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From research to clinical practice: Implementation of functional magnetic imaging and white matter tractography in the clinical environment

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A B S T R A C T
In the last two decades functional magnetic resonance imaging (fMRI) has dominated research in neuroscience. However, only recently has it taken the first steps in translation to the clinical field. In this paper we describe the advantages of fMRI and DTI and the possible benefits of implementing these methods in clinical practice. We review the current clinical usages of fMRI and DTI and discuss the challenges and difficulties of translating these methods to clinical use. The most common application today is in neurosurgery. fMRI and DTI are done preoperatively for brain tumor patients who are having tumors removed and for epilepsy patients who are candidates for temporal resection. Imaging results supply the neurosurgeon with essential information regarding possible functional damage and thereby aid both in planning and performing surgery. Scientific research suggests more promising potential implementations of fMRI and DTI in improving diagnosis and rehabilitation. These advanced imaging methods can be used for pre-symptomatic diagnosis, as a differentiating biomarker in the absence of anatomical measurements, and for identification of mental response in the absence of motor-sensory abilities. These methods can aid and direct rehabilitation by predicting the success of possible interventions and rehabilitation options and by supplying a measure for biofeedback. This review opens a window to the state of the art neuroimaging methods being implemented these days into the clinical practice and provides a glance to the future clinical possibilities of fMRI and DTI.

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1. Introduction

Over the past two decades the neuroscientific and medical communities have witnessed a tremendous growth in the field of noninvasive imaging of brain function. There is no doubt that fMRI – a functional imaging method that measures the hemodynamic changes in the gray matter occurring during physical, cognitive or emotional tasks – has attracted the most attention. The fMRI functional information is complemented by anatomical DTI tractography that provides valuable mapping of the white matter fiber tracts essential for intact flow of information to and between activity sites.

While fMRI has had an extreme impact on neuroscience, the practical application of these results in the clinical field is less clear, as fMRI is still in the earliest stages of its transition from research laboratories to clinical applications.

In this review we intend to briefly introduce fMRI and DTI, present the relevant terminology and discuss the implications of translating these methods into the clinical practice. We will describe the current use of fMRI and DTI as part of pre-brain surgery evaluation and review additional promising application of these imaging methods in medicine.

2. Methodological background

2.1. fMRI (Fig. 1)

Functional Magnetic Resonance Imaging (fMRI) is used to estimate and localize brain activation in the gray matter. The method is based on the neuro-vascular coupling – neural activity in a specific gray matter region of the brain will cause an increase in the blood consumption of that area. The increase in blood flow to the activated region alters the ratio between the deoxyhemoglobin and oxyhemoglobin. As deoxyhemoglobin is paramagnetic this change influences the signal registered in the MRI. This signal is called BOLD — Blood Oxygenation Level Dependant, as it reflects the oxygenation level of the brain tissue [1–3]. It is commonly assumed that changes in the BOLD signal reflect neuronal activity, although the exact relation between BOLD and neural activity and the physiological mechanisms involved are still under investigation [4].

Commonly whole brain images are acquired at relatively high temporal (2–3 s) and spatial (usually about 3 mm) resolution using gradient echo imaging sequences, either Eco-planer-imaging (EPI) or Spiral imaging. These sequences allow rapid rather than high contrast acquisition of brain volumes, necessary for capturing the physiological...
changes of interest. Functional images are later registered and superimposed on high-contrast anatomical images in order to improve identification of anatomical structures.

Subjects are required to perform one or more tasks and rest alternately during the scan. Activity is usually organized in blocks ("block design") in order to enhance signal. Alternatively, stimuli can be presented as single events ("event related design"). This paradigm is preferred when post-hoc single event analysis is required or in order to allow randomization. As the BOLD signal is created when there is a change in the blood flow, indicating a change in neuronal activity, different mental states are compared during the fMRI in order to create a contrast. As effects are based on small changes in signal with significant noise (from functional, physiological and mechanical origins) advanced preprocessing and statistical methods are required to identify activation.

