Diffusion Tensor Imaging and Drug Development

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Introduction

Non-invasive clinical MRI relies on the intrinsic behavior of water protons to provide a contrast between tissues. Various techniques are used to sensitize images to different contrast types such as T1- and T2-weighting, but these parameters are not directly linked to the functional physiology of the tissue being examined. Movement of water within and between cellular compartments can provide valuable information about tissue structure and function, and therefore, diffusion MRI has evolved into a sophisticated technique. In addition to providing the scalar diffusion coefficient from a purely isotropic medium, a more advanced MR technique, DTI, is capable of providing a quantitative, directionally-estimated diffusion parameter that is useful in regions of high anisotropy (or the degree from which diffusion deviates from a spherical distribution), for example, in the white matter tracts of the brain. These tensors can be related to the brain architecture, sensitive to pathophysiological conditions such as white matter tract injury and edema (Leung et al. 2004; Price et al. 2006).

Diffusion Magnetic Resonance Imaging

Diffusion MRI is an important imaging method, designed to sensitize images to the random translation motion of water molecules. The rate of diffusion of protons on these water molecules depends on many physical parameters including membrane permeability, extracellular volume fraction and local water concentrations

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(Latour et al. 1994). Because of these physical components influencing the path of the proton, the distribution of movement allows for a unique insight into the geometrical structure and organization of tissues being examined. Unlike other MR methodologies that require the use of exogenous contrast agents or alteration of basic MRI parameters for assessment of tissue T1 or T2 relaxation, diffusion is completely independent of these physical parameters or magnetic field.

Physical Concepts

Pulsed field gradients are a useful way to measure the diffusion of water protons because they are non-destructive, and in most cases with MR modalities, it is a non-invasive measurement (i.e., no chemical tracers are introduced or are necessary for sensitization of these images to diffusion). The modification to the Hahn echo for water diffusion measurement resulted in the Stejskal–Tanner's derivation for the effect of anti-phased, amplitude-matched, time-dependent field gradients in the presence of spin diffusion (Stejskal and Tanner 1965). The two gradient pulses of duration δ and amplitude G are separated by a diffusion time Δ. Following the 90° pulse, the first diffusion gradient pulse introduces a phase shift in the nuclei in the direction of its application. After a finite time period, a 180° refocusing pulse inverts the phase shift and the second amplitude-matched gradient induces phase shifts identical to those induced by the first gradient pulse. Stationary spins will be phased back to their original phase following the 180° pulse. If a spin has diffused from its position at the moment of the first gradient pulse, the second gradient pulse will fail to refocus the spin to its initial phase. A measure of the extent of locomotion a spin or a group of spins will undertake is represented by the diffusion coefficient. Signal attenuation resulting from this incomplete refocusing, or diffusion of spins is represented as:

$$S = S_0 e^{-bD} \tag{1}$$

where $b = -\gamma^2 G^2 \delta^2(\Delta - \delta/3)$, γ is the gyromagnetic ratio of a hydrogen proton and S_0 is the net magnetization of the system when no diffusion weighting is applied (i.e., $G=0$). The diffusion coefficient, D, is often referred to as the 'apparent' diffusion coefficient (ADC) because each voxel in an image may represent numerous tissue types, and measured diffusion coefficients may reflect motion of water molecules from both the intra- and extra-cellular compartments in those tissues.

A simple diffusion MRI experiment is usually acquired with diffusion-weighting in three orthogonal directions. One image, required for an accurate estimation of S_0, is acquired with no diffusion-weighting. The images acquired with diffusion-weighting are geometrically averaged to provide an average diffusivity (van Gelderen et al. 1994). The diffusivity of a group of spins is typically reflective of the directionally averaged ADC.

Diffusion Tensor Imaging

Although diffusion MRI provides valuable information regarding the average mobility of tissue water, the values are relegated to a single scalar parameter that does not reveal the underlying *directional* motion of water that arises due to physical barriers (e.g., cellular membranes). This section reviews the physical basis of a more advanced diffusion MR acquisition technique that is capable of evaluating the more comprehensive three-dimensional motion of tissue water in space.

