Methodology of diffusion-weighted, diffusion tensor and magnetisation transfer imaging

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ABSTRACT. MRI offers a number of opportunities to examine characteristics of tissue well below the spatial resolution of the imaging technique. The best known of these is diffusion imaging, which allows the production of images whose contrast reflects the ability of water molecules to move through the extravascular extracellular space. Less well-known, but increasingly important, is magnetisation transfer imaging, which produces contrast based on the ability of protons to move between the free water pool and local macromolecules. Both of these techniques offer unique information about the microscopic and molecular structure of tumour tissue. This article will briefly review the underlying theory and technical aspects associated with these imaging techniques.

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Diffusion imaging

Water molecules within the brain are constantly moving by diffusion or Brownian motion. Diffusion MRI is dependent on the fact that protons precess at the same rate if they experience the same magnetic field. A pulse gradient is applied before being refocused by a second pulse gradient; all protons that have not moved will be fully rephased causing no signal loss. Protons that have moved will be dephased and cause a drop in signal intensity that is dependent on the degree of diffusion weighting and the diffusion coefficient. The *b*-value gives the degree of diffusion weighting and is related to the strength and duration of the pulse gradient as well as the interval between the gradients. Diffusion-weighted signal changes are not sufficient to quantify these diffusion changes. Not only does the signal depend on the degree of diffusion weighting (*b*-value) but also the *T*₂ weighted signal and/or proton density. The gradient of the signal intensity (plotted on a logarithmic scale) is used as a measure of the diffusion coefficient. This coefficient measures all motional processes, such as flow and diffusion. As a result, the diffusion coefficient is referred to as the apparent diffusion coefficient (ADC). In regions where there is an increase in water diffusion, for example in regions of vasogenic oedema, there is a decrease in the diffusion-weighted signal with an increase in the ADC. Where protons accumulate, for example in areas of cytotoxic oedema where water is trapped within the cell, there is an increase in the diffusion-weighted signal and a decrease in ADC. Such changes accompany ischaemia, where energy failure causes failure of the Na⁺-ATPase pumps, thus leading to water accumulation within the cells. Experimental evidence suggests that the main determinant of the diffusion coefficient is the extracellular

volume fraction [1]. In tumours, the extracellular volume fraction can be affected by two processes (Figure 1).

1. *Vasogenic oedema*: produced due to defects in the blood–brain barrier. This causes a decrease in the diffusion-weighted imaging (DWI) signal and an increase in the ADC. ADC measurements correlate with the *T*₂ weighted signal intensity normalised to white matter (as an estimate of oedema) and the degree of enhancement on *T*₁ weighting images (as a marker of blood–brain barrier disruption) [2].
2. *Tumour cellularity*: increased cell numbers will restrict diffusion, reduce the extracellular volume fraction, increase DWI signal and reduce the ADC. Some studies have shown that there is an inverse relationship between cellularity and ADC [3, 4]. Stadnik et al [5] found that the ADC did not correlate with the number of cells, but did correlate with the volume of the extracellular space. Most studies have shown that tumours have higher ADC values than normal brain [3, 5–10] and the ADC decreases with increased tumour grade [3, 4].

High *b*-value diffusion imaging

The *b*-values used for most clinical studies (*i.e.* in the range up to 1500 s mm⁻²) have a monoexponential relationship between MR signal and *b*-value. Studies with higher *b*-values, up to 5000 s mm⁻², have shown that there is a biexponential relationship between signal and *b*-values; there appears to be a diffusion coefficient for a fast component of water diffusion and a coefficient for a slow component [11–13]. Although there was an initial suggestion that the fast component related to extracellular water diffusion and the slow component related to intracellular water, studies where the volume of the intra- and extracellular components were altered

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Figure 1. (a) A T_1 weighted gadolinium-enhanced image of an occipital glioblastoma shows a tumour that has a cystic component. (b) Diffusion-weighted imaging shows low signal in the cystic region (asterisk) whereas this has a high apparent diffusion coefficient (c). (d) A fractional anisotropy image with intact white matter tracts lateral to the tumour (arrow).

showed there was simultaneous changes in both coefficients [14].

