Bridging the gap between brain anatomy and function with diffusion MRI

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Abstract

Water diffusion MRI allows tissue structure to be probed and imaged at a microscopic scale well beyond the usual "millimetric" image resolution, providing unique clues to the fine architecture of neural tissues, and to changes associated with various physiological or pathological states. The leading clinical application of diffusion MRI has been in the study of acute brain ischaemia. With its unmatched sensitivity, diffusion MRI provides some patients with the opportunity to receive suitable treatment at a stage when brain tissue might still be salvageable. Moreover, because diffusion is anisotropic in brain white matter, reflecting its organization in bundles of myelinated axonal fibres running in parallel, diffusion MRI can be used to map out the orientation in space of the white matter tracks in the brain. Diffusion MRI is also a promising tool for the study of brain maturation and development.

Introduction

The ability to visualize anatomical connections between different parts of the brain, non-invasively and on an individual basis, has opened a new era in the field of functional neuroimaging. This major breakthrough for neuroscience and related clinical fields has developed over the past ten years through the advance of "diffusion magnetic resonance imaging" or D-MRI. The concept of D-MRI is to produce MRI quantitative maps of microscopic, natural displacements of water molecules that occur in brain tissues as part of the physical diffusion process. Water molecules are thus used as a probe that can reveal microscopic details about tissue architecture, either normal or in a diseased state.

The concept of molecular diffusion

Molecular diffusion refers to the random translational motion of molecules (also called Brownian motion), which results from the thermal energy carried by these molecules. Molecules travel randomly in space over a distance that is statistically well described by a "diffusion coefficient" (D). This coefficient depends only on the size (mass) of the molecules, the temperature and the nature (viscosity) of the medium.

"Diffusion MRI" is, thus, deeply rooted in the concept that, during their diffusion-driven displacements, molecules probe tissue structure at a *microscopic* scale well beyond the usual *millimetric* image resolution. During typical diffusion times of about 50-100 ms, water molecules move in brain tissues on average over distances around 1-15 μm, bouncing, crossing or interacting with many tissue components, such as cell membranes, fibres or macromolecules. Because of the tortuous movement of water molecules around those obstacles, the actual diffusion distance is reduced compared to free water. Hence, the non-invasive observation of the water diffusion-driven displacement distributions *in vivo* provides unique clues to the fine structural features and geometric organization of neural tissues, and to changes in those features with physiological or pathological states.

Imaging diffusion with MRI

Principles

While early water diffusion measurements were made in biological tissues using Nuclear Magnetic Resonance in the 1960s and 70s, it is not until the mid 1980s that the basic principles of diffusion MRI were laid out[1],[2;3], see for instance [4] for a review. MRI signals can be made sensitive to diffusion through the use of a pair of sharp magnetic field gradient pulses, the duration and the separation of which can be adjusted. The result is a signal (echo) attenuation which is precisely and quantitatively linked to the amplitude of the molecular displacement distribution: Fast (slow) diffusion results in a large (small) distribution and a large (small) signal attenuation. Of course, the effect also depends on the intensity of the magnetic field gradient pulses.

