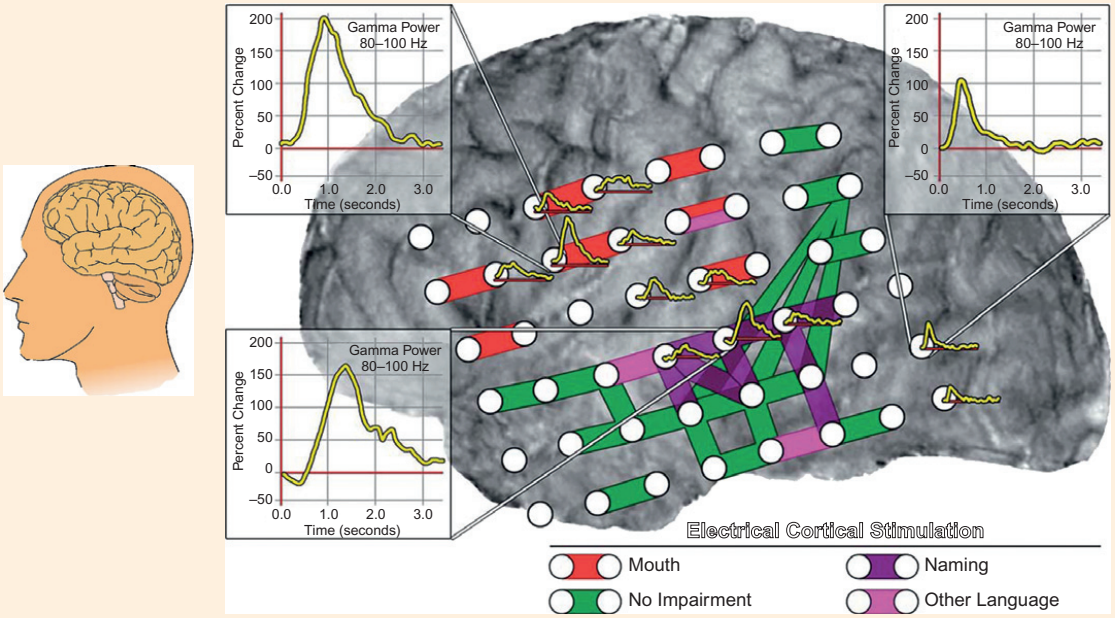
CHAPTER

5

Brain imaging

OUTLINE

LISTENING TO THE BRAIN



Direct electrical recording and stimulation of the left hemisphere of a waking patient. The patient feels no pain because the cortex has no pain receptors, and the incision is protected with local anesthesia. It is important for the patient to be conscious during exploratory surgery to help locate vital functions that must be protected. Notice that the surgeon has labeled electrodes for the mouth (white dots with red stripes) and for picture naming (dark purple stripes). The three graphs show the averaged electrical activity over three seconds after the patient is shown a visual object to name. Gamma activity (80–100 Hz) peaks the fastest in the posterior site, then near the motor cortex (red), and finally in the upper temporal lobe (purple). Can you guess why?

Source: *Crone et al., 2006.*

1.0 INTRODUCTION

The ability to directly observe the living brain has created a scientific turning point, much like Galileo's first glimpse of the moons of Jupiter. Humans have studied the sky for many centuries, but when glass lenses and telescopes were invented, the pace of discovery took off. But just as Galileo's telescope required constant improvement, our "brain scopes" have their limits. We should know their limits as well as their capabilities.

A perfect brain observer would keep track of tens of billions of neurons many times per second. The perfect observer should then be able to track the shifting interplay between groups of

neurons, with thousands of signals traveling back and forth. By analogy, a perfect spy satellite would see every human being on Earth as well as all the things we say to one another.

Such a perfect observer does not exist. We are more like distant space explorers beginning to observe a new planet. We pick up signals without knowing exactly where they come from, whether they are made by living creatures, what languages they speak, or even whether the signals mean anything.

We know that the brain has major pathways and maplike arrays of neurons and that single spikes as well as waves (oscillations) can travel between brain maps. Brain oscillations vary between 0.5 to 120 Hz (i.e., up to about 120 cycles per second), with occasional faster events. If we add in the neurotransmitters and neuromodulators that shape signal transmission, the potential number of signals is enormous.

Neurons have *electrical*, *magnetic*, *chemical*, and *anatomical* properties. Each of these can be measured. As you know from Chapter 3, every neuron can send a fast electrical signal down its axon. We can record this activity in the cell or in the surrounding fluid. The brain also has a rich fuel supply, and when a specific region of the brain is working harder, it needs extra fuel. Those facts give us all our brain measurement techniques: neurons, and networks of neurons, generate electrical and magnetic signals. Metabolic processes can be picked up using methods like PET and fMRI. The anatomical shape of brain structures can be detected by CAT scans and MRI. As a result, we can now see functional brain activities for speech, action control, motivation, sensory perception, and more.

1.1 Basics

Brain imaging has been a breakthrough technology for cognitive neuroscience, building on decades of cognitive psychology, behavioral conditioning, psychophysics, and brain science. Before imaging techniques matured, our knowledge came from animal studies and the haphazard injuries incurred by human beings. But brain injuries are extremely imprecise, and to locate the damage, neurologists often had to rely on postmortem examination of patients' brains—as in the case of Broca's and Wernicke's patients. The brain can often compensate for damage, so lesions change over time as cells die and adaptation occurs. Therefore, postmortem examinations do not necessarily reflect the injury at the time of diagnosis. Animal studies depend on presumed homologies—similarities across species—that were often not convincing. No other animals have language and other human specializations. It was therefore very difficult to understand how brain functions in animals mapped onto human cognition.

Today, we have perhaps a dozen techniques that are rapidly becoming more precise. Medical needs often drive this expensive technology because it applies to many organs in the body. As a result, we now have ways to study the distribution of billions of neurochemical receptors in the brain, the thickness of cortex, the great highway system of white fiber bundles, and, most important for cognitive neuroscience, the *functional* activity of the brain—the basis of its adaptive capacities. New advances are allowing scientists to investigate not only specific brain regions but also the dynamic pattern of connectivity between them. Some of the massive "wiring" of the brain is shown in the figure, but like the World Wide Web, the wiring

is only part of the story: ever-changing connections are being made that can alter in a fraction of a second.

1.1.1 *Accuracy in space and time*

Figure 5.1 shows today's methods and their accuracy in space and time. (See Chapter 1 for the spatial and time magnitudes of the brain.) Techniques like functional magnetic resonance imaging (fMRI), which records metabolic changes like blood oxygenation, have good spatial resolution and relatively poor time resolution. fMRI has a response time of about six seconds because the fMRI signal (called the BOLD signal) reflects a flow of oxygen-rich blood traveling to "hot spots" that are doing extra work. The changes in blood flow take several seconds to catch up with the neuronal activity. fMRI is therefore too slow for tracking single neurons and populations in "real time."

We do not have a complete census of all the neurons in the brain the way a human society might conduct a census of the whole population. We are always sampling from a very large set of active neurons. For that reason we cannot be sure that we know every single cell type in the brain, down to the smallest level. Brain anatomists are constantly discovering new specialized neurons in some local neighborhood. For example, the light receptors that adjust our body to sunlight and darkness were only discovered in recent years.

fMRI has very good spatial specificity compared to electroencephalography (EEG) and magnetoencephalography (MEG), which use electrical and magnetic signals, respectively.

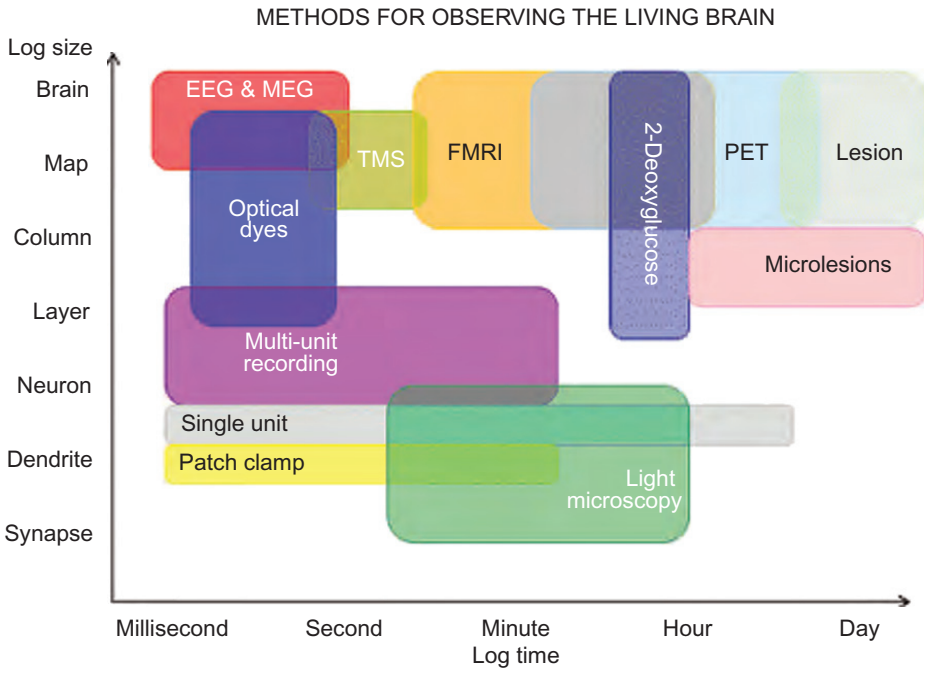


FIGURE 5.1 How good are current methods? Pros and cons of imaging techniques: differing imaging modalities have different resolutions. While some approaches have a very high temporal (time-based) resolution but a low spatial (space-based) resolution, other modalities have an opposite relation.

Thus, fMRI is used to localize brain functions. But EEG and MEG have excellent temporal resolution—almost instantaneous—and relatively poor spatial precision. They can track neuron population activity as quickly as tens and hundreds of milliseconds, but it is hard to know *which* set of neurons is doing it. fMRI is sometimes used in combination with EEG to obtain the best temporal *and* spatial precision. Combined measures may give us the best of both worlds.

1.1.2 A brain in a shoebox: coordinates

When sailors learned to draw imaginary lines of latitude and longitude to place a coordinate system around the earth, it became possible to specify any place with a precise "x" and "y" number. The earth's coordinate system became a major advance in navigation.

The shape of the brain is more complex than the earth's, but the strategy of placing it in a three-dimensional space is the same. Scientists can specify a precise location in the brain by placing it in a virtual shoebox so each point in the brain has a unique address in three orthogonal dimensions. Each point can be specified as x, y, and z. The best example is the Tailarach Coordinate System illustrated in Figure 5.2.

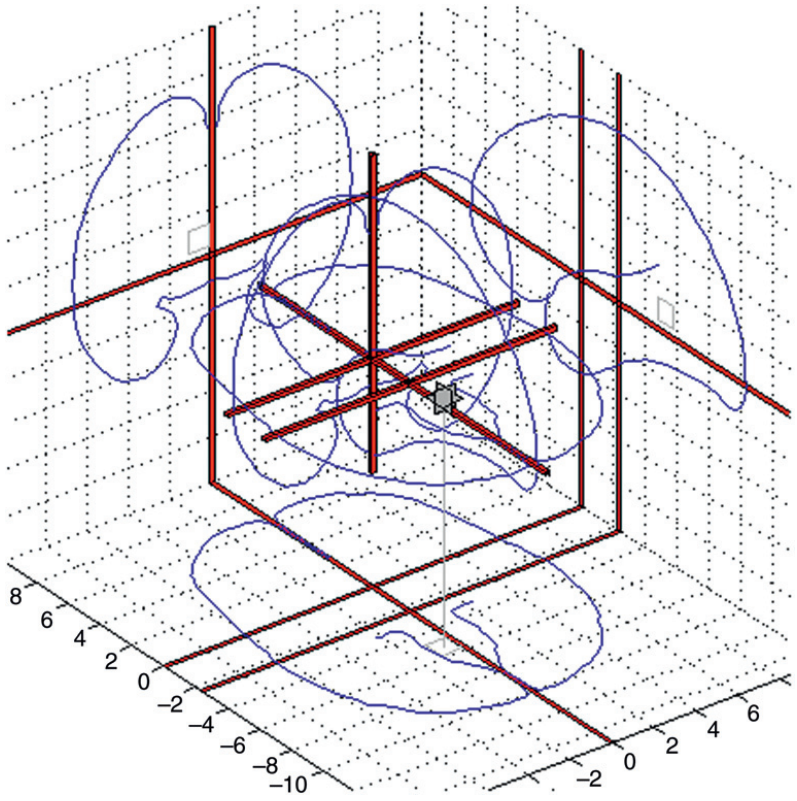


FIGURE 5.2 A coordinate system for the brain. The brain is typically imaged in three dimensions: axial, sagittal, and coronal (see Chapter 1). Putting the brain together into a three-dimensional image allows the coordinates to be determined across these three dimensions. Source: *http://neuroinf.imm.dtu.dk/old_brede/WOROI_96.html*

Different people have different brains. Just as our heads have distinctive shapes, so do the organs inside. We begin to lose neurons after birth, so infants have more neurons than older children, teenagers, or adults. On the other hand, brain myelination (the wrapping of long axons by white protective cells) keeps growing until about age 30. Serious illnesses, growth and aging, learning and exercise, brain injury, and even malnutrition can add or subtract tissue. The brain keeps changing.

