MRI in the study of brain functions: clinical perspectives

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fMRI can identify the regions of the brain associated with various functions.

Functional magnetic resonance imaging (fMRI) can be used to identify regions of the brain that are associated with certain perceptual, cognitive, emotional and behavioral functions such as sensorimotor, language, and memory. Although several MRI techniques have been developed for imaging functions of the brain, such as arterial spin label (ASL) [1–3], contrast agent enhanced imaging [4–6] and magnetic resonance spectroscopic imaging (MRSI) [7, 8], the most commonly used technique is based on blood oxygenation level dependent (BOLD) imaging [9–15].

BOLD imaging takes advantage of an endogenous paramagnetic contrast agent, deoxyhemoglobin, to detect MRI signal changes related to a change of deoxyhemoglobin concentration in the blood. The BOLD signal is sensitive to local changes of blood flow and to oxygen saturation in the microvasculature, both of which are coupled to local neuronal activity. In other words, an increase in neuronal activity is associated with a transient increase in local blood flow, and it is this increase that is measured with fMRI. A statistical comparison of images obtained during an activated condition with images obtained during a control condition can be used to reveal the activated brain regions that are specific to a particular mental task.

fMRI has several advantages over other neuroimaging modalities in studying brain functions [16–18], including:

- high spatial resolution (1–4 mm in-plane resolution)
- moderately high temporal resolution (0.1–1 s)
- noninvasive, easily repeatable technique with minimal preparation for the patient
- can obtain both functional and anatomical images in the same study session
- can be performed using most clinical scanners without adding significant costs.

For all of these reasons, fMRI has quickly become the most frequently used imaging modality for functional brain mapping in recent years, and has led to tremendous advances in the field of neuroscience.

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Clinical application

Since its introduction, fMRI has attracted interest in assisting both clinical diagnosis and management of patients who may have functional disruptions due to pathological conditions. Significant efforts have been made in developing clinical applications of fMRI for epilepsy surgery [19–23], diagnosis of schizophrenia [24–27], cerebral injury [28–31], and CNS pharmacology [32, 33]. The results of these studies have demonstrated the potential utility of fMRI in clinical services. However, unlike the wide acceptance of fMRI by the neuroscience community, the development of clinical fMRI is moving forward cautiously. Until now, clinical applications of this technique have been largely at the stage of controlled evaluation. Many issues that are unique to clinical fMRI still remain to be investigated [34, 35].

This article reviews both current applications and recent developments of fMRI, with an emphasis on clinical applications. It provides a brief summary of the biophysical principles and physiological bases of the fMRI method, and discusses its feasibility as a clinical tool. We also discuss the practical concerns in clinical fMRI such as patient preparation, study design, image acquisition and processing, and data analysis and interpretation. Finally, we address the potential challenges of clinical fMRI under pathophysiological conditions, and anticipate future developments.

Neuronal activity, metabolism and hemodynamics

There is an empirical correlation between local neuronal activity in the brain and local changes in hemodynamics [36–41]. Although it has been known for more than a century that increased neuronal activity leads to increased regional cerebral blood flow, cerebral blood volume and blood oxygen content, the underlying biochemical and physiological mechanisms of these processes are not fully understood. Nevertheless, it has been generally accepted that brain activation, hemo-

Imaging modality	Hemodynamic parameters measured	Contrast agent	Spatial resolution (mm*)	Temporal resolution (seconds)
PET	rCBF, rCBV	Radioactive tracer (^{15}O or ^{18}F)	10–30	60–120
SPECT	rCBF	Radioactive tracer (^{99}Tc or ^{123}I)	10–20	–
Optical (near infrared)**	Blood oxygenation	Hemoglobin and deoxyhemoglobin	2–10	< 1
fMRI	Blood oxygenation, rCBF	Deoxyhemoglobin or magnetically 'labeled' blood	2–4	0.1–3

* Spatial resolution is compared at in-plane resolution. A typical slice thickness used for fMRI exams is 5 mm, giving a voxel size of 3.7 x 3.7 x 5.0 mm^3 with FOV of 240 mm and an imaging matrix of 64 x 64.

** Optical imaging, and near-infrared spectroscopy in particular, has technical limitations in brain coverage. However, it can measure deoxyhemoglobin concentrations directly and quantitatively. Increased attention has been paid to developing this method for studying brain function.

