Chapter 5

MR Contrast Mechanisms and Pulse Sequences

Compared with other neuroimaging methods, MRI has extraordinary versatility for generating images of a wide range of different tissues. In this chapter, we consider the approaches used to create these different types of contrast. Static contrasts are sensitive to the type, number, relaxation, and resonance properties of atomic nuclei within a voxel. Typical static contrasts are based on density (e.g., proton density), relaxation time (e.g., $T_1$, $T_2$, $T_2^*$), chemical concentration (e.g., lactate or acetylcholine), and even content of a particular molecular type (e.g., macromolecules). We use images influenced by static contrast to determine brain anatomy in fMRI experiments. Motion contrasts are sensitive to the movement of atomic nuclei. Typical motion contrasts provide information about the dynamic characteristics of the protons in the brain, such as blood flow in MR angiography, water diffusion in diffusion-weighted imaging, or capillary irrigation in perfusion-weighted imaging. We will also discuss some of the most common techniques for collecting images rapidly, at the time scale needed for fMRI, and their associated pulse sequences.

A further distinction can be drawn depending on whether the contrast is derived from intrinsic properties of the biological tissues (i.e., endogenous contrast) or from the presence of foreign substances that have been introduced into the body (i.e., exogenous contrast). Nearly all fMRI experiments result in images that are derived from an endogenous contrast mechanism: the amount of deoxygenated hemoglobin within a brain region. An example of an exogenous contrast mechanism is the injection of gadolinium-DTPA, a rare earth compound that has extremely high magnetic susceptibility, and which greatly distorts the surrounding magnetic field. The use of exogenous agents is a common practice in clinical MRI for enhancing both static and motion contrasts, but it is less prevalent in functional studies due to the obvious safety issues associated with any injections. In the following sections, we will focus on endogenous contrast measures, especially those commonly used in structural and functional brain imaging. Potentially valuable advances in the application of exogenous contrast to fMRI are considered in Chapter 12, which covers advanced MRI techniques.
Static Contrasts and Related Pulse Sequences

Static contrast mechanisms have been widely used in MRI due to their ability to illustrate basic tissue characteristics. To understand how static contrast can be generated, we consider first the simple cases of $T_1$ and $T_2$ contrast. As derived in the previous chapters, there are two equations for magnetization after an initial excitation of a fully recovered spin system (Figure 5.1). Equation 5.1 describes the longitudinal magnetization:

$$M_z(t) = M_0(1 - e^{-t/T_1})$$

Equation 5.2 describes the transverse magnetization:

$$M_{xy}(t) = M_0 e^{-t/T_2}$$

There are two important factors that govern the time at which MR images are collected. The first factor is the time interval between successive excitation pulses, which is known as the repetition time, or TR. Often, consecutive excitations occur at time intervals not long enough to allow full recovery of the longitudinal magnetization. Under such short TRs, the subsequent transverse magnetization, which translates to detectable MR signal, should be described as

$$M_{xy}(t) = M_0(1 - e^{-TR/T_1}) e^{-t/T_2}$$

This equation illustrates that the MR signal depends not only on the original magnetization (which in turn depends on proton density) but also on the properties of the tissue being imaged, as expressed through both the $T_1$ and $T_2$ constants (Table 5.1). Shown in this table are rough values for the time constants $T_1$ and $T_2$ at a field strength of 1.5 T. Another value of interest is the $T_2^*$ value

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**Figure 5.1** Changes in longitudinal and transverse components of magnetization. (A) The time constant $T_1$ is usually on the order of 1 s, so recovery of longitudinal magnetization ($T_1$ recovery) occurs over a period of several seconds. (B) The time constant $T_2$ is typically on the order of a few tens of milliseconds, so decay of transverse magnetization occurs over a period of about 100 ms. The values used for $T_1$ and $T_2$ in these plots are similar to those for gray matter at field strengths used for fMRI studies.
TABLE 5.1 Rough Values for the Time Constants T₁ and T₂ at Field Strength of 1.5 T

<table>
<thead>
<tr>
<th></th>
<th>Gray Matter</th>
<th>White Matter</th>
<th>Cerebrospinal Fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₁</td>
<td>900 ms</td>
<td>600 ms</td>
<td>&gt;2000 ms</td>
</tr>
<tr>
<td>T₂</td>
<td>100 ms</td>
<td>80 ms</td>
<td>2000 ms</td>
</tr>
</tbody>
</table>

for gray matter, about 40 ms at 1.5 T, which determines the echo time (TE; see definition below) used for BOLD-contrast fMRI images. Note that the values given in the table are only approximate, as these constants will vary according to field homogeneity and other factors. Moreover, each constant changes with field strength: as field strength increases, T₁ gets longer, while T₂ and T₂* get shorter. We provide these approximate values as a guideline for thinking about the contrast mechanisms discussed in this chapter. In Equation 5.3, the term \((1 - e^{-TR/T₁})\) accounts for the incomplete recovery of the longitudinal magnetization, which will reach a steady state after repetitive excitations. If the TR is much longer than T₁, then this term approaches one (i.e., full recovery) and can be removed from the equation.

The second factor that governs the timing of MR image collection is the echo time (TE), which is the time interval between excitation and data acquisition (from the center of k-space). Remember that the MR signal received at the center of k-space has the greatest amplitude, as described in the previous chapter, so at that point it resembles an echo of the initial transmission. For simplicity, we can replace the term \(i\) with TE to give the MR signal for an image with a given TE.

\[
M_{xy}(t) = M_0 \left(1 - e^{-TR/T₁}\right) e^{-TE/T₂} \tag{5.4}
\]

Equation 5.4 provides the foundation for manipulating the signal from a particular tissue type by controlling TR and TE. However, in MRI we are interested in comparing MR signals from multiple tissue types. The signal difference between any two types of tissue is known as contrast. For tissue types A and B, the contrast between them, \(C_{AB}\), is simply the difference between the MR signals associated with each (Equation 5.5). The terms \(M_{0A}\) and \(M_{0B}\) are the original magnetization values for tissues A and B, \(T₁A\) and \(T₁B\) are the \(T₁\) values of A and B, and \(T₂A\) and \(T₂B\) are the \(T₂\) values of A and B.

\[
C_{AB} = M_{0A} \left(1 - e^{-TR/T₁A}\right) e^{-TE/T₂A} - M_{0B} \left(1 - e^{-TR/T₁B}\right) e^{-TE/T₂B} \tag{5.5}
\]

Proton-density contrast

One of the simplest forms of MR contrast is proton-density imaging. The net magnetization of each voxel reflects the total contribution from all of that voxel’s spins, most of which are hydrogen atoms (i.e., protons). Proton-density images, as the name implies, provide contrast based on the sheer number of protons in a voxel, which of course differs in different tissue types. To maximize proton-density contrast, researchers use pulse sequences that minimize \(T₁\) and \(T₂\) contrasts. To minimize \(T₁\) contrast, a pulse sequence must use either a very short or very long TR, and to minimize \(T₂\) contrast, a pulse sequence must use either a very short or very long TE. Logically, either long or short values for either parameter would work for proton-density-weighted images (i.e., images whose intensity depends primarily on relative proton density). In 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.

echo time (TE) The time interval between an excitation pulse and data acquisition (defined as the collection of data from the center of k-space), usually expressed in milliseconds.

proton-density imaging The creation of MR images that are sensitive to the number of protons present within each voxel.
practice, however, the use of extremely short TR or long TE values results in low MR signal. To maximize proton-density weighting while still recovering sufficient MR signal, pulse sequences are used that have very long TR values (Figure 5.2A) and very short TE values (Figure 5.2B). In practice, a TR greater than $T_1$ and a TE less than $T_2$ satisfy the criteria. If the TR used is much greater than the $T_1$ value of the tissue being imaged (e.g., two to three times as long), the protons will be nearly fully recovered after each excitation. Likewise, if the TE value is much less than the $T_2$ value (e.g., one tenth as long), there will be minimal decay before image acquisition.

**Thought Question**

How does the concept of proton density relate to the concept of net magnetization?

One disadvantage of using a very long TR is that it greatly increases imaging time. In many situations, such as when scanning patients who have difficulty tolerating lengthy MRI sessions, slow imaging sequences may not be feasible. To reduce acquisition time while still maintaining proton-density contrast, a smaller flip angle (less than $90^\circ$) may be used for excitation, to only partially tip the longitudinal magnetization toward the transverse plane. This will require less time to achieve full longitudinal recovery. The effect of using a smaller flip angle for partial excitation is illustrated in Figure 5.3, where it can be seen that a shorter TR can be used without introducing significant $T_1$ weighting (see below for the definition of a $T_1$-weighted image), effectively reducing the imaging time. In summary, to generate images sensitive to proton density, we must collect those images using a pulse sequence with a long TR and a short TE.
As long as there is sufficient $T_1$ recovery and minimal $T_2$ decay, any type of pulse sequence, including common gradient-echo (GRE) imaging and spin-echo (SE) imaging sequences, can acquire proton-density images. A gradient-echo sequence uses only gradients to generate the signal echo in the center of $k$-space. A spin-echo sequence, on the other hand, uses a second 180° electromagnetic pulse, called a refocusing pulse, to generate the signal echo. We will discuss examples of these types of sequences throughout this chapter.