2.2. DTI (Fig. 2)

Diffusion Tensor Imaging (DTI) is used to estimate the white matter tracks in the brain [5,6]. The method is based on diffusion — the random motion of water molecules in the extra and intra cellular spaces. The rules of diffusion state that the less spatial constraints the larger the diffusion will be. In the absence of local spatial constraints — as in the ventricles, the molecules will diffuse in all directions randomly (isotropic diffusion). However when the motion of the molecules is limited by tubular structures such as the axons, diffusion will be mainly directional — in the direction of axonal fibers rather than in a perpendicular plane (anisotropic diffusion). In DTI, a diffusion tensor, that is a $3 \times 3$ symmetric matrix, is used to describe the diffusion at each voxel. This model supposes the existence of one major direction of diffusion per voxel. The strength of local diffusion directionality, is usually quantified by the fractional anisotropy (FA) which allows us to distinguish between gray matter (low directionality and FA) and white matter (high directionality and FA); and to estimate the characteristics of the white matter fibers.

Additional information regarding the location and orientation of the fibers can be collected by methods of fiber tractography (FT): by integrating the orientation information along the main diffusion direction, virtual fiber tracts are reconstructed, providing a 3-d visualization of the white matter tracts. These axonal tracts can be reconstructed using functional activation regions derived by fMRI as seeds, thereby investigating connectivity between functional areas [7]. Pathology studies have shown a good overlap with DTI tractography for major white matter tracts [8].

Thus information derived about the micro-structure of the fibers using DTI is complemented by the information about their macro-structure derived using FT methods.

Two main approaches have been applied for DTI-FT: deterministic and probabilistic. In the first one, the principal direction of the diffusion tensor is tracked from voxel to voxel, starting form a seed voxel, until the FA falls below a preset threshold [9]. In this approach the point reached is not known a-priori but the tracking process, being deterministic, is fully repeatable. In the probabilistic approach, the tracking process is the result of consecutive directions sampled at random from a Gaussian probability density function whose covariance matrix is defined by the tensor at each voxel [10]. In this approach the connectivity between two areas of the brain can be tested by looking for the probability of the pathways that connect between these given regions.

3. Limitations of fMRI and DTI

Both fMRI and DTI are relatively accessible, non invasive methods providing high spatial resolution brain images (about 2 mm$^3$ voxels for DTI and 3 for fMRI). Both methods allow parallel imaging of the whole brain, promoting understanding of the complex networks and the interactions of various brain regions involved in performing a task. Although the temporal resolution of fMRI is limited to seconds (compared to milliseconds using single cell recording and EEG) it is sufficient to follow mental processes and thereby supplies a reasonable compromise between spatial and temporal resolution.

3.1. The reliability of the signal

fMRI does not measure directly the neuronal activity in a region, but rather provides an estimation of activity based on the hemodynamic changes in that region. This imposes constrains on the signal. The temporal resolution is limited by the relatively slow pace of hemodynamic changes, and the signal registered represents the average hemodynamic changes created by a sequence of neural events.
As opposed to fMRI, DTI measurements of local diffusion are also made in response to changes in local BOLD signal and signal is defined relative to baseline condition. The lack of an objective baseline creates difficulties in comparing results from different magnets and subjects, and even from the same subject in different sessions. In voxels where diffusion is isotropic (the random motion of water molecules) the fractional anisotropy (FA) is low and marked by a blue ball. In voxels where diffusion is anisotropic (the motion of water molecules has a preferred direction) due to structures such as fibers that limit the motion, the FA will be close to one and will be marked by an ellipsoid which will correlate with the flow of diffusion. DTI tractography does not allow for the tracking of individual fibers since their cross section is smaller than the voxel size by many orders of magnitude. At the scale of axonal bundles, however, large numbers of parallel axons contribute to the directional signal observed with DTI. As standard DTI assumes one main direction of diffusion per voxel, crossing fibers within one voxel are difficult to model. In the case where two or more differently oriented axons bundles crosses inside a voxel, DTI tractography will generally fail and tracking will stop or deviate from the correct direction. This problem is in the focus of current research and different advanced algorithms are proposed to improve tracking abilities. Moreover, the presence of abnormal tissues, e.g. tumors or edemas, may also perturb DTI tractography since these alternate the local microstructure in which diffusion occurs.