Physical Concepts

There exist some structures in which the diffusivity has a high directional dependence, or anisotropy. Anisotropy is a concept that was originally contemplated in vivo in the brain white matter and the spinal cord (Chenevert et al. 1990; Moseley et al. 1990). Diffusion anisotropy is quite high in asymmetric tissues like muscle fibers or white matter in the brain, which is primarily composed of collateral myelinated axonal fibers. This straightforward method of measuring diffusion may be considered a ground-level acquisition of the true geometrical and structural milieu of the system. A more sophisticated measure of diffusivity can be encoded into a diffusion tensor, or a three-dimensional representation of diffusion in the tissue:

$$\mathbf{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} \tag{2}$$

The diffusion tensor is derived from diffusivity measurements in at least six non-collinear directions. Since the tensor is positive and symmetric, with these six measurements, all the values within the matrix are known. Typically, many more directions are used to scan space more uniformly and avoid sampling direction biases, a paradigm that is necessary for more complex applications such as fiber orientation mapping (Jones et al. 1999; Papadakis et al. 1999).

Once the diffusion tensor components have been acquired, the tensor is diagonalized (off-diagonal terms of **D** are nulled), and the eigenvalues (λ), which correspond to diffusivity, and eigenvectors (ε), which correspond to the main diffusion directions, are provided. In an anisotropic system, the diffusion tensor can be graphically represented as an effective diffusion ellipsoid. The shape of the ellipsoid has a very useful physical interpretation. In a given system, very short diffusion times would result in a relatively isotropic tensor, and the ellipsoid would adopt a spherical geometry. Longer diffusion times might illuminate the true nature of the anisotropy in the system, allowing spins to reach their physical barriers and seek alternative

pathways, resulting in an ellipsoid with a more prolate geometry. Eigenvalues are the major, medium and minor axes of the ellipsoid, and the associated eigenvectors dictate the orientation with respect to the main magnetic field.

Several quantitative parameters can be derived from the tensor. The mean diffusivity (D) is the directionally averaged or mean-squared displacement of the molecule:

$$D = (\lambda_1 + \lambda_2 + \lambda_3)/3 \tag{3}$$

Another common parameter derived from the tensor is the fractional anisotropy, which is the fraction of the magnitude of the anisotropy in **D**:

$$\mathrm{FA} = \frac{\sqrt{3(\lambda_1 - \langle\lambda\rangle)^2 + (\lambda_2 - \langle\lambda\rangle)^2 + (\lambda_3 - \langle\lambda\rangle)^2}}{\sqrt{2(\lambda_1^{\,2} + \lambda_2^{\,2} + \lambda_3^{\,2})}} \tag{4}$$

where λ denotes the mean of the three eigenvalues. Fractional anisotropy ranges from 0 to 1, where 1 represents a completely anisotropic system.

The lattice index calculates the anisotropy in a voxel by incorporating the anisotropy value of its nearest neighbor. Though the index benefits from a relative reduction of noise in the measurement, it suffers from increased partial volume effects (Pierpaoli and Basser 1996).

The extent to which a tensor adopts a shape can be used in a quantitative manner, and the physical orientation of the lowest entropic path of water in the laboratory frame can be mapped to the RGB color vectors in order to display a qualitative visualization of the variation in anisotropy (Pajevic and Pierpaoli 1999). Fiber tracking or tractography is a technique that utilizes mathematical algorithms to identify neighboring voxels from seed regions that would likely be located within the same fiber tract (Conturo et al. 1999; Mori et al. 1999).

Diffusion Tensor Imaging in Human Brain Pathologies

Molecular motion of water is considered a direct reflection of physiology, as opposed to oxygenation (the BOLD effects), or contrast-enhanced MRI, where signal changes from exogenous contrast agent effects on the intrinsic T1 and T2 relaxation of tissue protons are indirectly correlated with concentration, and therefore, hemodynamic physiology. Changes in cell membrane permeability, active transport mechanisms, viscosity, tissue interstitial fluid pressure, and structural integrity of cellular networks may all contribute to alterations in the microscopic diffusion of water molecules, especially in the context of a therapeutic insult to normal and pathological tissue (Sugahara et al. 1999; Szafer et al. 1995).

