Inferring Structural and Architectural Features of Brain Tissue from DT-MRI Measurements

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ABSTRACT

Diffusion tensor magnetic resonance imaging is an imaging modality that measures the diffusion properties of water molecules in tissues noninvasively. Water diffusion is affected by tissue constituents, such as macromolecules, membranes, organelles, as well as by tissue microstructure, architecture, and organization. From the quantities measured with diffusion tensor-magnetic resonance imaging, one can infer information about brain tissue that cannot be obtained using conventional, compositional-based (eg, proton density and chemical spectroscopy), or relaxometry-based (eg, magnetization transfer, T1, T2, and T2) magnetic resonance imaging methods. Understanding the relationship between a measured water diffusion pattern and the underlying histological features of the tissue, however, is not simple. In the absence of a robust and comprehensive model of water diffusivity in biological tissues, the biological interpretation of diffusion measurements relies on empirical evidence. Herein, the properties of several diffusion tensor-derived quantities are reviewed, together with the experimental evidence that helps clarify their relationship with the underlying properties of brain tissue.*

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INTRODUCTION: DIFFUSION MEASUREMENTS IN BIOLOGICAL TISSUES

In the years preceding the advent of magnetic resonance imaging (MRI), magnetic resonance spectroscopists performed in vitro diffusion measurements in a variety of materials, including biological specimens. It was soon realized that interpreting the diffusion data obtained in tissues was more complicated than interpreting those in a bulk fluid. In a simple homogeneous fluid, diffusion is fully described by the diffusion coefficient (D), a constant that depends on the temperature and size of the diffusing molecule.[1] In biological tissues, D was found to be lower than that of bulk water at the same temperature,[2-8] and in certain tissues, including nervous tissue, D appeared to decrease with increasing diffusion time.[9,2] The former result indicated that tissue constituents somewhat interfere with the diffusion process (by hindering water diffusion), while the latter result suggested that this interaction is more complex than the simple effect of increased viscosity. Investigators tried to interpret these early experimental results on the basis of two models: the "restricted diffusion" model (sometimes referred to as the "obstruction" model) and the "hydration" model. The restricted diffusion model assumes that molecular self-diffusion in tissues is, for short diffusion times, essentially the same as that of the bulk fluid, but appears reduced when the diffusion time is long enough to allow the majority of the molecules to encounter physical barriers. Wang and Woessner[10,11] considered these barriers to be small impenetrable entities (macromolecules and small dense organelles), while Crick[12] included in the term "restriction" the effect exerted by permeable barriers (eg, the cell membranes). Cooper and colleagues[9] proposed that the reduction of D in biological tissues could result in part from the interaction of water with macromolecules. These authors based their interpretation on experiments with human blood fractions and ex vivo animal heart and liver, in which they observed a dependence of D on the degree of hydration of the tissue, with lower water diffusivity seen in the more dehydrated samples.

The development of a comprehensive biophysical model that could fully explain the diffusion properties of water in biological tissue has proven to be an elusive goal. Several experiments show that tissue constituents, such as macromolecules and membranes, all significantly affect water diffusion properties measured in tissues via MR methods. However, the early enthusiasm that MR diffusion experiments could be used to measure microstructural features of the tissue (eg, average cell size), the average distance between organelles, and membrane permeability[13] has been tempered by the difficulty of sorting out the effects of the geometrically and compositionally complex microenvironment of biological tissues, particularly in the brain. The same concept of a "diffusion coefficient" as a quantity that completely characterizes the diffusion process is not meaningful in biological tissues. In a homogeneous and isotropic fluid, each molecule has the same probability of traveling a certain distance in a given diffusion time. In tissues, the diffusional displacement of water molecules measured with MRI is the voxel-averaged result of individual displacements that may differ for each molecule depending on its interactions with the local microenvironment. For these

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reasons, the term "effective"[14,15] or "apparent"[16] diffusion coefficient (ADC) is commonly used in the MR diffusion literature when referring to Ds computed in biological tissues.[17]