An example of a proton-density gradient-echo sequence, which is often used due to its very fast acquisition rate, is shown in Figure 5.4A. Here, the excitation pulse is immediately followed by the data acquisition period (indicated by DAQ in the figure), so that there is little signal decay due to transverse relaxation. In addition, the very long repetition time allows the excited magnetization to fully recover before the subsequent excitation. A sample proton-density-weighted image is shown in Figure 5.4B. The highest signal is evident in the cerebrospinal fluid (CSF) and ventricles (e.g., at the center of the image), with less signal in the gray matter, even less signal in white matter, and the lowest signal in air. These intensity values are consistent with the relative densities of the tissues. The greatest tissue density, and hence the most protons, in the brain will be found in fluid-filled regions like the ventricles. Gray matter, which is composed of both cell bodies and the supporting vasculature, weighs proportionally less, and white matter, which is mostly axonal projections across the brain, weighs even less.

Proton-density images can be used as high-resolution reference images for determining anatomical structure in the brain. For this reason, they are often an important part of fMRI studies. In addition, the intensity values they provide can be used to improve algorithms for labeling different parts of the brain according to the types of tissue they contain (e.g., gray matter vs. white matter). Such segmentation approaches are often important when understanding how damage or atrophy in a region alters its functional properties, such as in the study of disease or aging. To facilitate tissue segmentation, proton-density images are frequently acquired at the same slice locations as $T_1$- or $T_2$-weighted images (see below) so that complementary anatomical information can be acquired.

**Figure 5.3** The use of a smaller flip angle in proton-density imaging. One approach for minimizing the acquisition time necessary for proton-density imaging is to reduce the flip angle of the excitation pulse. With a typical 90° excitation pulse the net magnetization (blue solid line) takes a long time to reach a near maximal level, as indicated by the blue dashed line. But if the flip angle of the excitation pulse is reduced, there is only partial excitation. In this latter case, the net magnetization (red solid line) reaches the same near maximal level much more rapidly, as indicated by the orange dashed line.

**gradient-echo (GRE) imaging** One of the two primary types of pulse sequences used in MRI; it uses gradients to generate the MR signal changes that are measured at data acquisition.

**spin-echo (SE) imaging** One of the two primary types of pulse sequences used in MRI; it uses a second 180° electromagnetic pulse to generate the MR signal changes that are measured at data acquisition.

**refocusing pulse** A 180° electromagnetic pulse that compensates for the gradual loss of phase coherence following initial excitation.

**segmentation** The process of partitioning an image into constituent parts, typically types of tissue (e.g., gray matter, white matter) or topographical divisions (e.g., different structural regions like Brodmann areas).
Figure 5.4 A pulse sequence used for proton-density imaging. The primary requirements for proton-density imaging are a very short TE and a very long TR, such as those used in this gradient-echo sequence (A). The resulting image (B) is brightest in voxels with high density (e.g., CSF within ventricles) intermediate in gray matter, and darkest in areas of low density (e.g., air, white matter). The data acquisition period is indicated by DAQ. In this and subsequent pulse sequence diagrams, the line labeled RF describes the signals sent via the radiofrequency head coil, while the lines labeled $G_x$, $G_y$, and $G_z$ describe the direction and strength of the gradients along each of the three cardinal axes.

$T_1$ contrast

While proton-density images have many uses, other forms of contrast emphasize differences in the relaxation properties of atomic nuclei. The most commonly used structural contrast for anatomical images of the brain is $T_1$ weighting. Images are called $T_1$-weighted, or $T_1$-dependent, if the relative signal intensity of voxels within the image depends on the $T_1$ value of the tissue. Figure 5.5 provides an example of the TR and TE values necessary to generate $T_1$ contrast. At very short TRs, there is no time for longitudinal magnetization to recover and thus no MR signal is recorded for either tissue. Conversely, at very long TRs, all longitudinal magnetization recovers for both tissues. So, at short and long TR values, the amount of longitudinal magnetization will be similar between the tissues. At intermediate TRs, however, there are clear differences between them (Figure 5.5A). The tissue that has a shorter $T_1$ value recovers more rapidly and thus has greater MR signal. For any two tissues that differ in $T_1$, there is an optimal TR value that maximally differentiates between them. To have exclusive $T_1$ contrast, we must also have a very short TE, to minimize $T_2$ contrast. When TE is much less than $T_2$, the term $e^{-TE/T_2}$ from Equation 5.4 becomes approximately equal to 1 (Figure 5.5B). Equation 5.5 then reduces to

$$C_{AB} = M_{0A}(1-e^{-TR/T_1A}) - M_{0B}(1-e^{-TR/T_1B})$$

In this case, $C_{AB}$ depends on TR but not TE. Note that the proton density of the tissues always contributes to the contrast, because the number of spins in the imaging volume determines the original net magnetization. In summary, to generate images sensitive to $T_1$ contrast, we must collect those images using a pulse sequence with intermediate TRs and short TEs.
Just as proton-density contrast can be generated with any type of pulse sequence, $T_1$ contrast will be evident using any pulse sequence that meets the above criteria (i.e., medium TR and short TE). In practice, both gradient-echo and spin-echo sequences are commonly used. Since a gradient-echo pulse sequence was used in the previous example, we show a spin-echo pulse sequence in Figure 5.6A. The hallmark of spin-echo sequences is the 180° refocusing pulse that is applied shortly after the initial 90° excitation pulse. The refocusing pulse corrects for phase dispersion due to $T_2$ effects, so that all spins are approximately in phase during the data acquisition period. This sequence elicits the most signal from white matter and bone marrow, due to their short $T_1$ values, and an intermediate amount of signal from gray matter. Since water has a very long $T_1$ value, very little signal is recovered from cerebrospinal fluid, which becomes nearly indistinguishable from air (Figure 5.6B).

To boost $T_1$ contrast, researchers often use a technique called inversion recovery, which begins the sequence with a 180° inversion pulse rather than the more common 90° pulse (Figure 5.7A). Because the inversion pulse flips the net magnetization to the negative state, it effectively doubles the dynamic range of the signal. To understand the advantage of inversion recovery, consider Figure 5.7B. Shown in red are typical effects of TRs from two different tissues on MR signal. By introducing an inversion recovery pulse, the range over which the signals must recover becomes twice as large (blue curves). This in turn increases the maximal $T_1$ difference that can be measured between the tissues. Inversion recovery is also useful for selectively eliminating the MR signal of a single tissue type. For example, by collecting images using a TR at which the longitudinal magnetization from CSF is zero (the "zero crossing," see arrow in Figure 5.7B), there will be no signal from CSF in any voxel. The suppression of CSF allows better assessment of other tissue types, such as gray and white matter.
Figure 5.6 A pulse sequence used for $T_1$-weighted images. The primary requirements for $T_1$ imaging are a short TE and an intermediate TR. Either gradient-echo or spin-echo sequences can be used. Shown in (A) is a spin-echo sequence. The resulting image (B) is brightest in voxels with short $T_1$ values (e.g., white matter and bone marrow), intermediate in gray matter, and darkest in areas with long $T_1$ values (e.g., CSF). DAQ, data acquisition period.

Figure 5.7 Use of inversion recovery to increase $T_1$ contrast. By including a 180° inversion pulse before a typical gradient-echo or spin-echo sequence (A), the net magnetization can be flipped to the negative state. As a result, the net magnetization must recover over twice the dynamic range, and thus the relative difference in $T_1$ recovery between the tissues is increased. As illustrated in (B), the $T_1$ contrast is much greater for the same pair of tissues following an inversion pulse (blue curves) than under normal conditions (red curves). The green and purple lines indicate the differences between red curves and blue curves, respectively. Inversion recovery sequences can also be used to eliminate MR signal from a tissue of a particular type, by collecting images at a TR that corresponds to the zero crossing for that tissue (arrow).
**T₂ contrast**

T₂-contrast images have maximal signal in fluid-filled regions, which is important for many clinical applications. Many tumors, arteriovenous malformations, and other pathological conditions show up most readily under T₂ contrast. High-resolution T₂ images are also used as anatomical references in fMRI studies, either in isolation or in conjunction with proton-density or T₁ images in a multi-contrast tissue segmentation algorithm. Thus, common clinical protocols include both T₁- and T₂-weighted images.

