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REVIEW

A MACROSCOPIC VIEW OF MICROSTRUCTURE: USING DIFFUSION-WEIGHTED IMAGES TO INFER DAMAGE, REPAIR, AND PLASTICITY OF WHITE MATTER

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Abstract—Since its introduction in the early 1990s, diffusion-weighted magnetic resonance imaging (MRI) has played a crucial role in the non-invasive evaluation of tissue microstructure of brain parenchyma *in vivo*. Diffusion anisotropy, in particular, has been extensively used to infer histological changes due to brain maturation and pathology, as it shows a clear dependence on tissue architecture. Although the resolution used in most studies lies in the macroscopic range, the information provided originates at the microscopic level and, as such, diffusion MRI serves as a microscope that can reveal profound details of tissue with direct clinical and research applications. The interpretation of diffusion parameters of white matter rests on what is known to drive diffusion anisotropy, namely axonal membranes, density and coherence, as well as myelin sheaths. However, these factors interact to modulate anisotropy, making interpretations potentially difficult. While there are numerous publications that report diffusion changes in response to particular, histologically confirmed tissue abnormalities in animal models of disease, the microscopic correlates of altered diffusion parameters due to neurological disorders in humans have been difficult to characterize. Animal models may provide insight into the mechanisms involved, but do not necessarily provide accurate representations of the human condition, making human diffusion MRI studies with direct histological confirmation crucial for our understanding of tissue changes secondary to neurodevelopment and disease. This work provides a synopsis of tissue characteristics that give rise to highly informative, specific diffusion patterns, and also of how methodological and artifactual aspects can provide erroneous diffusion measurements that do not accurately reflect tissue and may lead to misinterpretation of results. Examples of diffusion changes due to human conditions are provided to illustrate the wealth of applications of diffusion MRI in clinical and research fields.

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Abbreviations: CHARMED, composite hindered and restricted model of diffusion; DTI, diffusion tensor imaging; FA, fractional anisotropy; FWHM, full width at half maximum; fODF, fiber orientation distribution function; MD, mean diffusivity; MRI, magnetic resonance imaging; PDF, probability density function.

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Contents

INTRODUCTION

The self-diffusion of water molecules is random, but barriers present in tissue hinder such free motion and, in effect, impart a particular signature to the displacement profile of water molecules. Far from being a drawback, this provides a mechanism with which to probe the micro-structural organization of tissue. In tissue with highly organized and coherent microstructure, water does not diffuse equally in all directions, but rather follows a preferred direction and is thus anisotropic. The brain's white matter and peripheral nerves are composed of bundles of packed axons with similar orientations and have been extensively analyzed in terms of their diffusion properties. Neural tissue is, however, not the only tissue capable of imparting anisotropy to the diffusion of water molecules, as skeletal and myocardial muscle fibers, and potentially any other tissue with a regular and directional organization, also show this phenomenon. The biological mechanisms that produce diffusion anisotropy in nervous tissue are well understood and have been reviewed before (Beaulieu, 2002). Briefly, the main contributor to diffusion anisotropy is the presence of ordered cellular membranes, such as the axolemma, with the spacing between them within such a range that a water molecule is likely to encounter them several times within a short time period. Water molecules

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diffusing randomly at body temperature could potentially move as far as ten microns in 50 ms, providing ample opportunity for their interaction with axonal membranes. If the axons are spaced too far apart (or if the diffusion phenomenon is studied within a very small time window), water molecules will not have sufficient time to interact with the membranes, and diffusion anisotropy will appear to be reduced or not be evident at all. Semi-permeable barriers, such as the myelin sheaths that encapsulate certain axons, further modulate diffusion anisotropy. Thus, the diffusion profile is governed by the micro-architecture of the tissue (Pierpaoli et al., 1996), and if such architecture is coherent enough (and the diffusion profile is sampled appropriately), then the preferred direction of anisotropic diffusion will match the predominant orientation of the tissue.

Diffusion-weighted magnetic resonance imaging (MRI) allows the simultaneous assessment of water diffusion in a large number of samples (pixels) across an imaging plane (Lebihan and Breton, 1985; Merboldt et al., 1985; Taylor and Bushell, 1985; Le Bihan et al., 1986). Relating the signal in the presence of diffusion sensitization to that of an otherwise identical image, but lacking diffusion sensitization, provides a quantitative measure of the diffusion process in one dimension. If the experiment is repeated several times and the diffusion behavior is sampled in three dimensions, it is possible to reconstruct the diffusion profile on a pixel-by-pixel basis. As stated above, the preferred direction of diffusion on a given pixel (or voxel, in three dimensions) will relate to the tissue contained therein. White matter, being highly organized, will produce highly anisotropic diffusion profiles that follow the shape of major fiber bundles. Neighboring voxels belonging to the same structure will have similar preferred diffusion orientations: this is exploited by computational algorithms that enable the reconstruction of the three-dimensional trajectory of white matter bundles – a technique known as tractography (Mori and van Zijl, 2002). Neuroanatomical studies have benefited greatly from the use of tractography, as it is currently the only method available to delineate white matter pathways in the living human (Johansen-Berg and Behrens, 2006; Ciccarelli et al., 2008; Catani et al., 2012). Methodological aspects and applications of tractography are not covered here, as they warrant their own discussion.

Apart from providing the orientation of white matter fibers, the study of the diffusion of water molecules within each voxel provides a means to probe tissue microstructure in a non-invasive fashion in living tissue. It is of utmost importance, however, to acknowledge that MRI measurements of diffusion summarize an ensemble of water molecules that are simultaneously interacting with the tissue, and that a very large number of fibers may be present within the voxel. Thus, at each voxel (typically 2–3 mm in each dimension), diffusion MRI measurements provide information about the average characteristics of the tissue contained therein, bridging a spatial gap of three orders of magnitude. Fortunately, a leap of faith is not needed, as it has been demonstrated repeatedly that diffusion measurements are capable of providing accurate representations of tissue properties (Beaulieu, 2002). What is needed, however, is a solid knowledge of the mechanisms involved, as many confounding factors hamper a clear and proper interpretation of the diffusion profile (Tournier et al., 2011; Jones et al., 2012; Le Bihan and Johansen-Berg, 2012). This article highlights particular scenarios in which histological characteristics have been inferred in humans by diffusion MRI, with a strong bias toward those studies in which direct histological confirmation was obtained, and with selected references to the animal research literature to provide context.

INFERRING MICROSTRUCTURE NON-INVASIVELY

Considering the difficulties of obtaining histological confirmation of human imaging studies, most of what is known regarding the changes of water diffusion due to white matter pathology comes from animal models of disease, which are assumed to correspond to the human condition. While this may be the case in some circumstances, great care must be exercised in order not to over-interpret diffusion parameters (Jones et al., 2012). Other important sources to support the interpretation of quantitative diffusion parameters include autopsy specimens (Schmierer et al., 2007, 2008), and prior knowledge regarding histological changes in specific neurological diseases.

The most widely used descriptor of water diffusion is the tensor model, with its imaging application known as diffusion tensor imaging (DTI) (Pierpaoli et al., 1996). In this mathematical model, water diffusion is assumed to be Gaussian and unidirectional, and it is represented as an ellipsoid shaped by the eigenvalues of the tensor. The eigenvector associated with the largest eigenvalue therefore represents the principal diffusion direction of water molecules of the tissue within a given voxel, and the remaining two eigenvectors are oriented orthogonal to it. Hence, the ellipsoid is oriented parallel to the predominant direction of white matter fibers. Anisotropy indices such as fractional anisotropy (FA), volume ratio (VR), relative anisotropy (Sands, 1995; Basser and Pierpaoli, 1996; Pierpaoli and Basser, 1996), or the linear component of the ellipsoid (CL) (Westin et al., 2002) relate longitudinal and radial diffusivities, while the mean apparent diffusion coefficient (ADC) or mean diffusivity (MD) provide information about the overall diffusivity, regardless of directionality.

In general, the diffusion tensor model is readily interpreted based on what is known to drive diffusion anisotropy (Beaulieu, 2002): longitudinal diffusivity (i.e., that associated with the largest eigenvalue, and thus, reflecting the diffusivity along the white matter bundle) is affected by axonal damage, particularly fragmentation (Song et al., 2003; Concha et al., 2006; Budde et al., 2007; Sun et al., 2008; Zhang et al., 2009; Liu et al., 2013), while radial (or perpendicular) diffusivity conveys information regarding axonal density, myelin integrity, and axonal diameter, as well as fiber coherence

(Takahashi et al., 2002; Song et al., 2003; Sun et al., 2006; Concha et al., 2010; Choe et al., 2012; Qin et al., 2012).[1] It is important to note that radial diffusivity is affected by several independent micro-architectural features, and it is impossible to discern their specific contributions by means of the tensor model alone.

Axons and myelin are not the only components within the white matter, yet they have been given a pivotal role in the biological interpretation of the diffusion tensor. Glial cells, for example, are abundant in the white matter, but are rarely taken into consideration when interpreting diffusion parameters (Ronen et al., 2013). Recently, highly organized formations of glial cells in the scar surrounding traumatic brain injury were found to be responsible for elevating diffusion anisotropy to a much larger degree than axonal or myelin contributions (Budde et al., 2011). Also, there is ample evidence that white matter contains a variable number of neurons, which show a descending density gradient from superficial to deep white matter (Larriva-Sahd et al., 2002; Suárez-Solá et al., 2009; DeFelipe et al., 2010). The contribution of these ''ectopic'' neurons to diffusion anisotropy of white matter is generally neglected, although it may be relevant in particular conditions, such as schizophrenia, in which their density is increased (Eastwood and Harrison, 2005).

Given its assumptions, the tensor model is only applicable where a single fiber population exists, as crossing, ''kissing'' or fanning fibers will result in oblate or isotropic tensors. More importantly, the determination of the vector associated with the largest eigenvalue in the presence of multiple fiber populations is an ill-posed problem, thus making the terms ''axial'' and ''radial'' diffusivities meaningless, along with their analysis (Wheeler-Kingshott and Cercignani, 2009). An added complication is that regions of crossing fibers may show a seemingly paradoxical increase of diffusion anisotropy when one of the two fiber populations undergoes degeneration (Pierpaoli et al., 2001; Douaud et al., 2011). It has been recently demonstrated (numerically and experimentally) that complex fiber architecture modulates all aspects of the diffusion tensor, and that such modulations are dependent on the geometrical properties of such crossings: Mean diffusivity decreases by as much as 5% as the angle between two fiber populations widens, and as a function of the volume fraction of the two fiber populations (Vos et al., 2012). Thus, the paradoxical increase of diffusion anisotropy following degeneration of a fiber population in a region of crossing fibers may be accompanied by an increase of MD that could be better interpreted by methodological (rather than physiological) considerations.

The described relationships of axial and radial diffusivities with tissue characteristics may be overly simplistic, yet they have served as the basis for interpreting the tensor model in several conditions over the past two decades. In general and when properly analyzed (Jones and Cercignani, 2010), the tensor model is sufficient and highly informative in regions containing a single fiber orientation, such as the fornix or the corpus callosum. Despite the known limitations of the tensor model, its straightforward biological interpretation, as well as the fact that the required data are not very demanding (i.e., relatively few diffusion gradient directions are needed, with a b value on the order of 1000 s/mm^2) (Lebel et al., 2012), has made its use widespread for the inference of tissue abnormalities due to injury or pathology in humans. On the other hand, the recognition that more than two-thirds of the voxels in a typical brain data set contain more than one fiber population (Behrens et al., 2007; Jeurissen et al., 2012) suggests that the tensor model is inappropriate for whole-brain analyses. The most straightforward way to deal with this problem is to estimate multiple tensors within each image voxel (Kreher et al., 2005; Peled et al., 2006; Ramirez-Manzanares et al., 2007), but the solution through this approach is non-unique, as different parameterizations of the underlying tensors may equally explain the observed data. Alternatives to the tensor model (discussed in Section 3) can cope with many of the shortcomings of the diffusion tensor and are rapidly gaining ground for the study of white matter microstructure.

