Review Article

Diffusion MRI: From basic principles to clinical applications

Claude J Bajada, Geoff J M Parker, Matthew A Lambon Ralph, Lauren L Cloutman

Abstract

Diffusion MRI (dMRI) is widely used by clinicians and radiologists to diagnose neurological disorders, in particular stroke. The most commonly encountered diffusion technique in the clinic is simple diffusion weighted imaging and apparent diffusion coefficient (ADC) mapping. However, dMRI can tap into a wealth of data that is usually overlooked by clinicians.

Claude J Bajada MD, MSc*
Neuroscience and Aphasia Research Unit (NARU),
Division of Neuroscience and Experimental Psychology,
School of Biological Sciences;
The University of Manchester,
Manchester, UK
c.bajada@fz-juelich.de

Geoff J M Parker BSc, PhD
Manchester Academic Health Science Centre;
The University of Manchester,
Manchester, UK
Bioxydyn Limited,
Manchester, UK
Division of Informatics,
Imaging & Data Sciences,
School of Health Sciences.
The University of Manchester,
Manchester, UK

Matthew A Lambon Ralph BSc PhD
Neuroscience and Aphasia Research Unit (NARU),
Division of Neuroscience and Experimental Psychology,
School of Biological Sciences;
The University of Manchester,
Manchester, UK

Lauren L Cloutman BSc PhD
Neuroscience and Aphasia Research Unit (NARU),
Division of Neuroscience and Experimental Psychology,
School of Biological Sciences;
The University of Manchester,
Manchester, UK

**Corresponding Author*

While most of this 'additional' information is primarily used in a research setting, it is beginning to permeate the clinic.

Despite the widespread use of dMRI, clinicians who do not have radiological training may not feel comfortable with the basic principles that underlie this modality. This paper's aim is to make the fundamentals of the technique accessible to doctors and allied health practitioners who have an interest in dMRI and who use it clinically. It progresses to discuss how these measures can be used.

Keywords

diffusion MRI, diffusion tensor imaging, radiology, tractography

Introduction

Diffusion Magnetic Resonance Imaging (dMRI) is a well-established tool that is routinely used in clinical practice to identify an acute cerebral infarction and is increasingly used as an aid to tumour characterisation. Tractography (an extension of dMRI) has been used to identify the location of white matter tracts in pre-surgical planning. Other less widespread uses include the differentiation of intra-cranial cysts, the assessment of diffuse axonal injury and the assessment of demyelinating disorders.

In light of the increasing interest in diffusion imaging within the clinical community, this paper explains the basic principles of diffusion MR in order to give the reader a better appreciation of why dMRI can be used in the above conditions.

The review is split into three main sections. The first describes the physical process of diffusion, explains how it is measured using MRI, and describes the different measurements obtained from dMRI. The second describes how to use the obtained measurements to reconstruct the white matter tracts; tractography. The final section discusses different clinical applications of dMRI.

Basic principles

Diffusion

Water diffuses according to an apparently random, passive movement of molecules that collide and interact with one another. In a container (such as glass or vase) water molecules diffuse uniformly in all orientations (known as 'isotropic' diffusion) and without restriction. However, the brain is not structureless. In neural tissue the diffusion of tissue water is hindered by cell membranes and myelin sheaths.[1] In white matter, axons are often lined up in parallel, which hinders diffusion particularly perpendicular to the fibres, with greater diffusion in parallel with the fibre orientation (known as 'anisotropic' diffusion).[2] In grey matter, where the barriers are not highly ordered, this hindered diffusion is relatively more isotropic than in white matter.

Diffusion MRI

Water is an abundant source of hydrogen nuclei (protons), which are detectable by an MRI scanner. All hydrogen nuclei possess a quantum mechanical property known as spin, which determines their intrinsic magnetic moment; each proton can be considered loosely as a tiny bar magnet. If a container of water is put into a scanner, the magnetic moments of the protons on average align with the main magnetic field. If a 90 degree radio frequency (RF) pulse is turned on, the proton magnetic moments rotate into the plane perpendicular to the field (known as the transverse plane) and precess (rotate round their own axes) in synchrony (in-phase) with each other.

This is the source of the MR signal. After a period of time, the protons dephase (precess at different rates so moving out of phase) which causes signal to be lost gradually. Indeed, the time it takes for protons to dephase is called the T_2* relaxation time.

