Concise review paper / Point sur

What to expect from MRI in the investigation of the central nervous system?

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Abstract – Functional magnetic resonance imaging (fMRI) has appeared as a new tool that is very powerful for cognitive neuroscience, offering the potential to look at the dynamics of cerebral processes underlying cognition, non-invasively and on an individual basis. Work remains to be done to optimize the technique and to better understand its basic mechanisms, but one may expect to build in a foreseeable future a functional list of the main brain cortical networks implicated in sensory-motor or cognitive processes. Still, the real understanding of brain function requires direct access to the functional unit consisting of the neuron, so that one may look at the transient temporal relationships that exist between largely distributed groups of hundreds or thousands of neurons. Furthermore, communication pathways between networks, which are carried by brain white matter, must be identified to establish connectivity maps at the individual scale, taking into account individual variability resulting from genetic factors and cerebral plasticity. In this respect, MRI of molecular diffusion is very sensitive to water molecular motion and, thus, to tissue dynamic microstructure, such as cell size and geometry. Preliminary data suggest that diffusion MRI visualizes dynamic tissue changes associated with large neuronal activation and space orientation of large bundles of myelinated axons in the white matter. © 2000 Académie des sciences/Éditions scientifiques et médicales Elsevier SAS

imaging / brain / magnetic resonance / cognition / molecular diffusion

Résumé – Qu’attendre de l’IRM dans l’exploration du système nerveux central ? L’imagerie par résonance magnétique fonctionnelle (IRMf) est apparue comme un nouvel outil extrêmement puissant pour les sciences cognitives, offrant la possibilité d’examiner les aspects dynamiques des processus cérébraux liés à la cognition, de manière non invasive et à l’échelle de l’individu. Des progrès restent à accomplir pour optimiser la méthode et mieux en comprendre les mécanismes, mais on peut espérer disposer dans quelque temps d’une sorte de catalogue fonctionnel de l’ensemble des régions cérébrales indiquant l’implication de chaque région dans tel ou tel processus sensorimoteur ou cognitif. Pourtant, la compréhension du fonctionnement du cerveau humain requiert l’accès direct à l’unité fonctionnelle que constitue le neurone afin de mettre en évidence les relations temporelles transitoires qui existent entre des groupes de centaines ou de milliers de neurones largement distribués. D’autre part, les voies de communication entre réseaux, constituant la substance blanche, doivent être connues pour établir des cartes de connectivité anatomo-fonctionnelle entre régions à l’échelle individuelle, prenant en compte la très grande variabilité interindividuelle liée à des facteurs génétiques et à la plasticité cérébrale. L’IRM de diffusion, qui mesure les...
mouvements moléculaires de l’eau, est un marqueur très sensible à la structure dynamique des tissus, à l’échelon microscopique, comme l’agencement spatial et la taille des cellules. Des données préliminaires montrent que cette technique donne accès aux changements dynamiques tissulaires qui accompagnent une activité neuronale corticale importante et à l’orientation dans l’espace de gros faisceaux de fibres axonales myélinisées dans la substance blanche. © 2000 Académie des sciences/Éditions scientifiques et médicales Elsevier SAS

imagerie / cerveau / résonance magnétique / cognition / diffusion moléculaire

1. Introduction

The understanding of how the human brain works has, of course, considerable potential, not only for health care (huge amounts of money are spent each year in developed countries to manage or rehabilitate large populations of neurological and psychiatric patients or simply ageing populations), but also for improving human cognition in general (though optimized education, e.g. teaching of foreign languages, better communication between individuals, better understanding of social behaviours, etc.). Also the development of computer–human interfaces, which are invading our daily life (at work, at home, in our cars, etc.), would greatly benefit from this knowledge. New, ‘biological’ computers could be conceived, which could share some common features with the way our brain works. It is also, by any means one of the greatest dreams for human kind.

