In fMRI experiments, small but meaningful changes in brain activity lie buried within highly variable measurements. To understand how small fMRI signal changes are, even in the very best cases, consider the two brain images shown in Figure 8.1A and B. Both are $T_2^*$-weighted images taken from the same subject while the subject performed a hand-squeezing task, which is one of the most reliable and robust ways of evoking large BOLD signal changes. One image (Figure 8.1A) was taken while the subject was resting, while the other (Figure 8.1B) was acquired at the maximum of the BOLD hemodynamic response. These images appear nearly identical to the naked eye, despite an intensity change of about 5% in voxels within the primary motor cortex (Figure 8.1C and D). Figure 8.1E shows a plot of these signal changes over time. This discrepancy illustrates the first fundamental problem of fMRI data analysis: the measured BOLD signal change is very small compared with the total intensity of the MR signal.

Small absolute effects are not necessarily difficult to measure. Thermometers can reliably identify temperature changes of small fractions of a degree, while stopwatches can identify timing changes of a few milliseconds. Nor are they unimportant: a one percent increase in body temperature from absolute zero (approximately 3 K, 3°C, or 6°F) could have fatal consequences. However, there is a second fundamental problem for fMRI data analysis: the task-related change in the BOLD signal is very small compared with other sources of spatial and temporal variability across and within images. Figure 8.1D shows a map of the percent signal change between two brain images. The large variability across the image is readily apparent, especially in areas outside the brain or near its edges. Based on a single pair of images alone, it would be impossible to tell which increases in activity are due to the experimental task, and therefore meaningful, and which are due to other non-task-related sources.

In this chapter, we describe the sources of variability in fMRI data that can potentially mask the BOLD effect. Some variability results from temperature fluctuations in the MR scanner or the subject’s body, which can cause artifactual changes in the recorded signal. While a potential problem, thermal variability tends to be highly random and independent of the experimental task. More problematic are physiological effects like head motion or changes in heart rate or respiration, which can be temporally correlated with an experimental
Figure 8.1 Changes in fMRI activity over time. Shown here are two BOLD fMRI images, one taken at time point 45, while the subject was resting (A), and the other taken at time point 50, while the subject was squeezing both hands (B). Even though this slice contains the hand regions of the primary motor cortex, the images appear nearly identical. The numerical difference between these images is shown in (C), and the percent signal change is shown in (D), scaled with white representing a +5% change and black representing a -5% change. The time course of the voxel indicated by the crosshairs is shown in (E), with arrows indicating the time points of (A) and (B). TR = repetition time.

**preprocessing** Computational procedures that are applied to fMRI data following image reconstruction but before statistical analysis. Preprocessing steps are intended to reduce the variability in the data that is not associated with the experimental task, and to prepare the data for statistical testing.

manipulation. For example, the subject may move her head a small distance each time a visual stimulus is presented, due to the alerting or arousing properties of the image. Even if these problems are overcome, there may still be variation in the brain regions that are active during performance of the task due to strategic, practice, or fatigue effects. Given these many sources of variability, it often seems a wonder that we can identify any significant effects at all!

To minimize the effects of unwanted variability in the BOLD signal, nearly all fMRI studies incorporate preprocessing algorithms that compensate for specific sources of variability (e.g., head motion). Preprocessing steps can be considered separately from other aspects of data analysis because they are generally applied to all fMRI data in a similar manner, independent of the particular
experimental design. It is important to understand the causes of noise in fMRI data, along with the potential strategies for reducing that noise, so that fMRI researchers can improve the quality of their data and the validity of the inferences they draw from their results.

**Understanding Signal and Noise**

Consider the following analogy. You are at a party and a friend speaks to you. While straining to hear your friend, you also hear many other sounds, such as other conversations, loud music, or the hum of the air conditioner. What you understand depends not just on the loudness of your friend’s voice, but also on the loudness and character of these other sounds. In this analogy, we can refer to your companion’s speech as the signal and the other sounds that interfere with your ability to hear him as noise. Note that what constitutes signal or noise depends on your current interest. If you wanted to eavesdrop on an adjacent conversation, you may stop listening to your friend. The new conversation would become the signal, and your friend’s words would become noise. However, some sounds, like an air conditioner’s hum, are unlikely to ever become signals.

We can use this analogy to think about fMRI. When we present a stimulus, we hope to measure a response in the brain, just as you expected to hear your companion’s speech. However, in both cases the signal we hope to detect is mixed with other irrelevant sources of variability. We can improve our ability to detect the signal by increasing its amplitude or by decreasing the noise, that is, by increasing the signal-to-noise ratio (SNR). In fMRI studies, the definition of the signal also depends on our interests, as will be discussed in the next section. And, just like in the party environment, noise can come from multiple sources, each with different spatial and temporal properties. For these reasons, terms like signal-to-noise ratio can have different meanings in different contexts. We will begin by carefully defining important terms to minimize such confusion (Box 8.1).

**Signal and noise defined**

Recall that in an fMRI experiment, only one physical quantity is measured: the magnitude of the current in a detector coil. Thus far we have referred to this quantity as the MR signal. This quantity reflects both the change in net magnetization caused by the excitation pulse (signal) and fluctuations caused by thermal energy in the sample and the imaging hardware (noise). Because thermal noise tends to be evenly distributed throughout the image, MR physicists and engineers quantify a raw signal-to-noise ratio (raw SNR) by dividing the intensity of the image in a region that contains the object being imaged (the signal) by the intensity of the image in a region that is outside of the sample (the noise). Raw SNR is used to evaluate the performance of the scanner hardware, and institutions compare such measures of SNR when deciding which MRI scanner to purchase and when monitoring the quality of a MRI scanner over time. Engineers strive to maximize raw SNR by using more efficient detector coils and pulse sequences, and by shielding the scanner from outside interference.

While raw SNR is useful for evaluating scanner quality, other measures are more important for MRI and fMRI. Since we want to create maps of brain anatomy or function, we need to be able to characterize differences in MR signal within different regions of the brain, and not just between the inside and outside of the brain. For this purpose, we introduce a new measure, the con-
The remainder of this book focuses on the design, analysis, and interpretation of BOLD fMRI experiments, along with the relation of fMRI to other neuroscience techniques. It is therefore necessary to introduce key concepts that recur throughout the following chapters.

**Data Acquisition**

Functional and structural MRI differ in more than just contrast sensitivity. The goal of structural MRI is to distinguish different types of tissue. Each structural image collected provides a snapshot of the underlying tissue, so a single image may be sufficient for mapping brain structure if contrast-to-noise is sufficiently high. Functional MRI has a very different goal: to relate changes in brain physiology over time to an experimental manipulation. A single functional image provides no information about brain activity. Only by examining changes across images over time can we infer that our experimental manipulation has an effect. For this reason, fMRI data are collected as a time series that can then be examined for changes associated with the experimental task, such as voxels that increased (or decreased) their activation following the presentation of a stimulus. Unlike structural imaging, which attempts to minimize noise within an image, functional imaging benefits from minimizing noise across successive images. Functional MRI analyses attempt to detect small task-related changes in BOLD signal while ignoring signal fluctuations due to other factors.

Functional MRI data are generally organized in a hierarchical fashion (Figure 1). It is common in fMRI studies to run 12–20 subjects (sometimes called participants) in an experiment, with complex cognitive tasks running more subjects and simpler perceptual tasks running fewer. The number of subjects depends upon the power of the experimental design and the size of the expected BOLD effect. Usually each subject participates in a single experimental session lasting 1 to 2 hours, but some experiments, such as those testing memory or drug effects, may require multiple sessions separated by days or weeks. Each session includes collection of anatomical images and one or more runs of functional images. Depending on the experiment, each run may last from a few minutes to a few tens of minutes. Breaking the session into runs can minimize subjects’ fatigue, improve subjects’ compliance with task instructions, and provide opportunities to identify and correct problems.

Within each run, the functional data are acquired as a time series of volumes. In an experiment with a 1-second TR, there might be 600 volumes acquired during a 10-minute run and several times that number for the entire experiment. Note that the overall MR signal is elevated in the first few volumes in each run, because the net magnetization has not yet reached a steady state (Figure 2). Therefore, the first few volumes are often excluded from further analysis. Each volume comprises a variable number of slices, ranging from 1 to 4 in an experiment targeting a particular region, to 25 or more in a study designed to cover the entire brain. Each slice is acquired at a different point in time within the TR, but all data within the slice are effectively acquired at the same time. Slices contain thousands of voxels that together form an image of the brain. Due to the Fourier approaches used for reconstructing MR data, slices usually consist of a 2\(^n\)-by-2\(^n\) matrix of voxels, such as 64 \(\times\) 64 or 128 \(\times\) 128. Data for an fMRI experiment constitute a four-dimensional matrix: \(x\) by \(y\) by slice (\(z\)) by time point (e.g., 64 \(\times\) 64 \(\times\) 25 \(\times\) 1200).

**Figure 1** How fMRI data are organized.
events are sufficiently close together, special analysis procedures are required to separate their hemodynamic responses. There are also mixed designs that combine features from both types. The goal of some experiments is detection, or the determination of which brain regions are active during a task. In general, blocked designs have high detection power. Another goal is estimation, knowing how activation within brain regions changes over time. Event-related designs, especially those that use fast stimulus rates, have high estimation power. Issues related to experimental design are discussed in detail in Chapter 9.

With regard to the analysis of fMRI experiments, the key division is between voxelwise analysis and anatomical region-of-interest (ROI) analysis. In a voxelwise analysis, statistical tests are conducted on each voxel to evaluate its significance relative to the experimental hypothesis. Most fMRI studies use voxelwise approaches, and a number of software packages have been created to facilitate such analyses. In contrast, ROI analyses partition the brain into a smaller set of discrete regions, which are then individually analyzed for significance. ROI analyses can answer questions about the function of particular brain regions at a potential cost of spatial specificity. The core concepts of fMRI data analysis are introduced in Chapter 10.

time series A large number of fMRI images collected at different points in time.

subject A participant in a research study. Some journals and scientific societies prefer the term “participant,” to emphasize the voluntary nature of research.

session A single visit to the scanner by a subject. For fMRI studies, each session usually includes both structural and functional scans.

run An uninterrupted presentation of an experimental task, usually lasting 5 to 10 minutes for fMRI studies. It also refers to the set of functional images collected during that task presentation.

volume A single image of the brain, itself consisting of multiple slices and voxels.

slice A single slab of an imaging volume. The thickness of the slice is defined by the strength of the gradient and the bandwidth of the electromagnetic pulse used to select it.

voxel A three-dimensional volume element.

blocked design The separation of experimental conditions into distinct blocks, so that each condition is presented for an extended period of time.

event-related design The presentation of discrete, short-duration events whose timing and order may be randomized.

trial A single instance of the experimental manipulation.

mixed design A design that contains features of both blocked and event-related approaches.

detection Determination of whether activation of a given voxel changes in response to the experimental manipulation.

estimation Measurement of the pattern of change over time within an active voxel in response to the experimental manipulation.

voxelwise analysis The evaluation of statistical tests at the level of individual voxels.

region-of-interest (ROI) analysis Evaluations of hypotheses about the functional properties of brain regions (i.e., aggregated over a pre-determined set of voxels), often chosen to reflect a priori anatomical distinctions within the brain.

Experimental Design and Analysis

There are two basic types of experimental designs for fMRI: blocked designs and event-related designs. A blocked design presents two or more conditions in an alternating pattern (see the work of Kwong and colleagues described in the previous chapter). Most early fMRI studies used blocked designs. Blocks are typically about 10 to 30 s in duration, and there may be many alternations between different block types in a single run. An event-related design presents stimuli as individual events, or trials. The study by Blamire and colleagues in 1992 was the first to use an event-related design. If the interval between stimuli is sufficiently long (i.e., greater than about 10 s), the hemodynamic response decays to baseline after each stimulus. But, if.

