Cancer Imaging (2010) **10,** S163–S171
DOI: 10.1102/1470-7330.2010.9023

CI

e-med
www.e-med.org.uk

FOCUS ON: DIFFUSION AND FUNCTIONAL IMAGING

Wednesday 6 October 2010, 13:30–15:00

Diffusion-weighted and diffusion tensor imaging of the brain, made easy

T.A.G.M. Huisman

Division Pediatric Radiology, Johns Hopkins Hospital, Baltimore, MD, USA

Corresponding address: Thierry A.G.M. Huisman, MD, EQNR, FICIS, Professor of Radiology and Radiological Science, Medical Director Division Pediatric Radiology, Russell H. Morgan Department of Radiology and Radiological Science, 600 North Wolfe Street, Nelson, B-173, Baltimore, MD 21287-0842, USA.
Email: thuisma1@jhmi.edu

Abstract

Diffusion-weighted and diffusion tensor imaging (DWI/DTI) has revolutionized clinical neuroimaging. Pathology may be detected earlier and with greater specificity than with conventional magnetic resonance imaging sequences. In addition, DWI/DTI allows exploring the microarchitecture of the brain. A detailed knowledge of the basics of DWI/DTI is mandatory to better understand pathology encountered and to avoid misinterpretation of typical DWI/DTI artifacts. This article reviews the basic physics of DWI/DTI exemplified by several classical clinical cases.

Keywords: *Diffusion-weighted imaging; diffusion tensor imaging; vasogenic edema; cytotoxic edema; apparent diffusion coefficient; fractional anisotropy.*

Introduction

Diffusion-weighted imaging (DWI) is an advanced, functional magnetic resonance (MR) technique that has revolutionized diagnostic imaging. Although the first diffusion-weighted MR sequences were described as early as 1965 by Stejskal and Tanner, the demanding hard- and software requirements delayed introduction into clinical routine for many years. It was not until the mid-1980s that DWI became available on routine clinical MR scanners. Continuing development of hardware and software as well as the wider availability of ultra-high field MR units (3.0 Tesla) has made DWI one of the most important imaging tools in neuroradiology today. DWI has proved to be highly sensitive in the early identification of ischemic tissue injury, frequently before conventional MR sequences show pathology, opening up the time window for tissue salvaging interventions. DWI provides qualitative information by differentiating between vasogenic and cytotoxic edema and allows quantitative evaluation of lesions by measuring the apparent diffusion coefficient (ADC) and fractional anisotropy (FA), which are scalars of isotropic and anisotropic diffusion. Normal and abnormal microstructural brain development can also be studied using DWI based on the differential diffusion properties of the various tissues (FA scalars and tractography).

More recently, DWI sequences are being progressively applied outside the central nervous system. Whole-body DWI is being used for various musculoskeletal indications such as multifocal osteomyelitis, bone infarctions, metastatic disease and even for abdominal organ pathology. Respiratory gating, ultrafast imaging and powerful postprocessing tools allow imaging of organs that move, for example, as a result of respiration or spontaneous peristalsis.

The goal of this review is to summarize the essential basics of DWI that every radiologist should know and to provide better understanding of DWI findings encountered, facilitate recognition of artifacts that may mimic lesions and further advance new developments of DWI into clinical routine. Key references are listed[1–5].

1470-7330/09/000001 + 09

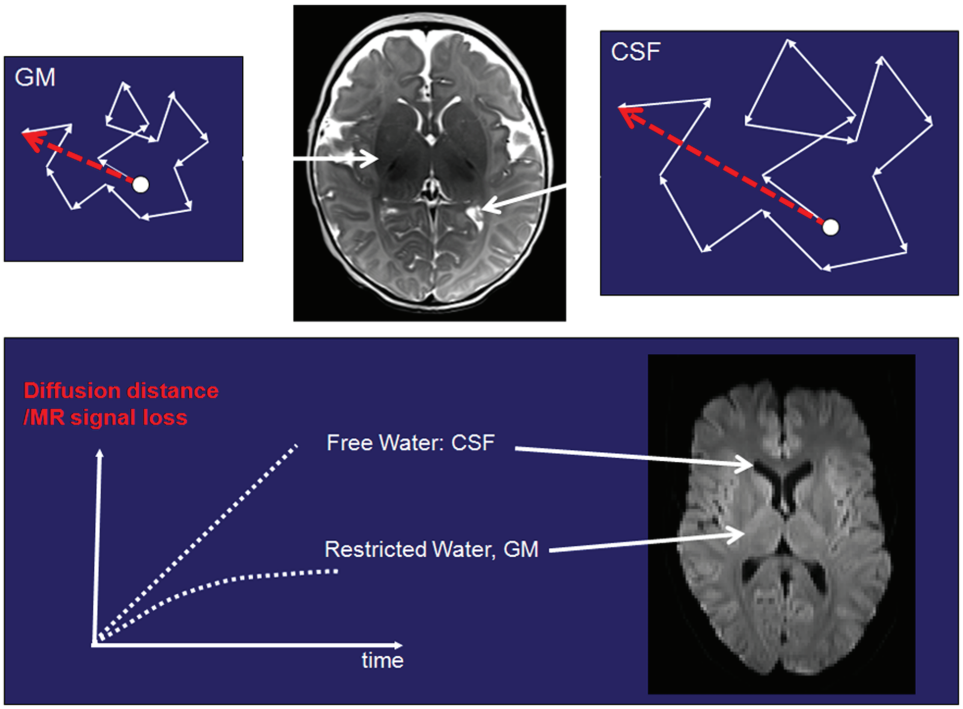

Figure 1 **Graphical display of water molecules moving at different rates through the gray matter and cerebrospinal fluid (CSF). The effective distance that water molecules travel in gray matter is smaller than in CSF (represented by the magnitude of the red arrow). The difference in travelled diffusion distance versus time is displayed in the lower graph. The faster the molecules move, the more distance is travelled, the more signal loss will occur if diffusion gradients are applied. Consequently the signal loss in the CSF is higher (hypointense) compared with the signal loss in the gray matter (hyperintense relative to the CSF).**

