interesting aspects of the information carried by their inputs. Theoretical analysis of a form of plasticity known as Hebbian indicates one way that this could happen in an unsupervised manner.

In 1949, Donald Hebb proposed that synapses should strengthen when a given presynaptic input to a neuron cooperates with a sufficient number of coactive inputs to cause that neuron to fire an action potential. Evidence for Hebbian synaptic plasticity has been obtained from many studies (Chapter 54). By itself, Hebbian plasticity would keep making synapses stronger and stronger, so some other form of plasticity must exist to prevent this from happening. Such compensatory forms of plasticity are called homeostatic, and experiments have revealed these forms of plasticity as well. Theoretical analysis indicates that a combination of Hebbian and homeostatic plasticity can adjust synapses, without any additional supervisory signal, so that they extract the combination of a neuron's inputs that is most highly modulated relative to other combinations (Figure 5–7). This is a reasonable candidate for the most interesting signal carried by those inputs, and thus, Hebbian plasticity provides a way for neurons to determine and extract such signals.

Synaptic Plasticity in the Cerebellum Plays a Key Role in Motor Learning

Although a detailed understanding of how the cerebellum contributes to complex human motor skills is lacking, a great deal is known about its role in simple forms of motor learning. Among the most thoroughly studied is a paradigm known as *delay eyeblink conditioning*, in which a neutral sensory stimulus such as a light or a tone is repeatedly paired with an aversive unconditioned stimulus (US) such as an air puff to the eye. After several days of such training, animals learn to close their eye in response to the previously neutral stimulus (the light or tone), known as the conditioned stimulus (CS), in anticipation of the US (the air puff). The timing of the eyelid closure is highly specific to the delay between the onset of the CS and the US.

Eyelid conditioning has been an extremely useful paradigm for understanding cerebellar function because it maps onto the structure of cerebellar circuitry in a particularly clear way (Figure 5–8). Information about the CS is first encoded by cerebellar granule cells and then relayed to Purkinje cells. The US is encoded by a completely separate input pathway, known as the olivocerebellar or climbing fiber system. In contrast to the many thousands of inputs from granule cells, each Purkinje cell receives a single powerful climbing fiber input from a brain stem nucleus known as the inferior olive. Electrophysiological recordings revealed that climbing fiber inputs to one particular region of the cerebellum signal the occurrence of the US, that is, a stimulus that is irritating to the cornea. This discovery was made possible by the fact that the climbing fiber evokes a distinct suprathreshold response in the Purkinje cell known as a complex spike.

A key to understanding how the cerebellum mediates learning was the discovery that the complex spike triggers plasticity at synapses between granule cells and Purkinje cells. Specifically, the co-occurrence of input from a presynaptic granule cell and a complex spike in the postsynaptic Purkinje cell results in a persistent weakening of the granule cell input, a form of plasticity known as cerebellar

