CHAPTER 8

Brain Monitoring and Manipulation

Today, . . . the Neurocentric Age is more deeply entrenched than ever. At the beginning of the twenty-first century, thousands of neuroscientists . . . continue to dismantle the brain, but they don't have to pull it from a corpse to do so. Instead, they can scan the positronic glow of neurons recalling the faces of friends, searching for a word, generating anger or bliss, or reading the minds of others.

—Carl Zimmer[†]

Few scientific developments have been more striking than the ability to image the functioning human brain. . . . Like the maps used by early explorers, our current understanding of brain function is riddled with errors, inconsistencies, and puzzles deserving of solution. Yet the difficulty in understanding the brain has only added to the excitement of the quest.

—Scott A. Huettel, Allen W. Song & Gregory McCarthy[††]

CHAPTER SUMMARY

This chapter:

- Introduces techniques used to look at the structure and function of the brain.
- Introduces manipulations of the brain including surgery, specialized disruption techniques, and drugs.
- Introduces basic experimental designs used to assess behavior and mental states during brain imaging or manipulation.

INTRODUCTION

Much of what we know about how the human brain works was discovered in experiments with non-human animals because that permits invasive techniques to probe brain function. Historically, the main way to understand human brain function was to investigate the particular impairments that followed from damage to a part of the brain by a stroke or some other accident. And the only way to know with certainty where the damage happened was to look at the brain after the patient died.

† Carl Zimmer, *Soul Made Flesh* 7 (2004).

†† Scott A. Huettel, Allen W. Song & Gregory McCarthy, *Functional Magnetic Resonance Imaging* 1 (2004).

In the last 20 years, however, medical imaging techniques derived from discoveries in physics have revolutionized medicine and neuroscience by giving physicians and researchers the ability to create images of the structure of the brain. These images permit localization of abnormalities in the brain caused by cancer, stroke, degeneration, traumatic brain injury, and the like. As you have already seen in previous chapters, courts are already encountering this type of imaging evidence.

In the 1980s and 1990s new technologies for probing brain function were invented that revealed the pattern of the energy utilization of the brain. Very soon experimental psychologists employed these methods with their array of tests to study behavior and mental representations. Through this research our understanding of human brain function increased tremendously — beyond the scope of a simple summary that can be offered here. But the important thing to note is that these advances have created powerful and dramatic opportunities (for better or for worse) for the introduction of this information about brain function into legal proceedings. Many believe that neuroscience may in some contexts usefully contribute to assessments of truth-telling, memories, pain and disability, competency, and criminal responsibility, to name just a few.

As important as neuroimaging has become, another dynamic area of neuroscience discovery we will look at in this chapter is just as important — how to change the brain.

Historically, the most powerful ways to change the brain have been through nutrition and education — as well as through drugs like stimulants (caffeine) and hallucinogens (mushrooms). Modern neuroscience offers specific drugs and devices to manipulate the brain even more directly through targeted stimulation or inhibition of particular neurotransmitter systems and brain centers.

The purpose of this chapter is to explain the basics of the most widely utilized brain monitoring and manipulation techniques so that you can recognize the results provided by the methods and understand how they are produced. This will prepare you to ask the right questions when such information arises in a legal setting. The next chapter will consider in more detail the limitations and cautions that should be kept in mind when considering such findings. Also, the Appendix provides a detailed guide on how to read an fMRI brain imaging study. In addition, we strongly encourage readers to review the coursebook web site for additional learning materials on these brain monitoring and manipulation techniques. In particular, the online resources offer color and interactive features that are not available in the hard copy text.

The chapter proceeds in four sections. In Section A, we review techniques for visualizing the structure of a living human's brain. In Section B, we introduce techniques for visualizing how those structures are functioning. In Section C, we discuss the research strategies that are employed to harness imaging technology for better understanding human cognition. We conclude in Section D with a discussion of direct interventions to modify human brain function.

A. BRAIN STRUCTURE

This section reviews four techniques available for visualizing the structure of a living human's brain.

1. X-Ray

In 1895, German physicist Wilhelm Röntgen was investigating the nature of cathode emissions. He noticed that when he shone cathode rays onto a distant wall, a glow could be seen even though solid objects blocked the path of the rays. He proposed that the glow was the result of a novel type of penetrating radiation, what was later termed the *X-ray*. To illustrate his findings, he published an image of the bones in his wife's hand.

X-rays are familiar, especially if you have ever had a broken bone. The electromagnetic waves that result in the X-ray image are absorbed to varying degrees by bone, brain and other tissues. Being less dense than other structures in the body, the brain does not show up clearly on an X-ray image. This variable absorption results in dark images when reflected against objects with little density, and lighter grey or even white when reflected against objects with greater density. This is why bones appear as white in an X-ray image: they are the densest material in the body.