DWI

DWI MR imaging provides image contrast based on differences in the magnitude of diffusion of water molecules within the brain. Diffusion represents the random thermal movement of molecules, also known as Brownian motion. Diffusion within the brain is determined by a variety of factors including the type of molecule under investigation, the temperature and the microenvironmental architecture in which the diffusion takes place. For example, diffusion of molecules within the cerebrospinal fluid (CSF) is less limited than diffusion of molecules within the intra- and intercellular space. By using the appropriate MR sequences that are sensitive for diffusion, these differences in diffusion rates (magnitude of diffusion) can be translated into image contrast (Fig. 1). Quantitative maps that display the spatial distribution of the diffusion rate within the brain are generated.

Typically, conventional MR imaging sequences are made sensitive to molecular diffusion by adding two extra gradients to a standard ultrafast MR imaging sequence, frequently a T2-weighted echo planar sequence. These diffusion gradients are equal in magnitude, symmetrically centered around a 180° refocusing radiofrequency pulse. The physical principle is analogous to that of phase contrast MR angiography (MRA). The first gradient causes molecules to acquire phase shifts; the second gradient cancels the gained phase shift by rephrasing, non-moving stationary spins. Moving spins however acquire an effective phase shift because their motion limits rephrasing by the second gradient. The higher the resultant spin dephasing, the more MR signal is lost. This principle also applies for diffusion-related motion of water molecules within the brain. As water diffusion is random, the resulting phase shifts accumulated by the diffusing water molecules are also at random leading to spin dephasing with resultant MR signal loss. Similar to blood flow, the degree of MR signal loss is determined by the degree of random motion (diffusion). The higher the degree of random motion (e.g. within CSF), the more MR signal loss, conversely the lower the degree of random motion (e.g. in gray or white matter), the lower the MR signal loss. The degree of MR signal decrease can be enhanced by increasing the strength and duration of the diffusion-encoding gradients. Diffusion gradients are characterized by the b value (s/mm^2) which is defined by the Stejskal-Tanner equation:

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3)$$

where γ is the gyromagnetic ratio, G, δ, Δ correspond to the amplitude, duration and interval of the diffusion gradient, respectively.

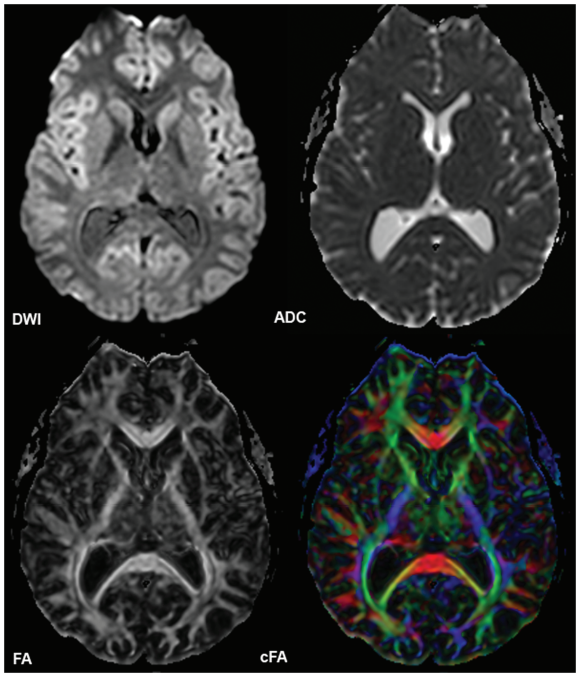

Figure 2 **Sample of an axial DWI, ADC, FA and color-coded (cFA) image of the brain. On DWI the cortex is slightly more intense than the white matter because of residual T2 effects (T2 shine through). The CSF is DWI hypointense. On the ADC map the cortex and white matter are equally intense because the T2 effect has been cancelled out. The gray and white matter are ADC hypointense compared with the CSF because diffusion is restricted within the brain and high in the CSF. The FA map shows high degrees of anisotropic diffusion along white matter tracts in the corpus callosum and internal capsule. A low degree of anisotropic diffusion is seen in the cortical and central gray matter (areas of isotropic diffusion). The color-coded FA maps display the predominant direction of diffusion, with left to right diffusion in the corpus callosum (red), superior-inferior diffusion in the internal capsule (blue) and anterior-posterior diffusion in the frontal white matter (green).**

Most frequently, images are acquired with a *b* value of 0 and 1000 s/mm^2. Because the diffusion gradients are added to a T2-weighted sequence, the measured MR signal equals the T2-signal intensity decreased by an amount of MR signal loss determined by the diffusion coefficient and strength of the applied diffusion gradient. The resulting signal intensity is typically mapped as a two-dimensional image (DWI map) for each voxel similar to conventional T1- or T2-weighted MR images (Fig. 2). The DWI map is consequently partially T2- and diffusion-weighted. The images acquired with a *b* value of 0 s/mm^2 is basically a pure T2-weighted image without diffusion weighting.

