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Summary

Diffusion imaging is a new imaging method based on Magnetic Resonance Imaging (MRI) that allows in vivo measurement of local diffusion properties of water molecules in the brain. Based on the Diffusion Tensor, it is increasingly used to characterize both grey and white matter. This can provide valuable information regarding cellular packing, cellular loss or regional edema in focal status epilepticus. Tractography is a method that reconstructs white matter neural tracts starting from any region studied. These imaging tools are increasingly used in clinical neurology and notably in epilepsy patients to detect subtle structural lesions that could be the cause of the epileptogenic activity. The precise and detailed knowledge of the trajectory of white matter tracts helps to plan difficult epilepsy surgical procedures and to better understand the propagation of epileptic seizures.

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Key words: Epilepsy, surgery, diffusion MRI, white matter tracts

Diffusions-Bildgebung bei Epilepsie

Die Diffusion-Bildgebung ist eine neue Bildgebungsmethode, die auf Magnet-Resonanz-Imaging (MRI) basiert und die *in vivo*-Messungen der lokalen Diffusionseigenschaften der Wassermoleküle im Gehirn erlaubt. Damit können wertvolle Informationen bezüglich zellulärer Dichte, Zellverlust oder regionale Ödeme durch fokalen Status epilepticus erhoben werden. Die Traktographie ist eine Methode, mit der neuronale Faserbahnen in jeder denkbaren Hirnregion rekonstruiert werden können. Die Bildgebungsmethoden werden mehr und mehr in der klinischen Neurologie und besonders bei Epilepsiepatienten verwandt, um subtile strukturelle Läsionen zu entdecken, die der epileptogenen Aktivität zugrunde liegen könnten. Das präzise und detaillierte Wissen der Bahnen in der weissen Substanz kann hilfreich sein, um schwierige epilepsiechirurgische Interventionen zu planen und die Propagation von epileptischen Anfällen besser zu verstehen.

Schlüsselwörter: Epilepsie, Chirurgie, Diffusions-MRI, weisse Substanz, Bahnen

Imagerie de diffusion appliquée à l'épilepsie

L'imagerie de diffusion est une nouvelle méthode basée sur l'Imagerie par Résonance magnétique (IRM) qui permet de mesurer *in vivo* les propriétés locales de diffusion des molécules d'eau dans le tissu cérébral. Basée sur le Tenseur de Diffusion, elle est utilisée de façon croissante pour caractériser la substance grise et la substance blanche cérébrale. Des informations importantes concernant la densité ou la perte cellulaire ou encore la présence d'un œdème local dans le cas d'un état de mal épileptique. La tractographie est une méthode de reconstruction des fibres nerveuses dans la substance blanche à partir de n'importe quelle région étudiée. Ces outils d'imagerie sont utilisés de manière croissante en neurologie clinique et notamment chez les patients épileptiques pour détecter des lésions structurelles subtiles sous-jacentes à une maladie épileptique. La connaissance précise et détaillée de la trajectoire des voies dans la substance blanche aide à planifier les interventions difficiles en chirurgie de l'épilepsie et à mieux comprendre la propagation de l'activité épileptique.

Mots clés : Epilepsie, chirurgie, IRM de diffusion, substance blanche, faisceaux d'axones

Introduction

Epilepsy affects 0.5-1% of the general population. Approximately 20% of all epileptic patients are said to be pharmaco-resistant because their seizures are not controlled by drug treatment. In some of these patients, surgical treatment can be proposed and can be superior to long-term drug treatment [1]. A non-invasive pre-surgical evaluation determines if surgical resection will control the seizures without any major risk of post-operative neurological or cognitive deficit [2, 3]. In patients with normal Magnetic Resonance Imaging (MRI), additional imaging tools are needed to locate the epileptogenic focus. In other patients, the presence of a large le-

sion (malformation, tumor) leads to abnormal development or displacement of important connecting neural pathways, while in other cases, it is the vicinity of important cortical and subcortical networks (motricity, language, vision) that makes surgical procedure very risky. Diffusion imaging and tractography are new developments of MRI that are increasingly involved in clinical diagnostic studies and non-invasive surgical planning and that aid in the management of difficult cases.