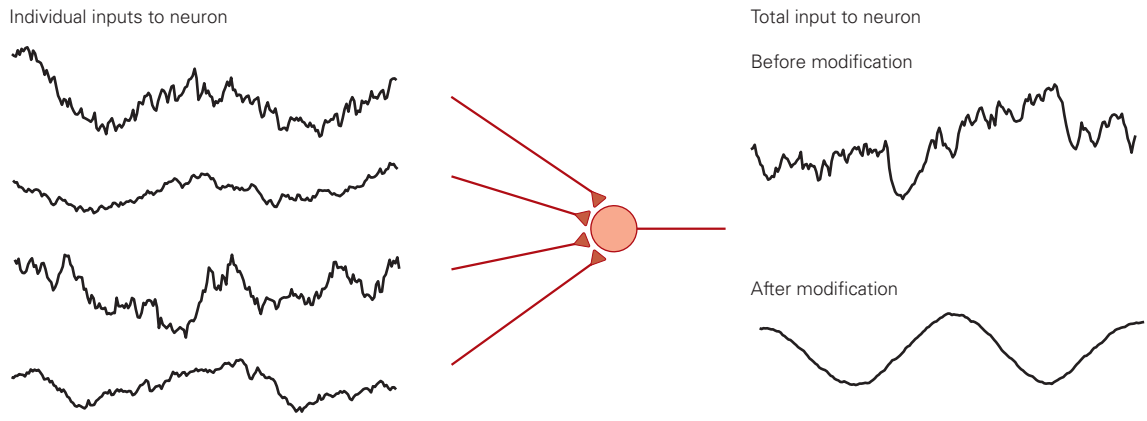

Figure 5–7 Hebbian plasticity can identify relevant input signals to a neuron. In this example, a neuron receives 100 inputs; firing rates for four of them are shown (*left*). Each of the input rates is noisy but contains, within the noise, a sinusoidal signal. The input rates are multiplied by synaptic strengths (**brown triangles**) and then summed to produce the total input to the neuron (*right*). Before Hebbian plasticity occurs, the synapses have random weights, resulting in the noisy trace; after modification, the total input reveals the underlying sinusoidal signal.

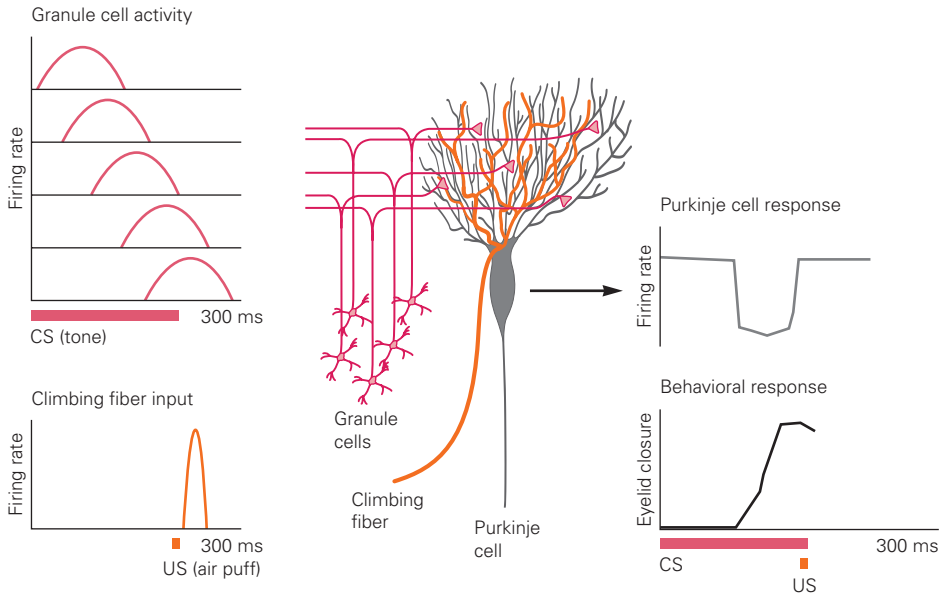

Figure 5–8 Hypothetical role of the cerebellum in eyeblink conditioning. Information about the conditioned stimulus (**CS**) and unconditioned stimulus (**US**) is relayed via mossy and climbing fiber pathways, respectively. Granule cell synapses active before presentation of the US are gradually weakened by long-term depression induced by climbing fiber input. This contributes to a pause in Purkinje cell firing that is precisely timed to occur just before the US. Since Purkinje cells are inhibitory, this pause excites downstream neurons in the cerebellar nucleus and red nucleus that drive eyelid closure.

long-term depression (Figure 5–8). Hence, for each occurrence of the US, the strength of granule–Purkinje cell synapses active immediately prior to the US is reduced. This plasticity leads to the gradual emergence of a learned pause in Purkinje cell firing due to the decrease in granule cell excitation just before the expected time of arrival of the US.

How does a decrease in Purkinje cell firing lead to a learned motor response? Purkinje cells are normally spontaneously active, and they inhibit their downstream targets. Purkinje cells in regions of the cerebellum receiving climbing fiber input related to noxious stimuli to the eye form synapses with neurons that indirectly activate the muscles that produce eyelid closure. Hence the learned pause in Purkinje cell firing causes the eyelid to close at just the right moment to protect the eye. Appropriate timing of the pause is thought to be mediated by a diversity of temporal response patterns in granule cells. Computer simulations have shown that learning of appropriately timed responses can be explained by plasticity in the granule–Purkinje cell synapse if individual granule cells are active at different delays after the CS or exhibit a variety of distinct, but repeatable, temporal patterns locked to the CS.

