Diffusion tensor imaging offers fresh approach to diagnosis of brain disorders

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The application of MR imaging to reveal diffusion characteristics of water in tissues was preceded by basic science MR methods for the determination of diffusion constants. In routine clinical MR imaging, most of the signal arises from water in tissue, and the visualization of changes in the diffusion properties of tissue water with MR imaging has become a useful, multifaceted tool to characterize tissue structure and to identify and differentiate disease processes.

Diffusion imaging also promises to further our understanding of brain disorders and abnormalities such as stroke, tumors, multiple sclerosis, and schizophrenia.

When it became evident that MR diffusion techniques could be implemented on clinical MR scanners to evaluate the mobility of water molecules, several important clinical and research applications emerged. Diffusion MR imaging as a technique was pioneered in 1986 by Le Bihan, and in 1990 Moseley conducted ground-breaking animal studies that demonstrated the value of diffusion imaging for the early detection of stroke.

These findings strongly supported the introduction of MR diffusion imaging as a novel diagnostic method. Its widespread application was impeded, however, by technical factors. The most important difficulty was motion sensitivity, which can cause severe ghosting artifacts or complete signal loss. As molecular displacement must be observed on the order of micrometers, it is no surprise that any motion—even unavoidable involuntary head motion or physiological, blood pressure-related pulsations of the brain tissue—would interfere with these measurements. The problem is even more serious when scans must be obtained in disoriented and confused stroke victims, whose head movements are excessive. The development of faster sequences that are more robust to...
bulk motion was largely inspired by the need to cope with motion sensitivity.

The development of diffusion-sensitive pulse sequences basically followed two directions: echo-planar imaging methods, which acquire a complete image within a single shot, and navigator methods, which acquire images in multiple shots but employ so-called navigator MR signals for each shot to detect and correct the bulk motion. While single-shot methods are extremely robust, the elevated sensitivity to magnetic field inhomogeneities may lead to image distortion artifacts in areas exhibiting large variations in magnetic susceptibility, as at interfaces between air, bone, and brain tissue. Spatial resolution is limited and signal averaging may be necessary. Navigator methods, in contrast, permit excellent spatial resolution with minimal image distortion artifacts and high signal-to-noise ratio, but they are not as robust and require acquisition times of 10 minutes or more. Furthermore, cardiac gating must be used, which makes the technique less attractive in a routine clinical setting.

At our institution, we have developed a special MR diffusion imaging method that obtains images line-by-line in multiple independent single-shot acquisitions (Figure 1). In terms of overall scan time, line scan diffusion imaging (LSDI) falls between the faster single-shot diffusion-weighted echo-planar imaging and the slower navigator methods. It is as robust to bulk motion as the single-shot echo-planar imaging methods, but it does not suffer from severe distortion artifacts at tissue interfaces. Unlike single-shot echo-planar imaging, LSDI does not require special gradient hardware and can therefore be implemented on cost-effective low-field systems that are not capable of acquiring single-shot echo-planar images.

With the development of techniques less prone to ghosting artifacts due to bulk motion, the exceptional value of diffusion imaging for the early detection of ischemic stroke in humans soon became evident. The demonstration of diffusion imaging’s diagnostic utility gave a boost to the study of cerebral vascular disease, in which the technique is used to evaluate early tissue changes following acute stroke as well as to study other brain disorders such as tumors.

**Brownian Motion**

The measurement of water diffusion in tissues begins with probing the movement of water molecules within the intricate tissue environment. In pure liquids such as water, individual molecules are in constant motion in every possible direction, due to random motion initiated by thermal energy. This phenomenon is commonly referred to as "Brownian motion." In tissues, however, the presence of various tissue components (larger
molecules, intracellular organs, membranes, cell walls) has the effect of damping the Brownian motion. In many tissues, when averaged over the macroscopic scale of image voxels, this restriction is identical in every direction—the diffusion is isotropic. In some very structured tissues, such as muscle or cerebral white matter, the cellular arrangement creates a preferred direction of water diffusion that is largely uniform across the entire voxel—the diffusion is anisotropic.

The diffusion coefficient is a measure of this molecular motion, and it can be determined with MR imaging techniques. MR diffusion imaging makes use of the strongest possible magnetic field gradients, which are of the order of 20 to 40 mTesla/m, with clinical scan systems. The magnetic field gradient is applied to “tag” spins according to their location in space. A second gradient applied at a later time then serves to probe how far, on average, the individual spins have moved between the time of the first and second gradient application. Each gradient is typically applied for a duration of several tenths of a millisecond, during which time the average water molecule in brain tissues may migrate 10 or more micrometers in a random direction. The irregularity of the motion entails a signal loss that can be used to quantify the diffusion constant.