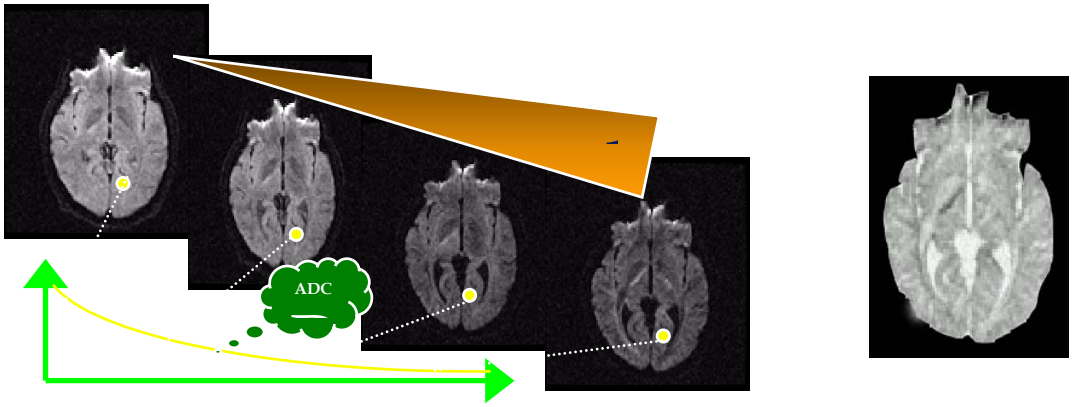

Figure 1: Diffusion-weighting. In practice different degrees of « *diffusion-weighted* » images can be obtained using different values of the b factor (*orange triangle*). The larger the b factor the more the signal intensity becomes attenuated in the image. This attenuation, though, is modulated by the diffusion coefficient: signal in structures with fast diffusion (e.g., water filled ventricular cavities) decays very fast with b, while signal in tissues with low diffusion (e.g., gray and white matter) decreases more slowly. By fitting the signal decay as a function of b, one obtains the ADC for each elementary volume (voxel) of the image. « *Calculated* » diffusion images (*ADC maps*), depending solely on the diffusion coefficient, can then be generated and displayed using a gray (or color) scale: High diffusion, as in the ventricular cavities, appears bright, while low diffusion is dark (*right*).

In practice, any MRI imaging technique can be sensitized to diffusion by inserting the adequate magnetic field gradient pulses [5]. By acquiring data with various gradient pulse amplitudes one gets images with different degrees of diffusion sensitivity (Fig. 1). Contrast in these images depends on diffusion, but also on other MRI parameters, such as the water relaxation times. Hence, these images are often numerically combined to determine, using a global diffusion model, an estimate of the diffusion coefficient in each image location. The resulting images are maps of the diffusion process and can be visualized using a quantitative scale.

Because the overall signal observed in a “diffusion” MRI image voxel, at a *millimetric* resolution, results from the integration, on a statistical basis, of all the *microscopic* displacement distributions of the water molecules present in this voxel it was suggested [6] to portray the complex diffusion processes that occur in a biological tissue on a voxel scale using a *global*, *statistical* parameter, the *Apparent Diffusion Coefficient* (ADC). The ADC concept has been largely used since then in the literature. The ADC now depends not only on the actual diffusion coefficients of the water molecular populations present in the voxel, but also on experimental, technical parameters, such as the voxel size and the diffusion time.

A major neurological application: Acute brain ischaemia

Although the first diffusion images of the brain were obtained in the mid 1980s, both in normal subjects and in patients [6], it was not until the mid 1990s that diffusion MRI

really took off. Initially, the specifications of the clinical MRI scanners made it difficult to obtain reliable diffusion images, as acquisition times were long (10 to 20 minutes) and the presence of the large gradient pulses required for diffusion also made the images very sensitive to macroscopic motion artefacts, such as those induced by head motion, breathing or even cardiac related brain pulsation [7]. Therefore, although diffusion MRI was shown to be potentially useful in the clinic, demonstrative clinical studies started only later, when better MRI scanners, equipped with echo-planar imaging (EPI) became available. Exploiting gradient hardware EPI makes it possible to collect a whole brain image in a single "shot" lasting a few tens of milliseconds and images of the whole brain in less than a second, virtually freezing macroscopic motion.

The most successful application of diffusion MRI since the early 1990s has been in acute brain ischaemia [8]. The application of diffusion MRI to patients with chronic infarct lesions was suggested early on [6;9]. However, a significant discovery was made later by Moseley et al. [10;11] who demonstrated that water diffusion significantly drops (by 30 to 50%) in ischaemic brain tissue within several minutes of the occlusion of the middle cerebral artery in the cat. This finding was soon confirmed by many groups using other animal models (see [12] and [13] for extensive reviews) and later in human patients with stroke [14][15] [16](Fig. 2) . Diffusion MRI today is the imaging modality of choice to manage stroke patients. However, although the decrease in water diffusion right after the ischaemic injury has been clearly established, its interpretation is still not fully understood, and its relationship with the severity of the ischemic damage and the clinical outcome remains a subject of study [13]. The diffusion drop is linked in some way to the cellular change in energy metabolism that ultimately leads to the decreased activity and then failure of the Na^+/K^+ pumps resulting in cytotoxic oedema [12]. Diffusion imaging offers great potential in the disease management of stroke patients: First, the development of pharmaceuticals for the treatment of stroke can be greatly facilitated, as drug effects can be assessed objectively and very quickly compared with long and costly clinical trials or animal model studies. With diffusion MRI used in combination with perfusion MRI, which outlines regions with decreased blood flow or increased blood mean transit times [17], and MR "angiography" (which provides images of the vasculature, showing occluded vessels), clinicians have in their hands invaluable tools to help them, at a very early stage when tissue is still

