# Clinical Applications of Functional MRI

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INTRODUCTION

Magnetic Resonance Imaging (MRI) of the brain is well-recognized for its excellent spatial resolution, allowing neuroanatomic structures to be viewed in sharp detail. Recently, it has become possible to modify a conventional MRI scanner to study the brain's function as well. This new technology, called functional Magnetic Resonance Imaging (fMRI), has brain researchers excited for several reasons.

First, the most commonly used fMRI technique called BOLD-fMRI (Blood-Oxygen-Level-Dependent fMRI) potentially offers imaging with a temporal resolution on the order of 100 milliseconds and a spatial resolution of 1-2 millimeters, which is much greater than that of PET and SPECT scanning.[1] This means that transient cognitive events can potentially be imaged and small structures like the amygdala can be more readily resolved. Next, unlike PET and SPECT, most fMRI techniques are noninvasive and do not involve the injection of radioactive materials so that a person can be imaged repeatedly. This may allow imaging of a patient repeatedly through different disease states (ie. imaging a bipolar patient through manic, depressive, and euthymic states) or developmental changes (ie. learning, cognitive stages of development, stages of grief recovery). It also allows for investigations in healthy children due to the low risk. Third, with fMRI, one can easily make statistical statements in comparing different mental states within an individual in a single session whereas PET and SPECT scans usually rely on making statistical statements about group differences between mental states. Thus, fMRI may be of important use in understanding how a given individual's brain functions and perhaps, in the future, making psychiatric diagnoses and treatment recommendations. It is, in fact, already starting to being used in presurgical planning to map vital areas like language, motor function, and memory[2-6]. Perhaps most important for the future clinical utility of fMRI is that it involves only some upgrading of conventional MRI machines and, thus, may be become widely available.
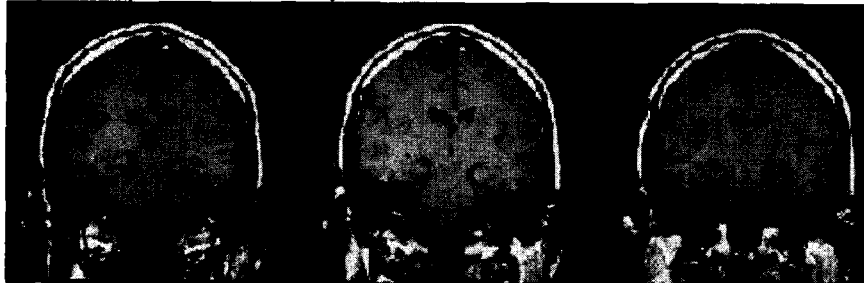
Below, we describe the principles underlying the different types of functional MRI and give examples of how each technology can be used in psychiatry research or clinical practice. The basic principles underlying all types of MRI were discussed in the previous section on structural imaging. Namely, we discuss the three main types of functional MRI:

(1) BOLD-fMRI which measures regional differences in oxygenated blood
(2) perfusion fMRI which measures regional cerebral blood flow
(3) diffusion-weighted fMRI which measures random movement of water molecules.

BOLD-fMRI (Blood-Oxygen-Level-Dependent fMRI)

BOLD-fMRI is currently the most common fMRI technique.

Here, the MRI scanner is tuned to resonate and image hydrogen atoms as in conventional MRI; however, T2*-weighted images are performed which take advantage of the fact that deoxygenated hemoglobin is magnetic whereas oxygenated hemoglobin is not.[6-8] Because of the magnetic properties of the unflipped magnetic deoxyhemoglobin molecule which causes rapid dephasing, T2* signal is retained longer in a region when it has more oxygenated blood

compared to when there is less oxygenated blood. Thus, an area with more oxygenated blood will show up more intense on T2*-weighted images compared to when there is less oxygenated blood around.

