# Principles and Applications of Functional Brain Imaging

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## Introduction

Functional imaging techniques are well established in both the nuclear medicine and positron emission tomography (PET) communities. While the informational content of these images can be high, limited availability (PET) and low spatial resolution limit their clinical applications. MR imaging can provide functional as well as anatomic information, in part because of the large number of intrinsic parameters that effect MR images contrast. These include proton density (r), relaxation times, T1 and T2, chemical shift, flow, magnetic susceptibility, diffusion, and others. While not functions of tissue per se, each of these parameters can be exploited to assess various functional activities of the body. This is best illustrated by MR angiography, where both time-of-flight and phase contrast methods depend on velocity (cardiovascular function) to provide contrast and thereby to represent vascular anatomy. Similarly, it can be argued that a positive Gd-DTPA CNS exam reflects abnormal function (integrity) of the blood brain barrier.

Synergistic developments in NRM instrumentation, image acquisition strategies and MR contrast agents have increased the availability of techniques for and approaches to functional MR imaging. Refinements in fast MR imaging techniques, e.g. fast gradient echo and echo planar imaging (EPI), have been especially important in this regard, given their success in reducing motion artifacts and their ability to increase the number of studies performed per patient examination (1). Of particular interest, real time imaging methods essentially freeze action, and thereby allow physiological motion, such as cardiac systole, to be evaluated. Most recently, these techniques have been used to obtain accurate assessments of tissue and organ hemodynamics, e.g. blood volume and flow, by use of both exogenous and endogenous contrast strategies. While the term 'fMRI' commonly refers to mapping of signal changes with some type of task paradigm, we use the term in its fuller sense, including imaging water mobility (via diffusion-weighted imaging, DWI), permeability of the blood brain barrier, and maps of relative cerebral blood flow and volume.

## Principles

The assessment of cerebral hemodynamics has been demonstrated using several MR approaches including: 1) serial imaging during the first pass transit of MR contrast agents; 2) the changes in oxy- deoxyhemoglobin concentration during neuronal activation; and 3) novel MR pulse

sequences to directly measure perfusion (2-5). The first two rely on magnetic susceptibility effects and require T2-weighted pulse sequences.

Susceptibility-based perfusion imaging uses EPI to visualize the rapid passage of a bolus of contrast agent. All MR agents have both T1 and T2 relaxation effects. While routine clinical use of Gd-based agents depends on their T1 relaxing effects (causing increased signal intensity on T1-weighted images), perfusion sensitive imaging uses the T2 effects, which dominate at higher concentrations. The passage of contrast agent causes a transient signal loss (T2 effects) which is proportional to the blood volume in each voxel. Thus, this approach is sensitive to tissue microvasculature. Relative cerebral blood volume maps can be generated by applying susceptibility physics and standard tracer kinetic principles. As with other intravascular tracer techniques, more than relative cerebral blood volume (rCBV) can be computed from the signal intensity vs. time curve. Contrast agent arrival time, time to peak change, and transit time can be calculated on a voxel-by-voxel basis. Over the past five years perfusion imaging* have demonstrated utility in various CNS applications including tumor detection and/characterization and assessment of acute stroke. (* Strictly specking, "perfusion imaging" is a misnomer, since contrast injection studies typically do not measure flow directly, but rather other hemodynamic parameters. Efforts are in progress to obtain true cerebral blood flow measurements using MR contrast agents.)

Equally exaction is the non contrast agent approach that demonstrates real time changes in MR signal in response to various neurological task activations. This blood oxygen level dependent contrast (BOLD) approach exploits the decrease in A-V oxygenation difference that accompanies regional increase in blood flow. This method utilizes changes in the levels of deoxyhemoglobin (the body's own contrast agent) to provide endogenous MR contrast (6). This increase in blood flow simultaneous with a reduction indeoxyhemoglobin concentration produces regional signal enhancement in the area of activation. In addition to cognitive neuroscience research, this approach is being used in pre-surgical planning in patients with CNS lesions.

Diffusion is the random, thermal motion of molecules (also known as brownian motion). The quantity D is a measure of diffusion, and is typically expressed in units of an area per unit time. The D for pure water at room temperature is about $2 \times 10^{-5}$ $cm^2/sec$. MR imaging can be made sensitive to intravoxel dephasing, and therefore diffusion, by the addition of gradient pulses to a standard spin-echo sequence. MRI has provided one of the first non-invasive *in vivo* methods for measuring a diffusion coefficient, which is known as the apparent diffusion coefficient (ADC). While diffusion and brain function may not appear to be closely linked, studies have demonstrated that the apparent diffusion coefficient changes in disease states.