The MR measurement fails to differentiate diffusion-related motion from blood flow, perfusion, bulk tissue, or tissue pulsation-related motion. Thus, the diffusion value obtained with this technique is not an actual diffusion coefficient, but only an apparent diffusion coefficient, or ADC. Diffusion-weighted images are inherently also T2 weighted, by nature of the long probing time of the magnetic field gradients. To separate confounding T2 relaxation and diffusion-related changes of the signal, it is therefore beneficial to calculate a map of ADC values.

In an acute stroke, the diffusion coefficient within the lesion is reduced by as much as 50% within minutes after the onset of ischemia (Figure 2). As a result, diffusion-related signal attenuation is diminished and the lesion appears bright. Twelve to 24 hours later, T2 changes also start to contribute to the lesion brightness. This effect, also called “shine through,” must be considered when trying to estimate the age of an ischemic lesion, particularly at a later stage, when ADC values revert.

**Restricted Diffusion**

Diffusion along one particular direction, as selected by the direction of the probing magnetic field gradient, could be different from the diffusion along another direction if the structural organization of the tissue is anisotropic. In the brain and spinal cord, diffusion anisotropy is attributed to the presence of myelinated white matter fiber tracts. The motion of tissue water across the multiple layers of myelin membranes that surround the axons is restricted. At the same time, water molecules are relatively free to move along the longitudinal direction of the axons.
To avoid fiber tract direction-dependent signal variations, image data from several acquisitions, with diffusion weighting along different directions, must be combined. Independent of the preferred diffusion direction, a minimum of three directions that are orthogonal (perpendicular) to each other must be sampled. The description of multidirectional tissue water diffusion apparently requires a more complex model in order to characterize it accurately. This more complex model uses the concept of a diffusion tensor and was introduced to the field of MR diffusion imaging by Basser et al.\textsuperscript{13}

Conceptually, the term "tensor" is a construct of physics and engineering; it was introduced to describe tension forces in solid bodies with an array of three-dimensional vectors. The tensors used to describe diffusion can be further conceptualized and visualized as ellipsoids, the three main axes of which describe an orthogonal coordinate system. The directions of the main axes represent the eigenvectors and their length the eigenvalues of the tensor.

The longest main axis of the diffusion ellipsoid represents value and direction of maximum diffusion, whereas the shortest axis denotes value and direction of minimum diffusion. If the three eigenvalues are equal, the diffusion is said to be isotropic and the diffusion tensor can be visualized as a sphere.

In MR diffusion tensor imaging (DTI), a tensor that describes diffusion in all spatial directions is calculated for each voxel. To correctly assess the diffusion tensor, data from at least six independent diffusion encoding directions are acquired for each voxel. Eddy currents that occur mainly due to the presence of diffusion gradients may result in a mismatch of the images obtained with diffusion weighting along different directions. Consequently, the determination of fiber direction may be unreliable. We have found, however, that the eddy current-related mismatch of images obtained with LSDI is minimal, unlike images obtained with single-shot echo-planar diffusion imaging.

White matter fiber tracts consist of a large number of densely packed myelinated axons. Within this myelinated white matter, the movement of water molecules is substantially restricted to directions that are perpendicular to the longitudinal axis of the axons. Consequently, in white matter tracts, the longest main axis is much larger than the other two and coincides with the direction of the fibers. Following Westin’s geometrical classification of the diffusion tensor,\textsuperscript{14} this type of anisotropic restricted diffusion is termed linear diffusion. If diffusion is restricted along one direction only and unrestricted along the other two directions, as between layers of tissue sheets, the term planar diffusion is used.

The basic ellipsoid model is idealized and does not necessarily reflect the
true diffusion behavior encountered in real tissues. At nerve fiber tract crossings, for example, the ellipsoid tensor model fails, since each fiber tract constitutes a preferred diffusion direction. Acquisition protocols that measure diffusion along a large number of directions, however, allow for a better description of the complex directional diffusion behavior in fiber tract crossings and in other heterogeneously organized tissue structures.\textsuperscript{15}

Various measures, such as the ratio between the longest and shortest axis of the diffusion ellipsoid, can be used to quantify anisotropy, thus describing the inequality of diffusion values among particular directions. On maps generated by these parameters, white matter tracts, which exhibit a high anisotropy index, appear bright. Gray matter and cerebrospinal fluid, on the other hand, are represented by dark shades according to their low or absent anisotropy.