MEASURING DIFFUSION IN ANISOTROPIC MEDIA: THE DIFFUSION TENSOR

Whereas in tissues with randomly composed microstructure, water diffusivity appears to be the same in all directions (isotropic diffusion), in tissues with an orderly oriented microstructure, such as brain white matter, the measured diffusivity of tissue water varies with the tissue's orientation (anisotropic diffusion, Figure 1).[6,18-21] Diffusion tensor MRI (DT-MRI) provides a measurement of an effective or apparent diffusion tensor (**D**) in each voxel of an imaging volume. This tensor quantity can be used to compute a three-dimensional displacement profile (ie, the surfaces of constant particle concentration that would result from releasing water molecules from a single point and allowing them to diffuse for a period of time) in anisotropic media (Figures 1 and 2). Within the limit of Gaussian diffusion, the displacement profile in anisotropic media can be described by an ellipsoid. DT-MRI provides the required information to construct a diffusion ellipsoid in each voxel of an imaging volume.[22,23]

From **D**, it is possible to calculate quantitative scalar and vector-valued parameters that characterize specific features of the diffusion process. These scalar quantities are designed to be rotationally invariant (ie, independent of the coordinate system in which the MR measurement is made the orientation of subjects in the magnet, and many of the specifics of the experimental design). The most basic rotationally invariant quantities are the three principal diffusivities (or eigenvalues) of **D**. They are the principal "apparent" diffusion coefficients measured along the three intrinsic-coordinate directions that constitute the local diffusion frame of reference in each voxel. Each eigenvalue is associated with a principal direction (eigenvector) that is also intrinsic to the tissue. The three eigenvectors of **D** are mutually perpendicular and coincide with the three axes of the diffusion ellipsoid. In each voxel, these eigenvalues can be sorted in order of decreasing magnitude ($\lambda 1$=highest diffusivity; $\lambda 2$=intermediate diffusivity; $\lambda 3$=lowest diffusivity). In anisotropic tissues consisting of ordered, parallel bundles, the largest eigenvalue, $\lambda 1$, represents the diffusion coefficient along the direction parallel to the fibers, while $\lambda 2$ and $\lambda 3$ represent the diffusion coefficients in the transverse directions.[22,23]

TRACE(D)

Trace(**D**) corresponds to the sum of the three eigenvalues of **D**, ($\lambda 1$, $\lambda 2$, and $\lambda 3$) (Figure 3). Trace(**D**) is a rotationally-invariant scalar measure that characterizes the orientationally averaged diffusivity of the tissue. In the literature, the quantity Trace(**D**)/3 is given different names such as, "Trace ADC," "mean ADC," "average ADC," "mean diffusivity," "orientationally averaged diffusivity," "orientationally averaged ADC," and represented by different symbols, such as $\langle D \rangle$ and $\overline{D}$. The use of such a variety of names to indicate the same quantity is confusing, and some of these commonly used names are imprecise or inappropriate. For example,

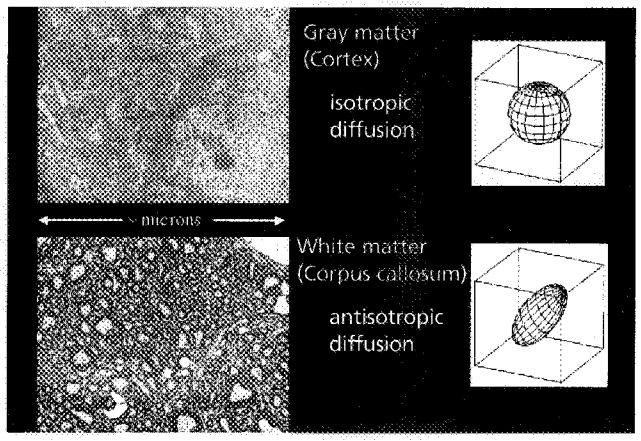

FIGURE 1. Electron micrographs of tissue samples taken from the cerebral cortex (top) and the corpus callosum (bottom) in cats. The dimension of the portion of tissue included in these micrographs is on the order of a few microns. This distance is consistent with the diffusional path length traveled by water molecules in a typical diffusion MRI study. The presence of fibrous structures, having consistent orientation across the voxel, causes water diffusion to be anisotropic in the corpus callosum (higher diffusivity in the direction parallel to the fibers than in the direction perpendicular to them). In gray matter, the lower degree of microstructural ordering is reflected by a more isotropic diffusion pattern.

MRI=magnetic resonance imaging.