For T₂-weighted, or T₂-dependent images, the amount of signal loss depends on the time between excitation and data acquisition, or echo time (TE). Again, an optimal combination of TR and TE exists for any two tissues to maximize the T₂ contrast between them (Figure 5.8). If an image is acquired immediately after excitation, such that the TE is very short, then little transverse magnetization will be lost regardless of T₂ and thus there will be no T₂ contrast. If the TE is too long, then nearly all transverse magnetization will be lost and still the image will have no T₂ contrast. But at an intermediate TE, the difference in transverse magnetization can be maximized (Figure 5.8B).

To have exclusive T₂ contrast, we must have a very long TR, so that the longitudinal recovery is almost complete and T₁ contrast is minimal (Figure 5.8A). When the TR is much greater than T₁, the term e⁻¹⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻~-~-⁻~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-~-\(C_{AB} = M_{0A}e^{-TE/T_{2A}} - M_{0B}e^{-TE/T_{2B}}\) (5.7)

In summary, to generate images sensitive to T₂ contrast, we must collect those images using a pulse sequence with a long TR and an intermediate TE.

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**Figure 5.8** Selection of TR and TE values for T₂ contrast. The use of long TR (A) and intermediate TE (B), shown as vertical, dashed orange lines, on two tissues (red and blue) will maximize the T₂ differences between tissues and minimize the T₁ differences between tissues. This combination provides T₂ contrast. The green lines show the relative contrast associated with different TR (A) and TE (B) values.
Figure 5.9 Creating $T_2$-weighted images. The primary requirements for $T_2$ imaging are an intermediate TE and a long TR. (A) Only spin-echo sequences (i.e., those containing a 180° refocusing pulse) can be used. The resulting image (B) is brightest in voxels with long $T_2$ values (e.g., CSF in ventricles) and darkest in areas with short $T_2$ values (e.g., white matter). (C) Restoring phase coherence using a 180° pulse. As time progresses following excitation, magnetic field inhomogeneities will cause a loss of phase coherence over time, as some spins (represented by rabbits) have fast precession frequencies and some (represented by turtles) have slow precession frequencies. If a 180° refocusing pulse is presented at time TE/2, the precession direction will be flipped. At the precise time TE, all of the spins will have their original phases (as indicated here by the return of the rabbits and turtles to their original locations).
Unlike proton-density or $T_1$-weighted images, $T_2$-weighted images can only be generated using spin-echo-based pulse sequences. Only spin-echo sequences allow true spin–spin relaxation that does not depend on the field inhomogeneity. A typical pulse sequence is shown in Figure 5.9A. The resulting brain image will be brightest in fluid-filled regions such as the CSF and ventricles, of medium brightness in gray matter, and darkest within white matter (Figure 5.9B). These intensity values are consistent with the relative $T_2$ values of the regions. Remember from the previous chapter that $T_2$ values depend on spin–spin interactions, and thus homogeneous tissues tend to have longer $T_2$ relaxation periods. For example, CSF has the longest $T_2$ value due to its high water content, gray matter has an intermediate $T_2$ value from its rich blood supply, and white matter has the lowest $T_2$ value (see Table 5.1).

**Thought Question**

Often, proton-density and $T_2$-weighted images are acquired within the same pulse sequence. What aspects of their pulse sequences make this possible?

Because the 180° pulse reverses the loss of phase coherence experienced by spins, spin-echo imaging has little sensitivity to static magnetic field inhomogeneities (e.g., $T_2^*$ effects). As shown in Figure 5.9C, differences in the magnetic field strength experienced by different spins cause loss of phase coherence over time, as some spins will precess faster and some slower. By introducing the 180° pulse at a time point exactly halfway between excitation and TE, the relative phase difference between the spins can be reversed. Therefore, the spins that precess faster will now be behind the spins that precess more slowly, so the faster spins will catch up at time TE. Spin-echo imaging can thus help eliminate the effects of magnetic field inhomogeneities around large blood vessels, minimizing the contaminating effects of those vessels. Another advantage of spin-echo imaging lies in its resistance to susceptibility artifacts, which are caused by magnetic field inhomogeneities near air–tissue interfaces in the brain, as found in the ventral frontal and temporal lobes.

**$T_2^*$ contrast**

Recall from Chapter 3 that there are two causes for transverse relaxation: spin–spin interaction ($T_2$) and changes in spin precession frequencies due to inhomogeneities in the magnetic field. The combined effect of these two factors on the decay of transverse magnetization is given by the time constant $T_2^*$. Although $T_2$ and $T_2^*$ are related, the former constant is always greater than the latter, so $T_2$ decay is always slower than $T_2^*$ decay. Quantitatively, the relationship between $T_2$ and $T_2^*$ is given by $1/ T_2^* = (1/ T_2) + (1/ T_2')$, where $T_2'$ reflects the dephasing effect caused by field inhomogeneity. Because it forms the basis for BOLD-contrast fMRI, there has been a rapid increase in use of $T_2^*$-based imaging protocols since 1990. As will be discussed further in Chapter 7, $T_2^*$-weighted (or $T_2^*$-dependent) images are sensitive to the amount of deoxygenated hemoglobin present, which changes according to the metabolic demands of active neurons. $T_2^*$-weighted imaging is therefore the contrast basis for fMRI. Anatomical imaging using $T_2^*$-weighted contrast can be used to generate images of the brain’s venous system (i.e., venograms; Figure 5.10), because of the high concentration of deoxygenated hemoglobin in venous blood.
Like $T_2$ contrast, $T_2^*$ contrast is provided by pulse sequences with long TR and medium TE values. An additional requirement is that the pulse sequence must use magnetic field gradients to generate the signal echo, because refocusing pulses will eliminate field inhomogeneity effects. Most commonly used are gradient-echo sequences, as illustrated in Figure 5.11. Note the similarity to the proton-density sequence shown in Figure 5.4, which differs only in its TE value. Here, an intermediate TE is used so that the image is sensitive to local field inhomogeneity and not just to the number of protons present. The pulse sequence shown can provide information about factors that decrease magnetic field homogeneity, such as the presence of deoxygenated hemoglobin. Because spin-echo pulse sequences have reduced $T_2^*$ sensitivity, they are less frequently used for BOLD-contrast fMRI.

**Chemical contrast**

The MR signal can be made sensitive to the concentrations of particular tissue chemicals. For neuroimaging, important brain chemicals include N-acetyl aspartate (NAA), creatine, glucose, and lactate, which play critical roles in regulating brain function, energetics, and metabolism. An important technique used to measure these substances is called chemical shift imaging. Because protons experience different shielding effects from the surrounding electrons in different molecules, their resonance frequencies vary slightly from one type of molecule to another. For example, the resonance frequencies of protons in NAA and water differ by about 2 parts per million (ppm), or roughly ~250 Hz in a typical 3.0 T scanner. The chemical shift therefore reflects the difference in proton resonance frequencies in different molecules. By quantifying the magnitude of MR signal at individual frequencies and resolving their spatial locations by spatial encoding, maps can be generated that reflect the concentrations of individual chemicals of interest (Figure 5.12). In practice, the pulse sequences used for chemical shift imaging

![Chemical contrast](image)

**Figure 5.10** An application of $T_2^*$-weighted image in generating a vein image, known as a venogram. This image illustrates the pattern of large and small veins present within a single horizontal slice. Venograms use phase discrepancies caused by local susceptibility ($T_2^*$) effects to map out the venous system. (Courtesy of Dr. Todd Parrish, Northwestern University, and Dr. E. Mark Haacke, Wayne State University.)

**Figure 5.11** A pulse sequence used for $T_2^*$-weighted images. Like $T_2$-weighted images, $T_2^*$-weighted images require an intermediate TE and a long TR. Gradient-echo sequences are most commonly used, because the refocusing pulses used in spin-echo images will eliminate the field inhomogeneity effects that form the basis of the $T_2^*$ effect.

chemical shift imaging  A technique for measuring the concentration of particular chemicals, based on subtle differences in the resonance of the protons they contain.
involve the acquisition of hundreds or thousands of data points within each excitation, on top of the normal requirements for spatial encoding discussed in the previous chapter (Figure 5.13). Thus, acquisition of high-resolution chemical shift images can very be time-consuming and is not commonly combined with standard fMRI studies.

**Thought Question**

Why can a conventional combination of frequency encoding and phase encoding not be used for chemical shift imaging?