While physicians have used X-rays to locate bone injuries for many years, new technology was developed to use X-rays to visualize soft tissues (at least to some degree). Thus, X-ray technology can be helpful to detect cysts or tumors in the brain. Moreover, by introducing dyes with higher density to increase the visual contrast, blood vessels can be observed.

2. Computed Axial Tomography

X-ray images are two-dimensional slices. *Computed Axial Tomography* (CAT or CT) computes the three-dimensional shape of the interior of the head from X-ray slices from all angles around the head. The math may be complicated, but the concept is simple; if you want to determine the position of each person in a glass room, you would need to walk all the way around to view each perspective. From the collection of these two-dimensional patterns, it is possible mathematically to reconstruct the three-dimensional composition of the interior of the head. Like X-ray images, high-density regions like bone are light, and low-density regions are dark. The typical spatial resolution for CT scanners is ~1cm. After the technology's advent in the early 1970s, CT scans became the standard of care for detection and diagnosis of neurological damage. Although complications from CT scans are rare, some patients can have severe reactions to dyes injected to visualize blood vessels.

3. Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI), first used on humans in 1977, provides images of the brain with great anatomical detail. Unlike other imaging technology, MRI uses no damaging radiation or injected tracers, making the procedure completely non-invasive and safe. More crucially, MRI reveals the inner structure of the brain with much more resolution than CT.

MRI takes advantage of the magnetic characteristics of the atoms that make up our bodies (and everything else). Atoms consist of a nucleus made of protons and neutrons surrounded by electrons. The subatomic particles spin on an axis; this makes them very tiny, weak magnets. The MRI scanner consists of a very large, powerful magnet shaped into a tube with a very thick wall. Magnet strength is

measured in units of *Tesla* (T). MRI scanners used today are typically either 1.5T or 3T. To appreciate the magnitude, a 3T magnet is roughly 80,000 times stronger than the Earth's magnetic field. So if you were to walk into the room containing the magnet, you could feel the keys in your pocket pulled toward the magnet. (This is why the procedure for MRI requires you to leave all metal outside the room.) Similarly, when placed into the scanner, the axis of rotation of the trillions and trillions of subatomic particles of the brain becomes aligned with the axis of the magnetic field just as compass needles align to the earth's magnetic field.

This alignment sets the stage for the MRI measurement. Patterns of periodic energy pulses are applied to the tissue. These pulses are just large enough to knock the protons in water molecules out of alignment with the magnet. However, like a spinning top that returns to its upright axis when it is wobbled, the axis of the spinning protons regains alignment with the magnetic field. As they realign, they release energy that can be detected as radio waves by sensors around the head.

Now, here's the amazing part that makes MRI work. The amount of time to realign and the amount of radio wave energy released by each spinning proton is proportional to the environment in which the proton finds itself. Recall from Chapter 7 that the CNS is organized into gray matter consisting of the cell bodies and dendrites of neurons and also glia and into white matter consisting of the myelinated axons of the neurons running from one part of the brain to another. It happens to be the case that the spinning proton realignment takes different amounts of time in gray and white matter. The MRI scanner can determine the location of each proton as it detects the energy that reemerges from it. By mapping the pattern of radio wave energy throughout the head, the scanner calculates a three dimensional representation of the brain's internal structure that distinguishes gray matter from white matter.

To analyze MRI signals, the scanner divides the brain into a three-dimensional grid, something like the pixels of computer display monitors. In fact, these 3D boxes are called voxels (volumetric pixels). Each voxel is 2 or 3 mm on each side, the size of a small pea, although newer methods resolve less than 1 mm. To appreciate the scale of this, recall that the cerebral cortex is generally just 2-3 mm thick.

MRI images provide a much clearer image of the brain than is possible with CT scans because the density of protons is much greater in gray matter than in white matter. Therefore, MRI scans make it possible to see the individual sulci and gyri of the cerebral cortex, the impressive size of the corpus callosum, and the fine detail of small, subcortical structures such as the basal ganglia. The spatial resolution of MRI images depends on the strength of the magnetic field and other components of the system. A 1.5T system produces images with a resolution of 1 mm. In addition, by adjusting various parameters of the process, it is possible to create images emphasizing different aspects of brain structure.

MRI is used primarily in clinical care to visualize brain structure and pathologies such as tumors and brain injury. More recently, anatomical MRI images have been introduced in the courtroom as evidence for claims of brain damage. It is important, therefore, to appreciate the factors that affect the quality of MRI images. On the one hand, the quality of the MRI system such as magnet strength and numerous other technical features can produce higher or lower quality images that emphasize different aspects of brain structure. So when you evaluate an MRI image critically, you need to ask questions about the settings of the equipment.

