Applications of Diffusion Tensor Imaging

Michael E. Moseley, PhD

Associate Professor of Radiology

Stanford University

Anisotropic DWI - Mapping of the Proton Diffusion "tensor". In neural ordered tissue, it is thought that water diffusion is mainly influenced by the presence of myelin sheaths and intracellular structures. Perpendicular to the fiber tracts, the cholesterol-laden myelin lipid bilayers might restrict or hinder the spins from diffusing through the normally highly permeable cytomembrane. Diffusion along the fiber is more or less determined by subcellular structures, such as the endoplasmatic reticulum, mitochondria, neuro-filaments and macromolecules. In addition to that, the entire complex of axons and stabilizing tissue (i.e., glia cells, astrocytes) is also assumed to influence diffusion due to the tortuosity of proton translation, but the uniform distribution of such cells throughout the brain might render this notion less important as initially anticipated.

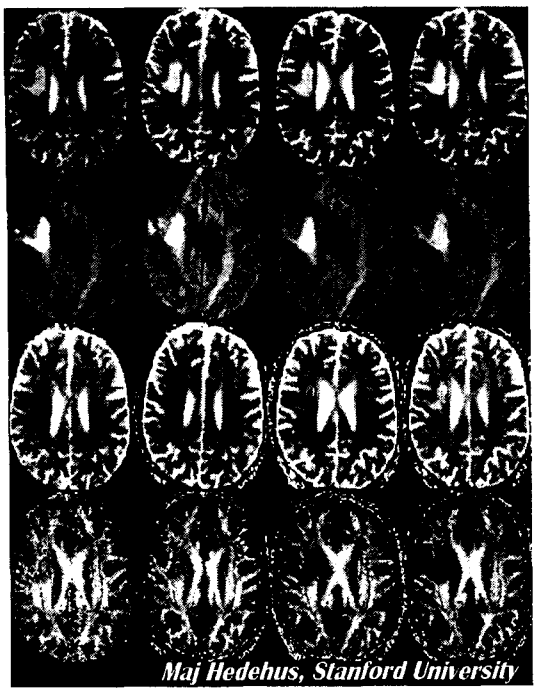
Diffusion "Anisotropy" Methods and Application to Neurologic Diseases. Diffusion anisotropy can be measured by determination of the so-called diffusion tensor (1-5). The tensor is essentially a map of directional vectors in 3D space, showing the preferential motion of water protons in oriented white matter. In order to acquire data for the diffusion tensor, diffusion must be measured along six or more non-collinear directions. For that purpose, a single-shot echo planar imaging (EPI) sequence was modified to allow diffusion sensitizing along any given direction. The use of fast and strong gradients (up to 30 mT/m) are needed to obtain b-values in the order of 1000 s/㎟ with a diffusion time of 32ms and an effective echo time in the order of 100ms.

A straight-forward method of obtaining six non-collinear directions are by applying identical gradients along the following six axes combinations: (x,y,z) = {(1,1,0), (0,1,1), (1,0,1), (-1,1,0), (0,-1,1), (1,0,-1)}. This scheme has the additional advantage, that the diffusion sensitizing gradients always are applied along two axes simultaneously, thus doubling the total b-value as compared to applying gradients along one direction only. The sequence was tested for functionality (correct ADC and anisotropy values) on phantoms and volunteers. We found, that using two b-values (0 and ~900) with two averages for b=0 and four averages for b=900s/㎟ for a slice thickness of 5mm was appropriate to ensure an appropriate signal-to-noise ratio at 1.5Tesla.

Based on the data in the diffusion tensor, diffusion coefficients along the principal directions of the white matter fibers and eigenvectors defining the orientation of such fibers can be calculated. Software was developed for this purpose, along with software for analyzing the degree of anisotropy, given by the so-called "fractional anisotropy" (FA). The ability of DTI to discriminate between white matter (high FA, bright) and gray matter (low FA, dark) is evident. The ability of DTI to show fiber directionality and coherence is demonstrated below (right below), where lines corresponding to the principal fiber directions are shown for two enlarged regions.

