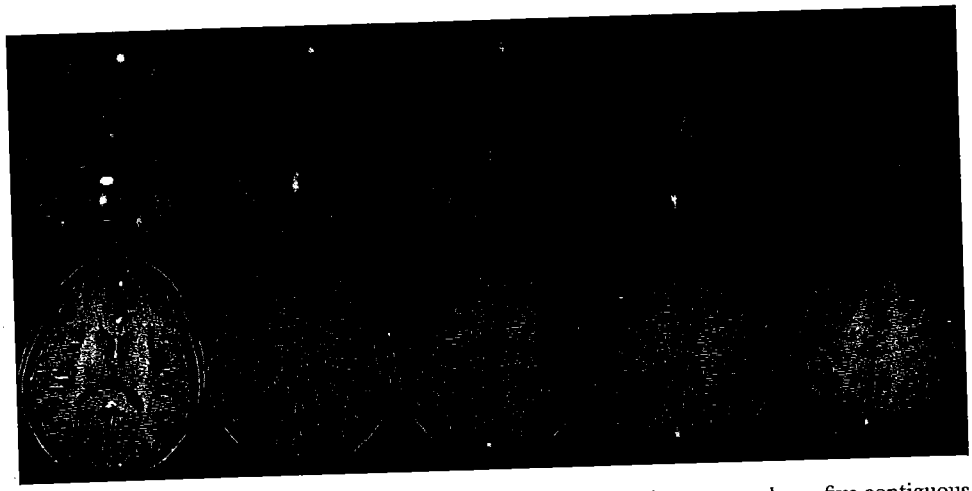

Figure 6.2. Arterial spin labeling images of cerebral blood flow. The top row shows five contiguous 8-mm sections through the brain collected with the QUIPSS II pulse sequence, and the bottom row shows conventional anatomical images for comparison. Note that the CBF is highest in gray matter, as would be expected. Averaging for the ASL images required 3 min of data acquisition. (Data courtesy of E. Wong.)

BLOOD OXYGENATION LEVEL DEPENDENT fMRI

Blood Susceptibility Depends on Deoxyhemoglobin Content

In contrast agent studies the susceptibility of the blood is manipulated by the experimenter. But nature has also provided an intrinsic physiological agent that alters blood susceptibility: deoxyhemoglobin. Fully oxygenated blood has about the same susceptibility as other brain tissues, but deoxyhemoglobin is paramagnetic and changes the susceptibility of the blood. As capillary and venous blood become more deoxygenated, field distortions around the vessels are increased, and the local signal decreases. And in a complementary fashion, if blood oxygenation increases the local MR signal also increases. This BOLD contrast is the basis of most of the fMRI studies of brain activation performed today.

The phenomenon of changes in blood oxygenation producing a measurable effect on MR images was first observed by Ogawa and co-workers (1990a). In this pioneering study they imaged the brain of a mouse breathing different levels of O_2, using a 9-T system with strong gradients to produce a voxel resolution of 65 μm in plane and a slice thickness of 700 μm. They found that when the mouse breathed 100% oxygen, the brain image was rather uniform and featureless. But when the animal breathed only 20% oxygen there was a dramatic change. Many dark lines appeared, outlining the major structures in the brain. The dark lines corresponded to the locations of blood vessels, and when the oxygenation of the blood was increased back to 100%, the lines reversibly disappeared. These investigators also noted that the signal loss around the vessels was greater with increased TE, and that the width of some of the lines grew larger as TE was increased, suggesting that the presence of the deoxygenated blood in the vessels affected the transverse relaxation

outside as well as within the vessels. The observed signal loss was interpreted to be a result of the change in the magnetic susceptibility of the blood vessel compared to its surroundings due to an increase in deoxyhemoglobin.

The fact that deoxyhemoglobin is paramagnetic, and that this creates magnetic field gradients inside and around the red blood cells, was well known (Thulborn et al., 1982), but this was the first demonstration that this phenomenon could produce a measurable effect in an MR image following a physiological manipulation. Subsequent studies in a cat model at 4 T using EPI further demonstrated that changes in brain oxygenation following respiratory challenges could be followed with GRE imaging (Turner et al., 1991).