Anisotropic diffusion and the diffusion tensor

Without barriers water will diffuse in all directions, a process referred to as isotropic diffusion. It is well recognised that in the brain water does not diffuse equally in all directions. Water will preferentially diffuse along axonal fibres [15–17] and have a higher diffusion coefficient when measured parallel than when measured perpendicular to axonal fibres [18]. Such directional water diffusion is called anisotropic diffusion. Diffusion

of a water molecule in white matter tracts can be described by an ellipsoid. Mathematically ellipsoids can be described in three dimensions by a tensor. The diffusion ellipsoid can be described by a symmetric 3×3 second-order tensor.

$$\overline{D}_{\text{eff}} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix} \quad (1)$$

To calculate the tensor, Basser et al [19] described a method that measured the diffusion coefficients in a minimum of six non-collinear directions (*i.e.* along the x ,

y , z , xy , xz and yz directions). Diagonalisation of the tensor matrix allows the tensor to be described by three eigenvalues (λ_1 , λ_2 , λ_3) that describe the size of the axes of the ellipsoid, and three eigenvectors (e_1 , e_2 , e_3) that describe their direction (Figure 1).

Quantifying the diffusion tensor

The advantage of using a tensor method to quantify diffusion is that the measures are rotationally invariant and not dependent on head positioning. This allows reproducible measurements that can be used in both cross-sectional and longitudinal studies. The simplest method of summarising the tensor is the mean diffusivity (D) that is defined by the equation:

$$D = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \quad (2)$$

Mean diffusivity is a measure of isotropic diffusion and is equivalent to the "average" ADC calculated from multiple gradient directions.

Various measures of anisotropic diffusion have been described, but the most commonly quoted in the literature is fractional anisotropy (FA). This is calculated from the following equation:

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

A comparative study of anisotropic indices showed that FA mapped diffusion anisotropy with the greatest detail and the best signal-to-noise ratio. The volume ratio (VR), a measure calculated from the ratio between the volume of the diffusion ellipsoid and the volume of a sphere of diameter D , provided the strongest contrast between low- and high-anisotropy areas at the expense of increased noise contamination and decreased resolution in anisotropic regions. The relative anisotropy (RA) proved intermediate in quality [20].

Although FA is the commonest index to be used in the literature, there are concerns that it might not be sensitive to changes in anisotropy. From the equation, it can be seen that FA could decrease either by a decrease in anisotropy or an increase in the isotropic component. This certainly occurs in stroke, where the FA increases in the acute period following a stroke [21]. As a result, other measures of anisotropy have been sought. The simplest measures use the eigenvalues, either alone or in combination. Other measures compare diffusion parallel to the principle axis of diffusion (defined as λ_1) to diffusion perpendicular to this (the average of λ_2 and λ_3). Reduction in parallel diffusion has been shown to be a marker of axonal damage, whereas an increase in perpendicular diffusion is a marker of demyelination [22]. More complex methods decompose the tensor into an isotropic component (referred to as p) and an anisotropic component (referred to as q) [23, 24]. Studies in tumours show a reduction in FA compared with normal tissue, and correlates with tumour cellularity, vascularity and cellular proliferation [25, 26]. This reduction is more marked for the lower grade (Figure 1),

possibly reflecting the presence of "organised" structures (e.g. pseudopallidation) within glioblastomas [27].

Magnetisation transfer

The majority of signal in MRI is due to protons that exist in water or fat. However, there are other protons in tissue such as those attached to macromolecules, e.g. myelin. These protons are invisible to conventional MRI due to their short T_2 relaxation times (approximately 20 μ s compared with approximately 80 ms in white matter as a whole). Thus the signal associated with macromolecular protons has decayed before it can be imaged.

Magnetisation transfer (MT) allows us to indirectly access the characteristics of these macromolecular protons. MT experiments tend to assume a two-pool (or binary spin bath) model of tissue [28] where protons are considered to exist in either the free proton or bound (or semi-solid) proton pool. The free pool includes tissue water where the mobility of the protons ensures a long T_2 relaxation time while the bound protons are those tightly bound to macromolecules, which causes the short relaxation times. These pools are considered to be in good contact meaning that cross-relaxation occurs and magnetisation is exchanged between the pools. MT takes advantage of this contact and the difference in the range of resonant frequencies associated with the two pools as shown in Figure 2. Free protons exhibit a small range of resonant frequencies whereas bound protons have a much wider bandwidth owing to variations in their microscopic environment.