Maps of diffusion rates are calculated from a combined analysis of the two images acquired with different *b* values ($b = 0$ and $b = 1000$ s/mm^2). By plotting the natural logarithm of the measured signal intensity versus the *b* values, the diffusion rate can be derived from the slope of this plot. The rate of diffusion is measured in units of area divided by time (e.g. square millimeters per second). The observed diffusion of molecules within biological environments is determined by a variety of known and unknown factors. This includes the previously mentioned microenvironmental architecture but also energy-dependent transportation mechanisms that enhance the motion of water molecules across cell membranes. To respect this variety of factors that influence the measured diffusion, the rate of diffusion in living systems is referred to as the ADC. The ADC values of the each voxel can be displayed as a two-dimensional ADC map (Fig. 2), similar to the DWI maps, revealing the spatial distribution of the different ADC values within a slice of brain tissue. Areas with a high rate of diffusion will have a high ADC value and consequently appear hyperintense on the ADC maps (e.g. CSF). Areas with restricted diffusion, like white or gray matter appear ADC hypointense. A major advantage of the ADC maps is that they are devoid of T2 effects that may mimic or obscure lesions on DWI images. In addition, the ADC values are not dependent on the field strength or sequence parameter used. The ADC value is an absolute quantitative measurement of translational water motion, which can be compared between serial examinations.

Diffusion is however a three-dimensional phenomenon with a direction and shape. The three-dimensional shape and magnitude of diffusion differ between various brain structures. The microstructural architecture as well as physiologic factors influence the diffusion of water molecules within the brain. Diffusion in white matter tracts is, for example, predominantly along the direction parallel to the long axis of tracts and limited in the direction perpendicular to the tract. This directional diffusion can be graphically represented as an ellipsoid or cigar, and is known as anisotropic diffusion (Fig. 3a). When the degree of diffusion is equal in all directions in space such as in CSF, where no cell membranes limit diffusion, the three-dimensional shape of diffusion can be graphically represented by a sphere and is known as isotropic diffusion (Fig. 3b).

The directionality of diffusion can be noted if diffusion-weighted images are acquired with diffusion-encoding gradients applied along different axes. If the direction of the diffusion-encoding gradient matches the principal direction of a white matter tract, the MR signal will be suppressed; the signal will remain intact or less suppressed if the white matter tract runs perpendicular to the diffusion-encoding gradient. This direction-selective signal loss may mimic lesions. Typically, this directionality can be compensated for by applying diffusion-encoding gradients along three orthogonal directions (*Dxx*, *Dyy*, *Dzz*) (Fig. 4a). By averaging the resultant diffusion-weighted images, the signal changes related to the directionality of diffusion are cancelled out. The signal

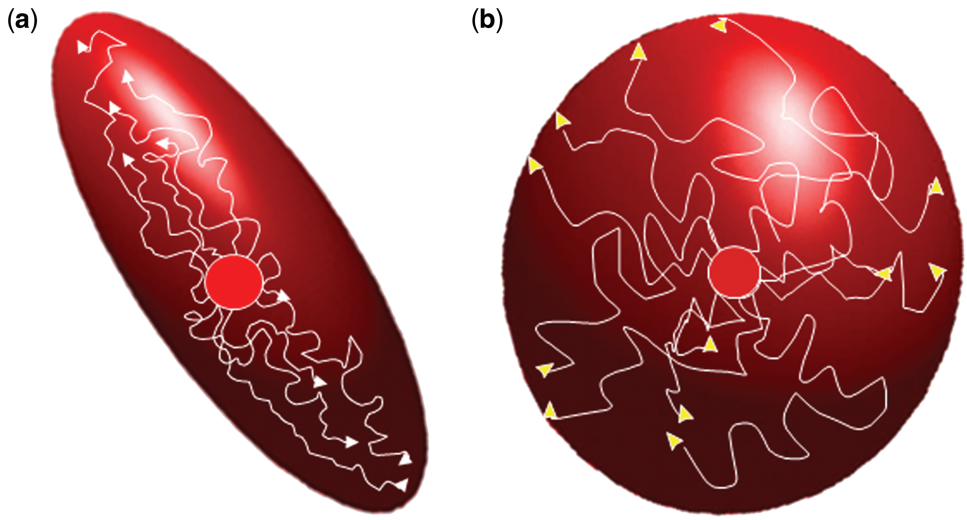

Figure 3 **Anisotropic diffusion (a) resembles a three-dimensional ellipsoid in space with predominant diffusion of molecules along the main axis of the ellipsoid and restricted diffusion perpendicular to the ellipsoid. Isotropic diffusion (b) can be represented by a sphere with equal diffusion in all directions in space. The arrows represent the motion of individual molecules.**