Individual brains therefore need individual images. MRI and CAT scans are used to take a snapshot of the three-dimensional brain at any particular moment. Figure 5.3 shows the smallest unit imaged using MRI: a "voxel." Figure 5.4 shows a brain navigation program with a screenshot of the standard coordinate system used in most MRI research.

Brain surgeons need to know where to remove disease-causing tissue and which regions need to be left untouched. Structural images from MRI and CAT scans give us a three-dimensional map of the brain. But maps are also essential for understanding functional measures, like EEG, MEG, fMRI, and deep brain recording. Typically, measures of brain structure and function are combined.

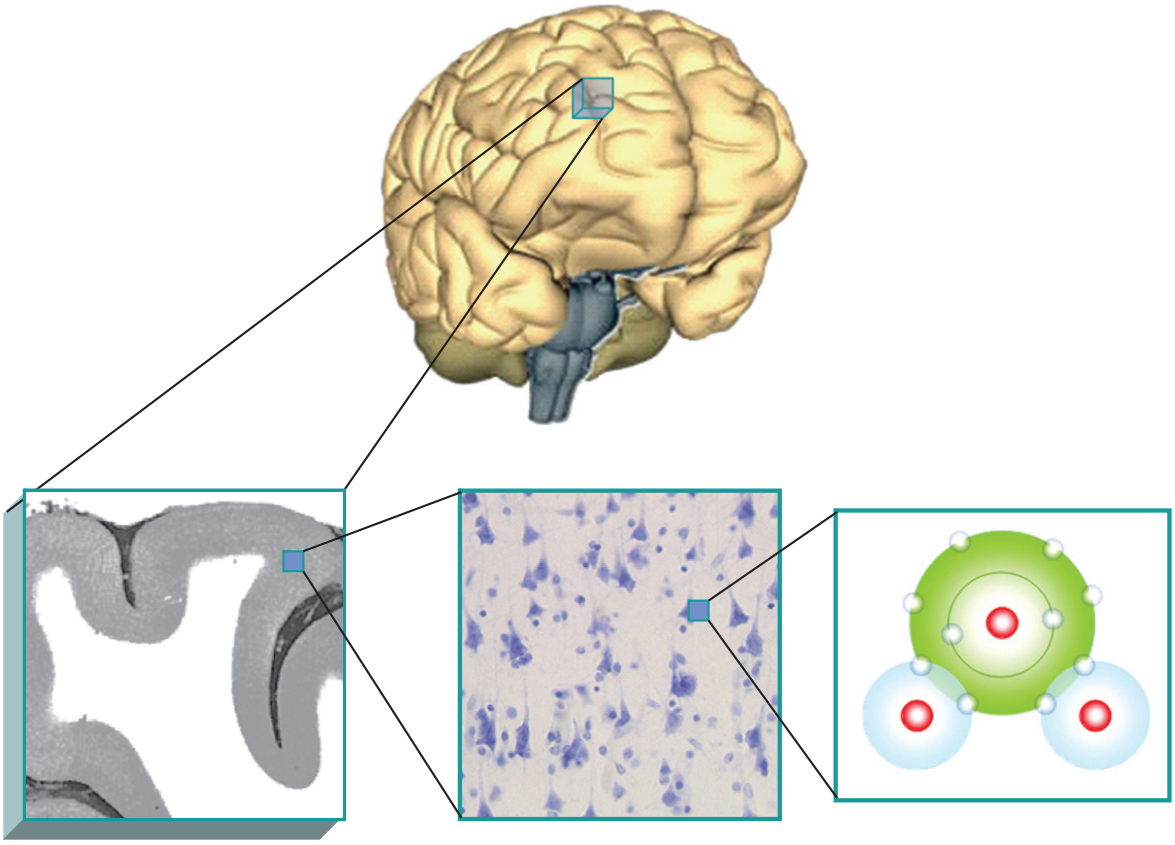


FIGURE 5.3 A single "voxel" gives the smallest unit of volume. The voxel is a representation of a volume in three-dimensional space. In the brain, the resolution of the MRI scanner determines how small the voxels can be. Higher magnetic field strength increase the spatial resolution and thus the ability to represent separate structures in the brain. Source: *Jones et al., 2002.*

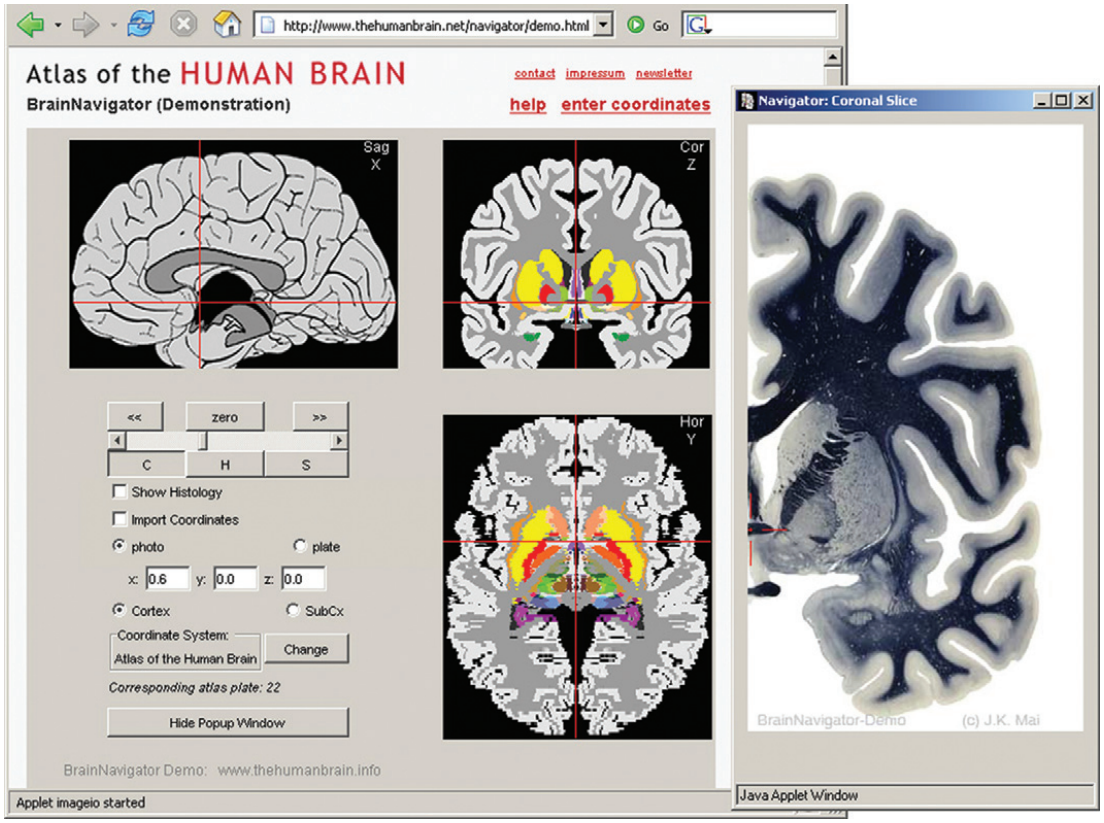


FIGURE 5.4 Brain navigation software allows the user to translate precise locations into conventional brain locations in order to compare results across patients. Notice the orientation of the standard slices. The x, y, and z coordinates are known as the Talairach system (Talairach & Tournoux, 1988). Anatomical landmarks like the corpus callosum can be seen in the upper left display. Source: *Talairach & Tournoux, 1988.*

1.2 Single neurons

Even with fast-improving imaging techniques, the most direct evidence about the living brain still comes from *intracranial* electrical recordings. One reason is that the electrical voltages in the brain are much greater than on the scalp—on the order of *millivolts* rather than *microvolts*. Surface EEG is filtered through a watery medium of brain tissue, skin, bone, and muscle. When you frown, the muscles above your eyes contract, and thin layers of muscle across the scalp stretch and adjust. Even eye movements have large effects on the scalp-recorded EEG. Thus surface EEG recordings mix many electrical sources, as well as being filtered through layers of tissue. About 99.9 percent of the signal strength is lost.

Direct brain recording therefore has a great advantage. The biggest drawback is that it requires invasive surgery. In humans it is never done without medical justification. However, many animal studies use direct brain recording, and these still provide much of the basic evidence.

Wilder Penfield and his colleagues pioneered electrocorticography (ECoG) in humans in the 1950s. Epileptics with uncontrolled seizures can benefit from surgical removal of seizure-causing

scars in the cortex. ECoG recordings can show where such "epileptogenic foci" are located. In addition, the surgeons need to know which areas to avoid damaging because they are vital for perception and language. ECoG exploratory studies are relatively safe and practical. Probing the cortical surface is generally pain-free because the cortex does not have pain receptors. The scientific benefits have been very important. ECoG studies in conscious humans are helping to uncover the neural basis of language, conscious perception, and voluntary control.

1.2.1 Recording and stimulating neurons

Single neurons have electrical and magnetic properties, like electrical batteries. We can measure the charge left in a battery and the amount of work it can do for us. We can also measure its magnetic field, as well as its chemistry and overall structure. Hubel and Wiesel (1962) recorded single feature-sensitive cells in the visual cortex of the cat—an achievement for which they received a Nobel Prize in 1981. More recent work has recorded in medial temporal lobes (Figure 5.5). Like every method, electrical recording of axonal firing has its limitations, but it continues to be a major source of information.

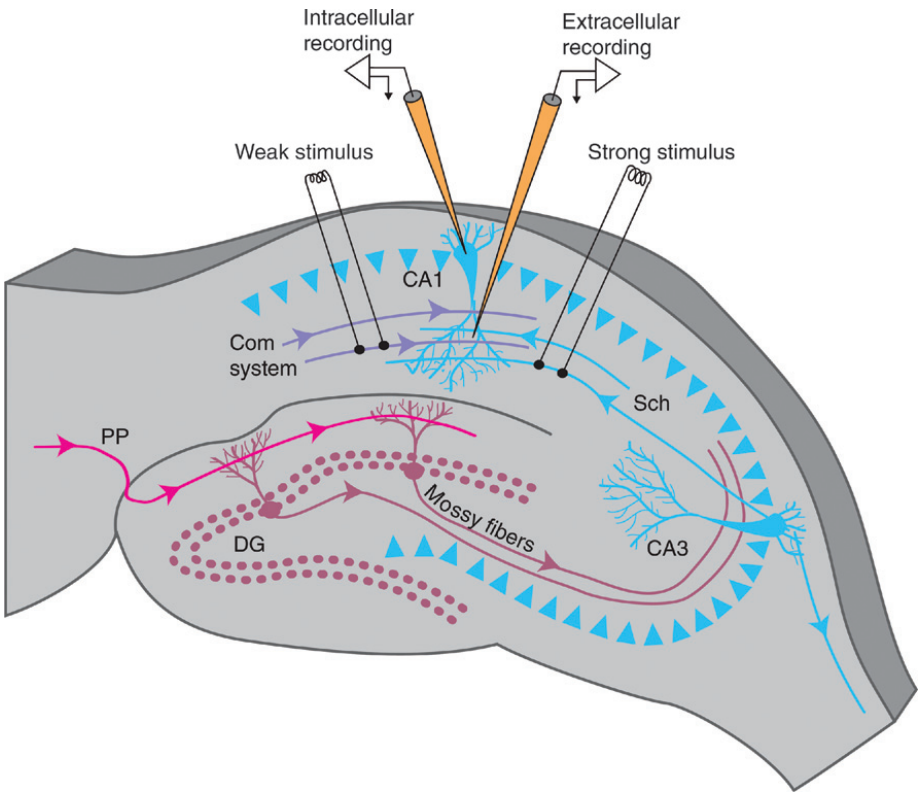


FIGURE 5.5 The voltage and current flow of neurons have been studied using microelectrodes inserted in the cell, compared to a reference electrode placed outside. Large numbers of neurons also generate electrical and magnetic fields, and because many neurons are lined up in parallel arrays, like vast fields of wheat or corn, their overall electrical and magnetic fields "point" in a consistent direction. Source: *Squire et al., 2002.*

Neurons fire a maximum of 1,000 Hz, but cortical neurons average about 10 Hz. We have no "universal census" of cortical neurons, so we do not know with certainty how representative the small samples we observe really are.

In many countries, deep electrode recordings are allowed in primates, such as the macaque monkey, under suitable ethical constraints. The macaque brain has some striking similarities to human brains. Single-neuron recording in the macaque prefrontal cortex may show working memory. In a typical experiment, a macaque is trained to fixate visually on a cross on a computer screen and to perform a delayed response to a visual stimulus. The animal is trained to wait for a moment before looking in the direction where a stimulus appears or, alternatively, to look in the opposite direction. We can then record the activity of a single prefrontal neuron in the three phases: the presentation of a visual stimulus, the period when the monkey keeps the location of the visual stimulus in working memory, and the response of looking in the opposite direction.

1.2.2 Single neuron recording in humans

Some of the most astonishing findings in the last ten years have come from single cell recordings in humans. This is ethically possible only when there is a medical necessity for the risks of surgery, like infection and brain damage. However, the technology for safe and effective epileptic surgery has been worked out over half a century.

Depth electrodes have been used in humans. Typically, these electrodes are implanted before surgery in a patient who has otherwise untreatable epilepsy. The implants can determine where epileptic foci begin at the onset of a seizure and where critical regions of the brain are located that must not be lesioned.