Due to technical challenges, direct evidence for such temporal representations has not yet been obtained for granule cells in the region of the mammalian cerebellum involved in eyeblink conditioning. However, a diversity of temporal patterns has been observed in granule cells in a structure analogous to the cerebellum in fish. More broadly, studies of the cerebellum, including those of eyeblink conditioning, provide a concrete illustration of how neural circuits can mediate learning though trial and error, even for learning more complex motor skills such as playing a musical instrument. Purkinje cells integrate a rich diversity of signals related both to the external world and internal state of the animal (conveyed by granule cells), with highly specific information about errors or unexpected events (conveyed by the climbing fibers). The climbing fiber acts as a teacher, weakening synapses that were active before, and hence could have contributed to errors. These changes in synaptic strength alter the firing patterns of Purkinje cells and, by virtue of specific wiring patterns, alter behavior such that errors are gradually reduced.

The cerebellum and cerebral cortex, including the hippocampal region, are foci of intense experimental and theoretical research on learning and memory. Technological advances are opening up new approaches for studying the contributions of synaptic actions, individual cells, and circuits to memory-related phenomena.

Highlights

1. Neural coding describes how stimulus features or intended actions are represented by neuronal activity. Decoding refers to the inverse process through which neural activity is interpreted to reveal the encoded signals. Mathematical decoding of neural responses can be used to interpret computations being performed by neural circuits and to drive prosthetic devices.
2. Neural circuits are highly interconnected, but a few basic motifs are used to characterize their functions and modes of operation. Feedforward circuits process information to extract structure and meaning from a sensory stream. Recurrent circuits can perform temporal processing and generate dynamic activity to drive motor responses.
3. Most neurons receive a finely tuned balance of excitatory and inhibitory inputs. Small changes in this balance in response to a sensory stimulus can evoke an action potential output.
4. Levels of neural activity must often be maintained for many seconds. Networks of recurrent excitation provide one mechanism to produce long-lasting changes in neural output.
5. Synaptic plasticity supports longer-lasting changes in neural circuits that underlie learning and memory. Hebbian plasticity can extract interesting signals from a complex set of inputs without the need for supervision (a "teacher"). Synaptic plasticity in the cerebellar cortex is driven by error signals (a form of supervision) and is used to tune motor responses and learn timing relationships.

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6

Imaging and Behavior

To explain an organism's behavior in biological terms, it is necessary to reconcile measures of biological processes (eg, action potentials, blood flow, release of neurotransmitters) with measures of cognitive and motor outputs. Relating biological and behavioral measures is challenging, however. Precise neural measurements and invasive techniques are possible in nonhuman animals, but many of these species have a relatively constrained behavioral repertory. Moreover, it is far more difficult to directly measure or invasively manipulate neural activity in healthy humans, the species with the most advanced and varied behavior. Thus, a central effort of modern neuroscience has been to develop new methods for obtaining precise biological measures from the human brain and for modeling human behaviors in nonhuman animals.

The dominant approach in humans for measuring biological processes and linking them to behavior is functional magnetic resonance imaging (fMRI). Other imaging methods for measuring human brain function such as electroencephalography, positron emission tomography, and near-infrared spectroscopy have their own strengths. However, fMRI is particularly well suited for studying the neural underpinnings of human behavior for several reasons. First, it is noninvasive: It does not require surgery, ionizing radiation, or other disruptive intervention. Second, it can measure brain function over short periods of time (in seconds), which allows it to capture dynamic aspects of mental processes and behavior. Third, it measures activity across the whole brain simultaneously, providing the opportunity to examine how multiple brain regions interact to mediate complex behaviors. Thus, the focus of this chapter is fMRI.

We start by explaining the technicalities of how an fMRI experiment works and how the data are typically collected. We then explain how fMRI data are analyzed

and how they provide insight into human behavior and thought. We then turn to a more conceptual overview of what has been learned from fMRI, using examples from the fields of perception, memory, and decision-making. Finally, we consider the strengths and limitations of fMRI and discuss what kinds of inferences about brain and behavior it can support.

Although the focus of this chapter is on imaging and behavior in the healthy brain, fMRI also has the potential to change the way we diagnose and treat psychiatric and neurological disorders. Virtually all such disorders (eg, autism, schizophrenia, depression, eating disorders) involve changes in large-scale circuit dynamics, in addition to the disruption of particular brain regions and cell types. Basic research into how healthy brain circuits mediate mental processes and behavior, combined with the ability to measure activity in these same circuits in clinical populations, holds tremendous promise for understanding disease and dysfunctional behavior.