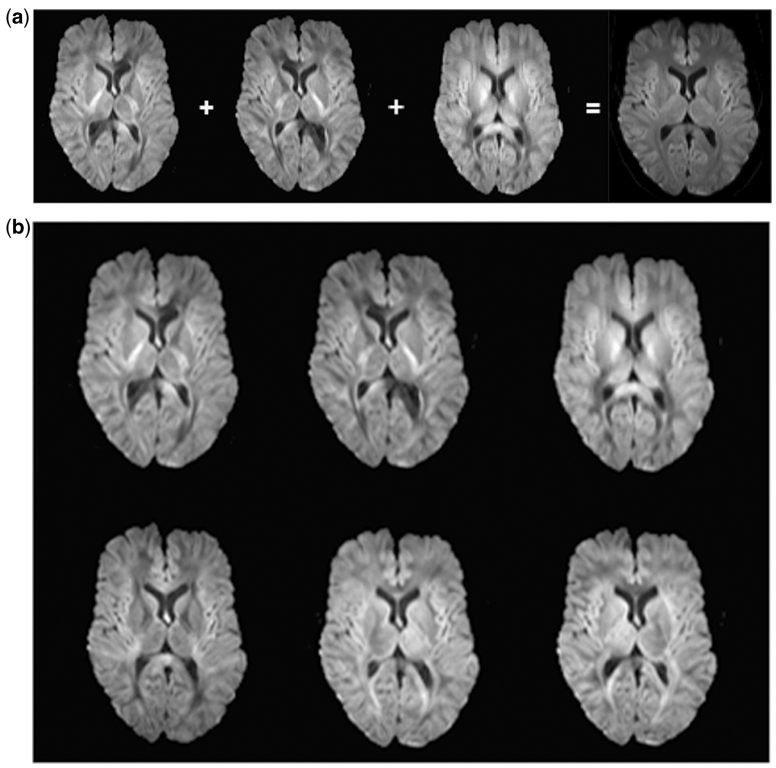

Figure 4 **(a) Raw DWI data acquired with diffusion-encoding gradients applied along the three principal axes in space (*Dxx*, *Dyy*, *Dzz*). The anisotropy of diffusion in the brain can be recognized by the differences in signal intensity of the various white matter tracts in relation to the applied diffusion gradient. The fourth image is the averaged trace of diffusion or DWI image that is used for clinical routine. (b) For diffusion tensor imaging, diffusion gradients are applied in six directions to fully sample the diffusion tensor in space. Consequently, six individual diffusion-weighted images are generated that are again averaged to render the trace of diffusion or diffusion-weighted image.**

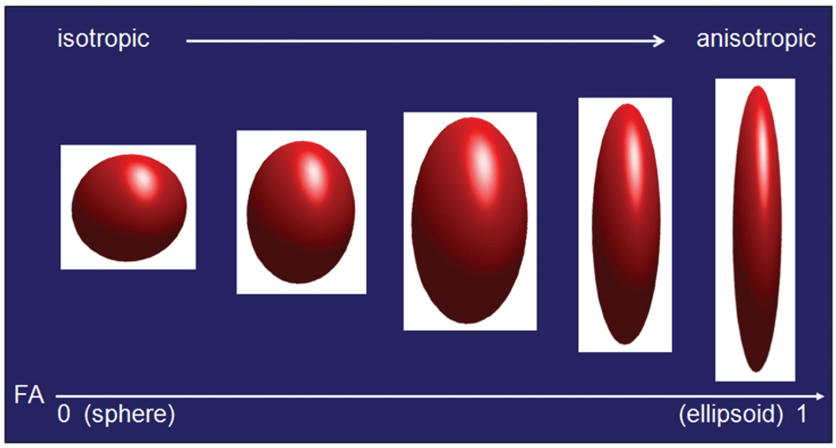

Figure 5 **Graphical display of the range of isotropic towards anisotropic diffusion as can be observed in the various regions of the brain. An FA value of zero represents complete isotropic diffusion (perfect sphere); an FA value of one represents the hypothetical case of complete anisotropic diffusion (narrow ellipsoid).**

intensity of the individual voxels in these maps, which are known as isotropic DWI images or trace of diffusion maps, are essentially the cube roots of the multiplied signal intensities of the three individual images acquired with a diffusion gradient in each of the three orthogonal directions.

Diffusion tensor imaging

Diffusion tensor imaging (DTI) analyses the three-dimensional shape of the diffusion, also known as diffusion tensor. The diffusion tensor of white matter or gray matter tracts should be considered as a three-dimensional structure with three principal diffusivities (eigenvalues, $\lambda 1$, $\lambda 2$, $\lambda 3$) associated with three mutually perpendicular principal directions (eigenvectors). The diffusion tensor harbors valuable information about the microstructure of brain tissue. The trace images give valuable information about the magnitude of diffusion, and the shape of the diffusion tensor may change independently from the overall size or magnitude of the diffusion tensor. A detailed analysis of the diffusion tensor may consequently render valuable information about various disease processes affecting the brain. A prerequisite for DTI is that the entire diffusion tensor is sampled. The tensor has three degrees of freedom and is represented by a 3×3 symmetric matrix (*Dxx*, *Dxy*, *Dxz*, *Dyx*, *Dyy*, *Dyz*, *Dzx*, *Dzy*, *Dzz*). The tensor can consequently be sampled by repeating a diffusion-weighted sequence along six different directions because *Dxy=Dyx*, *Dxz=Dzx* and *Dyz=Dzy* (Fig. 4b). A seventh measurement is performed with a low *b* value. These 7 measurements are the minimum required for solving for the diffusion coefficients that characterize the diffusion tensor.

Based on these data, as well as the DWI and ADC maps, a third map can be calculated: the FA map (Fig. 2). FA is defined as the ratio of the anisotropic component of the diffusion tensor to the whole diffusion tensor and serves as a rotationally invariant scalar that quantifies the shape of the diffusion tensor. FA varies between zero and one. Zero represents maximal isotropic diffusion as in a perfect sphere; one represents maximal anisotropic diffusion as in the hypothetical case of a long cylinder of minimal diameter (Fig. 5). The FA values can also be calculated on a voxel by voxel basis and mapped accordingly. Areas with a high degree of anisotropic diffusion (high FA value) are bright (e.g. corpus callosum, internal capsule), and areas with low anisotropic diffusion are dark (e.g. CSF or gray matter).

Sampling the diffusion tensor also gives information about the principal direction of diffusion (Fig. 6a). Consequently, next to the degree of anisotropic diffusion, the direction of diffusion can also be mapped. Typically, the FA maps can be color coded with red indicating a predominant left-right, green an anterior-posterior, and blue a superior-inferior anisotropic diffusion (Fig. 2). This color coding facilitates recognition of major normal and aberrant white matter tracts.

