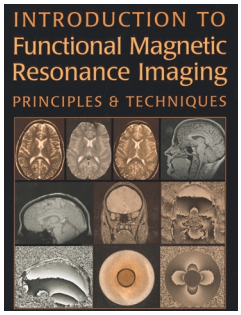
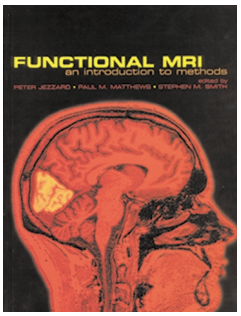
Functional MRI for beginners



An Introduction to Functional Magnetic Resonance Imaging: Principles and Techniques

by Richard B. Buxton
Cambridge University Press, 2002. $140
hardcover, pp 536
ISBN 0521581133



Functional Magnetic Resonance Imaging: An Introduction to Methods

by Peter Jezzard, Paul M. Matthews & Stephen M. Smith (Editors)
Oxford University Press, 2001. $195
hardcover, pp 408
ISBN 0192630717

Reviewed by Michael S. Beauchamp

In the ten years since it was first described, functional magnetic resonance imaging (fMRI) has made the leap from an esoteric technique to a staple of neuroscience research. Newspaper science sections are full of fMRI studies of lie detection, chocolate eating and romantic love. The ability to measure brain function (instead of the static anatomy imaged with traditional MRI) gives fMRI its name and is the key scientific reason for its growing popularity, but more pragmatic factors are also important. Chief among these is the availability of more than 13,000 clinical MR scanners, primarily located in North America, Europe and Asia. Of the 3,700 scanners in the United States, 58% are of sufficiently high field strength (1.5 Tesla) to allow imaging of the changes in cerebral vasculature related to neural activity that are the physiological basis for fMRI.

The core of an MR scanner consists of coils of superconducting wire that are continuously immersed in a bath of liquid helium to allow them to carry enormous volumes of electrical current without resistance, generating a magnetic field that serves to align hydrogen nuclei in the body's water molecules. Although it is thousands of times stronger than the Earth's magnetic field, there are no known health risks directly associated with the magnetic field in an MR scanner. A very rare indirect risk is that these large fields are always present (even when images are not being collected). This can lead to accidents in which ferrous metal objects are attracted with great force into the bore of the magnet. Hospitals repay the initial costs of the device (roughly $1.5 million) by billing patients and their insurers $1,000 or more for a clinical scan, usually performed during normal working hours. Since the discovery of fMRI, neuroscientists at some centers have negotiated with radiology departments to use the always-on scanners at greatly reduced rates in off-hours. On nights and weekends, investigators lugging homemade stimulus delivery devices invade the formerly empty MR centers, along with normal volunteers (often graduate students) willing to spend hours inside the claustrophobic and noisy magnet in order to obtain precious data.

Many of the first neuroscience discoveries made using fMRI were made by visual neuroscientists, who adapted stimulus protocols used for single-unit recordings from non-human primates to study human cortex with fMRI. Those with access to a scanner equipped their laboratories with a few UNIX workstations to analyze the MR data, and steered their research program headlong into fMRI. The explosive growth continued as psychologists and cognitive neuroscientists discovered fMRI. For scientist frustrated by the existence of many theories about brain function, but relatively few ways to choose among them, fMRI promised a new rigor and connection between psychological theory and brain function. The previous state of the art in functional brain imaging, positron emission tomography (PET), offers spatial and temporal resolution that is an order of magnitude poorer than that of fMRI. In addition, there are relatively few PET scanners because of their limited clinical utility and the need for nearby cyclotrons to generate the short-lived injected radioactive tracers used to measure brain activity. Whereas technical, geographic and bureaucratic obstacles often prevented neuroscientists from testing their theories using PET, the wide availability of MR scanners has democratized imaging.

The rapid growth of the field has created a demand for fMRI pedagogy, including two recent books that aim to provide an introduction to fMRI. *Functional Magnetic Resonance Imaging: An Introduction to Methods*, edited by Peter Jezzard, Paul M. Matthews and Stephen M. Smith, contains chapters by 31 experts. *An Introduction to Functional Magnetic Resonance Imaging: Principles and Techniques,* by Richard B. Buxton, is a single-author monograph. Both books begin with the poorly understood sequence of events that links neuronal activity to changes in the MR signal. Synaptic activity, because it is metabolically more demanding than action potential production, is thought to drive much of the fMRI response. Neurons and glial cells, taxed by ion flows and transmitter release and re-uptake, signal the vasculature to deliver more blood, leading to increases in cerebral blood flow and cerebral blood volume. This increase can be very focal, as demonstrated by the ability of fMRI to visualize ocular dominance columns (structures about 1 mm in size). Most fMRI studies use BOLD (blood oxygen level–dependent) imaging, which takes advantage of several serendipitous facts of nature. Whereas blood flow and blood volume in active cortex increase dramatically in comparison with resting cortex, the consumption of oxygen does not rise nearly as much. This means that in the vicinity of active cortex, blood is actually more oxygenated, resulting in a decrease in the amount of deoxyhemoglobin and an increase in oxyhemoglobin. Whereas deoxyhemoglobin is paramagnetic, decreasing the MR signal, oxyhemoglobin is diamagnetic and has little effect on the

Michael S. Beauchamp is in the Laboratory of Brain and Cognition, National Institute of Mental Health, Building 10 Room 4C104, Bethesda, Maryland 20892-1366, USA.
e-mail: mbeauchamp@nih.gov

MR signal. Therefore, the MR signal rises and falls with the amount of neural activity (although the vascular response to neural activity is very slow, resulting in a lag of several seconds for the MR signal to begin rising after neural activity commences, and 10–15 seconds for it to fall back to baseline after neural activity ceases.)