Figure 2. MR signal is elevated early in runs, before longitudinal magnetization reaches a steady state. Shown is a sample time course of activation in a single voxel for the first 20 images in a single run. Because of this increased activation, fMRI researchers often discard the first few images in a run, before they are even saved to disk. Note that although the steady-state activation looks very flat at this scale, there is about a 4% variation across time points, much greater than the typical BOLD response.
contrast-to-noise ratio (CNR). The magnitude of the intensity difference between different quantities divided by the variability in their measurements.

contrast (1) The intensity difference between different quantities being measured by an imaging system. It also can refer to the physical quantity being measured (e.g., T₁ contrast). (2) A statistical comparison of the activation evoked by two (or more) experimental conditions, in order to test a research hypothesis.

functional signal-to-noise ratio (functional SNR) The ratio between the intensity of a signal associated with changes in brain function and the variability in the data due to all sources of noise. Functional SNR is sometimes called dynamic CNR or functional CNR.

effect size The numerical difference between means divided by the standard deviation.

to contrast-to-noise ratio (CNR). Two properties of CNR are important to understand. First, CNR is always relative to some comparison within an image. As introduced in Chapter 1, the contrast of an MRI image refers to the physical property to which it is sensitive. An image sensitive to T₁ contrast will be bright for voxels with short T₁ values (like white matter) and dark for voxels with long T₁ values (like gray matter or cerebrospinal fluid). Thus, T₁-weighted pulse sequences have a very good ability to distinguish between gray and white matter (high CNR), but only a limited ability to distinguish between cerebrospinal fluid and air (low CNR). Second, CNR depends on the absolute difference in intensity divided by the shared variability. For example, for high CNR between gray and white matter not only must the mean voxel intensity be much higher for one tissue type (e.g., white matter for T₁ images), but also the signal should be relatively constant within each tissue type (see Figure 1.5 for examples).

For most fMRI experiments, however, CNR is unimportant. Typical T₂*-weighted images have intrinsically low contrast (see Figure 8.1A and B), making it hard to identify boundaries between different types of tissue. Instead, the important quantity for fMRI studies is functional signal-to-noise ratio (functional SNR). Some authors refer to this quantity as dynamic CNR or functional CNR. Here, we use the term “signal” to describe the difference in BOLD activation between two states of the brain caused by an experimental manipulation. Likewise, the term “noise” refers to the variability in those states over time. The concept of functional SNR is closely related to that of effect size in statistics, which refers to the difference between two conditions in units of standard deviation.

In summary, just as CNR reflects how easily we can see differences between tissues, functional SNR reflects how easily we can see differences between experimental conditions. For the remainder of this book, we will focus our discussion on the ability of fMRI experiments to detect meaningful changes in brain activity. We will use “SNR” to denote functional SNR, and “raw SNR” to describe the signal and noise directly measured by the detector coil. We will use “CNR” to refer to the contrast sensitivity of anatomical images.

Functional SNR

The functional SNR measured in an fMRI experiment depends on the amplitude of the task-related BOLD signal compared with non-task-related variability. As shown in Figure 8.2, a simple motor or visual task, like squeezing one’s hand or watching a flashing checkerboard image, may generate BOLD changes of several percent in the primary motor cortex, even with scanners at 1.5 T. However, if the hand is squeezed less frequently and less vigorously, or if the checkerboard is blurred and flashed at a slower rate, BOLD activity may decrease dramatically. In addition, signal magnitude also depends on the area being measured. Many experimental tasks evoke activity in a set of related brain regions, such as areas associated with perceptual and motor processing and those associated with working memory and decision-making. As a rule of thumb, task-evoked fMRI signal changes are largest in primary motor or sensory areas, and generally decrease in amplitude in regions associated with higher cognitive function.

Thought Question

Why might the amplitude of the BOLD response typically be larger in primary sensory and motor cortices than in brain regions associated with complex cognitive processes?
Figure 8.2 Effects of increasing functional SNR from relatively low to high levels. (A) Shown within the yellow box are three voxels in and adjacent to the primary motor cortex, during performance of a blocked-design hand-squeezing task. (B) The uppermost voxel has little to no task-related signal change (low SNR). Plotted at right are histograms comparing the frequency of occurrence of each MR signal range during the hand squeezing blocks (in red) and during resting blocks (in blue). (C) The distributions of activation during task and non-task periods are highly overlapping for this voxel. (D) The middle voxel has a medium SNR, but there is still substantial overlap between the distributions (E). However, the lowermost voxel (F) has a very high SNR, and the distributions have much less overlap (G). The red and blue lines below each graph indicate the means ± one standard deviation of each histogram. If the difference between the means is large enough compared with the standard deviation, as in the bottom graph, we can identify significant activation.

If a study compares two experimental conditions, such as a memory test comparing remembered and forgotten words, the difference in signals between conditions (for which the term "contrast" is also used) is almost always much smaller than the difference between the signal associated with each condition.
Figure 8.3 Using fMRI to examine relative activation. Signal changes in fMRI are rarely all or none, but are often a matter of degree. Shown are the hypothetical responses of a face-sensitive region of the brain to images of a face (red line) and a wrench (blue line). The responses to both stimuli are large compared with the difference between the two responses. The difference between two conditions is often called an experimental contrast.

and baseline (Figure 8.3). Consider the fusiform gyrus in the temporal lobe, which plays an important role in the perception of objects, including faces. If an fMRI subject views a single face presented in isolation, activity in the fusiform gyrus might increase by about 1.1% over baseline. Other stimuli, such as images of tools, may evoke lower-amplitude activation in this region. For example, an image of a wrench might evoke a 0.8% increase in signal. Thus, the difference in signal between the conditions would be 0.3%. The more similar the conditions are, the smaller the functional SNR for detecting a difference between them.

Researchers can improve functional SNR in two ways. First, one can increase the signal (i.e., improve the experimental power) by using a higher-field scanner or by collecting more data. These carry costs, however, by requiring a more expensive machine or longer scanning time. And, using a high-field scanner introduces some important disadvantages, like increased signal loss in ventral brain regions. Conversely, one can take steps to reduce noise. The most important factor is creating a good experimental design (see Chapter 9) that distinguishes task-related signal from task-unrelated noise. Researchers also strive to eliminate some of the many sources of noise in fMRI data through the application of corrective algorithms before the data are analyzed (i.e., preprocessing). We consider both approaches—increasing signal and minimizing noise—in the remainder of this chapter.

Effects of Field Strength on fMRI Data

In any MRI scan, the amount of net magnetization is proportional to the strength of the static magnetic field (see Chapter 3). Remember, however, that the signal we measure in fMRI does not depend solely on the net magnetization. Because the net magnetization must be tipped into the transverse plane to become measurable, other effects come into play, including $T_1$ and $T_2$ relaxation, pulse sequence parameters, motion-related contrast preparations (e.g., perfusion, diffusion), and susceptibility effects, all of which were discussed in
Chapters 4 and 5. These latter factors temper the gains associated with strong magnetic fields, with important consequences for BOLD fMRI.

**Field strength and raw SNR**

One solution for increasing the amplitude of the BOLD signal is to increase the scanner field strength. With increasing field strength, the energy difference between high- and low-energy states increases, causing more spins to align parallel with the static field and increasing net magnetization. The theoretical relationship between field strength and MR signal is simple: as static field strength increases linearly, raw signal increases quadratically (i.e., with the square of the field strength). Thus, a 3.0-T scanner measures four times as much raw signal as a 1.5-T scanner. For comparison, thermal noise increases linearly with the field strength, so a 3.0-T scanner measures twice as much thermal noise as a 1.5-T scanner. When we divide the quadratic increase in signal by the linear increase in noise, we find that the raw SNR only increases linearly with the field strength. Recall from Chapter 1 the first whole-body MRI scanner, used by Damadian and colleagues in 1977, and named “Indomitable.” The field strength of that scanner was only 0.05 T, resulting in a theoretical raw signal and a raw SNR that were only about one thirty-six hundredth and one sixtieth, respectively, as strong as in a modern 3.0-T scanner!

Indeed, researchers have demonstrated that both fMRI BOLD signal amplitude and functional SNR increase with increasing field strength. A very early fMRI study was reported in 1993 by Turner and colleagues, who compared visual cortex activation at 1.5 T and 4.0 T. Using a simple design that alternated blocks of flashing lights and darkness every 30 s, they found that the evoked MR signal within the visual cortex was much larger at 4.0 T than at 1.5 T, with signal changes of approximately 15% and 5%, respectively (Figure 8.4). These results suggested that raw SNR increases roughly linearly with field strength.

There are now numerous more recent examples of parallel fMRI data acquired at two or more field strengths, often 1.5 T and 3.0 T. The general findings are that signal amplitude increases with field strength, but that the relationship is usually less than linear (e.g., doubling the field strength might result in a 50% increase in amplitude). And, as we will discuss further below, increases in field

![Figure 8.4](image.png) An early study of field strength effects in fMRI. Turner and colleagues measured changes in visual cortex activity at 1.5 T and 4.0 T. Approximately 2–3 times as much signal was recorded at the higher field strength.
spatial extent  The number of active voxels within a cluster of activation (i.e., the size of the active region).

partial volume effects  The combination, within a single voxel, of signal contributions from two or more distinct tissue types or functional regions.

strength have consequences for physiological variability, which further temper the advantages of higher field strengths. In many cases, the advantages of newer MRI scanners for fMRI imaging come mainly from the ability to do parallel imaging with high-performance gradients rather than from higher field strengths (see Chapter 5 for examples).

Field strength and spatial properties of activation

Greater field strength has two main effects on the spatial distribution of activation: improved spatial specificity and increased spatial extent of activation. Improvements in spatial specificity are critical for many applications of fMRI. Many phenomena of interest have small spatial scale and thus are more identifiable at higher fields. Recently, Yacoub and colleagues used a 7.0 T scanner to reproducibly identify spatial patterns of activation that likely reflect ocular dominance columns (Figure 8.5), thus building on prior work at lower field strengths. Another intriguing example of spatial specificity comes from a 2007 study by Ress and colleagues of cortical layering. By collecting fMRI data at 3.0 T in very small voxels (less than 1 cubic millimeter), they found that the amplitude of the BOLD signal in a given voxel depended on its position within the gray matter, with the largest signal changes observed about 3 mm from the gray–white boundary. These advances come in part because these very small voxels are highly specific; they minimize partial volume effects (see Figure 7.15). If a small voxel is primarily composed of active neural tissue that is responsive to the experimental task, it will generate a larger BOLD signal change than the same amount of active neural tissue located within a larger voxel. For this reason, decreasing voxel sizes can result in larger BOLD signal changes from active voxels.

Increasing spatial specificity can result in better sensitivity to signal changes from small blood vessels. Because the $T_2^*$ value of blood decreases significantly with increasing field strength, the intravascular contribution, especially from the large vessels, drops out at high field strengths. Conversely, the extravascu-

Figure 8.5  Identification of ocular dominance columns using high-field (7.0-T) fMRI. Visual input from each eye is represented within the primary visual cortex in small (~1mm) columns that are organized in a roughly alternating pattern along the cortex. (A) To maximize the chances of identifying reliable ocular dominance patterns, Yacoub and colleagues selected thin slices that ran along the interhemispheric fissure, targeting a small area within the primary visual cortex (white box). (B) Shown are maps of voxels that responded most to stimulation of the left eye (blue) or right eye (red), in each of three separate fMRI sessions. (C) A substantial fraction of the voxels passed significance thresholds in all three sessions (same color scheme as in B), providing good evidence for the robustness of the measurements. (After Yacoub et al., 2007.)
lar signal from spins near large blood vessels increases linearly with field strength, while the signal from spins near small vessels increases quadratically (i.e., with the square of the field). Therefore, as field strength increases, the small-vessel extravascular component of the BOLD response increases faster than the large-vessel extravascular component. A schematic illustration of the different effects of field strength on these various BOLD signal components is given in Figure 8.6. This scheme suggests that the extravascular component of small vessels would prevail at very high magnetic fields.

Small vessels are more likely to be located near the neuronal activity of interest, and thus the BOLD response may be more spatially specific at higher field strengths. In 2001, Kruger and colleagues investigated the effects of field strength (1.5 T vs. 3.0 T) on functional SNR in different types of voxels during a combined visual and motor task. In addition to an overall increase in functional SNR, they found that functional SNR increased by a factor of about 1.8 in small regions of activation that may correspond to large blood vessels, and by a factor of about 2.2 in larger regions of active gray matter. This work demonstrated the tendency toward improved signal specificity near small vessels at high field strengths. Note, however, that the extravascular component originating around large vessels would still be present, despite its relatively reduced proportion in the overall BOLD signal (Figure 8.6). This will partially compromise spatial specificity.