This paper presents a brief technical survey of the physical and radiological principles of diffusion and its measurement, followed by a review of the application to epilepsy surgery. Four clinico-radiological vignettes illustrate the potential role of diffusion MRI in diagnostic and treatment of epilepsy, including epilepsy surgery.

Physical and radiological principles underlying diffusion imaging

Diffusion: physical introduction

In the human body, random motion of water molecules is caused by thermal energy. This molecular displacement is called *diffusion*. When the molecules can diffuse equally in all directions of a tridimensional space, the medium is described as *isotropic*, like the free diffusion of a drop of ink in a glass of water, which is limited only by the walls of the glass. In a biological structure, the water molecules are supposed to diffuse freely inside of the intra-cellular space and inside of the extra-cellular space, while the passage from one compartment to the other is limited but not excluded by cellular membranes. In a tissue where the intracellular volume is high compared to extracellular volume, the cell membranes limit long range diffusion compared to a tissue where the extracellular volume predominates. Therefore, the diffusion coefficient will be low in the former tissue and high in the latter. These structural properties can be used to detect regions of high intracellular volume like cell swelling in cytotoxic edema (early status epilepticus, acute stroke, ...) or abnormally packed neurons (disorders of brain development). Similarly, regions of increased extracellular volume can be detected and occur in vasogenic edema (late status epilepticus, subacute stroke) and cellular loss (gliosis).

In a highly organized structure like the brain, nerve fibres are tightly packed in white matter bundles. Therefore, the diffusion is favoured in certain directions and restricted in others because of resistance of the cellular membranes to the crossing of water molecules. The myelin sheets and intra-axonal skeleton (microtubules) seem to play a minor role in the diffusion properties. The diffusion in such structures is called *anisotropic*. A *Diffusion Tensor* is a mathematical representation to describe the diffusion properties of a tissue with 6 variables: 3 for the position at which the diffusion is measured and 3 for principal orthogonal directions to

represent anisotropic properties. This Diffusion Tensor can then be used to calculate the *mean diffusivity and fractional anisotropy* (directionality of the motion) [4, 5].

Measurement of diffusion with MRI

Magnetic Resonance Imaging (MRI) offers a unique tool to measure the diffusion properties through *Diffusion Tensor Imaging* (DTI), where additional gradients in the magnetic field are designed to display prominently the diffusion effect. The magnetic properties of the water molecules which move into a given volume element (voxel) during the acquisition sequence will be different from those of immobile molecules (phase shift), causing a decrease of the signal intensity. By measuring the diffusion properties at each position (voxel) in 3 perpendicular directions, the diffusion tensor can be obtained to determine the deriving mean diffusivity and fractional anisotropy. The *Diffusion Weighted Imaging* (DWI), *Apparent Diffusion Coefficient* (ADC) and *Fractional Anisotropy* (FA) [4 - 6] sequences that are now recorded in routine structural MRI can be derived from this tensor.

