2 means a rapid decay which produces a weak or dark signal.³ For example, cerebrospinal fluid (CSF) contains protons relatively far apart from each other and hence fewer interactions compared to fat, which allows for a longer time until equilibrium and hence a dark T1 but also a slower decay from parallelism and therefore a bright T2. T1 is generally utilized to assess morphology which includes anatomy, which is why it is also referred to as an anatomical sequence, as well as edema and fibrosis; T2 is more helpful to visualize edema and inflammation.⁴ Flair is T2 but fluid is attenuated, allowing regions of tissue close to fluid to be more

carefully visualized, such as the periventricular area.⁵ PD is when T1 and T2 are attenuated such that signal is produced based on the density of protons in tissue and is most frequently utilized for meniscal tears.^{6,7}

Diffusion-weighted is different from other MRI sequences in that it is designed to visualize water diffusion.^{1,8,9} Water has a unique diffusion pattern and rate depending on the cellular and tissue architecture.^{8,9} For example, intracellular water will interact with structures such as the cytoskeleton, enzyme complexes, and organelles whereas extracellular water will interact with proteins in the extracellular matrix as well as different orientations of cells. Since these cellular and tissue architectural properties can change with alterations in tissue integrity due to the injury-repair response, DWI can be utilized for evaluating damage to components of brain structure, even before abnormalities are illustrated on anatomical MRI.^{1,8} DTI is DWI but includes the mathematical models applied to DWI which provide a quantitative interpretation that DWI does not provide.

We can estimate cellularity and white matter microstructural organization based on DTI properties such as the degree of restricted diffusion or fractional anisotropy (FA), molecular diffusion rate or mean diffusivity (MD or apparent diffusion coefficient [ADC]), the diffusion rate along the main axis of diffusion known as axial diffusivity (AD or λ_{\parallel}), and the diffusion rate perpendicular to the main axis known as radial diffusivity (RD or λ_{\perp}).^{10,11} These metrics are most commonly used for relating diffusion to an underlying pathophysiology of white matter and are calculated based on eigenvalues in a DTI model as seen in Figure 1. Eigenvalues explain how spread-out data is in a given direction, and in this case, eigenvalues describe the diffusion properties of water on a 3D grid, or tensor, of tissue in each unit (known as a voxel) of an MRI image of the brain.¹² There are other variables including trace, relative anisotropy and more, though their applicability is limited currently. Understanding these main terms' definitions and impressions is crucial towards understanding DTI (Table 1).

DTI TERMINOLOGY

Fractional Anisotropy

Fractional anisotropy is measured from 0 to 1, with 0 being isotropic or the completely unrestricted diffusion of water that moves in any random direction, and 1 being anisotropic or the completely restricted diffusion of water in roughly one direction.¹¹ CSF is likely to have an FA closer to 0 (or isotropy) than grey or white matter

Voxel of an axon

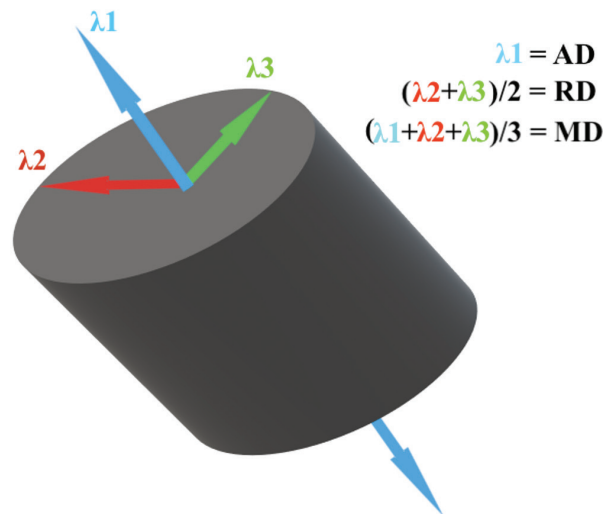


Figure 1. Eigenvalues and diffusion measures of a voxel of an axon. This schematic characterizes the eigenvalues of a tensor and how three of the most common diffusion measures are calculated.

of the brain for this reason, with white matter having a higher FA than grey matter.^{13–15} White matter is mainly composed of axons and its myelin from oligodendrocytes that form tracts such as the cortico-spinal tract or the corpus callosum (CC). Axons are assumed to be tubular and unidirectional structures of neurons encased by myelin that restrict the movement of molecules into or out of the axon which therefore establishes anisotropy. Grey matter, on the other hand, consists of neuronal cell bodies and their dendrites, as well as unmyelinated axonal terminals that interact with one of the 1,000 synapses every neuron has on average, which allow for a greater possibility of directions for diffusion of water molecules.¹⁶ This makes the grey matter FA less than that of white matter. However, not all white matter regions are created equal; the genu of the CC has a higher FA than other white matter tracts due to the highly organized fiber tracts within the CC.¹⁴ A decrease in FA often is interpreted to mean either axonal or myelin degeneration; how to distinguish between these two possibilities requires further data.^{15,17} This is because a reason for decreased FA may be due to an increase in RD or a decrease in AD and will be discussed later.¹⁸

