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Overview of Functional Magnetic Resonance Imaging

Gary H. Glover

Department of Radiology, Stanford University, Stanford, CA 94305

Synopsis

Blood Oxygen Level Dependent (BOLD) functional magnetic resonance imaging (fMRI) depicts changes in deoxyhemoglobin concentration consequent to task-induced or spontaneous modulation of neural metabolism. Since its inception in 1990, this method has been widely employed in thousands of studies of cognition for clinical applications such as surgical planning, for monitoring treatment outcomes, and as a biomarker in pharmacologic and training programs. Technical developments have solved most of the challenges of applying fMRI in practice. These challenges include low contrast to noise ratio of BOLD signals, image distortion, and signal dropout. More recently, attention is turning to the use of pattern classification and other statistical methods to draw increasingly complex inferences about cognitive brain states from fMRI data. This paper reviews the methods, some of the challenges and the future of fMRI.

Keywords

functional magnetic resonance imaging; fMRI

Introduction

Functional Magnetic Resonance Imaging (fMRI) is a class of imaging methods developed in order to demonstrate regional, time-varying changes in brain metabolism^{3,37,49}. These metabolic changes can be consequent to task-induced cognitive state changes or the result of unregulated processes in the resting brain. Since its inception in 1990, fMRI has been used in an exceptionally large number of studies in the cognitive neurosciences, clinical psychiatry/psychology, and presurgical planning (between 100,000 and 250,000 entries in PubMed, depending on keywords). The popularity of fMRI derives from its widespread availability (can be performed on a clinical 1.5T scanner), non-invasive nature (does not require injection of a radioisotope or other pharmacologic agent), relatively low cost, and good spatial resolution. Increasingly, fMRI is being used as a biomarker for disease^{33,36}, to monitor therapy⁵⁴, or for studying pharmacological efficacy⁶². Thus, it is of interest to review the fMRI contrast mechanisms, the strengths and weaknesses, and evolutionary trends of this important tool.

Address for Correspondence: Gary H. Glover, PhD, Lucas MRI Center, MC 5488, 1201 Welch Road, Stanford, CA 94305-5488, Tel: 1-650-723-7577, Fax: 1-650-723-5795, gary.glover@stanford.edu.

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Basis for fMRI

fMRI is of course based on MRI, which in turn uses Nuclear Magnetic Resonance coupled with gradients in magnetic field³⁸ to create images that can incorporate many different types of contrast such as T1 weighting, T2 weighting, susceptibility, flow, etc.⁷ In order to understand the particular contrast mechanism predominantly used in fMRI it is necessary to first discuss brain metabolism.

All the processes of neural signaling in the brain, including formation and propagation of action potentials, binding of vesicles to the pre-synaptic junction, the release of neurotransmitters across the synaptic gap, their reception and regeneration of action potentials in the postsynaptic structures, scavenging of excess neurotransmitters, etc., require energy in the form of adenosine triphosphate (ATP)⁵⁵. This nucleotide is produced principally by the mitochondria from glycolytic oxygenation of glucose, and its production results in carbon dioxide as a byproduct. When a region of the brain is up-regulated (i.e. *activated*) by a cognitive task such as finger tapping, the additional neural firing and other increased signaling processes result in a locally increased energy requirement, in turn resulting in up-regulated cerebral metabolic rate of oxygen (CMRO₂) in the affected brain region¹². As the local stores of oxygen in tissues adjacent to capillaries are transiently consumed by glycolysis and waste products build up, various chemical signals (CO₂, NO, H⁺) cause a vasomotor reaction in arterial sphincters upstream of the capillary bed, causes dilation of these vessels. The increased blood flow acts to restore the local [O₂] level required to overcome the transient deficit; however, for reasons that are still not fully understood more oxygen is delivered than is needed to offset the increase in CMRO₂. As a result, neural up-regulation results initially in a build-up of deoxygenated hemoglobin [Hb] and a decrease in deoxygenated hemoglobin [HbO₂] in the intra- and extravascular spaces, followed within a second or two by a vasodilatory response that reverses the situation to result in an increase in [HbO₂] and decrease in [Hb] over that in the resting condition^{13,22} (see Fig. 1). This sequence of processes is described as the hemodynamic response to the neural event.