Functional MRI Experiments Measure Neurovascular Activity

fMRI experiments enable investigators to track brain function based on changes in local blood oxygen levels that occur in response to neural activity. Like all forms of magnetic resonance imaging (MRI), fMRI requires both highly specialized equipment and sophisticated computer programs. In this section, we first consider the basic principles of how MRI can be used to image brain structure and then explain how fMRI extends this capability to image brain activity.

At the core of every MRI machine is a powerful magnet. The strength of the magnetic field is quantified in Tesla (T) units, and most modern MRI machines are 3T. The use of higher field strengths, such as 7T, offers some advantages, including the possibility of higher-resolution imaging of cortical layers. Such machines are not yet widespread, and layer-specific imaging is in its infancy, so we focus on the capabilities and configuration of 3T machines.

The outside of an MRI machine looks like a tunnel, known as the "bore" of the magnet. Subjects lie on a bed with their head in a helmet-like head coil, which receives signals from the brain. Visual stimuli are typically viewed through a mirror on the head coil angled toward a screen at the back of the bore. Auditory stimuli are presented through headphones. Behavior is typically measured in terms of manual responses with a button box and/or eye movements with an eye tracker. This apparatus constrains which experimental tasks are possible. However, fMRI is flexible in other ways, including that it can be performed and repeated without harm in many different types of subjects, from children to the elderly, whether healthy or suffering from a disorder.

What does fMRI measure? There are two fundamental concepts that we will discuss in turn, first magnetic resonance and then neurovascular coupling (Figure 6–1).

fMRI Depends on the Physics of Magnetic Resonance

In general, MRI exploits the magnetic properties of hydrogen atoms, the dominant source of protons in the body, specifically the way each atom's proton interacts with a strong magnetic field. A key property of protons is that they intrinsically rotate around an axis. This *spin* gives protons angular momentum and a magnetic dipole along the axis, their own north and south poles. Under normal circumstances, the directions of these dipoles are random for different protons. When placed in a strong external magnetic field, however, a subset of the protons (how many is proportional to the field strength) align with the direction of this field, which extends from foot to head when lying in an MRI bore.

An important step toward measuring a signal from protons is to push them out of alignment with this main field. To understand why, it is helpful to think about a familiar object, the gyroscope. If a still gyroscope is tipped out of vertical balance, it will just fall over. However, if you spin the gyroscope before tipping it, inertial forces will prevent it from falling over. The axis around which the gyroscope is spinning will itself begin to rotate around the vertical axis. This *precession* occurs because gravity exerts a vertical torque on the tilted gyroscope, pulling its center of mass down so that it pivots around its bottom point and traces out a circle in the transverse plane (looking from above). Something similar happens to a proton that is tilted with respect to the strong magnetic field: The field applies a torque and the orientation of the rotational axis precesses around the field direction. The speed of precession, or the *resonant frequency*, is determined by the Larmor equation, according to the field strength and a *gyromagnetic ratio* specific to each type of atom. In the case of a 3T magnet and hydrogen atoms, this speed is in the radiofrequency (RF) range.

But how do protons get tipped out of alignment in the first place to enable precession? The answer depends upon the same principle of torque. A second, weaker magnetic field is applied in a perpendicular direction (eg, front to back of the head), introducing