Mean Diffusivity

Mean diffusivity is an average of three eigenvalues (λ_1 , λ_2 , and λ_3), or the magnitude of diffusion across the

3D-axes.¹¹ The sum of the magnitude of the three eigenvalues is the trace, so other papers may describe MD as trace/3. It can be generalized then that a low MD corresponds to low diffusivity and high MD high diffusivity. White matter and grey matter generally have similar MD, and CSF has higher MD than either type of brain matter.¹³ While MD cannot be used to differentiate brain matters, it is sensitive to changes to the diffusion of water. Typically, if MD is higher than normal then it may reflect damage such as cytolysis as diffusion is less restricted.^{15,19} Such damage may be from the loss of integrity of fiber tracts or myelin damage.^{13,20} Cytotoxic edema, which can be from a redistribution of water extracellularly to intracellularly, would reduce cell-mediated water transport and therefore reduce MD.^{21,22} Changes such as greater myelination or axonal packing would reduce MD, while demyelination, axonal degeneration, and increases in CSF or vasogenic edema increase MD.^{13,15,20,22} Like FA, additional information is needed to interpret MD.

Axial Diffusivity

Axial diffusivity (AD or λ_1) is important for delineating between grey and white matter and for estimating changes to white matter specifically.¹¹ Because AD is assumed to be the parallel diffusion of water relative to a

tract, AD is very low in grey matter and much higher in white matter.²³ However, AD is more sensitive to white matter maturation and similarly axonal degeneration than it is to the tissue's myelination; in fact, having elevated or lower myelination does not change AD.²⁴ Barriers to the diffusion of water down the axon such as cellular debris and protein aggregation (ex. amyloidosis) would decrease AD.²⁵ On the contrary, having more neurofilaments which increase the axon's diameter and therefore the axonal caliber would enhance AD.^{24,26,27} Axonal packing (increased neurofilaments) is complicated by the changes in axonal diameters as well as myelination, so an absolute change in axonal packing may or may not be reflected in AD.^{15,26} Additionally, AD is positively correlated with CSF and cytotoxic edema which would increase the axon's diameter and mimic neurofilament assembly, and so changes to AD may reflect extracellular and intracellular alterations.¹⁵ A specific utilization of AD is in Wallerian degeneration; that is depicted by a decrease in FA and AD with an increase in RD (described subsequently) without a change in MD.²⁸ Generally, the interpretation for AD then is a marker of axonal injury, independent of myelination, but interpretation of changes in AD needs to be in the context of other conditions related to the intracellular and extracellular environments.

Table 1. This schematic depicts how changes in tissue integrity and architecture influence DTI measurements.

	FA	MD ($I_1+I_2+I_3$)/3	AD I_1	RD (I_2+I_3)/2
	FA is a summary measure of microstructural integrity. While FA is highly sensitive to microstructural changes, it is less specific to the type of change.	MD is an inverse measure of the membrane density, is very similar for both GM and WM and higher for CSF. MD is sensitive to cellularity, edema, and necrosis.	AD tends to be variable in WM changes and pathology. In axonal injury AD decreases. The ADs of WM tracts have been reported to increase with brain maturation.	RD increases in WM with de- or dysmyelination. Changes in the axonal diameters or density may also influence RD.
Gray Matter	↓	-	↓	↑
White Matter	↑	-	↑	↓
CSF	↓	↑	↑	↑
High myelination	↑	↓	-	↓
Dense axonal packing	↑	↓	-	↓
WM Maturation	↑	↓	↑	↓
Axonal degeneration	↓	↑	↓	↑
Demyelination	↓	↑	-	↑
Low SNR	↓	↑	↓	-

Source: From Tromp.¹⁵



Radial Diffusivity

Radial diffusivity [RD or $(\lambda_2 + \lambda_3)/2$] can also separate grey from white matter and is useful for estimating changes to white matter though more specifically in regards to myelin.¹¹ Opposite of AD, RD is very low in white matter and higher in grey matter because it measures diffusion of water perpendicular to λ_1 rather than parallel.^{23,27} One useful item, however, is that RD is also positively related to CSF and edema like AD, thus it is within reason that RD and AD both simultaneously increase if cytotoxic edema is occurring.²⁹ However, note that RD and AD can be age-related and increase simultaneously because of both myelin and axon loss.³⁰ One way to distinguish age-related white matter changes from edema is that RD is more sensitive to aging than AD, so a relatively equal change in both AD and RD is likely edema.³¹ Additionally, RD is more closely related to myelination than it is to axonal injury. Studies found that dysmyelinated shiverer mutant mice had increased RD but AD remained unchanged; demyelination also increases RD.^{32,33} Note that large enough axonal edema and inflammation may reduce water diffusivity after a period of time which would cause RD values to remain unchanged.²³ Therefore, analyzing RD either too early or too late may miss important data for the interpretation of myelin and oligodendrocyte cellularity.