On the other hand, recall that the MRI process works by detecting the location of protons aligning faster or slower after being made to wobble. If the head of the subject lying in the scanner moves, then this determination of location will be inaccurate and the image will be blurrier. (This is why researchers are always pleading with their subjects to lie still.) Scientists have developed methods to correct for head movement in the scanner, but the corrections are never as good as a perfectly still head. Head movements are especially an issue when higher resolution images are produced, because they require longer scan times. So when you evaluate an MRI image critically, you need to ask if the person was very still when the scan was done. An implication as well is that if the person being scanned wishes to be uncooperative for some reason, then by simply moving his head slightly, the individual will corrupt the image.

Finally, as a practical matter, the MRI scanning process can be stressful and expensive. First, to get an MRI scan, you must lay within the rather narrow tube in the center of the magnet. Many people feel anxious or claustrophobic. Second, as noted above, high-resolution scans can take as long as 30 minutes throughout which you must lay perfectly still. Third, the machine is very loud when the energy pulses are produced. Subjects are usually given earplugs. Fourth, MRI images cannot be obtained from people with magnetic metal in their body; this includes pacemakers, joint replacements, and cochlear implants. Machinists who have small metal shavings embedded in their skin after years in the shop are also disqualified for MRI scans. Finally, MRI equipment is expensive to obtain and maintain, so the scans are expensive.

4. Diffusion Tensor Imaging

Diffusion Tensor Imaging (DTI) is a method that relies on the same MRI equipment, but extracts even more information. DTI is used to make inferences about the axon pathways flowing through the white matter. DTI has been used in conjunction with MRI to study the developing and adolescent brain, where the formation of connections between neurons is of tremendous importance.

As with MRI, the mathematics of DTI is complicated, but the concept is simple. By way of analogy, recall the way water flows through a hose tube; specifically, the velocity of the water is higher along the axis of the tube than perpendicular to the axis. DTI is based on a similar observation. Axons are actually tubes through which the fluids of the neuron flow, and thus, by measuring the direction of diffusion of the water molecules with the spinning protons, it is possible to find parts of the brain where the diffusion or flow of the water is higher and lower. The diffusion is lower in the gray matter because the axons are not very well aligned. The diffusion is higher in the white matter where bundles of axons are aligned. When regions of high diffusion are found, the orientation of that diffusion can be determined. The DTI measure is found in each voxel. By tracing the direction of diffusion through neighboring voxels, in some cases it is possible to connect the dots and trace an axon bundle from one end to the other. For example, in the corpus callosum the diffusion direction is all in the medial-lateral axis because that is how all the axon bundles are oriented.

Scientists are developing ever more complex and effective algorithms to trace the axon bundles more accurately because this provides the opportunity to

examine the pattern of connections within living human brains. The connectivity analysis has limits, though. One of the most severe is sorting out voxels where fiber pathways cross over each other. So this information is very useful and exciting, but it must be interpreted with caution.

Even if its ability to trace connections in the brain remains limited, DTI provides other information in the simple magnitude of directional diffusion. Thus, one can map the brain according to where directional diffusion is high or low. One can also compare brains on this measure. For example, researchers have found that the magnitude of directional diffusion in white matter changes as the brain develops through early life.

B. BRAIN FUNCTION

1. Introduction

CT and MRI provide information about the structure of the brain, but they do not provide information about the activity of the brain. An array of other technologies are used to investigate brain function. These noninvasive methods measure either electrical signals from the surface of the head or local changes of blood oxygen levels, both indirect measures that are complexly related to the nerve impulses produced in the circuits introduced in Chapter 7. Collectively these methods have been referred to as *functional neuroimaging*.

The information collected with functional neuroimaging must be interpreted in the context of the processes occurring in the brain while the measurements are obtained. As you learned in Chapter 7, the occurrence of brain processes creates perception, emotion, and plans — indeed all of human psychology. Therefore, to obtain interpretable functional imaging data, the psychological task conditions must be designed very carefully.

One of the earliest and still common approaches to reporting functional imaging data involves creating a map of how different parts of the brain appear active in different tasks or states such as moving a finger, looking at pictures of faces, reading lists of nouns, thinking of verbs that go with those nouns, imagining playing tennis, weighing purchasing options, considering moral dilemmas, and determining whether a defendant is guilty. This can lead to conclusions that claim to pinpoint particular mental processes to distinct regions of the brain. This has been criticized as a modern form of phrenology, an idea popular over a century ago that claimed to map unique function to discrete areas of the cerebral cortex. As you learned in Chapter 7, the brain works because it is organized into many complex circuits spanning cortical and subcortical centers. Thus, although different parts of the brain contribute to different functions, do not be seduced by the fallacy of *exclusive* localization of complex function — as if single parts of the brain do just one thing.