Diffusion MRI, in general, is susceptible to imaging artifacts, such as image noise, geometric distortions due to eddy currents, motion artifacts (including pulsation), and ghosting. All these artifacts have a direct impact on the quantitative diffusion parameters and must be considered before attempting to provide biological interpretations of the data (Le Bihan et al., 2006; Jones and Cercignani, 2010). For example, an imaging voxel containing more than one tissue type will yield signal equal to the weighted average of its components. This artifact, known as partial volume, is most evident in voxels lying at the boundary between brain parenchyma and cerebrospinal fluid (CSF), which are prone to show fast and near-isotropic diffusion profiles due to their CSF signal contribution, obscuring the information from the tissue of interest (Concha et al., 2005; Metzler-Baddeley et al., 2012). This negative effect can be minimized by fitting the signal using a two-tensor model (Pierpaoli and Jones, 2004; Pasternak et al., 2009), or by nulling the CSF signal at the time of acquisition by means of an inversion pulse (Papadakis et al., 2002; Chou et al., 2005; Concha et al., 2005; Cheng et al., 2011). The smaller a brain structure, the greater the proportion of its voxels that may be affected due to partial volume (Vos et al., 2011), which highlights the importance of providing some form of control over this artifact in certain areas of the brain, such as the fornix or the pons.

Considering all the above, and regardless of the analytical method used, it must be stressed that diffusion MRI provides *indirect* information about tissue microstructure, and that several modeling assumptions, data acquisition limitations and image artifacts are likely to influence the resulting signal, and must be accounted for prior to making absolute claims about tissue integrity

[1] Too often, only MD and some sort of anisotropy index are reported, precluding the possibility to infer more details regarding tissue micro-architecture (Hasan, 2006). FA and MD are not enough to explain the shape of the tensor and are not orthogonal to each other (Ennis and Kindlmann, 2006): in general, the eigenvalues of the tensor should be reported for a more thorough interpretation of the results.

in the absence of direct histological confirmation (Jones et al., 2012).

White matter damage and repair

The evaluation of patients with acute ischemic stroke has been the hallmark application of diffusion MRI. This imaging technique has revolutionized the field, for it allows a prompt and accurate diagnosis followed by appropriate treatment. Its most important application is to identify patients with potentially salvageable parenchyma with the goal of providing treatment to those who could benefit from it, while safeguarding those patients in whom the treatment itself could produce further harm. Within minutes after an acute ischemic event, MD shows a marked decrease (Mintorovitch et al., 1991; Hjort et al., 2005), which is generally attributed to energy depletion, ionic imbalance, cellular shrinkage, release of excitatory aminoacids and a shift of water toward the intra-cellular space (cytotoxic edema) (Moseley et al., 1990; Benveniste et al., 1992; Liu et al., 2001; Sotak, 2004). It is still unclear how the increase of intracellular water results in hyper-intense signal on diffusion-weighted images (Duong et al., 2001; Ackerman and Neil, 2010; Budde and Frank, 2010; Badaut et al., 2011) as tortuosity is similar in the intra- and extracellular spaces (Duong et al., 1998), and reduced diffusivity following ischemia is not exclusive to either of the two compartments (Duong et al., 1998; Silva et al., 2002; Goodman et al., 2008). During cytotoxic edema, axons and dendrites adopt a beaded architecture (Murphy et al., 2008) that has been recently proposed to be a major contributor to the initial decrease of diffusivity following ischemia, due to the introduction of barriers (membranes) that hinder water mobility along these two neuronal structures (Budde and Frank, 2010). Further breakdown of the blood–brain barrier, damage to cell membranes, and vasogenic edema all have actions opposite to cytotoxic edema, pseudo-normalizing MD within the next 2 to 7 days (Knight et al., 1991; Duong et al., 1998; Gaudinski et al., 2008). Decreased MD is not associated with an established infarct (Liu et al., 2001), as tissue can potentially recover after reperfusion (Mintorovitch et al., 1991; Kidwell et al., 2000), although MD normalization following treatment does not guarantee tissue salvage (Li et al., 2002). Diffusion anisotropy is also time dependent with respect to stroke onset, with an initial slight increase in the hyper-acute phase (<5–7 h after onset), followed by a reduction within the next 24–36 h to values less than those found in non-affected tissue (Sorensen et al., 1999; Yang et al., 1999; Bhagat et al., 2006, 2008; Liu et al., 2007). While the mechanisms that increase diffusion anisotropy in the first few hours after stroke onset are still unclear, it has been suggested that cytotoxic edema could reduce the space between fibers and increase intra-axonal tortuosity, thus providing greater orientation-dependent barriers to diffusion (Sotak, 2002; Sen and Basser, 2005). Subsequent reduction of diffusion anisotropy is attributed to degradation of tissue microstructure in the chronic phases of stroke (Liu et al., 2007) and can be seen in areas remote from the lesion due to secondary degeneration of the white matter fibers (Pierpaoli et al., 2001). Diffusion MRI can be used to monitor the evolution of stroke and to predict functional outcomes depending on the site of the lesion and the quantitative diffusion parameters contained therein and in remotely connected regions (Jiang et al., 2010). Although already established as an invaluable clinical tool in the evaluation of ischemic stroke, diffusion MRI is extensively used in animal models of the disorder, providing crucial information on the patho-physiology of ischemic injury, with the great advantage that this newly generated knowledge is rapidly being integrated into patient care.

Diffusion MRI is a useful tool in the field of oncology, as some brain tumors infiltrate white matter, while others merely displace it, a difference that may translate into very different treatments. For example, the infiltration of gliomas into organized tissue disrupts its architecture by virtue of disorganized cellular growth, neuronal death and axonal loss, all of which can be evaluated with DTI (Goebell et al., 2006; Stadlbauer et al., 2006). In a study of 20 patients with a histologically-confirmed diagnosis of glioma (grade II and III), the quantitative histological characteristics of 77 biopsies were correlated with pre-operative DTI indices, and the authors demonstrated a clear negative correlation between FA and both tumor cell number and degree of infiltration (Fig. 1) (Stadlbauer et al., 2006). In a different study, the same authors reported that the tract count per voxel (as derived from whole brain tractography) also correlated with quantitative histology (Stadlbauer et al., 2010), a finding that is explained in part by the dependence of the tracking algorithms on FA values. Edema and fluid accumulation in solid tumors lead to an enlarged extracellular space and, in turn, to increased MD, while highly cellular tumors show the reverse pattern (Humphries et al., 2007; Fatima et al., 2013; Koral et al., 2013). Brain abscesses generally display low values of MD, which shows a strong negative correlation with the number of viable inflammatory cells in the medium (Mishra et al., 2005), and thus diffusion MRI can be used to differentiate them from necrotic brain tumors (Reddy et al., 2006). Grading of brain tumors and their response to treatment, although debatable (Padhani et al., 2009), has also been attempted with diffusion MRI (Chenevert et al., 2000; Hamstra et al., 2005, 2008; Sijens et al., 2007). In a recent study, pre-operative super-resolution track density imaging (Calamante et al., 2010) was related to the histological characteristics of 43 image-guided biopsies from 18 patients with glioblastoma (Barajas et al., 2013). In particular, the necrotic core of the tumors corresponded to decreased track density, while the surrounding (non-Gd-enhancing) tissue showed complex characteristics, including edema, microscopic hemorrhage, necrosis and invading glioma cells within white matter that led to a paradoxical increase in track density. Further, tractography can be used to plan surgical interventions that spare displaced white matter

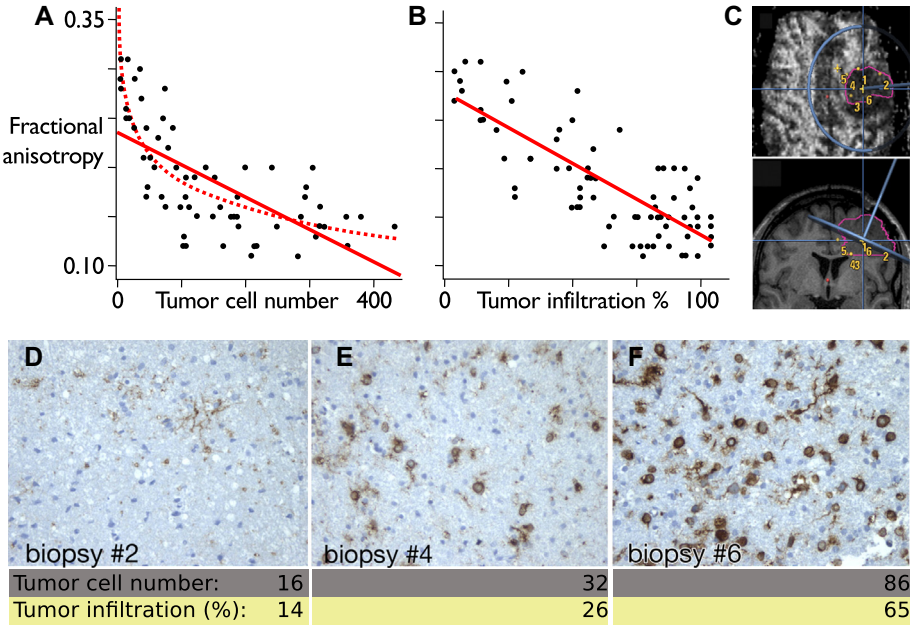

Fig. 1. Correlations between fractional anisotropy (FA) and quantitative histology of glioma biopsies. Pre-operative FA values show a negative correlation with tumor cell number (A) and tumor infiltration (B) defined as the ratio between tumor and non-tumor cells (n = 77 biopsies, 20 patients). (C) Biopsy sites are shown for a representative patient overlaid on an axial FA map (top) and a coronal T1-weighted image (bottom). The corresponding photomicrographs of three biopsies taken from the sites specified in C are shown in D–F. Tumoral cells are stained in brown over a hematoxylin–eosin stain, and the corresponding values (averaged over five fields) are shown below each field. (Modified from Stadlbauer et al. (2006), with permission from the author and the Radiological Society of North America).

fibers, thereby reducing secondary deficits brought about by their ablation [see, for example, (Leclercq et al., 2011)].

While computing correlations of diffusion parameters with histology is relatively straightforward in the case of biopsy specimens, the same is not true in the case of human fiber bundles affected by disease, for there are few scenarios where pre-operative imaging and subsequent procurement of white matter tissue is feasible. For example, the fimbria-fornix of 11 patients with temporal lobe epilepsy undergoing surgery was analyzed using DTI prior to surgery, which demonstrated reduced FA and increased radial diffusivity. Quantitative electron microscophic evaluation of the surgically resected tissue revealed a positive correlation between the surface area of axonal membranes and FA and a similar positive trend between FA and axonal density (Concha et al., 2010). Although myelin has been shown to modulate diffusion anisotropy (Gulani et al., 2001; Beaulieu, 2002), it did not play a role in the case of the fornix specimens, although other studies of ex-vivo human brains have proven its participation (Schmierer et al., 2007, 2008; Saksena et al., 2008). The direct confirmation of microstructural changes that were predicted by pre-surgical diffusion further validates the use of DTI to detect white matter pathology, particularly in the case of fiber bundles with a single fiber population.