With this technique, it is assumed that an area is relatively more active when it has more oxygenated blood compared to another point in time [1,6]. This is based on the principle that when a brain region is being used, arterial oxygenated blood will redistribute and increase to this area. This principle has one caveat: there is a time lag of 3-6 seconds between when a brain region is activated and blood flow increases to it [1,9,10]. During this time lag of 3-6 seconds, in fact, the activated areas experience a relative decrease in oxygenated blood as oxygen is extracted by the active regional neurons. Afterward, the amount of blood flowing to the area far outweighs the amount of oxygen that is extracted so that oxygenated blood is now higher. Although images can be acquired every 100 msecs with echoplanar (a type of rapid acquisition) BOLD fMRI, this predictable but time varied delayed onset of the BOLD response limits the immediate temporal resolution to several seconds instead of the 100 msec potential.[9] In the future, researchers may be able to improve the temporal resolution of fMRI by measuring the initial decrease in oxygenated blood with activation.[11]

BOLD fMRI is a relative technique in that it must compare images taken during one mental state to another to create a meaningful picture. As images are acquired very rapidly (ie. a set of 15 coronal brain slices every 3 seconds is commonly done in our lab), one can acquire enough images to measure the relative differences between two states to perform a statistical analysis within a single individual. Ideally, these states would differ in only one aspect so that everything is controlled for except the behavior in question.[10] Breiter et al.(1996), for example, scanned Obsessive-Compulsive Disorder patients and healthy controls during activated (ie. holding dirty washcloth) versus rest states (ie. holding clean washcloth).[12]

BOLD-fMRI paradigms generally have several periods of rest alternating with several periods of activation . Images are then compared over the entire activation to the rest periods. Images obtained over the first 3 to 6 seconds of each period are generally discarded due to the delay in hemodynamic response. Alternating paradigms are used because the signal intensity generated by the MRI scanner drifts with time.

With current technology, fMRI-BOLD is best used for studying processes that can be rapidly turned on and off like language, vision, movement, hearing, and memory.[9] The study of emotion is hampered by its slow and variable onset and its inability to be quickly reversed.[13,14]

Time (min)
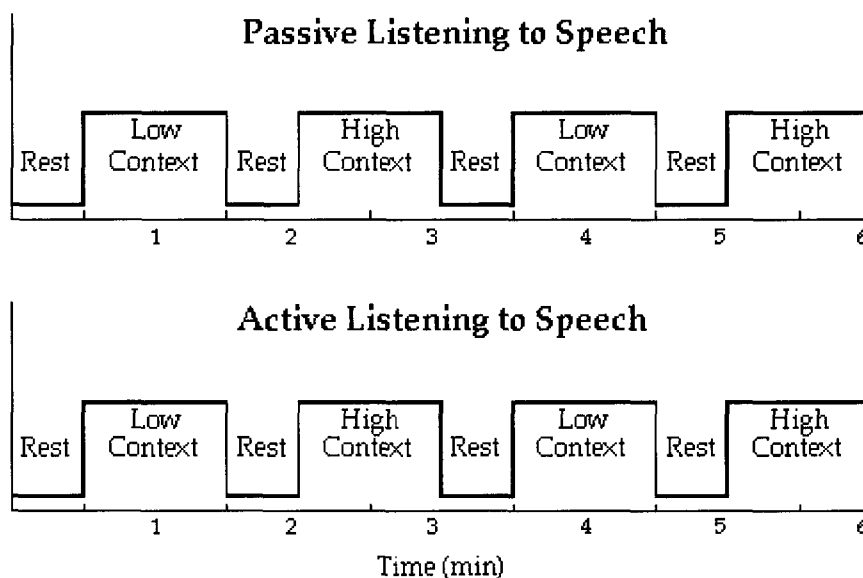
Some have, however, succeeded in using this technique to study emotional processes.[12,15] For example, Whalen et al. (1998)[16] used a backwards masking procedure to present 3 alternating conditions to 10 subjects: (1) a baseline condition where subjects would see a "+" sign, (2) a "happy" (H) condition where subjects would see repeated presentations of 33 msecs of a happy face followed by 167 msecs of a neutral face, and (3) a "fear" (F) condition where subjects would see repeated presentations of 33 msecs of a fearful face followed by 167 msecs of a neutral face. Here, fearful and happy faces were presented in such a way that 8 of the 10 participants could not identify them. Despite this unconscious processing, subjects had relatively increased amygdala activation with fearful faces and relatively decreased amygdala activation with the happy faces.
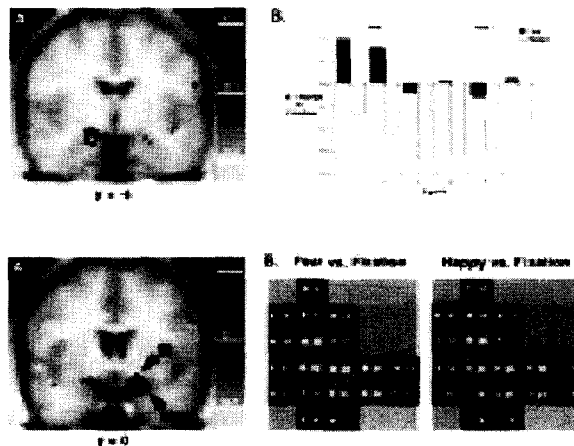
BOLD-fMRI is very sensitive to movement so that tasks are limited to those without head movement, including speaking. BOLD-fMRI is also limited in that artifacts are often present in brain regions that are close to air (i.e. sinuses) Thus, there are some problems in observing important emotional regions at the base of the brain like the orbitofrontal and medial temporal cortices. Another problem is that sometimes observed areas of activation may be located more in large draining veins rather than directly at a capillary bed near the site of neuronal activation.[6]