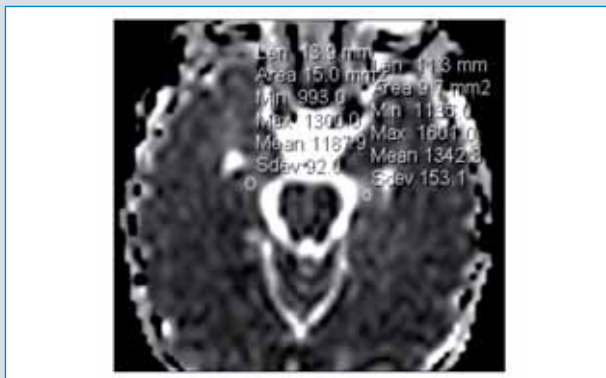
Tractography

This is a post-processing method used to display the data obtained from the DTI in order to represent white matter tracts in a 3D image or with colour coding. Starting from a given region of interest, the directions of maximal diffusion, assumed to be the direction of axonal bundles in the white matter, can be followed from one position to the next. In this way, pathways of facilitated water diffusion reflecting white matter neural tracts can be tracked across the brain. These pathways can be started at any "Region Of Interest" (ROI) in the brain: a ROI in the internal capsule or the motor cortex will give an image of the cortico-spinal tract; a ROI in the occipital lobe will give the optical radiation. The main problem of the technique is the measurement of fibre crossing because the diffusion has two "competing" peak-directions and the anisotropy is falsely reduced, making the tracking difficult. Recently, the measurement of diffusion in a greater number of directions has partly overcome the problem. State-of-the-art imaging includes *Diffusion Spectrum Imaging* and *Q-ball Imaging* that are not yet used routinely because of the duration of the acquisition and the need for specific MRI equipment and scientific expertise [4].

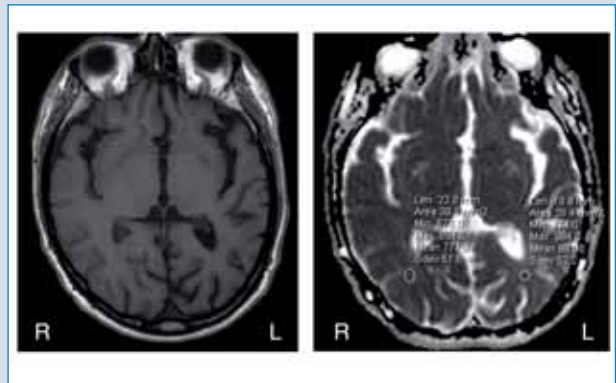
Diffusion MRI applied to epilepsy imaging

Structural brain modification associated with seizures

The occurrence of epileptic seizures can produce subtle morphologic changes in the brain. MRI can image these changes and their time course, especially after prolonged (status epilepticus) or very frequent seizures. In the acute phase, during (ictal) or shortly after (post-ictal) the seizure, cytotoxic edema causes cellular swelling, and therefore an increase of the intra-cellular space and water content. Consequently the free diffusion of water molecules is focally reduced and could be imaged through diffusion MRI. Focal swelling is associated with hyperintensity on T2-weighted/FLAIR imaging or reduced ADC coefficient. This phase of cytotoxic edema is followed by another phase of vasogenic edema, where the vessel permeability rises. Thereby, there is an increase of the extra-cellular volume, where water diffuses more easily compared to intra-cellular volume. The ADC coefficient is increased. After single seizures, MRI changes have been described but are less consistent. A study looking at diffusion-weighted focal changes less than an hour after single seizures identified focal changes after 50% of single partial complex and secondary generalized seizures. The involved region corresponded to the putative focus of the seizures only in a minority of the patients suggesting that the method probably revealed networks involved in the seizures rather than the zone of onset [7]. The final evolution can be towards a complete resolution of these changes suggesting only a transitory dysfunction or towards permanent abnormalities in the form of tissue atrophy and gliosis, a cellular loss reflected as an increase of the ADC (**Vignette 1**). A progression of these changes toward MRI changes compatible with hippocampal sclerosis can be seen after limbic status epilepticus (**Vignette 2**). The detection of



Vignette 1: Hippocampal lesion in temporal lobe epilepsy: Map of Apparent Diffusion Coefficient (ADC) in a patient with left-sided hippocampal sclerosis (axial view). The value of Mean ADC is higher on the affected side (1342.8 ± 153.1 vs 1187.9 ± 92) probably in relation to cellular loss and gliosis that increase the extracellular space.