Oncology

The clinical utility of diffusion MRI has been demonstrated quite extensively in brain tumors, where increased diffusion values were measured shortly after the initiation of treatment (Batchelor et al. 2007; Mardor et al. 2003) and in some cases, the magnitude of these changes corresponded to clinical outcomes (Chenevert et al. 2000; Hamstra et al. 2005). Diffusion MRI is thus being heralded as a surrogate marker of therapeutic response in human brain tumors. Diffusion tensor imaging is rapidly becoming a routine clinical imaging modality in neuro-oncology, partly because of its unprecedented insight into the white matter tract anatomy and the implications for treatment and surgical planning in the context of a tumor, and also because of its potential quantitative nature.

Field et al. has identified four distinct modes by which a cerebral neoplasm might alter the natural state of a white matter tract (Field et al. 2004; Jellison et al. 2004). The first pattern of alteration illustrates a mass that displaces the white matter tract as it develops and expands, but leaves the tract intact. The second pattern of alteration illustrates a mass that is not in contact with the fiber tract, but rather has a large edematous region that will not affect the tract location or orientation, but will induce a large reduction in fractional anisotropy. The third pattern, observed in only infiltrating gliomas, is characterized by a substantial reduction in the fractional anisotropy without a substantial bulk mass effect on displacement of the fiber tract. The fourth pattern, observed in both high and low grade malignant tumors, is characterized by a complete abrogation of anisotropy and directionality such that the fiber tract was no longer identifiable.

Head Trauma

Head trauma injuries can be defined as either focal or diffuse, with focal injuries resulting from an external force applied directly on the brain, while diffuse injuries result from shear strain due to a rapid acceleration and deceleration event followed by a sudden change in the momentum. The latter type of injury can be further identified with the extent of diffuse ischemia, histopathologic changes in edema with subsequent diffuse swelling or diffuse axonal injury (DAI). DAI manifests at the cellular level and is thus considered a microscopic injury (as opposed to focal injury, which is localized and can be identified macroscopically). A predictable exploratory evaluation of head injury is initiated with standard Computed Tomography (CT) imaging. This is followed in many cases by conventional MRI, which is typically invoked to identify diffuse lesions, though it is limited by low sensitivity for the extent of injury. Since DTI is capable of elucidating axonal white matter architecture, it outperforms both CT and conventional MRI for identifying DAI (Huisman et al. 2004; Lee et al. 2003; Ptak et al. 2003; Rugg-Gunn et al. 2001). This specificity can

have profound effects on the outcome of the injury because various categories of head trauma have different prognoses and treatment protocols. In general, most studies find that FA is significantly reduced in the posterior limb of the internal capsula, genu, stem and splenium of the corpus callosum, column of the fornix and the centrum semiovale in patients with head trauma compared to healthy, demographically-matched controls (Akpinar et al. 2007; Naganawa et al. 2004; Nakayama et al. 2006; Sidaros et al. 2008). In some cases, these values correlated with injury severity (Akpinar et al. 2007; Nakayama et al. 2006) or long-term outcome (Ptak et al. 2003; Sidaros et al. 2008), a finding that may ultimately lend FA the tenability to progress into a non-invasive biomarker for traumatic brain injury.

Huntington's Disease

Though few studies to date have been published, DTI has been shown to produce quantitative information, specifically, significant reductions of FA, in both white and gray matter in patients diagnosed with Huntington's Disease (Reading et al. 2005; Rosas et al. 2006), as well as in patients with suspected or known mutations in the Huntingtin gene (Kloppel et al. 2008). Pre-symptomatic (no cognitive impairment) carriers of the mutation in the Huntingtin gene are important components to this research because they provide a model for defining the pre-symptomatic versus early stage of pathophysiology when treatment is likely to be the most effective. DTI fiber tractography has been used to map the anatomical connections between the frontal cortex and the striatum, and significantly lower percentages of these connections were found in pre-symptomatic carriers. Furthermore, this particular metric was negatively correlated with the onset of symptoms. Thus, DTI indices may prove to be a valuable measure of the therapeutic outcome, identifying short to mid-term neurobiological changes.