While a single cell cannot tell us much about human cognition, a recent experiment provided some intriguing results regarding conscious and unconscious visual perception (Figure 5.6). While the spiking neuron is a plausible unit of brain activity, some scientists believe that graded dendritic currents in each neuron may do useful information processing; some argue for subcellular processes inside the cell; others point to nonclassical cells and synapses; and many scientists believe that real brain processes only take place at the level of *populations* of neurons. Therefore, recording axonal spikes is important, but it may not be the only important thing going on. Obviously, it's a risky business to jump from a single neuron to more than 10 billion in the vast forest of the brain.

2.0 ELECTRICAL AND MAGNETIC FIELDS

The brain has billions of neurons lined up more or less in parallel. The long pyramidal neurons of the cortex mostly point their axons inward to the thalamus, and later many axons join the great hubs and highways of the inner white matter. However, pyramidal cells have input dendrites that are mostly spread out horizontally, following the curve of the cortex. When pyramidal neurons fire a spike down the axons, their dendrites also change. Those flat and bushy horizontal "arbors" of dendrites are picked up as EEG activity at the scalp because their electrical fields happen to point outward.

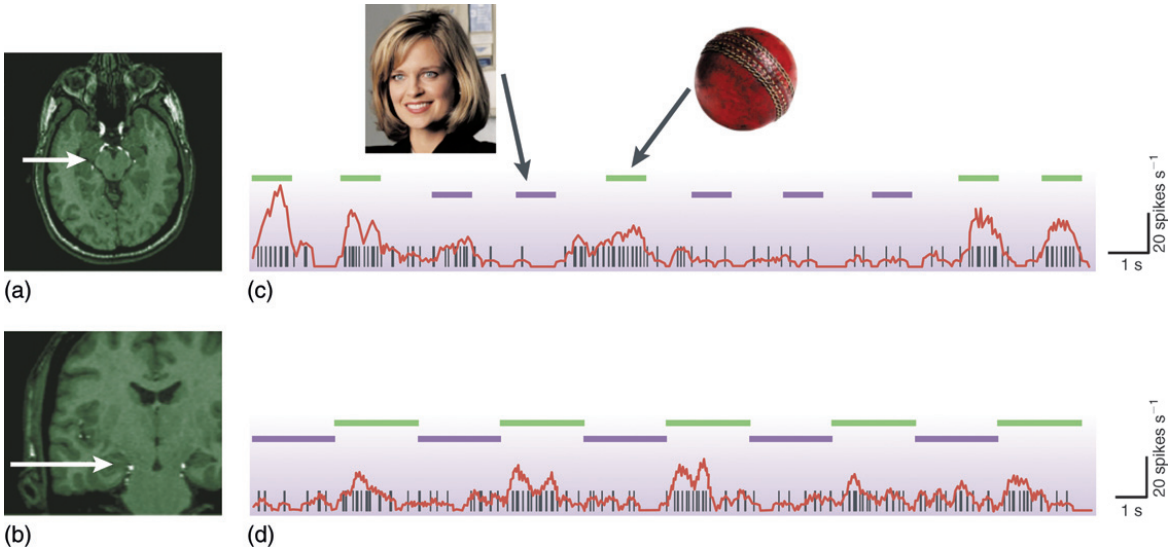


FIGURE 5.6 Single neurons reflecting conscious perception. A remarkable experiment in which both conscious and unconscious stimuli were shown simultaneously to two different eyes using a variant of binocular rivalry (see Chapter 6). In the upper row (c), the woman's face is conscious, but the ball is not; in the lower row (d), this is reversed. Peak firing rates, in red, during the time periods marked by the green horizontal bars, when the subject is reporting that the woman's face can be seen. The brain seems to determine which of the two simultaneous stimuli will become conscious when the signal reaches the object recognition areas in the cortex. The electrode locations are shown on the brain scans on the left (a, b). Source: *Rees et al., 2002.*

All streams of electrons generate both electrical and magnetic fields, which radiate at right angles to each other (Figure 5.7). Therefore, we can also pick up the brain's magnetic field—at least those components that conveniently point outward from the scalp. Most the field strength in the brain is not measurable from the outside. We just take advantage of radiating fields that can be picked up.

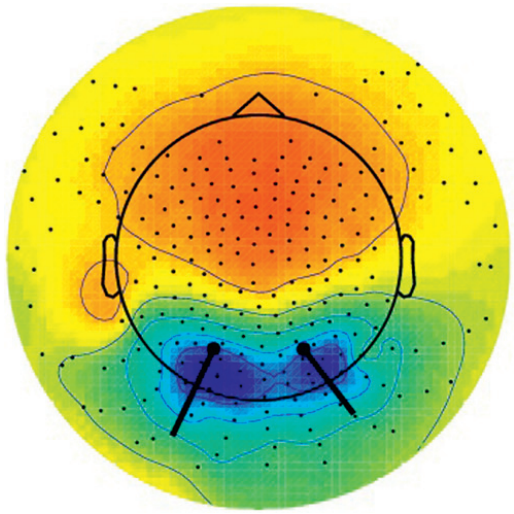


FIGURE 5.7 The brain radiates electrical and magnetic fields. Here is an example of a 252-channel EEG recording. The head is shown from above, with the front of the face on the top of the figure and the back of the head on the bottom. Dipoles are shown in black arrows, and their centers are shown in blue. Based on these data, what part of the brain do you think is active? Source: *Schwartz Center for Computational Neuroscience (http://sccn.ucsd.edu/eeglab/comp252.html), with permission.*

2.1 Electroencephalography: the electrical fields of the brain

Scalp EEG is a standard tool in medicine. When an accident victim comes into an emergency room with a head injury, scalp EEG is one of the first tests. With only 21 electrodes, a great deal can be observed, including gross brain damage, coma and stupor, sleep, waking, epileptic signals, and more. Computer programs for analyzing EEG are constantly improving.

The biggest difficulty in scalp EEG is locating the source of the recorded signal. The brain is a large, wet medium, and recording from the scalp results in a loss of 99.9 percent of the source. This is like trying to understand a watery planet where all the radio signals come from deep in the ocean and most of the signal power is lost before the satellite can pick it up.

The brain's electrical activity can be recorded through the scalp or on the surface of the cortex. Rather than picking up electrical activity direct from neurons, the electroencephalogram picks up the electrical field. The resulting record is an *electroencephalogram* (EEG). The EEG was discovered in 1929 by Hans Berger.

EEG is a relatively direct measure of the brain's electrical activity. But with tens of billions of cortical neurons firing about 10 Hz, we have several trillion electrical events per second. The raw EEG was therefore difficult to interpret before the advent of powerful computerized analysis.

However, when the EEG is averaged over a number of trials and " locked " to a specific zero point, like the onset of a stimulus, the averaged electrical activity yields elegant and regular waveforms. This event-related potential (ERP) is sensitive to large population activity that characterizes visual, auditory, and even semantic processes.

The brain can also be *stimulated* with electrical and magnetic energy. Today we can stimulate deep brain regions using microelectrodes, which are sometimes useful for treating severe depression and Parkinson's disease.

2.2 Analyzing the electroencephalogram

While the brain has about 100 billion cells, the cortex is now believed to have about 1,000 specialized regions, originally discovered by Brodmann (1909) and therefore still called Brodmann areas. They are the postal codes of the brain. Other major structures, like the thalamus, have their own regional organization.

Humans communicate by phone, radio, and television. Those techniques use different coding schemes, often with different waveforms (such as AM and FM radio). The brain seems to have many coding schemes. The visual cortex, for example, has "visuotopical maps": two-dimensional arrays of the visual input that begin with the retina and continue in the visual cortex with area V1. Higher-level maps have more abstract visual representations, like motion, color, faces, houses, and other objects. Since these arrays often correspond to one another, they are said to be "topographically mapped." A particular point on the retina, like your center of visual gaze, corresponds to the same point in the thalamus, V1, and higher visual maps. This is a *spatial* coding scheme, like a video camera or a computer screen.

The waveforms in Figure 5.8 show major bands (ranges) of waves in the EEG. These oscillations are believed to play important roles in the brain (See Box 5.1 for an interesting experiment using these EEG measures.). Notice the top oscillations, which represent "raw" (unprocessed) EEG, recorded from any electrode on the scalp. During the waking state, these oscillations look nearly random, as if they are generated by chance events. For that reason EEG was controversial for many years, until the emerging evidence showed that the choppy "ocean" of the brain consists of many regular waveforms (Figure 5.9).

When random snippets of EEG are averaged, the result is a straight line, since random positive and negative oscillations add up to zero. This fact is used in the event-related potential, discussed in the following.

The activity of large populations is another important level of analysis (Freeman, 2004; John, 2001). Spontaneous EEG shows different patterns of activation. For example, during deep sleep, the raw EEG shows large, slow waves. This indicates that large groups of neurons are synchronized on a very large scale throughout the brain. When the subject wakes up, this slow pattern is replaced by small, rapid electrical waves, indicative of rapid and

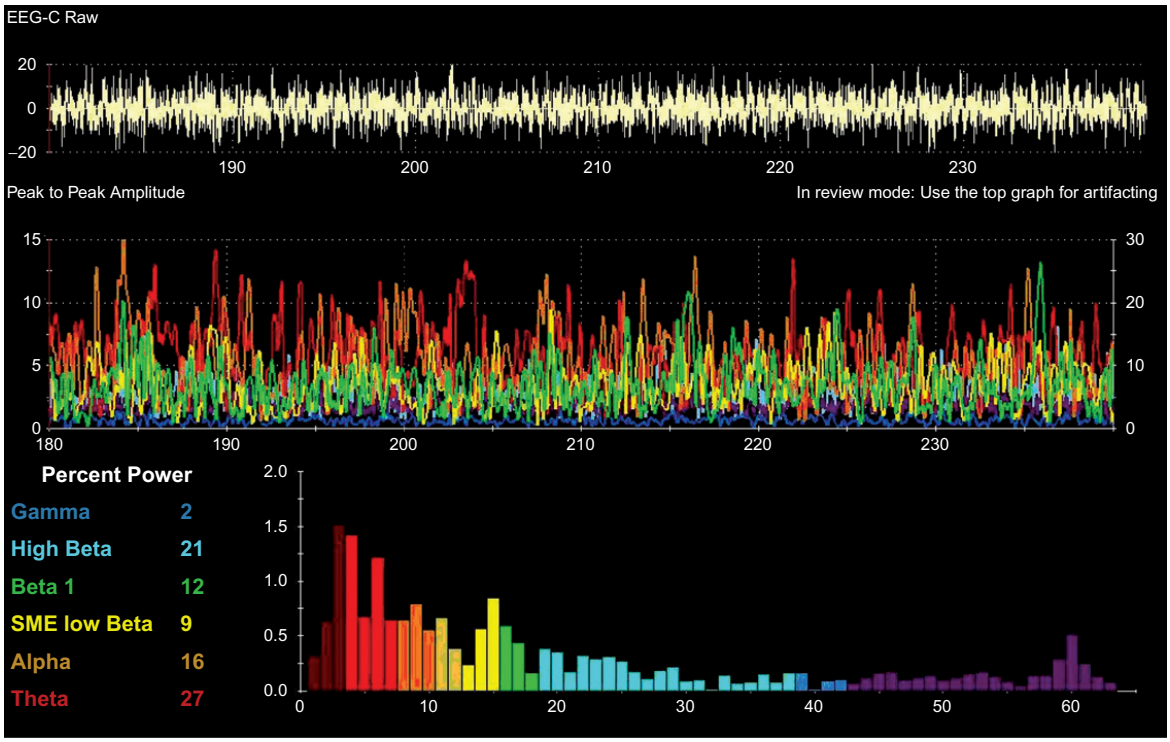


FIGURE 5.8 Regular rhythms in different parts of the brain are shown. A method called Fourier analysis allows us to decompose the density (or power) of regular waveforms that are buried in noisy EEG recordings. The graphs show the resulting power curves. The colors correspond to different frequency ranges. Source: *Zoran Josipovich, with permission.*