Table 1. Comparison of some imaging modalities and their measurements.

dynamics, and metabolic processes are coupled in both space and time.

The coupling of neuronal activity to alterations in the vascular system is the basis for a number of functional imaging methods currently used in studying brain function [42–44], including positron emission tomography (PET), single photon emission computed tomography (SPECT), optical imaging and fMRI (Table 1).

Questions concerning the relationship between the various hemodynamic and metabolic parameters to actual neuronal activation have stimulated some detailed studies of brain hemodynamics. For example, although most fMRI studies measure large-scale hemodynamic changes occurring within 2 to 7 seconds after neuronal events (hemodynamic response delay), studies at high field strengths have observed changes in these physiological parameters in as little as a few hundred milliseconds after neuronal stimulation [45, 46].

More recent data acquired by using equilibrium blood pool MRI agents suggests that Cerebral Blood Volume (CBV) changes appear to lag behind changes in Cerebral Blood Flow (CBF), suggesting a capacitance system within the capillary and postcapillary bed [47]. Similarly, it has been known for some time that there is a rapid onset of increased tissue oxygen in both primary sensory (visual) and higher-order (language) cortex in humans after stimulation [48–50], which may represent a different stage of neuronal event from that of the delayed response typically measured in the visual cortex. Some studies also report nonlinear correlations between the BOLD response and stimulation, suggesting a much more complex relationship between neuronal activity and hemodynamic response [51–53].

Therefore, the precise correlation between neuronal activity and hemodynamic response, and the exact temporal ordering between changes in oxygen metabolism and the hemodynamic parameters of blood flow and blood volume, are still to be fully defined. In fMRI, the BOLD signal is dependent on both the underlying physiological events and the imaging physics [54, 55]. The brain activation signal measured with fMRI is considered to be an indirect measurement of change in the deoxyhemoglobin concentration of the blood in the vicinity of local synaptic activity. Although it is sensitive, BOLD contrast is not a directly quantifiable measure of neuronal activity; for example, it does not have units of 'ml/min' or 'activity/second'.

BOLD imaging provides an indirect indication of neuronal activity.

However, measuring the time course of hemodynamic changes and the relationship of these physiological changes to the underlying neuronal activity will determine both the spatial resolution and the accuracy of the fMRI technique [56–57]. For clinical fMRI, these issues have important implications, because the mechanisms of hemodynamic coupling can be altered by diseases.

Imaging brain activation with MRI

Current fMRI methods are based on two technical advances in MRI that were achieved in the early 1990's. First, the emergence of fast imaging techniques, as represented by echo planar imaging (EPI)

at high field (1.5 T) [58, 59], allows a set of complete two-dimensional brain images to be acquired with a single radio frequency excitation. The commonly used single-shot EPI method is capable of very fast acquisition (< 100 ms/image) of multi-slice images. For example, it allows the entire brain to be covered by 28 slices, each with a slice thickness of 5 mm, in less than 3 seconds.

The introduction of EPI led to initial studies of the dynamic changes in cerebral blood volume using exogenous paramagnetic contrast agents, and was thus the key technical development leading to the first functional MR images of brain activity. It also led to other fast imaging methods, such as the spiral imaging method [61].

Subsequently, the method of using endogenous contrast agents was developed. One such endogenous contrast mechanism was based on the concept of altering the longitudinal proton magnetization of inflowing blood to create imaging contrast between 'tagged' protons of inflow blood (the tracer) and stationary protons of the tissue, thus measuring blood perfusion [1, 2]. This Arterial Spin Labeling (ASL) technique is capable of measuring regional Cerebral Blood Flow (rCBF) with high spatial and temporal precision. The other endogenous contrast mechanism was based on the observation of local changes in the magnetic susceptibility induced by changes in the deoxyhemoglobin content of the blood, i.e. Blood Oxygen Level Dependent (BOLD) contrast.