We have employed diffusion tensor imaging was performed on a 1.5T Signa (GE Signa Horizon EchoSpeed) using a spin echo EPI technique (FOV 24cm, 128x128 zerofilled to 256×256; TE/TR =106ms/6s, 18 oblique slices, slice thickness 5mm skip 0mm). The amplitude of the diffusion-sensitizing gradients was 1.4Gauss/cm with a duration and separation of 32ms and 34ms, respectively. This resulted in a b-value of 860s/㎟. Diffusion was measured along six non-collinear directions: (x,y,z) = [(1,1,0), (0,1,1), (1,0,1), (-1,1,0), (0,-1,1), (1,0,-1)]. For each gradient direction, four images were acquired and averaged. Two images with no diffusion weighting (b=0s/㎟) were acquired and a set of Inversion Recovery (IR) images for CSF nulling (TI~2100ms) were acquired with b=0/㎟; these images were used to unwarp the diffusion weighted images, which resulted in a more robust unwarping than using the non-IR b=0 images. The acquired images were reconstructed prior to averaging, giving NEX=4 for the high b-value and NEX=2 for b=0s/㎟. The diffusion tensor was determined for each pixel after which eigenvalues, eigenvectors and the FA was calculated.

Diffusion Anisotropy Methods and Application to Neurologic Diseases: Diffusion Tensor Imaging (DTI) in Disease. We have added DTI to a wide variety of brain MR protocols such as acute and chronic stroke, trauma, multiple sclerosis, premature babies as well as to a number of psychiatric protocols. Preliminary results from stroke patients suggest that the relationships of WM structure, together with ADC and T2, can critically improve the evaluation of cerebral ischemia progressing to infarction. An example in the evolution of stroke is shown below.



Left. Confirmed stroke imaged at 1, 2, 3 and 4 weeks post-ictum (columns 1-4). T2-weighted EPI images, diffusion weighted images and ADC maps all show the characteristic evolution of an ischemic injury to infarction: The T2-weighted hyperintensity (top row) is clearly visible at 1 week and beyond. The diffusion-weighted images (2nd row) show initial hyperintensity, corresponding to decreased diffusion that is also seen as hypointensity on the ADC maps (third row). The diffusion weighted image stays hyperintense as the T2 "shine-through" outweighs the ADC evolution from below-normal values to "pseudo-normal" and supernormal values beyond 2 weeks. The fractional anisotropy (FA, bottom row) is already decreased (0.24 ± 0.06) as compared to a corresponding region in the contralateral 0.35 ± 0.05) at one week and it continues to decrease over time (at 4 weeks: 0.08 ± 0.05, contralateral 0.33 ± 0.07), in good correspondence with the theory of WM structural degeneration. This assessment is not apparent from either the T2 or ADC maps.

Over the past decade, diffusion weighted imaging has become an important image modality in the clinical management of stroke and for investigation of mechanisms of neuronal damage in animal models of cerebral ischemia, and the diffusion weighted images or the ADC maps are evaluated routinely. However, despite the fact that Wallerian degeneration has been shown to decrease the degree of anisotropic water motion in peripheral nerve and DTI imaging has demonstrated a decrease in anisotropy in stroke patients, tensor measures are becoming an integral part of clinical studies.

DTI has also been used to assess the anisotropy in WM of schizophrenic patients (6). This study showed a gray matter volume deficit but normal white matter volume in schizophrenic patients as compared to normals. Contrarily, the fractional anisotropy was shown to be lower in white matter but not in gray matter in schizophrenic patients. This points to a compromised white matter integrity that is not discernible from structural MRI exams. The study identified a double dissociation: relative to controls, schizophrenics exhibited lower anisotropy in white matter, despite absence of a white matter volume deficit; in contrast to the white matter pattern, gray matter anisotropy did not distinguish the groups even though the schizophrenics had a significant gray matter volume deficit. The observed white matter abnormality suggests a possible compromise in the white matter integrity, which points to a potential substrate for functional disconnection or underdevelopment of the otherwise highly integrated neural networks. Thus, DTI is valuable in the evaluation of white matter health. We believe, that this DTI method will prove invaluable in a

wide variety of disorders that are expected to involve subtle white matter abnormalities.
Recently, reports of water proton diffusion anisotropy abnormalities have been reported in multiple sclerosis (MS) (7-8). Fillipi, et al. used DTI to examine the tissue damage in lesions and normal-appearing white matter (NAWM) and to investigate the magnitude of the correlation between DTI-derived metrics and clinical disability. DTI scans were obtained from 78 patients with relapsing-remitting, secondary progressive, or primary progressive MS and from 20 normal control participants. After creating mean diffusivity (D) and fractional anisotropy (FA) images and image coregistration, D and FA values were measured. The average lesion D was higher and the average lesion FA was lower than the corresponding quantities of the NAWM ($p < 0.001$). The values of enhancing and nonenhancing lesions were not different, whereas enhancing lesions had lower FA ($p < 0.001$). They concluded that DTI was able to identify MS lesions with severe tissue damage and to detect changes in the NAWM. They also indicate that DTI-derived measures are correlated with clinical disability, especially in patients with secondary progressive MS, thus suggesting a role for DTI in monitoring advanced phases of the disease.