### Brain Tumors

Diagnosis of CNS tumors has been greatly aided by the anatomic and contrast resolution of MR imaging. Characterization is more difficult, particularly because the T1 and T2 relaxation times of neoplastic tissue are not specific indicators of malignancy. PET studies of tumor metabolism using

$^{18}$FDG have shown the degree of glucose utilization to be a predictor of tumor prognosis. However, metabolism may not be the only or the best method to evaluate cancer. In order to continue growth, a tumor must induce new capillary vessels once it reaches a few millimeters in size; this is termed angiogenesis. Additional investigation has demonstrated that tumor angiogenesis is an independent predictor of relapse-free survival in primary breast carcinoma. Suseptibility-based MR perfusion imaging, with its sensitivity to the capillary bed, is therefore well suited for evaluating tumor angiogenesis *in vivo*.

The susceptibility contrast agent MR approach has provided several important features in patients with neoplastic discase (7). First, rCBV maps appear closely correlated to tumor grade, with low grade lesions showing low CBV (low MR signal), and more aggressive lesions demonstrating elevations of rCBV (increased MR signal). This is in accordance with the results of previous angiographic and PET studies, which found increased rCBV when studying high grade primary brain tumors. Second, in some lesions, significant regional heterogeneity of rCBV was apparent. High grade lesions in particular often showed considerable variation across the tumor. In lower grade lesions, focal high rCBV regions were often not apparent on conventional pre or post contrast T1- and T2-weighted images. These cases demonstrate that functional rCBV imaging may have an important role in guiding tumor biopsy. Despite the excellent correlation, interesting differences were apparent across the brain between these two modalities. Notably, MR rCBV images show relative insensitivity to large vessels such as the middle cerebral artery and central veins. This reflects the increased sensitivity of the MR approach to the microvasculature.

A third finding was quite surprising. In the majority of our tumor cases studied with both MR rCBV and PET $^{18}$FDG, there was good to excellent congruence between these maps (Figure 1). With both imaging modalities a focal "hot spot" is seen, showing congruence between the region of increased glucose uptake and the region of increased microvascular volume. This origin of this relationship is currently being explored. Based on our results and previous studies, we postulate a link between tumor metabolism, tumor angiogenesis and microvascular density, and tumor grade. Finally, MR rCBV maps were able to differentiate recurrent tumor from radiation necrosis (Figure 2).

Based on our experience (>500 patients) we concluded that MRI blood volume mapping will be useful in the classification process of gliomas, in selecting optimal biopsy sites, in separating radiation necrosis from areas of tumor regrowth, and in the planning of radiotherapy. Moreover, the finding that glucose uptake and capillary blood volume are closely correlated from tumor to tumor and between regions within the same tumor may assist our understanding of the mechanisms regulating tumor angiogenesis and its link with tumor energy demands. The use of high speed echo planar imaging techniques, which provide the necessary temporal resolution, are essential for these studies of the entire brain.