The BOLD contrast observed in vitro by Thulborn et al. [61] suggested that changes in blood oxygenation induce changes in MR signal intensity. Later, the effect was demonstrated in vivo by Ogawa et al., and was subsequently applied to the study of brain activation [9, 10]. BOLD imaging is based on the fact that deoxyhemoglobin, which is a paramagnetic molecule, induces a small local field inhomogeneity in the magnetic field of the MR scanner. As deoxyhemoglobin is confined to red blood cells, it acts as an endogenous paramagnetic contrast agent in the blood, which is modulated by variations in oxygen supply (blood flow) and oxygen consumption (tissue metabolism). The presence of deoxyhemoglobin causes a difference in the local magnetic field susceptibility between blood and surrounding tissue, which results in a T2* effect, i.e. a small signal drop. Consequently, a reduction in the deoxyhemoglobin concentration will produce a small signal increase. Thus, the activation-induced BOLD changes can described by a somewhat simplified model. Neuronal activity causes an increase in both blood flow and oxygenation, thereby decreasing the deoxyhemoglobin concentration, which leads to a small, but measurable, MR signal increase. It is the combination of endogenous contrast and rapid imaging technology that makes it possible to detect the activation-induced MR changes.

Areas with signal changes matching neurological stimuli can be identified.

The image acquisition method used for BOLD fMRI is designed for T2* weighting with a fast imaging readout. In most fMRI experiments the gradient echo method is used. TE is typically in the range of 20–40 ms, and TR is selected from 1000 ms to 4000 ms depending on the required temporal resolution. Although the use of short TR's (e.g. < 1000 ms) can improve temporal resolution, it decreases the BOLD signal and limits the number of slices that can be acquired. For this reason it is not generally used in clinical fMRI, which is performed on individual patients and therefore requires the greatest MR signal for both sensitivity and reliability.

Currently, single shot EPI is implemented by manufacturers on most state-of-art clinical systems and is widely used for fast image acquisition. Single shot EPI is preferred to multi-shot EPI, as it minimizes the motion artifacts that are more likely to occur in patients with functional impairment due to their physical condition. Spiral imaging, which is available on some systems, can also be used. Most fMRI exams use an imaging matrix of 64 x 64 and an FOV of 240 mm, giving an in-plane resolution of 3.7 x 3.7 mm.

Exam design and task paradigm

fMRI experiments rely on the ability to detect task-evoked signal changes in series of MR images, and to extract regions of activation using statistical techniques [62, 63]. Any areas with signal changes that correlate with the neurological stimuli can then be identified and compared with a corresponding high-resolution anatomical image. In general, there are two types of task paradigms: blocked ('boxcar') designs and event-related designs. Blocked designs use a boxcar waveform that has a control condition, e.g. resting, and a task condition, typically alternating every 10–30 s. Event-related designs use very brief stimuli, typically < 1 s in duration, against a background control condition.

Because event-related designs use very brief stimuli, they can be used to track the flow of neural processing through the brain [64, 65]. They can also be used to investigate differences in the onset of neural activity evoked by different types of stimuli. Furthermore, because the stimuli can appear randomly, they are statistically more efficient than blocked designs. Consequently, event-related fMRI has the potential to address a number of important cognitive questions that focus on the temporal behavior of the hemodynamic response, relative order, changes induced by modification of the experimental context, and intersubject differences. Today, most fMRI research on cognitive processes uses event-related experimental designs, but their application in clinical fMRI faces several technical challenges. First, complicated statistical models are often needed for deriving the functional maps, but this approach is becoming feasible with the inevitable increase in computer processing speed. Secondly, substantial validation and development remains to be done before event-related designs become widespread in clinical practice.

Currently, most clinical fMRI procedures use blocked designs. In addition to their simplicity, blocked designs are well suited to clinical fMRI because the primary goal in most clinical applications is to localize an activated brain region rather than define the pattern of connectivity throughout the brain. In fact, all major scanner manufacturers currently offer a so-called real-time fMRI capability, provided that the procedure uses a blocked design. This is often an optional software and hardware package that promotes the routine use of clinical fMRI. Nevertheless, because event-related designs offer greater flexibility, they are likely to gain wider acceptance in the future.

Practical concerns in clinical applications of fMRI

Although fMRI has been widely used in the field of neuroscience, some of the techniques may not be directly applicable in clinical circumstances, due to a variety of special considerations with respect to the patients.