By combining the directional information and magnitude of anisotropic diffusion of the individual voxels, the course of white matter tracts can be reconstructed. This technique relies on the assumption that voxels with a similar orientation of their principal anisotropic diffusion direction are likely part of the same white matter tract. Powerful postprocessing mathematical algorithms allow white matter tracts to be studied and visualized in vivo. This technique is also known as tractography (Fig. 6b). By increasing the number of diffusion-encoding gradients, complex crossings of white matter tracts within one voxel can be resolved. High-resolution, multitensor imaging (more than six diffusion directions) (Fig. 7) at high field strengths are currently combined with various

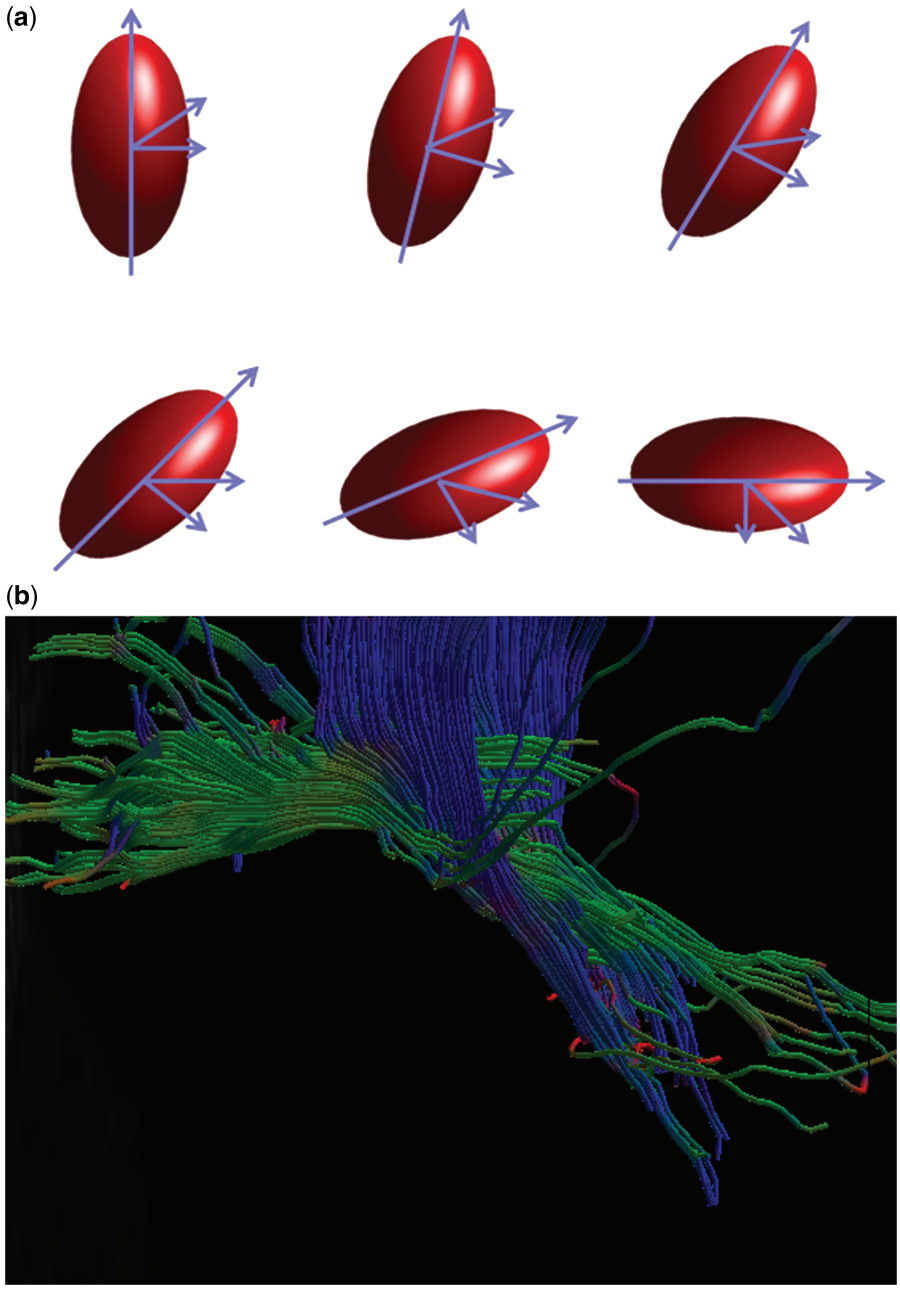

Figure 6 **(a) DTI allows the shape of the diffusion tensor in space (e.g. ellipsoid) to be calculated but also gives the orientation of the tensor in space. The tensor is represented by the three principal eigenvectors both in direction (orientation of the vector) and magnitude (length of the vector). Various orientations of the diffusion tensor are displayed, which provide information about the orientation of white matter tracts in the brain. (b) Based on the DTI data, fiber tracts can be reconstructed from the DTI data based on the identified direction and magnitude of the anisotropic diffusion within the individual voxels. This graph shows a crossing of descending corticospinal tracts (blue) and anterior-posterior (green) running tracts. Various left to right connecting tracts are seen in red.**