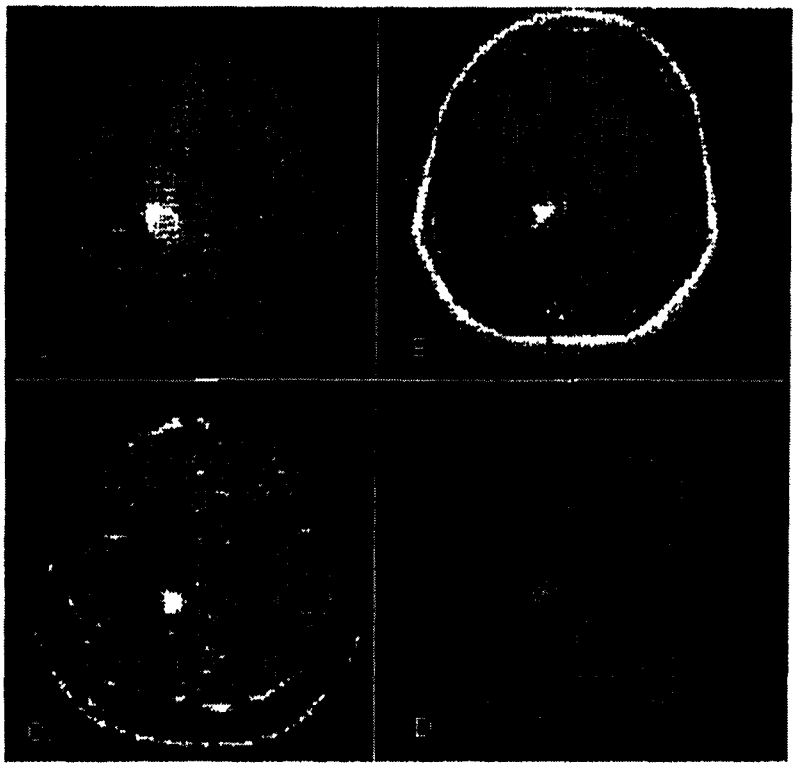

Figure 1. 47 y.o. male with known low grade oligodendroglioma status post treatment, now with new enhancement on routine MRI. A. T2-weighted image. B. Post-Gd T1-weighted image. C. rCBV map showing high rCBV focus. D. 18FDG PET showing increased metabolic uptake. Biopsy showed anaplastic astrocytoma.

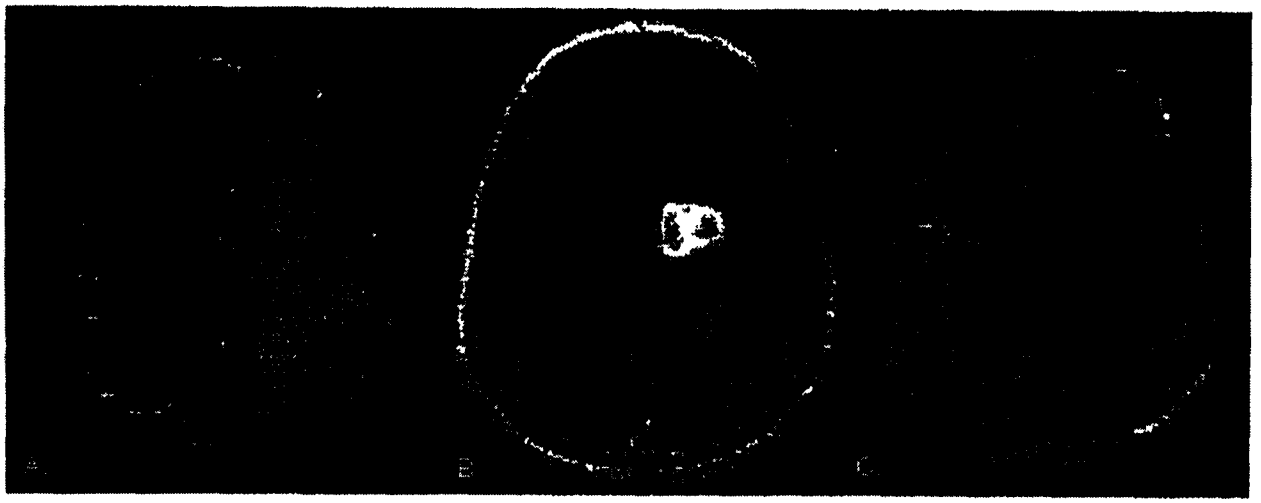

Figure 2. 42 y.o male with known grade 3/4 gliomas status post radiation therapy, now with enlarging mass and new enhancement. A. T2-weighted images. B. Post Gd T1-weighted image. C. rCBV map showing no increased rCBV. Biopsy showed radiation necrosis only, with no evidence of malignancy.

## Pre Surgical Planning

Forty patients with lesions near language and/or sensorimotor areas were studied by both fMRI and intraoperative direct cortical stimulation. Lesions included primary brain tumors, cavernous malformations, cortical heterotopia, and indeterminate pathologic diagnosis. All patients underwent sensorimotor activation studies and/or language activation. Functional MRI was performed using the susceptibility based BOLD contrast technique at 1.5T. Multislice T2*-weighted echo-planar images were obtained using an asymmetric spin-echo pulse sequence during alternating control and activation tasks. Sensorimotor tasks consisted of self-paced repetitive movements of the fingers, toes, or tongue. Language tasks included verb generation, passive reading, and object recognition. All language tasks were performed without overt speaking in order to minimize motion artifacts. Sites of functional activation were identified by statistical analysis of the signal time course on a voxel-by-voxel basis using the Kolmogorov-Smirnov test. The functional maps were coregistered, fused, and volume rendered with high resolution structural MR images. Multiple measurements of relative rCBF were also made by PET using inhaled $^{15}O$-$Co_2$ during rest and performance of the same tasks. Intraoperative primary sensorimotor and language mapping were performed by direct cortical stimulation using a hand-held bipolar stimulator (all cases) or depth electrode (one case) and were documented by photographs.