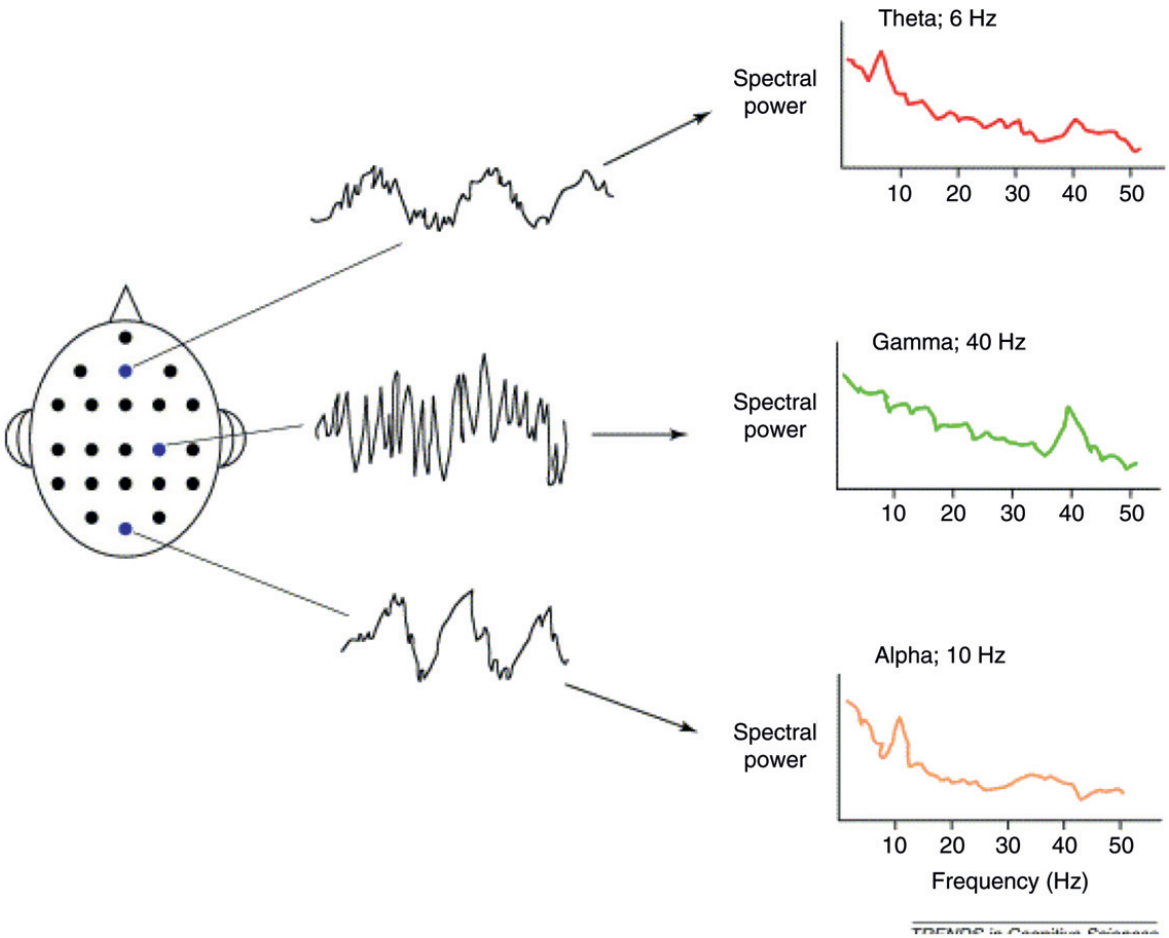


FIGURE 5.9 Some power spectra showing peaks at canonical EEG frequencies. Although any of the frequencies can occur at any electrode site, alpha power is often recorded at posterior sites, theta at frontal sites and gamma over sensory cortex. Source: *Ward, 2003.*

flexible information patterns of interaction in the brain. It is currently believed that cortical neurons do not fire at different rates during deep sleep compared to waking, but rather that waking EEG allows a far greater amount of interactive processing. Sleep is not a passive state, but a different operating mode of the brain, with its own functions. One of these is believed to be the consolidation of memories based on waking experiences (Hobson & Stickgold, 1995).

EEG has a millisecond time resolution, but its spatial resolution is rather poor. It is very difficult to locate the electrical source of the EEG signal. It helps to increase the number of electrodes and to use sophisticated analytical methods. However, EEG gives us little information about brain regions deep beneath the cortex.

2.3 Averaging the EEG

It makes sense to get the average annual income in a country. One reason is that there is variability between the poorest and wealthiest people. Another is that it helps to have one number to describe millions of people. The point of statistics is to simplify very large numbers to just a few. A similar approach works with the electrical activity of the brain, using the "event-related potential" (the word *potential* means "voltage"). Event-related potentials (ERPs) were discovered several decades ago, before high-speed computers were available to analyze the EEG. When a bright flash or a loud sound is presented to an animal or a human being, a wave of activity travels throughout the cortex and thalamus. That brain activity is "evoked" by the flash or the bang, and it is helpful to show the results starting with the moment of the stimulus. The evoked (that is, they occur in response to the event, in this case a flash or bang) potential waveforms are reflected in the EEG, but they tend to be swamped by other brain activity, much like a giant wave in the ocean that is invisible as long as it is swamped by other wave activity in the sea.

As just pointed out, the irregular or "random" component of the EEG drops out when multiple stretches of the signal are added up or averaged. However, the large and distinctive signals of the ERP do not drop to zero. Rather, they add up over each trial, showing up as the event-related potential (ERP). ERP peaks and valleys are quite regular and stable over time. They are believed to reflect large neuronal populations that are triggered by the input.

When we average over a number of half-second stretches of EEG, we obtain the ERP in Figure 5.10. EEG reveals brain patterns during sleep and waking, abnormalities during diseases like epilepsy, and even the brain areas that respond to music. A more recent technique, magnetoencephalography (MEG), is related to EEG and has provided new ways to image the human brain.

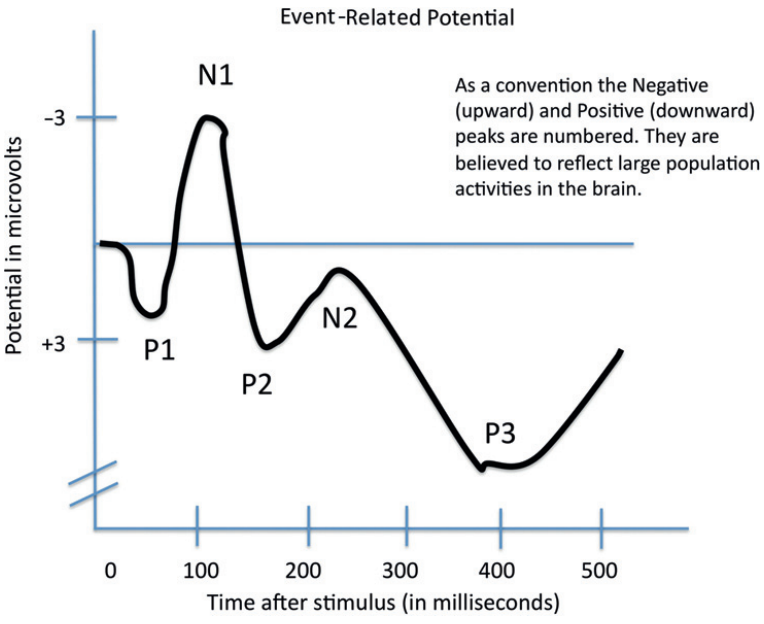


FIGURE 5.10 While the EEG is complex and irregular, averaging the EEG trace over multiple presentations of a stimulus reveals a remarkable degree of regularity, as shown in this event-related potential (ERP). Although the ERP is not completely understood, it appears to reflect large, successive neuronal population activities in the cortex and related structures. The timing and size of the major peaks and valleys are sensitive to many cognitive and emotional factors, including surprise. Similar averaging methods are used with other brain recording methods such as MEG. Source: *Baars.*

BOX 5.1

THE EEG OF MEDITATION

A study by Lutz *et al.* (2004, see Figure 5.11), using EEG, focused on the brain activity of experienced Buddhist meditators. EEG signals were recorded in expert meditators and control subjects during normal rest and during different stages of meditation. Three stages were used: rest, meditative state, and a pause stage between meditative states. Lutz *et al.* found that, during meditation, the group of experienced meditators had a dramatically higher level of gamma-band oscillations. The researchers also found long-distance phase synchrony between frontal and parietal areas in the brain. From these results, Lutz *et al.* speculate that meditative training enhances the integration of distant brain areas. Interestingly, the results showed that brain activation even at rest differed between the expert and naïve groups. This indicates that substantial meditative experience can alter the workings of the brain, although at present we can only speculate at the precise cause and effect relationships.

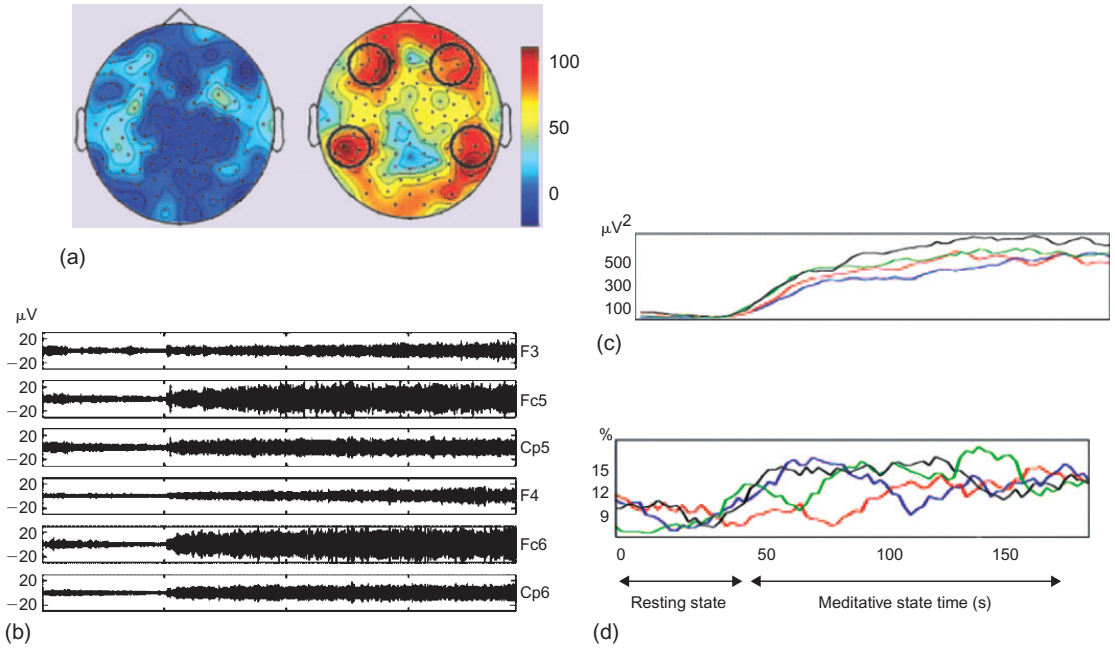


FIGURE 5.11 Measuring the effects of meditation: the study of Lutz and collegues (2004) shows that gamma power is much higher in practicing meditators (right) compared to non-meditating controls (left). The color scale indicates the percentage of subjects in each group that had an increase of gamma activity during the mental training. Source: *Lutz et al., 2004.*

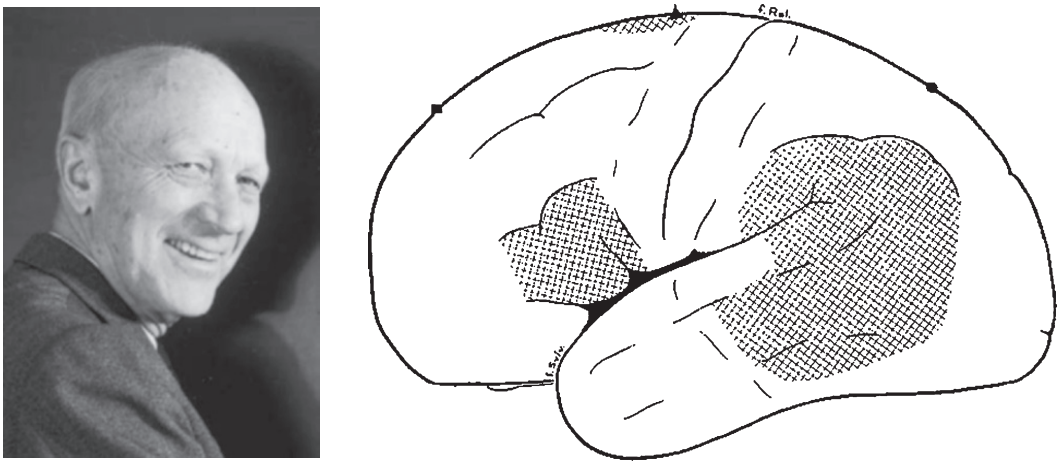


FIGURE 5.12 Left panel: Wilder Penfield. Penfield and colleagues devised open-brain neurosurgery for untreatable epilepsy in the 1950s. Right: Penfield's map of brain regions where electrical stimulation interferes with language. Notice how closely these regions correspond to the classical Broca's and Wernicke's patients studied a century before. Sources: *Adelman & Smith, 2004.*

2.4 Stimulating the brain

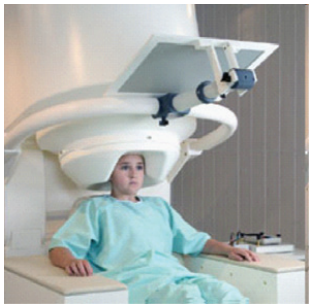
What if you could evoke neural activity in a safe fashion? Such a method would be especially useful to test causal relationships between neural activity and cognitive functions. Early work on direct electrical brain stimulation began with Wilder Penfield, a neurosurgeon at the Montreal Neurological Institute (Figure 5.12). Penfield and his colleagues treated patients with intractable epilepsy. In open brain surgery, patients can remain awake and responsive, since only local anesthetic is needed at the site. There are no pain receptors in the brain itself, so the cortex brain can be operated on without general anesthesia.