Each technique used for neuroimaging has pros and cons; each provides information in a particular range of space and time. Recording the nerve impulses in single neurons provides the highest resolution in space and time, but this requires invasive methods that can be employed only in serious clinical conditions in humans. The noninvasive methods sacrifice some time and space resolution but

offer the possibility of investigating human brain function. If interpretations remain limited within the bounds of the techniques, then the evidence obtained from each technique should converge on a unified and more nearly correct understanding of brain function and how it produces behavior.

2. Measuring Brain Electrical Signals

You learned in Chapter 7 that neurons signal to each other through nerve impulses. By inserting small electrical probes into the brain, the impulses from individual neurons can be recorded (*single-unit recordings*), as can the impulses from populations of tens or hundreds of neurons in a small region (*multi-unit recordings*). These electrical probes can also measure the fluctuations of electrical potentials associated with synaptic transmission in the local region (*local field potentials*). These measurements are obtained commonly in animal research studies, but they are also obtained from human patients during certain types of brain surgery to treat disorders such as Parkinson's disease or epilepsy. The patients are awake and interacting during surgery to help the surgeons locate the particular regions of the brain necessary for the treatment, and most patients give prior consent for research use of the recordings. The patterns of activity measured in the human brain resemble what is observed in animal studies. This engenders confidence that measurements of human brain signals can be compared usefully to what is found in more rigorously controlled experiments with animals.

Typically it is not possible to insert probes into the brain of humans. However, a very weak electrical signal can be recorded from the surface of the head. The recording is made by the *electroencephalograph* (EEG in which ''electro'' means electrical, ''encephalo'' means brain, and ''graph'' means display and measurement); it is closely related to the *magnetoencephalograph* (MEG). To understand EEG and MEG, we need to review the basic physics of electromagnetism. Electrical current happens when charged particles move in a circuit. The amount of current that can flow depends on the electrical potential or voltage present. If there is no voltage, it's like a dead battery; no charge can flow so no work can be done to run a computer or a brain. When current flows, an electrical field can be measured, and with every electric field an associated magnetic field is also created. You can learn how this is so in physics textbooks, but for our purposes this should be enough background information.

You learned in Chapter 7 that most of the neurons in the cerebral cortex are elongated neurons called pyramidal neurons. When the elongated pyramidal neurons are depolarized by their synaptic inputs, they become tiny batteries with a positive and a negative end. When millions of these neurons become polarized, they create an electrical field of sufficient strength to be measured on the surface of the head. This randomly oscillating electrical potential, or ''brainwave,'' can be measured easily with relatively inexpensive equipment. Much more expensive equipment can measure the magnetic field associated with the electric field; this is the MEG. The EEG and the MEG are two ways of recording the same brain processes, and, being less expensive, EEG is used much more commonly in the legal arena.

The EEG (and MEG) detect randomly rhythmic fluctuations of electrical signals produced by the brain that oscillate between peaks and troughs. Researchers can measure the interval between (or frequency of) successive peaks and troughs and also the amplitude from the peaks to the troughs. The frequency is measured in units of cycles-per-second (also known as Hertz or Hz)[1], and the amplitude is measured in units of microvolts (millionths of a volt). The frequency and amplitude of the brain signal oscillation varies with behavioral state. When subjects are alert, the EEG shows higher frequency and lower amplitude. As the brain becomes relaxed, the EEG shows lower frequency and higher amplitude. As the brain goes to sleep, the EEG shows even lower frequency and higher amplitude; however, the waves are interrupted with intermittent high frequency and high amplitude signals called spindles. When the brain suffers an epileptic seizure, the EEG exhibits pronounced series of high amplitude spikes. The information obtained from the EEG is invaluable for diagnosing and monitoring the treatment of epilepsy, sleep disorders and other neurological diseases. The EEG is also used to assess brain death in some states because a brain that cannot produce signals detected by EEG cannot produce behavior or consciousness. As you will learn in Chapter 10, this has important implications for the status of a person as living or dead, which touches on areas of the law such as wills, trusts, and estates, as well as insurance.

A recent and particularly exciting development is the use of brain waves in prosthetic devices. In Chapter 20 you will learn how sophisticated computer algorithms can read the brainwaves from a person who is totally paralyzed to guide a cursor on a computer monitor and to write emails, for example.