In this quest, neuroimaging has a crucial role, as the brain has the peculiarity of being organized on a spatially distributed basis. Although the brain ‘hardware’ is made up of about $10^{11}$ neurons and $10^{12}$ glial cells that are all working on the same basic principles, the nature of the processes performed by these cells at a ‘logical’ network level seems very different according to the location of these networks in the brain. Thus, although brain tissue is roughly homogeneous with regards its grey and white matter components, it is highly heterogeneous functionally. For instance, the regions of the occipital cortex are mainly dealing with visual processes, while some specific regions of the frontal cortex of the left brain hemisphere are involved in language production. In these conditions tools that map the different brain regions that are activated during a given cognitive task are extremely valuable. If these tools are, furthermore, non-invasive and do not interfere with brain function, allowing investigations to be performed in normal subjects, free of neurological or psychiatric disorders, it becomes obvious that functional brain imaging is irreplaceable when it comes to studying cognitive functions that have little or no equivalents in non-human primates.

This correlation between anatomy and function was revealed long ago, as stated in the famous Edwin Smith papyrus, which relates functional deficiencies in warriors to brain injuries, but was clearly outlined by the pioneer work of the French neurosurgeon Paul Broca on aphasia. The discovery that a frontal area of the left brain hemisphere was necessary for language production led to more than a century of observations of brain damaged patients, which has surprisingly revealed that functional deficits could be linked to specific brain regions. A breakthrough occurred when, in the 1970s, it became possible to look at the location of the lesions through non-invasive neuroanatomical imaging tools, i.e. X-ray computed tomography (CT) and magnetic resonance imaging (MRI) and not only during autopsy. It remains that only lesions resulting in clinically or neuropsychologically observable functional deficits could be studied. Also, there is, of course, no experimental control on the localization, degree and extent of the lesions that occur at random, some locations being common and other very infrequent.

But another giant step was made when the term ‘functional’ was added to brain imaging, allowing a more or less direct visualization of brain regions activated by sensory-motor or cognitive tasks in normal subjects. First, progress in computers had made it possible to produce functional maps out of the electric (or magnetic) activity of the brain. Then, in the middle of the 1980s positron emission tomography (PET) allowed local metabolic and blood flow changes associated with brain function to be observed for the first time in humans, and some neurotransmitters to be mapped out. Slightly later, MRI became ‘fMRI’ (for functional MRI) when it was shown that brain activity could be (indirectly) detected through the associated local modulation of the blood oxygen level. As MRI does not use any ionizing radiation it offers the great advantage of being repeatable at will on the same subjects. MRI scanners do not require extensive radiochemistry laboratories and are already available in most hospitals and many research facilities. Furthermore, as fMRI has a greater sensitivity, a better spatial and temporal resolution and is more widely available than PET, it has quickly gained popularity and become the method of choice for brain activation studies in normal subjects, as well as in patients, especially those undergoing neurosurgery. Another great asset is that high resolution anatomical images and functional images can be obtained during the same session using the same imaging modality, and functional and anatomical images may be easily matched. This approach has been extraordinarily successful, as can be seen from the existing literature body which is very large and rapidly growing, in assigning more or less specific roles to localized brain regions. The recent development of ‘event-related’ fMRI, which allows single cognitive events to be detected and localized on an individual basis,
gives access to increasingly subtle cognitive processes, such as consciousness.

It remains that there are limits to the knowledge one may gain from such brain imaging studies. Although an exhaustive knowledge (if at all possible) of a human ‘brainom’, i.e. a list of brain regions with associated functions, would certainly be an important first step, it is clearly not enough to understand how the brain works. Knowing that the ‘Broca’ area plays an important role (though not specific) in language production, for instance, is fundamental. However, the nature of the information processing taking place in this area which determines this role is totally unknown. The next step is thus to investigate whether and how neuroimaging may help us further to decipher a ‘neural code’. By crossing out neuroimaging data obtained using different paradigms activating a given brain area one may infer some of the specific functional features of the region. Though, it would be greatly beneficial to extend our approach down to the neuron level. Hence, the regional specialization of brain function should now be observed at a microscopic level, as this specialization may result from a differential organization of the neurons (and the glial cells) and their connections in local networks (each neuron has on average 10⁴ synapses). The demonstration of transient synchronization of neuronal activity in such local networks has been shown in animals by recording small neuron assemblies, but such results are, of course, very difficult to obtain in the human brain. These local networks are also macroscopically connected together throughout the brain by myelinated fibre tracts. Brain white matter should thus not be forgotten, as information is transported through it to be processed, in parallel and sequentially, by different cortical and subcortical regions. Efforts should thus be directed to extend neuroimaging capabilities with approaches to provide direct visualization of neuronal connections and synaptic activity with an improved spatial and temporal resolution. Recent advances in MRI have been encouraging in this regard.