APPLICATIONS OF DTI IN EVALUATING NEUROLOGICAL DISORDERS

While DTI has enormous potential for interpreting a macroscopic level of cellularity within white matter pathways, it is evident that other information is currently needed to make valid interpretations of its results that include but are not limited to pathophysiology, histology, anatomic neuroimaging, neuroanatomy, and careful consideration of the subject's clinical history. For example, important but often unappreciated clinical factors including elevated blood pressure and obesity appear to affect FA and AD respectively.³⁴ Basic neuroanatomy and neuroscience must also be utilized. A region of the hippocampus such as the dentate gyrus may entirely differ from the primary cornu ammonis in terms of cell density and cell type and therefore influences DTI data.³⁵

When understanding DTI and neuroimaging as it relates to aging, it is also important to analyze the changes in FA from posterior to anterior. Reports have observed a 'last in, first out,' meaning the last parts of

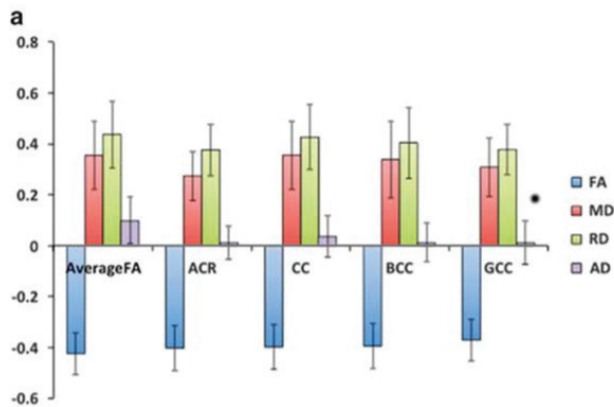
the brain to mature, such as the prefrontal lobe, are the first to degenerate in normal aging.^{36,37} FA is often higher in the posterior relative to the anterior. This concept is important because a lower FA in the posterior portion of the brain in an older adult relative to the prefrontal cortex of the brain, for example, may underlie a pathology such as Alzheimer's disease or Lewy body dementia.³⁶

Different regions also decline differently in normal aging,³⁸ though an overall global perspective should be taken as well to label either axonal injury or demyelination. In fact, one way of distinguishing between axonal injury from demyelination in either an acute or gradual pathophysiological process is to analyze whether or not the FA values are uniformly decreased globally within a tract or focally. Entire tracts of abnormally low FA signify axonal injury as the whole axon is dysfunctional, with focal differences owing to demyelination as each myelin sheath covers only a fraction of the axon. Readers of DTI literature should be cautioned in cases where researchers or clinicians are studying specific regions of interest (ROIs) and attempting to attribute it to either axonal injury or demyelination, as the results may only convey a small portion of information.

Clinical Research Examples: Schizophrenia

Our first example is from a 2018 study by Kelly et al,³⁹ where researchers from the Schizophrenia Working Group of the Enhancing Neuroimaging Genetics through Meta-Analysis consortium (ENIGMA-Schizophrenia) attempted to investigate white matter differences between 1963 adult subjects with schizophrenia and 2,359 healthy adult controls across the globe using DTI in a meta-analysis. As shown in Figure 2, the magnitude of the differences between the two groups in regards to FA, MD, AD, and RD through a post hoc analysis is described using Cohen's *d* effect size estimates and covariates including age, sex, and their interactions were accounted for. Across the average DTI measurement values and specifically in the anterior corona radiata (ACR), CC, body of corpus callosum (BCC), and genu of corpus callosum (GCC), FA was found to be lower in schizophrenia subjects than healthy controls, though MD and RD were higher ($p < 0.002$). AD was no different between schizophrenia subjects and healthy controls.

Numerous studies have suggested that a dysfunction in myelination due to an altered oligodendrocyte genotype contributes to schizophrenia.⁴⁰⁻⁴³ Myelin



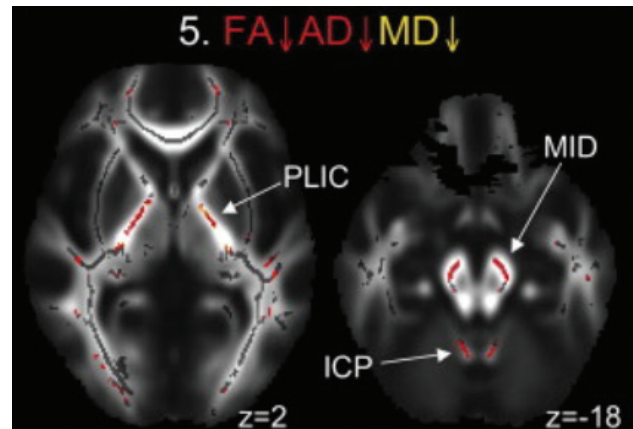
Source: Figure from Kelly et al³⁹

Figure 2. (a) Cohen's *d* effect sizes, after meta-analysis, for FA, MD and RD differences in schizophrenia patients versus healthy controls, after including age, sex, age × sex, age² and age² × sex as covariates for the top four ROIs showing the largest FA effects (average FA, BCC, CC, ACR and GCC). Error bars represent the 95% confidence intervals. The CC, ACR, and FA across the whole brain are among the measures that show most robust effects in cohorts worldwide.