Before the development of inexpensive, powerful computers, EEG data were recorded on very long strips of paper, and investigators did measurements by hand. As digital EEG recording and analysis became possible, a form of computer analysis has been developed known as quantitative EEG (QEEG). As described above, the EEG consists of rhythmic fluctuations. QEEG simply employs well-established algorithms that decompose such fluctuations into different frequency components.[2] The EEG is usually recorded from an array of dozens of electrical contacts arranged around the head. Based on what you learned in Chapter 7, it should not be a surprise that the brainwaves recorded over different regions of the brain differ in various ways.

The QEEG approach plots the magnitude of the different frequency components on an image of the head, usually in vivid colors. Some call this a ''brain

1. To facilitate communication between researchers, the frequency ranges of brain waves have been given an arbitrary nomenclature which is shown here for your reference. The unit of measurement of frequency is named for the German scientist, Hertz, and is abbreviated Hz. One Hz is one cycle per second.

Frequency range	Up to 4 Hz	4 to 8 Hz	8 to 13 Hz	13 to 30 Hz	30 to 100 Hz
Name	Delta	Theta	Alpha	Beta	Gamma

2. If you remember sine waves from mathematics, then you can appreciate that the EEG can be decomposed into a collection of sine waves with different frequencies and amplitudes. The quantitative determination of that collection of sine waves is just what QEEG does. If you do not remember sine waves, then you can think of QEEG as decomposing a musical chord into which keys on a piano were struck and how hard.

map,'' but you should appreciate that it is an image constructed from mathematical calculations performed on the brainwaves. These mathematical calculations are not supposed to correspond in any way to the operations that the brain actually performs. Nevertheless, researchers have found that the frequency content of the brainwaves varies with the location of the recording contacts and mental state. They have also found that the QEEG pattern varies across individuals but seems to be replicable when measured at different times from the same individual. Researchers are seeking to develop a database of the natural variability of QEEG patterns against which to judge deviations that may be informative clinically for diagnosis or measuring effects of medications. Many investigators employ the QEEG approach for research studies, and a thriving business provides access to this measurement for commercial purposes. In the neurolaw arena, as you have already seen in Chapter 6, courts are weighting the admissibility of QEEG in novel legal contexts.

Sophisticated computer analysis permits another approach using EEG that has been much more informative scientifically. Embedded in the rhythmic fluctuations of the EEG recording from a participant responding to stimuli to perform a task (such as press the right button if the stimulus displayed is an ''O'' and the left, if it is an ''X'') are small signals related to presentation of stimuli, production of responses and various cognitive processes. By using a computer to remove the random noise in the brain waves recorded over dozens of testing trials, investigators can observe and measure the electrical potential signals related to the events of the task. The more trials that can be sampled, the more reliable the signal that is known as an *event-related potential* (ERP). ERPs arise from the summed polarization of large groups of neurons responding collectively to the events. Scientists have described ERPs related to sensory processes, attention, memory, intention, body movements and monitoring of consequences. In other words, all of the cognitive processes described in Chapter 7 have associated ERPs through which the brain correlates can be studied.

The scientific foundation of ERPs is much stronger than that of QEEG. ERPs are commonly used in clinical settings. The visual and auditory ERPs are of particular importance in detecting, for example, multiple sclerosis, a disease arising from loss of axonal myelination. When demyelination occurs in the optic nerve, the early peaks of a visual ERP are delayed. In neurolaw, as we will see in Chapter 15, some have proposed using ERP measures for lie detection.

EEG provides good information about the timing of brain processes because it can measure neural events with millisecond (1000th of a second) resolution. On the other hand, it lacks resolution in space; it is difficult to determine where in the brain particular EEG signals arise. It is a very common tool, though, because EEG data can be obtained using equipment that is much less expensive than that necessary for the two neuroimaging tools discussed next.

3. Positron Emission Tomography and Single Photon Emission Computed Tomography

Unlike EEG and MEG, the techniques discussed in the next two sections measure neural events through local changes in blood flow and oxygen utilization that

correlate with local changes in neuronal activity. Blood flow delivers oxygen and glucose, the basic sustenance of neurons and glia, so when certain regions are more active and thus more demanding of energy, blood flow will be redirected towards these regions. Techniques based on this indirect measure are very popular because they result in vivid two-dimensional or three-dimensional images of localized brain activity.

Positron Emission Tomography (PET) requires injecting a radioactive tracer into a subject's blood stream while that person is engaged in a sensory, motor or cognitive task. The tracer will flow to all parts of the body, but PET measurements are based on the fact that more blood will flow to parts of the brain with more neural activity, so these areas will have preferential accumulation of the tracer. Being radioactive, the tracer emits subatomic particles as they degrade. These particles are detected by an array of sensors that provide information used to reconstruct the three-dimensional location from which the particle was emitted in the brain. Regions of more or less blood flow are identified by the detection of more or fewer particle emissions.

