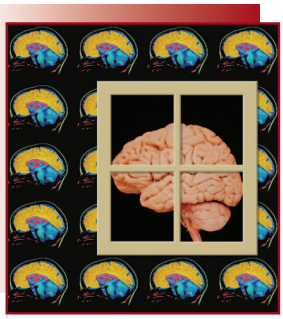

A Brief Introduction to Functional MRI

History and Today's Developments

BY JAMES J. PEKAR

In this issue, *IEEE Engineering in Medicine and Biology Magazine* focuses on modern methods for the analysis of data from functional magnetic resonance imaging (fMRI) studies. Accordingly, the guest editors have seen fit to begin with a brief article on the mechanisms and methods behind fMRI. In this context, it is worth noting that magnetic resonance imaging (MRI), in the first place, rests on a series of unlikely accomplishments: Who might have thought, at the turn of the last century, that the spin of subatomic particles could be detected in bulk matter using radio frequency (RF) energy, or that RF energy, with wavelengths of tens of centimeters, could be used to form exquisite images with submillimeter spatial resolution?

In 1924, Wolfgang Pauli suggested, on theoretical grounds, that particles could have intrinsic angular momentum, or spin. In the 1920s, Otto Stern and I.I. Rabi showed that beams of such particles, traveling in a vacuum through strong magnetic fields, would absorb RF energy in a narrow range of frequencies. Those beam experiments were the first measurements of spin resonance.

In 1946 Felix Bloch and Edward Mills Purcell showed that such spin resonance could be detected among nuclear spins in bulk matter; for this they shared the Nobel Prize in Physics in 1952. This phenomenon, dubbed *nuclear magnetic resonance* (NMR), turned out to be immensely valuable for chemistry because nuclei resonate with exquisite sensitivity to local electromagnetic fields and consequently serve as lucid reporters on their microenvironments.

Applications of NMR to chemistry grew rapidly, as did applications to living systems. In the late 1950s, scientists began applying NMR to isolated cells and excised tissues; by the late 1960s, NMR data were being acquired from intact animals [1]. In the early 1970s, scientists noted that such tissue NMR signals from water's hydrogen nuclei change in disease. A seminal contribution was made in 1973 when Paul Lauterbur [2] showed how NMR signals could be used to form an image, using a spatial gradient of the static magnetic field to yoke frequency to location, by causing the resonance frequency of nuclei to vary linearly with their spatial location. It is worth noting that these images are not diffraction limited in that, unlike, for example, optical or electron microscopy, we can use MRI to resolve features much smaller than the wavelength of the RF energy used. In 2004, Lauterbur shared the Nobel Prize in Physiology or Medicine with Peter Mansfield [3], who laid the foundation for snapshot MRI (image formation from data acquired in a fraction of a second). Richard Ernst introduced another central innovation [4] when, in 1975, he first demonstrated a Fourier rather than projection-based approach to magnetic resonance (MR) image encoding; for this (and other) work, he was awarded the Nobel Prize in Chemistry in 1991.

Development of commercial MR scanners took off in the 1980s, and by 1990, clinical MRI was of primary importance for brain tumors, stroke, and multiple sclerosis. In 1990, Ogawa [5] showed that these MRI water signals can be sensitized to cerebral oxygenation, using deoxyhemoglobin as an endogenous susceptibility contrast agent. Using gradient-echo imaging, a form of MRI image encoding sensitive to local inhomogeneity of the static magnetic field, Ogawa demonstrated (in an animal model) that the appearance of the brain's blood vessels changed with blood oxygenation. Within two years, his and two other groups had published papers using this blood-oxygenation-level-dependent (BOLD) contrast MRI to detect brain activation in humans [6]–[8], and, today, an explosion of studies use this so-called fMRI technique to map human brain function.

Of course, BOLD fMRI does not measure brain function directly. Rather, BOLD fMRI brain activation studies are the latest in a line of approaches, dating from the 19th century, which use brain perfusion as a proxy for brain function. Without making direct measurements of brain function (i.e., without measuring computations performed in neuronal cell bodies, action potentials traveling along axons, or neurotransmitter trafficking at synaptic junctions), these approaches take advantage of the phenomenon that increases in neuronal activity are accompanied by local increases in perfusion. Generally, these approaches map changes in perfusion (or its concomitants) to shed light on regional changes in brain activity. Specifically, BOLD fMRI sensitizes MRI acquisitions to the local decreases in deoxyhemoglobin due to reactive hyperemia [9] accompanying neuronal activation: Following an increase in

 0739-5175/06/$20.00©2006IEEE

neuronal activity, local blood flow increases (the mechanisms responsible for this neurovascular coupling are still being explored). The increase in perfusion, in excess of that needed to support the increased oxygen consumption due to neuronal activation, results in a local decrease in the concentration of deoxyhemoglobin. As deoxyhemoglobin is paramagnetic, a reduction in its concentration results in an increase in the homogeneity of the static magnetic field, which yields an increase in the gradient-echo MRI signal.

Given that BOLD fMRI does not measure brain activity directly but, rather, relies on neurovascular coupling to encode information about brain function into detectible hemodynamic signals, it may be useful to look at how most fMRI studies are designed and performed.