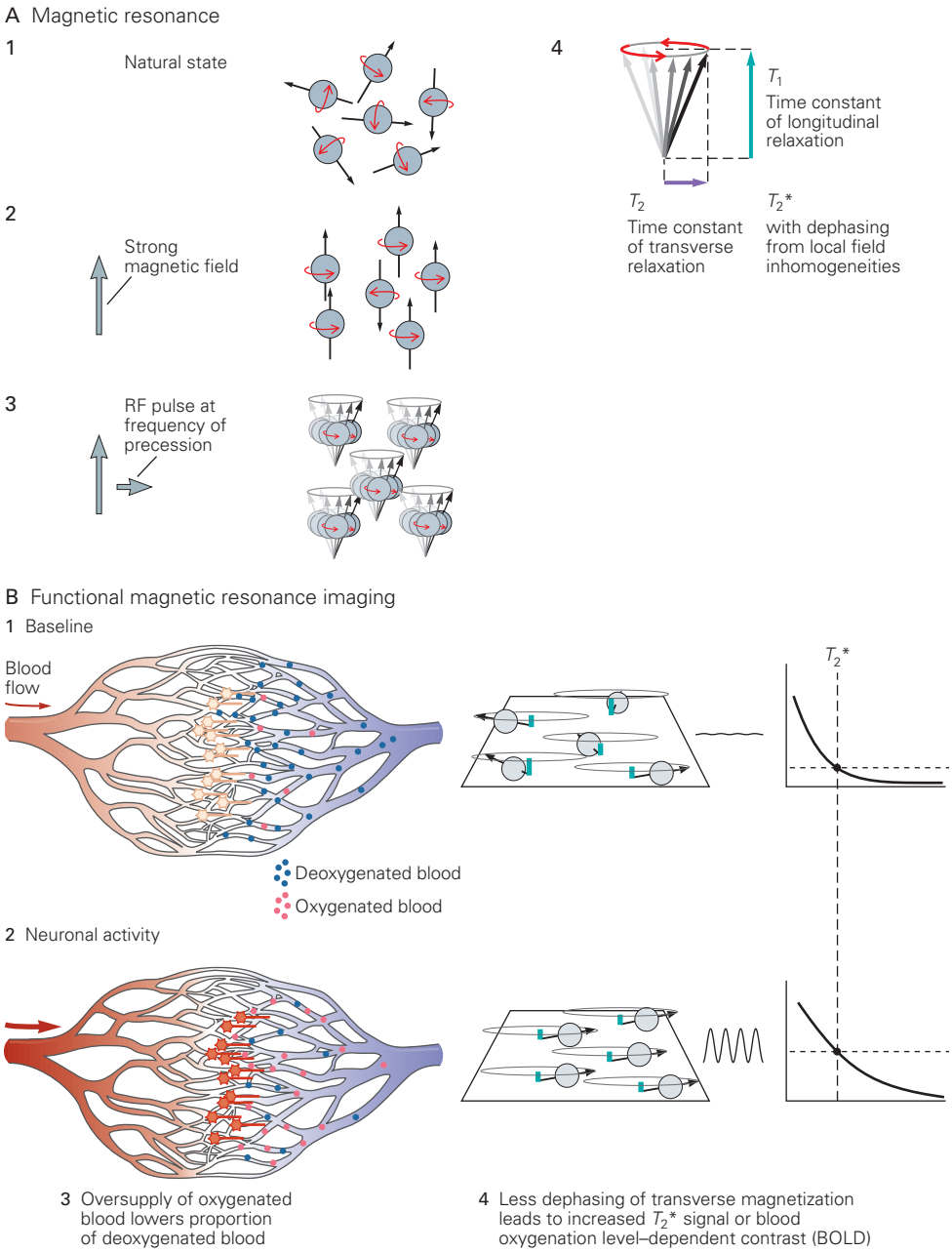

Figure 6–1 How fMRI measures neural activity.

A. Outside of the MRI environment, protons in hydrogen atoms in the brain spin around axes that point in random directions (**1**). When a brain enters the strong magnetic field of the MRI bore, a subset of these axes aligns with this field, which is known as longitudinal magnetization (**2**). These protons can be measured by transmitting a radiofrequency (**RF**) pulse that induces a weaker magnetic field perpendicular to the strong field. This misaligns the protons with the strong field, which now acts as a torque, causing the proton spin axes to precess in an arc on the transverse plane. The frequency of the RF pulse is chosen to resonate with the precession rate of the protons, which in turn depends on the strength of the magnetic field (**3**). When the RF pulse is stopped, the protons initially continue to precess synchronously, inducing alternating current at the same frequency in receiver coils surrounding the head. These signals can be used to generate an image by applying magnetic gradients that adjust the field strength in orthogonal directions across the brain. This results in different resonant frequencies at different points in the brain, allowing the source of the received signals to be identified. The transverse magnetization dissipates over time, and signal is lost. This relaxation occurs as the protons give off thermodynamic energy and their axes return to the longitudinal direction (T_1), and as the protons become desynchronized in the transverse plane from local interactions with other atoms and molecules (T_2), and because of inhomogeneities in the magnetic field (T_2^*) (**4**).