2. fMRI around year 2000

2.1. Principles

fMRI and PET rely on the common principle postulated at the end of the last century by Roy and Sherrington [1] that regional blood flow and metabolism are modulated by neuronal activity. The mechanisms and the rational of this link are still unclear and the object of many fundamental research studies. It seems that oxygen consumption increases only slightly during activation (less than 10 %) while blood flow increases much more (up to 50 %) [2]. It remains that, by different physical means, PET and fMRI provide quantitative or qualitative maps of changes in cerebral blood flow which are interpreted, on the basis of the above principle, in terms of regions being ‘activated’ (and sometimes ‘deactivated’) by sensorial, motor or cognitive tasks. While the basic design of most PET studies had centred on comparison of baseline to an active (test) condition, fMRI allowed an important departure from the single scan per condition study-design, into more flexible paradigms of multiple scans over varying time intervals and multiple conditions.

At the end of the 1980s pioneer studies showed that MRI could be sensitized to perfusion and blood flow [3]. From these initial studies it appeared that MRI could be used to detect brain activation. Indeed, it was shown that the concept of MRI of molecular diffusion (cf. below) could be extended to look at the displacement of water molecules in the pseudo-randomly orientated capillary network (IntraVoxel Incoherent Motion or IVIM imaging) [4]. Preliminary visual activation images were obtained with this method in 1986, but the BOLD concept developed later (see below) would soon prove to be much more sensitive, as the IVIM method requires a very high signal/noise ratio in the raw images. The IVIM approach remains, however, useful to separate the flow and oxygenation effects that occur during brain activation, as confirmed by recent results from our group.

The first successful visualization of brain activity with MRI was provided by Belliveau et al. [5] who, using an intravenous bolus injection of a paramagnetic contrast agent (Gadolinium-DTPA), looked at changes in primary visual cortex evoked by a flashing light stimulus. The transit of this bolus through the brain microvasculature results in a transient signal drop that may be measured in real time using echo-planar imaging (EPI). With EPI a complete image can be generated in as little as 25 ms [6]. From the time course of the signal change, one may derive approximate relative blood volumes in each voxel of the image. The bolus of contrast agent has to be injected twice, first, when the subject is at rest, and second, while performing a task. As it is known that, during brain activation, blood flow and blood volume locally increase in the activated regions, the two relative blood volume maps are thus compared (subtracted) to infer which areas of the brain have been activated. A major limitation of this technique is the need to inject a bolus of contrast agent for data acquisition in each condition and to wait for the elimination of the agent (several minutes) between each condition. Also, only one cognitive task can be studied at a time and repetitive studies are precluded. This first very successful attempt has, therefore, not survived the demonstration stage, as a much more flexible technique came at about the same time.