Currently, there are no indications for BOLD-fMRI in clinical psychiatry, although this technique holds considerable promise for unraveling the neuroanatomic basis of psychiatric disease. It may be of potential help in sorting out diagnostic heterogeneity and treatment planning in the future. Neurologists and neurosurgeons are beginning to use this technique clinically to noninvasively map language, motor, and memory function in patients undergoing neurosurgery.[2-6]

Perfusion fMRI

Two fMRI methods have been developed for measuring cerebral blood flow. The first method, called intravenous bolus tracking, relies on the intravenous (iv) injection of a magnetic compound such as a gadolinium-containing contrast agent and measuring its T2*-weighted signal as it perfuses through the brain over a short time period of time.[17-20]

Areas perfused with the magnetic compound show less signal intensity as the compound creates a magnetic inhomogeneity that decreases the T2* signal. The magnetic compound may be injected once during the control and once during the activation task and relative differences in blood flow between the two states may be determined to develop a perfusion image[17]; alternatively, one can measure changes in blood flow over time after a single injection to generate a perfusion map.[19] Belliveau et al. (1991) used the technique to create the first functional magnetic resonance maps of human task activation using a visual stimulation paradigm. They imaged the occipital lobe after injecting gadolinium-DTPA once during darkness and again during a flashing light to map the visual response. They made a statistical comparison between images obtained during visual stimulation versus those obtained during darkness to generate the now famous image.
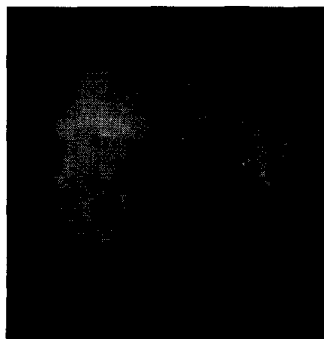
Although gadolinium-based contrasts are not radioactive, the number of boluses that can be given to an individual is limited by the potential for kidney toxicity with repeated tracer administration. This technique also only generates a map of relative cerebral blood flow, not absolute flow as in the next technique. Arterial spin labelling is a T1-weighted noninvasive technique where intrinsic hydrogen atoms in arterial water outside of the slice of interest are magnetically

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tagged ("flipped") as they course through the blood and are then imaged as they enter the slice of interest. [6,21-24]

Arterial spin-labelling is noninvasive, does not involve an iv bolus injection, and can, thus, be repeatedly performed in individual subjects. Also, absolute regional blood flow can be measured which cannot be easily measured with SPECT or BOLD-fMRI and requires an arterial line with PET. As absolute information is obtained, cerebral blood flow can be serially measured over separate imaging sessions such as measuring blood flow in bipolar subjects as they course through different disease states.[25] Absolute blood flow information may be important in imaging such processes as anxiety which may be hard to turn on and off. For instance, in social phobics, a relaxation task may be imaged on one day and anticipating making a speech may be imaged on the next day. Comparing these separate tasks in different imaging sessions would not be possible with BOLD-fMRI. The following figure shows an example of the arterial spin-labelling technique. While there is currently no clinical indication for this technique, it may soon be used clinically to help characterize the different stages of acute ischemic stroke.[26]
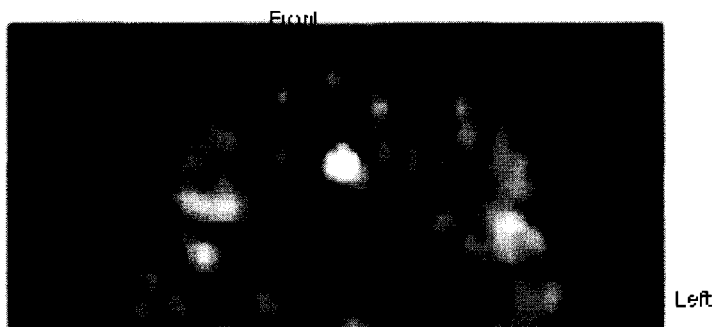