A second consequence of increased functional SNR is the increased spatial extent of activation (i.e., number of active voxels within a region). In their 1999 study, Yang and colleagues measured activity within the sensorimotor cortex while subjects performed a blocked-design finger tapping task at either 1.5 T or 4.0 T. Under optimum TR and TE parameters, there were approximately 70% more active voxels within the sensorimotor region at the higher field strength. Kruger and colleagues also found that spatial extent depends on field strength, with about 40% more voxels active across the motor and visual cortices at 3.0
T compared with 1.5 T. While these studies used simple visual and motor tasks, a 2003 study by Krasnow and colleagues examined the effects of field strength on several more complex tasks, including perceptual, memory, and emotional processing paradigms. They compared activity at field strengths of 1.5 T and 3.0 T and found that there were substantial increases in the number of activated voxels with increasing field strength. Increases of 35 to 83% were observed across multiple brain regions during a cognitive task, suggesting that detection power throughout the brain improves with increasing field strength.

These two consequences may appear contradictory: how can we gain spatial specificity at the same time as spatial extent increases? However, no true contradiction exists. The gain in spatial specificity comes from changes in the weighting of different vascular components. The large-vessel extravascular component does increase with field strength, but it does not increase as rapidly as the small-vessel extravascular component. The gain in spatial extent is an effect of increasing functional SNR, which in turn improves our estimates of whether a voxel’s activation matches our experimental hypotheses. We can use increased functional SNR in two ways. First, we can identify more voxels as active at the same statistical threshold. Or, by increasing our statistical threshold, we can improve our estimates of which voxels are active, without changing the spatial extent of activation.

**Thought Question**

What do the effects illustrated in Figure 8.6 predict for studies of the fMRI initial dip (see Chapter 7)?

**Challenges of high-field fMRI**

It is also important to realize that as field strength increases, the MR properties of spin systems change. For example, the relaxation parameters $T_1$ and $T_2^*$, which both affect signal recorded in fMRI experiments, change with increasing field strength. The parameter $T_1$ increases with field strength (by about 30% from 1.5 T to 3.0 T), and this could reduce the effective signal recovery for short TR values. The parameter $T_2^*$ decreases with increasing field strength, and this could reduce the time available to acquire a signal. Detailed measurements were reported in 2007 by Peters and colleagues, who found that $T_2^*$ values in gray matter were 22% shorter at 3.0 T and 60% shorter at 7.0 T, compared with values at 1.5 T. A more significant challenge comes from susceptibility artifacts that distort the uniformity of the magnetic field. Just as BOLD susceptibility effects increase with field strength, so too do signal losses in regions of the brain near air-tissue boundaries (Figure 8.7). These regions include the ventral frontal and temporal lobes, which are adjacent to air-filled sinuses. Without the use of specialized pulse sequences or equipment that can partially compensate for susceptibility-induced signal loss (see Chapter 5), imaging of these regions becomes more difficult or impossible at higher field strengths. Field inhomogeneity can also lead to geometric distortions that require specialized software and hardware for their correction.

At the time of publication of this Second Edition, the current standard for static field strength in fMRI studies is 3.0 T, although many institutions use scanners with lower (e.g., 1.5 T) or higher (e.g., 4.0 T or 7.0 T) field strengths. It is critical to emphasize that, while field strength is the most salient characteristic of an fMRI scanner, the quality of a scanner depends on many other factors.
Sources of Noise in fMRI

At a given field strength, the overall signal is mainly determined by the amount of net magnetization, which in turn reflects the number of atomic nuclei and their relaxation properties. However, the sources of noise are numerous and complex, varying over both time and space. Some sources of noise involve regular temporal variation, as can be seen in Figure 8.8, which presents the power spectrum of a single experimental run. A power spectrum shows what frequencies are present in a time series of data, and is created using the Fourier transform. Peaks within a power spectrum can be thought of as regular oscillations in the intensity of the given voxel, reflecting changes over time due to the respiratory cycle, cardiac pulsations, or BOLD activity. Spatial features of fMRI noise can be seen in Figure 8.9. The most striking feature of this set of images is that much of the anatomical structure of the brain was recovered, indicating that the variability inside the brain is much higher than the variability outside the brain. If noise were evenly distributed across the image, the image would be a uniform gray.

There are five main causes of temporal and spatial noise in fMRI: intrinsic thermal noise within the subject and the scanner electronics; system noise

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power spectrum A representation of the strength of different frequency components within a signal. The Fourier transform converts a signal (i.e., changes in intensity over time) into its power spectrum.
Figure 8.8 The power spectrum of an experimental voxel over a single run. The experimental task used an event-related design in which visual stimuli of 1-s duration were separated by intervals of 9 s. Plotted on the y-axis is the power at each frequency; i.e., how much did regular changes at that frequency contribute to the overall BOLD time course. Visible are clear peaks at the respiratory and cardiac frequencies. The accuracy of these peaks was verified by physiological monitoring. To detect such high-frequency changes, a single slice was sampled at a TR of 250 ms. Note that the lowest frequencies are excluded from this plot because the very high power at low frequencies obscures the effects shown. A small peak is evident near the task frequency of 0.1 Hz.

associated with imperfections in the scanner hardware; artifacts resulting from head motion, respiration, heart rate, and other physiological processes; variability in neuronal activity associated with non-task-related brain processes; and changes in behavioral performance and cognitive strategy. We discuss each of these sources of noise in the following sections.

Thermal noise

All MR imaging, whether anatomical or functional, is subject to thermal noise (also called intrinsic noise), which reflects the heat-related motion of electrons within the subject and within the scanner electronics. To understand the possible sources of thermal noise, recall from Chapter 2 the hardware that underlies the acquisition of MRI data. Following its excitation, the sample (e.g., the brain) emits a radiofrequency signal that is detected by the receiver coil. The signal then becomes an electric current that passes through a series of electronics hardware, replete with many conductors, resistors, and power amplifiers.
Within each component of the hardware, free electrons collide with atoms, resulting in an exchange of energy. The higher the temperature of the system, the more frequent the collisions and the more the current becomes distorted. Thermal noise also depends on the frequency bandwidth of the receiver and the resistance in the detector coil. Theoretical formulations of thermal noise by Edelstein and colleagues in 1986 showed that thermal noise increases linearly with field strength. So thermal noise will be approximately twice as large at 3.0 T as at 1.5 T.

Because the magnitude of thermal contributions to the MR signal varies randomly over time, thermal noise has no spatial structure. That is, the magnitude of thermal noise within a voxel is independent of its spatial location. However, the effect of thermal noise depends on the voxel’s signal amplitude. Consider a voxel within the brain that has very high raw signal (i.e., it appears bright on images). Thermal noise during image acquisition may add or subtract from the measured intensity values, resulting in a Gaussian distribution of intensity values over time. Now consider a voxel in air outside the brain;
system noise Fluctuations in MR signal intensity over space or time that are caused by imperfect functioning of the scanner hardware.

scanner drift Slow changes in voxel intensity over time.

that voxel has negligible raw signal (i.e., it appears dark on images). Thermal noise can only have an additive effect on that voxel. The resulting distribution will have a lower bound at zero and will be positively skewed (i.e., it will have a Rayleigh rather than a Gaussian distribution). A book published in 2002 by Buxton is listed in the chapter references, and gives a good discussion of the relationship between raw signal and thermal noise effects.

System noise

A second factor that contributes to variability in the measured fMRI signal is system noise, which generally describes variations or discrepancies in the functioning of the imaging hardware. Some common causes of system noise are static field inhomogeneities due to imperfect shimming, nonlinearities and instabilities in the gradient fields, and off-resonance or loading effects in the radiofrequency transmitter and receiver coils. One particularly important form of system noise is scanner drift (Figure 8.10). Although drift can result from any of several different sources, a common cause is changes in the resonant frequency of hydrogen protons associated with subtle changes in the strength of the static field. Even though it is powered by superconducting currents, the static field strength of the main magnet still drifts slowly over time, often on the order of a few tenths of a part per million per day. Expressed in terms of field strength and resonant frequency, such drifts might reflect an alteration in the main field strength on the order of 0.005 of a Gauss and variation in the resonant frequency by a few Hertz. This can lead to changes in global or local signal intensity over time. Similarly, instability in the gradient coils can cause the shape and location of the recorded images to change over time (see Chapter 4).

Problems with the radiofrequency coils can introduce several types of system noise. If the frequency of the excitation pulse does not match the resonant frequency of the sample, excitation will be inefficient and intensity variation may be introduced, causing the MR signal to fluctuate over time. Another

Figure 8.10 Scanner drift. Low-frequency changes in MR signal are collectively known as drift. Shown here is a roughly linear decrease in activation throughout a single run (each time point collected with TR of 1.5 s).
potential problem results from the fact that the receiver coil is coupled to the sample via mutual inductance, meaning that changes in the current or voltage distribution in the sample will induce corresponding changes in the current or voltage carried by the receiver coil. Thus, noise in the brain effectively reduces the sensitivity of the receiver coil. To minimize this problem, scanners match the impedance in the sample and the receiver coil. This matching process is referred to as achieving the dominant loading factor for the object being imaged (i.e., a particular subject's brain) so that optimal mutual coupling can be reached.

Some aspects of system noise are the responsibility of the MR center, because they affect all researchers who use a scanner. By ensuring that the MR scanner electronics are as stable as possible and by preventing extraneous radiofrequency signals from entering the scanner room, the research center can improve the consistency of fMRI data, both within and between sessions. Researchers should become familiar with the quality assurance procedures at their MRI center so that they can recognize problems as they arise and, in turn, provide feedback to the technical staff running the scanner.

**Motion and physiological noise**

So far we have considered thermal and system noise, which result from intrinsic properties of the scanning system. If we scan an inert object (e.g., a plastic ball filled with fluid or gel), we will still measure significant thermal and system noise. The human brain, on the other hand, is hardly inert. Muscles contract with each breath or heartbeat. Blood pulses through arteries and veins. The metabolic demands of neurons drive chemical reactions. This activity results in variations in fMRI signal due to motion artifacts and physiological noise.

Signal variability due to subject motion is common and extremely disruptive for fMRI studies. Throughout an experiment, a subject may shift the position of his head; move his shoulders, arms, or legs to become more comfortable; or swallow because of nervousness. In the best cases, small head motions can be partially corrected during data preprocessing, while in the worst cases, large motions may render data completely un-interpretable. In addition, small-scale motions result from the regular oscillatory activity of the heart and lungs. This activity is much faster and more periodic than large-scale head motion, introducing a different set of challenges. If the rate of sampling is fast enough, it may be possible to characterize and minimize motion due to heart and lung activity during preprocessing. But in most fMRI studies, motion due to cardiac activity, in particular, is too fast to be sampled effectively (i.e., for TRs >500 ms), and if the TR is long enough (i.e., >2500 ms), respiratory activity may likewise be under-sampled. Under those circumstances, the signal changes associated with these sources of motion are still present, but become distributed throughout the fMRI time series in a manner that may be difficult to identify or correct; this phenomenon is known as aliasing. Respiration also introduces variability in the fMRI signal through systematic distortions in the magnetic field. As the subject breathes, the expansion of the lungs casts a magnetic susceptibility "shadow," influencing field strength and homogeneity of the magnetic field, and altering signal intensity throughout the image (including areas outside the brain). This phenomenon was demonstrated by Raj and colleagues in 2001.

The effects of motion in fMRI are usually not due to motion during image acquisition, which would reduce the raw SNR. Recall from Chapter 5 that typical fMRI pulse sequences (e.g., spiral or echo-planar gradient-echo imaging)
Figure 8.11 Distribution of physiological noise. For one subject, images show brain anatomy (A), noise from all sources (B), physiological noise due to variation in blood flow and metabolic processes (C), and noise due to bulk head motion and cardiac and respiratory pulsations (D). Note that the noise in (C) is concentrated within gray matter, while that in (D) is more uniform, save for effects around the edge of the brain. (E, F) For comparison, the authors also collected data from a fluid-filled ball (i.e., a phantom). Overall noise levels are generally uniform throughout the phantom (E) and there is negligible physiological noise (F). (From Kruger and Glover, 2001.)

have very short TEs, often about 30 to 40 ms. There is little opportunity for motion to occur during such a short acquisition window. Motion causes problems because of variability across the time series of images, which is critical for functional SNR. A voxel near the edge of the brain, for example, may begin by containing mostly gray matter but end up, after motion, containing mostly cerebrospinal fluid. Note that if motion were completely random, the resulting reduction in SNR could be ameliorated by additional data collection. Motion is rarely random, however. It is often correlated with the experimen-
tal task; for example, when subjects catch their breath each time they press a response button. Motion also introduces both spatial correlations, since adjacent voxels move together, and temporal correlations, since movements are extended over time.