In a standard spin echo MRI, a 180 degree pulse rephases (realigns) the protons and causes reappearance of signal as an 'echo' (see http://www.drcmr.dk/BlochSimulator/ for a good simulation of the process). Not all signal is recovered in the echo; with the amount of signal remaining dependent of the intrinsic T_2 relaxation time. The application of diffusion gradients causes additional dephasing and signal loss.

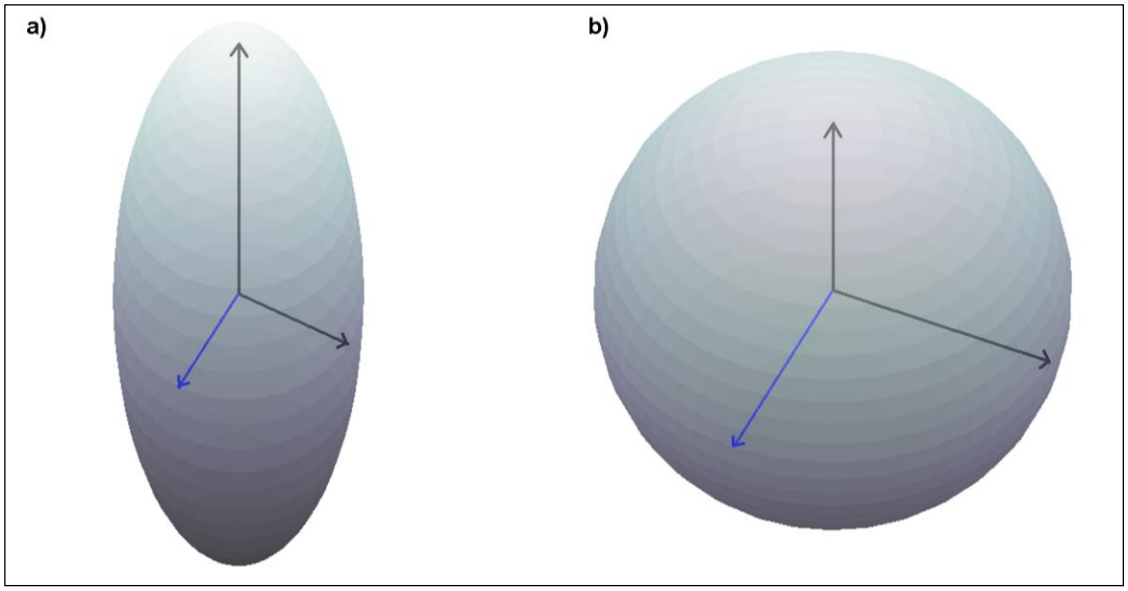
When a scanner is configured to detect diffusion, if a proton does not diffuse (i.e., stays in the same place), the signal is regained on application of the 180 degree pulse. If the proton diffuses, signal is lost.[3-5] Hence, image intensities in a diffusion weighted image are hypointense in regions where there is diffusion and relatively hyperintense where there is little diffusion.

The Diffusion MRI Measures

Multiple diffusion weighted images are typically acquired in a scanning session. Each diffusion weighted image (DWI) contains information about water diffusing in one specific orientation. Thus, to estimate the dominant orientation along which water is diffusing in every voxel, the information from all the orientations, sampled by the various individual diffusion-weighted images, is combined. By doing this, one can measure the amount of diffusion in each voxel and the orientation of that diffusion. This can be described mathematically by using a tensor. In this application, a tensor can be thought of as a sphere or ellipsoid that best describes the amount of diffusion and level of anisotropy in the voxel. For example, a voxel in which there is a large amount of isotropic diffusion can be modelled by a large sphere while a voxel where diffusion occurs preferentially along a white matter tract (anisotropic diffusion) can be modelled by an elipsoid that has its main axis parallel to the orientation of diffusion (Figure 1).