DTI is also a very sensitive tool for the detection of Wallerian degeneration, and the time course of the diffusion parameters reflects the underlying microstructural changes that occur during the degeneration process (Fig. 2). During the acute phases of degeneration (i.e., the first week after the primary lesion), axons within the fiber bundles fragment and form beaded structures (Kerschensteiner et al., 2005; Zhang et al., 2009; Qin et al., 2012) that hinder diffusivity along the axons, which translates into reduced anisotropy secondary to a decrease of the major eigenvalue (Thomalla et al., 2004, 2005; Concha et al., 2006; Liu et al., 2013). Next, over a period of several months, there is further axonal membrane breakdown, progressive degradation and phagocytosis of the myelin sheaths, glial proliferation and macrophage infiltration (particularly in the vicinity of the primary lesion) (Vaughn et al., 1970; Cook and Wisniewski, 1987; George and Griffin, 1994), and all these events lead to a minimization or disorganization of the barriers that normally restrict radial diffusivity, thus increasing the second and third eigenvalues (reducing anisotropy) –this has been extensively demonstrated in humans (Pierpaoli et al., 2001; Thomalla et al., 2004, 2005; Concha et al., 2006; Yu et al., 2009; Liu et al., 2013) and is in line with results in animal models (Zhang et al., 2009; Qin et al., 2012). The ability to stage Wallerian degeneration by characterizating the diffusion parameters of white matter enables DTI to be used as a tool for the prognosis of patients following stroke (Yu et al., 2009; Puig et al., 2010) and traumatic (Betz et al., 2012) or other (Naismith et al., 2010) acute brain injuries.

Multiple sclerosis (MS) is particularly amenable to study with diffusion-weighted MRI, as degradation of myelin, one of the modulators of diffusion anisotropy, is the hallmark of the disease (Fox, 2008; Rovira and

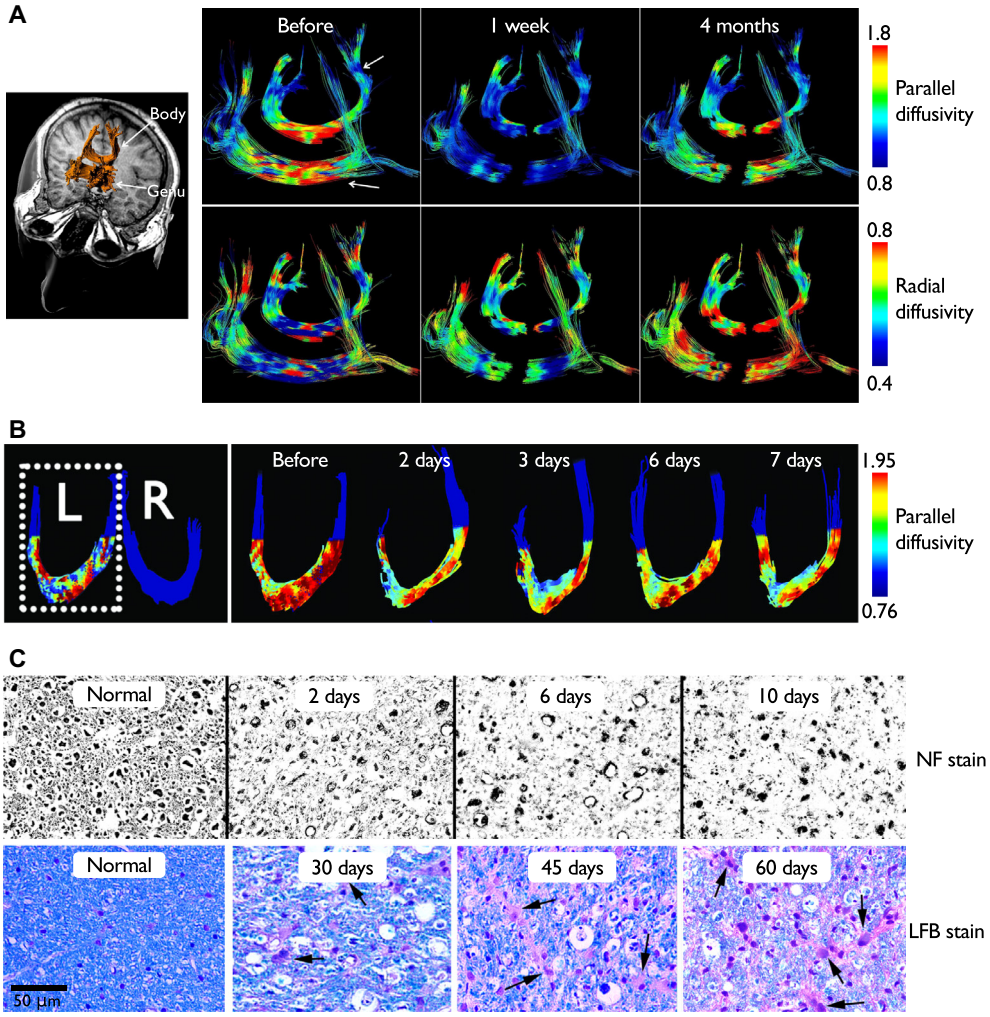

Fig. 2. Acute and chronic phases of Wallerian degeneration. (A) Diffusion parameters of the genu and body of the corpus callosum in a patient before and after surgical transection of the fibers. There is a marked decrease of parallel diffusivity at one week, with pseudo-normalization at 4 months, while perpendicular diffusivity shows a gradual increase over time. (B) The first week following transection of the fornix in a patient with temporal lobe epilepsy shows that the decrease of parallel diffusivity occurs immediately after the lesion. (C) Immunohistochemical analysis of the cortico-spinal tract in a feline model of Wallerian degeneration confirms the acute degeneration of axons, as revealed by the neurofilament protein stain (NF), and the chronic and progressive degradation of myelin evidenced by Luxol-fast blue stain (LFB). Arrows in bottom row of panel C indicate axonal debris (purple) that has been phagocytized by activated microglia. Adapted, with permission from the authors, from Concha et al. (2006) (A), Liu et al. (2013) (B) and Qin et al. (2012) (C).

León, 2008; Hygino da Cruz et al., 2011). There is, in addition, direct axonal damage (Trapp et al., 1998), which can further decrease diffusion anisotropy. Tissue inflammation is present in active lesions, and the degree to which the histological changes occur is extremely variable between lesions and among patients. Therefore, there are several imaging profiles of MS lesions with any given technique. The most severe and irreversible white matter lesions are clearly visible with conventional T1- and T2-weighted images, and show increased overall diffusivity and decreased anisotropy; these changes are more pronounced in the case of lesions that show post-Gd-enhancement or T1 hypointensity (Filippi et al., 2001). Diffusion MRI, however, has the advantage of being able to demonstrate MS lesions before conventional MRI (Rovaris et al., 2005). The diffusion abnormalities of these so-called ‘‘normal-appearing white matter’’ regions become more marked as the disease progresses and neurological disability increases (Rovaris et al., 2003; Garaci et al., 2007). Furthermore, the diffusion abnormalities cannot be solely attributed to secondary Wallerian degeneration of the axons affected within visible lesions (Rovaris et al., 2005; Saindane et al., 2007). Post-mortem examination of the brains of patients with MS demonstrated that reduced diffusion anisotropy and increased MD within white matter lesions correspond to reduced myelin staining and axonal count (Mottershead et al., 2003; Schmierer et al., 2007). Given that axonal loss is a key predictor of disease progression (Petzold, 2013), diffusion MRI should be able to provide clinically relevant prognostic information regarding progression and neuroprotection, but so far it has been insufficiently accurate to become clinically viable (Barkhof et al., 2009). This may be due to the fact that axonal loss does not occur in isolation, but in

combination with several other histological changes that may modulate diffusion in contrasting ways, such as myelin degradation, edema, inflammation, astrocyte hyperplasia, activation of the microglia, increased tissue water, and alterations in neurofilament phosphorylation (Werring et al., 2000). The contribution of inflammation and increased cellularity has been recently disentangled from axonal damage using a modified multi-tensor approach known as diffusion basis spectrum imaging (Wang et al., 2011). Moreover, animal models have shown that re-myelination can be measured with DTI, particularly through radial diffusivity (Sun et al., 2006), a feat that has been replicated in human spinal cord in MS patients who recover from a spinal cord relapse (Freund et al., 2010), reaffirming the utility of diffusion MRI in longitudinal assessments of subtle white matter changes in MS patients.

Evaluating recovery through diffusion-weighted MRI has received considerable attention recently with good reason, as it provides a non-invasive way to longitudinally monitor the effect of treatment. A longitudinal study of 22 patients with traumatic brain injury (Sidaros et al., 2008) showed that DTI parameters could be used as prognostic factors regarding the patients' recovery. Shortly after injury, the patients showed reduced FA and increased radial diffusivity in several white matter regions, particularly the cerebral peduncles, which correlated with the neurological state 1 year later. Moreover, the DTI parameters of the internal capsule and centrum semiovale showed normalization in patients with good outcomes, while elevated MD and a lack of FA normalization in the cerebral peduncle and corpus callosum were associated with limited recovery. Other studies have shown that quantitative diffusion parameters of the white matter, particularly of the corticospinal tract, are indicative of motor function several months following stroke (Watanabe et al., 2001; Cho et al., 2007; Schaechter et al., 2009; Qiu et al., 2011). The tissue at the periphery of post-ischemic necrosis undergoes drastic changes that can be modulated or accentuated by neuro-restorative therapy (Jiang et al., 2010). Following stroke induced in rodents, the border zone of the ischemic lesion shows an initial reduction of FA, followed by a normalization and even elevation that is commonly attributed to axonal and myelin regeneration. The reorganization of white matter can be modulated by certain treatments such as neural progenitor cell treatment (Jiang et al., 2006), sildenafil (Ding et al., 2008) or erythropoietin (Li et al., 2009), all of which result in increased FA (Dijkhuizen et al., 2012). However, it is important to recognize that reactive gliosis shows a high degree of directionality, which can also increase diffusion anisotropy (Li et al., 2005). Indeed, this phenomenon has been clearly demonstrated to also occur in the scar that surrounds experimentally injured brain tissue, where the contribution of gliosis to the variance of diffusion anisotropy was greater than that of axons (Budde et al., 2011), meaning that not all increases of diffusion anisotropy are signs of recovery.

Plasticity of white matter

Structural plasticity of the adult brain was classically considered small, if it existed at all. However, there is at present little doubt that the adult brain is capable of undergoing molecular, structural and functional changes, many of which form the bases of memory and learning processes, or certain neurological disorders (Taubert et al., 2012). Understanding these mechanisms, as well as their time course, is pivotal for the development of restorative and neuroprotective interventions to treat neurodegenerative disorders such as Parkinson's disease, or acute brain lesions such as stroke or traumatic brain injury. Longitudinal and non-invasive investigations are necessary, particularly to study high-order processes that are mostly evident in the human brain. Neuroimaging techniques, MRI and others, can fulfill this role, but diffusion MRI in particular, with its ability to confer information of the microscopic domain, seems specially suited to probe tissue changes that are not necessarily translated into gross morphological or metabolic modifications.