Other physiological sources of noise include fluctuations in blood flow, blood volume, and oxygen metabolism. In 2001, Kruger and Glover investigated the spatial distribution of physiological noise, separating it into one component (\( \sigma_B \)) associated with variability in the transverse relaxation rate and another component (\( \sigma_{NB} \)) associated with cardiac and respiratory motion. Since the former component, like BOLD contrast itself, results from susceptibility-related signal changes, its magnitude depends on TE. The latter component, in contrast, is independent of TE. Kruger and Glover found that the spatial distribution of these two components differed (Figure 8.11). The former was much greater in gray matter than in white matter, while the latter was equally distributed throughout the brain. Furthermore, \( \sigma_B \) was typically about twice as large as \( \sigma_{NB} \). Furthermore, they found that at 1.5 T, physiological noise makes up about 40% of the total noise, but at 3.0 T, physiological noise constitutes more than 52% of total noise.

These results suggest that physiological noise, rather than thermal or system noise, is the dominant source of variability in fMRI studies, especially at higher field strengths. Theoretical formulations suggest that thermal noise increases linearly with increasing field strength, but physiological noise increases quadratically with field strength. So, as field strength increases from 1.5 T to 3.0 T, raw signal will quadruple, thermal noise will double, and physiological noise will quadruple. These relations suggest that at very high field strengths, physiological noise may become dominant, and thus the improvement of functional SNR with increasing field strength may be considerably less than linear (Figure 8.12). More recent data from Triantafyllou and colleagues support this notion, indicating that at 7.0 T, the ratio of physiological to thermal noise becomes more than two to one. This suggests that, at high

![Figure 8.12 Changes in signal and noise with increasing static field strength. MR signal increases with the square of the field strength, while thermal noise increases linearly with field strength. The ratio of these quantities, raw SNR, thus increases linearly with field strength. However, because physiological noise increases with the square of field strength, functional SNR (which is dependent on both thermal and physiological noise) may reach an asymptote at high fields. Note that here the field strength is indicated in arbitrary units; the field strength beyond which such an asymptote would occur is not yet established.](image-url)
reaction time The time required for someone to make a simple motor response to the presentation of a stimulus. Note that this is distinct from response time, which applies to situations in which someone must choose between two or more possible responses.

response time The time required for someone to execute a choice between two or more possible responses. Note that this is distinct from reaction time, which applies to situations when only one possible response is present.

intersubject variability Variability in fMRI data across a set of subjects; it includes the factors associated with intrasubject variability, along with between-subjects differences in task performance and physiology.

intrasubject variability Variability in the fMRI data from a single subject associated with thermal, system, and physiological noise, as well as with variability in the pattern of brain activity during task performance.

fields, increases in physiological noise may counteract gains in signal, setting an asymptotic upper limit for functional SNR. Note that data indicate that this limit increases for small voxel sizes, for which there is still an improvement in functional SNR as field strength increases. Thus, high-field fMRI might be most useful for research that requires very good spatial resolution. For an example, see the article by Bodurka and colleagues in the Chapter References.

Non-task-related neural variability
In the party analogy described at the beginning of this chapter, we noted that other nearby conversations could make it difficult to hear your friend’s speech. However, unlike the other sources of noise discussed thus far, the words spoken in these other conversations represent legitimate signals that could, in principle, be of interest to you. Similarly, during any fMRI experiment there will be a surplus of ongoing cognitive processes, most of which are not anticipated by the experimenters.

Let us consider an fMRI experiment in which we stroked the thumb with a brush to investigate which brain areas are activated by somatosensory stimuli. At the same time that the subject’s brain experiences this discrete task-related sensory stimulus, the subject may also be hearing the sounds of the scanner gradients, receiving varying visual stimuli as he or she looks around within the scanner, recalling memories, or planning events as he or she thinks about appointments for later that day. All of these stimuli—internal and external—activate neural processes that incur metabolic demands and thus influence BOLD contrast. We only label these other processes as noise because they are unrelated to the stimulus of interest. However, under a different experimental design or analysis they could provide important information about brain function. This illustrates that the task-related responses in which we are interested occur within a highly active brain where routine neural processes are altering BOLD contrast at every moment.

Behavioral and cognitive variability in task performance
An additional source of noise in fMRI data comes from variability in how subjects perform the experimental task. (Box 8.2 considers other sources of interindividual variability, including potential differences in the form of the hemodynamic response.) In general, the more complex the task, the more performance will vary across time and across subjects. Performance is often measured by the time it takes to generate a response, known as reaction time or response time, depending on the experimental task. If the task simply requires the detection of a stimulus, the behavioral measure is known as reaction time and is typically around a few hundred milliseconds. But if the task requires the subjects to make some judgment about a stimulus, such as whether or not they remember it from earlier in the experiment, then the behavioral measure is known as response time. Since response times require additional cognitive processes, they are longer than reaction times. Depending on the experiment, response time may be as short as 300 ms or as long as several seconds. In any experiment, there will be both intersubject and intrasubject variability in reaction or response time (Figure 8.13). Variability in response time may have important consequences for the timing and amplitude of the BOLD signal. For examples, see the work of Menon and colleagues (Figure 7.24A) and Richter and colleagues (Figure 7.23), introduced in Chapter 7. To deal with this issue, many fMRI studies include reaction time, or some other behavioral measure, as a covariate in their analyses.
Figure 8.13 Variability in response time. Shown are histograms of response time data obtained during a target detection task conducted as part of an fMRI experiment. While the input stimulus was similar on every trial, the behavior differed dramatically from trial to trial. (A) The distribution of response times across approximately 10,000 trials collected from many subjects. Note that the distribution is highly positively skewed, with the shortest response times at about 400 ms and the mean at about 800 ms. (B) Distributions from two individual subjects. Note that even though these subjects were performing the same task, their patterns of performance were very different.

Performance can also be measured by examining the accuracy of responses. However, accuracy is frequently related to response time: subjects can perform most tasks more accurately when doing them more slowly. This relation is known as a speed-accuracy trade-off. Imagine that you are shown a series of photographs of faces and are asked to judge the emotion they are expressing. If you try to guess the emotion as quickly as possible, you will make many mistakes, especially on more complex emotions like disgust. Conversely, if you spend more time considering each face carefully, your accuracy will increase but your response times will slow. Because of these trade-offs, it is often reasonable to emphasize one factor as a constraint on behavior: “Respond as quickly as you can while maintaining a low error rate.” This reduces variability in error rates across subjects, especially if you provide feedback about errors and the target error rate. Accuracy should be emphasized when the characteristics of the response are critical (e.g., when classifying stimuli as correctly remembered or forgotten). Speed should be emphasized when the processes of interest would change if the subject is allowed unlimited time to respond. Experiments on attention often emphasize speed, because the effects of attention on behavior may change if subjects are allowed a long time to respond.

**Thought Question**

How could differences in task performance confound fMRI studies that compare different subject groups, such as young and elderly adults?
BOX 8.2 Variability in the Hemodynamic Response over Subjects and Sessions

In most fMRI experiments, it is assumed that the measured signal has similar temporal and spatial properties between subjects (and across brain regions), allowing researchers to apply a single analysis model throughout an experiment. Yet, the fMRI hemodynamic response might vary in different subjects because of differences in local vasculature, neuronal activity, or even the functional organization of small areas of cortex. If there is substantial intersubject variability in the hemodynamic response, then an analysis model that is appropriate for one subject (e.g., who has a hemodynamic response peak at 5 s) might be inappropriate for another (e.g., who has a hemodynamic response peak at 7 s). This could potentially lead to erroneous conclusions about brain function. While intersubject variability in fMRI data has been studied for more than a decade, clear conclusions about its sources have been surprisingly difficult to draw. For an extended discussion of how experimental limitations can lead to unwarranted conclusions about variability, refer to the article by Savoy, cited in the chapter references.

A good example of both the extent and implications of intersubject variability is found in a 2004 report by Handwerker and colleagues (which builds on earlier work by Aguirre and colleagues). Their subjects watched for infrequent, unexpected presentations of a flickering checkerboard, whereupon they would simultaneously press buttons on a response box and move their eyes to the location of the checkerboard. This design allowed the authors to compare hemodynamic responses in multiple anatomically defined regions of interest: the primary visual cortex, the primary motor cortex, and the frontal eye fields, which are important for the control of eye movements. They found that within a given individual, the hemodynamic responses in each region tended to be rather similar in onset, shape, and peak latency. However, striking differences were found in different individuals, with some individuals' responses peaking as early as 3–4 s, while those of other individuals peaked as late as 6–7 s (see Figure 1 for examples). These measured hemodynamic responses allowed the authors to simulate how intersubject differences could influence analyses.
BOX 8.2 (continued)

Figure 1 Intrasubject consistency and intersubject variability in the BOLD hemodynamic response. The reproducibility of the fMRI hemodynamic response has been examined in several experiments. Here, hemodynamic responses derived from four different brain regions are plotted for 20 subjects, within the same experiment. The task involved moving eyes and pressing buttons in response to an unexpected stimulus. Subjects are arranged according to the consistency of their BOLD responses across brain regions, from most consistent (upper left) to least consistent (lower right). All responses are normalized to a maximum amplitude of 1.0. Although there are substantial differences between individuals in the timing of their hemodynamic responses, with some peaking earlier and some later than the canonical hemodynamic response (lines), there is relatively good consistency in the timing of the hemodynamic response across regions within the same individual. (After Handwerker et al., 2004.)

They found that the detection of activated voxels was not dramatically influenced by the choice of hemodynamic response function (e.g., whether the function was derived from canonical data or from the subject's own data). However, the amplitude of the estimated activation was greatly reduced by a poor-fitting function. Thus, the authors concluded that using subject-specific functions may be beneficial, especially when conclusions are derived from the distribution of activation amplitudes across subjects. This may be especially important in cases where individual differences are of particular interest, such as when examining within-subject effects of a specific treatment.

A considerable number of studies have documented three aspects of temporal variability: (1) the same experimental task will evoke different hemodynamic responses in different subjects, (2) some of this variability reflects intersubject differences in task performance, and (3) residual variability in the shape and timing of the hemodynamic response is partially consistent across brain regions within a subject. Handwerker and colleagues showed that functions derived from subject-specific hemodynamic responses can improve analysis sensitivity compared with canonical functions derived from large numbers of subjects. However, what task should be used to develop the function is an open and important question, given that there will be intersubject variability in even simple motor and visual tasks. One intriguing possibility is calibrating the hemodynamic response using data from a breath-holding task, which evokes a state of hypercapnia (i.e., increased carbon dioxide) associated with large increases in BOLD signal.

In a 2007 report, Thomason and colleagues reported that using the magnitude of the breath-holding response to normalize the evoked BOLD responses both reduced inter-individual variability and increased the number of activated voxels in a working memory task. While the discussion so far has focused on temporal variability in fMRI data, it is also important to consider spatial variability. How much does the pattern of activation across regions differ from session to session? When different individuals perform complex cognitive tasks, differences in strategy may contribute to differences in measured activation, as outlined in the main text. Indeed, such individual differences are an important part of many fMRI studies. But, strategic differences should be relatively minimal when the same subject repeatedly performs a relatively simple task.

In a study reported by McConigle and colleagues in 2000, a single subject participated in 33 separate scanner sessions, each containing three blocked-design tasks: finger tapping, passive visual stimulation, and random-number generation. Every session was identically run on the same scanner, with the same room lighting and ambient sounds, with the same operator giving the same instructions. Indeed, the authors note that the subject had the same "I've done this before" thoughts before every session! When the activation maps were examined at standard significance thresholds, there were apparent differences in the pattern of activation, even in the passive visual task (Figure 2A). In some sessions, there was very robust activation along the calcarine sulcus, which encompasses the primary visual cortex. However, other sessions had almost no activated voxels. A natural interpretation of these results is that the spatial pattern of activation is highly variable from session to session, even under conditions most likely to lead to reproducible activation.