Pain

DTI has promoted a greater understanding of pain processing and control in fibromyalgia (Sundgren et al. 2007) and migraines (DaSilva et al. 2007), and the functional connectivity of the pain processing network (Hadjipavlou et al. 2006). Fibromyalgia is a chronic pain disorder characterized by widespread tenderness and sensitivity. The most pronounced differences observed using DTI were significant reductions in FA found within the right thalamic region, the magnitude of which were statistically greater in individuals classified as experiencing more intense clinical pain (Sundgren et al. 2007). However, there were no significant differences in FA compared to controls in any other region of the pain matrix (i.e., the primary and secondary somatosensory cortices, the insula, the anterior cingulate, the dorsal lateral pre-frontal cortex and the basal ganglia). In chronic migraine sufferers, changes

in the structures involved in the trigeminal pain processing pathway have been observed (DaSilva et al. 2007). Significant reductions in FA were observed in two subtypes of migraine sufferers (migraineurs with aura and migraineurs without aura) compared to controls. Additionally, lower FA values were observed in migraineurs with aura in the ventral trigeminothalmic tract and in migraineurs without aura in the ventrolateral periaqueductal gray matter. The changes observed in this study could be attributed to the increase in the axonal diameter and decrease in the myelination, and are not necessarily linked to lesion consolidation.

Stroke

The temporal evolution of stroke is categorized into the following phases, relative to the onset of symptoms: hyperacute (<12 h), acute (1–7 days), subacute (1–16 weeks), chronic (>16 weeks) phase. The ADC decreases within minutes after the onset of stroke and can remain depressed well into the acute stage of infarction before pseudonormalization and subsequent increases occur (Huang et al. 2001). One utility of DTI is that it can reliably differentiate between the white and gray matter, and therefore, it can be used in the quantification of the ADC in the gray and white matter separately. In fact, this method has been used to evaluate these differences over time, from the acute to subacute stage (Mukherjee et al. 2000).

FA is another metric that can reliably differentiate between the gray and white matter of infracted tissue (Munoz Maniega et al. 2004; Sorensen et al. 1999). Indeed, a stronger utility for DTI lies in its ability to quantify anisotropy in acutely, subacutely and chronically ischemic WM. The use of DTI in evaluating hyperacute stroke, however, has not delivered diagnostically useful information to date (Harris et al. 2004; Ozsunar et al. 2004).

DTI is used in the evaluation of subacute stroke and in the elucidation of Wallerian degeneration in the corticospinal tract (CST), demonstrating a negative correlation between FA and motor function (Moller et al. 2007). Another group reported reduced FA values in the CST resulting from acute anterior choroidal artery (AchoA) infarcts, and these values correlated with the long-term motor outcome (Nelles et al. 2008). Results led investigators to conclude that long-term recovery, ergo positive clinical outcome is related to the preservation of the integrity (i.e., anisotropy) of CSTs. Additionally, reduced FA in the superior longitudinal fasciculus and arcuate fasciculus are correlated with pronounced difficulty to repeat spoken language (Breier et al. 2008). Directionally encoded color maps and 3D tractography have been used to relate localization of stroke lesions with WM tracts (Lee et al. 2005; Lie et al. 2004; Yamada et al. 2004) and estimate the level of disruption or distortion of these tracts (Gillard et al. 2001; Parmar et al. 2006), an index which can have a significant impact on the prognosis and treatment of the patient. DTI has also been useful in understanding CADASIL, an autosomal dominant vasculopathy that causes recurrent ischemic events in the subcortical WM (Chabriat et al. 1999). Decreases in FA have been shown to parallel disease progression.