Learning and training induce many types of structural and functional changes in the gray and white matter in a time-dependent manner (Johansen-Berg et al., 2012; Zatorre et al., 2012); these may include neurogenesis, synaptogenesis, dendritic arborisation, axonal and synaptic sprouting, gliogenesis, angiogenesis and myelin formation (Blumenfeld-Katzir et al., 2011; Zatorre et al., 2012) Long-term effects of cortical plasticity or training result in macroscopic morphological changes that relate to remodeling of neural processes (Lerch et al., 2011), which can be detected through MRI in humans (Maguire et al., 2000; Draganski et al., 2004; Boyke et al., 2008; Driemeyer et al., 2008; Hyde et al., 2009) The white matter of highly trained individuals, such as musicians, shows differences in diffusion parameters from non-trained subjects in key areas of the brain (Bengtsson et al., 2005; Imfeld et al., 2009; Steele et al., 2013). Diffusion MRI of human adults who learned a complex visuo-spatial task (juggling) revealed increased diffusion anisotropy of the white matter underneath the intraparietal sulcus within a 6-week period (Scholz et al., 2009). Similarly, diffusion anisotropy of the white matter of the prefrontal cortex showed a positive correlation with learning performance of a balancing task in subjects within a two-month period (Taubert et al., 2010). These white matter changes are not restricted to motor-related brain regions, as the amount of training in a working memory task correlates positively with diffusion anisotropy of the corpus callosum and the white matter underneath the intraparietal sulcus (Takeuchi et al., 2010). In an animal model of spatial learning and memory which involved learning to navigate a water maze, there was evidence of decreased diffusivity in several brain structures, including the dentate gyrus, and the piriform and cingulate cortices, as compared to their baseline assessed five days earlier (Blumenfeld-Katzir et al., 2011). These changes were related to an increased immunoreactivity to synaptophysin and glial fibrillary acidic protein, as well as a substantial increase in the

number of astrocytic processes. In the same study, the corpus callosum showed a significant increase of diffusion anisotropy following training, which was related to an increase of myelin basic protein observed by immunohistochemistry. In follow-up human studies, it was shown that the MD of the hippocampus and parahippocampus decreased after being involved in only 2 h of a spatial learning task (playing a car-racing video game) (Sagi et al., 2012), and that these changes are echoed in the fornix (Hofstetter et al., 2013). These findings were supported by a similar paradigm in rodents, in which the same diffusion decreases were found, and were related to an increased number of synaptic vesicles, astrocytic processes, and expression of brain-derived neurotrophic factor evaluated through immunohistochemistry (Sagi et al., 2012) (Fig. 3). Other plastic changes such as synaptic reorganization and axonal sprouting can also occur in response to brain injury, as is the case of the hippocampus following status epilepticus (Sutula, 2002). In that case, the coherent organization of the newly formed axonal processes is capable of increasing diffusion anisotropy, as seen through high-resolution diffusion MRI, both ex-vivo and in the living animal (Kuo et al., 2008; Laitinen et al., 2010). Moreover, diffusion MRI is sensitive enough to demonstrate tissue abnormalities that lie beyond the classically recognized sites of alterations following status epilepticus in rats (Sierra et al., 2011; van Eijsden et al., 2011). Although the resolution needed for its application in humans is still not sufficient, these findings could be of great relevance for the diagnosis and follow-up of patients with temporal lobe epilepsy (Sutula et al., 1989) and other forms of brain injury. For a review of plastic changes of gray and white matter, evidenced with diffusion MRI and other neuroimaging methods, the reader is referred to (Zatorre et al., 2012).

WHEN THE TENSOR MODEL IS NOT ENOUGH

With the recognition that using typical resolution nearly 90% of the white matter voxels in the human brain contain crossing fibers (Jeurissen et al., 2012) and that the tensor model is inadequate under these circumstances, there is a definite need to find alternative ways to analyze the diffusion MRI signal that conveys information about complex tissue microstructure. There are several methods to deal with this problem (Tournier et al., 2011), but all have one thing in common, and that is their high demands in terms of data acquisition compared to DTI. Some *q*-space methods require several dozen diffusion gradient directions with one or more high *b* values (~2000–50,000 s/mm^2), which potentially translate into prohibitively long acquisition times (>25 min). Fortunately, recent developments in hardware, pulse sequence design and analytical methods (Tuch et al., 2002; Prčkovska et al., 2013) are progressively reducing

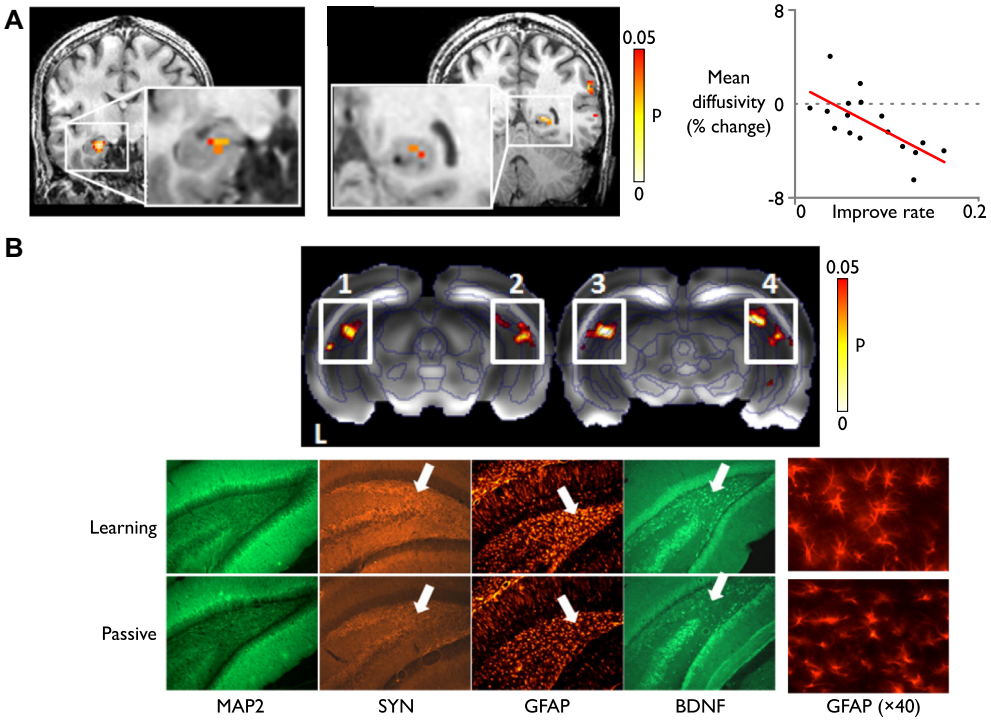

Fig. 3. Changes in mean diffusivity due to training. (A) Decreased mean diffusivity of the left hippocampus and right parahippocampus following 2 h of training on a spatial learning and memory task. There was a negative correlation between the subject's behavioral improvement rate and the change in mean diffusivity of the right parahippocampus (scatter plot). (B) Using a water maze task in rodents, there was also evidence of decreased diffusivity in homologous regions in trained animals, as compared to the passive group (top row; four of five clusters found are shown, 1–4). Immunohistochemical evaluation of the hippocampus (mid- and bottom rows) demonstrated regional differences (arrows) in immunoreactivity of synaptophysin (SYN), glial fibrillary acid protein (GFAP) and bran-derived neurotrophic factor (BDNF), but not microtubule-associated protein 2 (MAP2, a marker of dendrites) between the learning and passive group. Adapted, with permission from the author, from Sagi et al. (2012).

scan time,and the alternatives to DTI are becoming feasible in the clinical realm (Reijmer et al., 2012, 2013a,b; Liégeois et al., 2013). The advantages of non-tensorial approaches to tractography are evident and indisputable (Farquharson et al., 2013), and it is often absolutely necessary to be able to resolve crossing fibers in order to identify certain white matter bundles, such as the acoustic radiation, or the lateral aspects of the cortico-spinal tracts (Behrens et al., 2007). At the single voxel level it is possible to obtain diffusion anisotropy metrics similar to FA, although their biological interpretation has not been as thoroughly studied as their tensor counterpart (Fritzsche et al., 2010). For example, the generalized fractional anisotropy (GFA) index (Tuch, 2004), defined as the standard deviation divided by the root mean square of the diffusion orientation density function, provides a straightforward replacement for FA in non-tensorial data. By design it captures the anisotropy of all the fiber populations at once and, therefore, is unable to extricate tissue abnormalities in separate fiber populations. The construction of the entire diffusion probability density function (PDF) through one of the *q*-space methods [e.g., diffusion spectrum imaging (Wedeen et al., 2005) or *q*-ball imaging (Tuch, 2004)] allows the extraction of parameters that can be altered by pathology or development, such as the zero displacement probability, full width at half maximum (FWHM), root mean square displacement and kurtosis excess. For example, during the natural process of myelination of the spinal cords in rats, the PDF of the white matter becomes increasingly narrow, yielding increasing values of zero displacement probability and decreasing values of FWHM (Assaf et al., 2000). In contrast, an increased FWHM is associated with axonal damage and myelin degradation (Assaf et al., 2003; Biton et al., 2005, 2007). Excess kurtosis, particularly parallel to white matter fibers, is a highly sensitive indicator of degeneration following axotomy in a rodent model, both in the acute and chronic phases of degeneration (Farrell et al., 2010). In patients with multiple sclerosis, levels of N-acetylaspartate (a neuronal marker assessed by MR spectroscopy) correlates with zero displacement probability and FWHM not only in regions of white matter with frank abnormalities, but also in so-called normal-appearing white matter. Further, *q*-space diffusion parameters are more sensitive than DTI to detect these abnormalities (Assaf et al., 2005).

Using multiple *b* value images, the tensor model can be extended into diffusion kurtosis imaging (Jensen et al., 2005; Jensen and Helpern, 2010; Wu and Cheung, 2010), which provides similar information to the excess kurtosis metric derived from the diffusion PDF. More complex models have also been proposed that take into consideration the geometrical properties of tissue and assign different compartments in which diffusion behavior varies (Stanisz et al., 1997; Peled et al., 1999; Assaf et al., 2004; Jespersen et al., 2007; Alexander, 2008). In the composite hindered and restricted model of diffusion (CHARMED) (Assaf et al., 2004), the diffusion signal is separated into a fast-diffusing component, assumed to be extra-axonal, and a slow-diffusing component, assumed to be intra-cellular. The extra-axonal space poses some barriers to free diffusion and can indeed produce anisotropy, but with longer diffusion times, the mean water displacement increases linearly. In contrast, the slow-diffusing, intra-axonal water encounters barriers perpendicular to the fibers that cannot be overcome (i.e., the axolemma and myelin sheaths) and as diffusion times are increased, the water displacement gradually increases toward a plateau. This separation of intra- and extra-axonal diffusivities provides more detailed and accurate estimates of fiber microarchitecture. Further, an extension of the CHARMED model, AxCaliber, exploits the restricted diffusivity to infer the distribution of axon diameters within a given voxel, which correspond closely to those derived from electron microscopy (Assaf et al., 2008; Barazany et al., 2009). While the orientation of the fibers must be known a priori to derive axon diameters from AxCaliber, recently introduced restriction spectrum imaging (White et al., 2013) uses high *b*-value data to study the behavior and orientation of water diffusion within and outside neurites (axons and dendrites), thus providing a more thorough description of tissue organization. In an ex vivo preparation of rodent brain, restriction spectrum imaging was able to capture important structural details of cortical layers that corresponded to histology but were not evident through other diffusion MRI methods. Data requirements must be less strict when imaging the living human brain, for which adaptations of these analytical methods have been made. For instance, the average axonal diameter and density of large white matter bundles can be determined within acceptable acquisition times (Alexander et al., 2010) – while simulations showed the method performed well, and the results in humans are in line with known histological features, there is no direct evidence that the derived axonal metrics correspond to histology. Also, neurite dispersion and density (Jespersen et al., 2007) have been estimated in humans in under 30 min using high angular resolution and two non-zero *b* values (Zhang et al., 2012). As fractional anisotropy can be affected similarly by increased fiber dispersion or reduced fiber density (Tournier et al., 2011), each with very different origins and meanings, the ability to disambiguate the two conditions can provide important biological information, and the relatively short scan times required to acquire all the necessary data make this technique appealing for clinical research.