Patient preparation

The success of clinical fMRI depends entirely on its ability to assist in the diagnostic interpretation of an individual patient. Like any diagnostic test, it must have high sensitivity and specificity. Understanding both the pathological condition of the patient and the limitations of fMRI are important in identifying patients who would be good candidates for the procedure.

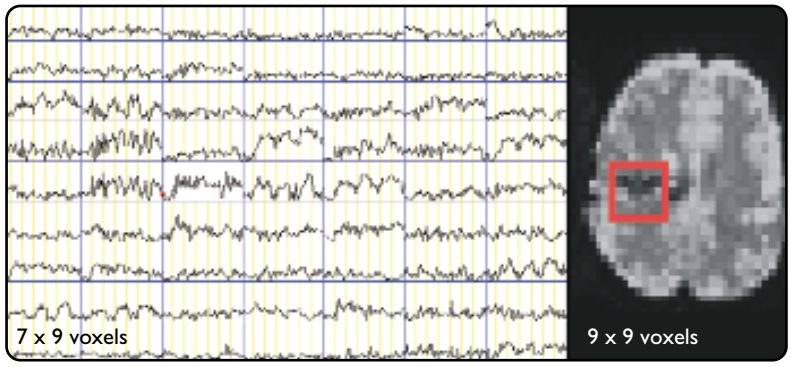


Figure 1. Possible 'false activation' was observed in the vicinity of an AVM when a patient performed left-handed thumb-to-index finger tapping. The AVM is located within the region of interest (ROI) indicated by the red box. The MRI signal time courses shown on the left were extracted from some voxels in the ROI, and appear to be correlated with a blocked task paradigm.

BOLD fMRI measures task-evoked hemodynamic changes, and the BOLD signal is detected in the vicinity of the venules and larger veins. Consequently, the ability of the BOLD technique to localize neuronal activity depends on the proximity of these vessels to the activated cortex. Thus any abnormality in the cerebral vasculature may affect the measurement of brain activation. For example, fMRI can be used to identify functionally intact regions in patients with an arteriovenous malformation (AVM), as part of preoperative planning. However, such a vascular malformation may alter the coupling of neuronal activity with the cerebral hemodynamics, and make it difficult to interpret the results. Figure 1 shows a 'false activation', (i.e. the signal time course appeared to be correlated with the task paradigm) at the periphery of an AVM when the patient performed a finger-tapping task.

When performing a clinical fMRI procedure, one will want to know several pertinent elements of the patient's history:

- what is the disease and what does the physician want to know about brain function?
- what is the patient's mental status (important if the patient must perform a task)?
- medications (these may alter the hemodynamics)
- what is the patient's physical condition?

Besides routine MRI screening procedures, additional preparations should be performed. For example, fMRI may require the patient's active participation during the exam, but most patients will be unfamiliar with the procedure. It is important to take additional time to explain the nature of the procedure, and sometimes to allow the patient to practice before the exam. If nothing else,

Successful clinical application of fMRI requires active patient participation.

this decreases anxiety and will improve the quality of the results. Patients who need fMRI exams often have a certain degree of functional impairment or may be in poor physical condition, so that additional supports may be necessary to physically stabilize the patient and minimize motion artifacts. Medications present a unique problem. There are few data on the effects of various medications in fMRI, so any particular medication may have an unexpected effect. However, some general guidelines can be offered. If it is medically prudent, CNS depressants (benzodiazepenes, barbiturates) should be withheld, as they may impair the patient's ability to perform a task. Antiseizure medications will generally not be withheld, but their use should be noted in the interpretation. Hemodynamic agents (beta-blockers, calcium channel blockers) are presumed to have some effect on the BOLD signal, but the effects are poorly understood. ACE-inhibitors and diuretics are less likely to have a direct effect.

Simple task paradigm

Clinical applications include surgical planning and disease management.

Clinical fMRI exams are generally performed on individual patients.The exam results are difficult to assess, as pathological conditions are likely to be different from one patient to another. Because of the physical condition of the patient, it is not practical to perform repeated fMRI exams, so that easy and simple tasks are desirable. In addition, routine clinical operation of an MRI facility demands that the examination be performed in a timely fashion.