In general, the use of DTI during the subacute to the chronic phases of stroke is better characterized. Along this continuum, FA becomes progressively more attenuated (Buffon et al. 2005; Yang et al. 1999; Zelaya et al. 1999). It has been suggested that sensitivity to these variable stages of ischemic proliferation may improve treatment and ultimately, provide clinicians with the ability to identify and potentially preserve viable tissue from irreversibly injured tissue (Ozsunar et al. 2004).

Multiple Sclerosis

Although conventional T1-weighted MR Imaging, Magnetic Resonance Spectroscopy and Magnetization Transfer imaging demonstrate a high sensitivity for identifying sclerotic lesions, DTI has gained momentum in this arena because it delivers structural information that can be correlated with disease outcome. DTI has been shown to differentiate the normal white matter in patients from MS compared to control subjects (attributed to axonal loss and/or gliosis) (Bammer et al. 2000; Ciccarelli et al., 2000; Filippi et al. 2001; Werring et al. 1999). It has also been shown to differentiate between acute and chronic lesions (Bammer et al. 2000; Ciccarelli et al., 2000; Filippi et al. 2001; Werring et al. 1999) and correlate with disability (Castriota Scanderbeg et al. 2000; Ciccarelli et al., 2000; Filippi et al. 2001).

Depression

DTI has also been used to correlate changes in FA with late-life depression. Specifically, reductions in FA have been observed in the frontal and temporal regions of the brain of patients with late-life depression compared to healthy, age-matched controls (Alexopoulos et al. 2002; Nobuhara et al. 2006; Taylor et al. 2004); furthermore, FA values were inversely correlated with severity of symptoms (Nobuhara et al. 2006).

Autism

DTI studies have shown decreased FA values in regions of the brain associated with social cognition, including areas important for face and gaze processing, (the fusiform gyrus and superior temporal sulcus) and areas important for emotional processing (anterior cingulate, amygdala, ventromedial prefrontal cortex) in subjects with autism compared to control subjects (Barnea-Goraly et al. 2004). Disruptions have also been observed in the superior temporal gyrus and temporal stem in autism, areas critical to language and social cognition (Lee et al. 2007). Such disruptions in the white matter tract organization have been attributed to abnormal levels of neurotrophic brain factors during brain development (Anderson et al. 1990; Vanhala et al. 2001).

Obsessive Compulsive Disorder

Some studies have observed reduced FA values in the rostrum of the corpus callosum in patients with OCD compared to normal subjects, and values were inversely correlated with symptom severity (Saito et al. 2008). Other studies have shown bilateral reduction in FA values in the anterior cingulate gyrus in patients with OCD compared to healthy controls. The same study found additional areas of altered FA that correlated with disease severity including the parietal lobes (supramarginal gyri), the right posterior cingulate gyrus and the lingual gyrus (Szeszko et al. 2005). One group showed that drug-naïve patients with OCD demonstrated a higher FA in the corpus callosum, and that following 12 weeks of pharmacotherapy, most of the areas investigated exhibited a "normalization" or pre- to post-therapy decrease in these FA values (Yoo et al. 2007). Such a discrepancy has been postulated to be related to drug-naïveté, treatment period or subject characteristic (e.g., age).

Schizophrenia

A very comprehensive review of 19 studies conducted between 1998 and 2004 has been published, covering mostly chronic, medicated patients with adult-onset schizophrenia demonstrating altered or abnormal FA, D and RA compared to healthy, demographically matched controls (Kanaan et al. 2005). The two most common types of analyses were ROI-based and voxel-based. The majority of studies employed the former, although the ROI-based methods are subjective, and it is imperative that repeatability/reproducibility of the method be demonstrated. Voxel-based analyses are more powerful when DTI is used as an exploratory device, and areas of abnormality are more diffuse or widespread than focal. Interestingly, there was a great diversity of anatomical regions studied, though the corpus callosum and cingulum tended to inspire the most interest. However, for as many studies that found significant decreases in FA in various regions, there were approximately an equal number that found no change or abnormality in FA in the same regions.