Diffusion tensor tractography is a new application that is extremely helpful diagnostically.\textsuperscript{16} It uses the principal diffusion direction measured with DTI to compute the pathways of complete nerve fiber tracts. The tracing is performed by first defining positions of interest in a white matter tract. By following repetitively and in small steps along spatially interpolated directions of maximum diffusion, the application defines a contiguous path that passes through the initial seed positions. Visualized with suitable software in three dimensions, these tracts depict the involved anatomy of white matter fiber (Figure 3). The departure from the basic assessment of the anisotropy of each diffusion ellipsoid to the more elaborate analysis of neighbor relations among diffusion ellipsoids opens the possibility for assessing in vivo axonal fiber connectivity and functional links between brain regions.

**Novel Diagnostic Applications**

Several applications of diffusion imaging are adding to our understanding of brain disorders. The phenomenon of restricted diffusion is of particular interest to studies that evaluate the integrity of white matter fiber tracts.\textsuperscript{17,18} Using geometry and the degree of anisotropy loss, researchers can document white matter tract alterations such as dislocation, swelling, infiltration, and disruption. These changes are characteristically present in various degrees and forms in brain tumors and other space-occupying lesions (Figure 4).

This detailed depiction of altered white matter anatomy can be used primarily for surgical or radiation therapy planning to avoid the injury of displaced but still intact fiber tracts. The cross-sectional size of these pathways yields a quantitative measure of connectivity between different brain regions. Diffusion tensor tractography, fused with conventional and functional image information, provides a powerful tool for neurosurgeons, especially when surgery takes place in the proximity of vital nerve fiber tracts.
To trace and map the passage of functionally relevant fiber tracts along the tumors is equally important to the mapping of cortical functions adjacent to tumors. Therefore, DTI and functional MR imaging (fMRI) are complementary techniques for surgical planning. The information gathered with these techniques helps the neurosurgeon to decide where tumor tissue can be excised without permanent neurologic consequences. Tractography with the aid of DTI is also valuable in other brain disorders that involve changes in white matter connectivity such as disruptions in connectivity and subsequent reorganization of nerve pathways that result from brain injuries, as with physical trauma or ischemia. Changes or disruptions of connectivity may also occur in diseases such as multiple sclerosis, HIV-1 infection, and schizophrenia as well as degenerative and metabolic conditions. Figure 5 shows an application to schizophrenia.

In addition to the directionality of diffusion, the amount of diffusion weighting generated by the probing gradients (denoted with the b factor) is a potential diagnostic measure. For routine clinical scans, b factors between 500 and 1000 sec/mm² are commonly used. The higher the b factor we choose, the more the contrast between tissues with different diffusion constants increases. With a b factor of 200 sec/mm², for example, a fresh stroke lesion may be barely distinguishable from normal tissue, whereas at a b factor of 1000 sec/mm², the contrast between lesion and normal tissue may reach a ratio of 2:1 or higher.

In the early days of diffusion imaging, it was thought that tumor detection and demarcation could be aided with MR diffusion imaging. Conventional diffusion imaging, however, while useful for the early detection of stroke, was never found to be particularly helpful for the characterization of tumors versus normal tissues, except in the case of cystic lesions. Once we exceed the normal range of b factors, however, some tumors exhibit a striking contrast to normal white and gray matter. It appears that the abnormal signal decay is prominent in tumors and may provide information different from that obtained with contrast-enhanced MR scans.

MR diffusion imaging has become a powerful, multifaceted tool both for very basic clinical needs and for advanced, specialized diagnosis and treatment planning. Current MR brain research would be unthinkable without these advances in MR diffusion imaging. In particular, DTI and nerve fiber tractography have opened up research possibilities in areas that hitherto relied largely on postmortem studies. For the first time, the intricate connective architecture of the most complex human organ can be studied noninvasively.

Other potentially important applications of MR diffusion imaging include characterization of cardiac muscle tissue architecture, liver disease
diagnosis, and temperature mapping. Technical advances such as improved spatial resolution, shorter scan time, and reduced artifacts are desirable, and further investments in software development are necessary to bring data processing tools developed at research laboratories closer to the clinical imaging practice. Once clinicians become comfortable with this technique, several new and interesting applications may emerge.

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