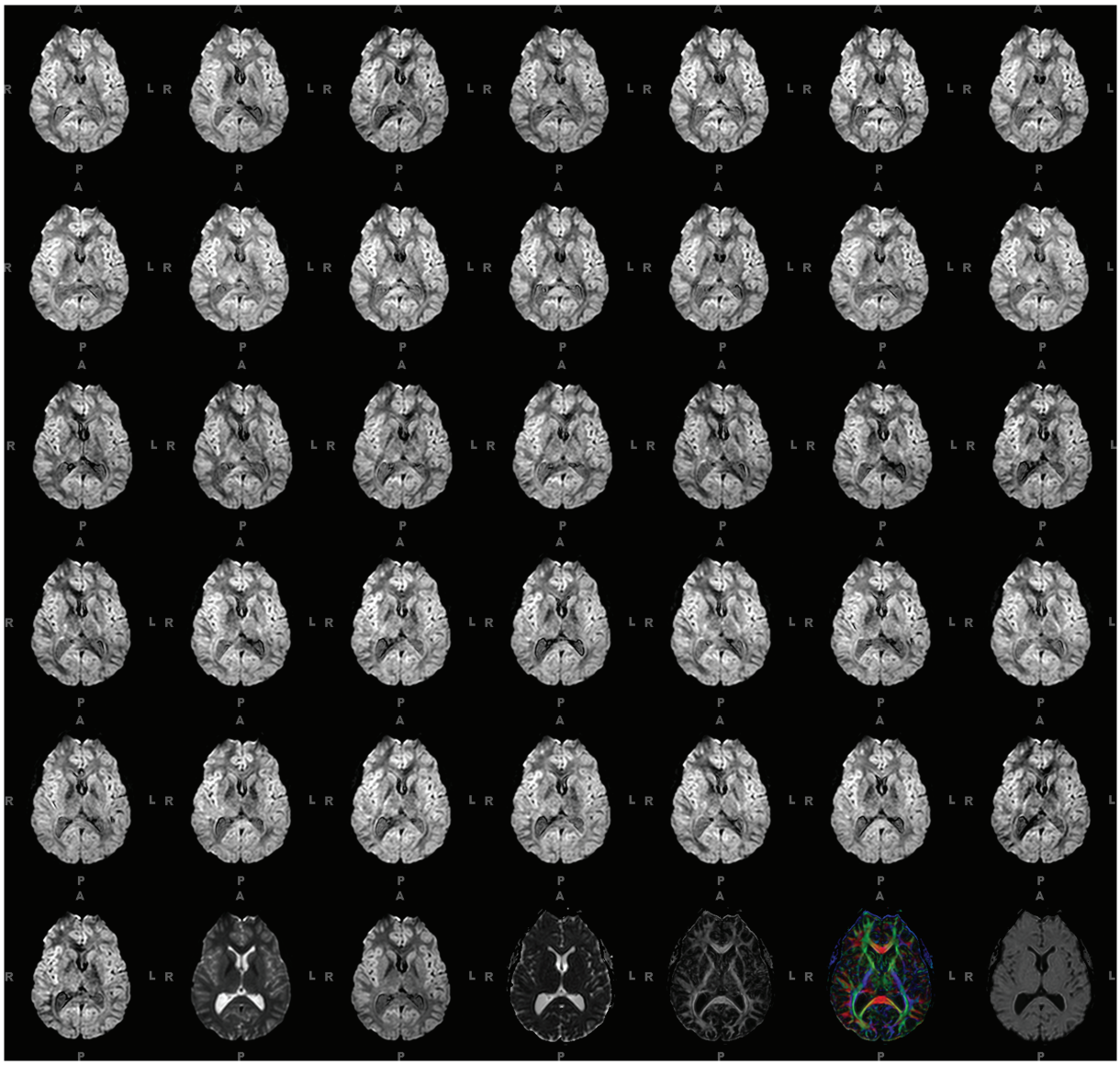

Figure 7 **In multitensor DTI, a significantly higher number of diffusion-encoding gradients are applied along multiple directions in space. This provides more detailed information about the course and crossing of white matter within the brain. In this example, 36 directions have been sampled. In the bottom row the various DTI maps that can be calculated are displayed.**

other advanced MR techniques to study connectivity within the brain. This may be particular helpful to discriminate between tumor-related white matter tract deviation versus infiltration and identification of compensatory rewiring of functional centers affected by adjacent brain tumors.

Why is DWI/DTI so helpful?

The true value and final significance of DWI and DTI for the evaluation of the diseased pediatric brain cannot yet be estimated. Research developments are continuously being translated in routine clinical imaging. The scientific literature on DWI/DTI and the number of applications keeps increasing. DTI revolutionized our understanding of tissue injury in vivo, development of white matter tracts and consequently functional connectivity within the brain. In addition, DWI/DTI allows diseases to be identified and quantified earlier; DTI scalars have proved to be valuable objective biomarkers of tissue injury, allowing treatment monitoring and may serve as a predictor of outcome.

In clinical routine, DWI/DTI has proved to be especially helpful in the early recognition of cerebral ischemia (Fig. 8). DWI/DTI may show tissue injury within 30 min