Using a single non-zero *b* value and multiple gradient directions, the fiber orientation distribution function (fODF) can be obtained through spherical deconvolution (Tournier et al., 2004). The amplitude of the fODF is proportional to the intra-axonal fraction, as well as to axonal diameter and spacing (Dell'Acqua et al., 2012; Raffelt et al., 2012). Convincing results have been obtained by simulation of fibers, and the applicability of this method has been shown in human data, proving it to be more sensitive than DTI parameters to identify

pathological changes in motor neuron disease (Raffelt et al., 2012). Nonetheless, no study has yet confirmed that the suspected mechanisms driving the changes in fODF amplitude truly correspond to histological changes.

CONCLUSIONS

Diffusion MRI is a powerful tool for the non-invasive assessment of tissue microstructure; it cleverly exploits the information regarding the behavior of water diffusion, using it to probe the microscopic environment while reporting at a macroscopic scale. It provides a window into the microscopic realm at each image voxel, while at the same time enabling the identification of macroscopic, long-range white matter pathways through tractography. The relative ease with which it can be applied to study the human brain has made it very popular among scientists and clinicians, and the technique is now available on virtually all modern scanners. As with any powerful tool, however, one must be aware of its reach and its limitations, keeping in mind that any inferences made about tissue microstructure arise from an indirect measurement, and must consider all the factors (biological and artifactual) that may influence the diffusion signal prior to making bold claims about white matter integrity.

The diffusion tensor model has been largely responsible for the widespread adoption of diffusion MRI since its introduction nearly two decades ago, likely due to its simplicity and clear biological interpretation. While DTI remains a valid tool for the analysis of particular brain regions and for testing carefully considered hypotheses, its limitations force us to look for extensions or alternatives for the analysis of diffusion MRI. As such, more complete models or even model-free approaches (some of them as seasoned as the tensor model) are gradually gaining a central role in the study of brain connectivity and tissue characteristic. As data acquisition times are shortened, imaging hardware is improved (or diffusion gradient requirements are relaxed), and histological correlates of complex water diffusivity are understood, these advanced methods are likely to dominate the diffusion MRI literature, and will surely provide us with more accurate and complete descriptions of human white matter microstructure *in vivo* during normal development and in the presence of pathology, recovery and plasticity.

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REFERENCES

Ackerman JJH, Neil JJ (2010) The use of MR-detectable reporter molecules and ions to evaluate diffusion in normal and ischemic brain. NMR Biomed 23:725–733.

Alexander DC (2008) A general framework for experiment design in diffusion MRI and its application in measuring direct tissue-microstructure features. Magn Reson Med 60:439–448.

Alexander DC, Hubbard PL, Hall MG, Moore EA, Ptito M, Parker GJM, Dyrby TB (2010) Orientationally invariant indices of axon diameter and density from diffusion MRI. NeuroImage 52:1374–1389.

Assaf Y, Blumenfeld-Katzir T, Yovel Y, Basser PJ (2008) AxCaliber: a method for measuring axon diameter distribution from diffusion MRI. Magn Reson Med 59:1347–1354.

Assaf Y, Chapman J, Ben-Bashat D, Hendler T, Segev Y, Korczyn AD, Graif M, Cohen Y (2005) White matter changes in multiple sclerosis: correlation of q-space diffusion MRI and 1H MRS. Magn Reson Imaging 23:703–710.

Assaf Y, Freidlin RZ, Rohde GK, Basser PJ (2004) New modeling and experimental framework to characterize hindered and restricted water diffusion in brain white matter. Magn Reson Med 52:965–978.

Assaf Y, Mayk A, Cohen Y (2000) Displacement imaging of spinal cord using q-space diffusion-weighted MRI. Magn Reson Med 44:713–722.

Assaf Y, Mayk A, Eliash S, Speiser Z, Cohen Y (2003) Hypertension and neuronal degeneration in excised rat spinal cord studied by high-b value q-space diffusion magnetic resonance imaging. Exp Neurol 184:726–736.

Badaut J, Ashwal S, Obenaus A (2011) Aquaporins in cerebrovascular disease: a target for treatment of brain edema. Cerebrovasc Dis 31:521–531.

Barajas RF, Hess CP, Phillips JJ, Morze CJV, Yu JP, Chang SM, Nelson SJ, McDermott MW, Berger MS, Cha S (2013) Super-resolution track density imaging of glioblastoma: histopathologic correlation. AJNR Am J Neuroradiol 34:1319–1325.

Barazany D, Basser PJ, Assaf Y (2009) In vivo measurement of axon diameter distribution in the corpus callosum of rat brain. Brain 132:1210–1220.

Barkhof F, Calabresi PA, Miller DH, Reingold SC (2009) Imaging outcomes for neuroprotection and repair in multiple sclerosis trials. Nat Rev Neurol 5:256–266.

Basser PJ, Pierpaoli C (1996) Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B 111:209–219.

Beaulieu C (2002) The basis of anisotropic water diffusion in the nervous system – a technical review. NMR Biomed 15:435–455.

Behrens TEJ, Berg HJ, Jbabdi S, Rushworth MFS, Woolrich MW (2007) Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? NeuroImage 34:144–155.

Bengtsson SL, Nagy Z, Skare S, Forsman L, Forssberg H, Ullen F (2005) Extensive piano practicing has regionally specific effects on white matter development. Nat Neurosci 8:1148–1150.

Benveniste H, Hedlund LW, Johnson GA (1992) Mechanism of detection of acute cerebral ischemia in rats by diffusion-weighted magnetic resonance microscopy. Stroke 23:746–754.

Betz J, Zhuo J, Roy A, Shanmuganathan K, Gullapalli RP (2012) Prognostic value of diffusion tensor imaging parameters in severe traumatic brain injury. J. Neurotrauma 29:1292–1305.

Bhagat YA, Emery DJ, Shuaib A, Sher F, Rizvi NH, Akhtar N, Clare TL, Leatherdale T, Beaulieu C (2006) The relationship between diffusion anisotropy and time of onset after stroke. J Cereb Blood Flow Metab 26:1442–1450.

Bhagat YA, Hussain MS, Stobbe RW, Butcher KS, Emery DJ, Shuaib A, Siddiqui MM, Maheshwari P, Al-Hussain F, Beaulieu C (2008) Elevations of diffusion anisotropy are associated with hyper-acute stroke: a serial imaging study. Magn Reson Imaging 26: 683–693.

Biton IE, Duncan ID, Cohen Y (2007) q-space diffusion of myelin-deficient spinal cords. Magn Reson Med 58:993–1000.

Biton IE, Mayk A, Kidron D, Assaf Y, Cohen Y (2005) Improved detectability of experimental allergic encephalomyelitis in excised swine spinal cords by high b-value q-space DWI. Exp Neurol 195:437–446.

Blumenfeld-Katzir T, Pasternak O, Dagan M, Assaf Y (2011) Diffusion MRI of structural brain plasticity induced by a learning and memory task. PLoS One 6:e20678.