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**Macromolecular contrast**

So far in this chapter we have discussed the generation of images with contrast based on the properties of individual atomic nuclei or small molecules. Contrast can also be based on the interactions between molecules. For example, the magnetization of the protons in macromolecules (e.g., proteins) can

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**Figure 5.12** Chemical shift images and spectra. Shown in the top row are images representing the concentrations of three brain chemicals: choline (A), creatine (B), and NAA (C) in a patient with a brain tumor (location shown with white arrow on the T2 MRI image in D). The graphs show the underlying atomic spectra, identified by measuring the shifts in the resonant frequencies of nearby protons caused by these chemicals. Compared to a voxel in the unaffected hemisphere (E), a voxel within the tumor (F) exhibits increased levels of choline and creatine, compared to NAA. (Courtesy of Dr. Dikoma Shingui at Cornell University Medical School.)

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**Figure 5.13** A chemical shift imaging sequence. Instead of sequentially applied frequency and phase encoding gradients, chemical shift imaging employs simultaneous phase encoding gradients along both $G_x$ and $G_y$ to resolve spatial locations. During the data acquisition window (DAQ), the scanner acquires a large number of data points over an extended period of time to resolve spectral frequency changes (i.e., changes in the resonant frequencies of protons caused by local chemical concentrations).
magnetization transfer An MR imaging technique that uses an off-resonance excitation pulse to saturate the MR signal from large molecules; the subsequent influence of that pulse upon free protons in water indicates the concentration of those large molecules.

Figure 5.14 Conceptual illustration of the generation of magnetization transfer contrast. Protons in macromolecules have a wide range of resonant frequencies (purple distribution), reflecting the varied local magnetic environments experienced by protons in different parts of the molecules. In contrast, the resonant frequencies of protons in water have a much tighter distribution (blue) around the Larmor frequency (black line). Here, we illustrate the process of magnetization transfer in four steps. An off-resonance excitation pulse (Step 1, red) will provide energy to protons in some of the macromolecules, while not affecting the protons in normal water. Over a short period of time, some of the magnetization of those macromolecules will be transferred to the surrounding water molecules (Step 2, green), reducing the MR signal obtained from protons in those water molecules in a subsequent image (Step 3, red). By determining the magnitude of signal loss in a particular voxel, researchers can estimate the concentration of the targeted macromolecules (Step 4, orange).

influence that of nearby water molecules, a phenomenon known as magnetization transfer.

Like chemical shift imaging, magnetization transfer depends on differences between molecule types, specifically differences in the proton resonance frequencies due to various shielding effects. In particular, the resonance frequencies of protons within water molecules have a fairly narrow range, typically about 100 Hz. However, protons in macromolecules can have resonance frequency ranges of several thousand Hz. These two distinctly different frequency distributions allow the selective excitation of some protons within macromolecules without exciting those in water, through the use of specialized pulse sequences (Figure 5.14). The first step in this process is the delivery of an off-resonance excitation pulse that provides energy to protons in some of the macromolecules while not affecting the protons in normal water. After a short time interval (e.g., a few tens of milliseconds), some of the magnetization will transfer into protons in the water surrounding the macromolecule. If a second excitation pulse is delivered after this magnetization transfer occurs, the overall MR signal will be lower than it would be without the magnetization transfer. Because the amount of magnetization transfer is directly proportional to the concentration of the targeted macromolecule, the reduction in MR signal provides a measure of macromolecule concentration.

Many years after its first demonstration, magnetization transfer is now widely used to generate contrast based on the macromolecular properties of brain tissues. The resulting images often have significant clinical impact. For example, magnetization transfer can be used to detect changes in the myelination of the brain's white matter (Figure 5.15), since myelin is composed of specific macromolecules (i.e., lipids and proteins). Magnetization transfer has been used to study
the maturation of myelin in pediatric brains and to investigate myelin disorders such as multiple sclerosis (which is associated with demyelination).

**Motion Contrasts**

The human body is inherently dynamic. Within the vascular system, for example, water molecules are in constant motion, flowing as rapidly as one meter per second in large arteries. Water also diffuses within and among cells, such as along axons in white matter. Pulse sequences sensitive to motion provide important information about the brain, including both structural and functional information. Structural techniques include MR angiography and diffusion tensor imaging, which are often used for mapping the neurovascular system and white-matter tracts, respectively. Functional techniques include diffusion imaging, which maps the motion of water molecules over time, and perfusion imaging, which maps blood flow through capillaries. These techniques are collectively known as motion-weighted contrasts.

**MR angiography**

Magnetic resonance angiography, or MRA, provides images of the structure of blood vessels through noninvasive MRI (Figure 5.16). In classic angiography, a contrast agent is injected into the bloodstream through an inserted catheter. X-ray images are then collected with and without the contrast agent present to generate a difference image (i.e., angiogram) that maps the vascular system. Although angiography provides good vascular images, it is a very invasive procedure, requiring both the insertion of a foreign substance and exposure to ionizing radiation. Because MRA does not require ionizing radiation, it can be used to noninvasively detect, diagnose, and aid in the treatment of many types of medical problems, including cardiac disorders, stroke, and vascular disease.

![Figure 5.16 A sample magnetic resonance angiography (MRA) image.](image)
bolus  A quantity of a substance that is introduced into a system and then progresses through that system over time.

time-of-flight (TOF) MRA  A type of MR angiography that generates contrast by suppressing signal from spins within an imaging plane so that voxels with inflowing spins (i.e., those with blood vessels) have high signal. MRA also complements fMRI studies by identifying major blood vessels that may confound experimental results. If identified, the data from these vessels can be removed from analyses to improve the localization of activity to the capillary bed.

MRA can be performed using either exogenous or endogenous contrast. In some clinical settings, exogenous contrast-enhancing agents are used to increase the vessel signal. For a typical contrast-enhanced MRA, a small quantity (or bolus) of a gadolinium-based contrast agent is injected into the patient’s bloodstream. The gadolinium itself is not visible on MR images, but it radically shortens the $T_1$ recovery period for nearby blood, allowing the use of specialized pulse sequences with extremely short TRs (three to seven milliseconds) and TEs (one to three milliseconds). The short TR saturates the signal from stationary tissues but not from the gadolinium-enhanced blood, while the short TE minimizes $T_2$ decay. Depending on the delay between bolus injection and image acquisition, the contrast agent may travel through different components of the vascular system, so the images can be calibrated to provide information about arterial or venous networks.

In research settings, MRA is usually performed using noninvasive endogenous contrast. There are two primary techniques for endogenous contrast MRA. The most common is time-of-flight (TOF) MRA, which involves the generation of signal based on blood displacement. The underlying principle of the TOF technique is spin saturation. By repeatedly and frequently applying excitation pulses or gradient pulses to a single imaging plane, the signal within that plane can be suppressed. Thus, tissues whose spins remain within the plane, such as gray or white matter, will produce little MR signal and will appear to be very dark on TOF images. Blood vessels, however, are constantly replenished with new spins from outside the plane. These spins have not experienced the excitation or gradient pulses, and thus they contribute normal levels of MR signal. TOF images are typically acquired in the axial (i.e., horizontal, relative to the brain itself) plane and can be reformatted to other planes for ease of viewing.

The TOF signal is proportional to the amount of blood that enters the slice (Figure 5.17). If a completely new column of blood enters the slice every TR, the TOF signal will be at its maximum. But if blood flow is weak or absent, then the TOF signal will be much reduced. Consequently, TOF MRA is a flow-dependent imaging technique. Because of this, the TR and slice thickness of a TOF image must be chosen based on the expected flow.

Figure 5.17  Schematic illustration of the signal-generation mechanism for TOF magnetic resonance angiography. In TOF MRA, repeated excitation pulses saturate the MR signal from spins within a plane, as shown by the blue rectangle at left. Then there is a waiting period during which voxels with flow (e.g., blood vessels) have new spins introduced, while voxels without flow (e.g., white matter) do not. The amount of MR signal recorded following excitation and acquisition is greatest for voxels that had the most new spins enter during the waiting period.
To acquire MRAs with TOF contrast, a specialized pulse sequence is required (Figure 5.18). As described in the preceding paragraphs, the imaging plane is presaturated by the electromagnetic excitation pulse and gradient saturation pulses. After a brief waiting period during which fresh blood can enter the plane, the MR signals are acquired by a gradient-echo acquisition technique, so that only the signal from this new blood will be present.