Indeed, the most common approach to fMRI of brain activation has been the one using ‘blood oxygen level-dependent’ (BOLD) contrast [7–9]. Although oxyhaemoglobin is diamagnetic, i.e. not visible in the MRI signal, deoxyhaemoglobin, which is paramagnetic owing to the presence of four unpaired electrons [10], becomes slightly magnetized in the presence of the magnetic field of the MRI scanner. Deoxyhaemoglobin is confined to red cells and behaves as a natural, endogenous paramagnetic contrast agent present in the blood stream at high concentration and modulated by variations in oxygen supply (blood flow) and oxygen utilization (tissue metabolism), as ini-
tially shown in animal models [11, 12]. As in the case of a paramagnetic contrast agent, deoxyhaemoglobin induces a small change in the magnetic susceptibility of the blood compared to that of the surrounding tissue. This blood/tissue difference in magnetization accelerates the magnetic relaxation of water protons, which results in a small signal drop. During brain activation, the large increase in blood flow, which overcompensates a small increase in oxygen consumption, results in a net decrease in the blood deoxyhaemoglobin concentration which, in turns, leads to a small (a few percent), but measurable signal increase.

The local mechanisms underlying the BOLD signal change and its relationship with brain activation are still not fully understood, but several theories have been devised taking into account the geometry of the capillary network, red cell flow, the strength of the magnetic field and the type of MRI sequence used. Work is in progress to better understand the relationship between the fMRI signal and the blood oxygenation state [13]. In any case, one should bear in mind that brain activation is seen with fMRI through a haemodynamic window and, thus, indirectly. Furthermore there is a delay of up to seconds between the visible haemodynamic response and the presumed peak of the neuronal activity which limits the temporal resolution of the method (although MRI images can be physically acquired in less than 100 ms). Recent studies, however, have shown that it could be possible under particular conditions to deconvolve the BOLD response time course to achieve a resolution of a few hundred milliseconds. Similarly, the fMRI spatial resolution is limited, because the vessels at the origin of the BOLD response feed or drain territories the size of which is well above the ultimate possible resolution of MRI images. The size of the vessels responsible for the BOLD effect depends on the imaging technique and the magnet field strength and may vary from microns to millimeters.

2.2. Applications of fMRI

The heart of a fMRI study is, of course, the paradigm, the purpose of which is to answer a cognitive question, either from a neuroscience or from a clinical standpoint. Two issues are important: the design of the paradigm and how it will be performed by subjects. It is not possible to obtain ‘absolute’ activation maps, but only ‘contrast’ maps which highlight the regions that have been differentially activated between two or more cognitive conditions. These conditions must be very well defined and controlled. The timing of the paradigm is also critical, as it has to coincide with the MRI signal acquisition. So far, most fMRI studies have alternated periods of ‘rest’ and ‘activated’ periods (block paradigm design). This has already been an improvement over PET, where only two conditions are usually compared. The possibility of alternating activation and rest periods increases the contrast-to-noise ratio of the fMRI data, provided one processes those data properly by taking into account the dynamic aspect of the response of the brain to the paradigm (see below). However, there are still limitations: habituation and fatigue effects may interfere, while some studies, e.g. on memory or inducing a long lasting response (taste [15], oculo-vestibular system [16], etc.) may preclude any alternation of resting and activated states. Ideally, subjects should be free to perform tasks at their own pace. These difficulties have been recently resolved through the development of ‘event-related’ fMRI [14]. It is now possible to produce activation maps from single task events and on an individual basis. This new approach allows stimuli to be presented on a pseudo-random basis, eliminating anticipation or habituation effects. Subject performance, such as reaction times, may also be recorded and used to optimize data analysis on an individual and event basis.

An important step in fMRI is, indeed, data processing. If images are not processed with great care, lack of sensitivity and specificity may lead to incorrect results, that is some activated regions are not detected and, inversely, some regions found to be activated are not real. It is not unusual to generate between 10 000 and 20 000 images per subject in a single session, representing whole brain data sets acquired at a few second intervals for several runs lasting a few minutes. Images have also to be registered for head motion, as any mismatch may wipe out small BOLD responses. Basically, all the images are transformed by a combination of translations and rotations, so that they all fit with one of them arbitrarily chosen as a mask. Similar algorithms have been designed for PET, but the requirements for fMRI are much more severe, given that the BOLD effect is small and spatial resolution is higher. Other correction schemes may be used, such as dewarping to fix the geometrical distortion observed in the images acquired with EPI and normalization of the images in a standardized frame, such as the Talairach co-ordinate system, for anatomical localization. Then the brain regions where the signal changed in synchrony with the paradigm time course must be detected on a statistical basis. Several methods and statistical tests have been proposed, but the most popular approach rests on the calculation of the correlation between the BOLD response and an idealized waveform derived from the paradigm. The endpoint is the generation of maps where activated pixels are displayed using a colour scale according to their degree of statistical significance and overlaid on the matching high resolution anatomical images. Ascribing statistical significance in fMRI data, however, is not a trivial issue, as one must consider the degree of correlation that exists between successive time points and adjacent pixels due to the haemodynamic nature of the MR signal response [17].