Using simple blocked designs, robust activation can be detected in the primary motor, sensory, and visual cortex for individual patients. Language function can be evaluated, although the cortical network of activity is more distributed. The study of higher order cognitive functions such as memory, emotion and attention in individual patients is still challenging. This is an area of active research, requiring collaborative efforts between neuroscientists, clinicians and MRI physicists in order to further advance clinical fMRI. It is our hope that developments in both MRI techniques and neuroscience can soon provide more sensitive imaging methods and task designs for clinical use.

fMRI helps preserve functional areas during biopsy, surgery or therapy.

Postprocessing and data analysis

Postprocessing of clinical fMRI data generally adopts the approach used in conventional fMRI studies, which includes the following steps:

- realigning the functional images in the time series to correct for motion artifacts
- registering functional images on the anatomical images
- statistical analysis to correlate functional image time series to the design paradigm
- superimposing a functional map on high-resolution images for anatomical assignments.

Because clinical fMRI is usually used for investigating individual patients, it is not generally necessary to normalize the images to a standard brain atlas. Motion correction is particularly important in clinical fMRI. Commonly used rigid body transformation algorithms can be applied quickly. Most of the artifacts can be detected reliably and, at least in part, be reduced or eliminated with the help of mathematical algorithms and appropriate pulse sequences. There are significant efforts in progress to improve the reliability by developing methods that apply more accurate motion corrections, such as reducing physiological variations by using either the navigator imaging method, or by applying corrections during image reconstruction [66, 67].

Current clinical applications of fMRI

The current clinical applications of fMRI include surgical planning, functional assessment in brain tumor management, monitoring functional change, and investigation of the neural basis of mental illness.

Surgical planning

The ability to localize functional foci of the brain makes fMRI particularly useful for preoperative planning. The primary use of fMRI is to non-invasively identify functional areas of cortex in order to preserve their function during brain biopsy, resective surgery or radiation therapy [68–70]. In the surgical treatment of epilepsy, significant efforts have been made to develop the fMRI method as a replacement for the traditional intracarotid amytal procedure, also known as the Wada test. Task paradigms such as picture naming, word generation or simple fMRI rhyme detection have been developed to determine hemispheric dominance for language in epileptic patients [19–23, 68].

Results derived from the fMRI examinations were compared with those obtained on the same patients using the standard Wada test, stereotactic intra-

cerebral EEG stimulations and recordings, as well as outcomes of temporal lobectomy. These studies demonstrated that the fMRI examination generates robust responses in the language areas, and is a feasible method for determining hemispheric language dominance.

Other neurosurgical interventions may use fMRI for functional guidance. For example, implantation of a neurotrophic electrode for a 'locked-in' patient was guided by fMRI in combination with an imaginary finger-tapping task [71, 72]. The implantation of the electrode at the location identified by the fMRI exam (Figure 2) established a direct interface between the patient's brain and a device that was used to assist the patient with communication. Recently, efforts have also been made to develop an intraoperative MRI device that facilitates a noninvasive, real-time, functional MR examination in the surgical suite that can improve the efficiency and precision of the surgery [73].

Functional assessment in brain tumor management

In the clinical management of a brain tumor patient, fMRI can play an important role, ranging from cortical mapping to guiding stereotactic biopsy and tumor resection, and assessing functional plasticity in relation to the lesion [74–76].

Figure 3 shows two examples in which fMRI was used to identify the language area in patients with a brain lesion. A confrontation naming task was used in which the patient was instructed to generate sentences for line-drawn pictures of animals. fMRI exams were successful in identifying the language areas in both patients, and provided needed spatial information for the surgical planning.