A second technique is velocity-encoded phase contrast (VENC-PC) MRA, which uses gradient fields to produce a difference in precession phase between the vasculature and the surrounding tissue. The amount of the phase difference that accumulates depends on the relative velocities of the moving spins and the strength and duration of the applied gradient. That is, spins changing positions rapidly over time will precess more rapidly, and thus gain precession phase, relative to spins that stay in roughly the same place. By measuring phase differences in each of three orthogonal directions, a map of three-dimensional flow can be created. Typical VENC-PC protocols involve the acquisition of two sets of images: one with a strong gradient and the other with either no gradient or a gradient in the opposite direction. The difference between these images indicates the magnitude of the phase difference at each voxel, and thus the brightness at each voxel is proportional to flow. Voxels with stationary spins will not give signals, since there are no phase differences between the images, whereas voxels with rapidly moving spins will produce bright signals due to the large phase differences. The VENC-PC technique, unlike TOF, does not depend on TR or slice thickness, because it acts on the blood already present in the imaging slice.

Since the VENC-PC technique relies on relative phase, it is sensitive to the strength and duration of the gradients used. Imagine that the gradients are set up so that a flow velocity of 20 cm/s corresponds with a phase change of 180°. If a given vessel, such as a large artery, has a very fast flow rate of 40 cm/s, the resulting phase angle change will be 360°. As in basic geometry, an angle of 360° cannot be distinguished from one of 0°, so this fast-flowing artery would appear to have no flow whatsoever! This problem, known as velocity aliasing, demonstrates the importance of choosing appropriate velocity-encoding parameters. If the gradient is too strong, as in the above example, fast-flowing vessels may not be identified. But if the gradient is too small, the ability to resolve differences between slow-flowing vessels will be compromised. If the choice of gradient strength is matched to the expected velocities of blood in the different vessel types, then selective imaging of different parts of the vascular system is possible.

To acquire MRAs with VENC-PC contrast, a pulse sequence like the one in Figure 5.19 is necessary. Here, the velocity-encoding gradients are inserted.
Figure 5.19 Pulse sequence used for VENC-PC MRA. This technique uses spatial gradients to induce changes in spin phase. The magnitude of the phase difference between a pair of images (e.g., one with gradients versus one without) provides information about the velocity of spins within each voxel.

after the excitation pulse but before the phase image acquisition. Note that they are bipolar in shape, which has no effect on static tissue. When this pulse sequence is repeated twice, once with velocity-encoding gradients and once without (or with opposite gradients), flow-dependent phase contrast will be generated.

**Diffusion-weighted contrast**

At all temperatures above absolute zero, thermodynamic effects cause molecules to move randomly. The motion of molecules due to thermodynamic effects is known as diffusion (Figure 5.20). In gases and liquids, molecules can move relatively freely, as when a dye spreads through a glass of water or when the smell of freshly baked bread wafts through a house. In solids, however, the motion of molecules is restricted, and thus diffusion is much slower. The abundance of water molecules in the human body makes it possible to perform diffusion-weighted imaging using MRI. And, because of the different cellular environments experienced by different water molecules, diffusion-weighted MRI can provide a new dimension of image contrast based on the mobility of those molecules, in terms of both the magnitude and direction of their diffusion.

If the magnetic field were perfectly homogeneous, the effect of diffusion would be hardly visible, as the water molecules would experience the same

**diffusion** The random motion of molecules through a medium over time.

Figure 5.20 Diffusion. Over time, molecules within gases or liquids will move freely through the medium. This motion is known as diffusion. Shown here are sample random paths that could be taken by molecules within a medium that allows isotropic (i.e., the same in every direction) diffusion. As time passes, molecules become increasingly distant from their starting location.
magnetic field regardless of their position over time. However, when magnetic fields are inhomogeneous, due to either intrinsic non-uniformity or to externally applied gradients, water molecules experience different magnetic fields as they diffuse. This causes a loss of phase coherence, which in turn attenuates the MRI signal. Unlike the loss of phase coherence due to static magnetic field inhomogeneity (i.e., T\textsubscript{2}* effects), this loss cannot be recovered even with spin-echo pulse sequences. Because diffusion is random, the path taken by each molecule cannot be reversed. Thus, the refocusing pulse of a spin-echo sequence cannot recover signal lost to diffusion.

Diffusion weighting is the application of controlled gradient magnetic fields to quantify the amplitude and direction of diffusion. The presence of diffusion-weighting gradients further attenuates the MR signal beyond that caused by common T\textsubscript{2} relaxation. Assuming equal, or isotropic, diffusion along all directions (Figure 5.21A), the attenuation effect \(A\) due to diffusion weighting is given by the exponential

\[ A = e^{-\int_0^T D(\gamma G(t))^2 dt} \]  

(5.8)

In this equation, \(D\) is the apparent diffusion coefficient, or ADC (i.e., the measured value of the diffusion coefficient), \(G\) the strength of the external diffusion-weighting gradient, and \(T\) the duration of the diffusion-weighting gradient. We can define the degree of diffusion weighting as the b factor:

\[ b = \int_0^T (\gamma G(t))^2 dt \]  

(5.9)

To further simplify Equation 5.8:

\[ A = e^{-bD} \]  

(5.10)

Equation 5.12 quantifies the mean diffusivity within a voxel without providing directional information. But water molecules in the brain do not diffuse equally in all directions. Most water is contained within tissues that have considerable structure, such as the long processes of axons or the narrow walls of blood vessels. Unequal, or anisotropic, diffusion (Figure 5.21B) refers to the preference in some tissues for water molecules to diffuse in one direction or another. In anisotropic diffusion, the motion of molecules over time does not resemble a sphere, in which molecules move equally in every direction, but instead resembles an ellipsoid whose long axis indicates the fastest axis of diffusion. The diffusion ellipsoid is mathematically described as a three-dimensional tensor, which is a collection of vector fields governed by three principal axes (Box 5.1).

The ability of diffusion weighting to attenuate a signal based on its ADC can be very useful in fMRI for understanding the origins of the detected brain...
BOX 5.1 Diffusion Tensor Imaging

A particularly important form of diffusion-weighted imaging is diffusion tensor imaging (DTI), which quantifies the relative diffusivity of water in a voxel into directional components. For example, white matter, which is composed mostly of nerve fibers, shows prominent anisotropy, such that water molecules diffuse most quickly along the length of the fiber and most slowly across the width of the fiber. A scalar quantity known as the fractional anisotropy (FA) can be computed for each voxel to express the preference of water to diffuse in an isotropic or anisotropic manner. FA values are bounded by 0 and 1 and are calculated using equation below, where $D_x$, $D_y$, and $D_z$ represent the three principal axes of the diffusion tensor:

$$FA = \frac{\sqrt{(D_x - D_y)^2 + (D_y - D_z)^2 + (D_z - D_x)^2}}{\sqrt{2(D_x^2 + D_y^2 + D_z^2)}}$$

FA values approaching the maximum of 1 indicate that nearly all of the water molecules in the voxel are diffusing along the same preferred axis, while FA values approaching the minimum of 0 indicate that the water molecules are equally likely to diffuse in any direction. Fractional anisotropy provides important information about the composition of the tissue within a voxel. Notably, some neurological diseases, such as multiple sclerosis and vascular dementia, are characterized by potentially severe white-matter pathology. The resulting axonal damage can be identified as decreased FA values in affected voxels.

To determine the coefficients of diffusion along different directions (i.e., axes of a diffusion tensor), we need to apply controlled gradients in a pulse sequence. These gradients must be balanced in time to preserve the MR signal. In spin-echo sequences (Figure 1A), this balance is achieved by presenting the gradients before and after the refocusing pulse. In gradient-echo sequences (Figure 1B), successive positive and negative gradients are applied. In an ideal isotropic medium, application of a gradient along any axis would be sufficient for measuring the ADC. However, the brain contains many tissues that constrain diffusion, and thus diffusion-weighting gradients must be applied in many directions to quantify the diffusion tensor. In practice, at least six different directions are needed to account for the six degrees of freedom in spatial coordinates and angles for any given tensor. Many new DTI sequences collect data from diffusion-weighted gradients in 15, 32, or even more directions.

**Thought Question**

Why are the gradients used in the spin-echo pulse sequence of the same sign, while the gradients used in the gradient-echo sequence are of opposite signs?