dysfunction is reported in subcortical white matter tracts of the prefrontal cortex in schizophrenia patients post-mortem.⁴⁰ In a DTI study, schizophrenia patients had low FA, high MD, high RD, and no difference in AD values in the ACR of the prefrontal cortex as well as the CC compared to controls that may be related to altered motor behavior.^{39,44,45} So at first glance, the low FA and high MD from 2018 Kelly et al can signify axonal damage, demyelination, or edema. AD is unchanged, so axonal injury or edema is unlikely, which only leaves demyelination which is consistent with the RD value and histological data. This exact relationship has been found in patients with white matter hyperintensities experiencing cognitive impairment, where researchers also concluded it was consistent with demyelination.⁴⁶

Clinical Research Examples: White Tract Variations

The second example is a study by Burzynska et al, in 2010 who compared DTI data from 63 healthy adults in their seventh decade of life from 80 other healthy adults in their third decade to discover whether or not there exists age-related DTI measurement variations using tract-based spatial statistics.³⁸ Figure 3 illustrates lower FA, AD, and MD values in older patients compared to younger patients in the posterior limb of the internal capsule, inferior cerebellar peduncles, and midbrain white matter ($p < 0.01$, 2-tailed).



Source: Figure from Burzynska et al³⁸

Figure 3. Patterns of age-related differences in diffusivity parameters. Within voxels showing a significant age-related reduction in FA (in blue, $p < 0.01$, 2-tailed), we distinguished five patterns (in red, $p < 0.01$, 2-tailed) ... (5) decreases in AD... showed additional increase in AD and a decrease in MD, respectively, are overlaid in orange. PLIC: posterior limb of the internal capsule; MID: midbrain WM; ICP: inferior cerebellar peduncle. The numbers indicate the z-axis coordinate in MNI152 space (mm).

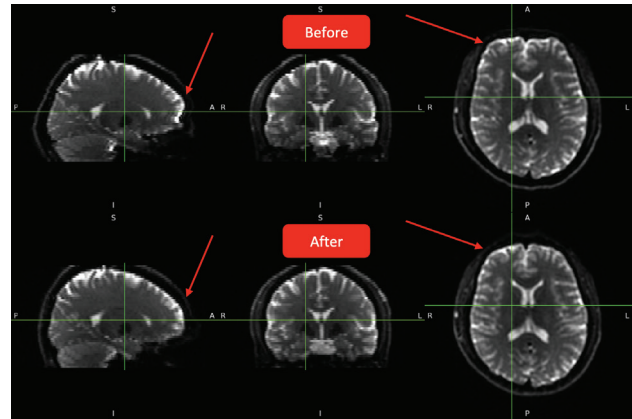
While this was one of only five patterns found in this investigation, we will be focusing on the aforementioned pattern for purposes of education. A low FA can mean either axonal or myelin degeneration, but that is generally accompanied by a high MD, which is not found in this case. Wallerian degeneration does not fit this pattern as described earlier. If gradual and chronic enough, cytotoxic edema or inflammation could be why RD was insignificantly impacted, but AD would have been higher. A low MD signifies low diffusivity, so while there may be axonal or myelin injury, it is possible that gliosis, a creation of more or larger glial cells, is occurring as a reaction to injury. Gliosis and resulting glial scars would also inhibit axon regeneration which may explain the low AD. RD is unchanged since gliosis is largely related to a hypertrophy of astrocytes and microglia, with little net change in oligodendrocytes and hence myelin. The discrepancy between the FA and MD in the study by Burzynska et al was thought to be due to gliosis.³⁸ One study found that gliosis could not be concluded based on AD and RD, though that investigation was done with a small sample size *ex vivo* in subjects with cerebral amyloid angiopathy without known postmortem interval and was largely exploratory and subject to false-positives.⁴⁷ Though this example leads us to conclude

gliosis, aging is subject to decreased white matter, demyelination, and axonal loss that can appear as unique DTI patterns regionally, which Burzynska et al describe in their investigation.³⁸

Clinical Research Examples: Infarcts

In our final example, an investigation by Zhao et al, in 2019 investigated differences with a Student's *t*-test between subjects with leukoaraiosis (LA) and lacunar infarct subjects from two hospitals in China using subjects' DTI scans.⁴⁸ Lacunar infarct subjects had DTI values of (FA: 0.35 ± 0.03 , MD: 0.40 ± 0.05) and LA subjects corresponded to (FA: 0.32 ± 0.02 , MD: 1.08 ± 0.03) in normal appearing white matter, with a statistically significant difference between the two groups ($p < 0.05$).