Another anticipated application of tensor mapping is in the depiction of WM changes in mild to moderate trauma (9). DTI maps the degree of directionality of water movement in white matter tracts, and is sensitive to abnormalities in the white matter integrity, composition or local ordering. Therefore, we predict that DTI can assess the degree and location of diffuse axonal injury even at the early stages in mild to moderate traumatic brain injury. Since DTI maps the composition or local ordering in white matter regions such as the corpus callosum or internal capsule, structures known to be particularly susceptible to diffuse axonal injury (DAI), we expect DTI to be sensitive to diffuse axonal injury even at early stages of axonal degradation. If so, DTI will provide a powerful tool for improved diagnosis at time of presentation and for non-invasive, longitudinal studies of diffuse axonal injury and possibly further classification of DAI with respect to anatomical location and severity. Finally, we fully anticipate that DTI will provide a much-needed look at early trauma and disease effects in the spinal cord (10-11).

Perhaps the one area where DTI is producing new results that will likely alter the field of psychiatric imaging is in the prediction of cognitive and motor performances. Klingberg, et al. (12) published an important paper in which diffusion tensor magnetic resonance imaging (MRI) was used to study the microstructural integrity of white matter in adults with poor or normal reading ability. Subjects with reading difficulty exhibited decreased diffusion anisotropy bilaterally in temporoparietal white matter. Axons in these regions were predominantly anterior-posterior in direction. No differences in T1-weighted MRI signal were found between poor readers and control subjects, demonstrating specificity of the group difference to the microstructural characteristics

measured by diffusion tensor imaging (DTI). White matter diffusion anisotropy in the temporo-parietal region of the left hemisphere was significantly correlated with reading scores within the reading-impaired adults and within the control group. The anisotropy reflects microstructure of white matter tracts, which may contribute to reading ability by determining the strength of communication between cortical areas involved in visual, auditory, and language processing.

In other studies relating the DTI exam to the correlation of motor performance, the role of normal and abnormal aging have begun to explore the use of DTI. In a series of studies comparing DTI-observed changes in normal aging compared to the changes seen in suspected cases of Alzheimer's Dementia (AD), Stebbins, et al., (30-31) examined frontal-lobe FA in selected regions-of-interest (corrected for atrophic differences) in 10 younger and 10 older healthy participants. Participants were group matched for education and pre-morbid IQ. DTI was performed using a diffusion weighted single-shot spin-echo echo-planar sequence using the anatomical slice prescription from a high resolution FSE series. The DTI data were processed to provide fractional anisotropy (FA) with the group DTI data analyses performed using SPM'99. Immediately before scanning, each subject's reasoning performance was measured from a Raven's Matrices exam. The investigators found that the frontal FA was significantly reduced in older compared to younger participants ($p<.0001$). When the investigators then correlated the measured FA with cognitive skills, the reasoning performance was significantly correlated with frontal FA ($p<.0001$) while other cognitive parameters such as mental status, education and pre-morbid IQ did not significantly correlate with frontal FA. In a separate but related study (31), Urresta, et al., from the same group examined alterations in FA in Alzheimer's disease (AD). Participants consisted of 10 healthy older right-handed subjects and 10 patients with a diagnosis of probable AD. In those patients with suspected AD, the measured FA was significantly decreased ($p<0.05$) in white matter areas corresponding bilaterally to the frontal lobes, the superior longitudinal fasciculus, and the temporal stem. Compared to the effects of normal aging on white matter integrity, these results show a further disease-induced deterioration in the microstructure of frontal and temporal lobe white matter, but not in the subcortical white matter tracts. The investigators concluded that decreases in frontal white matter microstructural integrity measured by DTI FA values occur in older participants independent of atrophic changes. The correlation with reasoning performance supports a role for frontal white matter integrity in this ability.