Tractography is an advanced application of DTI. Based on the estimated diffusion tensors, the longest axis of the diffusion ellipsoid (e.g., the most preferred direction of diffusion) can be used to guide the tracking of nerve fibers as they travel between functionally associated brain regions (Figure 2A). By following these directions and continuously connecting the long axes in space, we can construct images of complete nerve fibers and form maps of structural connectivity (Figure 2B). A high-resolution example of the major fiber tracts is shown in Figure 2C. More advanced acquisition techniques, such as diffusion spectrum imaging (DSI)

![Figure 1 Pulse sequences used for diffusion-weighted imaging. Shown are sample pulse sequences used for diffusion-weighted spin-echo imaging (A) and diffusion-weighted gradient-echo imaging (B). Note that the spin-echo sequence has a refocusing pulse between two gradients of similar sign, while the gradient-echo sequence alternates gradients of opposite sign.](image-url)
Box 5.1 (continued)

Figure 2 Fiber tracking using diffusion tensor imaging. DTI allows the measurement of the relative motion of water molecules within a voxel. (A) Each voxel is represented by an ellipsoid whose dimensions reflect the rate of diffusion, with spheres reflecting isotropic diffusion and narrow ellipses showing diffusion along a preferred axis. White-matter tracts can be reconstructed from these data using algorithms that find continuous tracks of diffusion across voxels, as indicated schematically for a hypothetical five-by-six set of voxels. Visible in red is a curve obtained by tracing diffusion axes across adjacent voxels. (B) An image showing, in three dimensions, a sample set of oval diffusion tensors used to generate maps of fiber tracts. (C) An image of DTI tractography that illustrates major fibers. Shown here are the superior longitudinal fasciculus (SLF), the superior fronto-occipital tract (SFO), the inferior fronto-occipital tract (IFO), the uncinate fasciculus (UNC), and the inferior longitudinal fasciculus (ILF). (D) An image created using diffusion spectrum imaging to improve the fine separation of crossing fiber tracts. Shown are the distortions in the normal pattern of white matter caused by a large brain tumor (yellow), compared with the pattern in the healthy side. (B courtesy of Dr. Guido Gerig, University of Utah; C courtesy of Dr. Susumu Mori, Johns Hopkins Medical School; D courtesy of Dr. Isaac Tseng, National Taiwan University Hospital.)

and high angular resolution diffusion imaging (HARDI), can resolve multiple tensors to improve fiber tracking at regions with complex, crossing sets of white-matter tracts. DSI can be used to resolve detailed white-matter structure, as shown in Figure 2D. In this image the normal pattern of the genu and splenium of the corpus callosum are altered by a large brain tumor.

In the context of fMRI, DTI can aid in determining the connectivity between various activated regions, to help infer their potential hierarchy in functional pathways. To date, DTI has been used most commonly in studies of memory and of visual function (e.g., see Figure 3). The development of DTI tractography is still at an early stage. New technical developments may lead to improvements in the quantitative assessment of white-matter integrity (and volume). This will greatly broaden its application for fMRI researchers.

(continued on next page)
**BOX 5.1 (continued)**

**Figure 3** DTI tractography guided by areas of BOLD fMRI activation. Shown in the left column (panels A–C) are 3-D representations of the core regions of the human visual system, all functionally defined using fMRI. Some of these regions process basic features like line edges and their position (V1, V2) and more complex features like form, color, and motion (V3, V3A/VP, V4v, V5/hMT+). Other regions are selective for particular types of object processing (FFA: faces; PPA: places). Panels D–J provide examples of the fiber tracts, measured using DTI, that connect pairs of these regions (blue lines). (From Kim et al., 2006.)

**diffusion tensor imaging (DTI)** The collection of images that provide information about the magnitude and direction of molecular diffusion. It is often used to create maps of fractional anisotropy.

**fractional anisotropy (FA)** The preference for molecules to diffuse in an anisotropic manner. An FA value of 1 indicates that diffusion occurs along a single preferred axis, while a value of 0 indicates that diffusion is similar in all directions.

**tractography** The identification and measurement, often using diffusion tensor imaging, of white matter tracts that connect distant brain regions.

signals. Figure 5.22 illustrates the spatial distribution of ADCs within brain activations, with large vessels that have large ADCs distributed along the surface of the brain, while low ADC values are located in deep brain regions.

**Perfusion-weighted contrast**

The human brain requires oxygen for metabolism (see Chapter 6). To ensure a constant supply, hemoglobin molecules carry oxygen through the bloodstream to all parts of the brain. The irrigation of tissues via blood delivery is known as perfusion, and the family of imaging procedures that measure this process are...
known as perfusion MRI. Perfusion is expressed as the volume of blood that travels through a tissue mass over time. In the human brain, gray-matter perfusion is approximately 60 mL/100 g/min, and white-matter perfusion is lower, about 20 mL/100 g/min. Unlike the MRA techniques described in the section on MR angiography, which are often used to measure the properties of large blood vessels for clinical reasons, perfusion MRI is used most frequently to generate images of blood flow in capillaries and other small vessels.

Perfusion MRI may use either exogenous or endogenous contrast. Exogenous contrast approaches use intravascular contrast agents that freely perfuse through the vascular system. The attenuation of the MR signal in each voxel is proportional to the amount of the contrast agent present. Thus, signal changes can be interpreted as a function of perfusion, and images can be created that depict different perfusion properties, such as the relative cerebral blood flow (rCBF), relative cerebral blood volume (rCBV), and mean transit time (mTT). As their names imply, relative blood flow and relative blood volume express changes in how much blood comes into a voxel, and how much blood is contained within a voxel, respectively. The mean transit time measures how quickly blood passes through a particular voxel and can indicate brain regions with
arterial spin labeling (ASL) A family of perfusion imaging techniques that measure blood flow by labeling spins with excitation pulses and then waiting for the labeled spins to enter the imaging plane before data acquisition.

Continuous ASL. A type of perfusion imaging that uses a second transmitter coil to label spins within an upstream artery while collecting images.

Pulsed ASL. A type of perfusion imaging that uses a single coil both to label spins in one plane and to record MR signal in another plane, separated by a brief delay period.

Labeling plane. The plane in which initial excitation pulse(s) are applied during perfusion imaging.

Imaging plane. The plane in which changes in MR signal are recorded during perfusion imaging.

delayed blood flow. The use of exogenous contrast agents provides very high signal changes but has limited use for research because of its invasiveness.

Endogeneous contrast perfusion imaging is noninvasive and is therefore used in fMRI research. Contrast is generated through the clever use of radiofrequency pulses to magnetically label, or tag, protons in blood water molecules before they reach the tissue of interest. This approach is known as arterial spin labeling, or ASL, of which there are two types: continuous and pulsed. Continuous ASL typically uses additional hardware, like a labeling coil, to saturate spins in upstream blood, such as in the carotid arteries of the neck (Figure 5.23A). Following this labeling process, the blood travels to the brain and enters the imaging slice. The brain images are then acquired in the presence of the labeled blood. Next, the labeling coil is turned off and a second set of images is acquired without the presence of the labeled blood. The difference between the two sets of images reflects only the blood flow, as any tissue that does not contain flow will be similar in the two conditions. A drawback of the continuous ASL technique is the requirement for a second transmitter coil to label the inflowing blood.

An alternative approach, pulsed ASL, uses a single coil both to label blood in the labeling plane and to record the MR signal change in the imaging plane (Figure 5.23B and C). Labeling pulses are broadcast for a brief period, followed by a delay and then image acquisition. The delay period must be calibrated to account for the distance between the labeling plane and imaging plane, so the labeled bolus of blood water will enter the imaging plane during image acquisition.

Regardless of the ASL method used, labeling blood only alters the longitudinal magnetization. Thus, we can describe the endogenous perfusion signal quantitatively by modifying the $T_1$ term of the Bloch equation (Equation 4.1). To do so, we introduce an additional term, $f(M'(t) - M_0)$, that accounts for the effects of blood flow:

$$\frac{dM(t)}{dt} = \frac{M_0 - M_x(t)}{T_{1app}} + f(M'(t) - M_0)$$ (5.11)

Figure 5.23 Perfusion imaging mechanisms. (A) Continuous ASL techniques use an upstream transmission coil to saturate spins in an artery that feeds the brain. Images collected following spin saturation can be compared with images in the absence of saturation to determine flow into the imaging plane. There are two primary types of pulsed ASL techniques, EPISTAR (B) and FAIR (C). EPISTAR relies on alternating two labeling planes that are equidistant from the imaging plane, one below the plane that includes feeding arteries and one above the plane that does not include any feeding vessels (i.e., is outside the head). FAIR alternates between labeling the entire brain and just the imaging plane. For either of the pulsed ASL techniques, differences between the two sets of images can be attributed to flow into the imaging plane.
In this equation, \( f \) is the blood flow in mL/g/sec and \( T_{1app} \) is the apparent \( T_1 \) value in the presence of blood flow. \( T_{1app} \) can be calculated from \( 1/T_{1app} = 1/T_1 + f/\lambda \), where \( \lambda \) is the blood–brain partition coefficient. This coefficient describes the movement of some substance between the vascular system and the brain, within a standardized time interval; its typical value for water is about 0.9 mL/g. Because the blood is labeled with an inversion pulse, its magnetization, \( M(t) \), is given by \(-M_0\) so that the difference between the two conditions becomes:

\[
\frac{dM(t)^{\text{label}}}{dt} - \frac{dM(t)^{\text{control}}}{dt} = -\frac{M(t)^{\text{label}} - M(t)^{\text{control}}}{T_{1app}} + f(-2M_0) \quad (5.12)
\]

and thus the signal remaining in the final perfusion image would be:

\[
M(t)^{\text{label}} - M(t)^{\text{control}} = -2T_{1app} f M_0 / \lambda \quad (5.13)
\]

This equation defines the relationship between the measured perfusion signal and blood flow in the brain.