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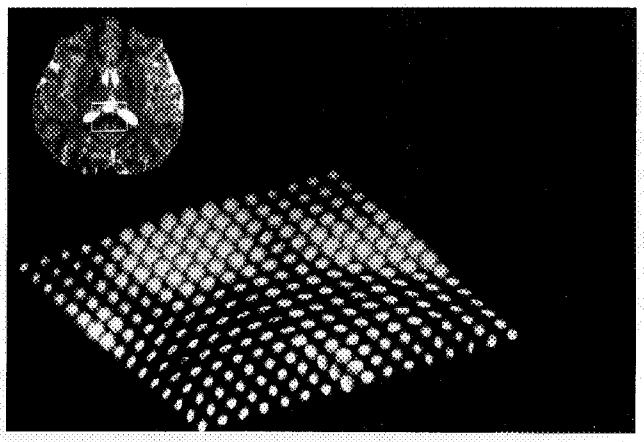

FIGURE 2.[24] Diffusion ellipsoids computed in the human brain from a DT-MRI study. Diffusion ellipsoids are constructed in each voxel of the region shown in the T2-weighted image at the top-left of the figure. Voxels with large, spherical ellipsoids contain CSF; voxels with smaller, spherical ellipsoids contain gray matter; and voxels with prolate ellipsoids contain white matter. In the corpus callosum, the orientation along which the apparent diffusivity is a maximum corresponds to the expected fiber orientation in this region.

DT-MRI=diffusion tensor magnetic resonance imaging; CSF=cerebrospinal fluid.

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Trace ADC is not meaningful, given that the ADC is a scalar quantity, not a tensor. We hope that with time the DT-MRI community will agree on a more uniform and precise terminology.

Trace(**D**) has been found to be quite uniform in normal brain parenchyma across diverse brain regions,[24] and even across mammalian species.[25,26] This regional homogeneity makes Trace(**D**) a particularly good parameter to use to detect structural abnormalities in vivo since its value appears to be so tightly controlled under normal conditions. Trace(**D**) is also relatively well behaved statistically. Noise in the diffusion-weighted images increases the variance of Trace(**D**) but does not alter its mean value at the typical signal/noise of clinical diffusion measurements. This implies that standard parametric statistical tests, such as analysis of variancem, can be used to test differences in Trace(**D**).[27] The most important clinical use of Trace(**D**) is in the assessment of cerebrovascular diseases, in particular in acute ischemia where tissue water diffusivity decreases significantly shortly after the onset of the ischemic event.[28,29] More recently, Trace(**D**) has become widely used to investigate a variety of neurological disorders, including epilepsy, multiple sclerosis, dementia, neurodegenerative disorders, normal brain development, and aging.

Several factors can potentially affect the value of Trace(**D**) in nervous tissue, and changes in Trace(**D**) cannot be unequivocally associated with specific changes in the structural of physiological state of the tissue (perhaps with the exception of a largely reduced value of Trace(**D**) that is indicative of severe cellular metabolic impairment). Properties of the tissue microenvironment that could potentially affect Trace(**D**) include the degree of tissue hydration, relative size of the extra- and intracellular compartments, geometry of cell bodies and processes, membrane permeability, integrity of cell membranes, and cell-packing density. The sensitivity of Trace(**D**) to the degree of cellularity is suggested by recent observations in multiple sclerosis and brain tumors. In multiple sclerosis, relatively low values of Trace(**D**) have been observed in active plaques that have increased cellularity due to the accumulation of inflammatory cells[30,31] and in tumors a significant inverse correlation between Trace(**D**) and cellularity has been found.[32]

INDICES OF DIFFUSION ANISOTROPY

Several diffusion anisotropy indices derived from the DT have been proposed in the literature. The most intuitive and simplest rotationally invariant indices are ratios of the principal diffusivities,[22] such as the dimensionless anisotropy ratio $\lambda 1/\lambda 3$ that measures the relative magnitudes of the diffusivities along the fiber-tract direction and one transverse direction. The main problem with using anisotropy indices defined from the eigenvalues of the tensor sorted in order of magnitude (sorted eigenvalues) is their extreme susceptibility to noise. Noise in the diffusion-weighted images not only increases the variability of the sorted eigenvalues, but also introduces a significant bias in their mean values.[25] The severity of this bias depends on the degree of overlap in the distributions of the eigenvalues. If we were to use standard statistical tests to analyze their distributions in a region of interest, we would erroneously conclude that statistically significant differences exist between $\lambda 1$ and $\lambda 2$, as well as between $\lambda 2$ and $\lambda 3$, even in an isotropic medium in which no differences are expected between them.