To obtain information about the role of brain areas in performing experimental tasks, the tracer is administered twice: once during a control condition, and once during an experimental condition. The difference in blood flow between the testing conditions measures the degree of involvement of different parts of the brain in a given experimental task. Thus, if the experimental condition involves presentation of visual stimuli and the control condition is darkness, then the brain image will show elevated blood flow in visual processing areas in occipital cortex. On the other hand, if the experimental condition involves generating verbs in response to nouns and the control condition is just repeating nouns, then the brain image will show elevated blood flow in language processing and production areas in temporal and frontal cortex. Finally, if the experimental condition involves imagining producing a sequence of finger movements and the control condition is actually producing the sequence of finger movements, then the brain image will show elevated blood flow in an area of frontal cortex responsible for planning movements.

The major advantage of PET is obtaining information about local processes within the human brain. This information is more elaborate than just blood flow, because PET allows researchers to use different kinds of radioactive tracers. The tracers can be incorporated into compounds used naturally by the brain (such as glucose or water to look at metabolic use) or into molecules that bind to receptors or other sites of drug action. For example, the location and density of dopamine receptors can be measured with PET. Thus, PET can be used to trace the pathway of any compound in the human brain as long as it can be labeled with a radioactive tracer. New tracers are being synthesized to explore various molecules and processes with dozens in clinical use and hundreds in research use. The most common tracer used for clinical PET scanning is *fluorodeoxyglucose* (also called FDG or fludeoxyglucose) because it reveals the utilization of glucose. Researchers have also used PET to obtain images of the location where particular neurotransmitters such as dopamine are more concentrated.

The technique has many disadvantages. First, radioactive tracers must be injected into the blood stream. Beyond the potential health risks posed by

the radiation, a facility must have the equipment and expertise necessary to produce the radioactive tracers because they degrade at a rapid rate. Second, the resolution of PET in time is very low because ~40 seconds is needed to count enough particles to derive the map of brain activity; this means that rapid changes in brain state that could be observed through EEG or MEG will be invisible to PET. Third, the resolution of the activity maps in space is very coarse, on the order of centimeters; this means that variation across individual neurons or local circuits that could be observed with single-unit recordings will be invisible to PET. A sense of higher resolution can be obtained by superimposing PET images on structural MRI images from the same subject.

While the use of PET in research has decreased with the development of functional MRI (described below), PET offers particular advantages in clinical settings for diagnosis of brain disease. In neurolaw, PET scans have been allowed in criminal trials as evidence, as we saw in Chapter 2 to locate a cyst in the skull of Herbert Weinstein.

Like PET, *Single Photon Emission Computed Tomography* (SPECT) traces the emission of a radioactive tracer injected into the bloodstream. Unlike PET, SPECT uses tracers that do not decay rapidly. Using SPECT, researchers effectively take a snapshot of brain activity at the moment the tracers are injected. Thus, relative to PET, SPECT has less spatial resolution and no timing resolution. However, SPECT is more affordable and thus more widely available, so it may appear more often in neurolaw cases.

4. Functional MRI

Functional Magnetic Resonance Imaging (fMRI) is a specialized application of MR technology to measure levels of brain activity indirectly through changes in regional blood flow. You learned above that MRI is based on the magnetic spin properties of atoms in the brain. Recall now that blood transports oxygen from the lungs to the body using a protein called *hemoglobin*. Oxygen is bound to hemoglobin (becoming *oxyhemoglobin*) in the lungs and transports it to the organs of the body where it is released from hemoglobin (becoming *deoxyhemoglobin*). fMRI is based on the fortunate fact that oxyhemoglobin is not magnetic but deoxyhemoglobin is magnetic and perturbs the local magnetic field. This difference is the basis of fMRI, because the scanner can detect regions with relatively more oxyhemoglobin relative to deoxyhemoglobin as a consequence of demands from neural activity. This signal is called the *blood-oxygenation level-dependent* (BOLD) signal.

The typical fMRI study uses roughly 200,000 voxels, 100,000 of which enclose the cerebral cortex and underlying white matter. The BOLD signal measured in each voxel is compared between a baseline period and an active period. This is just like the comparison described for PET above. To create the fMRI image a color is assigned to each voxel according to the magnitude of the BOLD signal during a test period compared to the magnitude of the BOLD signal during a control baseline period. While the color assignments are completely arbitrary, it has become standard to use hot colors (red and yellow) to represent increased BOLD and to use cool colors (blue and green) to represent decreased BOLD.