Tensors describe both the level of isotropy and the magnitude of diffusion in any orientation in every voxel of the brain. These metrics are derived by 'decomposing' the tensor into three eigenvectors (orientation) and three eigenvalues (magnitude).[6]

Figure 1: *Ellipsoids depicting an anisotropic (a) and isotropic (b) tensor. The arrows represent the eigenvectors. The length of each of those vectors is called its eigenvalue. Note that all vectors are at 90 degrees to each other.*



Apparent Diffusion Coefficient

The Apparent Diffusion Coefficient (ADC) is a measure of the amount of diffusion occurring in a given voxel of the brain. A measured diffusion coefficient differs from the true diffusion coefficient of a substance depending on the conditions in which it is measured and the type of medium within which diffusion occurs hence the term apparent diffusion coefficient is used. ADC is calculated from one or more diffusion weighted image in combination with an image with no diffusion weighting. Since the DWI still has T_2 weighting it is not a pure measure of diffusion. If a tissue has a long T_2, then it will appear bright on a DWI despite there being relatively unrestricted diffusion (T_2 shine through). The ADC map is a pure, mathematically calculated, measure of diffusion and hence not affected by T_2 weighting. If a single diffusion weighted image is used in the generation of the ADC value then the ADC will be dependent on the orientation of the diffusion sensitisation within that image. The ADC values along the six main orientations (xx, yy, zz, xy, xz and yz) are the values that form the diffusion tensor matrix.

Mean diffusivity

The mean diffusivity (MD) is a measure of the average amount of diffusion that occurs in a voxel irrespective of whether the diffusion is isotropic or anisotropic. It is rotationally invariant since it is the average ADC in three orthogonal directions (xx, yy and zz) of the diffusion tensor. There are two ways to calculate an MD map. The first approach requires a minimum of three diffusion sensitised images in orthogonal orientations to be produced, hence a full tensor of six directions does not need to be estimated. However, if a full tensor is estimated then MD is the average of the three eigenvalues of the tensor. Both these approaches give identical results (apart from measurement error). MD maps are clinically often referred to as (rotationally invariant) ADC maps. MD is affected by the cellularity of a voxel, and the presence or absence of oedema or necrosis.[7]

Longitudinal diffusivity

Longitudinal or axial diffusivity (AD) is a more specific measure of diffusion. While MD is the average amount of diffusion in all directions, AD is the measure of diffusion occurring along the principal eigenvector of the diffusion tensor and is therefore another term for the principal eigenvalue. A decrease in AD is often associated with a disruption of white matter integrity. For example, in axonal injury, damage and debris could impede diffusion in the principal orientation.

Radial diffusivity

Radial diffusivity RD is a measure of the

amount of diffusion occurring perpendicular to the principle eigenvector. RD is often interpreted in an inverse fashion to AD; that is an increase in RD is associated with possible white matter integrity damage such as demyelination or axonal injury, as barriers to the radial diffusion of water, such as myelin and axon membranes are damaged or destroyed.[8] RA and AD together make up MD.

Fractional anisotropy

Fractional anisotropy (FA) is a measure of the level of orientational anisotropy of water diffusion in each voxel. FA varies between zero (if all eigenvalues are equal - a totally isotropic voxel) and 1 (if only one eigenvalue is non-zero). FA is frequently considered to be related to white matter integrity as axonal damage is expected to lead to increased diffusivity in directions radial to the axis of axons and fibre bundles. DTI studies often investigate the change in FA in differing neurological conditions with the assumption that a decrease in FA is caused by damaged white matter.[9] The use of FA and MD can give complementary information that enriches ones understanding of the underlying structure of the brain. However, these metrics do not directly measure microstructure and any interpretation as such must be made with caution

Advanced measures

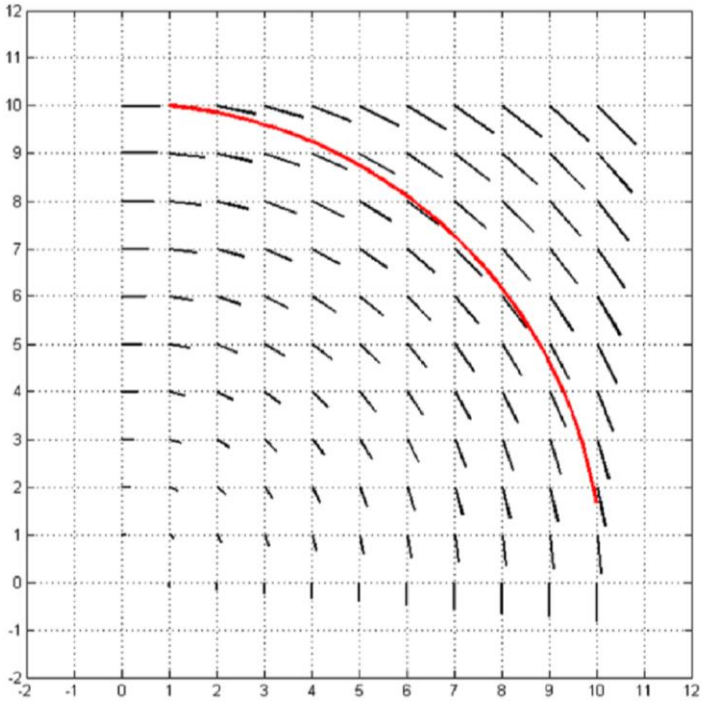
The tensor is not the only mathematical way to describe diffusion in voxels. In fact, many more complicated and arguably more precise methods of modelling diffusion exist.[10] As an introductory text, however, it is beyond the scope of this review to go into details. The measures described above are still the most commonly used, but it is important to be aware that diffusion MRI has the potential to give even more information than is discussed here.