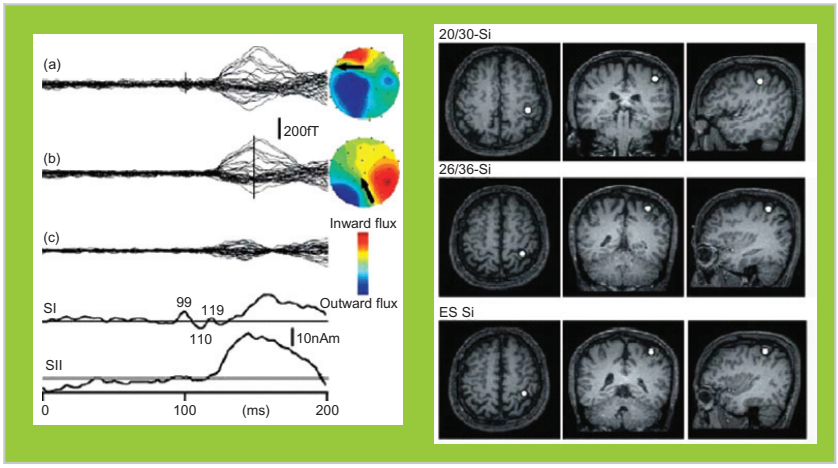
2.4.1 A safe way of interfering with brain function: transcranial magnetic stimulation (TMS)

It is now possible to stimulate brain lesions in healthy subjects. Without cutting a person's brain, we can alter the brain's level of activity locally. Brief magnetic pulses over the scalp either inhibit or excite a region of cortex. For example, if you stimulate the hand area of the motor cortex, the subject's hand will move and twist. Applying an inhibitory pulse over the same area will cause subjects to have difficulty moving their hands. This is called *transcranial magnetic stimulation* (TMS) or, as one leading researcher called it, "zapping the brain" (Cowey & Walsh, 2001). TMS appears to be generally safe. By applying TMS, we can test causal hypotheses about the contribution of specific brain regions to cognitive processes. Since the TMS works at the millisecond scale, it is also possible to study how rapid waves of processing develop. Recent TMS studies emphasize that magnetic pulses rarely have simple, local effects. Rather, like other kinds of brain stimulation, magnetic pulses often trigger off widespread activities, depending on the subject's expectations and ongoing goals.

2.5 Magnetoencephalography: magnetic fields of the brain

Magnetoencephalography (MEG) measures the magnetic field produced by electrical activity in the brain (Figure 5.13). Its spatial resolution is now approaching a few millimeters, while its temporal resolution is in milliseconds. Because of the physics of magnetism, MEG is highly sensitive to dendritic flow at right angles to the walls of the sulci (the cortical folds). MEG results must be superimposed upon a structural image of the living brain. MEG uses a process called *magnetic source imaging* (MSI) to coregister the magnetic sources of brain activity onto anatomical pictures provided by MRI. MEG has the advantage of being entirely silent and noninvasive. As we will see, MRI is quite noisy, and, of course, depth electrodes require surgery. Thus, MEG is attractive for use with children and vulnerable people. MEG is easy for young children to tolerate as long as they can stay relatively still.





Magnetic field

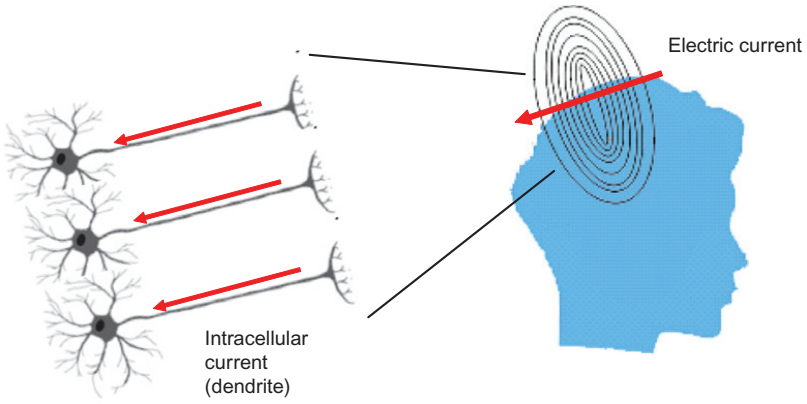


FIGURE 5.13 Magnetoencephalography and its analysis. The subject is placed in the scanner that has a large set of shielded sensors. The signals are derived from ionic currents flowing in the dendrites (bottom). Action potentials do not produce an observable field. Upper middle: Magnetic fields following painful (touch) stimulation, where (a) shows the recorded data, and (b) and (c) display residual magnetic fields obtained after filtering the somatosensory processing signals from the recorded data. The bottom two lines show the time course of the source strengths during the painful stimulation. Upper right: Source locations of the MEG data overlaid on MR images. Source: *VSM MedTech.*

3.0 FUNCTIONAL NEUROIMAGING: A BOLD NEW WORLD

EEG and MEG measure brain activity fairly directly. Other neuroimaging methods use indirect measures, such as blood flow or regional oxygen level. Currently, the most popular method is fMRI (Figure 5.14) and especially the kind that measures the oxygen level of the local blood circulation (called BOLD, for **b**lood-**o**xygen **l**evel **d**ependent activity).

When neurons fire, they consume oxygen and glucose and secrete metabolic waste products. An active brain region consumes its local blood oxygen supply, and as oxygen is consumed, we can see a small drop in the BOLD signal. In a fraction of a second, the loss of regional oxygen triggers a new influx of oxygen-rich blood to that region. Here, we see a recovery of the signal. However, as the compensatory mechanism overshoots, flooding more oxygenated blood into the area than is needed, we also see that the signal rises high above the baseline. Finally, as unused oxygen-rich blood flushes out of the region, we can see a drop in the BOLD signal back to the baseline (Figure 5.15).

Thus, as the oxygen content of blood produces changes, we can measure neural activation indirectly. The BOLD signal comes about six seconds after the onset of neuronal firing. The relationship between neural activation and the BOLD fMRI signal is shown in Figure 5.16. Note that these studies frequently use a block design, where a certain task is cycled on and off and the BOLD signal is measured across the ON and OFF blocks.

Positron emission tomography (PET) was developed much earlier than MRI or fMRI, and it provides a measure of metabolic brain activity (Figure 5.17). PET is used less often for research today because it is very expensive, requiring a cyclotron. It also requires subjects to be injected with a radioactive tracer. For nonmedical investigations, MRI and fMRI have

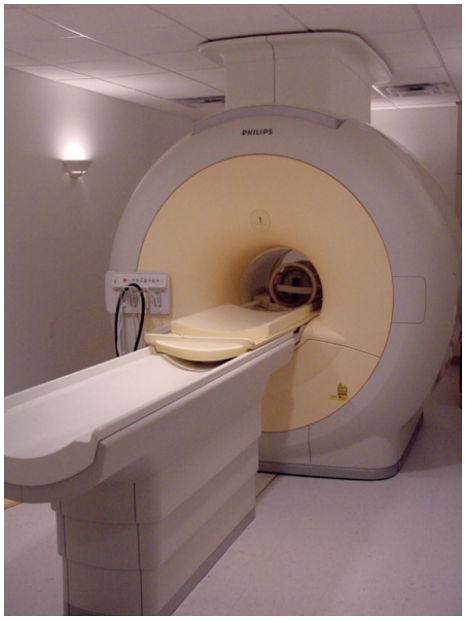


FIGURE 5.14 An MRI scanner. For both MRI and fMRI recording, the subject is lying down on the narrow bed that is then drawn into the core of the scanner. Source: *Sharma & Sharma, 2004.*

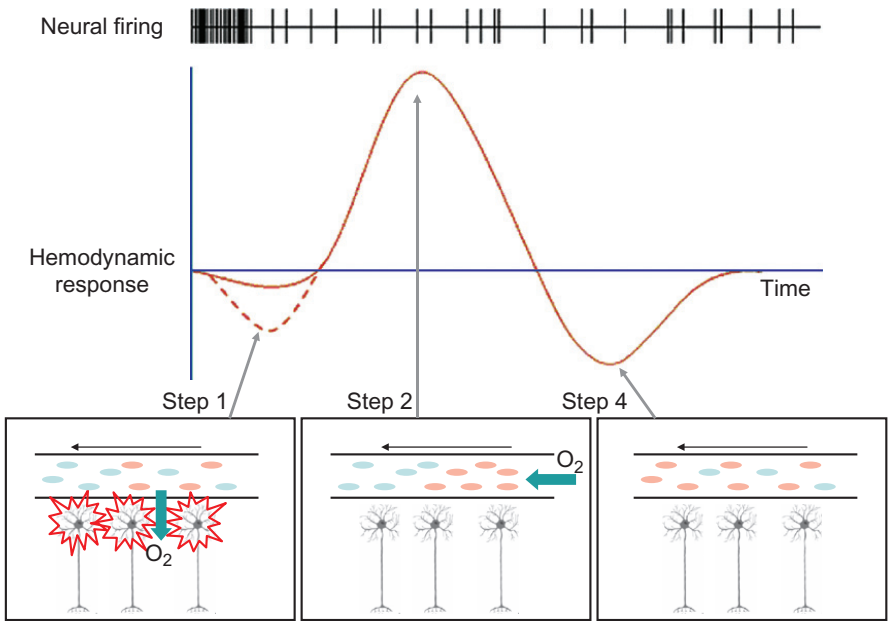


FIGURE 5.15 MRI and functional MRI. Top: The blood oxygenated-level dependent (BOLD) signal simplified in four steps. Step 1: increased neural activation leads to an increase in the consumption of oxygen from the blood, leading to a lower level of oxygenated blood and more deoxygenated blood, leading to a drop in the BOLD signal. Step 2: the vascular response to the increase in oxygen consumption leads to a dramatic increase in new, oxygenated blood at the same time as the oxygen consumption drops due to the decreased levels of neuronal activation. Step 3: a normalizing of flow and deoxy/oxyhemoglobin levels (not shown). Step 4: a poststimulus undershoot caused by the slow recovery of blood volume. Source: *Thomas Ramsoy, 2010, with permission.*

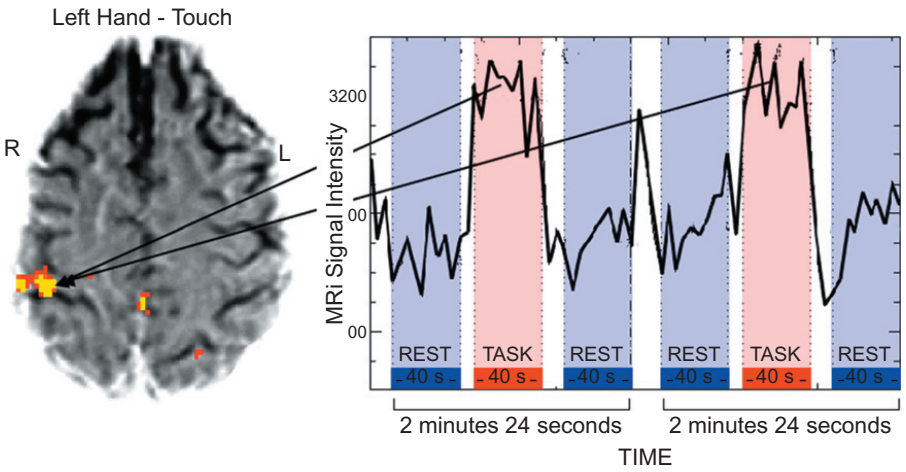


FIGURE 5.16 fMRI shows the activity of the brain, using a blocked design, where a stimulus is presented in blocks separated by a resting state, the BOLD signal cycles on and off as neural activity changes. Source: *Robinson, 2004.*

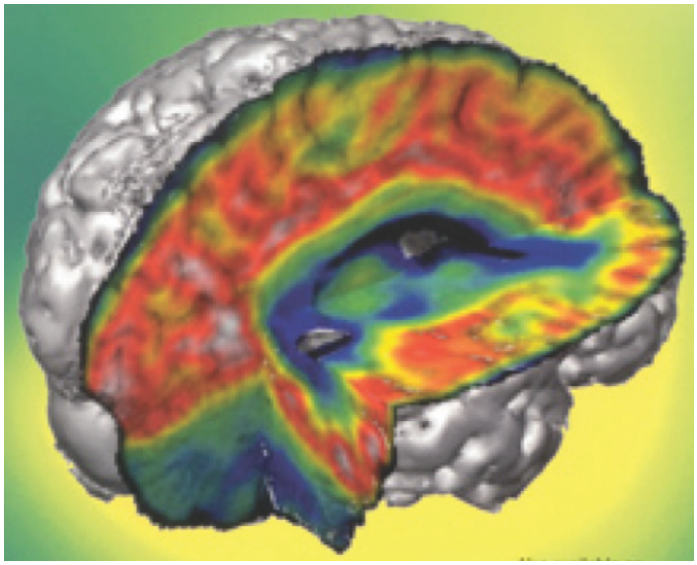


FIGURE 5.17 Positron emission tomography. PET measures metabolic activity in the brain. Here is an example of levels of metabolic activity across brain areas due to a certain neuroreceptor. The metabolic activity detected by PET has been coregistered with an MRI image that shows the brain anatomy. Source: *Adams et al., 2004.*

largely taken over the research field (Figure 5.18). However, PET is still important because different tracers can be linked to different molecules. The distribution of neurochemicals can therefore be determined.

Today, it is not possible to have high spatial and high temporal resolution at the same time using the same recording device. There is a tradeoff. Methods like fMRI and PET tell us *where* in the brain something is happening. EEG, MEG, and single cell recordings show millisecond changes in the brain. In any study, it is important to ask why the authors chose a particular method and what they observed—or might have missed—by the choices they made. In the best cases we can see different methods showing convergent results.

3.1 Regions of interest

Finding your way around the brain is not easy. An even harder task is figuring out which areas play which roles in major cognitive processes such as language, attention, and vision. One way is to define regions of interest (ROIs) ahead of the study and make predictions about expected activity in ROIs.