Since this review, between 2005 and 2008, at least 16 more studies emerged, with an emphasis on a first episode and early-onset (onset before the age of 18) demographic; the remaining 44% of the studies still focused on adult-onset schizophrenia. Although many regions were evaluated, the corpus callosum was a common focus. For the most part, these studies found significant or trend-level decreases in FA in the corpus callosum (or the study's particular region of focus, e.g., the optic radiation) in the first episode (Cheung et al. 2008; Friedman et al. 2008; Karlsgodt et al. 2008; Szeszko et al. 2005), early-onset (Ashtari et al. 2007; Kumra et al. 2005; Kyriakopoulos et al. 2008) and the adult onset schizophrenia (Buchsbaum et al. 2006; Butler et al. 2006; Hao et al. 2006; Kuroki et al. 2006; Shergill et al. 2007; Tang et al. 2007). Only one study from each demographic found no change in the regions studied (Jones et al. 2005; Kendi et al. 2008; Price et al. 2005) using both ROI- and voxel-based methods.

Alzheimer's Disease

DTI has been widely used to understand the pathophysiology of Alzheimer's disease (AD), and areas of abnormal white matter FA are consistently observed in the frontal (Bozzali et al. 2001; Head et al. 2004), parietal (Bozzali et al. 2001; Medina et al. 2006) and temporal (Bozzali et al. 2001; Takahashi et al. 2002; Xie et al. 2006) cortices. It has been shown that the corpus callosum is also affected with reductions in FA in both the genu (Head et al. 2004; Xie et al. 2006) and the splenium (Medina et al. 2006; Rose et al. 2000). The superior longitudinal fasciculus is commonly affected as well (Rose et al. 2000; Xie et al. 2006). Studies have also shown that the posterior cingulate gyrus, which is associated with episodic memory performance, may also contribute to neurodegeneration. Reduced anisotropy may result in decreases in acetylcholine since these fibers are an important component to the cholinergic system, providing a possible reason why procholinergic drugs may be so effective in the treatment of AD.

One study found that the lattice index was significantly reduced in the splenium of the corpus callosum and in the superior longitudinal fasciculus in patients with probable AD compared to healthy controls, and that these reductions correlated positively with the mini-mental state examination (MMSE) scores (Rose et al. 2000).

Mild cognitive impairment (MCI) rests within the continuum of cognitive decline from normal aging to AD. Similar regions are affected by losses in anisotropy between MCI and AD (Fellgiebel et al. 2004; Medina et al. 2006; Zhang et al. 2007), though attenuation of FA is more pronounced in AD (Fellgiebel et al. 2005; Zhang et al. 2007). Such sensitivity has engendered hope that DTI will be a useful methodology to aid in the early diagnosis of AD.

On the mechanism of WM inhomogeneity of AD, it is postulated that a reduced FA in combination with increased ADC values are derived from Wallerian degeneration or ischemic alterations that lead to axonal damage, gliosis and WM rarefaction (Stahl et al. 2007).

Recent efforts have been made to understand differences in the population of mutation carriers that increase the risk of developing AD. Lower FA values were observed in the mean whole brain WM, columns of the fornix, area of the perforant pathways bilaterally and the left orbitofrontal lobe in carriers of the familial Alzheimer's disease (FAD) mutation in the preclinical stages (some MCI) of the disease (Ringman et al. 2007). Additionally, lower FA values were observed in the columns of the fornix and in the left orbitofrontal lobe in carriers of the FAD mutation in the pre-symptomatic stages (no observable cognitive impairment) of the disease.

DTI and Drug Development

The path to FDA approval of a new pharmaceutical agent or device is made treacherous by various levels of research and development (R&D), with only a handful entering preclinical testing (5%). Only 0.1% of the original group will successfully survive

clinical trials and move on to a regulatory review. The time it takes to finalize the process can range from 10 to 12 years, and the cost is prohibitively expensive (> $500 million) (Bolten and DeGregorio 2002).