In summary, Diffusion tensor imaging (DTI) is a promising new technique for the assessment of white matter (WM) structural integrity and connectivity. The movement of water in brain is hindered by the presence of cell membranes, myelin sheaths surrounding axons, and other structures, particularly so in white matter tracts where the apparent water diffusion is highly anisotropic, since diffusion parallel to axons and myelin bundles is considerably faster than that

perpendicular to the axons. Tensors (a mathematical construct useful for describing multidimensional vector systems) are ideal for describing proton diffusion restricted by white matter tracts, by indicating the direction and the magnitude of restriction. This in turn offers an index of directional coherence of fiber tracts or integrity of cellular structure. Based on the diffusion tensor, several quantitative and absolute measures can be determined and mapped, such as the apparent diffusion coefficient (ADC), the degree of anisotropy (e.g., fractional anisotropy, FA) and measures of the correlation in orientation between a given pixel and its surrounding neighbors (e.g., the lattice anisotropy, LA).

REFERENCES

1. Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G. Diffusion tensor MR imaging of the human brain. Radiology 1996; 201: 637-648.
2. Conturo TE, McKinstry RC, Akbudak E, Robinson BH. Encoding of anisotropic diffusion with tetrahedral gradients: A general mathematical diffusion formalism and experimental results. MRM Magn Reson Med 1996; 35: 399-412.
3. Basser PJ, Pierpaoli C. Estimating the principal diffusivities (eigenvalues) of the effective diffusion tensor. In: Proc 5th ISMRM Vancouver, CAN, 1997; 3: 1739.
4. Pierpaoli C, Basser PJ. Toward a quantitative Assessment of diffusion anisotropy. Magn Reson Med 1996; 36: 893-906.
5. Pajevic S, Pierpaoli C. Color schemes to represent the orientation of anisotropic tissues from diffusion tensor data: Application to white matter fiber tract mapping in the human brain. Magn Reson Med 1999; 42: 526-540.
6. K.O. Lim, M. Hedehus, M.E. Moseley, A.J. de Crespigny, E.V. Sullivan and A. Pfefferbaum. Compromised White Matter Tract Integrity in Schizophrenia Inferred from Diffusion Tensor Imaging, Archives of General Psychiatry. 56, 367-374, 1999.
7. D.J. Werring, C.A. Clark, G.J. Barker, A.J. Thompson and D.H. Miller. Diffusion tensor imaging of lesions and normal-appearing white matter in multiple sclerosis. Neurology. 52:1626-32, 1999.
8. Filippi M, Cercignani M, Inglese M, Horsfield MA, Comi G. Diffusion tensor magnetic resonance imaging in multiple sclerosis. Neurology 2001 Feb 13;56(3):304-11.
9. Ford JC, Hackney DB, Alsop DC, Jara H, Joseph PM, Hand CM, Black P. MRI characterization of diffusion coefficients in a rat spinal cord injury model. Magn Reson Med 1994; 31: 488-494.

10. Zientara GP, Murphy BP, Maier SE, Huppi PS, Barnes PD, Volpe JJ, Jolesz FA. Diffusion tensor MRI of the human cervical spinal cord in vivo in preterm newborns. In: Book of abstracts: International Society of Magnetic Resonance in Medicine 1999. Vol 2, Philadelphia, PA: International Society of Magnetic Resonance in Medicine, 1999; 1099.
11. Bammer R, Augustin M, Simbrunner J, Kooijman H, Ebner F, Stollberger R, Hartung HP, Fazekas F. In-vivo diffusion-weighted interleaved echo-planar imaging of the human spinal cord. In: Book of abstracts: International Society of Magnetic Resonance in Medicine 1999. Vol 2, Philadelphia, PA: International Society of Magnetic Resonance in Medicine, 1999; 993.
12. T. Klingberg, M. Hedehus, E. Temple, T. Salz, J.D.E. Gabrieli, M.E. Moseley and R.A. Poldrack. Microstructure of temporo-parietal white matter as a basis for reading ability: evidence from diffusion tensor magnetic resonance imaging. Neuron. 25, 493-500, 2000.
13. Stebbins GT, Carillo MC, Medina D, deToledo-Morrell L, Klingberg T, Poldrack RA, Moseley ME, Karnil O, Wilson RS, Bennett DA, Gabrieli JDE. Frontal White Matter Integrity In Aging And Its Role In Reasoning Performance: A Diffusion Tensor Imaging Study. Abstract, Society Functional Neuroimaging, 2001 Abstract.
14. Urresta F, Medina D, deToledo-Morrell F, Gabrieli JDE, Klingberg T, Moseley ME, Wilson RS, Bennett JD, Stebbins G. In Vivo Detection Of White Matter Changes In Alzheimer's Disease With Diffusion Tensor Imaging. Abstract, Society Functional Neuroimaging, 2001 Abstract.