Thus, there are two primary consequences of increased neural activity, and both can be detected by MRI: increased local cerebral blood flow (CBF) and changes in oxygenation concentration (Blood Oxygen Level Dependent, or BOLD contrast). The change in CBF can be observed using an injected contrast agent and perfusion weighted MRI, first demonstrated by Belliveau⁶, or non-invasively by arterial spin labeling (ASL)²⁵. However, ASL suffers from reduced sensitivity, increased acquisition time and increased sensitivity to motion compared with the BOLD contrast method, and its use has therefore centered on obtaining quantitative measurements of baseline cerebral blood flow (CBF) for studies modeling the neurobiological mechanisms of activation^{12,22} or calibration of vasoreactivity⁴, rather than in routine mapping of brain function.

The second mechanism, termed Blood Oxygenation Level Dependent (BOLD) contrast, was first demonstrated in rats^{48,50} and later in humans^{3,37,49,52}, and is the contrast that is used in virtually all conventional fMRI experiments. BOLD contrast results from the change in magnetic field surrounding the red blood cells depending on the oxygen state of the hemoglobin. When fully oxygenated, HbO₂ is diamagnetic and is magnetically indistinguishable from brain tissue. However, fully deoxygenated Hb has 4 unpaired electrons and is highly paramagnetic⁵⁹. This paramagnetism results in local gradients in magnetic field whose strength depends on the [Hb] concentration. These endogenous gradients in turn modulate the intra- and extra-vascular blood's T₂ and T_{2*} relaxation times through diffusion and intravoxel dephasing, respectively. Using a gradient refocused echo (GRE) MRI pulse sequence⁷, the acquisition is made sensitive to T_{2*} and T₂. At 1.5T and

3T, the T2* contrast is predominant and is largest in venules⁶¹, while at higher field strength the diffusion-weighted contrast of T2 relaxation becomes more important and, because signals are generated preferentially in capillaries and tissue with spin-echo acquisitions, provides greater spatial specificity^{57,64}. Since most fMRI is currently performed at 3 Tesla or below, BOLD fMRI utilizes primarily GRE methods because of the increased T2* contrast¹⁰.

Task activation fMRI studies seek to induce different neural states in the brain as the visual, auditory or other stimulus is manipulated during the scan, and activation maps are obtained by comparing the signals recorded during the different states. Therefore, it is important to collect each image in a snapshot mode to avoid head motion and physiological processes of respiration⁸ and cardiovascular functions^{15,16} from injecting noise signals unrelated to the neural processing being interrogated. Generally, most fMRI is performed using an Echo Planar Imaging (EPI) method⁴³, which can collect data for a two dimensional image in approximately 60 ms at typical resolutions ($3.4 \times 3.4 \times 4 \text{ mm}^3$ voxel size). Typically, whole brain scans with ~ 32 2D slices are acquired with a repetition time (TR) of 2s/volume. Each voxel in the resulting scan produces a time series that is subsequently analyzed in accordance to the task design.

The fMRI experiment

The typical fMRI task activation experiment utilizes visual, auditory or other stimuli to alternately induce two or more different cognitive states in the subject, while collecting MRI volumes continuously as described above. With a two-condition design, one state is called the experimental condition, while the other is denoted the control condition, and the goal is to test the hypothesis that the signals differ between the two states. Using a block design, the trials are arranged to alternate between the experimental and control conditions, as shown in Fig. 2, with each block typically being a few tens of seconds long. The block design is optimum for detecting activation, but a jittered event-related (ER) design is superior when characterization of the amplitude or timing of the hemodynamic response is desired^{11,41}. In the ER design, task events are relatively brief and occur at non-constant inter-trial intervals with longer periods of control condition, which allows the hemodynamic response to return more fully to baseline. Jittering the timing serves to sample the hemodynamic response with higher temporal frequency in the overall time series, but may also be used to induce a desired cognitive strategy, e.g., to avoid an anticipatory response or maintain attention.

The degree to which valid inferences can be drawn from the measured time series data depends in large part on careful design of the task. The investigator must take care that only the effect of interest changes between experimental and control conditions, while confounding effects such as attention and valence are maintained constant or irrelevant. In some studies this is straightforward, such as the use of a sensory task for presurgical mapping, wherein the goal is only to localize activation so that important brain functions can be maintained after surgery. In this case the signal intensity is of minor interest as long as it is adequate to characterize the functional substrates to be preserved during surgical intervention. In many other cases, however, comparative inferences are desired such as parametric studies of the influence of task difficulty on a cognitive process, and thus control of such factors as learning, adaptation, and salience must be considered.