Buxton, an MR physicist at University of California, San Diego, spends most of his book elaborating on the biophysics of MRI, especially the physical principles linking changes in blood flow to changes in the MR signal. Scanners can be thought of as large computers driven by pulse sequence programs that first create the MR signal and then collect it. This flexibility means that there are a vast number of possible pulse sequences that can measure different physical properties of the tissue being imaged (as opposed to PET imaging, where the signal comes from not-easily-manipulable radioactive decay and is read out by detectors that operate in only a few modes). Different pulse sequences have different applications. For instance, the echo-planar imaging (EPI) pulse sequences usually used for fMRI are very loud (because the rapidly changing magnetic field causes parts of the scanner to vibrate), making it difficult to conduct sleep studies. Buxton clearly explains burst imaging pulse sequences that allow relatively quiet data acquisition. Pulse sequences used for BOLD fMRI provide results only as percentage change in arbitrary MR units. Buxton has been a leader in the development of arterial spin labeling pulse sequences, which provide quantitative estimates of blood flow that were previously obtainable only with radioactive tracer techniques such as PET. Spin labeling techniques may also have some advantages over BOLD techniques. (Because they measure arterial blood rather than venous blood, they may be more spatially specific.) However, the vast majority of published papers (all 21 of the fMRI studies published in the past year in *Nature Neuroscience*) use some form of BOLD-EPI because it is more sensitive than the alternatives—according to Buxton, eight times more sensitive than quiet-burst imaging sequences. When searching for slight changes in brain activity, even a small difference in sensitivity can mean the difference between experimental success and failure. This explains the current rush to replace the 1.5 Tesla clinical scanners initially used for fMRI with 3 Tesla scanners that promise greater sensitivity. After spending millions of dollars for a new high-field scanner, neuroscientists are reluctant to use a less-sensitive pulse sequence, hence the *de facto* standardization on BOLD-EPI.

One area that has seen tremendous innovation is the field of experimental design and its conjoined twin, data analysis, two subjects that receive only a cursory mention from Buxton but receive a thorough treatment in Jezzard's book. In traditional block-design neuroimaging experiments, stimuli are grouped together in blocks, which makes studies of unexpected stimuli (among other things) difficult. In event-related designs, stimuli are presented in rapid succession in pseudorandom order, allowing mixtures of novel and repeated stimuli, *post-hoc* sorting by behavioral response (*e.g.* correct or incorrect discriminations) and a host of other interesting manipulations. Randy Buckner and David Donaldson write an excellent chapter on recent advances in experimental design, including the use of combination block and event-related designs. These hybrid designs allow an examination of brain areas that respond to slow state changes (for instance, as the subject changes from a behavioral set of encoding stimuli to a behavioral set of retrieving previously presented stimuli) and to individual stimuli (for instance, as each item is stored or retrieved). Because the hemodynamic response to any single stimulus lasts about 15 seconds, the responses to stimuli presented more rapidly than this will overlap and must be separated. This requires sophisticated statistical techniques more common in signal processing than in biomedical research. Data analysis is probably the most confusing part of fMRI research to the novice, with methods sections that are often either uselessly skimpy ("data was analyzed with package X") or impenetrable ("data was analyzed using the following 15 steps", without rationale). The Jezzard book helps reduce the confusion, with excellent chapters by Stephen Smith showing the effects of common post-processing steps and explaining their use. A more advanced chapter by Keith Worsley covers the ins and outs of various statistical analyses.

It would take a superhuman intellect to write expertly about the vast breadth of fMRI, and Buxton wisely concentrates on the areas he knows best, although this leads to a slanted view of fMRI. For example, he devotes as much space to quantum mechanics as to event-related fMRI, not unreasonable from a physicist's perspective but less useful to a neuroscientist. Both the Jezzard and Buxton books are well written and should find a prominent place in the cubicles of aspiring and established fMRI researchers. It is important that everyone who uses fMRI understand the fundamental physical principles of the method, a strength of the Buxton book. On a day-to-day basis, however, most fMRI researchers think little about physics and spend their time designing experiments and analyzing data, areas Buxton barely touches on. In contrast, Jezzard's book covers the broad range of topics most useful to a neuroscientist, from low-level (principles of MRI in Jezzard's chapter) to high-level (the use of fMRI to determine connections between different brain areas in the chapter by Karl Friston and Christian Büchel). For a comprehensive overview of fMRI that includes applications, readers should also consider a book edited by Peter Bandettini and Chrit Moonen entitled *Functional MRI* (Springer, 1999).

After understanding the methods, readers may want to learn more about how fMRI has been applied to their neuroscience area of interest. *Handbook of Functional Neuroimaging of Cognition* (eds. Roberto Cabeza and Alan Kingstone, MIT Press, 2001) contains chapters by luminaries on the functional neuroimaging of semantic memory, perception, attention and other broad topics. Researchers might also wish to explore the many courses and workshops that have sprung up, some of which provide hands-on time with an MR scanner. Massachusetts General Hospital and the Medical College of Wisconsin have offered short courses in fMRI since 1994, where attendees may ask questions of experts (such as whether the experiments they have dreamed up are reasonable) and may even perform pilot fMRI studies of their own. The fMRI Experience, a meeting that is now in its fourth year, is aimed at introducing postdoctoral fellows and students to this promising field.

As newcomers apply fMRI to more neuroscience disciplines, its use seems certain to grow. The safety and noninvasiveness of fMRI are especially likely to fuel discoveries in fields that require longitudinal studies, such as psychiatric disorders and development. In psychiatric populations, patients can be scanned as their symptoms ebb and flow, giving insight into the neural substrates of disorders and the effects of treatment. In development, longitudinal studies will give an idea of how the brain networks for language, perception and memory found in adults are formed during childhood and adolescence.