Vignette 2: High sensitivity of diffusion images in cryptogenic epilepsy: This 46 year-old patient suffers from chronic left-sided temporo-occipital status epilepticus of cryptogenic origin. T1-weighted image shows only a discrete left-sided cortical and subcortical atrophy (axial view, left panel). The ADC map shows significantly higher values of Mean ADC in the left than right temporo-occipital white matter (891.6 ± 52.2 vs 777.9 ± 51.6 ; axial view, right panel). This allows more precise localisation of the structural abnormalities and precise monitoring of the disease.

the permanent structural abnormalities can be sometimes seen already after 2 months (hippocampal sclerosis) even in the absence of acute modifications of the MRI signal. On the other hand, resolution of the diffusion abnormalities can be seen after status epilepticus, preceding or following functional recovery. A precise knowledge of the timing of these changes needs to be addressed with serial imaging in larger group of subjects.

Lateralisation and localisation of the epileptogenic focus

One of the biggest expectations, regarding any new imaging tool involved in presurgical work-up of epilepsy, is that this new tool could help localizing the epileptogenic focus or any underlying structural abnormality that was not revealed by other imaging tests. “Interictal” and “post-ictal” imaging can be useful localizing subtle lesions and epileptogenic foci and they can be of great help if the standard imaging tests are normal or show multiple abnormalities.

In the case of temporal lobe epilepsy, lateralisation of the focus with the help of diffusion imaging was highly correlated with the presence of unilateral hippocampal sclerosis on conventional MRI but could not help to lateralize the focus when the conventional MRI was not conclusive [8]. In extra-temporal epilepsy, reports describe diffusion abnormalities in brain regions compatible with the seizure electro-clinical pattern in patients that have normal conventional MRI [8, 9]. Resection and histopathological analysis revealed subtle gliosis and a very good outcome confirming that the seizure onset zone was linked with the diffusion abnormalities [10].

In temporal lobe epilepsy with unilateral hippocampal sclerosis, diffusion imaging showed that structural abnormalities extend far beyond the sclerotic hippocampus to involve large regions on the ipsilateral temporal lobe, contralateral hippocampus and even frontal areas. However, these extensive findings do not seem to indicate a worse surgical outcome [11] and could even be reversible: in about half of the patients who underwent temporal lobe surgery and became seizure free, post-operative imaging showed a resolution of the diffusion abnormalities in the contralateral hippocampus [12]. In an interesting study with diffusion MRI in patients investigated with intracerebral electrodes, ADC abnormalities (probably reflecting gliosis or cellular loss) were better correlated with seizure onset zones than FA abnormalities that reflected rather a distant disorder of white matter connections. Moreover, the correlation was better in extra-temporal epilepsy (83%) than in temporal epilepsy (20%). Thus, diffusion imaging could help to choose electrode placement in difficult cases of cryptogenic partial epilepsy [13].

In patients with temporal lobe epilepsy, some studies show a correlation between findings of DTI and clinical characteristics: interictal psychosis correlates with lower FA in both frontal and temporal regions, higher mean diffusivity in bilateral frontal regions [14]; epigastric aura is associated with lower diffusivity ipsilateral to the epileptogenic focus and a positive history of febrile seizure is associated with bilateral higher anisotropy [15].

Trauma and post-traumatic epilepsy

Increase of the mean diffusivity and decrease of the fractional anisotropy can be measured in widespread brain regions after brain trauma and the affected territories can be much more extensive than those seen on standard MR images. These changes reflect cell loss, diffuse axonal injury and secondary Wallerian degeneration in the corresponding regions, allowing to map precisely the post-traumatic damages [16]. Moreover, a greater extent of the abnormalities observed with diffusion imaging seem to be correlated with a greater risk of developing post-traumatic epilepsy [17].

Brain development and congenital malformations

Diffusion imaging is particularly promising to study patterns of brain development. Increases in fractional anisotropy precede the appearance of myelin. Decrease in ADC reflects the progressive increase of the size of neurons and glial cells.