Boyke J, Driemeyer J, Gaser C, Büchel C, May A (2008) Training-induced brain structure changes in the elderly. J Neurosci 28:7031–7035.
Budde MD, Frank JA (2010) Neurite beading is sufficient to decrease the apparent diffusion coefficient after ischemic stroke. Proc Natl Acad Sci 107:14472–14477.
Budde MD, Janes L, Gold E, Turtzo LC, Frank JA (2011) The contribution of gliosis to diffusion tensor anisotropy and tractography following traumatic brain injury: validation in the rat using Fourier analysis of stained tissue sections. Brain 134:2248–2260.
Budde MD, Kim JH, Liang H-F, Schmidt RE, Russell JH, Cross AH, Song S-K (2007) Toward accurate diagnosis of white matter pathology using diffusion tensor imaging. Magn Reson Med 57:688–695.
Calamante F, Tournier J-D, Jackson GD, Connelly A (2010) Track-density imaging (TDI): super-resolution white matter imaging using whole-brain track-density mapping. NeuroImage 53:1233–1243.
Catani M, Dell'Acqua F, Bizzi A, Forkel SJ, Williams SC, Simmons A, Murphy DG, Thiebaut de Schotten M (2012) Beyond cortical localization in clinico-anatomical correlation. Cortex 48:1262–1287.
Chenevert TL, Stegman LD, Taylor JMG, Robertson PL, Greenberg HS, Rehemtulla A, Ross BD (2000) Diffusion magnetic resonance imaging: an early surrogate marker of therapeutic efficacy in brain tumors. J Natl Cancer Inst 92:2029–2036.
Cheng Y-W, Chung H-W, Chen C-Y, Chou M-C (2011) Diffusion tensor imaging with cerebrospinal fluid suppression and signal-to-noise preservation using acquisition combining fluid-attenuated inversion recovery and conventional imaging: comparison of fiber tracking. Eur J Radiol 79:113–117.
Choe AS, Stepniewska I, Colvin DC, Ding Z, Anderson AW (2012) Validation of diffusion tensor MRI in the central nervous system using light microscopy: quantitative comparison of fiber properties. NMR Biomed 25:900–908.
Cho S-H, Kim DG, Kim D-S, Kim Y-H, Lee C-H, Jang SH (2007) Motor outcome according to the integrity of the corticospinal tract determined by diffusion tensor tractography in the early stage of corona radiata infarct. Neurosci Lett 426:123–127.
Chou MC, Lin YR, Huang TY, Wang CY, Chung HW, Juan CJ, Chen CY (2005) FLAIR diffusion-tensor MR tractography: comparison of fiber tracking with conventional imaging. AJNR Am J Neuroradiol 26:591–597.
Ciccarelli O, Catani M, Johansen-Berg H, Clark C, Thompson A (2008) Diffusion-based tractography in neurological disorders: concepts, applications, and future developments. Lancet Neurol 7:715–727.
Concha L, Gross DW, Beaulieu C (2005) Diffusion tensor tractography of the limbic system. AJNR Am J Neuroradiol 26:2267–2274.
Concha L, Gross DW, Wheatley BM, Beaulieu C (2006) Diffusion tensor imaging of time-dependent axonal and myelin degradation after corpus callosotomy in epilepsy patients. NeuroImage 32:1090–1099.
Concha L, Livy DJ, Beaulieu C, Wheatley BM, Gross DW (2010) In vivo diffusion tensor imaging and histopathology of the fimbria-fornix in temporal lobe epilepsy. J Neurosci 30:996–1002.
Cook RD, Wisniewski HM (1987) The spatio-temporal pattern of Wallerian degeneration in the rhesus monkey optic nerve. Acta Neuropathol (Berl) 72:261–267.
DeFelipe J, Fields RD, Hof PR, Hoistad M, Kostovic I, Meyer G, Rockland KS (2010) Cortical White Matter: Beyond the Pale Remarks, Main Conclusions and Discussion. Front Neuroanat 4.
Dell'Acqua F, Simmons A, Williams SCR, Catani M (2012) Can spherical deconvolution provide more information than fiber orientations? Hindrance modulated orientational anisotropy, a true-tract specific index to characterize white matter diffusion. Hum Brain Mapp (Published online ahead of print).
Dijkhuizen RM, van der Marel K, Otte WM, Hoff EI, van der Zijden JP, van der Toorn A, van Meer MPA (2012) Functional MRI and diffusion tensor imaging of brain reorganization after experimental stroke. Transl Stroke Res 3:36–43.
Ding G, Jiang Q, Li L, Zhang L, Zhang ZG, Ledbetter KA, Panda S, Davarani SPN, Athiraman H, Li Q, Ewing JR, Chopp M (2008) Magnetic resonance imaging investigation of axonal remodeling and angiogenesis after embolic stroke in sildenafil-treated rats. J Cereb Blood Flow Metab 28:1440–1448.
Douaud G, Jbabdi S, Behrens TEJ, Menke RA, Gass A, Monsch AU, Rao A, Whitcher B, Kindlmann G, Matthews PM, Smith S (2011) DTI measures in crossing-fibre areas: increased diffusion anisotropy reveals early white matter alteration in MCI and mild Alzheimer's disease. NeuroImage 55:880–890.
Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A (2004) Neuroplasticity: changes in grey matter induced by training. Nature 427:311–312.
Driemeyer J, Boyke J, Gaser C, Büchel C, May A (2008) Changes in gray matter induced by learning—revisited. PLoS One 3:e2669.
Duong TQ, Ackerman JJ, Ying HS, Neil JJ (1998) Evaluation of extra- and intracellular apparent diffusion in normal and globally ischemic rat brain via 19F NMR. Magn Reson Med 40:1–13.
Duong TQ, Sehy JV, Yablonskiy DA, Snider BJ, Ackerman JJH, Neil JJ (2001) Extracellular apparent diffusion in rat brain. Magn Reson Med 45:801–810.
Eastwood SL, Harrison PJ (2005) Interstitial white matter neuron density in the dorsolateral prefrontal cortex and parahippocampal gyrus in schizophrenia. Schizophr Res 79:181–188.
Farquharson S, Tournier J-D, Calamante F, Fabinyi G, Schneider-Kolsky M, Jackson GD, Connelly A (2013) White matter fiber tractography: why we need to move beyond DTI. J. Neurosurg.:1–11.
Farrell JAD, Zhang J, Jones MV, Deboy CA, Hoffman PN, Landman BA, Smith SA, Reich DS, Calabresi PA, van Zijl PCM (2010) Q-space and conventional diffusion imaging of axon and myelin damage in the rat spinal cord after axotomy. Magn Reson Med 63:1323–1335.
Fatima Z, Motosugi U, Waqar AB, Hori M, Ishigame K, Oishi N, Onodera T, Yagi K, Katoh R, Araki T (2013) Associations among q-space MRI, diffusion-weighted MRI and histopathological parameters in meningiomas. Eur Radiol 23:2258–2263.
Filippi M, Cercignani M, Inglese M, Horsfield MA, Comi G (2001) Diffusion tensor magnetic resonance imaging in multiple sclerosis. Neurology 56:304–311.
Fox R (2008) Picturing multiple sclerosis: conventional and diffusion tensor imaging. Semin Neurol 28:453–466.
Freund P, Wheeler-Kingshott C, Jackson J, Miller D, Thompson A, Ciccarelli O (2010) Recovery after spinal cord relapse in multiple sclerosis is predicted by radial diffusivity. Mult Scler Houndmills Basingstoke Engl 16:1193–1202.
Fritzsche KH, Laun FB, Meinzer H-P, Stieltjes B (2010) Opportunities and pitfalls in the quantification of fiber integrity: what can we gain from Q-ball imaging? NeuroImage 51:242–251.
Garaci FG, Colangelo V, Ludovici A, Gaudiello F, Marziali S, Centonze D, Boffa L, Simonetti G, Floris R (2007) A diffusion longitudinal MR imaging study in normal-appearing white matter in untreated relapsing-remitting multiple sclerosis. Am J Neuroradiol 28:475–478.
Gaudinski MR, Henning EC, Miracle A, Luby M, Warach S, Latour LL (2008) Establishing final infarct volume: stroke lesion evolution past 30 days is insignificant. Stroke J Cereb Circ 39:2765–2768.
George R, Griffin JW (1994) Delayed macrophage responses and myelin clearance during Wallerian degeneration in the central nervous system: the dorsal radiculotomy model. Exp Neurol 129:225–236.
Goebell E, Paustenbach S, Vaeterlein O, Ding X-Q, Heese O, Fiehler J, Kucinski T, Hagel C, Westphal M, Zeumer H (2006) Low-grade and anaplastic gliomas: differences in architecture evaluated with diffusion-tensor MR imaging. Radiology 239:217–222.

Goodman JA, Ackerman JJH, Neil JJ (2008) Cs + ADC in rat brain decreases markedly at death. Magn Reson Med 59:65–72.
Gulani V, Webb AG, Duncan ID, Lauterbur PC (2001) Apparent diffusion tensor measurements in myelin-deficient rat spinal cords. Magn Reson Med 45:191–195.
Hamstra DA, Chenevert TL, Moffat BA, Johnson TD, Meyer CR, Mukherji SK, Quint DJ, Gebarski SS, Fan X, Tsien CI, Lawrence TS, Junck L, Rehemtulla A, Ross BD (2005) Evaluation of the functional diffusion map as an early biomarker of time-to-progression and overall survival in high-grade glioma. Proc Natl Acad Sci U S A 102:16759–16764.
Hamstra DA, Galbán CJ, Meyer CR, Johnson TD, Sundgren PC, Tsien C, Lawrence TS, Junck L, Ross DJ, Rehemtulla A, Ross BD, Chenevert TL (2008) Functional diffusion map as an early imaging biomarker for high-grade glioma: correlation with conventional radiologic response and overall survival. J Clin Oncol 26:3387–3394.
Hjort N, Christensen S, Sølling C, Ashkanian M, Wu O, Røhl L, Gyldensted C, Andersen G, Østergaard L (2005) Ischemic injury detected by diffusion imaging 11 minutes after stroke. Ann Neurol 58:462–465.
Hofstetter S, Tavor I, Moryosef ST, Assaf Y (2013) Short-term learning induces white matter plasticity in the fornix. J Neurosci 33:12844–12850.
Humphries PD, Sebire NJ, Siegel MJ, Olsen ØE (2007) Tumors in pediatric patients at diffusion-weighted MR imaging: apparent diffusion coefficient and tumor cellularity. Radiology 245: 848–854.
Hyde KL, Lerch J, Norton A, Forgeard M, Winner E, Evans AC, Schlaug G (2009) Musical training shapes structural brain development. J Neurosci 29:3019–3025.
Hygino da Cruz Jr LC, Batista RR, Domingues RC, Barkhof F (2011) Diffusion magnetic resonance imaging in multiple sclerosis. Neuroimaging Clin N Am 21:71–88.
Imfeld A, Oechslin MS, Meyer M, Loenneker T, Jancke L (2009) White matter plasticity in the corticospinal tract of musicians: a diffusion tensor imaging study. NeuroImage 46:600–607.
Jensen JH, Helpern JA (2010) MRI quantification of non-Gaussian water diffusion by kurtosis analysis. NMR Biomed 23:698–710.
Jensen JH, Helpern JA, Ramani A, Lu H, Kaczynski K (2005) Diffusional kurtosis imaging: the quantification of non-Gaussian water diffusion by means of magnetic resonance imaging. Magn Reson Med 53:1432–1440.
Jespersen SN, Kroenke CD, Østergaard L, Ackerman JJH, Yablonskiy DA (2007) Modeling dendrite density from magnetic resonance diffusion measurements. NeuroImage 34:1473–1486.
Jeurissen B, Leemans A, Tournier J-D, Jones DK, Sijbers J (2012) Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. Hum Brain Mapp (Published online ahead of print).
Jiang Q, Zhang ZG, Chopp M (2010) MRI of stroke recovery. Stroke 41:410–414.
Jiang Q, Zhang ZG, Ding GL, Silver B, Zhang L, Meng H, Lu M, Pourabdillah-Nejed-D S, Wang L, Savant-Bhonsale S, Li L, Bagher-Ebadian H, Hu J, Arbab AS, Vanguri P, Ewing JR, Ledbetter KA, Chopp M (2006) MRI detects white matter reorganization after neural progenitor cell treatment of stroke. NeuroImage 32:1080–1089.
Johansen-Berg H, Baptista CS, Thomas AG (2012) Human structural plasticity at record speed. Neuron 73:1058–1060.
Johansen-Berg H, Behrens TE (2006) Just pretty pictures? What diffusion tractography can add in clinical neuroscience. Curr Opin Neurol 19:379–385.
Jones DK, Cercignani M (2010) Twenty-five pitfalls in the analysis of diffusion MRI data. NMR Biomed 23:803–820.
Jones DK, Knösche TR, Turner R (2012) White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. NeuroImage. http://dx.doi.org/10.1016/j.neuroimage.2012.06.081.
Kerschensteiner M, Schwab ME, Lichtman JW, Misgeld T (2005) In vivo imaging of axonal degeneration and regeneration in the injured spinal cord. Nat Med 11:572–577.
Kidwell CS, Saver JL, Mattiello J, Starkman S, Vinuela F, Duckwiler G, Gobin YP, Jahan R, Vespa P, Kalafut M, Alger JR (2000) Thrombolytic reversal of acute human cerebral ischemic injury shown by diffusion/perfusion magnetic resonance imaging. Ann Neurol 47:462–469.
Knight RA, Ordidge RJ, Helpern JA, Chopp M, Rodolosi LC, Peck D (1991) Temporal evolution of ischemic damage in rat brain measured by proton nuclear magnetic resonance imaging. Stroke J Cereb Circ 22:802–808.
Koral K, Mathis D, Gimi B, Gargan L, Weprin B, Bowers DC, Margraf L (2013) Common pediatric cerebellar tumors: correlation between cell densities and apparent diffusion coefficient metrics. Radiology 268:532–537.
Kreher BW, Schneider JF, Mader I, Martin E, Hennig J, Il'Yasov KA (2005) Multitensor approach for analysis and tracking of complex fiber configurations. Magn Reson Med 54:1216–1225.
Kuo L-W, Lee C-Y, Chen J-H, Wedeen VJ, Chen C-C, Liou H-H, Tseng W-YI (2008) Mossy fiber sprouting in pilocarpine-induced status epilepticus rat hippocampus: a correlative study of diffusion spectrum imaging and histology. NeuroImage 41:789–800.
Laitinen T, Sierra A, Pitkänen A, Gröhn O (2010) Diffusion tensor MRI of axonal plasticity in the rat hippocampus. NeuroImage 51:521–530.
Larriva-Sahd J, Condés Lara M, Mart±nez-Cabrera G, Varela-Echavarria A (2002) Histological and ultrastructural characterization of interfascicular neurons in the rat anterior commissure. Brain Res 931:81–91.
Lebel C, Benner T, Beaulieu C (2012) Six is enough? Comparison of diffusion parameters measured using six or more diffusion-encoding gradient directions with deterministic tractography. Magn Reson Med 68:474–483.
Lebihan D, Breton E (1985) Imagerie de Diffusion In Vivo par Résonance Magnétique Nucléaire. XXX CR Acad Sci Paris 301:1109–1112.
Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M (1986) MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. Radiology 161:401–407.
Le Bihan D, Johansen-Berg H (2012) Diffusion MRI at 25: exploring brain tissue structure and function. NeuroImage 61:324–341.
Le Bihan D, Poupon C, Amadon A, Lethimonnier F (2006) Artifacts and pitfalls in diffusion MRI. J Magn Reson Imaging 24:478–488.
Leclercq D, Delmaire C, Menjot de Champfleur N, Chiras J, Lehéricy S (2011) Diffusion tractography: methods, validation and applications in patients with neurosurgical lesions. Neurosurg Clin N Am 22:253–268.
Lerch JP, Yiu AP, Martinez-Canabal A, Pekar T, Bohbot VD, Frankland PW, Henkelman RM, Josselyn SA, Sled JG (2011) Maze training in mice induces MRI-detectable brain shape changes specific to the type of learning. NeuroImage 54:2086–2095.
Liégeois FJ, Mahony K, Connelly A, Pigdon L, Tournier J-D, Morgan AT (2013) Pediatric traumatic brain injury: language outcomes and their relationship to the arcuate fasciculus. Brain Lang. http://dx.doi.org/10.1016/j.bandl.2013.05.003 [Epub ahead of print].
Li F, Liu K-F, Silva MD, Meng X, Gerriets T, Helmer KG, Fenstermacher JD, Sotak CH, Fisher M (2002) Acute postischemic renormalization of the apparent diffusion coefficient of water is not associated with reversal of astrocytic swelling and neuronal shrinkage in rats. Am J Neuroradiol 23:180–188.
Li L, Jiang Q, Ding G, Zhang L, Zhang ZG, Li Q, Panda S, Kapke A, Lu M, Ewing JR, Chopp M (2009) MRI identification of white matter reorganization enhanced by erythropoietin treatment in a rat model of focal ischemia. Stroke J Cereb Circ 40:936–941.
Liu K-F, Li F, Tatlisumak T, Garcia JH, Sotak CH, Fisher M, Fenstermacher JD (2001) Regional variations in the apparent diffusion coefficient and the intracellular distribution of water in rat brain during acute focal ischemia. Stroke 32:1897–1905.
Liu M, Gross DW, Wheatley BM, Concha L, Beaulieu C (2013) The acute phase of Wallerian degeneration: longitudinal diffusion