Figure 2. A schematic diagram of the resonance characteristics of the free and bound proton pools in tissue. The frequency 0 is equivalent to the Larmor frequency of water ($\sim 42.6 \text{ MHz T}^{-1}$) and the offset frequency for the magnetisation transfer (MT) pulse is usually in the order of 2 kHz. The protons with resonant frequencies (RF) encompassed by the shaded box are the only ones affected by this pulse. The width of the box will depend on the bandwidth of the pulse.

A portion of the bound protons can be saturated by the application of an "off resonance" radiofrequency pulse prior to the imaging sequence. That is to say a pulse at a frequency offset from the water resonance so that it only affects protons within the bound pool (Figure 2). This pulse is large compared with those used in the imaging sequence so the protons are saturated. Magnetisation exchange between the two pools then occurs so some of the free protons are now saturated, leading to a reduction in signal compared with an identical sequence without the off resonance pulse.

This effect can be used to alter image contrast, as tissues may show different size MT effects, or the signal from images with and without the pulse can be combined to produce the magnetisation transfer ratio (MTR):

$$MTR = (M_0 - M_S) / M_0 \times 100\% \quad (4)$$

where M_S and M_0 are the signal with and without the off resonance pulse respectively. The MTR is a dimensionless quantity and given in units of % or percentage units (pu).

The MTR is a function of a number of tissue-specific parameters, but also varies with the sequence parameters used. The strength and frequency of the off resonance pulse, the repetition time, echo time and the hardware used affect the MTR, making it heavily dependent on the specific scanner and sequence used [29].

A simple model that describes the MTR is:

$$MTR \propto k f_b T_1 \quad (5)$$

where k is the relaxation constant between the two pools, f_b is the fraction of protons in the bound pool and T_1 the

longitudinal relaxation time of the tissue. This model shows a limitation of the MTR; inflammation would cause an increase in free protons (a reduction in f_b) and an increase in T_1 ; these changes tend to cancel out reducing the sensitivity of the MTR to this pathology.

Recently a more complex analysis of MT (qMT) has been proposed [30], where multiple images, each weighted by a MT pulse of different offset frequency and power are used to estimate a series of parameters, including f_b , the relaxation times of the two pools and the cross-relaxation rate, which should be sequence independent and allow greater insight to pathological changes.

In normal brain the MTR is lowest in cerebrospinal fluid (as there are few bound protons) then increases through grey matter to white matter, which contains large amounts of myelin and, hence, a large bound proton fraction. MT imaging has been used to improve cardiac images by altering the contrast between the myocardial wall and blood chamber, but the main use of the technique has been in the brain. MT is of particular interest here as common pathological processes, such as inflammation and demyelination will alter the relative sizes of the two proton pools and result in changes to the MTR and qMT parameters, for example in multiple sclerosis lesions (Figure 3) and normal appearing white matter [31, 32]. A reduction in the MTR and f_b has been seen both in the acute phase (where inflammation increases the amount of free water) and in the chronic phase of the disease as demyelination and axonal loss reduce the number of bound protons. A decrease in the

Figure 3. A magnetisation transfer ratio (MTR) map of a subject with multiple sclerosis. Note the white matter lesions (arrowed), which manifest as areas of reduced MTR.

Figure 4. A magnetisation transfer ratio (MTR) map of a subject with a glioma; the tumour can be seen as the area of reduced MTR in the front left of the image. Also note the area of heavily reduced MTR, which indicates a cyst within the tumour.

MTR is the typical response to pathology, as tissue destruction and/or an increase in free water occur, and has been seen in diseases such as Alzheimer's [33] and HIV [34]. A decrease in the MTR compared with grey and white matter has been reported for many lesion types, with cysts having a lower MTR than benign and malignant tumours (Figure 4) [35].