Diffusion imaging is therefore very informative in developmental disorders. It can reveal very subtle areas of *cortical dysplasia* through changes in mean diffusivity reflecting abnormally packed cells or through abnor-

mal anisotropy of the underlying white matter bundles, caused either by disturbed connectivity or by ectopic neurons located in the white matter [18, 19]. The abnormal pattern seen in diffusion imaging is often more extensive than the malformation seen on standard MRI. This suggests that the malformed area and possibly the epileptogenic focus may not be restricted to abnormal regions seen on standard MRI. This reflects histopathological findings that show more widespread abnormal tissue than the extent seen on MRI. It could also explain the frequent bad outcome of epilepsy surgery in patients with cortical dysplasia or periventricular heterotopia.

Periventricular Nodular Heterotopia (PNH) or *Band Heterotopia* (BH) is a condition where some neurons did not migrate from the subependymal region toward the cortex, but stayed packed around the ventricle or in the subcortical regions, sometimes producing an appearance of “double cortex”. In these patients, epilepsy can arise from the heterotopia themselves or from other brain regions that appear normal on the standard MRI. Histopathological studies show that there are generally other sites of brain development disorder, either in the overlying cortex or at distant sites [20, 21]. The study of the connectivity of those structures indicates that white matter tracts run through or end within the band heterotopia [22], confirming histopathological studies and the fact that there is often no focal neurological deficit in these patients.

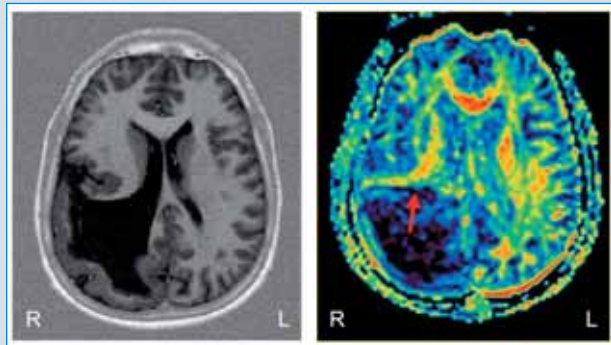
The precise description of the abnormal trajectory or morphology of the main white matter tracts with the help of tractography is also very important when epilepsy surgery is contemplated in a patient with a disorder of brain development. Isolated cases of various origins (cerebral palsy, agenesis of the corpus callosum, schizencephaly, polymicrogyria and other pediatric encephalopathies) are well documented in the literature [23 - 26].

Another particularly interesting condition is *Tuberous Sclerosis*, a genetic condition with skin lesions and multiple cerebral malformative lesions (tubers) that can be very epileptogenic. However, the phenotype is not strongly related to conventional MR patterns. Epilepsy surgery can sometimes significantly improve the seizures if the epileptogenic tuber can be identified even though the malformations are diffuse and multifocal. Interestingly, epileptogenic tubers have increased ADC values in the white matter underlying them, when compared to non-epileptogenic tubers, whereas the largest tuber identified by conventional and decreased FA values was less accurate [27, 28].

Tractography

In case of neurosurgical procedures in the context of a large lesion or malformation, the anatomical pathways might follow unusual trajectories or start

from atypical cortical regions. The in vivo representation of important white matter tracts, such as the cortico-spinal tract, can greatly help neurosurgical intervention for epilepsy or any other indication (**Vignette 3**). In temporal lobe epilepsy surgery, the main feared complication, besides memory decline, is post-operative visual field defect. This defect is correlated with the extent of temporal lobe that is removed (from the anterior pole) but individual variation can be important. A recent study showed that the optical radiation can be represented for individual patients and that a patient with a resection volume including part of the radiation had a post-