In the case of fiber crossing, probabilistic tractography may supply better results. A representative example is the case of the motor fibers that cross with the Superior Longitudinal Fascicle (SLF) before reaching the motor cortex. Using deterministic FT, the lateral fibers of the motor tract, spanning from the hands to the tongue, can usually not be reconstructed due to the significant decrease in FA at crossing points with the SLF. Probabilistic tractography was shown to cross successfully the SLF thereby providing a more complete mapping of the motor tracts [11]. Multi-tensor models have also been shown to provide improved results with regards to standard DTI for the reconstruction of the motor tracts [12]. This last approach assumes that more than one tensor is present in each voxel, allowing for the representation of crossing fiber tracts. The advantage of the multi-tensor method over the probabilistic one is the fact that it avoids time consuming random sampling process.

3.2. The quantitative value of the signal

fMRI is based on detecting changes in local BOLD signal and signal is defined relative to baseline condition. The lack of an objective baseline creates difficulties in comparing results from different magnets and subjects, and even from the same subject in different scans. As opposed to fMRI, DTI measurements of local diffusion are quantitative measurements with a physical meaning easily enabling intra and inter-subject comparisons.

3.3. Paradigm and analysis constraints

fMRI as a functional measurement is highly dependent on paradigm. Only functions directly addressed during scanning can be investigated and the task chosen significantly influences the results. For example, significant differences are found between the maps generated by different language tasks (such as verb generation vs. category generation) resulting in different lateralization of language dominance [13]. Tasks are limited to those possible to perform in the magnet and by the need to avoid head motion. This imposes difficulties on studying motor systems, speech, achieving natural conditions and studying conditions and patients that are susceptible to involuntary movements. As many tasks commonly involve a group of functional processes the choice of baseline is critical and interpretation of results must be done with much caution.

In most functional mapping tasks, fMRI requires some voluntary collaboration on the patient side. For example, in the mapping of specific motor areas, the patient is required to move repeatedly the corresponding body part. Therefore, patients under general anesthesia or suffering from impaired cognitive abilities (e.g. Alzheimer) or simply young children cannot be considered for fMRI mapping. DTI mapping, on the other hand, does not require any voluntary action from the patient, except for the need to minimize patient motion.

Data analysis includes many user defined variables, and the extent that these choices affect results is not entirely clear at the present time. The high variability in paradigms and analysis methods between research centers limit the ability to compare results and create optimal imaging methods.

4. fMRI and DTI as clinical tools

The success of fMRI and DTI in mapping human activity to brain areas, tracking white matter fibers and identifying pathological conditions arise the promise of applying these abilities to the clinical practice, to improve the treatment of individual patients.

A basic difference between the use of fMRI and DTI for research and for clinical practice is that while research is done on the group
level and the focus is on the effects common to all subjects (the differences between subjects are considered noise); in clinical practice we focus on a specific patient and are most interested in those differences between subjects. This makes interpretation of the results much more difficult and restricts the progression from scientific discoveries to clinical applications. Often results that are significant on a group level do not hold true for each and every subject, and thereby no information regarding a specific patient can be deduced from the imaging results. In order to enable the use of fMRI and DTI as a diagnostic tool standard norms in healthy patients are required. In the scientific imaging world there are no standard fMRI paradigms and different centers use different paradigms to identify the same brain functions [for a comparison of some common methods: 14,15]. This diversity may contribute to the expansion of scientific knowledge but makes it difficult to apply this knowledge to a clinical setting.

Furthermore as noted above, fMRI does not measure the neuronal activity directly but rather the changes in the hemodynamic properties of the region. Differences between subjects may be a result of physiological differences in the BOLD signal rather than differences in neural activity [16, for effect of specific parameters see: 17,18]. Specifically, the reliability of fMRI at estimating brain processing is based on research in healthy subjects, and may not be accurate in patients. The neuro-vascular coupling may be influenced by the proximity of vascular tumors [19,20], by epilepsy related lesions [21], disease [22] or medication [e.g., 23].