B. Magnetic resonance can be used to estimate neuronal activity in *functional* MRI because of the magnetic properties of blood. When a brain region is in a baseline state, there is a higher proportion of deoxygenated to oxygenated blood than when the region is active. Deoxygenated blood interacts with the magnetic field, causing local inhomogeneities that distort the rate of precession and disrupt the synchrony of protons in the transverse plane, leading to more rapid T_2^* decay and lower BOLD signal (**1**). Neuronal activity leads to metabolic demand (**2**), which in turn results in the delivery of excess oxygenated blood (**3**). Oxygenated blood does not interact with the magnetic field, and so the increased amount in active brain regions reduces field inhomogeneities. In turn, this reduces the dephasing of protons precessing in the transverse plane, leading to slower T_2^* decay and higher BOLD signal (**4**).

another torque that pulls protons away from alignment with the strong field. This misalignment causes precession about the direction of the strong field by allowing the strong field to act as a torque. Complicating matters, this precession makes protons a moving target for the weaker magnetic field that is needed to cause misalignment in the first place. This is solved by generating the second field using a transmit coil in the MRI machine, through which alternating current is passed to deliver an RF pulse at the resonant frequency of the protons. This induces a perpendicular magnetic field that rotates in lockstep with the precession. This RF pulse is sustained as long as needed to generate a specified change in the spin orientation of protons away from the strong field direction (eg, 90°). This change is known as the *flip angle* and is often chosen to maximize signal according to the Ernst equation.

Once the desired flip angle has been achieved, the RF pulse is stopped in order to measure the composition of tissue. At this point, protons are precessing around the strong magnetic field and tilted heavily into the transverse plane. This is akin to a bar magnet spinning on a table, where the north and south poles take turns passing any given location. If a coil is placed nearby, the spinning magnet induces a current in the wire that reverses as the poles alternate. This is what the receiver head coil in an MRI machine measures: alternating current induced by protons precessing synchronously (note: this is the same principle as described earlier for how the transmit coil works, just reversed). The amount of current indicates the concentration of precessing protons.

Critically, the frequency of these measured signals reflects the speed of precession, which in turn depends on the strength of the magnetic field experienced by the tissue. This can be used to generate three-dimensional images by imposing different gradients on the magnetic field (think of a staircase from higher to lower strength) that cause the Larmor frequency to vary systematically over space in the brain. During fMRI, one gradient is applied in a specific direction to select a slice of brain tissue. The RF pulse can be tailored to the resonant frequency for the exact field strength at this gradient step, such that only protons in this slice are excited. The same logic is used with additional gradients in orthogonal directions to impose a two-dimensional matrix on the selected slice, with each unit volume in the matrix or *voxel* having a unique frequency and phase. The head coil receives a composite signal with a mixture of these frequencies, but the signal can be decomposed to identify protons at every voxel in the slice.

There is another important property of precessing protons that contributes to MRI: The alternating current induced in the head coil begins to decay right after the RF pulse. There are different sources of decay. One source is that precessing protons give off thermodynamic energy (heat) to the surrounding tissue, just like a gyroscope will eventually lose energy to friction and topple over. As this occurs, the spin orientation of protons gradually relaxes back to the direction of the strong magnetic field, causing them to precess less in the transverse plane and thus generate less signal. This is called longitudinal relaxation and occurs with time constant T_1. A second type of decay occurs while protons are still precessing in the transverse plane. Individual protons are surrounded by a variable neighborhood of other atoms, which carry their own weak magnetic fields. This subtly changes the field strength the proton experiences, causing its Larmor frequency to vary unpredictably. Whereas right after the RF pulse protons precess in synchrony, these local interactions cause some protons to precess faster or slower. Because they get increasingly out of sync, the induced current alternates less reliably and signal is lost. This is called transverse relaxation and occurs with time constant T_2. This dephasing of protons can also result from inhomogeneities in the strong magnetic field itself, including how it is distorted by tissue placed into the field. The signal decay from both local interactions and field distortions has time constant T_2^* (pronounced "T2-star").