Analysis methods

Once the images have been acquired, the time series data must be processed to obtain maps of brain activation. Because the BOLD contrast is small (< 1% in many studies of higher cognitive processes)³⁵, simply averaging images over the experimental and control

conditions and then subtracting (as sketched in Fig. 2) is inadequate to reliably determine differences because noise will compete to render false positives and negatives. The noise results from thermal sources in the subject and electronics, bulk motion of the head, cardiac and respiratory-induced noise, and variations in baseline neural metabolism. Because the noise can sometimes be larger than the signal of interest, fMRI analyses compare the signal difference between the states using a statistical test. These tests result in an activation map that is a function of the probability that the brain states differ. The statistical test for activation can utilize a general linear model (GLM)^{27,63}, cross-correlation with a modeled regressor², or one of several data-driven approaches such as independent components analysis (ICA)¹⁴. The models against which the acquired data are tested include the experimental design of interest as well as “nuisance regressors” of no interest such as signal drift, motion, and noise reflected in global or white-matter signals. In all cases, the activation testing is preceded by a series of preprocessing steps.

The steps in pre-processing can include all or some of the following: 1) time-slice correction, to eliminate differences between the time of acquisition of each slice in the volume; 2) motion coregistration, in which affine head motion is detected and the time series of volumes is resampled to register each time frame to a reference frame, such as the first or middle time series point; 3) correction for physiological noise from breathing and cardiovascular function^{8,15}, low pass and/or high pass temporal filtering to improve the statistics while removing spectral components of no interest; 4) spatial smoothing to improve the signal to noise ratio (SNR) and improve the normality of the noise distribution; 5) pre-whitening to correct for autocorrelation in the time series³⁵. The analysis of fMRI data continues to be a subject of intense research at this time, and is one about which numerous books have been written, to which the reader is referred for further information (e.g. Sarty⁵⁶).

Comparisons with other functional imaging modalities

fMRI can be compared to other imaging methods used to obtain functional assessment of brain metabolism in terms of spatial and temporal resolution and availability. The primary alternatives are Positron Emission Tomography (PET), Near Infrared Spectroscopy (NIRS), ElectroEncephalography (EEG) and MagnetoEncephalography (MEG)³⁵.

1) Spatial resolution

Resolution in fMRI is limited primarily by SNR because of the necessity for rapid acquisition of time series information. For MRI, $SNR \propto p^2 w \sqrt{T_{acq} N}$, where p is the pixel size, w the slice thickness, T_{acq} is the k-space readout time and N is the number of time frames. Thus, as T_{acq} is reduced for single shot imaging (typically 20–30ms) the pixel size must be increased over that for conventional anatomic imaging to maintain an acceptable SNR. Accordingly, the typical fMRI pixel size is 3–4 mm, although with higher field magnets (7T) a pixel size of 500 microns or less may be readily achieved⁵⁷. The resolution of PET is limited by the size of the gamma ray detectors as well as the positron-electron annihilation range, and is typically ≥5–10 mm. NIRS resolution is low (10–20 mm) and limited predominantly by the strong scatter and attenuation of IR photons (which also limits the depth of cortex that can be imaged within a banana-shaped region connecting optodes), the modest density of optodes and the ill-conditioned inverse problem of reconstructing 3D maps of [Hb] from scalp recordings²⁰. The resolution in EEG and MEG is similarly limited to > 10–20 mm by the fact that a unique reconstruction of dipoles is not possible from scalp-based measurements of electrical or magnetic distributions and models and regularization must be employed for model estimation. Unlike EEG, MEG does not have the confound that

scalp recordings may be spatially distorted by heterogeneous electrical conduction paths within the brain/skull.

2) Temporal resolution

fMRI's temporal resolution is limited by hemodynamic response time; typically the BOLD response has a width of ~3s and a peak occurring ~5–6s after the onset of a brief neural stimulus. This is much slower than the underlying neural processes, and temporal information is thereby heavily blurred. Nevertheless, by jittering event-related stimuli and using appropriate analysis methods¹¹ temporal inferences in the 100ms resolution range can be achieved⁵¹. PET scans require minutes to complete because of the low count rates of injected radio nuclides, so changes in neural processes can only be studied by repeated scanning. Like BOLD, NIRS reports changes in blood oxygenation and, exacerbated by low SNR of NIR photons in the brain, has temporal limitations similar to those of fMRI. EEG and MEG, on the other hand, have millisecond temporal resolution and can easily capture the dynamics of evoked responses that last a few ms to several hundred ms. Multimodal approaches combining fMRI and EEG use fMRI maps as spatial priors to reconstruct high temporal resolution electrophysiology, thereby gaining resolution in both dimensions²¹.

Strengths and weaknesses of fMRI

From the discussion above, a primary strength of fMRI is its relatively high spatial resolution and availability. In addition, it is readily available to both clinical and academic researchers, is noninvasive, and can provide high resolution anatomic scans in the same session to use for localization, vessel identification,⁴⁵ or development of maps of white matter connectivity through the use of diffusion tensor imaging (DTI)⁵.