Depending on its nature, a brain lesion may have several effects on neighboring white matter fiber tracts: the tract may be dislocated, infiltrated/disrupted or remain unchanged [24]. This demonstrates the importance of fiber tracking in patients but nevertheless imposes a challenge for the commonly used tracking algorithms since known anatomical landmarks cannot be used. Moreover, the ability to correctly tract and evaluate the microstructure of a fiber may be disrupted by partial voluming — evaluating the diffusion parameters in voxels that include both tumor tissue and white matter [25].

5. Pre-surgical evaluation

The best established and most promising clinical application of fMRI and DTI is for pre-surgical planning. The aim is to provide the surgeon with functional information about the area that surrounds the tumor, which is crucial to correct planning of surgery. Preoperative fMRI and DTI mapping are not sufficient, and to achieve maximal accuracy intra-operative deep cortical stimulation (DCS) is performed during the surgery (awake craniotomy). The fMRI mapping is used to guide the neuro-stimulation and thereby can significantly shorten the surgery time. For patients who cannot undergo awake craniotomy fMRI is essential as the surgeon must rely exclusively on pre-operative mapping during surgery.

Preoperative functional imaging is necessary since the current functional knowledge about brain organization cannot be reduced to the individual level. The rough localization of different activation areas and white matter tracts are known (for example the primary motor cortex (M1) in the precentral gyrus) but the interpersonal differences in both brain function and structure require functional mapping for every subject. This individual mapping is even more important in patients who have a brain pathology which may cause cortical reorganization [26–29].

Although language functions are usually located in the left hemisphere, variability exits. Wada test [also known as intracarotid sodium amobarbital procedure, see 30 for review] was traditionally used to identify the dominant hemisphere. Currently fMRI is replacing the WADA test in pre-surgical evaluation. Several studies have compared lateralization indexes created by fMRI with WADA test lateralization and have found high correspondence between the two measures [e.g., 31,32]. Moreover, fMRI seems to provide a better predictive index of post surgery condition [33,34]. Additionally, in contrast to the WADA test which provides only a binary answer regarding language lateralization, fMRI can provide detailed information about language function areas, as well as information about the localization of other functions in a non invasive way.

In order to validate the mapping produced by fMRI its results can be compared with those of intra-operative DCS. It is important to note that while fMRI can identify the whole network of areas that participate in a specific task, not all of them are necessary for that task. Therefore we expect to find differences between those two methods. In brain systems with highly predictable and consistent localization such as the visual and motor systems, fMRI is relatively straightforward, and current procedures are highly successful in providing accurate localizations [35]. Other systems such as the language system, however, are far more variable and are highly dependent on paradigm and statistical analysis [e.g., 36,37, for review see: 38].

Functional loss can be caused not only by gray matter deficits, but also by damage to white matter fibers connecting functional areas. DTI uniquely supplies information regarding the location of relevant fibers and aids in preventing functional damage. A good spatial concordance was demonstrated, even in the presence of tumors, between intra-operative sub-cortical mapping obtained by DCS, and the motor and language fibers reconstructed by DTI [24].

Both fMRI and DTI mapping can be overlaid to a reference anatomical MRI scan and displayed on a neuro-navigation system used during the surgery. This computer assisted technology allows the surgeon to perform the surgery with continuous information about the relation between his position and the location of major fiber tracts and functional areas. However, the location of functional regions and fibers may change during surgery by the brain drift and removal of tissue and tumor. This drawback cannot be corrected by peri-operative imaging as the complexity of fMRI and DTI analyses makes it impossible to achieve rapid results with adequate accuracy.

In recent years several reviews have been published describing fMRI feasibility for brain tumor patients who are having their tumors removed [39] and for epilepsy patients who are candidates for temporal resection [40,41].