3.1.1 Coregistration of functional activity on a structural scan

The first step is to define the living brain anatomically to make out different areas, connections, and layers of organization. Structural MRI gives us a tool to map out brain structure, including the axonal (white matter) connections between brain regions. MRI shows structure but not function.

Look again at Figure 5.16, where the BOLD signal for a blocked fMRI design is presented. On the right side of Figure 5.16, we see an image with two yellow "hot spots," reflecting increased fMRI activity. The color is arbitrarily chosen to indicate the degree of activity. In order to pin down the location of the yellow hot spots, we need to superimpose the functional image

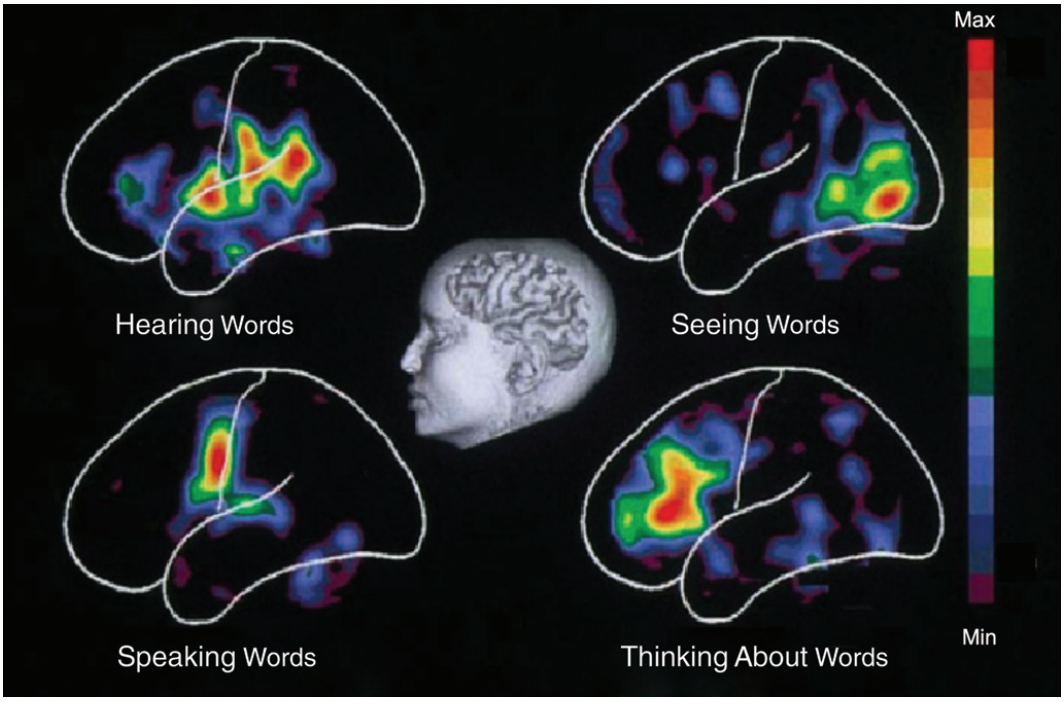


FIGURE 5.18 A classical PET finding: visual versus auditory brain activity. Brain metabolic activity is shown as noted on the right side of the figure, with red and yellow colors showing higher activity and blue and green colors showing lower activity. These early PET scans show results for hearing, seeing, speaking, and internally generating words. Notice that the auditory, visual, motoric, and speech production regions appear to be activated for the respective conditions. For example, in the "hearing words" condition, auditory regions in the temporal lobe show a high level of activity, while in the "seeing words" condition, visual regions in the occipital lobe show a high level of activity. Note that in these early studies, the results are shown on a brain outline template. Current studies use fMRI with enhanced ability to show brain function coregistered onto anatomical images. Source: *Posner & Raichle, 1997.*

on the structural MRI, which has a better spatial resolution. In a process called *coregistration*, the functional and structural images are aligned to each other. Coregistration ensures that the two images end up in the same space using the same metric. With higher spatial resolution we can ask questions that are anatomically specific.

Another approach is to mark ROI on the structural image alone to constrain the statistical analysis. Newer MRI machines with higher magnetic field strength now make it possible to look at the cellular organization of the living brain and to compare brains between groups of people (e.g., people with schizophrenia and healthy subjects).

3.1.2 Subtraction methods for defining functional activity differences

Different layers of cortex have either local or distant connectivity, so layer information is useful to find out how cortical regions interact. Because the brain is remarkably active at all times, it is still a challenge to isolate fleeting, task-related activity. One common method is

subtraction between fMRI conditions—for example, the brain's response to the task of interpreting Arabic numerals (1, 2, 3, . . .) is compared to its response to the same numbers when they are spelled out (one, two, three, . . .). Subtraction is used because it tends to remove most of the "irrelevant" brain activity that would otherwise drown out the signal of interest. It is much like comparing a choppy sea before and after a whale swims by. If you want to see the waves generated by the whale alone, you might subtract a record of the waves alone. It is the *difference* between the two conditions that matters (Figure 5.19).

Subtracting conditions can have unwanted consequences. There might be important things going on in both conditions. In addition, the variance of experimental and comparison conditions might be different, there might be interactions between independent variables, and so

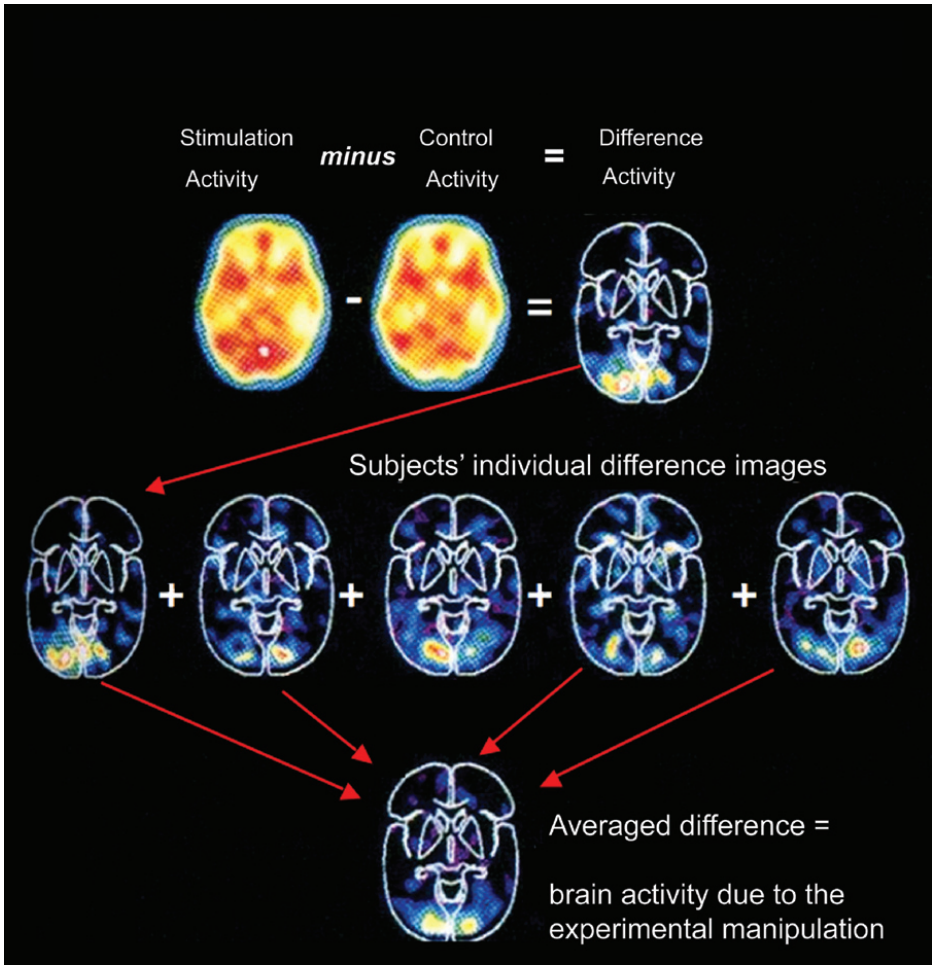


FIGURE 5.19 PET and fMRI subtraction methods. The brain has constant dynamic background activity. To remove this background activity, the PET or BOLD signal for an experimental task is subtracted, point by point, from a closely matched control task. Individual scans of the differences are then averaged and used to find the group average. Source: *Posner & Raichle, 1997.*

on. Another approach therefore is *parametric variation*, in which the variance for each main variable and their interactions can be separated statistically. For example, if you study working memory (WM), instead of subtracting brain activity during working memory from activity without it, one can study how gradually increasing the WM load leads to changes in neural activation. Since statistical testing must be done for every point of interest in the scan over every unit of time, this is a large data set.

3.2 The resting brain: intrinsic brain processes

As neuroimagers began to study different cognitive functions, the main approach was to use a contrastive, subtractive approach. Here, the neural activation during a given cognitive function, such as speech production, was compared to a period where subjects were instructed to relax and "do nothing." Such active-versus-rest comparisons showed powerful effects.

Yet there is a hidden assumption in these studies. If you are asked just to lie still and "rest," what will you do? Will your mind be a blank screen? A great deal of evidence shows that people just go back to their everyday thoughts, images, and feelings. You might be thinking about something that happened the day before or that you need to do later, or you might just daydream a bit. You are likely to have inner speech, visual imagery, episodic memories coming to mind, and so forth. For the brain, that is not "rest." Instead, the experimental comparison is really between two active states of the brain. One is driven by experimental task demands, while the other reflects our own thoughts, hopes, feelings, images, inner speech, and the like. In some ways, spontaneous activity may tell us more about the natural conditions of human cognitive activity than specific experimental tasks. Both are important.

The use of MRI to produce both precise anatomical images and to provide functional maps of brain areas has revolutionized the field.

3.3 Structural changes in the brain: taxi drivers

The best science is done by combining imaging techniques with genuine creativity. A lot of creativity goes into the selection of functional variables. What is the best way to understand vision? To understand selective attention and conscious cognition? A great deal of ingenuity has been devoted to those questions. Let us consider a few examples. Taxi drivers are well known for their ability to know their way around a city. They know not only how to get from A to B, but they also know the most efficient way to get there. Such ability to navigate through a complex road system depends on our spatial ability. Studies have shown that the hippocampus, a part of the medial temporal lobe, plays an important part in the navigational memory of places and routes. Rats with lesions to the hippocampus have been known for decades to perform disastrously on spatial tests. Birds and other animals that bury or hide their food at multiple places have larger hippocampi than nonstoring animals. Therefore, one question that arises when we think about taxi drivers is, are the brain regions responsible for spatial navigation more developed in taxi drivers than in other people? Indeed, it has been found that part of the hippocampi of taxi drivers was larger than the same region in a group of people

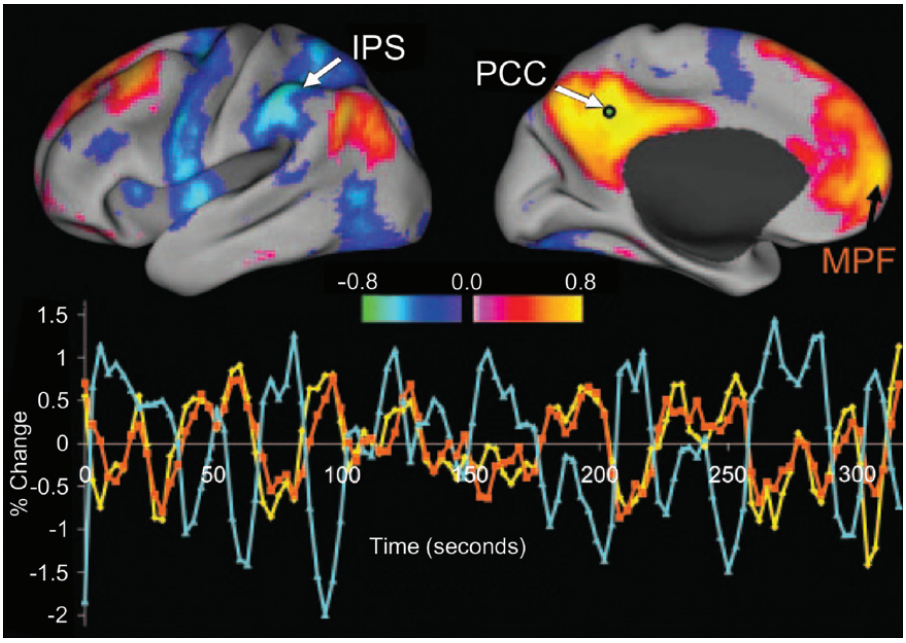


FIGURE 5.20 The brain is an active place. This fMRI shows spontaneous brain activity in both the left (shown as a lateral view on the left) and right (shown as a midline view on the right) hemispheres. The bottom shows this activation over 300 seconds (5 minutes). While such "task-unrelated" activity is different from typical experimental tasks, we know that humans are constantly thinking, imagining, feeling, anticipating, remembering, and talking to themselves without being given a specific task to do. Source: *Fox et al., 2005.*

with a different background. Okay, you might be thinking, but what if people with large hippocampi choose to be taxi drivers and not vice versa?

Here, the study showed that the size of the hippocampus depended on how long people had been working as taxi drivers. In other words, the longer you work as a taxi driver (and use your spatial navigation ability), the bigger your relevant part of the hippocampus will become.