It is not the object of this article to review the numerous results that have been obtained in just a few years with fMRI in the field of cognitive neuroscience. Let us say simply that earlier studies demonstrated that a robust localized, stimulus-dependent fMRI signal change could be recorded in primary visual, somatosensory and motor cortices using simple paradigms [5, 9, 18, 19]. Second generation studies have explored the relationship between specific stimulus–task parameters and the evoked fMRI signal changes in cortex [20, 21], basal ganglia [22] and
cerebellum [23], and examined specific prediction derived from previous electrophysiological or psychophysiological studies. fMRI has also been used to study cognitive processing and look at brain areas that subserve the reception and production of speech, for instance using word generation paradigms [24–26], and related modes of symbolic communication relating to the representation of knowledge (e.g. visual imagery [27]). fMRI has also opened up novel approaches to the study of the effects of experience on the brain, i.e. learning and memory [28].

Third generation studies are based on ‘event-related’ fMRI paradigms, which have become extremely flexible, allowing individual responses to single trials to be investigated for the first time (figure 1). It is now becoming possible to assess differences between brain responses (strategy) and not only average effects. The neural bases of consciousness can be investigated (subliminal stimulation [29]). Some recent results have shown that some basic mental processes, although still very simple, could be unravelled from the fMRI images, suggesting that, perhaps, in some well-defined conditions, studies of this kind could sometimes open a window to subjective mental experience which, of course, raises important ethical questions [30]. The use of event-related fMRI to look at the chronometry of brain activation (temporal order of the activated foci) remains an open issue, although recent results have suggested that temporal differences of a few milliseconds could be seen.

fMRI also has promising applications for clinical neurology, neurosurgery and perhaps psychiatry. For example, it allows non-invasive presurgical mapping of brain tissue to be removed or spared, as in the case of brain tumours [31] or intractable temporal epilepsy [32]. Language studies have suggested that fMRI could be used to assess brain lateralization of language, replacing invasive techniques such as the Wada test which is based on intracarotid amobarbital injection and the use of subdural electrodes positioned intraoperatively [26]. Because fMRI is non-invasive and does not involve exposure to radiation, it confers the advantage of repeatability in a single patient. Testing of patients individually will allow clinicians to follow changes in brain function over the course of a progressive disease, during recovery from injury or stroke, or in response to a treatment. For instance, as it has been shown that movement of the non-dominant hand is associated with ipsilateral as well as contralateral motor cortical activation [20], reorganization of sensory-motor cortex following unilateral brain injury could thus be monitored. Also, recent animal studies [33] suggest that the effects of psychopharmacological drugs could be detected using BOLD fMRI.

So as to give all its potential, fMRI today requires co-operation between multidisciplinary teams (physics, instrumentation, statistics and image processing, neurobiology, physiology, psychology, anatomy, neurology, psychiatry, etc.). Methods, which are still being developed, can then be optimized to answer specific cognitive or clinical questions. These questions are also better formulated to accommodate, in their pertinence and their experimental design, the present limitations of the technique.