Because BOLD contrast derives from the sluggish hemodynamic response to metabolic changes, a significant weakness is its low temporal resolution. Another problem is signal dropout and/or spatial distortion in frontal orbital and lateral parietal regions, caused by the ~9 ppm difference in magnetic susceptibility at interfaces between air and brain tissue¹⁸. This can result in erroneous lack of BOLD signal in ventral, temporal and PFC regions important in many cognitive studies. Many methods have been developed to diminish these susceptibility losses, although most involve some tradeoff of SNR in magnetically uniform brain regions^{18,19,31,34,58,60,65}. Other weaknesses include the scanner's loud noise associated with switched magnetic fields, which can cause confounds in studies of audition^{28,29} and resting state networks³⁰; however, methods using interleaved scanning/stimulus delivery epochs can avoid these problems, albeit with some loss of flexibility in experimental design^{26,28}. Finally, the high magnetic fields require customized stimulus delivery and subject response systems, again limiting flexibility and complicating multimodal experiments such as concurrent EEG recording.

Future of fMRI

For the most part, the MRI physics and technology development behind BOLD fMRI acquisitions are mature, and the tradeoffs between acquisition speed, resolution, SNR, signal dropout and contrast are well understood. Over the years, a number of investigators have attempted to develop alternatives to BOLD contrast using direct neural current detection⁹, although by now it is understood⁴² that the weak size of the neural current signal relative to physiological noise makes a breakthrough unlikely. Another alternative is the use of diffusion weighted imaging to demonstrate activation-related changes in populations of bound vs. free water distributions^{39,40}. A potential advantage is that such diffusion related changes may have more rapid responses than BOLD methods. However, again the signals are weaker than BOLD contrast and their biophysical origin is still unclear⁴⁶. Other

experiments have reported the use of spin echo rather than gradient echo acquisitions of BOLD contrast, especially at higher fields where T2* is foreshortened⁵⁷.

While a modest research effort will continue in improving acquisition technology, the bulk of research in the development of fMRI has shifted to its application to answering more complex questions in cognitive neuroscience. One promising area is that of using activation maps as input to classification and state change algorithms to predict or classify cognitive behavior, such as predicting brain states^{44,53} (also see, e.g. Norman for a review⁴⁷). Other emerging uses of fMRI include the development of quantitative measures, i.e. biomarkers for disease or monitoring behavioral modification such as reading disorders. A cautionary note, however, is that because of the small BOLD responses typical of cognitive processes, most studies are limited to employing group statistics to make inferences about populations rather than about individuals. Thus fMRI's use in quantifying individual characteristics may continue to be limited to those tasks for which relatively strong BOLD responses are observed, such as primary sensory systems. Resting state networks and their modification by disease conditions such as Alzheimer's, depression and other psychiatric disorders³² are gaining attention. However, there is growing awareness that these networks may be much more complex in their spatio-temporal dynamics than previously thought¹⁷, and much more work is indicated to understand their role and utility in predicting individual behavior/physiology. Finally, feedback derived from real-time fMRI has been shown to allow subjects to learn pain-reduction strategies²⁴, enhance sensorimotor control²³ and to control relevant brain regions in mood disorder experiments⁵³. The reader is also referred to Bandettini¹ for additional considerations regarding the future of fMRI.

Conclusions

Functional MRI has enjoyed an exciting development course with an exponential growth in published studies since its inception in the early 90's, and it has become commonplace for clinical uses such as presurgical planning, fundamental cognitive neuroscience investigations, behavior modification and training. Informed by fMRI, more sophisticated modeling of brain networks is certain to lead to new levels of understanding of the human brain.