Notice how imaginative the taxi driver example was. It is usually easier to randomly select human subjects (usually undergraduate students!) to stand for the entire human population. But the fact is that there are differences in age, particular abilities and talents, and other cognitive capacities among "average" subjects. One important implication is that the size of brain structures may change with specific experiences (Figure 5.21) (Maguire et al., 2000). That claim has now been supported for other brain regions as well. The taxi driver study is therefore an excellent example of creative selection of comparison conditions.

3.4 Connectivity and causality

White matter fiber tracts are the vast internal highway system of the cortex. We can visualize these fiber tracts using an MRI method called *diffusion tensor imaging* (DTI). DTI uses water flow along the axons surrounded by white myelin to measure the relative direction of white matter tracts (Figure 5.22). DTI helps us to understand brain connectivity patterns

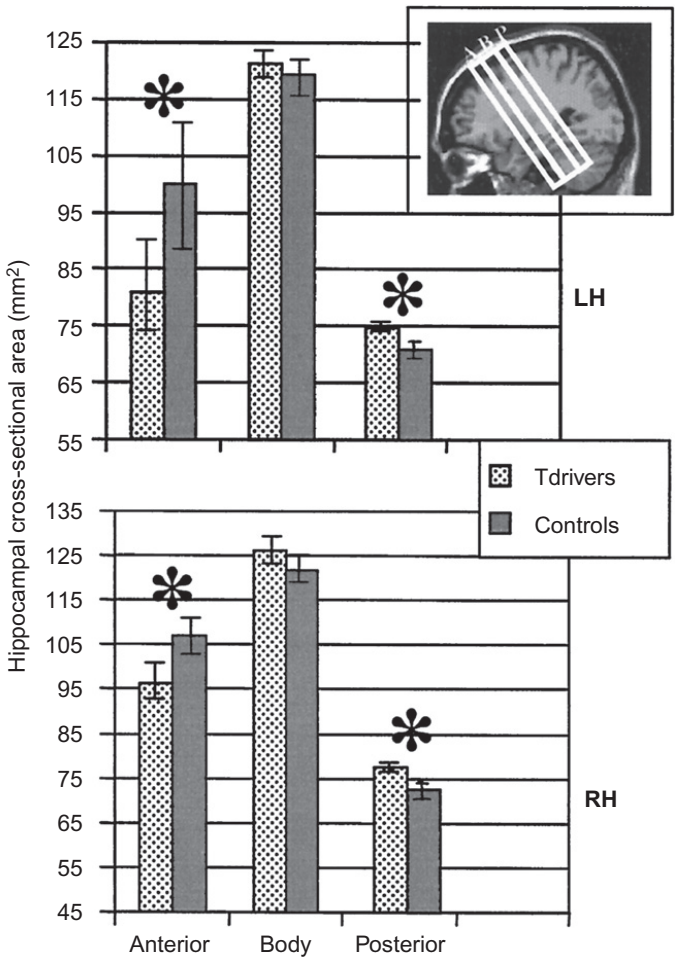


FIGURE 5.21 Memory and hippocampus size. Maguire and colleagues (2000) showed that London taxi drivers showed substantial differences in the size of a spatial mapping region of the brain, the posterior hippocampus. Source: *Maguire et al., 2000.*

in the healthy brain, as well as investigate these patterns in individuals with brain diseases that affect white matter, such as multiple sclerosis.

By far the largest fiber bundle in the brain is the corpus callosum (see Chapter 4), which connects the two hemispheres; but there are many other fiber bundles or tracts that connect regions within the hemispheres. The view of the vast array of white matter tracts is shown in Figure 5.23, with a midsagittal (center-line) view of the fiber tracts that extend upward from the spinal cord to the cortex. These fiber tracts make up the vertical "traffic arteries" that flow to and from the cortex and that provide the connective pathways throughout the central nervous system.

A recent study investigated the correspondence between white matter and gray matter, and the results are presented in Figure 5.24. Constructed maps of peripheral white matter tracts are presented at the top of the figure, and their corresponding cortical gray matter regions are shown below. Note that Figure 5.24 shows the same information across three views of the brain: from the front or anterior perspective (a and d), from the same or lateral perspective (b and e), and from the back or posterior perspective (c and f).

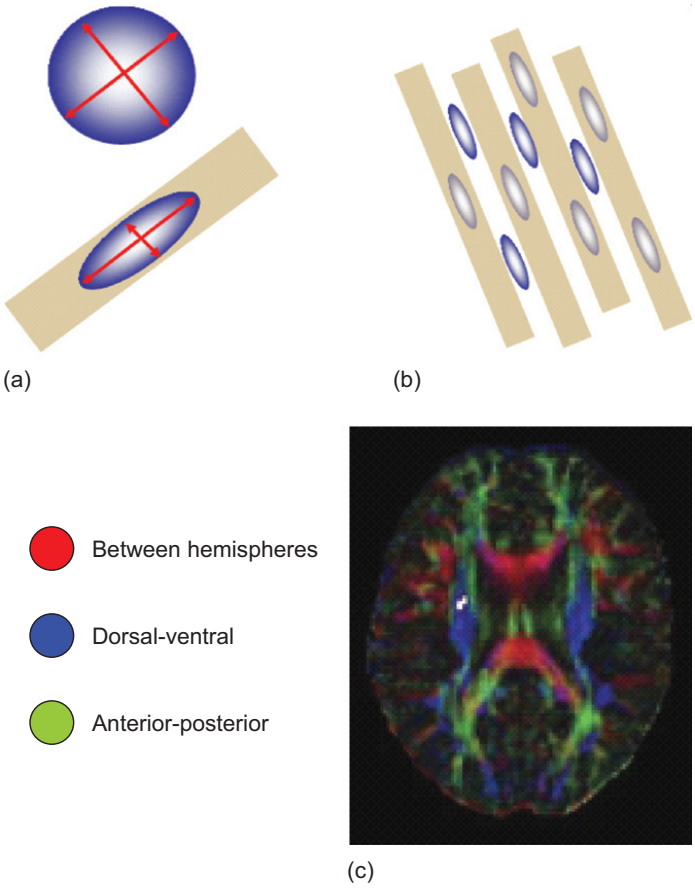


FIGURE 5.22 Diffusion of water depends on the local environment. (a) In the free and unrestricted medium (i.e., a glass of water), water can diffuse freely. The diffusion is *isotropic*—that is, it has the potential to move in all directions. If the water molecule is physically restricted, it can no longer move freely in any direction. This diffusion is *anisotropic*, meaning it cannot move in any direction. In a medium of fibers such as the brain's white matter (schematically shown in (b)), water molecules are highly restricted by the axonal fibers. In this way, it is possible to visualize the fiber tracts of the brain and to estimate the integrity of white matter within a given region. (c) Such visualization produces the typical colored DTI brain image that displays different trajectory trends in regional white matter. Source: *Thomas Ramsoy, 2010, with permission.*

4.0 CORRELATION AND CAUSATION

We typically combine brain and behavioral observations. We can present visual images on a screen and have the subject read aloud or meditate. Thus we typically observe a *correlation* between behavior and brain activity. In methods with high spatial resolution, such as fMRI, different tasks show local increases or decreases in the BOLD signal, indicating that the brain works more in some regions than others (see Figure 5.16).

We can take the example of the Counting Stroop Task, in which subjects are asked simply to count the number of words shown on a screen. On some occasions a word like *dog* is shown three times. The subject should say "three," which is not difficult. However, we can introduce a conflict between the words shown and the number of words. If we show the word *one* four times, there is an automatic tendency for expert readers (like college students) to say the word "one." But the correct answer is "four." This is very much like the Color-Naming Stroop Task. Subjects take longer to answer correctly, since they must inhibit their automatic tendency to read the words on the screen.

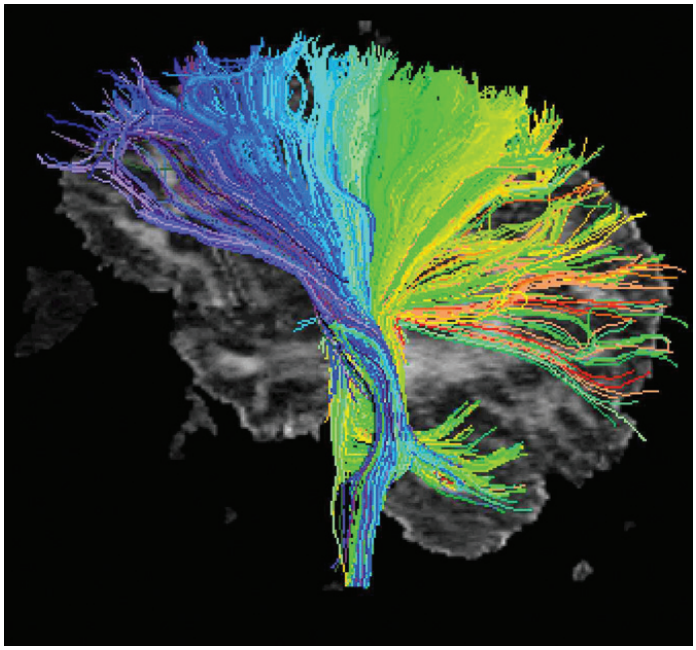


FIGURE 5.23 A fountain-like image of the white fiber tracts. This beautiful spray of neuronal tracts results from an MRI imaging technique called diffusion tensor imaging (DTI), which allows us to view the white (myelinated) fiber tracts. These are the vertical traffic arteries that flow from the cortex (especially frontal regions, shown in blue), down the spinal cord, and upward from the spinal cord to the rear half of the cortex, shown in yellow and green. Most of the volume of cortex is taken up by these massive fiber tracts. Source: *Maria Lazar, with permission.*

Zheng and Rajapakse (2006) reported the BOLD activity during the Stroop task (Figure 5.25). While many brain regions show activation during both conditions, frontal parts of the brain were more active during the conflict condition. This Stroop task result has now been found many times for conflictual tasks. One of the major roles of prefrontal cortex is to resolve conflicting tendencies, like the automatic tendency just to read words, against the tendency to follow the experimental instructions. Thus we have a correlation among (a) frontal activation, (b) longer reaction times, (c) a sense of subjective effort, and (d) a greater number of errors in the conflict condition. These are significant results, since there are many real-life conditions where conflicting tendencies need to be regulated.

However, so far we have no way to test *causal* hypotheses among the many brain regions that are involved in any complex task. For example, we know that the task requires visual word recognition, response preparation, choosing between two possible answers, perhaps detecting conflict, stopping the wrong answer from being said, selecting the right answer instead, and so on. An approach called *dynamic causal modeling* (DCM) is used to analyze causal relationships. Zheng and Rajapakse (2006) performed DCM on the brain activation they found in both word counting tasks. As you can see in Figure 5.25, DCM suggested that each task had a different activation pattern. Although many of the same regions of the brain are active during both tasks, their relative connectivity and contribution were altered. Interestingly, the analysis also showed that the interference condition recruits wider activity than the control condition. This is another common finding for mentally effortful conditions (Duncan & Owen, 2000).

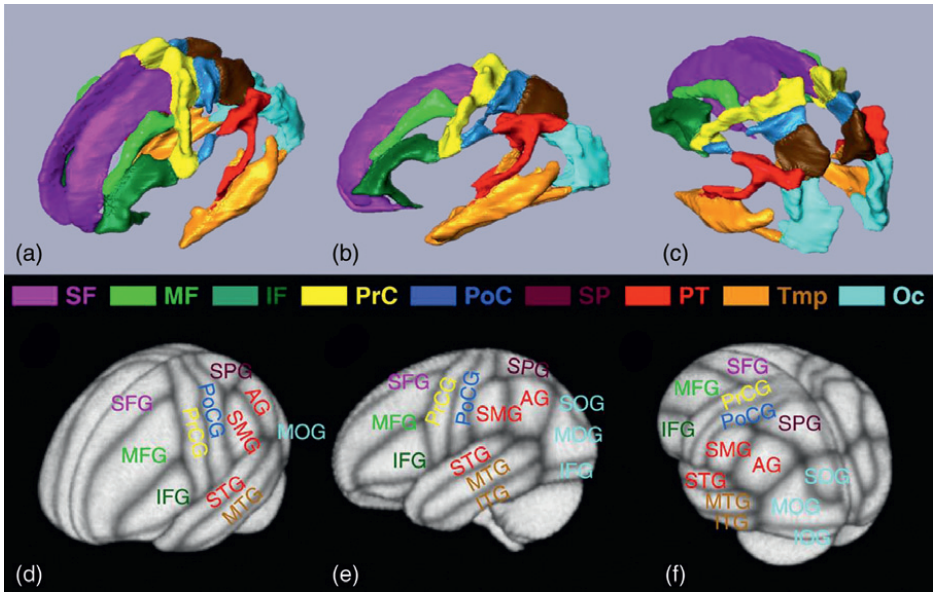


FIGURE 5.24 Diffusion tractography brings out the corpus callosum and other large fiber tracts. Notice that we are looking at a cutaway image of the brain, in which the right hemisphere is intact. We can see the green-marked fibers projecting upward in front and yellow-marked ones projecting toward the rear. Different artificial colors are assigned by computer to different directions of travel of the fiber highways (shown in (a), (b), and (c) – which are views of the same data, just shown in different angles. (a) shows the fiber tracts with a view from the front of the brain, (b) shows the same with a view taken from the side of the brain, and (c) shows same with a view from the read of the brain). The c-shaped or banana-shaped structures in section (b) are the corpus callosum (the "calloused body"), which looks white to the naked eye. The corpus callosum contains about 100 million fibers, running sideways from one hemisphere to the other. Millions of cells in the left hemisphere connect to a corresponding point in the right hemisphere. Figures (d), (e), and (f) show the same views of the brain as those shown in (a), (b), and (c), in this case the entire brain surface is shown along with labels of these anatomical regions such as SFG - Superior Frontal Gyrus, and MFG - Middle Frontal Gyrus. Source: *Huang et al., 2005.*

4.1 Why we need multiple tests of brain function

According to some media headlines, brain scientists recently discovered the parts of the brain used for deception and lying. This kind of headline comes from studies like the one shown in Figure 5.26. It shows fMRI differences between brain regions that had greater BOLD activity when people were telling the truth (green) and cortical areas when they were made to tell a lie. Such experiments often use playing cards and ask a group of subjects to "lie" by reporting a different card than the one they actually see.