This example is a nuanced example as it requires the attempt to distinguish a white matter hyperintensity as either LA or an acute lacunar infarction. Not only do they have a similar pathological basis owing to small-vessel disease and being age related, but also patients with acute lacunar infarcts are often predisposed to LA.⁴⁹⁻⁵¹ Symptoms of the stroke can assist physicians in identifying the specific white matter abnormality as a lacunar infarct from the other lesions associated with LA, but a lacunar infarct can be silent as well.^{50,52} Additionally, a more sudden, local symptom such as dysarthria is more attributable to a lacunar infarct than LA, which has been related to gradual cognitive decline.^{52,53} In this final DTI example study, it was found that patients with acute lacunar infarcts had higher FA and lower MD than LA patients.⁴⁸ The reason regarding the lower MD in the infarct was that the cytotoxic edema that occurred acutely decreased the ability for water diffusion, but over time MD would be increased once the edema is resolved. While ischemic injury may be thought to increase cellular damage and thus increase MD, this is dependent on the phase of injury and whether edema is present or not. A lower FA as seen in LA subjects may be two reasons: (1) because damage to white matter tracts typically reduces FA and (2) because LA lesions are in close proximity to the lateral ventricles, which contain elevated quantities of CSF. These FA and MD relative values are also subject to change depending on the condition of the stroke. A higher FA and lower MD like in this example are noted in the acute phase but may normalize during the subacute phase before MD increases and FA decreases once chronic, as indicative of structural disorganization.⁴⁸ A chronic lesion would be the same intensity to CSF, as Gore, Bansal, and Asuncion



Source: Images courtesy of Tugan Muftuler, PhD.

Figure 4. Before and after distortion correction caused by tissue susceptibility variations. Effect is most notable in the frontal lobe.

described.⁵³ This example should promote a well-rounded view for how to make an impression of DTI results.

Limitations

There are a number of limitations both to the interpretation of DTI and to DTI itself. Data may be distorted if not properly processed, an example of which is illustrated in Figure 4. This can be said for motion correction, as it is natural for the patient to shift during the image acquisition.^{11,54} Beyond background noise, which can be controlled via smoothing the dataset, eddy currents are natural opposing diffusion gradients and artifacts that can skew the voxels, known as shearing, or change the size of the brain volumes, which is called scaling.^{11,55} To view motion and eddy currents, they can only be illustrated in video and are available in the citation.⁵⁶ Any DTI software should be researched to ensure that the eddy currents are corrected for; specific MR hardware is also capable of correcting for eddy currents. Ghosting is also a type of noise that makes repeated versions of parts of the brain in the image and reduces proper visualization; if the percent signal ghosting is greater than 3% then it may obstruct the image.⁵⁷ Ghosting can be due to patient motion, blood flow, and other respiratory and cardiac effects that if understood may be helpful for not only controlling for those factors but in interpreting the data afterwards. Fortunately, ghosting is now corrected by a majority of modern scanners and is rarely seen anymore, though an example can be found in the citation.⁵⁸

In research and clinical interpretation, a comprehensive understanding of the patient cohort data and pathology is challenging but necessary as the influences of the DTI output are multifactorial. Partial volume effects from studying in an area of both white matter and grey matter can make the interpretation of results very uncertain and very challenging.^{11,59} A heterogeneity of different fiber types within the same voxel can be minimized though using multi-tensor models that Soares, Marques, Alves, Sousa explain in their 2013 article.¹⁹ Because partial volume effects can create a confounding bias in DTI measures, not taking partial volume effects into account can be devastating for valid impressions. Ozturk et al in 2008 cited partial volume effects as a potential reason for the high variability in DTI measurements found in deep white matter structures.⁶⁰ As for tissue architecture, crossing fibers with different directions would be expected to decrease FA, not due to either myelin or axonal cellularity. With 45–90% of white matter voxels containing a crossing fiber, it further reinforces the idea that other tools or modifications are needed to interpret DTI results.^{61,62} For example, utilizing high-angular resolution diffusion imaging can measure an orientation distribution function and create a version of FA known as generalized FA that is more geared towards fiber crossings.⁶³ Finally, the most challenging dynamic to overcome is that complex diseases may demonstrate demyelination, axonal damage, and inflammation simultaneously. Currently, the solutions again are using DTI in conjunction with other medical tools along with a robust clinical understanding.

CONCLUSION

DTI is an essential tool towards diagnosis and understanding pathology in white matter. Its ability to estimate minute structural properties has made for a vast application both in research and clinically, though interpretation may be complicated and limited in some instances. This literature review has offered through basic scientific concepts guidance for not only medical students but also members across educational backgrounds to better enable them to make fair DTI inferences in clinical research. Because DTI is now an established tool in medicine and research, medical students, graduate students, and residents may need to become more familiar with DTI as its use widens.

Conflict of interest and funding

The authors have not received any funding or benefits from industry or elsewhere to conduct this study.