While calculating ratios of the principal diffusivities requires us to sort the eigenvalues according to their magnitude, other invariant anisotropy indices can be constructed so that they are independent of the way we order the eigenvalues. One such index is the volume ratio (VR).[25] VR has a simple geometrical interpretation: it represents the volume of an ellipsoid whose semi-major axes are the 3 eigenvalues of **D** divided by the volume of a sphere whose radius is the orientationally averaged diffusivity, <D>. Since the volume of the ellipsoid approaches 0 as anisotropy increases, the values of VR range between 0 and 1, where 0 indicates the highest anisotropy and 1 represents complete isotropy. Often the complement of VR, 1-VR is used for consistency with other anisotropy indices for which 0 corresponds to isotropy and 1 to the highest anisotropy. Other invariant measures of diffusion anisotropy that do not require sorting of the eigenvalues have been proposed, such as the relative anisotropy (RA)[33] and the fractional anisotropy (FA).[33] Different anisotropy indices differ in their susceptibility to noise and their dynamic range of sensitivity. FA for example has a very good sensitivity to small differences in anisotropy for low levels of anisotropy, whereas VR provides a strong contrast between low and high anisotropy.[34] In general, the eigenvectors of **D** do not appear in the definition of anisotropy indices. This is not surprising because diffusion anisotropy is intrinsically related to the eigenvalues of **D**, which determine the shape of the diffusion ellipsoids, not to the eigenvectors of **D**, which specify their orientation. Some authors, however, have proposed anisotropy indices that use the directional information contained in the diffusion tensor in order to improve the accuracy and precision of the esti-

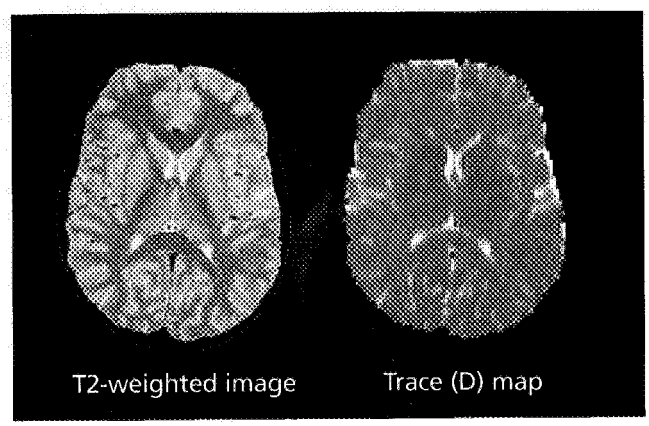

FIGURE 3. Axial T2-weighted image of healthy volunteer (left), and the corresponding Trace(**D**) map (right). White and gray matter have similar values of Trace(**D**).

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mation of anisotropy. The "lattice" anisotropy index, for example, is affected by the degree of orientational coherence of the diffusion ellipsoid in the reference voxel with those in neighboring voxels (Figure 4).[25,35] Furthermore, anisotropy indices that exploit the orientational coherence of eigenvectors that are computed in the same voxel from serial measurements of DT have been recently proposed.[36]

Other rotationally invariant scalars quantities can be constructed from the DT to measure different features of anisotropic diffusion. One of these measures is the skewness of the eigenvalues (Figure 4).[37,38] While anisotropy indices measure the degree to which the diffusion ellipsoid's shape deviates from being spherical, the skewness of the eigenvalues measures whether the ellipsoid is prolate (cigar-shaped) or oblate (pancake-shaped) This is shown in Figure 5. Prolate water-displacement profiles are typically found in white matter regions with parallel arrangement of fibers, such as the corpus callosum and pyramidal tract. Oblate ellipsoids correspond to white matter regions having a particular architectural arrangement of fibers, such sheets of parallel fibers with different orientations, or bundles of fibers that are randomly oriented in a plane. Oblate water-displacement profiles are found in the centrum semiovale and subcortical white matter regions (Figure 6).[21] Diffusion anisotropy is determined by the presence of fibrous structures, such as axons in white matter. Local architectural features of white matter, such as the distribution of orientations of axons within a voxel strongly affect diffusion anisotropy (Figures 4 and 7).[24,25] Architectural features of the tissue had never been considered as possible factors influencing diffusion anisotropy until reliable measurements of diffusion