6. Brain tumors

The aim of neurosurgical treatment of brain tumors is the complete removal of the pathologic mass without sacrificing the functions of the brain and while maintaining the patient's quality of life. According to the precise tumor localization, a specific test is tailored to each patient. Fig. 3 describes pre-surgical fMRI and DTI tractography which were performed for a 52 year old male patient with a recurrent left frontal glioblastoma multiforme (WHO grade 4). Functional imaging included motor tests (movement of hand, leg and tongue), a set of language processing tests (verb generation from visually presented objects, verb generation from auditory presented words and sentence generation from visually presented words), and reconstruction of language and motor fibers. Results clearly identified language related activation in the left hemisphere in the vicinity of the tumor and proximity of the superior longitudinal fasciculus to the tumor. This information supported the need to perform an awake craniotomy using cortical stimulation in order to completely remove the tumor while retaining functionality. It also contributed to the decision to approach the surgery anteriorly. During the operation the functional mapping enabled the surgeon to focus on stimulating relevant areas, thus reducing surgery time. The intra-operative cortical stimulation mapping demonstrated Broca's area by induction of speech arrest during 60 Hz electrical stimulation (6 mA) with the bipolar electrode in the same area defined pre-operatively with fMRI. The patient recovered from the surgery with no residual damage.
As atypical language organization (i.e. bilateral or right dominance) is replacing the WADA test in evaluating laterality. fMRI lateralization following the surgery [44,45].

Measurements including pre-surgical neuropsychological assessment, language lateralization index, and the extent of the hippocampal formation were compared to those of functional imaging. It was reported that the asymmetry index measured by fMRI during memory encoding tasks, is the best predictor of the degree of damage following surgery [40,52]. Evidence showing the ability of fMRI to activate the amygdala and predict post-operative emotional disturbances is promising, but additional work is necessary before this can be implemented as a routine clinical service [53].

Temporal lobe resection may cause visual field deficit due to damage to the optic radiation and especially to the Meyer loop [53]. A probabilistic extension of DTI tractography has been shown to provide an accurate mapping of Meyer’s loop in good match with published post-mortem studies [54].

Epilepsy surgery is not limited to anterior temporal lobe resection and in the case of drug resistant focal epilepsy lesionectomy may be preformed. As in resections of tumors, fMRI and DTI are used to supply information regarding functional regions and fibers in vicinity of lesions.

8. Advanced fMRI and DTI methods — future directions

Advanced methods are currently being developed to surmount the limitations of standard analysis. Connectivity fMRI (cMRI) allows evaluation of the functional connections between regions and study the ways in which information is transmitted and integrated across brain networks. For instance dynamic causal modeling (DCM) is based on modeling the hemodynamic properties of the BOLD signal and estimating the connections between regions in a predefined network. These methods allow assessment of causality and makes inferences about the direction of influence between regions [55]. Other methods of connectivity use advanced computational methods (such as ICA) to identify functionally synchronized networks without prior knowledge [56]. Connectivity analysis does not require a task and can be preformed while the subject is in rest (resting state fMRI) [57–60]. As this method does not require cooperation of the patient it may expand the options of functional mapping and allow clinical imaging for patients who are currently unable to perform the tasks of a functional MRI scan [61].

In order to improve fiber tracking, richer representation of diffusion is sought that enables for many diffusion directions representation in the same voxel. High angular resolution diffusion imaging (HARDI) has been proposed for this purpose [62]. Recently, it has been shown that the HARDI signal can be reconstructed independently using a spherical tomographic inversion called the Funk–Radon transform. The resulting imaging method, termed q-ball imaging, can resolve multiple intravoxel fiber orientations and does not require any assumptions on the diffusion process such as Gaussianity or multi-Gaussianity as with tensor based approaches [63]. The main limit to the clinical applicability of these new methods is the prolonged scanning time required to sample the large number of diffusion directions required for the HARDI method.

9. Additional clinical applications — future potential

A unique advantage of functional imaging is the possibility of identifying mental processing that is not dependant on measurable...
behavior. This characteristic can be used for early and accurate diagnosis, to predict the benefit of therapy and even to assist in selecting the most appropriate treatment.