tensor imaging of the fornix following temporal lobe surgery. NeuroImage 74:128–139.
Liu Y, D'Arceuil HE, Westmoreland S, He J, Duggan M, Gonzalez RG, Pryor J, de Crespigny AJ (2007) Serial diffusion tensor MRI after transient and permanent cerebral ischemia in nonhuman primates. Stroke 38:138–145.
Li Y, Chen J, Zhang CL, Wang L, Lu D, Katakowski M, Gao Q, Shen LH, Zhang J, Lu M, Chopp M (2005) Gliosis and brain remodeling after treatment of stroke in rats with marrow stromal cells. Glia 49:407–417.
Maguire EA, Gadian DG, Johnsrude IS, Good CD, Ashburner J, Frackowiak RSJ, Frith CD (2000) Navigation-related structural change in the hippocampi of taxi drivers. Proc Natl Acad Sci 97:4398–4403.
Merboldt K-D, Hanicke W, Frahm J (1985) Self-diffusion NMR imaging using stimulated echoes. J Magn Reson 1969(64):479–486.
Metzler-Baddeley C, O'Sullivan MJ, Bells S, Pasternak O, Jones DK (2012) How and how not to correct for CSF-contamination in diffusion MRI. NeuroImage 59:1394–1403.
Mintorovitch J, Moseley ME, Chileuitt L, Shimizu H, Cohen Y, Weinstein PR (1991) Comparison of diffusion- and T2-weighted MRI for the early detection of cerebral ischemia and reperfusion in rats. Magn Reson Med 18:39–50.
Mishra AM, Gupta RK, Saksena S, Prasad KN, Pandey CM, Rathore D, Purwar A, Rathore RKS, Husain N, Jha DK, Jaggi RS, Husain M (2005) Biological correlates of diffusivity in brain abscess. Magn Reson Med 54:878–885.
Mori S, van Zijl PC (2002) Fiber tracking: principles and strategies – a technical review. NMR Biomed 15:468–480.
Moseley ME, Cohen Y, Mintorovitch J, Chileuitt L, Shimizu H, Kucharczyk J, Wendland MF, Weinstein PR (1990) Early detection of regional cerebral ischemia in cats: comparison of diffusion- and T2-weighted MRI and spectroscopy. Magn Reson Med 14:330–346.
Mottershead JP, Schmierer K, Clemence M, Thornton JS, Scaravilli F, Barker GJ, Tofts PS, Newcombe J, Cuzner ML, Ordidge RJ, McDonald WI, Miller DH (2003) High field MRI correlates of myelin content and axonal density in multiple sclerosis – a post-mortem study of the spinal cord. J Neurol 250:1293–1301.
Murphy TH, Li P, Betts K, Liu R (2008) Two-photon imaging of stroke onset in vivo reveals that NMDA-receptor independent ischemic depolarization is the major cause of rapid reversible damage to dendrites and spines. J Neurosci 28:1756–1772.
Naismith RT, Xu J, Tutlam NT, Trinkaus K, Cross AH, Song S-K (2010) Radial diffusivity in remote optic neuritis discriminates visual outcomes. Neurology 74:1702–1710.
Padhani AR, Liu G, Koh DM, Chenevert TL, Thoeny HC, Takahara T, Dzik-Jurasz A, Ross BD, Van Cauteren M, Collins D, Hammoud DA, Rustin GJS, Taouli B, Choyke PL (2009) Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia (New York) 11:102–125.
Papadakis NG, Martin KM, Mustafa MH, Wilkinson ID, Griffiths PD, Huang CL, Woodruff PW (2002) Study of the effect of CSF suppression on white matter diffusion anisotropy mapping of healthy human brain. Magn Reson Med 48:394–398.
Pasternak O, Sochen N, Gur Y, Intrator N, Assaf Y (2009) Free water elimination and mapping from diffusion MRI. Magn Reson Med 62:717–730.
Peled S, Cory DG, Raymond SA, Kirschner DA, Jolesz FA (1999) Water diffusion, T(2), and compartmentation in frog sciatic nerve. Magn Reson Med 42:911–918.
Peled S, Friman O, Jolesz F, Westin C-F (2006) Geometrically constrained two-tensor model for crossing tracts in DWI. Magn Reson Imaging 24:1263–1270.
Petzold A (2013) Biomarkers of disease progression. In: Wilkins A, editor. Progressive multiple sclerosis. London: Springer. p. 115–146.
Pierpaoli C, Barnett A, Pajevic S, Chen R, Penix LR, Virta A, Basser P (2001) Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. NeuroImage 13:1174–1185.
Pierpaoli C, Basser PJ (1996) Toward a quantitative assessment of diffusion anisotropy [erratum appears in Magn Reson Med 1997 Jun; 37(6):972]. Magn Reson Med 36:893–906.
Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G (1996) Diffusion tensor MR imaging of the human brain. Radiology 201:637–648.
Pierpaoli C, Jones DK (2004) Removing CSF contamination in brain DT-MRIs by using a two-compartment tensor model. In: Presented at the 12th annual meeting of the International Society for Magnetic Resonance in Medicine, Kyoto, Japan, p. 1215.
Prčkovska V, Achterberg HC, Bastiani M, Pullens P, Balmashnova E, Ter Haar Romeny BM, Vilanova A, Roebroeck A (2013) Optimal short-time acquisition schemes in high angular resolution diffusion-weighted imaging. Int J Biomed Imaging 2013:658583.
Puig J, Pedraza S, Blasco G, Daunis-i-Estadella J, Prats A, Prados F, Boada I, Castellanos M, Sánchez-González J, Remollo S, Laguillo G, Quiles AM, Gómez E, Serena J (2010) Wallerian degeneration in the corticospinal tract evaluated by diffusion tensor imaging correlates with motor deficit 30 days after middle cerebral artery ischemic stroke. Am J Neuroradiol 31:1324–1330.
Qin W, Zhang M, Piao Y, Guo D, Zhu Z, Tian X, Li K, Yu C (2012) Wallerian degeneration in central nervous system: dynamic associations between diffusion indices and their underlying pathology. PLoS One 7:e41441.
Qiu M, Darling WG, Morecraft RJ, Ni CC, Rajendra J, Butler AJ (2011) White matter integrity is a stronger predictor of motor function than BOLD response in patients with stroke. Neurorehabil Neural Repair 25:275–284.
Raffelt D, Tournier J-D, Rose S, Ridgway GR, Henderson R, Crozier S, Salvado O, Connelly A (2012) Apparent fibre density: a novel measure for the analysis of diffusion-weighted magnetic resonance images. NeuroImage 59:3976–3994.
Ramirez-Manzanares A, Rivera M, Vemuri BC, Carney P, Mareei T (2007) Diffusion basis functions decomposition for estimating white matter intravoxel fiber geometry. IEEE Trans Med Imaging 26:1091–1102.
Reddy JS, Mishra AM, Behari S, Husain M, Gupta V, Rastogi M, Gupta RK (2006) The role of diffusion-weighted imaging in the differential diagnosis of intracranial cystic mass lesions: a report of 147 lesions. Surg Neurol 66:246–250 [discussion 250–251].
Reijmer YD, Brundel M, de Bresser J, Kappelle LJ, Leemans A, Biessels GJ (2013a) Microstructural white matter abnormalities and cognitive functioning in type 2 diabetes A diffusion tensor imaging study. Dia Care 36:137–144.
Reijmer YD, Freeze WM, Leemans A, Biessels GJ (2013b) The effect of lacunar infarcts on white matter tract integrity. Stroke 44:2019–2021.
Reijmer YD, Leemans A, Heringa SM, Wielaard I, Jeurissen B, Koek HL, Biessels GJ (2012) Improved sensitivity to cerebral white matter abnormalities in Alzheimer's disease with spherical deconvolution based tractography. PLoS One 7:e44074.
Ronen I, Ercan E, Webb A (2013) Axonal and glial microstructural information obtained with diffusion-weighted magnetic resonance spectroscopy at 7T. Front Integr Neurosci 7.
Rovaris M, Gass A, Bammer R, Hickman SJ, Ciccarelli O, Miller DH, Filippi M (2005) Diffusion MRI in multiple sclerosis. Neurology 65:1526–1532.
Rovaris M, Iannucci G, Cercignani M, Sormani MP, De Stefano N, Gerevini S, Comi G, Filippi M (2003) Age-related changes in conventional, magnetization transfer, and diffusion-tensor MR imaging findings: study with whole-brain tissue histogram analysis. Radiology 227:731–738.
Rovira À, León A (2008) MR in the diagnosis and monitoring of multiple sclerosis: An overview. Eur J Radiol 67:409–414.
Sagi Y, Tavor I, Hofstetter S, Tzur-Moryosef S, Blumenfeld-Katzir T, Assaf Y (2012) Learning in the fast lane: new insights into neuroplasticity. Neuron 73:1195–1203.

Saindane AM, Law M, Ge Y, Johnson G, Babb JS, Grossman RI (2007) Correlation of diffusion tensor and dynamic perfusion MR imaging metrics in normal-appearing corpus callosum: support for primary hypoperfusion in multiple sclerosis. Am J Neuroradiol 28:767–772.