3. What can we expect from MRI beyond the ‘decade of the brain’?

Functional MRI (fMRI) has thus appeared as a very powerful tool for cognitive neurosciences, offering non-invasive access to the cortical and subcortical networks involved in sensory-motor and high order cognitive processes on an individual basis. Works remains to be done to better understand mechanisms underlying BOLD fMRI, to improve its sensitivity and spatial/temporal resolution and to optimize image acquisition strategies. Important issues related to the coupling of neuronal firing and the haemodynamic response remain unsolved. Also, image processing and data analysis are becoming critical steps and improved, more sensitive and powerful models and algorithms must be developed, on a statistical and an anatomical ground, for instance, to combine data gathered by complementary mapping methods (fMRI, PET, ERPs, MEG, etc.). One may thus expect to obtain in a foreseeable future a global picture of the localization of the brain...
networks involved in most sensory-motor or cognitive processes, as well as their connections. Some groups have also started to build large computerized data bases [34, 35] to link information on localization of activated foci and paradigms, receptor and biological data, as obtained from animal studies or clinical data from patients.

Though, as stated in the Introduction, the understanding of how the human brain works goes far beyond this initial (but important) ‘exploration’ step. Ideally one should have access to the functional unit, the neuron, or at least to small ensembles of neurons. So far, neuronal activity (action potentials) can only be recorded in animal models or preparations (besides recordngs made intraoperatively in patients). Unfortunately, these studies are not easy to perform and analyse, even in animals. Furthermore, only a few ‘units’ can be looked at simultaneously in a given cortical region. One may dream of a non-invasive imaging method allowing the gap between animal studies based on single unit recordings and macroscopic human studies to be bridged. A first step, however, would be to determine, on an individual basis and at a microscopic scale, the neuronal networks involved in well-defined processes. To do so, one must be able to directly visualize neuronal activity (and not remote vascular effects), precisely identify the location of the active neuronal assemblies on the cortical ribbon, and visualize the connections between these assemblies. Given the high variability in gross and microscopic brain anatomy between individuals determined by the combination of genetic and plasticity factors, one cannot rely anymore at this microscopic scale on general concepts and atlases, such as the Brodmann areas and the Talayrac space, but one must gain access to individual cyto- and myeloarchitectonic data.

3.1. Aims

The challenge is thus to develop a method that could provide non-invasively in the human brain images of neuronal activity, directly and not through blood flow modulation, with exquisite spatial and temporal resolution. Today, methods based on electric (EEG) or magnetic (MEG) brain activity are responding somewhat to the above criteria, especially for their temporal resolution (1 ms). However, the determination of the number of electric dipoles contributing to the signal and their localization in the brain remains very difficult. Optical methods, such as near infrared spectroscopy (NIRS), is also promising, but must be performed invasively to reach a fine spatial resolution. One must, therefore, find a suitable physiological, physical or chemical event taking place during activation directly at the neuron or synaptic level, which can be measured and localized through imaging. This method would extend and ease current studies in animals and would improve our approach of the higher cognitive processes in humans. One must find a suitable physiological, physical or chemical event taking place during activation directly at the neuron or synaptic level, which can be measured and localized through imaging.

A second major issue is to visualize communication pathways between cortical and subcortical networks on an individual basis and to investigate how information is processed among distributed networks (functional integration). If action potentials originating from different regions have to arrive with some degree of synchrony in another region, transit time between these regions must be accounted for. It is thus crucial to have maps of the axonal fibres that connect brain regions, both from an anatomical (wiring) and a functional (information transit) standpoint. As these fibres could be considered as ‘delay lines’ the length and speed capacity (which depends on the degree of their myelination) must be known. One must, therefore, shift our attention towards the white matter and not only the cortex to assess anatomical, as well as functional brain connectivity. As large variations may exist between subjects owing to genetic and plasticity reasons, white matter data must be obtained on an individual basis. Parameters, such as the degree of myelination or the fibre length, might be important to evaluate how fast information may transit from one area to another. Also, the possibility of matching the acquisition of specific cognitive capabilities with the degree of myelination at a given age in children appears extremely promising to understand how the brain develops normally or pathologically. The possibility of investigating brain development through non-invasive neuroimaging would appear as a new, extended concept, following studies of functional deficits in brain-disease patients and functional expression in normal adults.