fMRI Perfusion Image (ml/min/mg tissue)
Heavy Cocaine Abuser
MUSC Picker EPI 1.5 Tesla Scarner

At this point, arterial spin-labelling has some limitations in that it takes several minutes to acquire information on a single slice of interest. Therefore, one must have a specific brain region that one is interested in examining. Also, as it currently takes several minutes to acquire a single slice, it would be tedious obtaining enough images on this slice within a single session to make a statistical statement on a given subject. Thus, this does not appear to be a useful mapping technique within individuals unless scanner acquisition time is shortened.

Diffusion-Weighted Imaging

Diffusion-weighted imaging is very sensitive to the random movement of 1H in water molecules (brownian movement),[26] The amount of water diffusion for a given pixel can be calculated and is called the apparent diffusion coefficient (ADC). Areas with low ADC values (ie. low diffusion) appear more intense. ADC values are direction sensitive. For instance, if images are taken perpendicular to myelin fiber tracts like the optic chiasm, arcuate fasciculus, or corpus callosum, ADC values will be lower than if the images are taken along the length of these fibers. This is thought to be because there is little diffusion across myelin sheaths.[27] Thus, ADC direction sensitivity permits detection of myelination and may allow researchers to understand in greater detail myelin development in infants. On the other hand, this direction sensitivity hampers the study of diffusion in other processes as ADC values differ, depending on the imaging plane (axial, coronal, or sagittal). There are now ways to calculate average ADC values incorporating all planes for each pixel, removing "artifacts" due to the direction of acquisition. Removing the directional diffusion sensitivity has been helpful in studying stroke.

While it is currently unclear how diffusion-weighted imaging will be useful in studying psychiatric disorders, it hold great promise for changing the clinical management of acute ischemic stroke by potentially refining the criteria for patients most likely to b The study of emotion is hampered by its slow and variable onset and its inability to be quickly reversed.[13,14] enefit from thrombolytic therapy. [28-30]
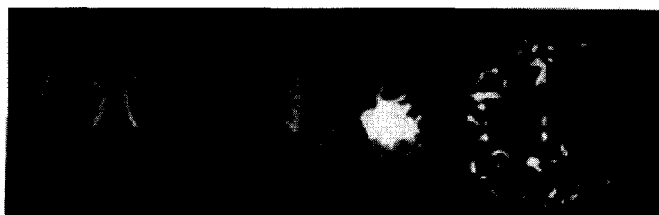
In the early post-stroke period, ADC values are heterogeneous in the ischemic region and the presence of areas that have only mildly diminished ADC values may indicate salvageable tissue. In this way, diffusion-weighted imaging may help reveal the likelihood of whether thrombolytic therapy may be useful. In addition, while ADC values continue to decrease over the first week post stroke, old strokes have ADC values that are normal or high. This allows distinction of old from new strokes which are often difficult to characterize with structural imaging and clinical exam alone when old and new strokes appear in the same brain region.

CONCLUSIONS

While there are currently no clinical indications for ordering any of these fMRI techniques, they hold considerable promise for unraveling the neurocircuitry and metabolic pathways of psychiatric disorders in the immediate future and in helping in psychiatric diagnosis and treatment planning down the road. Their first widespread clinical use will likely be in neurosurgical planning and perhaps, the management of acute stroke. As these techniques are generally noninvasive, can be performed on upgraded conventional MRI scanners, and are less expensive than acquiring a cyclotron to perform PET, they have a greater chance of becoming available in most hospitals over the next several years. Once fMRI techniques are perfected, they will likely offer considerable advantage over PET and SPECT scanning in all aspects except receptor-ligand studies which cannot currently be performed with fMRI. We hope that this article provides you with the necessary background to understand the current fMRI techniques and to more easily evaluate articles in this rapidly developing field.

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