Saksena S, Husain N, Das V, Pradhan M, Trivedi R, Srivastava S, Malik GK, Rathore RKS, Sarma M, Pandey CM, Gupta RK (2008) Diffusion tensor imaging in the developing human cerebellum with histologic correlation. Int J Dev Neurosci 26:705–711.

Sands DE (1995) Vectors and tensors in crystallography. Dover.

Schaechter JD, Fricker ZP, Perdue KL, Helmer KG, Vangel MG, Greve DN, Makris N (2009) Microstructural status of ipsilesional and contralesional corticospinal tract correlates with motor skill in chronic stroke patients. Hum Brain Mapp 30:3461–3474.

Schmierer K, Wheeler-Kingshott CAM, Boulby PA, Scaravilli F, Altmann DR, Barker GJ, Tofts PS, Miller DH (2007) Diffusion tensor imaging of post mortem multiple sclerosis brain. NeuroImage 35:467–477.

Schmierer K, Wheeler-Kingshott CAM, Tozer DJ, Boulby PA, Parkes HG, Yousry TA, Scaravilli F, Barker GJ, Tofts PS, Miller DH (2008) Quantitative magnetic resonance of postmortem multiple sclerosis brain before and after fixation. Magn Reson Med 59:268–277.

Scholz J, Klein MC, Behrens TEJ, Johansen-Berg H (2009) Training induces changes in white-matter architecture. Nat Neurosci 12:1370–1371.

Sen PN, Basser PJ (2005) A model for diffusion in white matter in the brain. Biophys J 89:2927–2938.

Sidaros A, Engberg AW, Sidaros K, Liptrot MG, Herning M, Petersen P, Paulson OB, Jernigan TL, Rostrup E (2008) Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: a longitudinal study. Brain 131:559–572.

Sierra A, Laitinen T, Lehtimäki K, Rieppo L, Pitkänen A, Gröhn O (2011) Diffusion tensor MRI with tract-based spatial statistics and histology reveals undiscovered lesioned areas in kainate model of epilepsy in rat. Brain Struct Funct 216:123–135.

Sijens PE, Heesters MAAM, Enting RH, van der Graaf WTA, Potze JH, Irwan R, Meiners LC, Oudkerk M (2007) Diffusion tensor imaging and chemical shift imaging assessment of heterogeneity in low grade glioma under temozolomide chemotherapy. Cancer Invest 25:706–710.

Silva MD, Omae T, Helmer KG, Li F, Fisher M, Sotak CH (2002) Separating changes in the intra- and extracellular water apparent diffusion coefficient following focal cerebral ischemia in the rat brain. Magn Reson Med 48:826–837.

Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH (2003) Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. NeuroImage 20:1714–1722.

Sorensen AG, Wu O, Copen WA, Davis TL, Gonzalez RG, Koroshetz WJ, Reese TG, Rosen BR, Wedeen VJ, Weisskoff RM (1999) Human acute cerebral ischemia: detection of changes in water diffusion anisotropy by using MR imaging. Radiology 212:785–792.

Sotak CH (2002) The role of diffusion tensor imaging in the evaluation of ischemic brain injury – a review. NMR Biomed 15:561–569.

Sotak CH (2004) Nuclear magnetic resonance (NMR) measurement of the apparent diffusion coefficient (ADC) of tissue water and its relationship to cell volume changes in pathological states. Neurochem Int 45:569–582.

Stadlbauer A, Buchfelder M, Salomonowitz E, Ganslandt O (2010) Fiber density mapping of gliomas: histopathologic evaluation of a diffusion-tensor imaging data processing method. Radiology 257:846–853.

Stadlbauer A, Ganslandt O, Buslei R, Hammen T, Gruber S, Moser E, Buchfelder M, Salomonowitz E, Nimsky C (2006) Gliomas: histopathologic evaluation of changes in directionality and magnitude of water diffusion at diffusion-tensor MR imaging. Radiology 240:803–810.

Stanisz GJ, Wright GA, Henkelman RM, Szafer A (1997) An analytical model of restricted diffusion in bovine optic nerve. Magn Reson Med 37:103–111.

Steele CJ, Bailey JA, Zatorre RJ, Penhune VB (2013) Early musical training and white-matter plasticity in the corpus callosum: evidence for a sensitive period. J Neurosci 33:1282–1290.

Suárez-Solá ML, González-Delgado FJ, Pueyo-Morlans M, Medina-Bolívar OC, Hernández-Acosta NC, González-Gómez M, Meyer G (2009) Neurons in the white matter of the adult human neocortex. Front Neuroanat 3:7.

Sun S-W, Liang H-F, Cross AH, Song S-K (2008) Evolving Wallerian degeneration after transient retinal ischemia in mice characterized by diffusion tensor imaging. NeuroImage 40:1–10.

Sun S-W, Liang H-F, Trinkaus K, Cross AH, Armstrong RC, Song S-K (2006) Noninvasive detection of cuprizone induced axonal damage and demyelination in the mouse corpus callosum. Magn Reson Med 55:302–308.

Sutula T (2002) Seizure-induced axonal sprouting: assessing connections between injury, local circuits, and epileptogenesis. Epilepsy Curr 2:86–91.

Sutula T, Cascino G, Cavazos J, Parada I, Ramirez L (1989) Mossy fiber synaptic reorganization in the epileptic human temporal lobe. Ann Neurol 26:321–330.

Takahashi M, Hackney DB, Zhang G, Wehrli SL, Wright AC, O'Brien WT, Uematsu H, Wehrli FW, Selzer ME (2002) Magnetic resonance microimaging of intraaxonal water diffusion in live excised lamprey spinal cord. Proc Natl Acad Sci U S A 99:16192–16196.

Takeuchi H, Sekiguchi A, Taki Y, Yokoyama S, Yomogida Y, Komuro N, Yamanouchi T, Suzuki S, Kawashima R (2010) Training of working memory impacts structural connectivity. J Neurosci 30:3297–3303.

Taubert M, Draganski B, Anwander A, Müller K, Horstmann A, Villringer A, Ragert P (2010) Dynamic properties of human brain structure: learning-related changes in cortical areas and associated fiber connections. J Neurosci 30:11670–11677.

Taubert M, Villringer A, Ragert P (2012) Learning-related gray and white matter changes in humans: an update. Neurosci Rev J Bringing Neurobiol Neurol Psychiatry 18:320–325.

Taylor DG, Bushell MC (1985) The spatial mapping of translational diffusion coefficients by the NMR imaging technique. Phys Med Biol 30:345.

Thomalla G, Glauche V, Koch MA, Beaulieu C, Weiller C, Rother J (2004) Diffusion tensor imaging detects early Wallerian degeneration of the pyramidal tract after ischemic stroke. NeuroImage 22:1767–1774.

Thomalla G, Glauche V, Weiller C, Rother J (2005) Time course of wallerian degeneration after ischaemic stroke revealed by diffusion tensor imaging. J Neurol Neurosurg Psychiatry 76:266–268.

Tournier JD, Calamante F, Gadian DG, Connelly A (2004) Direct estimation of the fiber orientation density function from diffusion-weighted MRI data using spherical deconvolution. NeuroImage 23:1176–1185.

Tournier J-D, Mori S, Leemans A (2011) Diffusion tensor imaging and beyond. Magn Reson Med 65:1532–1556.

Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mörk S, Bö L (1998) Axonal transection in the lesions of multiple sclerosis. N Engl J Med 338:278–285.

Tuch DS (2004) Q-ball imaging. Magn Reson Med 52:1358–1372.

Tuch DS, Reese TG, Wiegell MR, Makris N, Belliveau JW, Wedeen VJ (2002) High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. Magn Reson Med 48:577–582.

Van Eijsden P, Otte WM, van der Hel WS, van Nieuwenhuizen O, Dijkhuizen RM, de Graaf RA, Braun KPJ (2011) In vivo diffusion tensor imaging and ex vivo histologic characterization of white matter pathology in a post-status epilepticus model of temporal lobe epilepsy. Epilepsia 52:841–845.

Vaughn JE, Hinds PL, Skoff RP (1970) Electron microscopic studies of wallerian degeneration in rat optic nerves. I. The multipotential glia. J Comp Neurol 140:175–205.

Vos SB, Jones DK, Jeurissen B, Viergever MA, Leemans A (2012) The influence of complex white matter architecture on the mean diffusivity in diffusion tensor MRI of the human brain. NeuroImage 59:2208–2216.

Vos SB, Jones DK, Viergever MA, Leemans A (2011) Partial volume effect as a hidden covariate in DTI analyses. NeuroImage 55:1566–1576.

Wang Y, Wang Q, Haldar JP, Yeh F-C, Xie M, Sun P, Tu T-W, Trinkaus K, Klein RS, Cross AH, Song S-K (2011) Quantification of increased cellularity during inflammatory demyelination. Brain 134:3590–3601.

Watanabe T, Honda Y, Fujii Y, Koyama M, Matsuzawa H, Tanaka R (2001) Three-dimensional anisotropy contrast magnetic resonance axonography to predict the prognosis for motor function in patients suffering from stroke. J Neurosurg 94:955–960.

Wedeen VJ, Hagmann P, Tseng W-YI, Reese TG, Weisskoff RM (2005) Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. Magn Reson Med 54:1377–1386.

Werring DJ, Brassat D, Droogan AG, Clark CA, Symms MR, Barker GJ, MacManus DG, Thompson AJ, Miller DH (2000) The pathogenesis of lesions and normal-appearing white matter changes in multiple sclerosis: a serial diffusion MRI study. Brain J Neurol 123(Pt 8):1667–1676.

Westin CF, Maier SE, Mamata H, Nabavi A, Jolesz FA, Kikinis R (2002) Processing and visualization for diffusion tensor MRI. Med Image Anal 6:93–108.

Wheeler-Kingshott CAM, Cercignani M (2009) About ‘‘axial’’ and ‘‘radial’’ diffusivities. Magn Reson Med 61:1255–1260.

White NS, Leergaard TB, D'Arceuil H, Bjaalie JG, Dale AM (2013) Probing tissue microstructure with restriction spectrum imaging: histological and theoretical validation. Hum Brain Mapp 34:327–346.

Wu EX, Cheung MM (2010) MR diffusion kurtosis imaging for neural tissue characterization. NMR Biomed 23:836–848.

Yang Q, Tress BM, Barber PA, Desmond PM, Darby DG, Gerraty RP, Li T, Davis SM (1999) Serial study of apparent diffusion coefficient and anisotropy in patients with acute stroke. Stroke 30:2382–2390.

Yu C, Zhu C, Zhang Y, Chen H, Qin W, Wang M, Li K (2009) A longitudinal diffusion tensor imaging study on Wallerian degeneration of corticospinal tract after motor pathway stroke. Neuroimage 47:451–458.

Zatorre RJ, Fields RD, Johansen-Berg H (2012) Plasticity in gray and white: neuroimaging changes in brain structure during learning. Nat Neurosci 15:528–536.

Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC (2012) NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. NeuroImage 61:1000–1016.

Zhang J, Jones M, DeBoy CA, Reich DS, Farrell JAD, Hoffman PN, Griffin JW, Sheikh KA, Miller MI, Mori S, Calabresi PA (2009) Diffusion tensor magnetic resonance imaging of wallerian degeneration in rat spinal cord after dorsal root axotomy. J Neurosci 29:3160–3171.

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