These animal studies in which blood oxygenation was manipulated by the experimenter suggested that natural physiological processes that alter the oxygenation of blood also might be detectable with MRI. Kwong and co-workers reported a demonstration of mapping activation in the human brain using gradient echo MR imaging during visual stimulation and a simple motor task (Kwong et al., 1992). In these experiments a 1-min stimulus period alternated with a 1-min rest period, and EPI images were collected throughout several periods of stimulus and rest. The GRE signal in the visual cortex increased by about 3–4% during the photic stimulation, and a similar increase was observed in the hand motor area during a hand-squeezing task. This report, and several others published shortly afterward (Bandettini et al., 1992; Frahm et al., 1992; Ogawa et al., 1992), marked the beginning of functional human brain mapping based on the BOLD effect.

At first glance, the observation of a signal increase during activation seems somewhat surprising because it implies that the blood is more oxygenated in areas of focal brain activation. Ogawa et al. (1990a) in their original paper had earlier speculated that the deoxyhemoglobin effect could be used to monitor regional oxygen usage, suggesting that more active regions would appear darker because of increased deoxyhemoglobin resulting from higher oxygen consumption. However, this plausible prediction turned out to be wrong because of the nature of the physiological changes that occur during brain activation. As discussed in Chapter 3, earlier positron emission tomography studies by Fox and co-workers (Fox and Raichle, 1986; Fox et al., 1988) had found a pronounced mismatch between the increases in blood flow and oxygen metabolism during brain activation: CBF increases much more than $CMRO_2$. As a result, the delivery of oxygen to the capillary bed is substantially increased, but less is removed from the blood, so the blood is more oxygenated.

Our picture of the BOLD effect is then as follows. In the normal awake human brain about 40% of the oxygen delivered to the capillary bed in arterial blood is extracted and metabolized. There is thus a substantial amount of deoxyhemoglobin in the venous vessels, and so the MR signal is attenuated from what it would be if there were no deoxyhemoglobin. When the brain is activated, the local flow increases substantially, but oxygen metabolism increases only a small amount. As a result, the oxygen extraction is reduced, and the venous blood is more oxygenated. The fall in deoxyhemoglobin concentration leads to a signal increase. At 1.5 T the increase is typically small (a few percent or less). Nevertheless, with careful statistical

analysis such small changes can be reliably detected. At higher fields, such as 4 T, the signal changes are much larger, in the range of 5–15%.

Mapping Brain Activation with BOLD Signal Changes

Since the discovery that brain activation creates small changes in the local MR signal through the BOLD effect, a number of imaging approaches have been used to measure it. The prototype brain mapping experiment consists of alternating periods of a stimulus task and a control task (Bandettini et al., 1993). For example, in one of the most often repeated experiments, a subject rapidly taps the fingers of one hand against the thumb for a short period (e.g., 30 s) and then rests for the same period. This cycle is repeated several times. Throughout these stimulus/control cycles dynamic echo planar images are collected covering all or part of the brain. For a typical implementation the EPI images are acquired rapidly in a single-shot mode, requiring 100 ms or less for each image acquisition, and the spatial resolution is low compared to conventional MR images (e.g., $3 \times 3 \times 5$ mm). In this multislice dynamic imaging, images of each of the chosen slices are acquired in rapid succession, and after a repetition time TR this set of images is acquired again. The image acquisition is repeated at regular intervals of TR throughout the experiment, while the subject alternates between stimulus and control tasks.

This set of images can be thought of as a four-dimensional data set: three spatial dimensions plus time. For example, Figure 6.3 shows a single slice through the motor area from such a study in which eight cycles of 16 s of finger tapping were alternated with 16 s of rest. With TR = 2 s, 128 images were collected covering the eight cycles. The figure shows a high-resolution anatomical image and one image from the dynamic EPI series. The signal time courses for a block of 3×3 pixels of the dynamic images are also shown. These data are analyzed to identify areas of activation by examining the signal time course for each individual pixel with the goal of identifying pixels in which the signal shows a significant change between the stimulus and control periods. In Figure 6.3 the eight-cycle pattern is clearly evident in a few pixels, but often changes that are not apparent to the eye are nevertheless statistically significant. Because the signal changes due to the BOLD effect are small (only a few percent at 1.5 T), this statistical analysis is a critical aspect of interpreting BOLD data and is described in more detail in Chapter 18. The end result of the statistical analysis is a decision for each voxel of whether or not there was a significantly detectable activation, based on whether a calculated statistic, such as the *t*-statistic or the correlation coefficient, passed a chosen threshold.