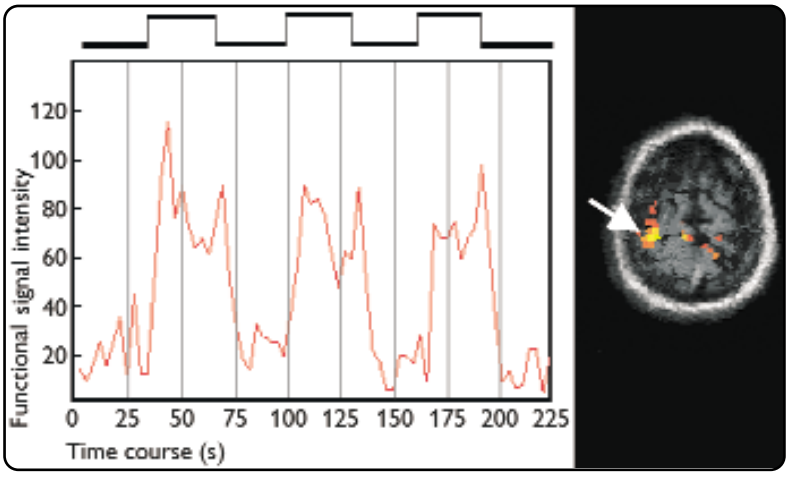


Figure 2.
BOLD signal time course. The signal time course on the left was recorded at a site (arrow) in the posterior parietal lobule (PPL) of a 'locked-in' patient performing imaginary finger tapping. The site was selected for implanting a neurotrophic electrode that extracts brain signals for interfacing with a computerized communication device.

However, fMRI has potential limitations in the study of brain tumors. The presence of edema, tumor mass and radiation-induced tissue damage affect the microvasculature surrounding the lesion. One must therefore be especially careful in the interpretation of data from an fMRI exam for the guidance of surgical procedures, especially for areas directly adjacent to tumors.

Monitoring functional change

fMRI may also be used to monitor recovery, disease progression, treatment efficacy, and the response to medication [77, 78]. Functional motor studies are useful in investigating the recovery of motor ability after brain injury such as stroke. This may be useful information for the design of rehabilitation therapy. For example, fMRI has been used to map short- and long-term cortical reorganization after spinal cord injury (Figure 4). Applications of fMRI to study neurological impairments that are not associated with structural abnormalities, such as learning problems, dyslexia [79], and motor neuron diseases, are currently in progress.

fMRI can monitor recovery, progression and response to treatment.

Figure 3. fMRI in preoperative planning.
Figure 3a. Preoperative planning for brain biopsy in a patient with a lesion (arrow) in the left frontal lobe (Broca's area). Significant bilateral language activation was observed in this patient.
Figure 3b. fMRI was used to determine the language area and its relation to the tumor for a patient with glioblastoma (arrow).

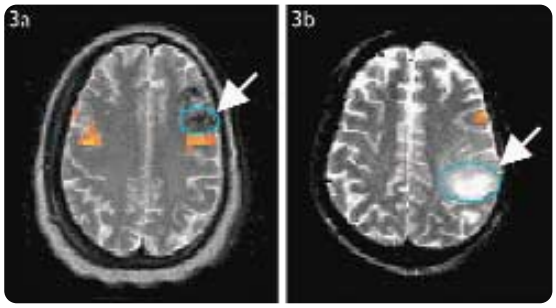
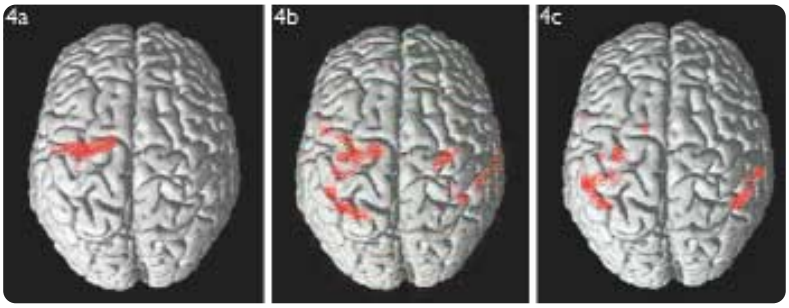


Figure 4. Functional reorganization of motor area was observed in the patients with short term and long term spinal cord injury (sci).
Figure 4a. Control.
Figure 4b. Two years after sci.
Figure 4c. More than 10 years after sci.



Psychiatric disorders

Because of its close ties to neuroscience, fMRI has been used since its invention to investigate the neural basis of mental illness. Most of the major illnesses, e.g. schizophrenia and major depression, appear to represent disordered neural systems widely distributed in the brain. Because of this, there is no single brain region associated with a particular mental illness. However, a few consistent findings have emerged that hold promise for the development of clinically useful fMRI in psychiatry.

There appears to be potential for the clinical use of fMRI in psychiatry.