Finally, the last component is linked to the cortex. If the global principle of functional segregation, i.e. correspondence between localization and function is generally accepted at a macroscopic scale, the identification at the microscopic level of the segment of the cortical ribbon actually activated by a given task remains a challenge. The labelling of these segments through anatomical landmarks, such as gyri and sulci, or references to atlases, such as the Talairach space, is very coarse, given the extreme variability of these landmarks among individuals. Classification of cortical areas according to Brodmann nomenclature has been convenient, but one has to keep in mind that this nomenclature was established at the beginning of the century from a single dead brain. Here also, the variability between individuals is great, reflecting the combined effects of genetic expression and plasticity. Thus, the only way to describe ‘functional’ segments along the cortical ribbon is to identify microscopic landmarks of these segments [36] non-invasively and on an individual basis. This approach would not only help scientists to communicate when they have to describe activated foci, but would also provide some light on the link between the local network architecture and the kind of information processing taking place there. Efforts should thus be made to develop tools that give access to individual cytoarchitecture.

In the last part of this article, we will examine how MRI, and especially MRI of water diffusion in the brain, may, in part, meet some of these expectations.
3.2. Diffusion MRI

Diffusion MRI provides quantitative data on water molecular motion, a very sensitive marker of tissue structure, at a microscopic scale, such as cell size or cell orientation in space [37]. Preliminary data have shown that diffusion MRI could visualize changes in tissue microstructure, which could arise during large, extraphysiological neuronal activation and to the spatial orientation of major myelinated axonal tracks in white matter. In this part we will examine how diffusion MRI might play a key role in neuroimaging by providing direct information on synaptic activity and on brain connectivity.

Diffusion MRI was introduced in 1985 [3]. This method allows images representing the spatial distribution of the diffusion coefficient of a molecular species (most often water) to be obtained on a quantitative basis. It has quickly appeared as a very powerful tool to look at tissue microstructure, as diffusion-driven water molecular displacements are in the order of micrometers during typical measurement times (e.g. 100 ms). Diffusion may be restricted or impeded by obstacles, such as membranes, fibres, myelin, etc. One may thus have access to microscopic information, although image resolution remains on a millimetric scale. Also, diffusion can be measured in an absolute quantitative way, which is exceptional with MRI and allows comparative studies (between subjects, research centres or hospitals, or over time) to be performed, for instance to monitor disease progress or recovery or drug effects. In neurology, diffusion MRI has shown enormous potential in two important clinical domains: stroke and white matter.

3.2.1. Brain ischemia

In animal models, the water diffusion coefficient is decreased within minutes after arterial occlusion in the ischemic territory [38]. This decrease is linked to the cytotoxic edema and the cell swelling that results from the metabolic shutdown and the failure of membrane ionic pumps. The diffusion slowdown is thought to come from the shrinkage of the extracellular space, which leads to an increased tortuosity, but this mechanism has not been fully elucidated. In human patients diffusion MRI clearly shows ischemic regions within the first hours, well before conventional MRI images (based on T1 and T2 relaxation) become abnormal in relation to vasogenic edema [39, 40]. Clinical evaluation is in progress to assess the potential of diffusion MRI in combination with perfusion MRI in the management of stroke patients at the acute stage (reperfusion and neuroprotection therapies) [41].

3.2.2. White matter

Water diffusion in white matter is anisotropic: diffusion is faster in the direction of the axons than in the perpendicular direction. The respective contribution of the geometric, parallel arrangement of the fibres, the presence of myelin and glial cells and the intra- and extracellular water pools to this anisotropy is still under investigation, but impressive results have been obtained. Maturation of myelin fibres in early infancy [42] and even in premature babies and newborns [43, 44] can be monitored. Inflammatory or destructive processes of the white matter, such as multiple sclerosis can be evaluated, as well as Alzheimer disease [45] or Creutzfeld-Jacob disease [46]. A major breakthrough has been diffusion tensor imaging (DTI) which allows the direction in space of the myelin fibres to be determined with very good accuracy and mapped out in the whole brain [47, 48].