One major purpose of cognitive neuroscience is identifying function with structure—that is, seeing whether specific brain locations do specific things for us. In that process, however, we must be very clear about the kinds of inferences that we can make from the evidence. The popular media may not be quite as careful as scientists need to be. Do you believe that the green areas in Figure 5.26 are really the "truth-telling" areas of the brain?

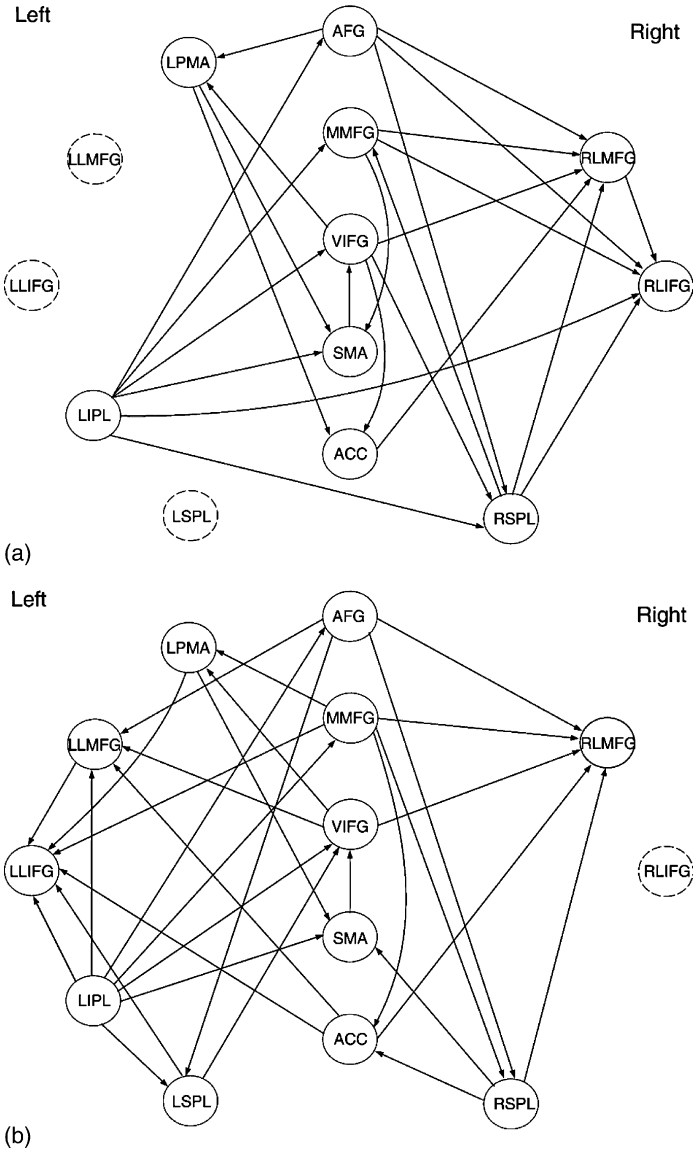


FIGURE 5.25 Causal relationships between brain activities during the Stroop task. Brain activity during simple counting with no interference is shown at the top (a), and the activation during counting with interference is shown at the bottom (b). Each circle represents a region of the brain. As can be seen, interference (b) leads to the engagement of a more widespread network than the control condition (a). This change in causal coupling between brain areas is seen in spite of the fact that many of the same areas are activated in both conditions. Note also that some of the connections are lost between the control (a) and interference (b) conditions. Source: *Zheng & Rajapakse, 2006.*

4.2 Brain damage and causal inferences

Historically, Paul Broca discovered patients who were unable to speak and also showed damage to the left frontal lobe. However, their ability to comprehend language was relatively spared. About the same time, Carl Wernicke made the discovery that damage to different regions of the left hemisphere was associated with the ability to understand language, while their ability to speak was intact. Today, we call this complementary pair of facts a *double dissociation*.

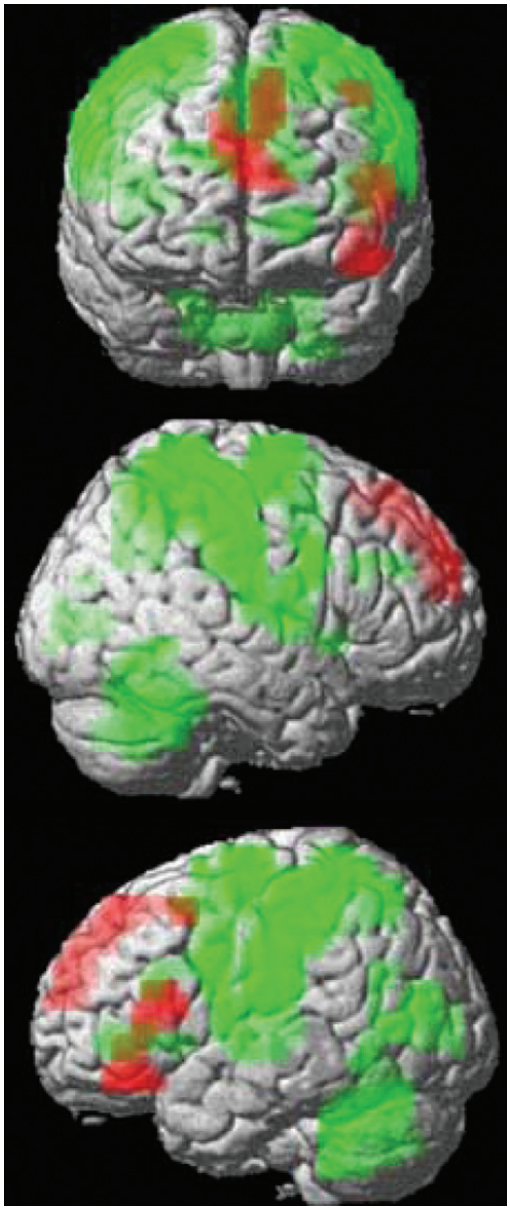


FIGURE 5.26 Are these the truthful and deceptive areas of the cortex? fMRI differences between cortical areas that had greater BOLD activity when people were telling the truth (green) and cortical areas when they were made to tell a lie (red). Is this the truth-telling cortex (green) and the lying cortex (red)? Why or why not? Source: *Davatzikos et al., 2005.*

Brain damage is correlational, since we cannot produce it and test its results in humans. Nevertheless, after a great deal of debate and controversy, there is no serious doubt today that one important function of Broca's area is the production of speech and likewise that one important function for Wernicke's region is speech comprehension (Figure 5.27). Lesions near Broca's area can lead to *dysarthria*, a condition where the control of mouth and tongue movement is disrupted but language production is still intact. Thus we have three lesions that lead to three different speech problems: one seems to be important for language

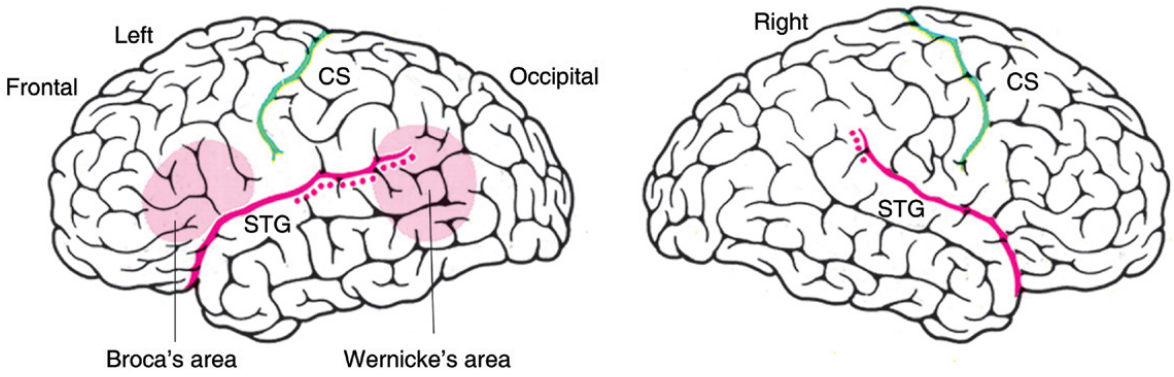


FIGURE 5.27 Language area lesions. Lesions to either Broca's or Wernicke's arear produce very different effects on language. Abbreviations: CS = "central sulcus," STG = "superior temporal gyrus." Source: *Standring et al., 2005.*

comprehension; another is vital for language production; and a third region is important for the motor commands to produce vocal expressions.

Brain injuries in humans happen for a host of reasons, ranging from car accidents to strokes. Accidental lesions do not neatly follow the borders between brain regions. To test brain-mind hypotheses, it is preferable to be much more precise about exactly where in the brain deficits occur. In order to do this, studies have been conducted in experimental animals, typically rats and monkeys. However, language is a species-specific function for humans, and we have no direct parallels in other species. Safer brain interventions for the human brain are being explored, including TMS, electrical field stimulation, and even color lasers.

Very precise lesions have been studied in monkeys and rats for many years. For example, Buckley and Gaffan (2006) made precise lesions in different areas of the medial temporal lobe (MTL) in macaque monkeys. Very specific damage to the *perirhinal* cortex (meaning "near the smell cortex") caused monkeys to make more errors on a visual object discrimination task. Lesions to surrounding areas did not produce this deficit. The harder the discrimination task became, the more errors the lesioned monkeys made. Yet the monkeys performed normally in simple visual discriminations among different colors, shapes, and orientations. This suggests that the perirhinal cortex may have a specific *causal* role in processing complex visual objects, like faces. A variety of human studies now support this finding. Animal studies have often played this pioneering role, allowing us to pick up leads that are later tested in humans.

5.0 SUMMARY

Brain techniques measure single neurons to large cortical regions, brain structure, dynamic brain activity, and connectivity. The advent of brain imaging has transformed the study of human cognition. New and more refined methods are constantly being produced. One recent advance is using multiple methods in the same study to optimize the tradeoffs between direct and indirect measures of brain activity.

6.0 STUDY QUESTIONS AND DRAWING EXERCISES

1. Label the differences between the brain scans in Figure 5.28, and describe the reasoning of the subtraction method for each image.
2. Define the BOLD response. What does BOLD stand for?
3. What is the time lag between neural activity and a BOLD response? Between neural activity and an EEG response?
4. What are the pros and cons of single cell recording in the brain?
5. What problem might arise when brain activity in a cognitive task is compared to a resting baseline?
6. What does Figure 5.26 tell us about lying and the cortex?

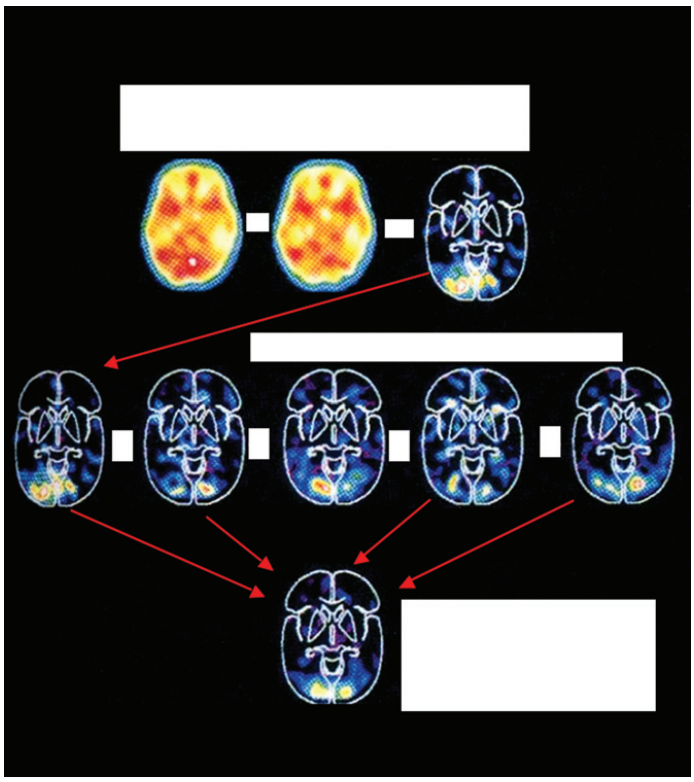


FIGURE 5.28 Drawing exercise. A reproduction of Figure 5.19 shown without labels for use in the drawing exercises. Source: *Modified from Posner & Raichle, 1997, with permission.*