salvageable, to assess lesion severity and extension, and to customize a therapeutic approach (pharmacological or interventional to individual patients [18], as well as to monitor patient progress on an objective basis, both in the acute and the chronic phase [19], and to predict clinical outcome [20-23].

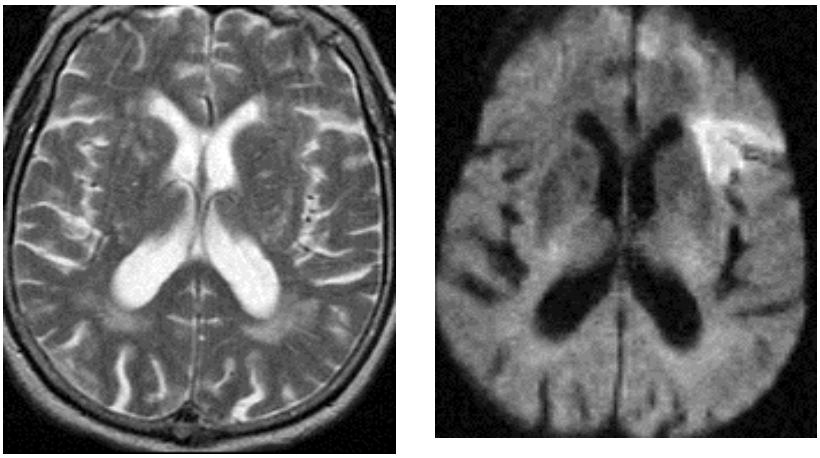

Figure 2: Acute brain ischaemia. A major clinical application of diffusion MRI has been acute brain ischemia. Images (*left*: conventional T2w-MRI) and (*right*: diffusion-weighted image) were obtained a few hours after the onset of aphasia in patient. The diffusion image clearly shows the infarcted tissue with an intense signal corresponding to reduced water diffusion in the ischemic territory.

Diffusion anisotropy in white matter: Towards brain connectivity studies

The diffusion tensor

Diffusion is truly a three-dimensional process, therefore, water molecular mobility in tissues is not necessarily the same in all directions. This diffusion *anisotropy* may result from the presence of obstacles that limit molecular movement in some directions. It is not until the advent of diffusion MRI that anisotropy was detected for the first time *in vivo*, at the end of the 1980s, in spinal cord and brain white matter [24;25]. Diffusion anisotropy in white matter grossly originates from its specific organization in bundles of more or less myelinated axonal fibres running in parallel: Diffusion in the direction of the fibres (whatever the species or the fiber type) is about 3-6 times faster than in the perpendicular direction. However the relative contributions of the intra-axonal and extracellular spaces, as well as the presence of the myelin sheath, to the ADC, and the exact mechanism for the anisotropy is still not completely understood, and remains the object of active research (see, for instance, [26] for a recent review). It quickly became apparent, however, that this anisotropy effect could be exploited to map out the orientation in space of the white matter tracks in the brain, assuming that the direction of the fastest diffusion would indicate

the overall orientation of the fibres [27]. The work on diffusion anisotropy really took off with the introduction in the field of diffusion MRI of the more rigorous formalism of the *Diffusion Tensor*, by Basser et al. [28;29]. With *Diffusion Tensor Imaging* (DTI), diffusion is no longer described by a single diffusion coefficient, but by an array of 9 coefficients which fully characterize how diffusion in space varies according to direction (see, for instance, [30] for a recent review on DTI). Hence, diffusion anisotropy effects can be fully extracted and exploited, providing even more exquisite details on tissue microstructure.