Yet, this interpretation was challenged by the authors themselves in a 2005 reanalysis of their original data. Two conclusions of this new study are especially important. First, inter-session variability was of similar magnitude to intra-session variability, and this conclusion held across a range of different statistical packages and analysis approaches. If inter-session variability were of much greater magnitude, for comparison, it would pose problems for
Figure 2 Reproducibility of fMRI activity across sessions. In what is likely a record, a single subject participated in 33 fMRI sessions, each containing simple motor, visual, and cognitive tasks. The experimental procedures were repeated in exactly the same manner at every session, right down to repeating the quite familiar experimental instructions. (A) Initial analyses suggested that there were different patterns of activation evoked in different sessions, based on the voxels passing conventional significance criteria. Shown here are data from the 33 visual-task sessions, each thresholded at a level of \( p < 0.05 \) and corrected for full-brain cluster significance. (B) A subsequent reanalysis by the same authors demonstrated that the activation differences that were found between sessions were largely an effect of using a relatively conservative threshold. When the significance threshold was relaxed by 33%, the patterns of activation became much more similar across sessions. (From Smith et al., 2005; data in A initially published by McGonigle et al., 2000.)

studies that involve repeated scanning of the same subject (e.g., before and after treatment). Second, they found that the apparent variability across sessions was largely an artifact of statistical thresholding. When using a slightly reduced threshold, the pattern of activation seemed much more similar across sessions (Figure 2B). It is important to emphasize that these two figures display the same activation map; they differ only in what parts of that map are shown in color and what are omitted. Considered in this new light, the authors make a compelling case that fMRI data can be highly reproducible across many sessions. In summary, data from the same subject may show significant temporal and spatial variability. However, much of that variability results from the same sources—scanner noise, physiological noise, and strategic variation—as intra-session variability.

Strategy changes are another source of task-induced variability. In many cognitive tasks, there may be more than one strategy that can be used to solve a task. When making decisions, some subjects may use specific heuristics (e.g., selecting the option that seems most familiar to them), whereas others may
adopt a more analytic approach (e.g., comparing the costs and benefits of every option). Such individual differences in strategy may be identifiable based on differences in the pattern of fMRI activation. (Evidence in support of this has come from several studies showing both inter-individual variability and intra-individual consistency across a number of fMRI tasks.) When planning an experiment, fMRI researchers should consider what strategies a subject might use to solve the task. If multiple strategies are possible, then there should be some way of identifying when different subjects (or even the same subject, at different times) employ particular strategies. To gain insight into how subjects may approach a task, researchers should always use themselves as pilot participants (in the behavioral task) before recruiting fMRI subjects.

Good training of research subjects can also reduce unwanted behavioral variability. Providing clear instructions improves the subjects’ understanding of the experimental task, while practice before the fMRI session allows subjects to attain a steady-state performance level before entering the scanner session. These practice sessions ahead of time—or even during anatomical imaging—minimize the learning effects or strategy changes that typically occur at the beginning of an experiment.

**Preprocessing**

As described in the previous chapters, one can consider fMRI data as consisting of a 3-D matrix of volume elements (voxels) that is repeatedly sampled over time. A single experiment might have an imaging volume of 64 × 64 × 30 voxels that is sampled every 2 seconds for a total of 10 minutes, resulting in 300 time points per voxel. A straightforward way of analyzing such a data set would be to extract the raw time course for each voxel and compare each of these time courses to some hypothesis using a test of significance. While this approach does indeed form the basis of much fMRI data analysis, it contains some hidden assumptions, which we will discuss in more detail in Chapter 10. Notably, it assumes that each voxel represents a unique and unchanging location in the brain and that the sampling of that voxel occurs at a regular known rate. These assumptions, though seemingly plausible, are always rendered incorrect by the sources of variability described earlier in this chapter.

Here, we discuss a series of computational procedures, collectively known as preprocessing, that operate on fMRI data following image reconstruction but prior to statistical analysis. Similar preprocessing algorithms are generally applied, regardless of the experimental design (e.g., the same procedures would be used for a blocked design study of language and an event-related study of memory). Preprocessing has two principal goals: to remove uninteresting variability from the data and to prepare the data for statistical analysis. If done correctly, preprocessing steps can greatly increase the functional resolution of an fMRI experiment.

**Quality assurance**

An important and often underutilized aspect of preprocessing is quality assurance (QA) testing. Quality problems can (and will) arise on even the best-maintained scanner. If a subject’s data are corrupted by extreme scanner noise, or by some problem with data acquisition, that subject may have to be excluded from further analyses, incurring both scientific and financial cost. Even more worrisome are hidden quality problems. The prevalence of automated statis-
Figure 8.14 Common artifacts found in MR images. An important goal for quality assurance programs is the identification of image artifacts that can corrupt MR data. (A) Radiofrequency leakage resulting from an ungrounded electrical connection can cause “white pixels” in $k$-space, resulting in grating patterns on reconstructed images. (B) Variations in the local properties of the field can cause intensity variations across an image, such as the brightening of the center of the image compared with the periphery.

tical packages has made it possible for investigators to preprocess, analyze, and combine data across subjects without ever examining an individual subject’s data. Without QA testing, unnoticed problems might propagate into the final results of an experiment, with potentially disastrous consequences.

The first rule of QA is simple: examine your data. Many common artifacts are readily visible in the raw images, even under a cursory examination (Figure 8.14). An effective way of viewing experimental data is as a time-series movie, in which an entire experimental run is shown, one volume after another, in a rapid sequence. Because our visual system is very good at picking up changes between successive images, many types of problems will appear as we view the sequence. Radiofrequency noise, for example, can show up as repeating patterns on top of the data, while head motion can appear as rapid jerks. Although visual inspection of fMRI data should be a regular part of any QA procedure, it is not in itself sufficient for ensuring data quality. Researchers should also apply statistical tests that evaluate the quality of collected fMRI data. These can include calculations of the mean image intensity, the raw SNR (over space), or the image intensity divided by the standard deviation over time (as a rough approximation of functional SNR). Some analysis packages and many imaging centers have developed quality assurance testing, some of which can be run automatically and in real time during fMRI sessions.

Though not strictly part of preprocessing, frequent tests of a single object, often called a phantom, are important for ensuring data quality. Phantoms (Figure 8.15) are typically balls or cylinders filled with a homogeneous fluid or gel, although they can have internal structure (including some that roughly mimic brain anatomy). Daily scanning of the same phantom with the same pulse sequences will indicate changes in the scanning environment, since the data should look identical across sessions. Imaging centers should regularly scan phantoms so that they will identify problems with scanner hardware as soon as possible.

Finally, while we emphasize quality assurance in the context of data acquisition, that concept should pervade all aspects of fMRI research. Problems or
Figure 8.15 Examples of phantoms and their appearance on MR images. Phantoms are fluid- or gel-filled shapes that are used for testing MR scanners. They may be homogeneous (A), or have internal structure (B, C). Shown below each phantom in (D, E, F) are structural MR images collected using each of these phantoms. (Phantoms courtesy of General Electric Corporation.)

mistakes can appear during any stage of fMRI experimentation: at data collection, following preprocessing, during final analyses, or even when preparing results for publication. Without a diligent QA program, problems with data quality will corrupt experimental results and frustrate investigators.

**Slice acquisition time correction**

Most fMRI data are acquired using pulse sequences of the form described in Chapter 4: slice selection using radiofrequency excitation, followed by simultaneous data collection from throughout that slice (i.e., using echoplanar or spiral techniques). To collect data from the entire brain, a typical pulse sequence might acquire 30 or more slices within a TR of 1.5 to 3.0 s, depending on the
ascending/descending slice acquisition The collection of data in consecutive order, so that slices are acquired sequentially from one end of the imaging volume to the other.

interleaved slice acquisition The collection of data in an alternating order, so that data are first acquired from the odd-numbered slices and then from the even-numbered slices, to minimize the influence of excitation pulses upon adjacent slices.

temporal interpolation The estimation of the value of a signal at a time point that was not originally collected, using data from nearby time points.

capabilities of the scanner. In virtually all fMRI scanning, the slices are acquired with equal spacing across the TR. One approach is to use ascending/descending slice acquisition, in which the slices are collected consecutively (e.g., 1-2-3-4-5-6-7-8-9-10-11-12). Most fMRI studies now use interleaved slice acquisition, in which the scanner first collects all of the odd-numbered slices and then collects all of the even-numbered slices to avoid cross-slice excitation. If there were 12 slices in the imaging volume, numbered from 1 at the bottom of the brain to 12 at the top, an interleaved acquisition sequence would collect the slices in the order 1-3-5-7-9-11-2-4-6-8-10-12. One potential problem for interleaved acquisition is that adjacent parts of the brain are acquired at non-adjacent time points within the TR (Figure 8.16). Thus, assuming that the interleaved example above had a TR of 3 s and that slice 1 was acquired at 0 s, slice 2 would not be acquired until 1.5 s later. In effect, an identical BOLD response in these two regions would seem to occur earlier in the latter slice, posing problems for simple analyses (especially in event-related experimental designs) if uncorrected.

Thought Question
In most fMRI pulse sequences, the slices are equally spaced throughout a TR. Can you think of a type of experiment in which researchers might concentrate all of the slices at the beginning of the TR, so that there is a period of time in which no acquisition takes place? (Hint: Refer to Chapter 2 to consider what the subject experiences each time a slice is acquired.)

The most common approach for dealing with slice-timing discrepancies is correction via temporal interpolation during preprocessing. Interpolation uses

Figure 8.16 Effects of slice acquisition time on the hemodynamic response. Imagine that a single brain region, shown in red (A), is uniformly active following presentation of a stimulus. This region spans three slices, 15 to 17, within the imaging volume, which is acquired with a standard interleaved sequence (i.e., that first acquires the odd-numbered slices and then acquires the even-numbered slices) (B). Because the slices within this region are acquired at different times within the 3 s TR, the hemodynamic response within the slices will have different time courses. The signal recorded from the different slices is plotted against the time each slice was acquired in (C). Yet, without correcting for the time of acquisition of each slice, the time courses would seem to differ dramatically across slices (D). The hemodynamic response in slice 16 (acquired late in the TR) appears to peak earlier than those in the surrounding slices (acquired early in the TR), even though the underlying activity is identical.
information from nearby time points to estimate the amplitude of the MR signal, for every slice, at a single point within the TR (e.g., the onset or middle). Sinc interpolation is most often used, because it accounts best for noise-related variability in fMRI data (see Chapter 4 for a discussion of this function). It is important to emphasize that interpolation techniques are intrinsically imperfect; any attempt to recover the missing information will be limited by the variability in the experimental data, particularly variability that is not associated with the task. Another approach is to create separate analysis models for each slice, effectively moving slice-acquisition correction from preprocessing to data analysis. This latter approach may be preferable if the experiment targets specific brain regions, but it can make some forms of post hoc analyses (e.g., extracting a mean time course from a region that spans slices) more challenging.

Head motion: an overview

Probably the most damaging (and frustrating) problem for fMRI studies is head motion. To appreciate how little head motion is required to render data meaningless, examine the data shown in Figure 8.17. Note the large intensity difference between adjacent voxels in panel B. Now imagine that the subject moves his head almost imperceptibly, shifting by only 5 mm (i.e., the width of a single voxel) to the right. Even such a tiny movement has a drastic effect on the data, as shown in panel C. Because the scanner acquires images at absolute spatial locations, not relative to the brain’s position, head motion can cause a given voxel to contain signal from two very different types of tissue (e.g., gray matter and ventricle). This can cause very large apparent changes in raw signal over time, leading to spurious motion-related activations that often form a distinctive ring pattern around the edges of the brain (Figure 8.18). Moreover, head motion can cause a loss of data at the edges of the imaging volume. Most fMRI protocols use fields of view that are substantially larger than the brain, such as 20 or 24 cm, so movements within the plane of data acquisition do not move the brain outside of the imaging volume. But large through-plane movements can cause a portion of the brain (e.g., portions of the superior frontal and parietal lobes) to move out of the imaging volume, with an irreversible loss of data from the affected regions. Researchers often acquire additional slices around the edges of the area of interest, whether

![Figure 8.17 Effects of head motion on fMRI data. Large intensity transitions exist at tissue boundaries, including the edges of the brain (A). Here we demonstrate the effects of head motion on voxel intensity. The magnified views show the position of the brain before head motion (B) and after a movement of one voxel to the right (C). The numerical intensity values for the voxels within the blue square are shown below. Note that the intensity in a given voxel may change by more than a factor of 5 due solely to head motion. This compares to a change of only 1 to 2% for real brain activity.](image)
Figure 8.18  Edge effects of head motion in fMRI analyses. Because the intensity transitions in the brain are greatest at its edges, head motion often results in systematic rings of artifactual activation around the edges of the brain. Shown are activation maps, in four axial slices, derived from the analysis of a motor task generally similar to that described in Figure 8.1. Here, however, the brain moved forward by two voxels at the beginning of one stimulus onset, and remained forward for 4 s. This causes large changes in signal intensity around the edges in the brain; for example, voxels at the back of the brain changed from high intensity to low intensity as a result of the movement. Thus, these voxels had a significant decrease in activation (plotted in a blue-to-white colormap) due entirely to the movement, and these movement-related effects dwarf the significant task-related increases in activation (plotted in a red-to-yellow colormap) within motor cortex.

the full brain or just a single region, so that small through-plane movements can be corrected.