Volume rendering of the registered functional and strctural images effectively demonstrated the three-dimensional relationships among cortical surface topography, tumor, and sites of functional activation. Each task within each subject activated localized regions in the contralateral precentral and postcentral gyri on both PET and fMRI, concordant with previous reports in normal subjects. Overall, there was good concordance between functional locaalization by fMRI, PET, and direct cortical stimulation. fMRI may eliminate the need for the Wada test for language localization and reduce or eliminate the time at surgery for direct cortical stimulation studies.

## Acute Stroke

While conventional CT and MR are excellent modalities for detecting and characterizing CNS disease in general, they fail to reliably detect acute ischemia or infarction at its earlist stages. Diffusion-weighted MRI (DWI) has been shown to be sensitive to early ischemic changes in brain (8.9) but does not directly detect ischemia itself as does susceptibility-based perfusion imaging (10). DWI has also demonstrated abnormalities in conditions other than ischemia animal models and therefore may lack specificity in humans. Using EPI, a variety of groups have developed and tested DWI (11,12) and perfusion sensitive techniques (13,14) in humans and animals with cerebral ischemia. We have developed a protocol that acquires T1, T2, diffusion, MRA, BBB integrity and perfusion sensitive imaging in 30 minutes (14 minutes of data acquisition) in the setting of acute stroke (15).

Eleven patients were imaged with an average time from onset of symptoms of 6 (range:2-10) hours. The diagnosis of acute cerebral infarction was confirmed in 9 of 11 patients by follow-up clinical and imaging studies; the symptoms of the other two patients resolved quickly and had

negative follow up exams. In the 9 patients with infarct, 8 has normal CT and 7 had normal MR exams in the acute phase; one patient showed subtle loss of the gray-white junction on CA at 3 hours post ictus, and two patients has subtle gyral hyperintensity (at 3 and 7 hours post ictus) on MR imaging. Five patients had intravascular enhancement on post-gdolinium T1-weighted imaging. In 9 patients with infarct, the DWI and perfusion sensitive MR exams demonstrated clear abnormalities in the acute phase that were confirmed by follow-up conventional imaging. Eight of the nine patients with confirmed acute infarct demonstrated markedly reduced flow signal in the appropriate MCA. However, the degree of flow signal reduction did not correlate with the size or location of the infarct.

The DWI and perfusion sensitive MR were consistent with three general categories:

(1) abnormalities of similar size and location on acute and follow-up studies;

(2) initial DWI smaller than perfusion sensitive MR abnormality, with a final infarct size larger than either;

(3) initial DWI smaller than perfusion sensitive MR abnormality, with a final infarct size between that of the DWI and perfusion sensitive MR abnormalities.

Pathophysiologically, the first group may indicate there may not be additional tissue at risk for the current vascular occlusion: collateral flow will limit the infarct size to the lesion already seen on the DWI. The second pattern's initial mismatch may represent a small infarct surrounded by additional tissue at risk; without effective treatment the infarct grows over time to involve even more tissue, perhaps due to excitotoxic, inflammatory, or free radical mechanisms in additional to secondary vascular mechanisms. The third patterns also shows a mismatch, but eventual infarct size smaller than the initial perfusion sensitive MR abnormality. This may represent successful limitation of the infarct size due to recruitment of collateral flow. Both of the patients who exhibited this pattern in our early data were kept hypertensive after their cerebral infarct for the purpose of maintaining collateral flow. The presence of perfusion sensitive MR abnormalities support the work in animal models indicating the DWI alone amy not be sufficient for determining the presence of extent of cerebral ischemia, since there appears to be a threshold effect before tissue becomes abnormal on DWI despite low rCBV. The combination of DWI with perfusion sensitive MR may help identify brain tissue still at risk for infarction in acute stroke patients and thereforee will be more powerful than either of these two techniques used individually. With these tools to investigate the natural history of stroke, understanding of the pathophysiology of cerebral ischemia in humans should increase. This in turn should enable improved rational therapy design.

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