Biomarkers, or a biological marker of a normal or pathological process or indicator of response to therapy, can be employed in any stage of R&D, from the drug discovery to Phase IV clinical trials. DTI is considered a functional imaging method (as opposed to molecular imaging method) because it measures tissue water mobility and is related to cellular density. In order for some quantitative DTI parameter to be considered a useful biomarker for response to therapy, among other things, it must be sensitive and specific (i.e., have a high predictive value) and it must produce information about the best time to image post-therapy. Because DTI is such a new method, clinical experience is still accumulating, and thus its link to more established clinical outcomes such as improvements in patient symptoms or in survival is not yet well established. This has not prevented investigators from studying these relationships and even proposing DTI as a surrogate marker. However, until diffusion or DTI is qualified for use as a surrogate marker in a particular disease, its greatest application may be in testing biological hypotheses in humans, and in improving our understanding of how disease and intervention interact. Here we will describe in detail one application, brain oncology and briefly highlight other disease potentials as well.

Oncology

A key question in oncology is response rate, in the context of therapeutic trials. There is precedence, albeit very little, for the use of DTI in measuring tumor response to therapy. The most compelling example is from a group that attempted to correlate the mean diffusivity, D, and the fractional anisotropy in a low-grade glioma to metabolite concentrations obtained from chemical shift imaging, a multi-voxel spectroscopic acquisition method (Sijens et al. 2007). This particular study was a case report of a single, 65 year-old male subject with a low-grade glioma. The subject was treated with 200 mg/m^2/day temozolomide and imaged after every 6, 9 and 12 cycles of therapy. The highest levels of choline were localized in the center of the tumor and systematically decreased in the center and over the whole tumor volume with treatment. The lowest levels of NAA were also localized in the center of the tumor, though only moderate increases in NAA were observed throughout the treatment regimen. Nevertheless, a positive correlation between relative concentrations of NAA and the fractional anisotropy ($p < 0.001$) was demonstrated, suggesting a re-emergence of existing, functional axonal structures concomitant with response to therapy. Additionally, a negative correlation was demonstrated between relative choline concentration and D ($p < 0.001$), suggesting a decrease in tumor cellularity and altered membrane phospholipid metabolism.

Another important contribution to drug development in brain neoplasia is the ability of DTI to resolve vasogenic edema and infiltrative tumor (Lu et al. 2003; Lu et al.

2004). This is increasingly important because anti-angiogenic therapies (or therapies that target tumor-associated microvessels) rapidly alleviate edema. Resolution of this edema may result in a lack of tumor enhancement, possibly leading to a misinterpretation that the tumor is responding to therapy. Thus, in the light of the influx of antivascular and antiangiogenic therapies, it would be prudent to have a non-invasive imaging method that can reliably differentiate between edema and tumor tissue. One group hypothesized that the mean diffusivity and the fractional anisotropy are significantly altered in the peritumoral regions of both high-grade gliomas and metastatic brain lesions, and further that the magnitude of fractional anisotropy changes in the peritumoral region of high grade gliomas are greater due to tumor infiltration (Lu et al. 2003). Compared to normal, contralateral brain tissue, the mean diffusivity in the peritumoral region of both the glioma and the metastatic lesion increased ($p<0.005$), and the fractional anisotropy decreased ($p<0.005$). The mean diffusivity was significantly lower in the glioma than in the metastatic lesion ($p<0.005$), but there was no statistical difference between the two types of lesions in the fractional anisotropy. Nevertheless, statistical differences are apparent between the normal tissue and the peritumoral edema, and thus, it is conceivable that resolution of tumor infiltration from edema may soon be possible with more advanced diffusion approaches.