REFERENCES

1. Serai SD. Basics of magnetic resonance imaging and quantitative parameters T1, T2, T2*, T1rho and diffusion-weighted imaging. *Pediatr Radiol* 2022; 52(2): 217–27. doi: 10.1007/s00247-021-05042-7
2. Elster AD. An index system for comparative parameter weighting in MR imaging. *J Comput Assist Tomogr* 1988; 12(1): 130–134. doi:10.1097/00004728-198801000-00025
3. Young IR, Szeverenyi NM, Du J, Bydder GM. Pulse sequences as tissue property filters (TP-filters): a way of understanding the signal, contrast and weighting of magnetic resonance images. *Quant Imaging Med Surg* 2020; 10(5): 1080–120. doi: 10.21037/qims.2020.04.07
4. Dekkers IA, Lamb HJ. Clinical application and technical considerations of T1 & T2(*) mapping in cardiac, liver, and renal imaging. *Br J Radiol* 2018; 91(1092): 20170825. doi: 10.1259/bjr.20170825
5. Kates R, Atkinson D, Brant-Zawadzki M. Fluid-attenuated inversion recovery (FLAIR): clinical prospectus of current and future applications. *Top Magn Reson Imaging* 1996; 8(6): 389–96.
6. Farshad-Amacker NA, Jain Palrecha S, Farshad M. The primer for sports medicine professionals on imaging. *Sports Health* 2013; 5(1): 50–77. doi: 10.1177/1941738112468265
7. Sano T, Widmalm SE, Yamamoto M, Sakuma K, Araki K, Matsuda Y, et al. Usefulness of proton density and T2-weighted vs. T1-weighted MRI in diagnoses of TMJ disk status. *Cranio*. 2003; 21(4): 253–8. doi: 10.1080/08869634.2003.11746259
8. Huisman TAGM. Diffusion-weighted and diffusion tensor imaging of the brain, made easy. *Cancer Imaging* 2010; 10(1A): S163–71. doi: 10.1102/1470-7330.2010.9023
9. Winston GP. The physical and biological basis of quantitative parameters derived from diffusion MRI. *Quant Imaging Med Surg* 2012; 2(4): 254–65. doi: 10.3978/j.issn.2223-4292.2012.12.05
10. Alexander AL, Hurley SA, Samsonov AA, Adluru N, Hosseinbor AP, Mossahebi P, et al. Characterization of cerebral white matter properties using quantitative magnetic resonance imaging stains. *Brain Connect* 2011; 1(6): 423–46. doi: 10.1089/brain.2011.0071
11. Rajagopalan V, Jiang Z, Stojanovic-Radic J, Yue GH, Pioro EP, Wylie GR, et al. A basic introduction to diffusion tensor imaging mathematics and image processing steps. *Brain Disord Ther* 2017; 6: 2. doi: 10.4172/2168-975X.1000229
12. Basser PJ. Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. *NMR Biomed* 1995; 8(7–8): 333–44. doi: 10.1002/nbm.1940080707