The major advantages of MT imaging and the MTR are that they are relatively easy to implement (MT is available from all major manufacturers), can be applied to both spin-echo and gradient-echo sequences and also easy to post-process, a subtraction is all that is required. MT is also a relatively high SNR technique and can be performed in clinically acceptable times. The parameters calculated from qMT can also be directly linked to specific pathological processes. However, qMT analysis is more complex and requires more images to be acquired, increasing the imaging time. Other disadvantages are that the MTR is very sequence dependent so values are not comparable between centres, specific absorption rate considerations can limit the strength of the MT pulse used, particularly at ≥ 3 T and the oversimplified tissue model used. Despite these, MT imaging, the MTR and qMT have shown considerable utility, in particular in demyelinating diseases, such as multiple sclerosis.

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References

- Latour LL, Svoboda K, Mitra PP, Sotak CH. Time-dependent diffusion of water in a biological model system. *Proc Natl Acad Sci USA* 1994;91:1229–33.
- Muti M, Aprile I, Principi M, Italiani M, Guiducci A, Giulianelli G, et al. Study on the variations of the apparent diffusion coefficient in areas of solid tumor in high grade gliomas. *Magn Reson Imaging* 2002;20:635–41.
- 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;22:1081–8.
- Sugahara T, Korogi Y, Kochi M, Ikushima I, Shigematu Y, Hirai T, et al. Usefulness of diffusion-weighted MRI with echo-planar technique in the evaluation of cellularity in gliomas. *J Magn Reson Imaging* 1999;9:53–60.
- Stadnik TW, Chaskis C, Michotte A, Shabana WM, van Rompaey K, Luytbaert R, et al. Diffusion-weighted MR imaging of intracerebral masses: comparison with conventional MR imaging and histologic findings. *AJNR Am J Neuroradiol* 2001;22:969–76.
- Bulakbasi N, Kocaoglu M, Ors F, Tayfun C, Ucoz T. Combination of single-voxel proton MR spectroscopy and apparent diffusion coefficient calculation in the evaluation of common brain tumors. *AJNR Am J Neuroradiol* 2003;24:225–33.
- Castillo M, Smith JK, Kwok L, Wilber K. Apparent diffusion coefficients in the evaluation of high-grade cerebral gliomas. *AJNR Am J Neuroradiol* 2001;22:60–4.
- Lam WW, Poon WS, Metreweli C. Diffusion MR imaging in glioma: does it have any role in the pre-operation determination of grading of glioma? *Clin Radiol* 2002;57:219–25.
- Maier SE, Bogner P, Bajzik G, Mamata H, Mamata Y, Repa I, et al. Normal brain and brain tumor: multicomponent apparent diffusion coefficient line scan imaging. *Radiology* 2001;219:842–9.
- Guo AC, Cummings TJ, Dash RC, Provenzale JM. Lymphomas and high-grade astrocytomas: comparison of water diffusibility and histologic characteristics. *Radiology* 2002;224:177–83.
- Burdette JH, Durden DD, Elster AD, Yen YF. High b-value diffusion-weighted MRI of normal brain. *J Comput Assist Tomogr* 2001;25:515–19.
- Clark CA, Le Bihan D. Water diffusion compartmentation and anisotropy at high b values in the human brain. *Magn Reson Med* 2000;44:852–9.
- Clark CA, Hedehus M, Moseley ME. In vivo mapping of the fast and slow diffusion tensors in human brain. *Magn Reson Med* 2002;47:623–8.
- Niendorf T, Dijkhuizen RM, Norris DG, van Lookeren CM, Nicolay K. Biexponential diffusion attenuation in various states of brain tissue: implications for diffusion-weighted imaging. *Magn Reson Med* 1996;36:847–57.
- Moseley ME, Cohen Y, Kucharczyk J, Mintorovitch J, Asgari HS, Wendland MF, et al. Diffusion-weighted MR imaging of anisotropic water diffusion in cat centralnervous system. *Radiology* 1990;176:439–45.
- Doran M, Hajnal JV, van Bruggen N, King MD, Young IR, Bydder GM. Normal and abnormal white matter tracts shown by MR imaging using directional diffusion weighted sequences. *J Comput Assist Tomogr* 1990;14:865–73.
- Chenevert TL, Brunberg JA, Pipe JG. Anisotropic diffusion in human white matter: demonstration with MR techniques in vivo. *Radiology* 1990;177:401–5.
- Le Bihan D, Turner R, Douek P. Is water diffusion restricted in human brain white matter? An echo-planar NMR imaging study. *Neuroreport* 1993;4:887–90.
- Basser PJ, Mattiello J, LeBihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. *J Magn Reson B* 1994;103:247–54.
- Papadakis NG, Xing D, Houston GC, Smith JM, Smith MI, James MF, et al. A study of rotationally invariant and symmetric indices of diffusion anisotropy. *Magn Reson Imaging* 1999;17:881–92.
- Green HA, Pena A, Price CJ, Warburton EA, Pickard JD, Carpenter TA, et al. Increased anisotropy in acute stroke: a possible explanation. *Stroke* 2002;33:1517–21.
- 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;20:1714–22.
- Pena A, Green HAL, Carpenter TA, Price SJ, Pickard JD, Gillard JH. Enhanced visualization and quantification of magnetic resonance diffusion tensor imaging using the p:q tensor decomposition. *Br J Radiol* 2006;79:101–9.
- Price SJ, Pena A, Burnet NG, Jena R, Green HA, Carpenter TA, et al. Tissue signature characterisation of diffusion tensor abnormalities in cerebral gliomas. *Eur Radiol* 2004;14:1909–17.
- Beppu T, Inoue T, Shibata Y, Kurose A, Arai H, Ogasawara K, et al. Measurement of fractional anisotropy using diffusion tensor MRI in supratentorial astrocytic tumours. *J Neurooncol* 2003;63:109–16.
- Beppu T, Inoue T, Shibata Y, Yamada N, Kurose A, Ogasawara K, et al. Fractional anisotropy value by diffusion tensor magnetic resonance imaging as a predictor of cell density and proliferation activity of glioblastomas. *SurgNeurol* 2005;63:56–61.
- Inoue T, Ogasawara K, Beppu T, Ogawa A, Kabasawa H. Diffusion tensorimaging for preoperative evaluation of tumor grade in gliomas. *Clin Neurol Neurosurg* 2005;107:174–80.