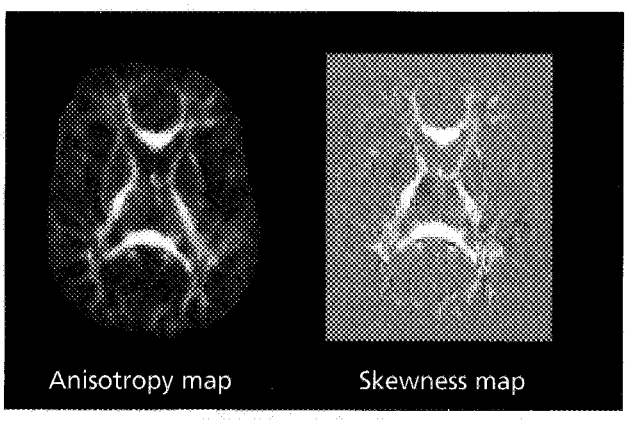

FIGURE 4. "Lattice" anisotropy index map (left) and "skewness" map for the same brain slice shown in Figure 3. In the anisotropy map, bright voxels indicate high anisotropy. White matter regions having a homogeneous distribution of signal intensity in the T2-weighted image have heterogeneous water diffusion properties that depend on the architectural arrangement of the fibers. For example, the corpus callosum has very high anisotropy, while subcortical white matter regions have lower anisotropy despite their similar T2-weighted signal intensity. In the skewness map, voxels with positive skewness are bright, while voxels with negative skewness are dark.

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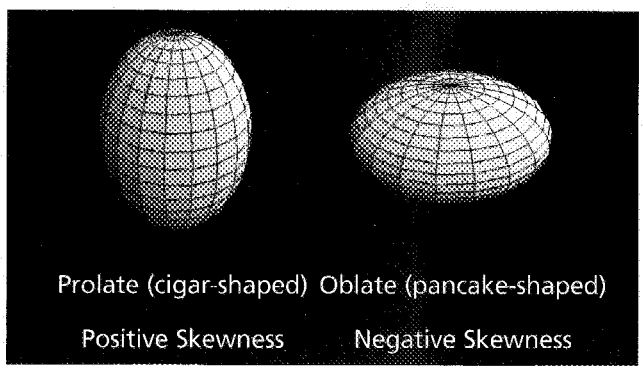

FIGURE 5. Two different anisotropic diffusion displacement profiles that can be found in different white matter regions in the human brain: prolate and oblate.

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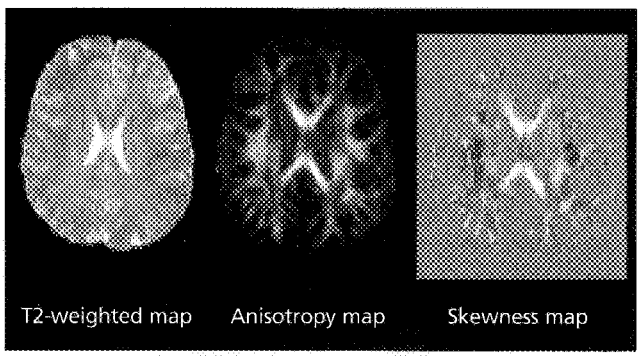

FIGURE 6. In Figure 4, few white matter voxels have negative skewness. This figure shows a more rostral section of the same brain in Figure 4, with several voxels in the centrum semiovale having negative skewness.

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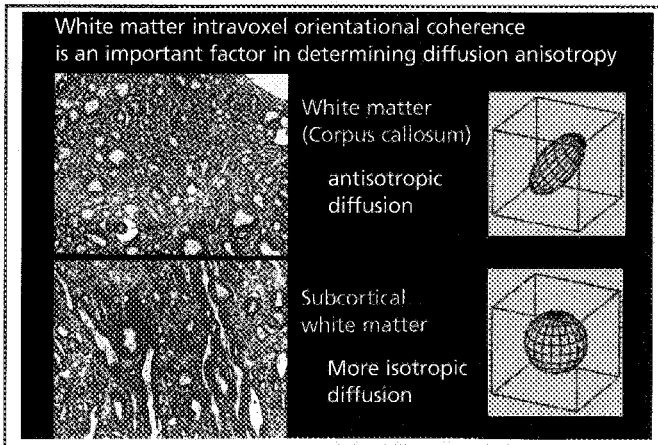

FIGURE 7. Electron micrographs of tissue samples taken from the corpus callosum (top) and the subcortical white matter (bottom) in cats. This figure underscores the importance of white matter architecture in determining the degree of diffusion anisotropy. Diffusion anisotropy is high in white matter regions, such as the corpus callosum, having coherently oriented fibers. Subcortical white matter regions, where fiber orientation is more incoherent, typically show low anisotropy values.