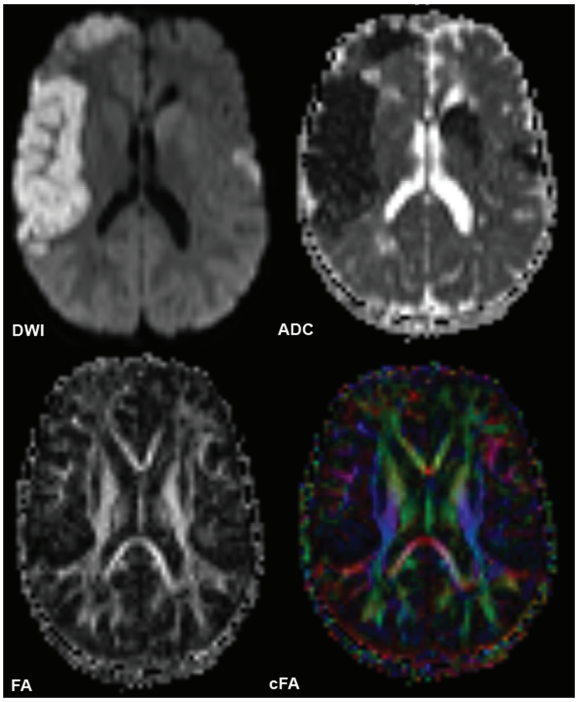

Figure 8 **Example of a 6-year-old boy with an acute bilateral, right dominant ischemic infarction. DWI shows several areas of restricted diffusion with matching ADC hypointensity (usually irreversible cytotoxic edema) in the distribution of the middle and anterior cerebral arteries. On the FA maps a reduced anisotropic diffusion is seen especially in the right middle cerebral artery infarction indicating ongoing loss of fiber tract integrity and cytotoxic edema.**

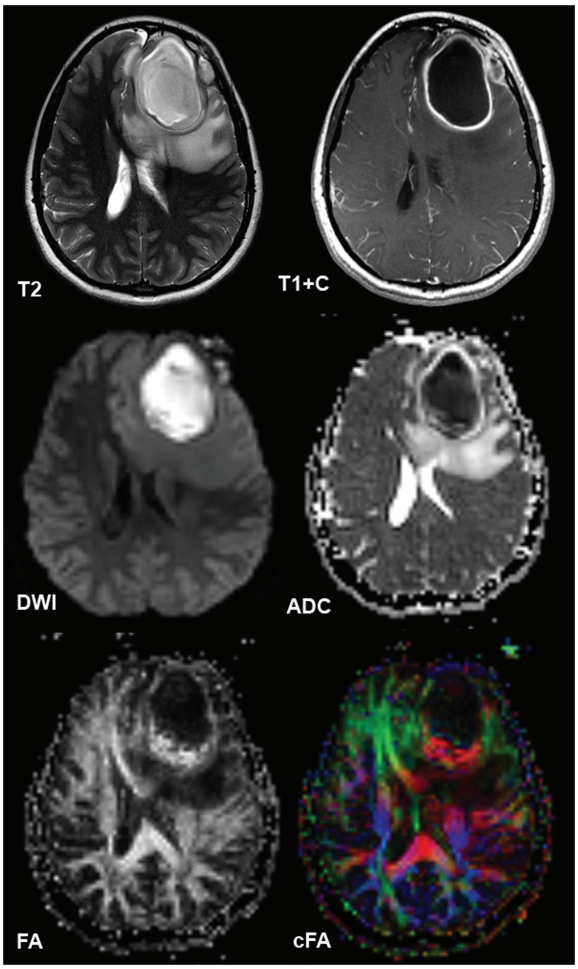

Figure 9 **Example of a 13-year-old boy with a large frontal and epidural brain abscess. T2-weighted and contrast-enhanced T1-weighted images reveal a large, centrally cystic lesion with peripheral enhancement and extensive perifocal white matter edema. The contents of the lesion are DWI hyperintense and ADC hypointense indicating restricted diffusion confirming a large abscess. The perifocal white matter edema is ADC hyperintense compatible with (usually reversible) vasogenic edema. The FA maps show the displacement of adjacent white matter tracts as well as increased isotropic diffusion in the areas of the vasogenic edema.**

of vessel occlusion, before conventional T1- or T2-weighted sequences show pathology. By combining the DWI/DTI data with perfusion-weighted imaging (PWI), tissue at risk for imminent infarction can be identified. Typically the core of infarction is characterized by a matching area of DWI/PWI abnormality surrounded by an area of oligemic tissue without matching diffusion abnormality (penumbra). If the oligemia persists, this area of DWI/PWI mismatch may evolve into infarction. Recognition of these differential areas of oligemia has initiated various neuroprotective treatment options as well as interventions. In addition, lesions with restricted diffusion (e.g. cytotoxic brain edema) and increased diffusion (vasogenic edema) can be differentiated using DWI/DTI (Fig. 9). This may have prognostic significance because cytotoxic edema (e.g. in ischemia) is frequently irreversible; vasogenic edema (e.g. infectious) may be reversible. Moreover, analysis of the DTI scalars may also help to differentiate between an abscess and a necrotic tumor (Fig. 10) or between an arachnoid cyst and an epidermoid cyst (Fig. 11) within the basal cisterns. The time evolution of the ADC and FA scalars in cerebral stroke also helps to date lesions. In ischemia, a pseudo-normalization of the ADC values may be seen at 10 days of ischemic injury.

Analysis of the ADC/FA scalars allows normal and abnormal brain maturation to be studied in children. ADC values are known to decrease with progressive brain maturation/myelination and FA values increase. These scalars may be altered in a variety of focal and diffuse white and gray matter diseases including metabolic diseases, leukodystrophies, autoimmune diseases, traumas and therapy-induced brain injury. This