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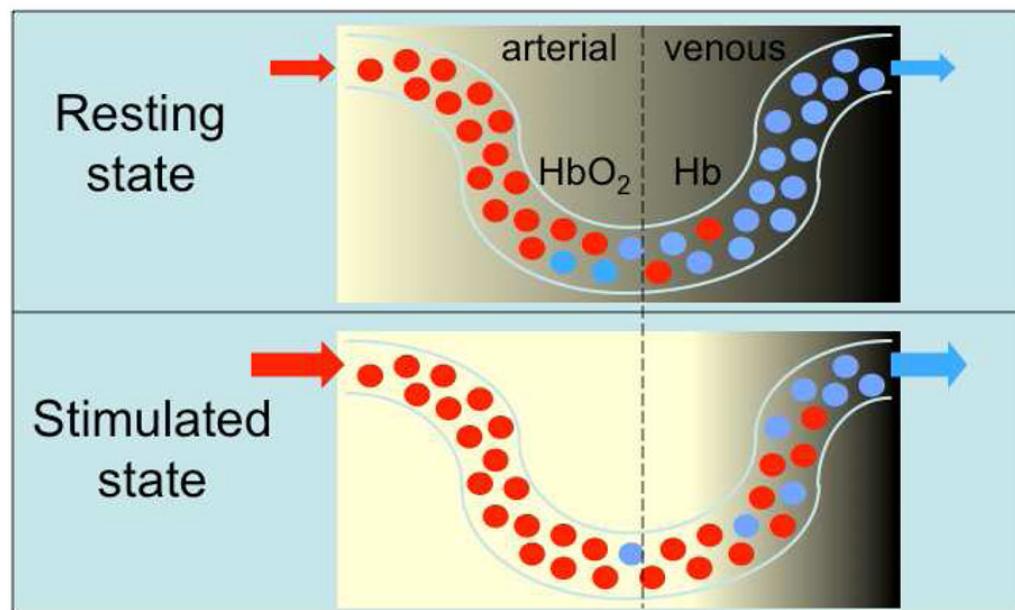


Figure 1.

Sketch of brain tissue containing a capillary during rest (top) and activation (bottom). Red and blue circles represent red blood cells that are fully oxygenated (HbO_2) and fully deoxygenated (Hb), respectively. The MRI signal is depressed in the venous side of the capillary due to the paramagnetic susceptibility of the Hb acting as an endogenous contrast agent (shown darker). In the stimulated condition, increased blood flow causes the Hb to be swept out and replaced by HbO_2 , causing a BOLD signal increase.

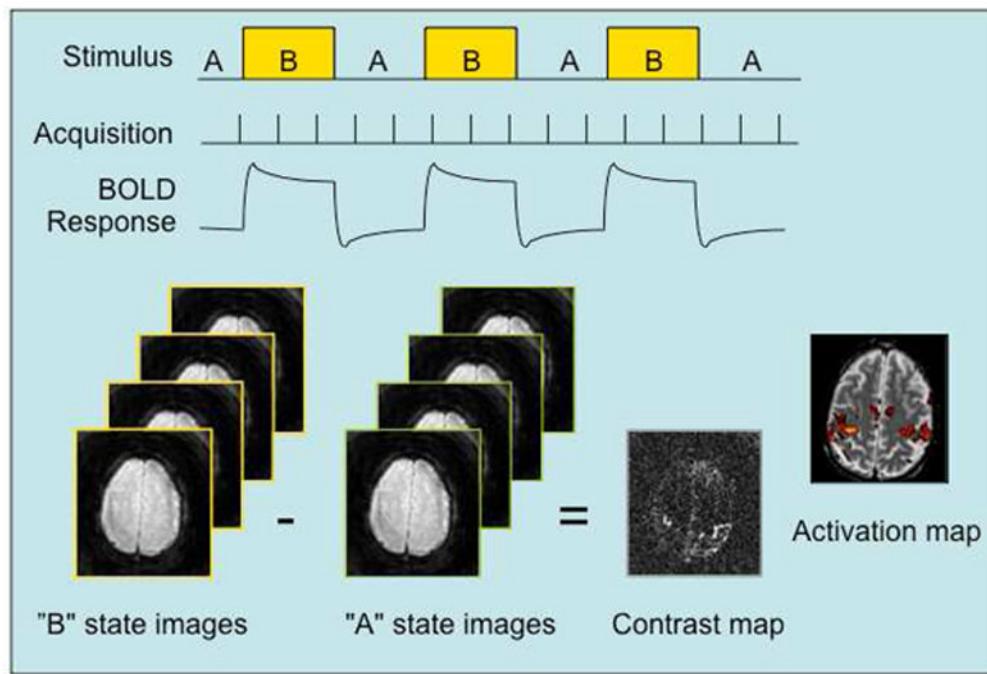


Figure 2.

Block design fMRI experiment. A neural response to the state change from A to B in the stimulus is accompanied by a hemodynamic response (as shown in Fig. 1) that is detected by the rapid and continuous acquisition of MR images sensitized to BOLD signal changes. Using single- or multi-variate time series analysis methods, the average signal difference between the two states is computed for the scan and a contrast map generated. A statistical activation map is finally obtained using a suitable threshold for the difference; the map depicts the probability that a voxel is activated given the uncertainty due to noise and the small BOLD signal differences.