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anisotropy became possible with DT-MRI. The measured diffusion anisotropy is also likely to be affected by white matter structural features, such as axonal diameter, fiber-packing density, and degree of myelination. However, a precise relationship between these structural features and diffusion anisotropy has yet to be established.

EIGENVECTORS, WHITE MATTER FIBER ORIENTATION MAPPING, AND TRACTOGRAPHY

The eigenvectors of the DT provide unique directional information that can be used to infer features of living tissue. In particular, the eigenvector e1, associated with the largest eigenvalue, $\lambda 1$, represents the direction parallel to a bundle of fibers within a voxel. We can use measurements of this eigenvector in each voxel to construct vector maps of white matter fiber direction within an imaging volume (Figure 8).[25,24,39-44] Moreover, from this discrete 3D vector field, one can calculate trajectories of different fiber tracts in a manner similar to that used in fluid mechanics to obtain fluid streamlines from a discrete velocity vector field.[45-50] In the brain, fiber-direction mapping is useful to identify and differentiate anatomical white matter pathways that have similar structure and composition but different spatial orientation.[44,51-53] Historically, such studies of the brains structural anatomy could only be performed using histological methods.[54] Several groups have presented white matter orientation maps of the human brain that clearly depict the main association, projection, and commissural white matter pathways. Even in the brainstem, which is a relatively small anatomical structure, motor and sensory pathways can be easily identified and differentiated from the transverse pontine fibers and cerebellar peduncles.[53]

Recently, DT-MRI has come to be increasingly used in the neurosciences community to study connectivity noninvasively in the living human brain. There are still many open questions about whether this goal can be achieved by currently available methods, because inferring continuity of particular pathways from diffusion measurements in regions where different fiber bundles intersect is problematic. Nevertheless, robust algorithms for fiber-tracking using DT-MRI data have been proposed recently and can be used to explore the potential usefulness of DT-MRI in assessing brain connectivity and degenerative changes of neural tissue.[45-50]

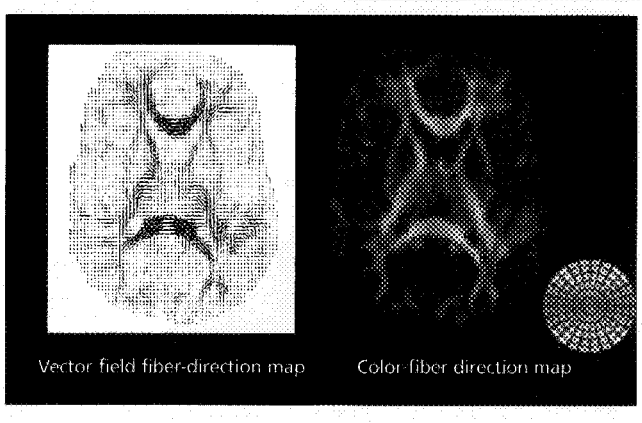

FIGURE 8. "Fiber-orientation" maps for the same brain slice shown in Figure 3. Both maps are constructed assuming that the orientation of highest diffusivity (principal eigenvector) represents the orientation parallel to a bundle of fibers within a voxel. The map on the left shows the projection of the principal eigenvector in the image plane in each voxel. The length of each segment is proportional to the degree of anisotropy. The map on the right shows a DEC map constructed.[52,53] In these maps, bright voxels correspond to regions where water diffusion is anisotropic (white matter); dark voxels indicate regions where water diffusion is isotropic (mostly gray matter and CSF). Different colors code for different fiber-tract orientations: the left-right, anterior-posterior, and superior-inferior orientation are respectively associated with pure red, green, and blue. Colors resulting from combinations of red, green, and blue indicate fibers oriented obliquely.

DEC=direction-encoded color; CSF=cerebrospinal fluid.

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CONCLUSION

Diffusion-weighted MRI was first performed in living tissue more than 10 years ago.[55] Subsequently, numerous experimental and clinical studies have shown that MRI measurements of water diffusion in tissues provides valuable information on tissue pathophysiology previously unattainable with any other noninvasive imaging technique. Although large scale clinical DT-MRI studies are only beginning to be undertaken, there is already a large body of experimental evidence suggesting that this technique provides unique information about brain anatomy, microstructure, organization, and architecture. CNS

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