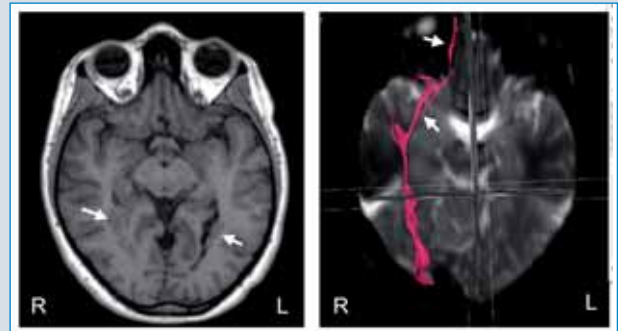


Vignette 3: Tractography for surgical planning: 30 year-old patient with pharmaco-resistant complex partial epilepsy in the context of a posterior hemi-hemi-megalencephaly (axial T1-weighted image, left panel). The neurological exam is normal. Diffusion Tensor Imaging (axial view, right panel,) shows the localization of the cortico-spinal tracts that is anterior to the malformation (red arrow). A multilobar parieto-temporo-occipital resection starting posterior to the central sulcus was performed. The patient is seizure free since then and suffers only from a mild visual field deficit.

operative visual deficit whereas another with surgery sparing the radiation did not [29]. Tractography of the optical radiation, as well as other white matter bundles of nervous fibers can thus be used to tailor neurosurgical interventions. A patient with an epileptogenic malformation (periventricular nodular heterotopia) adjacent to the optical radiation also benefited from tractography of this radiation to allow a safe resection of the epileptogenic malformation with no post-operative deficit [30]. In case of cortical development disorders, aberrant white matter connections could lead to atypical seizure propagation, and discordant results of non-invasive imaging tests used to locate the epileptogenic focus (**Vignette 4**).

Diffusion imaging also gives insight into functional organisation of the brain in healthy subjects and epileptic patients. In epileptic patients with atypical language lateralisation, structural diffusion tensor imaging revealed an asymmetric fraction of anisotropy, with lower values in the left hemisphere, which was not found in other patients without atypical language organisation. Moreover, the mapping of tracts from or to a specific

cortical area gives information about the connections and neuronal network involved. The corticospinal tract can be tracked down from the motor cortex defined by fMRI [31].



Vignette 4: Tractography from periventricular nodular heterotopia. This 25 year-old woman suffers from weekly complex partial hypermotor seizures suggesting fronto-temporal seizures. A non-invasive presurgical work-up revealed bilateral brain developmental disorder in the form of bilateral periventricular nodular heterotopia (white arrows, T1-weighted image, left panel). The ictal/interictal EEG neuropsychological tests and ictal SPECT showed a bilateral anterior temporal focus with right predominance. This axial view shows the tracking of white matter fibres from/ to the heterotopia. The tracts project anteriorly towards the orbito-frontal and anterior temporal structures suggesting aberrant connectivity (pink tract with white arrows, left panel). This could help understand the discrepancy between the results of the different tests. A posterior projection from the heterotopia is also present and seems to connect the heterotopia with the visual cortex.

Future perspectives

In epilepsy surgery planning, the precision of tractography will increase with the development of algorithms solving the problem of fibre crossing. The knowledge of the white matter tracts will be combined with other imaging modalities into neuro-navigation devices helping the monitoring of surgery with imaging during the operation and predicting the occurrence of post-operative deficits, especially when combined with brain areas activated during fMRI tasks.

In research, tractography of the nervous fibres connecting varying brain areas could be assessed by fMRI or EEG to study their functional connectivity in cognitive or other brain functions. Recent studies even suggest that diffusion MRI could detect changes related to the activity of cortical neurons and could therefore be used as a functional imaging tool [32]. Moreover, knowledge of the electrical conductivity assessed by diffusion MRI will enable more precise models of the seizure propagation in fundamental neuroscience research [33].

Conclusion

Diffusion MRI and tractography are new MRI methods, relying on the displacement properties of the water molecules in the brain that are entering research and clinical activity at a tremendous pace. The improvement of the imaging of fibre crossing and of the time necessary to obtain a good quality image allows very sensitive detection of structural and functional abnormalities as well as the representation of nervous fibres in the brain. More research is needed to understand precisely the meaning of abnormal results and how they are causally related to epilepsy.

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