28. Edzes HT, Samulski ET. Measurement of cross-relaxation effects in proton NMR spin-lattice relaxation of water in biological-systems—hydrated collagen and Muscle. *J Magn Reson* 1978;31:207–29.
29. Tofts PS, Steens SCA, Cercignani M, Admiraal-Behloul F, Hofman PAM, van Osch MJP, et al. Sources of variation in multi-centre brain MTR histogram studies: body-coil transmission eliminates inter-centre differences. *MAGMA* 2006;19:209–22.
30. Morrison C, Henkelman RM. A model for magnetization-transfer in tissues. *Magn Reson Med* 1995;33:475–82.
31. Filippi M, Campi A, Dousset V, Baratti C, Martinelli V, Canal N, et al. Magnetization-transfer imaging study of normal-appearing white-matter in multiple-sclerosis. *Neurology* 1995;45:478–82.
32. Davies GR, Tozer DJ, Cercignani M, Ramani A, Dalton CM, Thompson AJ, et al. Estimation of the macromolecular proton fraction and bound pool T-2 in multiple sclerosis. *Multiple Sclerosis* 2004;10:607–13.
33. Ridha BH, Symms MR, Tozer DJ, Stockton KC, Frost C, Siddique MM, et al. Magnetization transfer ratio in Alzheimer disease: comparison with volumetric measurements. *Am J Neuroradiol* 2007;28:965–70.
34. Ge Y, Kolson DL, Babb JS, Mannon LJ, Grossman RI. Whole brain imaging of HIV-infected patients: quantitative analysis of magnetization transfer ratio histogram and fractional brain volume. *Am J Neuroradiol* 2003;24:82–7.
35. Pui MH, Wang YD. Diffusion and magnetization transfer MRI of brain infarct, infection, and tumor in children. *Clin Imaging* 2005;29:162–71.