- 13.** Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G. Diffusion tensor MR imaging of the human brain. *Radiology* 1996; 201(3): 637–48. doi: 10.1148/radiology.201.3.8939209
- 14.** Mädler B, Drabycz SA, Kolind SH, Whittall KP, MacKay AL. Is diffusion anisotropy an accurate monitor of myelination? Correlation of multicomponent T2 relaxation and diffusion tensor anisotropy in human brain. *Magn Reson Imaging* 2008; 26(7): 874–88. doi: 10.1016/j.mri.2008.01.047
- 15.** Tromp D. DTI scalars (FA, MD, AD, RD) – how do they relate to brain structure? *The Winnower*; 2016.
- 16.** Hawkins J, Ahmad S. Why neurons have thousands of synapses, a theory of sequence memory in Neocortex. *Front Neural Circuits* 2016; 10: 23. doi: 10.3389/fncir.2016.00023
- 17.** Beaulieu C, Allen PS. Determinants of anisotropic water diffusion in nerves. *Magn Reson Med* 1994; 31(4): 394–400. doi: 10.1002/mrm.1910310408
- 18.** Boretius S, Escher A, Dallenga T, Wrzos C, Tammer R, Brück W, et al. Assessment of lesion pathology in a new animal model of MS by multiparametric MRI and DTI. *Neuroimage* 2012; 59(3): 2678–88. doi: 10.1016/j.neuroimage.2011.08.051
- 19.** Soares JM, Marques P, Alves V, Sousa N. A hitchhiker's guide to diffusion tensor imaging. *Front Neurosci* 2013; 7: 31. doi: 10.3389/fnins.2013.00031
- 20.** Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage* 2003; 20(3): 1714–22. doi: 10.1016/j.neuroimage.2003.07.005
- 21.** Field AS, Hasan K, Jellison BJ, Arfanakis K, Alexander AL. Diffusion tensor imaging in an infant with traumatic brain swelling. *AJNR Am J Neuroradiol* 2003; 24(7): 1461–64.
- 22.** Schaefer PW, Buonanno FS, Gonzalez RG, Schwamm LH. Diffusion-weighted imaging discriminates between cytotoxic and vasogenic edema in a patient with eclampsia. *Stroke* 1997; 28(5): 1082–5. doi: 10.1161/01.str.28.5.1082
- 23.** Winklewski PJ, Sabisz A, Naumczyk P, Jodzio K, Szurowska E, Szarmach A. Understanding the physiopathology behind axial and radial diffusivity changes-what do we know? *Front Neurol* 2018; 9: 92. doi: 10.3389/fneur.2018.00092
- 24.** Budde MD, Xie M, Cross AH, Song SK. Axial diffusivity is the primary correlate of axonal injury in the experimental autoimmune encephalomyelitis spinal cord: a quantitative pixelwise analysis. *J Neurosci* 2009; 29(9): 2805–13. doi: 10.1523/JNEUROSCI.4605-08.2009
- 25.** Dijkhuizen RM, de Graaf RA, Tulleken KA, Nicolay K. Changes in the diffusion of water and intracellular metabolites after excitotoxic injury and global ischemia in neonatal rat brain. *J Cereb Blood Flow Metab* 1999; 19(3): 341–9. doi: 10.1097/00004647-199903000-00012
- 26.** Feldman HM, Yeatman JD, Lee ES, Barde LHF, Gaman-Bean S. Diffusion tensor imaging: a review for pediatric researchers and clinicians. *J Dev Behav Pediatr* 2010; 31(4): 346–56. doi: 10.1097/DBP.0b013e3181dca8b
- 27.** Aung WY, Mar S, Benzinger TL. Diffusion tensor MRI as a biomarker in axonal and myelin damage. *Imaging Med* 2013; 5(5): 427–40. doi: 10.2217/iim.13.49
- 28.** O'Dwyer L, Lambertson F, Bokde ALW, Ewers M, Faluyi YO, Tanner C, et al. Multiple indices of diffusion identifies white matter damage in mild cognitive impairment and Alzheimer's disease. *PLoS One* 2011; 6(6): e21745. doi: 10.1371/journal.pone.0021745
- 29.** Kim JH, Loy DN, Liang HF, Trinkaus K, Schmidt RE, Song SK. Noninvasive diffusion tensor imaging of evolving white matter pathology in a mouse model of acute spinal cord injury. *Magn Reson Med* 2007; 58(2): 253–60. doi: 10.1002/mrm.21316
- 30.** Madden DJ, Bennett IJ, Burzynska A, Potter GG, Chen NK, Song AW. Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. *Biochim Biophys Acta* 2012; 1822(3): 386–400. doi: 10.1016/j.bbadis.2011.08.003
- 31.** Davis SW, Dennis NA, Buchler NG, White LE, Madden DJ, Cabeza R. Assessing the effects of age on long white matter tracts using diffusion tensor tractography. *Neuroimage* 2009; 46(2): 530–41. doi: 10.1016/j.neuroimage.2009.01.068
- 32.** Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage* 2002; 17(3): 1429–36. doi: 10.1006/nimg.2002.1267
- 33.** Song SK, Yoshino J, Le TQ, Lin SJ, Sun SW, Cross AH, et al. Demyelination increases radial diffusivity in corpus callosum of mouse brain. *Neuroimage* 2005; 26(1): 132–40. doi: 10.1016/j.neuroimage.2005.01.028
- 34.** Allen B, Muldoon MF, Gianaros PJ, Jennings JR. Higher blood pressure partially links greater adiposity to reduced brain white matter integrity. *Am J Hypertens* 2016; 29(9): 1029–37. doi: 10.1093/ajh/hpw026
- 35.** Stolp HB, Ball G, So PW, Tournier J-D, Jones M, Thornton C, et al. Voxel-wise comparisons of cellular microstructure and diffusion-MRI in mouse hippocampus using 3D Bridging of Optically-clear histology with Neuroimaging Data (3D-BOND). *Sci Rep* 2018; 8(1): 4011. doi: 10.1038/s41598-018-22295-9
- 36.** Douaud G, Groves AR, Tamnes CK, Westlye LT, Duff EP, Engvig A, et al. A common brain network links development, aging, and vulnerability to disease. *Proc Natl Acad Sci* 2014; 111(49): 17648–53. doi: 10.1073/pnas.1410378111
- 37.** Bender AR, Völkle MC, Raz N. Differential aging of cerebral white matter in middle-aged and older adults: a seven-year follow-up. *Neuroimage* 2016; 125: 74–83. doi: 10.1016/j.neuroimage.2015.10.030
- 38.** Burzynska AZ, Preuschhof C, Bäckman L, Nyberg L, Li SC, Lindenberger U, et al. Age-related differences in white matter microstructure: region-specific patterns of diffusivity. *Neuroimage* 2010; 49(3): 2104–12. doi: 10.1016/j.neuroimage.2009.09.041
- 39.** Kelly S, Jahanshad N, Zalesky A, Kochunov P, Agartz I, Alloza C, et al. Widespread white matter microstructural differences in schizophrenia across 4322 individuals: results from the ENIGMA Schizophrenia DTI Working Group. *Mol Psychiatry* 2018; 23(5): 1261–9. doi: 10.1038/mp.2017.170
- 40.** Flynn SW, Lang DJ, Mackay AL, Goghari V, Vavasour IM, Whittall KP, et al. Abnormalities of myelination in schizophrenia detected in vivo with MRI, and post-mortem