An important factor to include in the statistical analysis of BOLD data is that the metabolic activity producing the change in blood oxygenation and the BOLD effect lags behind the stimulus itself. That is, one must assume some model for the hemodynamic response to stimulation, and a typical assumed form is a delayed trapezoid. Figure 6.4 illustrates a correlation analysis of the dynamic BOLD data in Figure 6.3. The hemodynamic response (i.e., the BOLD signal change) is modeled as a trapezoid with 6-s ramps and a delay of 2 s after the start of the stimulus, and the

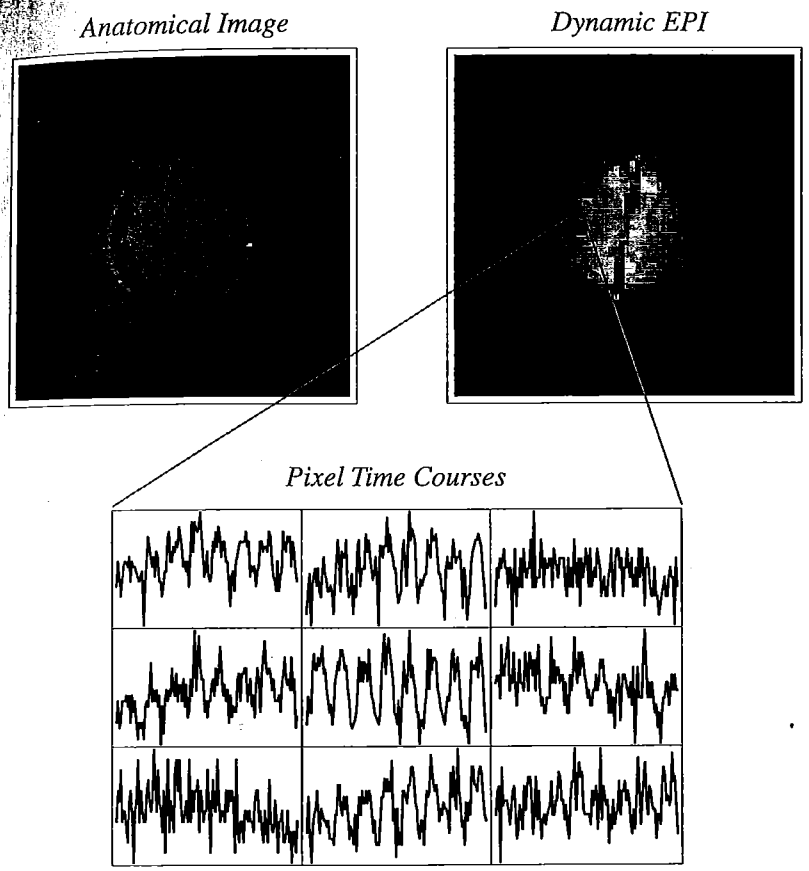

Figure 6.3. BOLD signal changes. On the left is a high-resolution anatomical image (256 × 256 matrix) cutting through the central sulci and the hand motor and sensory areas. On the right is one image from a series of 128 low-resolution dynamic images (64 × 64 matrix) collected every 2 s with EPI. The signal time courses from a 3 × 3 block of pixels is shown at the bottom. During the data acquisition the subject performed eight cycles of a bilateral finger tapping task, with one cycle consisting of 16 s of tapping followed by 16 s of rest. Several pixels show clear patterns of signal variation that correlate with the task. (Data courtesy of L. Frank.)

correlation of this model function with the measured pixel time course is calculated for each pixel. Those pixels that show a correlation coefficient greater than a chosen threshold value are designated as activated pixels and are then displayed in color overlayed on a gray scale image of the underlying anatomy. The gray scale image could be one of the EPI images from the dynamic time series or a higher resolution structural image acquired separately, such as a volume acquisition. Only the pixels that pass the chosen statistical threshold are colored, and for these pixels the color used typically reflects either the value of the statistic (e.g., the correlation coefficient) or a measure of the degree of signal change (e.g., percent signal change) (Bandettini et al., 1993).