There are several characteristic forms of head motion (see Figure 8.19 for examples). Many fMRI experiments are partitioned into multiple runs to reduce subject fatigue and, in some cases, to overcome hardware constraints on data acquisition. During the breaks between runs, subjects typically relax and talk to the experimenters, often resulting in considerable head motion. When different experimental conditions are separated in different runs (e.g., in studies of memory encoding and retrieval), motion can have differential effects across conditions. Within runs, subjects often make numerous small movements of the head. During a one- to two-hour session, while the subject lies in a small space, he or she will become increasingly tired and restless. Experimental stimuli themselves may cause head motion. Many experimental tasks require subjects to make motor responses, usually by moving a joystick or pressing a button, which may in turn lead to head motion. Anyone who has been a subject in an MRI study has experienced momentary drowsiness, only to be startled into alertness by the next stimulus. Motion effects that co-occur with stimulus presentation pose challenges for analysis and preprocessing techniques, because in these cases it is difficult to separate real brain activation from artifacts of motion. Within-run and between-runs movements are sometimes corrected separately because of their different spatial properties.

Even though head motion is an inherently spatial problem, it can have consequences for activation timing. Motion through the slice plane (i.e., along the z-dimension for most fMRI studies) will change the pattern of excitation across the brain. Recall that for functional pulse sequences, like gradient-echo
Figure 8.19 Plots of head motion over an experimental session. Shown are plots of translational (A) and rotational (B) head motion from a single fMRI session. By convention, translational effects comprise movements from left-to-right (x-axis), forward-to-back (y-axis), and top-to-bottom (i.e., in the slice acquisition direction; z-axis). Rotational effects comprise turns around the x-axis (pitch), around the y-axis (roll), and around the z-axis (yaw). This experiment consisted of seven runs, each of 410 images, with a TR of 1500 ms. Large motions between runs are visible as vertical lines on the plot; for example, see the vertical line near image 2050 that reflects an upward through-plane movement. Note that these are the estimated motion values at each point in time, and thus can be influenced by a number of factors besides head motion itself, as indicated in the text.

EPI, each excitation pulse is targeted to one slice at a time. But if the head moves during the acquisition of a single volume, then some of the slices may miss the excitation pulse, whereas others will experience two (or more) excitation pulses in rapid succession. The former will experience more T₁ recovery than expected,
whereas the latter will experience less $T_1$ recovery, changing the relative BOLD signal recorded from each. Motion also influences the timing of activation, potentially by a second or more in a typical interleaved slice acquisition.

**Prevention of head motion**

Like many other problems, head motion is more easily prevented than corrected. Most laboratories use head restraints of some form (Figure 8.20). The most effective but difficult-to-use option is the bite bar (Figure 8.20A and B). As its name implies, a bite bar immobilizes the head by requiring the subject to clamp his or her teeth firmly on a dental mold, which in turn is solidly attached to the scanning hardware. With the jaw immobilized, potential head movement becomes very limited. Some subjects dislike using bite bars, and this both increases the likelihood that a participant will end a session prematurely, and discourages participation in the first place. Systems that use mold-

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**Figure 8.20** Head restraint systems. Because severe head motion can render fMRI data useless, several systems for head-immobilization exist. Shown in (A) is a standard volume head coil with two motion-restraint systems. Attached to the top of the head coil is a bite bar, while at the bottom is a vacuum pack. When the bite bar is used (B), the subject clenches his teeth on a dental mold that has been customized to his bite pattern. This greatly restricts the effective motion of the head. Thermoplastic masks (C) mold to the subject's face, and are anchored to a static support. Vacuum packs (D) contain many soft foam beads within a plastic casing. When air is pumped out, the pack hardens to form a shell around the contours of the subject's head. (C from Med-Tec.)
able plastic or mesh to create a mask around the subject’s head (Figure 8.20C) are usually tolerated better. Such masks passively restrict head motion without requiring jaw clenching and are individually molded to each participant’s physiognomy. Mask systems take time to customize for each subject, especially thermoplastic devices that must be heated and cooled before scanning. Another disadvantage is that some subjects may feel claustrophobic due to the high degree of immobilization.

Vacuum-pack systems combine good motion prevention with improved patient comfort (Figure 8.20D). The vacuum pack consists of a large number of soft beads within a flexible plastic casing. Once the subject is positioned in the scanner, the pack is fitted around the sides of the head and its air is pumped out, which hardens the vacuum pack into a form-fitting shell molded to the contours of the skull. Since the face is left open, the risk of claustrophobia is not increased significantly. In fact, many subjects report that they prefer the vacuum system to no restraint at all, because its head support allows them to relax their neck muscles. Vacuum packs, and similar systems that use static padding, provide a reasonable compromise between restriction and comfort.

While restraint systems play an essential role in preventing head motion, probably the most important factor is subject compliance. When subjects become uncomfortable, they may terminate the session or move to relieve soreness or pain. Working to maximize the subjects’ comfort and interest in the study greatly improves the chances of acquiring a complete data set that is not corrupted by excessive motion. Researchers should regularly talk to their subjects; even a simple “How are you doing?” after each run will help prevent anxiety and the accompanying motion. We have also found that taping down the subjects’ foreheads will help to reduce head motion. Although a single piece of tape cannot prevent a subject from moving his or her head, it provides the subject with feedback (in the form of changes in tension) when he or she moves.

Head motion can also be minimized through subject training. At many centers, subjects participate in training sessions within an MRI simulator, or mock scanner, that is constructed from the parts of a decommissioned scanner (Figure 8.21A). Recorded scanner noises can be played within the bore of the simulator for added realism, and (at some centers) head position can be monitored.

Figure 8.21 Use of a mock scanner system for prevention of head motion. By acclimating potential subjects to the MRI environment in a simulated or mock scanner (A), head motion and other subject compliance problems can be greatly reduced. (B) An adolescent subject with a head-tracking system around her forehead. If she moves her head beyond a threshold amount, the movie that she is watching through the mirrored glasses will stop playing.
coregistration  The spatial alignment of two images or image volumes.

reference volume  A target image volume to which other image volumes are to be aligned.

rigid-body transformation  A spatial transformation that does not change the size or shape of an object; it has three translational parameters and three rotational parameters.

translation  The movement of an object along an axis in space (in the absence of rotation).

rotation  The turning of an object around an axis in space (in the absence of translation).

cost function  A quantity that determines the amount of residual error in a comparison.

mutual information  In the context of MRI, the amount of information about one image that is provided by knowledge of another image.

itor (Figure 8.21B). Mock-scanner training can make subjects more relaxed and comfortable during their real scanning sessions. Subjects who cannot tolerate confinement in the mock scanner, or who cannot avoid moving their heads over the course of the mock scanning session, can be excused from further participation.

**Correction of head motion**

When the head moves during an experiment, some of the images will be acquired with the brain in the wrong location. The goal of motion correction is to adjust the series of images so that the brain is always in the same position. The general process for spatially aligning two image volumes is called coregistration. For motion correction, successive image volumes in the time series are coregistered to a single reference volume. Because the brain's size and shape do not change, a rigid-body transformation is often used. Rigid-body transformations assume that the size and shape of the two objects to be coregistered are identical, and that one can be superimposed exactly upon the other by a combination of three translations (i.e., moving the entire image volume along the \( x \), \( y \), and \( z \)-axes) and three rotations (rotating the entire image volume through the \( x-y \), \( x-z \), and \( y-z \) planes). The assumption of rigid-body movements is generally plausible in fMRI studies, although inhomogeneities in the magnetic field may lead to differential scaling of images depending on their position in the scanner.

To determine the likely amount of head motion, computer algorithms identify the set of translation and rotation parameters that provides the best match to a reference volume, such as the first image acquired in the session (Figure 8.19). The mathematical measure of how well one image matches another is determined by a similarity measure, or cost function. In the ideal case of perfect coregistration between the corrected volume and the reference volume, a voxel-by-voxel subtraction would yield a difference of zero. A simple cost function, then, could be the sum of absolute intensity differences between voxels in the corrected and reference volumes. Since large differences are much more problematic than small differences, other cost functions weight large movements more heavily. Different cost functions are sensitive to different aspects of the data. For example, in 2001 Freire and Mangin reported that using the sum of squared differences as a cost function can sensitize the coregistration to the presence of large task-related BOLD activations, and this can shift the images and introduce spurious activations at high contrast borders. Other cost functions that minimize the mutual information between volumes are less sensitive to such task-related effects. Mutual information is a measure roughly analogous to correlation, which considers how well a voxel's intensity in the reference volume predicts, or reduces the uncertainty about, the intensity of a voxel in the corrected image. Unlike the sum of squared deviations, mutual information does not assume that the intensities within the coregistered images must match. Motion correction is sometimes done on smoothed images to minimize the effects of noise within the image on the cost function.

Regardless of the cost function chosen, the goal of coregistration is to find the transformation at which the smallest value of the cost function is obtained. It is not computationally feasible to compare, with high precision, all possible ways in which the head could move for each of hundreds of volumes acquired during an experiment. Thus, to minimize computational costs, realignment algorithms use iterative approaches that include an initial rough estimation followed by more precise refinement. While faster than testing all possible
movements, these algorithms have the minor disadvantage of potentially identifying a local minimum in the cost function, rather than the global minimum corresponding to the true motion.

Once a set of realignment parameters is determined, the next step is to resample the original data to estimate the values that would have been obtained had there been no head motion. This process is called spatial interpolation and is similar to the temporal interpolation described earlier in the chapter. However, whereas temporal interpolation only considers the single dimension of time, spatial interpolation considers the three dimensions of space. Simple trilinear interpolation assumes that each interpolated point should be a weighted average of all adjacent points. More complex sinc interpolation is optimal for well-sampled images, but may introduce artifacts if the data are not band-limited; that is, if there are important spatial frequencies in the brain that are not represented in the image.

Most researchers minimize the effects of head motion during preprocessing by using co-registration algorithms or, less frequently, by removing motion-related components from the data with filtering techniques (e.g., independent components analysis). It is also possible to isolate motion effects within experimental analyses. Including the calculated motion parameters as regressors reduces the amount of error (i.e., unaccounted-for variability) in the analysis model, which can increase the experimental power for detecting effects of interest. In a 2005 study, Johnstone and colleagues demonstrated that the inclusion of motion parameters in the experimental model can have a positive effect on the sensitivity of the analysis to true activations, especially within event-related designs. However, as already noted, head motion is often correlated with the experimental task, so including motion parameters in analysis models can also remove task-related activity.

Motion correction has become a standard part of fMRI preprocessing and is now used in nearly all published fMRI studies. The major software packages for fMRI analysis all include some form of motion correction, although the algorithms differ from package to package. When different motion correction approaches have been systematically compared, both on simulated and real fMRI data, the results have been equivocal. To a first approximation, all major packages do a creditable job correcting for motion, in that they all provide significant and measurable increases in the amplitude and specificity of BOLD activation. However, no one approach seems demonstrably superior to the rest. This suggests that the current approaches to motion correction provide robust and effective methods for improving fMRI data quality, although future advances remain possible. One target for future study will be using motion parameters to estimate the history of excitation of each voxel, potentially leading to changes in the predicted BOLD signal changes. While not part of most current approaches, the inclusion of spin history effects may become a standard part of preprocessing in the coming years.