The Reconstruction of White Matter Tracts

Tractography is a computational method that allows the virtual reconstruction of white matter tracts [11]. This paper will focus on a brief discussion of the most straightforward type of tractography, deterministic streamline tractography using tensors. A short reference to more advanced tractography algorithms will be given at the end of this section.

In tractography, each voxel can be modelled with a tensor and the principal orientation (eigenvector) is determined. An algorithm builds up a stepwise streamline from a seed (starting) voxel going through the most likely pathway through each voxel (see Figure 2).[12]

Figure 2*: in this deterministic approach, you can see that each voxel has one direction associated with it. A streamline (red) can thus be propagated from the seed voxel (1,10) and a 'tract' generated.*



Tractography has the advantage over gross dissection and tracer studies that it is non-invasive and that it is easily repeatable on the same individual. The same process can be carried out by different individuals and using different algorithms to ensure that a consistent result is obtained. It is the only method that is available to investigate human white matter tracts in-vivo. It is with this in mind that one must assess its limitations.

Data obtained from dMRI is determined by the diffusion of water. Algorithms infer white matter tracts from the way water diffuses around them, therefore some of the tracts obtained may be false tracts (false positive) while sometimes the algorithm may not reconstruct a tract that is really present (false negative). This can also occur because diffusion data contain noise, which results in errors in the tractography process. Errors can also occur in voxels that have more than one fibre population within them, since it can be difficult to determine configuration of the fibres that caused the observed diffusion (for example, the points at which two or more fibre bundles cross or diverge). Since deterministic tractography only uses the principal fibre direction for propagation, it is liable to rather large errors in these ambiguous or noisy voxels.[13] Also, since the algorithm does not allow for quantification of errors in the tract, confidence in the resultant tracts is unknown[14]. Such algorithms are poorly suited to deal with configurations such as crossing and kissing fibres because deterministic tractography computes the most likely streamline between two parts of the brain, without allowing for any form of branching or divergence.[14] Other, more advanced, methods to perform tractography exist and have been developed to tackle some of the issues discussed. These include using advanced non-Gaussian approaches to model intra-voxel diffusion such as constrained spherical deconvolution[15] and using probabilistic algorithms to perform the tractography.[13-14] While an in-depth discussion of these techniques is beyond the scope of this short primer, the interested reader is referred to[13-14] for more information.

Tractography is still being validated by comparing outputs with invasive dissection of tracts. Although to date there has been a high degree of agreement between dissection and diffusion tractography studies it is still not recommended for routine clinical use. [16-18]

Clinical Applications

Stroke

Within a few minutes of an acute ischaemic event, cytotoxic oedema accumulates within the infarct which translates into a lower MD. There are two common approaches that are used to identify these regions of reduced diffusion that imply an area of infarction in an acute stroke: MD measurement and assessment of the DWI signal (which also contains T_2 information).

In stroke, hindered diffusion is relatively hyperintense in a diffusion weighted image. In the MD map, on the other hand, each voxel contains the value of the MD, hence an area with hindered diffusion has a low MD and looks dark. Diffusion MRI can be used to accurately diagnose hyperacute stroke. This is in contrast to CT or conventional MRI where a stroke lesion may take hours to appear. Diffusion MRI is often used alongside perfusion techniques to assess a diffusion-perfusion mismatch.[19]

Tumours

MRI is a standard tool in the diagnosis and follow-up for tumours. MD mapping is increasingly being investigated as a marker for tumour cellularity and thus tumour grade, where a decrease in MD corresponds to higher cellularity.[20] It has also been investigated as a possible method for differentiating between brain mass effect and oedema from tumour and its infiltration, however results have been mixed.[21-22] These findings are yet to be validated for routine clinical use.