This basic paradigm is widely used, but there are many variations. Single-shot EPI is the most commonly used image acquisition technique because it has desir-

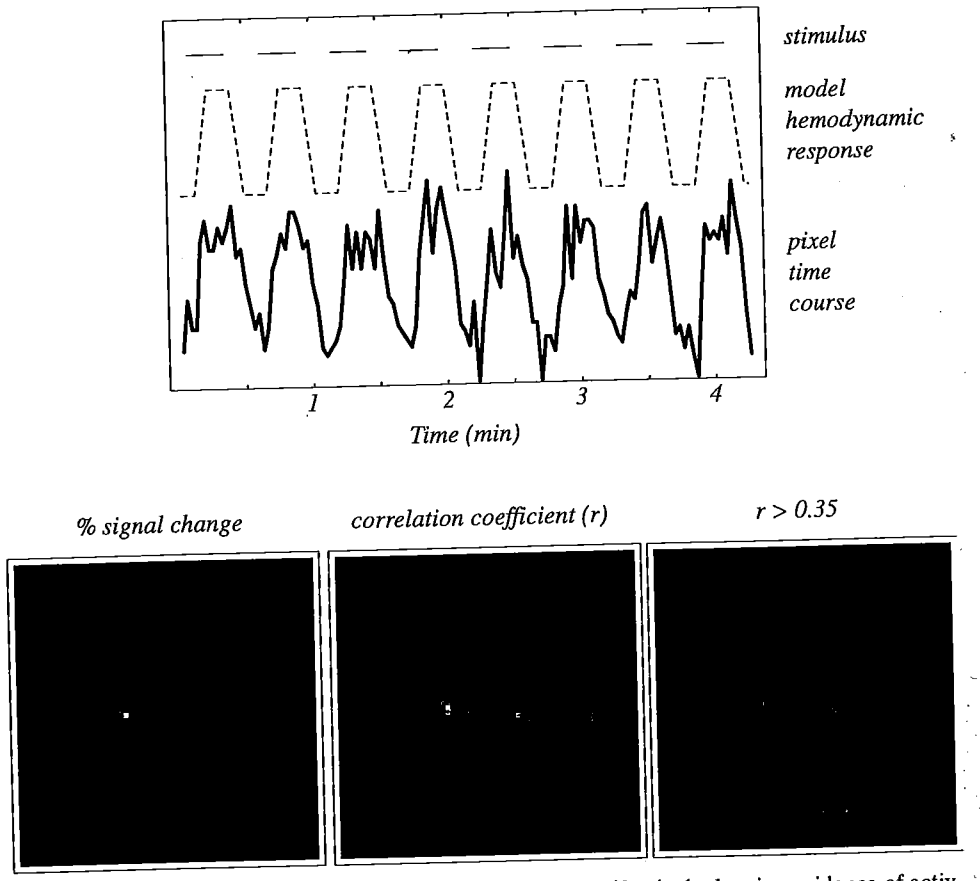

Figure 6.4. Correlation analysis of dynamic EPI data to identify pixels showing evidence of activity. The hemodynamic response is modeled as a trapezoid, with 6-s ramps and a delay of 2 s from the beginning of the stimulus (top). By correlating the model function with a pixel time course, the signal change (left image) and the correlation coefficient r can be calculated (middle image). The pixels passing a threshold of $r > 0.35$ are highlighted on the anatomical image (right image). For this final display the 64×64 calculated image of r was interpolated up to 256×256 to match the high-resolution image.

able features of rapid data acquisition and a high SNR. But multishot EPI and conventional 2D and 3D GRE imaging also are used. Both GRE and SE images exhibit BOLD effects, although the GRE signal is more sensitive because the signal changes produced by activation are larger. However, because the SE signal changes are more likely to reflect microvascular changes, they may give a more precise spatial map of the areas of activation. In addition, asymmetric spin echoes (ASE) are sometimes used because the ASE signal is intermediate between the GRE and SE signals in terms of both overall sensitivity and sensitivity to the microvasculature. The basic block design of stimulus trials is often used, but single-trial (Dale and Buckner, 1997) and continuously varying (Sereno et al., 1995) stimulus paradigms have also been developed.