**Distortion correction**

As we learned in Chapter 5, functional images often suffer from geometric or intensity distortions that preclude simple matching to the high-resolution structural images. The most common cause of such distortions is field inhomogeneities. Static field inhomogeneities usually cause geometric distortions, although they can also lead to signal losses under severe conditions. Excitation field inhomogeneities (i.e., uneven excitation or reception across space) usually cause intensity variations within the image. To ensure that images pro-
Figure 8.22 Correction of geometric distortions in functional images. In this image of a spherical phantom (A), there is obvious geometric distortion. To correct for the distortion, a map of magnetic field intensity is acquired (B). The intensity map can be used to generate a corrected image (C).

To provide a true and undistorted representation of the functional neuroanatomy, researchers use specialized acquisition techniques and computational algorithms that correct the acquired images to account for these distortions.

A common method to prevent non-uniformity within the static magnetic field is magnetic field shimming. By adjusting many first-, second-, and higher-order magnetic field gradients generated by shimming coils (see Chapter 2), most field distortions can be corrected and a reasonably homogeneous field can be created. However, when shimming conditions cannot be optimized, especially at very high magnetic field strengths, residual magnetic field inhomogeneities may remain significant enough to induce noticeable geometric distortions (Figure 8.22). An alternative approach, called magnetic field mapping, can be adopted to provide explicit knowledge of the static magnetic field. A field map of the main magnetic field can be created by acquiring two images of the signal phase with slightly different echo times. The difference between the phase images is proportional to the strength of the field at any given location. If the field is completely uniform, then the phase difference induced by the different echo times will be the same in all voxels, and the resulting image will be a uniform gray. Field maps can be determined for a phantom or human brain and can be incorporated into the image reconstruction routine to correct for any geometric distortions.

**Thought Question**

Why does acquiring images of the spin phase at two different echo times provide a measure of local magnetic field strength?

A common method to prevent non-uniformity in the excitation field is to construct very homogeneous volume transmitter and receiver coils. While the physical principles for producing such coils are well worked out (see Chapters 2 and 3 for additional discussion), in practice, even the best-constructed volume coils have residual intensity variations across space. This problem is exacerbated by the use of high-sensitivity surface coils, which by design intro-
duce large, spatially dependent intensity variations. Thus, it would be useful to have explicit knowledge of the excitation field, so intensity compensation algorithms can be applied post hoc, based on such knowledge. To create a map of the excitation field, a large uniform object (e.g., a water-filled phantom) is placed in the center of the magnetic field. For each voxel in the phantom, the recorded signal depends on two factors: the number of spins (e.g., hydrogen nuclei in a proton-density scan) and the strength of the excitation field at that location. The number of spins should be approximately constant across the phantom, since it is homogeneous; thus, any differences in intensity across the image will be due to variations in the strength of the excitation field.

New techniques can correct for intensity variations even when the user does not have explicit knowledge of the imperfections in the static or excitation fields. These techniques can be especially useful when field maps are not available (i.e., for previously acquired images). One promising technique is based on bias field estimation. This technique is used to estimate a map of intensity variations across space (i.e., the bias field) using the distorted image itself. Because the image reflects a combination of the true data (e.g., the actual number of protons or the real changes in blood oxygenation) and the distorting effects of the bias field, researchers must estimate the bias field by making assumptions about the properties of the noise and the smoothness of the signal. This determines the most likely pattern of distortions and thus recovers an estimate of the true data. An example of bias field correction is shown in Figure 8.23. Common methods rely on Markov random field models and their associated expectation-maximization algorithms to create a map of global and local signal gradients. While a detailed explanation of these methods is beyond the scope of this book, we refer interested readers to the Guillemaud and Brady reference listed at the end of the chapter.

**Figure 8.23** Bias field estimation and correction. There is a decrease in MR signal at the bottom (indicated by arrows) of this structural image (A). To correct for this signal loss, the relative intensity of the magnetic field is estimated (B), and a correction factor is applied to the original image. The low-signal region is corrected in the resulting image (C).
Bias field estimation and correction can substantially improve aspects of analysis that are dependent upon image uniformity. For segmentation algorithms to be accurate, different tissue types need to have similar values throughout the brain. Large bias field differences can cause discrepancies in gray/white contrast in different locations. Intensity values can be normalized throughout the brain by estimating and correcting for such inhomogeneities, thus improving the accuracy of segmentation.

Functional–Structural Coregistration and Normalization

The spatial and temporal corrections described in the previous sections ensure that each voxel contains data from a single brain region, as sampled at regular intervals throughout the time series. Such corrections are sufficient for analyses of the functional data from a single subject. Yet in most experiments, researchers want to understand how activation corresponds to the underlying neuroanatomy. Unfortunately, functional data typically are of low resolution and of little anatomical contrast, and they have geometric and intensity distortions, as we discussed above. Because of these limitations, we must often map our functional data onto high-resolution and high-contrast structural images. To facilitate this mapping, coregistration algorithms link the functional images to high-resolution structural images from the same subject.

Even if brain activity can be well localized within a subject through coregistration, there remains the problem of comparing activation between individuals, whether in the same study or in different studies. Some subjects have very large brains, while others have very small brains, and there is wide variation in shape, orientation, and gyral anatomy. For intersubject comparisons to be feasible, images of each subject’s brain must be transformed so that they are the same size and shape as all of the others. This process is called normalization. Coregistration and normalization are important preprocessing steps for most fMRI studies, especially those that use voxel-based (i.e., not anatomical region-of-interest) analyses.

Functional–structural coregistration

The differences between functional and structural images of the same brain region are striking. A typical functional image appears as a relatively undifferentiated and blurry blob, with only the ventricles and the barest outlines of gray matter distinguishable (Figure 8.24A). High-resolution structural images appear remarkably detailed by comparison, with clear outlines of the different sulci and gyri and distinct boundaries between the gray and white matter (Figure 8.24B). This additional detail provides several advantages. Whereas anatomical boundaries are difficult, if not impossible, to identify on functional images (e.g., the Sylvian fissure is difficult to find in the functional image), such boundaries and regions of interest can be easily located on structural images. Because the size, shape, and sulcal patterns of the brain are much more distinct on structural images, it is beneficial to use information from structural images to guide the normalization of functional images. As mentioned above, the computational processes that map two types of images (e.g., functional and structural) on to each other are known as coregistration.

One may question the necessity of functional–structural coregistration, because both types of image are typically acquired in the same scanner ses-
sion. Yet, in many cases the two types of image are acquired at different locations, either because different slices were wanted for each, or because the subject moved slightly between their acquisitions. A rigid-body transformation may be conducted for coregistration in which a cost function is minimized. However, because structural and functional images often have different, sometimes even opposite, contrasts, some cost functions, such as the sum of squared differences, are not appropriate. Cost functions based on mutual information, for example, can overcome this problem. Moreover, some pulse sequences used to acquire functional images may introduce subtle geometric distortions; for example, echo-planar functional images may be slightly stretched along one axis relative to a high-resolution structural image obtained from the same subject in the same session. If present, these distortions cannot be corrected by the six-parameter rigid-body transformation that we use for motion correction. If the distortion is linear, such that all voxels are similarly stretched along one or more axes, then a nine-parameter linear transformation can be used. In this transformation, three additional parameters are introduced to account for scaling differences along the x-, y-, or z-axes. If the distortion is more complex, with regions of greater and lesser stretching, then more-complex warping algorithms must be employed.

**Spatial normalization**

The human brain has remarkably variable morphology. The average adult brain is approximately 1300 cubic centimeters (cc) in volume, with values ranging from 1100 cc to 1500 cc (Figure 8.25). Thus, two subjects in the same fMRI experiment may differ in overall brain size by 30% or more. This difference is proportionally much smaller than the range in total body mass, which normally varies by about a factor of two or three in the adult population. There is also substantial variation in the shape of the adult human brain. For example, some people have brains that are longer and thinner than others. The differences may be especially pronounced in particular regions. The organization
of gyri and sulci is sufficiently variable that even major landmarks, like the calcarine sulcus that divides the primary visual cortex, can have different positions and orientations in different individuals.

Normalization is a form of coregistration, except that here the image volumes to be compared differ in shape fundamentally rather than as a result of image distortion. The goal of normalization is to compensate for these shape differences by mathematically stretching, squeezing, and warping the images of each brain so that they are the same as those of every other brain. The concept of normalization should be familiar to anyone who has watched as computerized morphing programs transform one person's face into another's. Most
fMRI analysis packages include modules that normalize data into a common space. Although these programs are largely automated, researchers should always check the output of automated steps, as errors in normalization will propagate throughout the rest of the analyses.

Normalization of data within a study allows for the combination of data from different individuals. Furthermore, if data from two different studies have been normalized in the same fashion, then the areas of activity found in each study can be compared. For this reason, many journals encourage the reporting of experimental data as coordinates within a common normalization scheme, or stereotaxic space. The most widely used stereotaxic space is Talairach space, which was created by the French physician Jean Talairach and colleagues, and is based on a simple stereotaxic framework derived from measurements on a single brain, that of an elderly woman. The origin of the space is set at the midpoint of the anterior commissure, with the x- and y- axes defined by the horizontal plane connecting the anterior and posterior commissures (Figure 8.26). While the standardization provided by this framework has been extraordinarily important for neuroscience, the use of a single brain presents many problems, notably that the brain used was unrepresentative of the population at large. A better approach has come from recent attempts at creating probabilistic spaces using combined data from hundreds of individual scans. A commonly used-space was created by the researchers at the Montreal Neurological Institute, and was based on the anatomies of more than one hundred individuals. The template for MNI space has been scaled to match landmarks within the well-established Talairach atlas. Most normalization algorithms are based on such probabilistic templates. See the article by Chau and McIntosh in the Chapter References for an interesting comparison of these template spaces.

To warp a given brain to a template, normalization algorithms determine the overall size of the brain, as well as its gross anatomical features. Some algorithms also require the identification of key landmarks in the brain, such as major sulci; this may be done automatically, or require user input. Some researchers

Figure 8.26 Typical coordinate axes for fMRI data. The most common axes for fMRI data define the x-axis as left to right and the y-axis by connecting the anterior and posterior commissures. The z-axis is perpendicular to the plane created by the other two lines.
cytoarchitecture The organization of the brain on the basis of cell structure.

filter Within the context of fMRI, an algorithm for removing temporal or spatial frequency components of data.

advocate surface-based normalization approaches. In these, the cerebral cortex, which is effectively just a large ~5 mm-thick sheet folded into a complex topography, is unfolded and blown up into a balloon shape. Surface-based approaches can have significant advantages in separating activations that are near to each other in volume space but not near each other in neural space (e.g., activation from voxels on opposite sides of a sulcus), especially if functional SNR is high.

Even if normalization algorithms were able to transform the images of two brains into the same stereotaxic framework, this would not mean that the brains would have activation in exactly the same voxels. Remember that normalization is based on gross morphological features of brains. These gross features do not necessarily indicate functional divisions between brain areas. More predictive of brain function are the regional cellular properties, or cytoarchitecture, which are usually not visible in MR images. Just as sulci and gyri are highly variable between individuals, so too are the boundaries between cytoarchitectonically distinct regions. For an example of the quantification of individual differences in the cytoarchitectonic organization of the human brain, see the work of Rajkowska and Goldman-Rakic in the Chapter References.

Normalization is a powerful technique that enables the testing of complex hypotheses with improved statistical power, and its positive impact on functional neuroimaging cannot be overstated. However, there are some caveats. Variability in brain features across individuals introduces theoretical constraints on normalization. Nearly all normalization approaches are based on subject samples drawn from the standard population of fMRI participants: young, typically college-age adults who are healthy and neurologically normal. Many other groups systematically differ from this population in the properties of their brains. The brains of elderly individuals may have atrophy, manifested as sulcal widening and enlarged ventricles. Young children may have differently-shaped brains, due to delayed maturation of some regions (e.g., the frontal cortex), and their images may have different contrast properties associated with reduced neuronal myelination. Male and female brains also differ in subtle ways. Thus, normalizing functional results between different subject groups may mask important group differences.