The description of the method here will be as simplified as the procedure is not. Because this method is becoming so important for law, though, we must consider carefully what is actually done. Particular limitations of this technique are considered in more depth in the next chapter and in the Appendix. You must appreciate that fMRI images with ''hot'' and ''cool'' spots are not just photographs of the brain.

fMRI brain images are constructed through a complex sequence of computerized analytical steps. One of the first is called *slice-timing correction*. The entire brain is scanned in a series of successively measured 2D slices. Accordingly, the last slice is obtained after the first in the sequence. Slice-timing correction accounts for this time difference across the brain scan slices. This is particularly important for event-related designs in which the BOLD signal changes are measured relative to particular testing events. Another processing step is *motion correction* that adjusts for incidental head movements produced during the scan. Next, if the scans from multiple individuals will be compared directly, then differences in brain size and shape must be accounted for. This is accomplished through *coregistration* that involves adjusting the size and shape of different parts of individual brains to bring them into registration with each other. Commonly, this is done by transforming each subject's brain to match the size and shape of a standard brain, like distorting each person's face to map it onto one standard face. A French physician named Talairach established a popular standard based on postmortem sections of a 60-year-old female. She happened to have a smaller than average brain, though, so most subjects' brains must be adjusted considerably, and that introduces some error. Such standards of measurement are necessary for science, and the error introduced from these standardization procedures is well known and accounted for. Finally, the raw BOLD signals have incidental, noisy variation across the voxels, so another processing step involves smoothing across voxels to remove the random noise.

Once all of that pre-processing is done, the real analysis can begin. Many approaches have been developed for discovering voxels or sets of voxels that exhibit more or less BOLD signal in relation to testing events and inferred mental states. Let us note here that higher or lower BOLD signal does not necessarily correspond to higher or lower counts of nerve impulses; this can be difficult to remember because so often BOLD signal is referred to simply as ''activation.'' One popular approach is known as a *general-linear model* (GLM). A GLM identifies voxels with BOLD signal changes that relate to specific events in a task. Typically this analysis results in patterns of voxels located in particular parts of the brain that have BOLD signal changes that are statistically related to an testing variable such as a task condition or an experimental or diagnostic group. A second approach is known as *independent component analysis*. Independent component analysis describes how different regions interact with each other instead of which region has more or less BOLD signal. A third powerful approach is known as *multi-voxel pattern analysis* (MVPA). MVPA searches for patterns of BOLD signal across all or many voxels throughout the brain. This approach is sometimes referred to as ''brain reading'' because different voxel patterns can be used to distinguish specific mental states. The computer tools for this analysis originate from a specialty in artificial intelligence known as machine learning.

Brain images differ from photographs in other ways too. The brain images one sees are nearly always comparisons (often referred to as contrasts) between two

different behavioral states. In ''activation paradigms,'' for instance, subject responses are typically measured and compared between two or more task conditions during a series of scans conducted in a single experimental session. Regional differences in the measured signal between various tasks are considered to reflect differences in the amount of local neuronal activity associated with performance of those tasks. However, the fMRI signal is very weak and can be corrupted by numerous problems with the machine (such as gradual changes of the strength of the magnetic field) and with the subject (for example, moving the head). Hence, a relatively standard set of ''pre-processing'' steps is performed to prepare the data for the actual analysis. These steps include accounting for incidental movements of the subject's head, for differences in the size and shape of different subjects' brains, for incidental distortions in the strength of the magnetic field through the brain, and for the timing of the information obtained in each voxel that are obtained in sequential slices through the brain, as well as smoothing the signal through time and across adjacent voxels to remove incidental noise.

A multitude of approaches to analyzing fMRI data have been developed and more are invented every year as this method develops further. One approach employs basic statistical methods to identify voxels in which the BOLD signal varies significantly with specific events or experimental manipulations. Such a finding is then interpreted as an indication of a regionally-specific ''activation'' associated with an experimental condition or group. Other approaches seek to identify networks of brain regions that collectively co-vary with condition or group. Yet another approach takes advantage of differences between individual subjects to identify differences in patterns of brain activation.

fMRI has significant advantages relative to PET. First, fMRI uses signals intrinsic to the brain rather than signals originating from exogenous, radioactive probes. This means that subjects can be tested repeatedly with fMRI, which provides an opportunity to obtain more data from each individual. Second, fMRI offers better spatial resolution than PET (a few millimeters compared to almost a centimeter); this allows more clarity about the location of brain damage or other events. Third, fMRI offers better temporal resolution than PET (a few seconds compared to many seconds or minutes). This allows for more informative studies of cognitive processes as described in the next section.

To be clear, though, the temporal resolution of fMRI is far inferior to ERP measurements described above. To address this, researchers are combining EEG and fMRI in the same subjects. Based on these advantages MRI devices have become ubiquitous in clinical settings, and in Chapter 1 you learned about a vivid neurolaw application of fMRI research with convicted criminals using a device carried to prisons in a tractor trailer.