Because the continuous ASL method uses a second transmitter coil to label blood, the images can be acquired with any standard spin- or gradient-echo pulse sequence. To achieve the maximal signal difference, the echo time (TE) must be kept as short as possible, which minimizes signal loss due to \( T_2^* \) or \( T_2 \) relaxation effects.

Pulsed ASL techniques require specialized pulse sequences to label the blood. One type of pulsed ASL is called EPISTAR (echo-planar imaging at steady state with alternating inversion recovery). In EPISTAR, alternating off-center inversion pulses are used to select labeling planes below and above the imaging plane (Figure 5.24A). For odd-numbered scans, the labeling plane is in the neck, below and upstream from the imaging plane. For even-numbered scans, the labeling

(A)

RF — 180° — 90° — 180° — DAQ

\( G_x \)

\( G_y \)

Odd scan

Alternating distal inversion

Even scan

(B)

RF — 180° — 90° — 180° — DAQ

\( G_x \)

\( G_y \)

Odd scan

Alternating proximal inversion

Even scan

Figure 5.24 Pulse sequences for pulsed ASL imaging. Shown are typical pulse sequences used for the EPISTAR technique (A) and the FAIR technique (B). Both techniques require alternating between different labeling planes, as shown for the \( G_z \) gradient at left.
plane is at an equal distance above the imaging plane, and can actually be outside of the brain. This is necessary to ensure that the inversion pulse has a similar effect on the spin system in both the odd and even scans.

EPISTAR is directionally specific, in that it is only sensitive to spins flowing from the labeling plane to the imaging plane. A second type of pulsed ASL, FAIR (flow-sensitive alternating inversion recovery), is not directionally specific (Figure 5.24B). For odd scans, the entire brain is labeled. For even scans, only the imaging plane is labeled. The difference between the odd and even scans reflects those spins that flow into the imaging plane from anywhere else in the brain; thus FAIR is insensitive to the direction of flow. However, flow within the plane will be similar between scans and does not contribute to the image. Because the inversion pulse is present for both acquisitions, its effect within the imaging plane is identical.

Like the diffusion imaging techniques described in the previous section, perfusion imaging can be used to create images of brain function (Figure 5.25), providing potentially complementary information to standard BOLD contrast.

Figure 5.25 Comparison of perfusion and BOLD contrasts. Shown are an anatomical reference image (A), and a resting-state perfusion map from the same slice (B). During a simple motor task, there were significant increases in perfusion within the primary motor cortex (C, oval highlight). These perfusion-related increases generally were similar to those obtained using BOLD contrast (D, circle highlight), but were more spatially specific. In all images, absolute signal intensity is shown using a grayscale color map. (From Luh et al., 2000.)
Fast Imaging Sequences for fMRI

For anatomical images of the brain, contrast is more important than speed of acquisition, since structural parameters such as size and shape change little over the course of a single scanning session. However, understanding the function of the brain requires images to be acquired very rapidly, at approximately the same rate as the physiological changes of interest. Fast pulse sequences have been developed that can be used to acquire very large numbers of images within short periods of time; for example, state-of-the-art sequences may allow the acquisition of 20 or more images per second. These sequences typically use variants of the gradient-echo approach described in Chapter 4 and are sensitive to T2* contrast. The basic principles underlying these sequences are described in the remainder of this chapter.

Echo-planar imaging

The first human MR images were acquired using a laborious voxel-by-voxel procedure. The image shown in Figure 1.12 took about 4 hours to acquire, and was collected at the slothlike pace of about two minutes per voxel. To put the current methods in perspective, a modern pulse sequence that results in the acquisition of 20 image slices per second, collects data at a rate that is approximately 10,000,000 times faster than the rate of acquisition of the first MR image. The development of fast MR imaging can be traced to the work of Peter Mansfield and colleagues at the University of Nottingham. At that time, the traditional method for acquiring images was to fill up k-space in a line-by-line fashion, which necessitated a large number of separate excitations for even a moderate-resolution image. In 1977, Mansfield proposed a new method, known as echo-planar imaging (EPI), in which the entire k-space is filled using rapid gradient switching, following a single excitation. For this technique, Mansfield shared the Nobel Prize in Physiology or Medicine in 2003.

Early MRI scanners were very limited in terms of the strength of the gradients that they could produce and the slow rate with which they could change the gradients. While high-static-magnetic field scanners were available by the early 1980s, advanced gradient technology was not common until the late 1980s and early 1990s. The maturation of gradient technology has made EPI the most commonly used fast imaging method in functional MRI. The basic EPI pulse sequence has changed little since its development by Mansfield (Figure 5.26A). Since all of k-space must be filled following a single excitation pulse, the data must be acquired before significant T2* or T2 decay can occur. However, to

Figure 5.26 An EPI pulse sequence (A) and its k-space trajectory (B). The black arrow in the k-space trajectory represents the initial negative Gx and Gy gradients used to move to the bottom left of k-space. The subsequent gradient changes are highlighted in different colors for easy comparison between the pulse sequence and its k-space representation. Note that the directions of the gradients are changed rapidly over time to allow the back-and-forth trajectory through k-space.
achieve reasonable spatial resolution, a relatively large $k$-space must be sampled, which takes time. To meet these constraints, the $k$-space must be filled very rapidly. This requires a very strong gradient system. For EPI to be practical, gradients of about 2.5 Gauss/cm are sufficient, but stronger whole-body systems now exist that can produce gradients of up to 5 Gauss/cm. The use of very strong gradients can shorten the scan time required for one image to less than 20 ms.

To fill $k$-space, EPI uses an unconventional pattern in which alternating lines are scanned in opposite directions. This switchback approach taxes the gradient hardware heavily, since different sets of gradients must be cycled to enable the 90° turns in the $k$-space pattern. This pattern is also inefficient in that data collected while transitioning from one line of $k$-space to another (i.e., the vertical lines in Figure 5.26B) are not used in the image-creation process. Furthermore, the raw data obtained from the EPI acquisition must be sorted and realigned to remove the influence of the zigzag trajectory before being reconstructed using a Fourier transform. Without such realignment, serious artifacts can arise (Figure 5.27).

The most common EPI artifacts result from imperfections in the magnetic fields, either static or gradient, used to collect the images. Small- and large-scale static field inhomogeneities can result in signal losses and geometric distortions, respectively, and are discussed in Chapter 4. Figure 5.28 shows a set of typical EPI images, each a single axial (i.e., horizontal) slice, with the lowest parts of the brain in the upper left of the figure. Visible are significant losses in MR signal in the ventral frontal lobes and inferior medial temporal lobes, due to magnetic susceptibility artifacts resulting from the field inhomogeneities present at the boundaries between brain tissues and nearby, air-filled cavities. The signal loss in the ventral frontal region results from the nasal and oral cavities, which sit just under the frontal lobe, and the loss in the inferior medial temporal region results from the auditory canals below.

Geometric distortion is also present in EPI images, due to the long time spent acquiring the data from $k$-space after each excitation. In anatomical images, which have short data acquisition intervals, small field variations in the image plane may cause only sub-pixel distortions. But in EPI images with long readout periods, there can be noticeable distortions of up to several pixels. A long readout time makes the system more prone to geometric distortions due to both the reduced sampling frequency and the reduced strength of the gradients used during data acquisition. Variation in the magnetic field along a single in-plane direction (e.g., $x$ or $y$) causes stretching and shearing of the otherwise circular phantom image (Figure 5.29A–C). Rarely, however, will geometric distortion be in a single direction; instead, gradient variation usually changes across the image in a complex fashion, resulting in more-complex patterns of distortion. A further problem results from small field variations along the $z$ (i.e., slice-selective, or through-plane) direction, which cause off-resonance excitation and thus severe signal losses (Figure 5.29D).