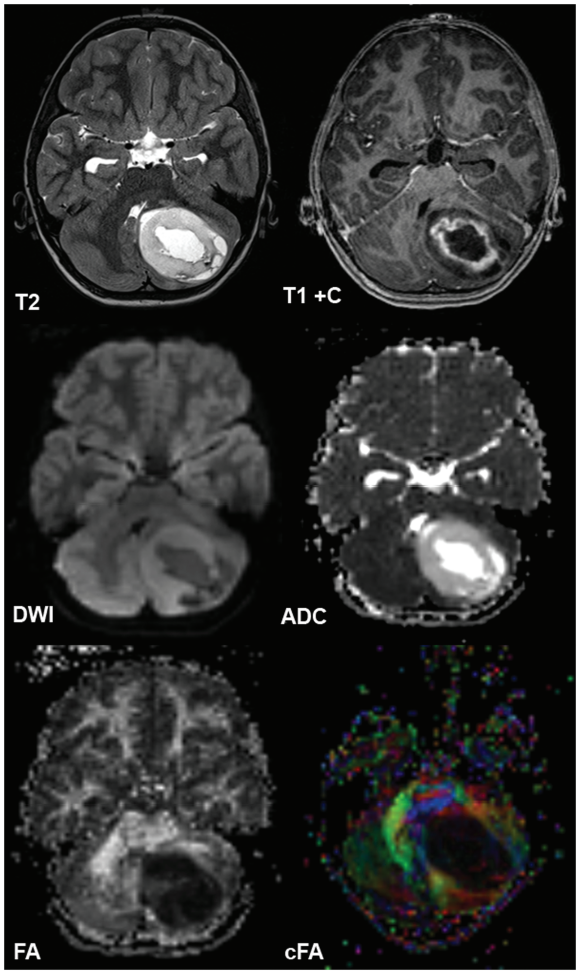

Figure 10 **Example of a 10-year-old female with a left cerebellar pilocytic astrocytoma. The T2- and contrast-enhanced T1-weighted images reveal a large peripherally solid, partially contrast enhancing, centrally necrotic/cystic tumor in the left cerebellar hemisphere. DWI and ADC maps show an increased diffusion within the cystic component excluding abscess formation. The FA maps show a lack of internal diffusion directionality as characterized by the FA hypointensity. The green-encoded white matter tracts in the middle cerebellar peduncle are compressed; the internal fiber architecture of the brainstem is preserved but mildly displaced.**

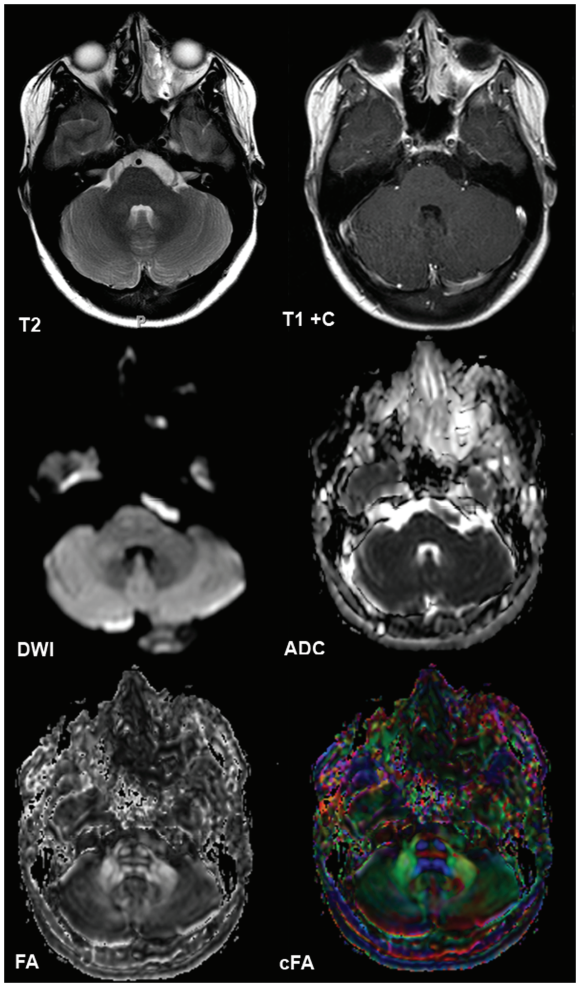

Figure 11 **Example of a 13-year-old female patient with an epidermoid in the left parapontine cistern. The lesion is T1- and T2-isointense with the CSF, limiting detection of the exact extent of the lesion. The epidermoid can easily be recognized on the DWI maps because of the restricted diffusion within the lesion due to the high cellularity (DWI hyperintense, ADC hypointense, FA slightly hyperintense).**

quantitative information may guide treatment and predict outcome. Tractography studies help to better understand the complex normal and abnormal neuronal networking within the brain. This may be of essential significance in the planning of tumor resection and potential of postoperative neurological recovery.

Many future applications are to be expected. A thorough understanding of the basics of DWI/DTI is essential to take full advantage of this exciting technology and to further advance functional neuroimaging.

References

[1] Huisman TA. Diffusion-weighted imaging: basic concepts and application in cerebral stroke and head trauma. Eur Radiol 2003; 13: 2283–97. doi:10.1007/s00330-003-1843-6. PMid:14534804.

[2] Huisman TA, Tekes A. Advanced MR brain imaging. Why? Pediatr Radiol 2008; 38: S415–32. doi:10.1007/s00247-008-0895-9. PMid:18470451.

[3] Huisman TA, Schwamm LH, Schaefer PW, *et al.* Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. AJNR Am J Neuroradiol 2004; 25: 370–6.

[4] Huisman TA, Boltshauser E, Martin E, Nadal D. Diffusion tensor imaging in progressive multifocal leukoencephalopathy: early predictor for demyelination? AJNR Am J Neuroradiol 2005; 26: 2153–6.

[5] Poretti A, Boltshauser E, Loenneker T, *et al.* Diffusion tensor imaging in Joubert syndrome. AJNR Am J Neuroradiol 2007; 28: 1929–33. doi:10.3174/ajnr.A0703. PMid:17898198.