Multiple Sclerosis

The most commonly used MRI sequence in multiple sclerosis (MS) is the fluid attenuated inversion recovery sequence (FLAIR). However, demyelinating disorders such as MS also have an impact on diffusion measures. The two most commonly used measures are FA and MD. FA generally decreases while MD typically increases in MS lesions, with subtle alterations in the normal appearing white and grey matter also being detectable.[23]

RD and AD (more detailed measures of diffusion in white matter tracts than MD, see above) can help in differentiating between pure demyelination and axonal injury that includes inflammation.[8,24] Demyelination alone increases RD

with no impact on AD while axonal damage and inflammation can decrease both measures.

These measures are not reliable in areas of complex white matter architecture such as in regions with complex fibre structure (e.g., crossing fibres).

Diffuse Axonal Injury

In traumatic brain injury (TBI) patients, dMRI has been investigated for diagnosis of axonal injury. When axons are damaged, their configuration is no longer as highly structured as in the healthy brain due to damage to membranes, alterations to the myelin sheath, replacement of axons and/or infiltration by other cell types, and the accumulation of cellular debris. Each of these factors can cause a decrease in FA. It has been suggested that a decrease in FA may be a biomarker for a poor cognitive prognosis in TBI.[24-25]

It is important to note that, while in many cases a decrease in FA is caused by damage to axons in certain areas such as when there are two populations of fibres going in different directions, damage to one fibre population can lead to a paradoxical overall increase in FA rather than a decrease. This is due to the initial presence of two separate fibre populations with different orientations leading to an average low FA as there is not one single dominant diffusion orientation. If one population is damaged or removed, the other population becomes dominant, with a subsequent higher average axonal orientation consistency and therefore higher FA.

Intra-cranial Cysts

Diffusion imaging can be used to differentiate epidermoid from arachnoid cysts. MD or DWI are the usual measures of choice. Since an arachnoid cyst is filled with cerebrospinal fluid (CSF), the MD will be very high (due to unrestricted diffusion) while DWI will be hypointense. The inverse pattern is seen in epidermoid cysts.[26]

Surgical Planning

Tractography is a promising technique for pre-surgical planning. Surgeons can reconstruct tracts of interest prior to the surgery in order to know where (or where not) to target their intervention.[27] While the images rendered by tractography algorithms look convincing, the limitations described above make it not recommended for routine clinical use outside a research setting.[18]

Conclusion

Many clinicians utilise diffusion imaging in their practice. This brief review summarised the basic principles of the modality and has introduced some of the ways in which this MR modality is currently being used. It is hoped that this primer will prove invaluable to anyone wanting to improve their interpretation of dMRI images and those who are interested in using these techniques for research or clinical application.

Acknowledgements

CJB was supported by a DTP studentship from the BBSRC (BB/J014478/1). The authors would like to thank Dr Malcolm Vella for comments on a previous draft of this manuscript.

References

1. Beaulieu C. The basis of anisotropic water diffusion in the nervous system – a technical review. NMR in Biomedicine. 2002 2002;15(7-8):435-55.
2. Le Bihan D. The 'wet mind': water and functional neuroimaging. Physics in medicine and biology. 2007 Apr 7;52(7):R57-90.
3. Stejskal EO, Tanner JE. Spin Diffusion Measurements: Spin Echoes in the Presence of a Time-Dependent Field Gradient. J Chem Phys. 1965;42(1):288.
4. Winston GP. The physical and biological basis of quantitative parameters derived from diffusion MRI. Quantitative imaging in medicine and surgery. 2012 Dec;2(4):254-65.
5. Mukherjee P, Berman JI, Chung SW, Hess CP, Henry RG. Diffusion tensor MR imaging and fiber tractography: theoretic underpinnings. AJNR Am J Neuroradiol. 2008 Apr;29(4):632-41.
6. Nucifora PGP, Verma R, Lee S-K, Melhem ER. Diffusion-Tensor MR Imaging and Tractography: Exploring Brain Microstructure and Connectivity. Radiology. 2007 2007/11/01/;245(2):367-84.
7. 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.
8. 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 Nov;17(3):1429-36.