3.3. Prospect

These two fields of applications exemplify the sensitivity of diffusion MRI to microscopic tissue features, such as cell volume, spatial organization and orientation. This sensitivity makes diffusion MRI a strong candidate for the future development expected in functional neuroimaging.

For instance, a very different approach, compared to BOLD fMRI, would be to investigate whether the diffusion coefficient itself changes during neuronal activation. This diffusion effect would likely reflect transient microstructural changes of the neurons or the glial cells during activation. The possibility to observe such effects would have a tremendous impact, as they would be directly linked to neuronal events, in contrast to the blood flow effects which are indirect and remote. Several facts have led us to this hypothesis: a) water diffusion in the brain is exquisitely sensitive to changes in cell size, as shown in acute ischemia where cell swelling due to cytotoxic edema results in a 30–50 % drop in diffusion. Similarly, changes in cell volume induced by osmotic agents are accompanied by changes in water diffusion (an increase in volume leads to a decrease in diffusion and vice-versa) [49, 50]; b) the hyperstimulation of the cortex in rats using chemical agents (bicuculline) or ions (K+), as well as status epilepticus [51] results in a marked decrease in water diffusion. This decrease in water mobility propagates along the cortex at a speed of 1–3 mm/min, in parallel to observed findings based on elementary electrical recordings (spreading depression) [52, 53]. This functional activity (although extraphysiological) also leads to an increase in cell volume, which has been suggested as a possible mechanism for the diffusion drop; c) optical recordings in the cat visual cortex during physiological stimulation have shown transient changes in photon scattering, in synchrony with activation [54]. Here also, the mechanism is not clear, but transient changes in the size of the axonal cone of emergence have been reported. Rapid shifts of solvated ions might also be responsible for this effect. It is important to notice that the photon scattering change starts immediately at the onset of activation (within 1–3 ms) and disappears quickly at the end. These data have thus encouraged us to think that neuronal activation could be detected directly from related changes in tissue structure, e.g. cell swelling, by monitoring water diffusion. Of course, the first challenge is to evaluate the importance of the effect (which has now been observed in tissue preparation by
several investigators) and whether diffusion imaging would be sensitive enough to detect it.

On the other hand, diffusion tensor MRI is about to provide data on brain connectivity at the individual level, as the feasibility of white matter fibre tracking with diffusion tensor MRI has now been clearly established by several groups [55, 56]. As water diffusion is directionally dependent in white matter (anisotropy), one may reverse the situation and infer the spatial orientation of the white matter fibres from sets of MRI images sensitized to diffusion along multiple directions. It is then becoming possible to gather quantitative data on fibre orientation on a voxel basis and infer connectivity between neighbouring voxels, and by extension, between activated foci on the cortex. Work remains to be done to improve the method and increase its spatial resolution. In our laboratory we have been able to gather data on major tracts [57], such as the corpus callosum, the arcuate fasciculus, the pyramidal tract, the optic radiations or even some U-fibres (figure 2).

The combination of fMRI and diffusion MRI also offers considerable potential in the study of brain development to investigate how the acquisition of cognitive or social behaviours is linked to the myelination of specific brain regions or fibre tracts.

4. Conclusion

MRI has already found a fundamental place in the exploration of human cognition, in normal subjects, as well as in patients, exploiting the relationship between brain anatomy and function, and between neuronal activation and blood flow. Efforts should be made to further develop neuroimaging methods to reach in vivo and non-invasively a spatial resolution of clusters of hundreds of neurons and a temporal resolution of a few milliseconds. New physical or chemical phenomena directly linked to neuronal and synaptic activity must be found that are accessible via MRI or other imaging modalities. With these enhanced features available, it is clear that neuroimaging and MRI in particular will play a key role in the understanding of the 'neural code', complementary knowledge acquired from genetics and molecular biology.

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