For BOLD fMRI, image data are typically acquired slice-wise using single-shot echo planar imaging (EPI), the snapshot imaging method proposed by Mansfield. A frequency-selective RF pulse is applied in the presence of a static magnetic field gradient to selectively excite nuclear spins in a virtual slice; the slice-select gradient is then turned off, and the signals from these spins are encoded along the dimensions of the slice using rapidly switched magnetic field gradients. Within approximately 50 ms, a dataset is acquired, which, when Fourier transformed, will yield an image of the slice in question. This is rapidly repeated for all the slices (typically around 30–40) in the brain, such that a complete multislice volume is built up within a time of repetition (TR), after which the process is repeated. For a typical TR of 2 s, if 200 volumes are acquired, then we have a volume movie consisting of 200 volumes of the brain (each consisting of 30–40 slices) acquired over 400 s. During these 400 s, a neurobehavioral paradigm is played out in which the research participant is exposed to sensory stimuli or asked to perform some set of mental and motor tasks or some combination of them. So we have a situation where 400 s of temporally structured brain activity (e.g., watching flashing lights every other 30 s, tapping one's fingers every other 20 s, reading words, or solving math problems) are accompanied by the acquisition of a brain volume movie with 2 s temporal resolution (see Figure 1).

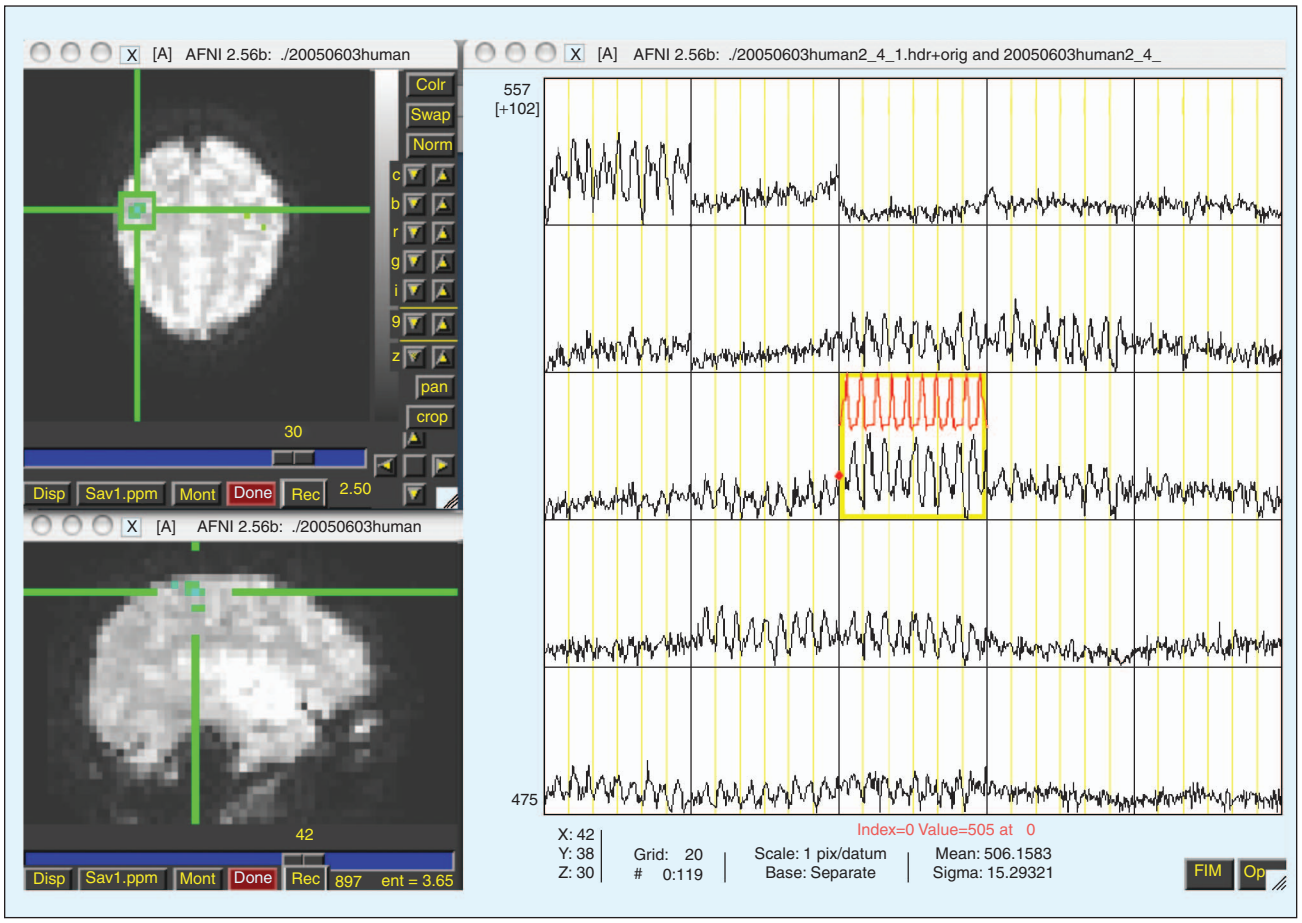

Fig. 1. Sample fMRI data (from an alternating hand-squeezing paradigm). Over a period of 240 s, a participant engaged in a paradigm consisting of alternating 6 s of rest, 6 s of left hand squeezing, 6 s of rest, and 6 s of right hand squeezing. Instructions were provided visually. Data were acquired at 3.0 T using single-shot echo planar imaging of axial slices. Note the relatively poor spatial resolution and contrast (compared to anatomical MRI). The right-hand figure graphs single-voxel raw data from a 5×5 grid of voxels in one axial slice. Note how the paradigm-related signal changes can be easily seen by the naked eye, even though no preprocessing has been performed on these data. The red curve shows the ideal time course (convolution of paradigm timing with assumed hemodynamic impulse response function) used to calculate the activation map shown overlaid in color. Data acquired at the F.M. Kirby Research Center for Functional Brain Imaging (http://mri.kennedykrieger.org); the figure is a screen shot from the AFNI program (http://afni.nimh.nih.gov).