Variability in brain features across individuals also introduces practical constraints on normalization. Many patient groups have a specific local pathology associated with their disorder, while patients with tumors may have brains that are apparently normal in most regions but have severe distortions in the lesion area. Since most normalization approaches attempt to minimize the differences between the subject’s brain and some template, abnormal features may reduce the accuracy of the matching process. Some normalization approaches have been developed for non-typical subject populations, but this remains an area of considerable interest. By its very nature, normalization emphasizes that which is common among individuals and de-emphasizes that which is unique. Small but meaningful variations among individuals’ functional neuroanatomy may be lost through this process. Investigators interested in individual differences may wish to consider alternatives to normalization, such as subject-based region-of-interest analyses.

Temporal and Spatial Filtering

Filters are used to remove or retain different frequency components that are present in a composite signal. Filters can operate on 1-D temporal data, such as a voxel’s time course of intensity changes, and on 2- or 3-D spatial data, such as adjacent voxels in a BOLD-contrast image volume. In neuroimaging, filters
are used to remove uninteresting variation in the data that can be safely attributed to noise sources, while preserving signals of interest. Thus, filtering can be used to increase functional SNR. Moreover, by reducing the dimensionality of the data, filters can reduce the problem of multiple statistical comparisons. In this section, we will explore both uses of filters in fMRI preprocessing.

**Temporal filtering**

The use of temporal filters can substantially improve the quality of fMRI data by improving functional SNR. To describe how temporal filters work, we will begin by reintroducing the concept of the frequency spectrum of a signal. Consider a time series of data recorded from a single voxel, which describes the behavior of the voxel in the time domain. The same data can be converted, using a Fourier transform, to the frequency domain. The frequency range that is present in a sampled signal depends on its sampling rate, which is given by the TR for fMRI data. The maximum frequency that can be identified, or the Nyquist frequency, is equal to one-half of the sampling rate. For example, if the sampling rate is 0.5 Hz (TR of 2000 ms), any frequencies in the underlying signal higher than 0.25 Hz would not be present in the sampled data. Instead, power at those frequencies would be aliased, or artifactually present at other frequency values. Because of the Nyquist limitation, we must sample the brain at twice the rate of any phenomenon of interest.

**Thought Question**

Based on what you learned in earlier chapters, what disadvantages are there for collecting images at very high temporal resolution (short TR)?

In the example shown in Figure 8.27, there is considerable power at about 0.025 Hz, which approximately corresponds to the task frequency. These two

![Figure 8.27](image_url)
graphs show exactly the same data, only transformed from one domain to another. In our analyses, we want to keep information about changes in the data that occur at the task frequency, but minimize changes in the data that occur at other frequencies. That is, we wish to reduce the contribution of noise from other frequency ranges. Suppose that we knew, based on physiological measurement that a subject breathed every 4 seconds (0.25 Hz), on average, during this run (see Figure 8.8 for an example). Since we are not interested in breathing, we would like to remove the effects of breathing from the data. But how? To reduce the influence of breathing, we construct a temporal filter that selectively attenuates frequencies around 0.25 Hz but leaves other frequencies essentially intact. This is called a band-stop filter, since it attenuates a range or band of frequencies. A low-pass filter leaves low frequencies intact while attenuating high frequencies, and a high-pass filter stops only low frequencies.

The choice of filter depends on what sort of variability should be eliminated. Typical heart rates during an fMRI experiment vary, but are often between 1.0 and 1.5 Hz. The rate of respiration is slower, about 0.2 to 0.3 Hz. For comparison, a typical experimental design might present alternating blocks of 12 s of task and 12 s of rest, for a total presentation rate of 0.04 Hz. A low-pass filter that excluded frequencies above 0.2 Hz could remove physiological oscillations without significantly reducing the ability to detect the task effect of interest. However, if the experiment used a fast event-related design in which stimuli were presented more rapidly (i.e., every few seconds), the task and respiration would be at similar frequencies, and such filtering would be extremely difficult. Changes of very low frequency are also observed in fMRI experiments, such as those related to scanner drift. These changes often take the form of near linear increases or decreases in absolute signal over the course of a several-minute experimental run. Such very slow changes can be extremely problematic for fMRI experiments, especially those using long-interval blocked designs. High-pass filtering of the data can remove slow drift-like trends. It is important to recognize that none of these factors, whether task, physiology, or drift, contributes to only a single frequency. For example, if the time course is not sufficiently well sampled, a high-frequency factor like heart rate could be aliased to a lower frequency, perhaps within the task range. All these factors provide energy at many frequencies, and as a result, temporal filtering should be done with caution.

An additional temporal consideration for fMRI analysis is the presence of temporal autocorrelation. That is, in all fMRI data series, the amplitude of the BOLD signal at past time points could be used to predict its amplitude at future time points. These regularities, if unaccounted for, can reduce the validity of the statistical models used for fMRI analyses. To minimize the effects of temporal autocorrelation, fMRI analysis packages use prewhitening algorithms that effectively eliminate that portion of the BOLD signal that is predicted by the previous time points. If successful, the residual signal (which can be used for fMRI analyses) becomes white noise, such that each time point is unrelated to its predecessors. This can greatly improve the ability to identify task-related signal changes. While prewhitening can be highly valuable for fMRI data, its effectiveness depends on the ability to accurately estimate the degree of autocorrelation, and researchers have developed multiple methods for this estimation. An alternative approach, precoring, involves the introduction of specific autocorrelations into the dataset. Although precoring is generally less effective than prewhitening, it can be more successful when the temporal autocorrelation cannot be well estimated.
Spatial filtering

In many fMRI analyses, low-pass spatial filters are employed to reduce the high-frequency spatial components and "smooth" the images. The most common spatial smoothing technique is the introduction of a Gaussian filter. A Gaussian filter has the shape of a normal (or "bell-curve") distribution. When a Gaussian spatial filter is applied, it effectively spreads the intensity at each voxel in the image over nearby voxels. The width of the filter refers to the distance of its effect: a narrow filter spreads data over only a few voxels, while a wide filter spreads data over many voxels. Spatial filter width for fMRI data is generally expressed in millimeters at half of the maximum value (full-width-half-maximum, or FWHM).

What are the advantages of spatially filtering fMRI data? The foremost advantage can be understood in terms of the principle of matched filters, which indicates that using a filter of the same frequency as the signal of interest maximizes SNR. This is similar to the concept of the band-stop filter for temporal data described in the previous section. In fMRI images, the width of the signal of interest can be understood in a literal sense: the typical spatial extent of regions of activity. If there were no spatial correlation in fMRI data, so that one could not predict whether a voxel is active based on whether its neighbors are active, then spatial filtering would reduce SNR. However, all fMRI data have spatial correlation, due both to functional similarities between adjacent brain regions and to blurring introduced by the vascular system. The cerebral cortex itself has a depth of about 5 mm, so activation of even a single cortical column can result in two or three active voxels, depending on their size. Additional spatial correlation is introduced when comparing subjects. Because all subjects' brains differ in shape and size, and potentially in functional organization, areas of activation are rarely represented in exactly the same voxels. Instead, combining data from many subjects distributes activation across a range of voxels. By using a filter that matches the expected spatial correlation of the data, one can increase SNR considerably with a minimal loss of spatial resolution. These advantages of spatial smoothing may become more important as field strength increases. As discussed earlier in the chapter, at high field strengths (e.g., greater than 3.0 T) most noise is physiological rather than thermal. Recent research using a 7.0-T scanner suggests that collecting high-resolution data and then smoothing to a desired lower resolution improves functional SNR, compared with collecting data at the lower resolution directly.

A second advantage of spatial filtering lies in improving the validity of statistical techniques. During the analysis of any fMRI dataset, there will be an enormous number of statistical tests. In a typical functional imaging volume, there may be more than 100,000 voxels, each of which is evaluated for significant differences in signal. If the threshold for significance is set at \( \alpha < 0.05 \), as is frequently done for psychological or medical experiments, then there should be more than 5000 voxels that show significance due to chance alone. This is known as the multiple comparison problem, and is discussed in detail in Chapter 10. But if the data are spatially correlated, then there may be many fewer local maxima that exhibit significant activation (Figure 8.28). In addition to its effects on false-positive rates, smoothing provides the additional benefit of improving the validity of experimental tests by making parameter errors more normal. Any derived parameter, such as the significance value measured at a single voxel, can be considered to be a combination of its true value along with some error. Many common statistical tests assume that error in measurement is normally distributed. Smoothing increases the normality
of data, because averaging of multiple observations tends toward the normal distribution, regardless of the properties of the individual observations (i.e., due to the Central Limit Theorem). Therefore, smoothing can have a positive effect on fMRI statistical analyses.

These advantages of spatial filtering can be particularly valuable for areas of the brain with low functional SNR. Parrish and colleagues conducted a set of simulations to determine the approximate SNR values needed to detect a BOLD signal change of a given amplitude, and to see how detection power changes with spatial filtering. They then applied those calculations to an fMRI time series measured for a clinical patient with a vascular malformation near the boundary between the parietal and occipital lobes. Then they repeated their analysis using a 6-mm Gaussian filter. Detection power increased considerably throughout the brain. Where before there was reduced functional SNR near the malformation and the inferior frontal lobe, now there was sufficient power to detect a response through nearly all of the brain. Note that spatial filtering provides an increase in SNR at a cost of reduced spatial resolution.

The primary disadvantages of spatial filtering result from the imperfect match between filter width and activation extent. If the filter used is too large, then meaningful activations could be attenuated below the threshold for significance. This is especially problematic when targeting very small brain regions, such as structures within the midbrain, where only a single voxel may be significantly active. If the filter used is too small, then it will have little positive effect on SNR, while reducing spatial resolution. Typical filter widths for fMRI are about 6 to 10 mm FWHM (i.e., about two to three voxels), although greater or lesser smoothing may be needed, depending on the noise level of the data. It is important to emphasize that spatial smoothing is beneficial for voxel-wise
analyses but has little effect on region-of-interest (ROI) analyses (see Chapter 10). In ROI approaches, the experimenter constructs bounded functional regions for subsequent analysis. The edges of these regions are considered to be meaningful, so their blurring may introduce unwanted variability into the data.

Summary

The core challenge of fMRI analyses is the detection of relatively small task-related variability, or signal, within large non-task-related variability, or noise. Three quantities are important: raw signal-to-noise ratio (raw SNR), contrast-to-noise ratio (CNR), and functional signal-to-noise ratio (functional SNR). Raw SNR depends on the magnitude of signal measured by the scanner compared with thermal noise. CNR depends on the intensity difference between two tissues of interest compared with the variability in intensity within one tissue. Functional SNR determines our ability to detect signal changes associated with experimental effects of interest, and is critical for many aspects of fMRI. While raw SNR scales linearly with the strength of the magnetic field, functional SNR scales less than linearly with field strength due to several sources of noise. Thermal and system variability in scanner hardware contribute to all types of MRI imaging but are much less important than physiological variability for fMRI, especially at high field strengths.

The steps used for minimizing the contributions of non-task-related variability are collectively known as preprocessing. Initial quality assurance tests are important for preventing and diagnosing data problems. Temporal and spatial preprocessing steps correct for variability due to differences in the timing of slice acquisition and in the spatial position of voxels, respectively. The most insidious cause of spatial error is head motion, which can introduce severe artifacts into the analyses, if not prevented or corrected. Spatial errors resulting from inhomogeneities in the static magnetic field or radiofrequency coil can be corrected through mapping or estimation of the resulting distortion field. To improve spatial localization of activity, images may be transformed both by functional–structural coregistration and by normalization. Functional MRI coregistration matches functional data to higher-resolution structural images, enabling the better anatomical localization of activity within a subject. Normalization mathematically warps subjects’ brains to a standard stereotaxic framework, allowing for better comparisons between individuals within a study, as well as allowing the reporting of data derived from common coordinates, for comparisons between studies. Functional resolution can be improved by the judicious use of temporal and spatial filtering. Temporal filtering can remove selected noise components, such as those introduced by physiological processes, and can correct for low-frequency scanner drift. Spatial filtering can increase functional SNR, reduce apparent noise, and increase the validity of comparisons between subjects. However, improperly applied filters can significantly reduce the quality of the data.

Suggested Readings


description of different components of physiological noise.

differences in BOLD responsivity as a function of the depth from the cortical surface,
which corresponds to different layers of neurons.

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and inter-subject variability in fMRI experiments.

Thieme, New York. This atlas has become extraordinarily influential as a reference for
brain anatomy and function.

* Indicates a reference that is a suggested reading in the field and is also cited in this
chapter.

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