Another group investigated the use of DTI to detect changes in the mean diffusivity (D) and fractional anisotropy in the genu and splenium in the corpus collosum following 45 weeks of radiation therapy (Nagesh et al. 2008). Significant increases in D and decreases in fractional anisotropy were observed ($p<0.001$) over time, suggesting disruption of the white matter architecture. Furthermore, both the perpendicular ($\lambda_{\perp}$) and parallel ($\lambda_{\parallel***}$) diffusivities increased significantly ($p<0.002$ and $p<0.04$, respectively) in a dose-dependent manner, suggesting systematic white matter injury or demyelination. Although this study has not demonstrated the DTI utility in providing a means of measuring tumor response to therapy, such a study will aid in establishing a method by which the extent of radiation-induced white matter injury and axonal degradation will be measured.

One group capitalized on a new analytical method, capable of separating the tensor into its isotropic (p) and anisotropic (q) components,

$$p = \sqrt{3}D \tag{5}$$

$$q = \sqrt{(\lambda_1 - D)^2 + (\lambda_2 - D)^2 + (\lambda_3 - D)^2} \tag{6}$$

thereby providing a method to delineate between the whole tumor region and any surrounding normal tissue infiltrated by glioma cells (Field et al. 2004). Based on the relative size of each component, three different patterns of abnormal growth emerged: (1) diffuse – the extent of isotropic diffusion (p) was greater than the extent of anisotropic diffusion (q); (2) localized – the extent of the isotropic and anisotropic regions were predominantly comparable, and tumor infiltration progressed only in regions where this symmetry failed and; (3) minimal – both regions were comparable.

Other Applications

For other brain pathologies (e.g., depression, OCD, schizophrenia and stroke), the use of DTI as an alternative metric of response to therapy is notional and is still preliminary. In a late-life depression study, patients treated with citalopram achieved remission (or failure to meet DSM-IV criteria for a depressive disorder), a factor which was correlated with significantly higher fractional anisotropy values in the right frontal matter compared to patients that demonstrated an overall lower fractional anisotropy in the same region (Alexopoulos et al. 2002). In drug-naïve patients with OCD, 12 weeks of therapy with citalopram resulted in the "normalization" of FA in the corpus callosum and internal capsule (Yoo et al. 2007), corresponding very well with an improvement in all clinical measures of response employed. Though it has been suggested that dosage of antipsychotic drugs correlate with the degree of reduced FA in the WM of schizophrenic patients (Okugawa et al. 2004), to our knowledge, there are no studies that directly correlate therapy with changes in FA over time.

For stroke, currently the main focus is to establish a method for staging an ischemic lesion in the hope that an accurate diagnosis is made and consequently, an appropriate treatment can be applied. The status of the lesion throughout the various phases of damage is critical to establishing the most effective treatment program.

Regarding research on the remaining pathologies (Alzheimer's and Huntington's disease, MS, autism and pain), available treatments are unfortunately still not disease-modifying. For example, there is no cure for Alzheimer's disease; but a program of drugs that maintain or improve cognitive function and/or slow progression of the disease, in addition to some metric like FA capable of assessing the efficacy of those drugs can have a profound effect on the quality of life for the patient. In general, since the pathophysiology of these disorders consistently manifests as an attenuation of the FA derived from DTI, any changes following successful curative or palliative therapy of these pathologies would likely result in the "normalization" or return of FA to normal values (or values comparable to contralateral normal tissue or healthy control tissue), and thus, DTI will continue to simulate a natural curiosity for its therapeutics use.

Limitations

A DTI dataset is most typically acquired using single-shot echo-planar imaging (EPI) sequence because of the inherent sensitivity of diffusion MRI to small bulk motion (e.g., head motion). Unfortunately, the trade-off for motion insensitivity is sensitivity to field inhomogeneities (Jezzard and Balaban 1995) and eddy currents (Jezzard et al. 1998), both of which affect the diffusion measurement. Furthermore, diffusion is intrinsically signal-to-noise limited. Work continues to focus on improvement of these limitations.

Concluding Remarks

Most of the studies mentioned in this chapter are low-power and preliminary, and thus, the results must be reviewed with aggressive criticism. However, with the continued improvement in the technical limitations, the potential for diffusion remains strong.

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