The anterior cingulate cortex has become a focal point for the pathophysiology of major depression. There is some evidence that depression is associated with hyperactivity in this region and that effective pharmacological treatment is associated with a normalization of activity [79]. Similarly, the anterior cingulate has been shown to be less active in schizophrenic patients [80]. However, in both of these examples the difference between patients and controls was statistical. Using fMRI for individual diagnosis of mental illness is not yet state-of-the-art. Because psychiatry does not currently have any reliable diagnostic test, the development of a reliable test that could be used on an individual basis would represent a major breakthrough.

Future developments and their clinical potentials

Although we need to continue validating current clinical applications of fMRI, and improve its reliability, it is anticipated that clinical application of fMRI can be significantly improved with the rapid developments in the following areas.

Very high field clinical MRI systems

3.0 T MRI systems provide better temporal resolution and sensitivity.

Both MR signal intensity and BOLD contrast increase as a function of field strength. Using 3.0 T scanners, which are currently available from all major manufacturers, anatomical images can be achieved with sub-millimeter resolution. With increased signal-to-noise and T2* weighting, functional imaging can be performed with both better temporal resolution and better sensitivity.

The improved functional and anatomic information obtainable at high field strength has helped to promote the rapid development of 3.0 T clinical scanners [82–84].

The 3.0 T clinical scanner will soon be commonplace in the United States, as most MRI scanner manufactures have obtained approval for routine use from the US Food and Drug Administration.

The availability of very high field strength will enhance the ability of clinical fMRI to perform reliable functional studies on individual patients, and improve the efficiency of fMRI exams in general. High-resolution fMRI can be used for mapping functional brain organization, ranging from large cortical networks to small nuclei, and even cellular layers.

Quantitative fMRI and measurement of rCBF

Perhaps the biggest challenge to BOLD fMRI is its inability to quantify the BOLD signal itself. Quantification is particularly important if clinical fMRI is to be used to diagnosis, prognosis and treatment. A method with great potential for quantitative fMRI is the ASL technique. This is a type of perfusion MRI that can be used for noninvasive measurement of the rCBF change associated with brain activation [2–4].

Several technical refinements are needed, including correct measurement of transit and trailing times [85], as well as improvements in temporal resolution and data processing, but quantitative ASL perfusion MRI is expected to be widely applied in clinical fMRI in the future.

Another promising method for quantitative measurement of rCBF is dynamic perfusion imaging with bolus injections of exogenous contrast agents such as gadolinium chelate or superparamagnetic iron oxide nanoparticles [6, 86]. These agents can greatly expand the capability of fMRI and provide accurate measurement of task-induced rCBF change.

Application of susceptibility contrast physics and standard 'bolus-tracking' kinetic principles allows the calculation of relative cerebral blood volume maps and mean transit time parameters, which are related directly to the hemodynamic response.

Another advantage of using exogenous contrast agents for perfusion fMRI is improvement in temporal resolution without the long labeling and inversion times needed in the ASL method.

Event-related design

The event-related task paradigm is capable of studying functional organization and temporal variations of hemodynamic response. Its applications in neurosciences have facilitated the development of new imaging acquisition methods and algorithms for data processing and analysis. The combination of real-time fMRI capability and integrated triggering devices has now been applied in clinical systems such as the Philips Intera system, making it possible to perform routine event-related fMRI in the clinic setting. Future development of clinical fMRI will soon adopt the event-related approach in order to investigate broad clinical issues such as disruption of functional connectivity [87, 88].

Combining fMRI and other imaging methods

Another direction for the future development of fMRI is the integration of other imaging methods, such as magnetic resonance spectroscopy (MRS), diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI). When these modalities are integrated they will provide a multifunctional view of the brain. For example, MRS can measure levels of various neuronal metabolites, such as N-acetyl aspartate (NAA), creatine (CRE), choline (CHO) and lactate (LAC), thus providing metabolic information associated to the regional brain activity.

Many brain diseases, such as brain tumors, temporal lobe epilepsy, schizophrenia as well as other neurodegenerative diseases often demonstrate abnormalities in the MRS exam. MRS can therefore be readily used to correlate biochemical processes of neuronal cells and functional assessments done by fMRI exam [89, 90].

Although dynamic measurement of task-induced metabolic changes using MRSI remains difficult, the recent development of fast MRSI such as 3D MRSI and MRS-EPI may make this feasible [8].

Functional assessments can be correlated with metabolic processes.

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