**Spiral imaging**

While EPI enables fast image acquisition, its speed is constrained by the physical limitations of the MR scanner gradient hardware. A new family of fast imaging sequences, called spiral imaging, utilizes a very different trajectory in $k$-space from that of EPI. Spiral imaging sequences use sinusoidal changes in the gradients (Figure 5.30A) to trace a corkscrew path through $k$-space that typically begins at the center and winds its way to the perimeter (Figure
5.30B). This can be much less taxing on a gradient system compared with EPI sequences, and can reduce the time needed to collect an image. An additional advantage is that all points sampled along the spiral trajectory are used for reconstructing the final image, improving the efficiency of the acquisition. A disadvantage of spiral imaging is that the k-space data do not follow a Cartesian grid. This necessitates an additional step in which the acquired data points are interpolated back onto a Cartesian grid so that a Fourier transform can be used to reconstruct the image. While this consumes additional

Figure 5.27 Artifacts due to the misalignment of EPI images. If the raw k-space data from an EPI acquisition are not realigned to remove the influence of the back-and-forth trajectory, significant image distortions can arise (A). (B) The corrected image of a phantom.

Figure 5.28 Signal loss due to susceptibility artifacts in EPI images. Shown here is a series of slices within an EPI image volume collected using a 4-T scanner (TE: 40 ms). In areas of the brain near interfaces between air and tissue, such as near the sinuses and auditory canals (arrows), there is significant signal loss due to magnetic field inhomogeneities.
Figure 5.29 Effects of small field variations on EPI images. A normal EPI image (A) will be distorted by small variations in magnetic field strength along a single direction. If the variation is along x (B) or y (C), the image is systematically stretched or sheared. If the variation is along the slice selection axis z (D), the excitation is off-resonance and the MR signal intensity is reduced.

Figure 5.30 Spiral imaging. As illustrated here, spiral imaging pulse sequences use sinusoidally changing gradients (A) to generate a curving path through k-space (B).
Figure 5.31 Signal losses due to susceptibility artifacts in spiral images. Compared with anatomical images (A), spiral images (B) exhibit regions of signal loss similar to those of EPI images (compare with Figure 5.28).

time during data processing, it is a small price to pay for the (often considerable) increase in acquisition rate.

**Thought Question**
The echo time (TE) is defined as the interval between excitation and the collection of the center of k-space. How do EPI and spiral sequences differ in where the TE falls within the duration of the data acquisition window?

Spiral images have the same vulnerability as EPI to signal losses in inhomogeneous regions, as shown in Figure 5.31. In addition, even though the spiral readout is more efficient than EPI in filling up k-space, it is still considerably longer than that used in conventional anatomical imaging methods, and thus spatial distortions are also present. The types of spatial distortion, however, are quite different from those found in EPI. Because of the non-Cartesian k-space sampling scheme, the regular distortion pattern seen in EPI images is usually not present in spiral images (Figure 5.32). For example, linear field variations in the x- or y-direction commonly shear and stretch entire EPI images. These same linear field variations would cause asymmetric compression in one dimension in spiral images. Due to the rotational symmetry between the x- and y-coordinates in spiral imaging, the artifact caused by the field variation along x (Figure 5.32B) is simply a 90°-rotated version of that caused by the field variation along y (Figure 5.32C). Another potential problem is that the spatial re-sampling necessitated by the spiral trajectory may blur the image. Like EPI, spiral imaging is also influenced by field inhomogeneities along the z-direction, resulting in severe signal losses (Figure 5.32D).
(A)

(B)

(C)

(D)

Figure 5.32 Effects of small field variation on spiral images. A normal spiral image (A) is distorted by small variations in magnetic field strength along a single direction, although the pattern of distortion is different from that of EPI. If the variation is along $x$ (B) or $y$ (C), the image is systematically compressed along the $y$-direction or $x$-direction, respectively. As with EPI, however, variation along the slice selection direction (D) causes a reduction in overall MR signal intensity.

Signal recovery and distortion correction for EPI and spiral images

As discussed above, a central weakness of BOLD fMRI, whether using EPI or spiral sequences, is its vulnerability toward magnetic field inhomogeneities. The air and bones in the sinuses and auditory canals have distinctly different magnetic susceptibilities compared with nearby brain tissues, leading to large magnetic field inhomogeneities and thus image artifacts. Specifically, in gradient-echo acquisitions, marked signal loss will be observed in EPI or spiral images; while in spin-echo acquisitions, significant geometric distortions will be seen. Since gradient echo imaging techniques are widely used in fMRI experiments, the resulting inability to measure fMRI signal in ventral brain regions
Figure 5.33 Use of a passive local shim (intra-oral graphite) to reduce susceptibility artifacts. Whereas images sensitive to $T_1$ contrast (A) can provide relatively good signal from throughout the ventral brain, images sensitive to $T_2^*$ contrast (B) show marked signal reductions in the ventral frontal lobe and ventral temporal lobe, due to susceptibility artifacts caused by the different magnetic properties of neighboring air and tissue. One approach for dealing with these signal losses is the introduction of a passive shim, such as a specially constructed mouth insert containing diamagnetic graphite (C, showing sample shims of different sizes and profiles). When placed in the mouth, these shims minimize susceptibility differences and thus ameliorate loss of signal in the ventral frontal lobes (D). Note that signal loss in the ventral temporal lobes (i.e., that caused by the auditory canals) is unaffected. (From Wilson et al., 2003.)

has been of significant concern. So, how can fMRI researchers who are interested in those regions compensate for these problems?

To prevent MR signal loss, we need to find effective means to compensate for the field inhomogeneities at boundaries between air and tissues. There are three types of compensation methods, all involving the shimming of the magnetic field (see Chapter 2 for an introduction to shimming). A relatively straightforward and effective approach is to introduce materials (e.g., pieces of graphite placed in the mouth) to provide passive local shims (Figure 5.33). However, the associated discomfort and inconvenience can make this a less-than-desirable option for many fMRI participants. A second option is the addition of active local shims, often using looped electrical circuits, to compensate for field inhomogeneities (shown in Figure 5.34). Yet, these can cause imaging artifacts and safety concerns. Third, since many of these intrinsic inhomogeneities induce gradient fields along the z-direction (i.e., inferior to superior), the pulse sequence can incorporate a z-shim gradient. Because this approach relies on the existing scanner hardware, it can provide good recovery of signal without consequences for the subject (Figure 5.35).

For spin-echo sequences that use a refocusing 180° pulse to generate MRI signal, magnetic field homogeneity is less critical for image quality, and thus there is much less signal loss due to inhomogeneities when using these
sequences. But because the spatial encoding is still achieved through gradient fields, magnetic field inhomogeneities can still shift the voxels in space and introduce large geometric distortions in the image. One important method for correcting such spatial shifts involves the use of a magnetic field map. The map is derived from two images acquired at slightly different TEs, and can be used subsequently to remove distortions from the images (Figure 5.36).

**Summary**

There are two general types of contrast for magnetic resonance imaging of the brain. Static contrast provides information about the number or content of atomic nuclei, while motion contrast describes how atomic nuclei move within a region of interest. Each basic type may use either endogenous mechanisms that rely on naturally occurring properties of biological tissue or exogenous mechanisms that typically involve the injection of compounds to greatly distort the magnetic field. Every contrast mechanism has associ-
Figure 5.35 Use of a pulse sequence with a compensatory $z$-gradient to reduce susceptibility artifacts. Shown in (A) are two representative axial slices acquired using gradient-echo echo-planar imaging. Visible is the typical pattern of susceptibility-induced signal losses in frontal and inferior temporal regions (indicated by arrows). (B) The same slices, here acquired using a single-shot susceptibility compensation sequence. Much greater signal is present in the regions of susceptibility artifact, and anatomical details are clearly visible within those regions. Both pairs of images were collected at 4.0 T from the same subject.

Figure 5.36 Use of a map of magnetic field strength to correct for image distortion. (A) One frequent consequence of magnetic field inhomogeneity is image distortion, shown here as skewing of the frontal lobes because of the underlying susceptibility artifact. By recording a map of magnetic field strength (B), correction algorithms can be applied to minimize that distortion (C).
ated pulse sequences describing the gradient changes and radiofrequency pulses that are used to collect the MR signal. By varying the parameters of a given pulse sequence, images can be collected that are sensitive to one form of contrast or another. Common static contrasts include proton-density, $T_1$-weighted, $T_2$-weighted, and $T_2^*$-weighted. In fMRI experiments, these static contrasts are typically used for the collection of high-resolution images that provide anatomical detail. The use of $T_2^*$-weighted contrast also provides the foundation for high-temporal-resolution studies of functional changes in the human brain. Motion contrasts include MR angiography, diffusion weighting, and perfusion imaging. Diffusion and perfusion imaging, in particular, have potential for providing information about brain physiology that can be complementary to that gained with BOLD fMRI. Gradient-echo imaging is the most common form of fMRI pulse sequence, for which both echoplanar and spiral imaging are used.

Suggested Readings


Chapter References