9. Kochunov P, Thompson PM, Lancaster JL, Bartzokis G, Smith S, Coyle T, et al. Relationship between white matter fractional anisotropy and other indices of cerebral health in normal aging: tract-based spatial statistics study of aging. NeuroImage. 2007 Apr 1;35(2):478-87.
10. Seunarine KK, Alexander DC. Chapter 4 - Multiple Fibers: Beyond the Diffusion Tensor. In: Johansen-Berg H, Behrens TEJ, editors. Diffusion MRI. San Diego: Academic Press; 2009. p. 55-72.
11. Catani M, Howard RJ, Pajevic S, Jones DK. Virtual in Vivo Interactive Dissection of White Matter Fasciculi in the Human Brain. NeuroImage. 2002 2002/09//;17(1):77-94.
12. Alexander AL. Deterministic White Matter Tractography. In: Jones DK, editor. Diffusion MRI : Theory, Methods, and Applications: Theory, Methods, and Applications. USA: Oxford University Press; 2010. p. 383 - 95.
13. Parker GJM, Haroon HA, Wheeler-Kingshott CAM. A framework for a streamline-based probabilistic index of connectivity (PICo) using a structural interpretation of MRI diffusion measurements. J Magn Reson Imaging. 2003 2003/08//;18(2):242-54.
14. Parker GJM. Probabilistic Fiber Tracking. In: Jones DK, editor. Diffusion MRI : Theory, Methods, and Applications: Theory, Methods, and Applications. USA: Oxford University Press; 2010. p. 396 - 408.
15. Tournier JD, Yeh CH, Calamante F, Cho KH, Connelly A, Lin CP. Resolving crossing fibres using constrained spherical deconvolution: Validation using diffusion-weighted imaging phantom data. NeuroImage. 2008 Aug 15;42(2):617-25.
16. Menjot de Champfleur N, Lima Maldonado I, Moritz-Gasser S, Machi P, Le Bars E, Bonafe A, et al. Middle longitudinal fasciculus delineation within language pathways: a diffusion tensor imaging study in human. European journal of radiology. 2013 Jan;82(1):151-7.
17. Sarubbo S, De Benedictis A, Maldonado IL, Basso G, Duffau H. Frontal terminations for the inferior fronto-occipital fascicle: anatomical dissection, DTI study and functional considerations on a multi-component bundle. Brain Struct Funct. 2013 Jan;218(1):21-37.
18. Duffau H. Diffusion tensor imaging is a research and educational tool, but not yet a clinical tool. World neurosurgery. 2014 Jul-Aug;82(1-2):e43-5.
19. Barber PA, Darby DG, Desmond PM, Yang Q, Gerraty RP, Jolley D, et al. Prediction of stroke outcome with echoplanar perfusion- and diffusion-weighted MRI. Neurology. 1998 Aug;51(2):418-26.
20. Chen LH, Liu M, Bao J, Xia YB, Zhang JQ, Zhang L, et al. The Correlation between Apparent Diffusion Coefficient and Tumor Cellularity in Patients: A Meta-Analysis. PLoS ONE. 2013 Nov 11;8(11).
21. Kono K, Inoue Y, Nakayama K, Shakudo M, Morino M, Ohata K, et al. The role of diffusion-weighted imaging in patients with brain tumors. AJNR Am J Neuroradiol. 2001 Jun-Jul;22(6):1081-8.
22. Maier SE, Sun Y, Mulkern RV. Diffusion imaging of brain tumors. NMR Biomed. 2010 Aug;23(7):849-64.
23. Inglese M, Bester M. Diffusion imaging in multiple sclerosis: research and clinical implications. NMR in Biomedicine. 2010 Aug;23(7):865-72.
24. Lerner A, Mogensen MA, Kim PE, Shiroishi MS, Hwang DH, Law M. Clinical applications of diffusion tensor imaging. World neurosurgery. 2014 Jul-Aug;82(1-2):96-109.
25. Kinnunen KM, Greenwood R, Powell JH, Leech R, Hawkins PC, Bonnelle V, et al. White matter damage and cognitive impairment after traumatic brain injury. Brain : a journal of neurology. 2011 Feb;134:449-63.
26. Newcombe VF, Das T, Cross JJ. Diffusion imaging in neurological disease. J Neurol. 2013 Jan;260(1):335-42.
27. Powell HWR, Parker GJM, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CAM, et al. MR tractography predicts visual field defects following temporal lobe resection. Neurology. 2005 Aug 23;65(4):596-9.