- with analysis of oligodendrocyte proteins. *Mol Psychiatry* 2003; 8(9): 811–20. doi: 10.1038/sj.mp.4001337
- 41.** Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophr Res* 2004; 67(2–3): 269–75. doi: 10.1016/S0920-9964(03)00181-6
- 42.** Mitkus SN, Hyde TM, Vakkalanka R, Kolachana B, Weinberger DR, Kleinman JE, et al. Expression of oligodendrocyte-associated genes in dorsolateral prefrontal cortex of patients with schizophrenia. *Schizophr Res* 2008; 98(1–3): 129–38. doi: 10.1016/j.schres.2007.09.032
- 43.** Alba-Ferrara LM, de Erausquin GA. What does anisotropy measure? Insights from increased and decreased anisotropy in selective fiber tracts in schizophrenia. *Front Integr Neurosci* 2013; 7: 9. doi: 10.3389/fnint.2013.00009
- 44.** Clark KA, Nuechterlein KH, Asarnow RF, Hamilton LS, Phillips OR, Hageman NS, et al. Mean diffusivity and fractional anisotropy as indicators of disease and genetic liability to schizophrenia. *J Psychiatr Res* 2011; 45(7): 980–8. doi: 10.1016/j.jpsychires.2011.01.006
- 45.** Walther S, Federspiel A, Horn H, Razavi N, Wiest R, Dierks T, et al. Alterations of white matter integrity related to motor activity in schizophrenia. *Neurobiol Dis* 2011; 42(3): 276–83. doi: 10.1016/j.nbd.2011.01.017
- 46.** Min ZG, Shan HR, Xu L, Yuan DH, Sheng XX, Xie WC, et al. Diffusion tensor imaging revealed different pathological processes of white matter hyperintensities. *BMC Neurol* 2021; 21(1): 128. doi: 10.1186/s12883-021-02140-9
- 47.** van Veluw SJ, Reijmer YD, van der Kouwe AJ, Charidimou A, Riley GA, Leemans A, et al. Histopathology of diffusion imaging abnormalities in cerebral amyloid angiopathy. *Neurology* 2019; 92(9): e933–43. doi: 10.1212/WNL.00000000000007005
- 48.** Zhao D, Wang Z, Cheng Y, Yuan Z, Rene F, Liu H, et al. A DTI study of leukoaraiosis and the differential diagnosis between leukoaraiosis and acute lacunar infarction. *CNS Neurosci Ther* 2019; 25(9): 1064–7. doi: 10.1111/cns.13191
- 49.** Miyao S, Takano A, Teramoto J, Takahashi A. Leukoaraiosis in relation to prognosis for patients with lacunar infarction. *Stroke* 1992; 23(10): 1434–8. doi: 10.1161/01.str.23.10.1434
- 50.** Wardlaw JM. What causes lacunar stroke? *J Neurol Neurosurg Psychiatry* 2005; 76(5): 617–9. doi: 10.1136/jnnp.2004.039982
- 51.** Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson Ó, et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility – Reykjavik study. *Brain* 2011; 134(Pt 11): 3398–407. doi: 10.1093/brain/awr253
- 52.** Te M, Zhao E, Zheng X, Sun Q, Qu C. Leukoaraiosis with mild cognitive impairment. *Neurol Res* 2015; 37(5): 410–14. doi: 10.1179/1743132815Y.0000000028
- 53.** Gore M, Bansal K, Khan Suheb MZ, Asuncion RMD. Lacunar stroke. StatPearls Publishing; 2022. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK563216/> [cited 27 February 2023].
- 54.** Baum GL, Roalf DR, Cook PA, Ciric R, Rosen AFG, Xia C, et al. The impact of in-scanner head motion on structural connectivity derived from diffusion MRI. *Neuroimage* 2018; 173: 275–86. doi: 10.1016/j.neuroimage.2018.02.041
- 55.** Leemans A, Jones DK. The B-matrix must be rotated when correcting for subject motion in DTI data. *Magn Reson Med* 2009; 61(6): 1336–49. doi: 10.1002/mrm.21890
- 56.** eddy – a tool for correcting eddy currents and movements in diffusion data. FSL. Available from: <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/eddy> [cited 4 March 2023].
- 57.** Phantom test guidance for use of the large MRI phantom for the ACR accreditation program. 2018. Available from: <https://www.acraccreditation.org/-/media/acraccrreditation/documents/mri/largephantomguidance.pdf> [cited 4 March 2023].
- 58.** Nyquist (N/2) ghosts. Questions and answers in MRI. Available from: <http://mriquestions.com/nyquist-n2-ghosts.html> [cited 4 March 2023].
- 59.** Alexander AL, Hasan KM, Lazar M, Tsuruda JS, Parker DL. Analysis of partial volume effects in diffusion-tensor MRI. *Magn Reson Med* 2001; 45(5): 770–80. doi: 10.1002/mrm.1105
- 60.** Ozturk A, Sasson AD, Farrell JA, Landman BA, da Motta AC, Aralasmak A, et al. Regional differences in diffusion tensor imaging measurements: assessment of intrarater and interrater variability. *AJNR Am J Neuroradiol* 2008; 29(6): 1124–7. doi: 10.3174/ajnr.A0998
- 61.** Jeurissen B, Leemans A, Tournier JD, Jones DK, Sijbers J. Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. *Hum Brain Mapp* 2013; 34(11): 2747–66. doi: 10.1002/hbm.22099
- 62.** Sarwar T, Ramamohanarao K, Zalesky A. Mapping connectomes with diffusion MRI: deterministic or probabilistic tractography? *Magn Reson Med* 2019; 81(2): 1368–84. doi: 10.1002/mrm.27471
- 63.** Tuch DS. Q-ball imaging. *Magn Reson Med* 2004; 52(6): 1358–72. doi: 10.1002/mrm.20279