With diffusion tensor imaging (DTI) diffusion data can be analysed in three ways to provide information on tissue microstructure and architecture for each voxel [4;31]: 1/ The mean diffusivity, which characterizes the overall mean-squared displacement of molecules and the overall presence of obstacles to diffusion; 2/ the degree of anisotropy, which describes how much molecular displacements vary in space and is related to the presence and coherence of oriented structures; 3/ the main direction of diffusivities, which is linked to the orientation in space of the structures. For instance, it has been pointed out that in stroke the average diffusion and the diffusion anisotropy in white matter had different time courses, potentially enhancing the use of D-MRI for the accurate diagnosis and prognosis of stroke [13].

Brain connectivity

Studies of neuronal connectivity are important to interpret functional MRI data and establish the networks underlying cognitive processes. Basic DTI provides a means to determine the overall orientation of white matter bundles in each voxel, assuming that only one direction is present or predominant in each voxel, and that diffusivity is the highest along this direction. Three-dimensional vector field maps representing fiber orientation in each voxel can then be obtained back from the image date through the diagonalization (a mathematical operation which provides orthogonal directions coinciding with the main diffusion directions) of the diffusion tensor determined in each voxel. A second step after this “inverse problem” is solved consists in “connecting” subsequent voxels on the basis of their respective fibre orientation to infer some continuity in the fibers (Fig.3). Several algorithms have been proposed (see [32] for a review). Line propagation algorithms reconstruct tracts from voxel to voxel from a seed point [33;34]. Another approach is based on regional energy

minimization (minimal bending) to select the most likely trajectory among several possible [35]. In any case, one has to keep in mind that at this stage only white matter bundles made of somewhat large number of axons are visible (and not intracortical connections).

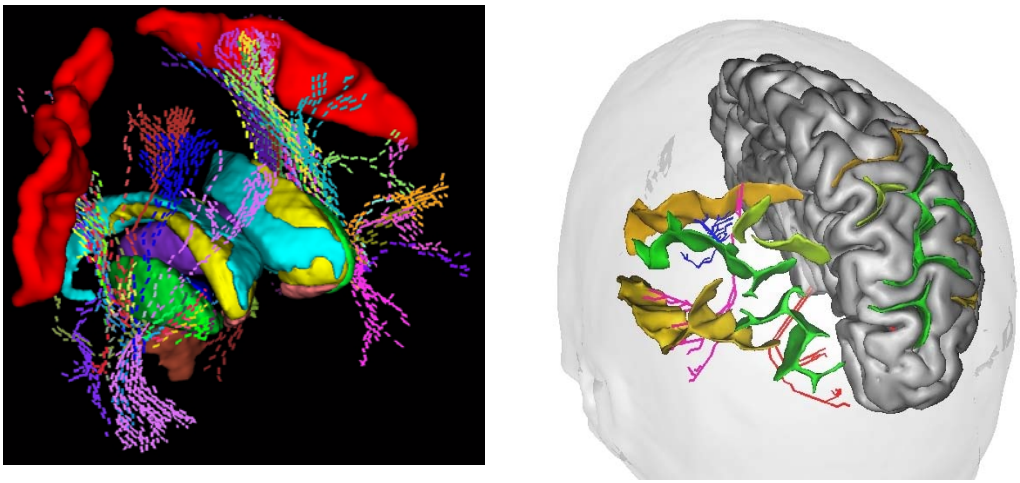

Figure 3: Fiber tracking. Several approaches have been developed to « connect » voxels after white matter fibers have been identified and their orientation determined. Left: 3D display of the motor cortex (red), central structures and connections. Right: 3D display from MRI of a brain hemisphere showing sulci and connections. (Courtesy of JF Mangin and C. Poupon, SHFJ/CEA).