These different sources of decay are important because T_1 and T_2 time constants vary depending on tissue type. MRI can thus exploit signal decay to identify gray matter, white matter, fat, and/or cerebrospinal fluid. Depending on the configuration and timing of RF pulses, gradients, and other parameters set on the MRI machine (collectively known as a *pulse sequence*), the signals received from different voxels can highlight the contrast between tissues with different T_1 values (T_1-weighted image) and/or different T_2 values (T_2-weighted image). For example, white matter is brighter than gray matter in T_1-weighted images and vice versa for T_2-weighted images.

The standard pulse sequence for measuring brain function is the echo planar imaging (EPI) sequence. EPI has two desirable properties for fMRI: It is extremely fast, allowing an entire slice to be acquired from one RF pulse in less than 100 ms, and it is sensitive to T_2^*, which, as we will see later, is how MRI measures neural activity. When designing an fMRI study, several parameters of the EPI sequence need to be chosen, including how many slices to acquire in the brain volume (typically 30–90); how much time per volume (repetition time, typically 1–2 s); what voxel resolution to use (typically 2–3 mm in each dimension); and

whether to use parallel acquisition (eg, acquire multiple parts of a slice and/or multiple slices at once). These choices are interdependent, imposing trade-offs between speed, precision, and signal-to-noise.

fMRI Depends on the Biology of Neurovascular Coupling

We have described general principles of magnetic resonance, but what about the second part of the story, neurovascular coupling? Active neurons consume energy obtained from oxygen in blood. Thus, when a brain area is active, blood oxygenation drops in that moment. To replenish these metabolic resources, the flow of blood to the local area increases over the next few seconds. Supply exceeds demand, and so, counterintuitively, there is a higher proportion of oxygenated (versus deoxygenated) blood in active brain areas.

To link this to magnetic resonance, remember that T_2^* decay reflects dephasing of protons caused by field inhomogeneities. Blood has different magnetic properties depending on oxygenation: Deoxygenated blood interacts with the magnetic field because the iron in hemoglobin is unbound, whereas oxygenated blood in which the iron is bound to oxygen does not. Deoxygenated blood thus causes faster T_2^* decay and reduces signal relative to oxygenated blood. This difference in signal is referred to as the *blood oxygenation level–dependent* (BOLD) contrast. Putting everything together, increased signal in a voxel measured with an EPI sequence indicates recent neuronal activity because of the relative increase in local blood oxygenation that accompanies such activity. The temporal profile of this BOLD response, known as the *hemodynamic response function*, looks like a bell curve with a long tail, peaking around 4 to 5 seconds after local neural activity and returning to baseline after 12 to 15 seconds.

There are many more details about the physics and biology of fMRI. In addition, our understanding of how it all works is still evolving. For example, it is unclear whether BOLD is more closely tied to the firing of individual neurons or to the activity of neural populations. Likewise, it may be difficult to distinguish whether increased blood oxygenation is caused by increases in local excitation or inhibition. More generally, the mechanisms of neurovascular coupling—how the brain knows when and where to deliver oxygenated blood—remain mysterious, with a growing focus on the functional role of astrocytes. There is also the possibility of obtaining better temporal and spatial resolution by measuring the initial consumption of oxygen at the precise site of neuronal activity (the "initial dip"), reflected in an immediate and focal rise in deoxygenated blood rather than the delayed and more diffuse oversupply of oxygenated blood. Nevertheless, even with an incomplete understanding, fMRI has utility as a tool to localize changes in neural activity in the human brain induced by mental operations.

Functional MRI Data Can Be Analyzed in Several Ways

When performing an fMRI experiment, researchers link the neurovascular measurements described earlier to cognitive tasks programmed into a computer script that a human subject performs. The script generally produces a series of *runs* that correspond to a continuous period of data collection (ie, several fMRI volumes in a row), typically lasting 5 to 10 minutes. Within each run, several *trials* are presented to the subject, often by showing a visual stimulus or playing an auditory stimulus. Depending on the task, the subject may, for example, passively view or listen to the stimulus, make a decision about it, or store it in memory. A button press or eye movement response is often collected as a behavioral index of cognitive processing on that trial. These trials are typically drawn from two or more task *conditions*, which determine the stimulus type, task difficulty, or other experimental parameters. In a basic subtraction design, trials are divided between an experimental condition and a control condition, which are identical but for one critical difference whose neural basis is being investigated. Trials usually last 2 to 10 seconds, often separated by a variable or "jittered" interval of several seconds. In all, such sessions typically last up to 2 hours.