9.1. Presymptomatic diagnosis

In many neurodegenerative diseases detection of the disease in the preclinical stage is critical. The potential ability of fMRI as a tool for Alzheimer’s disease (AD) early diagnosis was demonstrated in apo-E4 gene carriers. fMRI identified an increase in activation in the bilateral medial prefrontal cortex, left fusiform and right perisylvian cortex whilst carrying out memory and language tasks in apo-E4 carriers relative to a control group. At this stage apo-E4 carriers had no clinical symptoms and behavioral results were similar to those of the control group [64]. In another group of patients fMRI imaging was shown to predict the development of AD: The level of increased activation in the hippocampus while performing a memory task in mild cognitive impairment (MCI) patients was found to predict the mental decline that occurred during the following four years [65]. These results demonstrate the great potential of diagnostic fMRI to identify the earliest indicators of the disease before the start of cognitive impairment. These tests together with genetic testing can allow for early intervention that may prevent mental damage.

9.2. Differentiating biomarker

One of the difficulties in psychiatric clinical work is the lack of diagnostic anatomical measurements. fMRI may assist with the psychiatric diagnosis — it has been noted that the right prefrontal fMRI activation in untreated schizophrenia patients is different from both non-schizophrenic psychosis patients and patients with depression at the first outbreak of illness [66]. If these group results can be confirmed and validated as a marker for individual subjects, psychiatrists would have a diagnostic tool that could help identify schizophrenic patients during their first attack, and by defining prognosis, would help in more rational treatment planning for these patients. An additional promising direction is connectivity analysis: characteristic patterns of connectivity in the default mode network (DMN) were found for different mental conditions such as autism [67], post-traumatic syndrome [68] and schizophrenia [69]. It may be possible to use this measure to for early and exact diagnosis [for review see: 70].

9.3. Identification of mental response in the absence of motor-sensory abilities

A recently published study described the use of fMRI in communicating with coma patients. Using fMRI, Monti et al. [71–76] showed that some patients diagnosed as being in a chronic vegetative state could perform willful mental tasks: in one case the researchers were even able to communicate with the patient [77]. Default Mode Network (DMN) connectivity was shown to correlate with level of consciousness [78], DTI can demonstrate brain abnormalities missed by conventional radiological assessment [79] and was shown to not only distinguish between different levels of consciousness but also correlate with Coma Recovery Scale [80]. These results require reassessment of the diagnosis of coma patients (Fig. 5) and have consequences for the treatment and rehabilitation of patients in whom aware neural activation was found. These results also raise philosophic questions regarding the meaning of human awareness.

9.4. A predictive tool in the clinical assessment of the possibilities for successful intervention

The ability of fMRI and DTI to evaluate the intactness of brain systems in the absence of peripheral input can be used in pre-surgery decision making. Success of novel therapies in restoring the absent input does not always achieve the desired improvement in patient’s abilities. This may be due to cortical changes that occur following deprivation. We recently demonstrated this in the case of MM who after 40 years of blindness went through implantation of cornea and corneal stem cells. However although he regained his retinal image, his visual abilities remained severely limited and he did not rely on vision for daily life. fMRI demonstrated impaired visual induced activity in MM’s occipital areas and DTI showed that the diffusivity in his visual pathways was significantly different from those of sighted controls [81]. Performing these tests prior to surgery could have predicted the consequence of the intervention.

9.5. Biofeedback

Following the development of methods for real-time analysis of the fMRI signal [82–87] it is possible to use fMRI for biofeedback [88–90]. It was demonstrated that fMRI can aid in controlling the level of pain experienced in healthy control subjects and in chronic pain patients. Moreover, the effect was significantly better than that

![Fig. 5. Imaging results of imagery task in control (above) and coma patient (below): tasks included mental humming of a tune (a), visual imagery of objects (b), imagery of playing tennis (c) and mental navigation (d). Tasks activated distinct regions, similar to control subjects, in a 22 year old patient in minimal conscious state suffering from anoxic brain damage following drowning.](image-url)
achieved by hydraulic mechanisms based on measurements from the autonomic system [91]. While the autonomic system reflects the total sum of brain activation and may be influenced by many factors, by using fMRI it is possible to distinguish between different processes and focus on relevant regions only.

These examples demonstrate the tremendous potential of translation of fMRI methods to the clinical setting. The incorporation of these promising applications relies not only on developments in neuroscience, but also on the development of a less expensive fMRI which could be accessible to the broader population. The major challenge ahead is to bridge the gap between the world of research and the clinical setting and to develop clinical applications for scientific research which will result in improved treatment and care for patients.

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References