White matter diseases

The potential of “plain” diffusion MRI in neurology has also been studied in brain tumour grading [36-38], trauma [39], hypertensive hydrocephalus [40], AIDS [41], eclampsia [42], leukoaraiosis [43;44], migraine [45] and diseases of the spinal cord in animals [23;46-48] and humans [4950]. These clinical studies have been motivated by the very high sensitivity of D-MRI to microstructural changes in tissues, so that anomalies can be detected before changes in more conventional images contrasted by the T1 or T2 relaxation times. In some cases, specific (though often speculative) mechanisms underlying physiopathology (oedema, Wallerian degeneration, neurotoxicity, swelling, and so on) could be put forward, but a clear association between ADC findings and those microstructural tissue alterations remains difficult to demonstrate. Animal models, tissue modelling and computer simulations may help.

In white matter, any change in tissue orientation patterns inside the MRI voxel would probably result in a change in the degree of anisotropy. There is a growing literature body supporting this assumption: Many clinical studies carried on patients with white matter diseases have shown the exquisite sensitivity of DTI to detect abnormalities at

an early stage or to characterize them in terms of white matter fibre integrity. In the white matter, diffusion MRI has already shown its potential in diseases such as multiple sclerosis [51]. However, DTI offers more through the separation of mean diffusivity indices, such as the trace of the diffusion tensor, which reflects overall water content, and anisotropy indices, which point towards myelin fibre integrity. Examples include multiple sclerosis [52-55], leukoencephalopathies [56;57], Wallerian degeneration, HIV-1 infection [58], Alzheimer disease [59;60], or CADASIL [61] (see [62] for a review).

However, D-MRI could also unravel more subtle, functional disorders that do not necessarily translate into anatomical anomalies. For instance, anisotropy measurements may highlight subtle anomalies in the organization of white matter tracks otherwise not visible with plain, anatomical MRI. The potential is enormous for patients with functional symptoms linked to disconnectivity, for instance, in patients with psychiatric disorders (see [63] for a review). Links between cognitive impairments and abnormal connectivity in white matter based on DTI MRI data have also been reported in frontal regions in schizophrenic patients [64,65], in the corpus callosum and the centrum semiovale in chronic alcoholic patients [66], in left temporo-parietal regions in dyslexic adults [67], and in specific disconnection syndromes [68].

Brain development

Over the course of life, white matter matures and declines. Effects of ageing on white matter ordering can now be studied [66;69], but DTI can also be used to monitor the myelination process in foetuses, babies and during childhood [70]. DTI has clearly an important potential for the pediatric population [71]. It has been shown that the degree of diffusion anisotropy in white matter increases during the myelination process [7273;74], so that diffusion MRI could be used to assess brain maturation in children [75], newborns or premature babies [73;76], as well as to characterize white matter disorders in children [77]. Research on brain development has been exploding recently. Advances in neuroimaging have certainly contributed to this expansion, as data can now be obtained non-invasively in newborns or even before birth. Of particular interest is the observation with DTI that water diffusion in white matter in the brain changes dramatically during development, both in terms of average and anisotropic diffusion. For white matter during postnatal development, the degree of water

diffusion anisotropy follows the myelination process [71], but the effect is small compared with the prenatal stage where large anisotropy is observed even before axons get myelinated [78]. The combined effects of the axon packing in the fibre bundles and the thickness of the myelin sheath on the degree of anisotropy have still to be described in detail, but DTI already represents an outstanding tool to study brain development in animals and humans. Grey matter migration disorders may also be assessed [79;80].

Conclusion

Many tissue features at the microscopic level may influence NMR diffusion measurements. Great care is, however, necessary to properly interpret diffusion MRI data and infer accurate information on microstructure in biological tissues, such as effects of restriction, membrane permeability, hindrance, anisotropy. It remains that, even in its current stage, D-MRI is the only approach available to track brain white matter fibers non-invasively. D-MRI should thus have a tremendous impact on brain function studies. D-MRI has also been used to demonstrate subtle abnormalities in a variety of diseases including multiple sclerosis and schizophrenia, and is currently becoming part of many routine clinical protocols. With the development of powerful improvements to D-MRI tools, such as diffusion spectroscopy of metabolites, diffusion tensor imaging or *q*-space imaging, one may expect to reach new levels and break new grounds in the already flourishing field of diffusion imaging.

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