Each fMRI session produces a large amount of raw data, with BOLD responses sampled thousands of times at hundreds of thousands of locations in the brain. How are these data translated into insights about cognition and behavior? Numerous approaches to fMRI analysis are possible (Box 6–1), but for the most part, they break down into three categories (Figure 6–2). We first describe preprocessing steps common to all three types and then explain how each is conducted and what it can tell us.

fMRI Data First Need to Be Prepared for Analysis by Following Preprocessing Steps

Before the data can be analyzed, they must be prepared for processing. This is accomplished with a series of

Box 6–1 Brain Imaging as Data Science

Compared to many areas of science, the basic methods of brain imaging have enjoyed remarkable standardization. A major reason for this has been the availability of widely adopted software packages since the earliest days of fMRI in the mid-1990s. These packages were created and released by research groups, and—before it was fashionable—most were open-source.

At first, they included tools for preprocessing, alignment, analysis models, and statistical corrections. They have since incorporated new tools developed by researchers, including nonlinear alignment, field map correction, nonparametric statistics, and parallelization.

As a result, virtually all fMRI researchers use one or more of these packages, at least for part of their analysis pipeline. The following are popular free software packages for fMRI analysis:

AFNI: https://afni.nimh.nih.gov

FSL: https://fsl.fmrib.ox.ac.uk

SPM: https://www.fil.ion.ucl.ac.uk/spm

Beyond these specialized packages, fMRI is increasingly being viewed through the more general lens of data science. There are two reasons for this. First, fMRI produces a huge amount of data, both within each session but also aggregated across the thousands of studies that have been conducted. Making sense of fMRI data can thus be considered a big-data problem. Second, the data are incredibly complex and noisy, and the cognitive signals of interest are weak and hard to find. This creates a data mining challenge that has inspired many computer scientists.

The most concrete manifestation of this trend is the rise of machine learning in fMRI analysis. Other points of contact with data science include the challenges associated with the real-time analysis of streaming data, the application of network analysis and graph theoretic approaches, the use of high-performance computing clusters and cloud systems, and the growing practice of researchers publicly sharing data (eg, https://openneuro.org), code (on services such as GitHub), and educational materials (eg, https://brainiak.org/tutorials). Thus, the field of brain imaging will continue to benefit from advances in computer science, engineering, applied math, and statistics.

steps referred to as *preprocessing*. Preprocessing seeks to remove known sources of noise in the data, caused by either the subject or the MRI machine. Standard practice includes five basic steps known as motion correction, slice-time correction, temporal filtering, spatial smoothing, and anatomical alignment.

Motion correction seeks to address inevitable noise in the data due to a subject's head movement. Even the best subjects move their heads a few millimeters over the course of a scan, such that the voxels across three-dimensional brain volumes become somewhat misaligned. This movement can be corrected for using a spatial interpolation algorithm that lines up all of the volumes within each run. This algorithm quantifies the amount of movement at each point during the scan, including the translation in the x, y, and z dimensions, and the amount of rotation about these axes (*pitch*, *roll*, and *yaw*, respectively). These six time courses can later be included in the data analysis as *regressors*, to further remove motion artifacts.

Slice-time correction is applied to deal with differences in the timing of the acquisition of samples across different slices. EPI sequences collect the slices that make up each brain volume sequentially, often in an interleaved order to avoid contamination of adjacent slices. Thus, there is a large difference in the timing of the first- and last-acquired slices of the same volume, which are closer in time to the preceding and subsequent volumes, respectively, than to each other. Correcting for this difference in the timing of the slices can be accomplished with temporal interpolation to estimate what the signal would have been if all slices were acquired simultaneously.

Temporal filtering and *spatial smoothing* aim to increase the signal-to-noise ratio. Temporal filtering removes components of the time course in each voxel that are highly likely to be noise rather than meaningful variance, such as very low frequencies (>100-second period) that typically result from scanner drift. Spatial smoothing applies a kernel (typically 4–8 mm wide) to blur individual volumes, averaging out noise across adjacent voxels and improving the odds that functions will overlap across subjects after anatomical alignment.

This *anatomical alignment* is accomplished by registering data across runs and subjects, usually with simple transformations (eg, shift, rotate, scale), to a standard template such as Montreal Neurological Institute or Talairach space. Typically, fMRI data are