C. TASK DESIGN IN FUNCTIONAL IMAGING

1. Introduction

The brain is constantly active, blood is always flowing, and most of the brain's regulation of blood flow is not related to particular tasks or cognitive states. Accordingly, a BOLD signal in a brain area in and of itself tells us that the cells

in that area are functioning—but what does that function actually mean? How do we know whether someone is in pain, is remembering a vivid memory, or is exercising self-control? Answering questions like these are not easy, and as the next chapter explores, one should use great caution in evaluating research that claims to do mind reading. But cognitive neuroscientists are making important advances, and to understand how they are doing this we need to review experimental design.

Researchers use many experimental designs. But one described below is the *block design* study, using *subtraction* techniques. In block designs, subjects lie in the scanner while they see alternating blocks (groups) of images or text on the screen in front of them. The blocks are designed so that the only difference between them can be labeled as the cognitive process of interest. For example, an experimenter might alternate between showing the subject a set of images of places and a set of images of faces. The researcher compares the brain activity of the subject when she is looking at places versus when she is looking at faces. This comparison is carried out by ''subtracting'' the brain activity while looking at places from the activity while looking at faces. The difference that's left over after the subtraction is thought to be the additional brain activity for processing faces.

Similar designs have been used for investigating complex cognitive states, even states as mysterious as ''love.'' But whether such designs are truly informative and appropriate for a given mental state remains an open question. Experimental design should be scrutinized just as carefully as the technology used to carry out the experiment. This section provides a general introduction to the details of those designs.

2. Functional Decomposition and Experimental Design

Complex cognitive tasks are composed of numerous sub-operations. For instance, most commonly a subject receives instructions (e.g., press this key after one stimulus and another key after a different stimulus), perceives stimuli (perhaps the different stimuli are difficult to distinguish), performs certain cognitive operations (such as remembering the instructions), and responds overtly in some prescribed way (pressing this and not that key). *Functional decomposition* refers to the conceptual breakdown of a task into its component operations, carving the task at its functional joints.

Carefully considered functional decomposition lies at the heart of successful neuroimaging experiments. The ideal experiment creates conditions that hold most functional components as fixed as possible and manipulate just one variable at a time. In this way, differences in activation between scan conditions can be clearly attributed to the manipulated variable. The experimental design must be informed by knowledge derived from previous psychological studies of the component operations and their relationships. The coursebook web site provides additional resources related to psychological research in areas such as attention, memory, emotions, and so forth.

3. Task Types

Three types of tasks are used in neuroimaging activation studies. (1) The target task requires the participant to perform the sequence of operations of interest

(e.g., decide whether a scenario explained in a short paragraph is a crime). (2) The comparison tasks require participants to perform a sequence of operations that differs from the target task in a critical and informative manner (e.g., decide whether the same scenario involves a male or a female actor); more than one comparison task may be necessary. (3) The baseline task requires the participant to perform a very basic sequence of operations (or even nothing at all) (e.g., read a paragraph of the same length as the experimental scenarios to control for the eye movements and basic comprehension that occurs during reading).

Investigators then contrast the activation in different parts of the brain between the different types of task. The contrast of brain activation between the target or comparison tasks and the baseline tasks reveals the brain regions that are involved in accomplishing the additional operations (like interpreting a scenario as opposed to just moving eyes and reading). If the baseline task is not designed correctly, then the activation observed in the target and comparison tasks can be misleading. For example, if the baseline task required simply fixing gaze on a single letter in the middle of the screen, then the brain activation in the target and comparison tasks would be derived not only from the operations of reading and interpreting the scenario but also simply moving the eyes.

The contrast of brain activation between the target and comparison tasks is intended to reveal the brain regions that are involved in accomplishing the specific operation of interest (in this case, judging guilt versus innocence) while accounting for all of the other operations necessary to perform the overall task (moving eyes, sitting upright, breathing, etc.). If the comparison task is not designed correctly, then the activation observed in the target task can be misleading. For example, if the comparison task required simply reading a paragraph silently, then the brain activation in the target task could be derived not only from the operation of judging guilt vs. innocence but also from just interpreting the text.

Selection of the tasks involved in a study is critically important, strongly affecting its interpretability and outcome. Baseline tasks are typically chosen to be simple operations that lack the demands of the target and comparison tasks. Many researchers use baseline tasks in all their studies, regardless of the study's goal. This makes it easier to begin to find common patterns of activation across numerous studies, and allows the possibility of future meta-analyses. Regardless the choice of baseline task, it is of primary importance to be aware of the cognitive operations required by that task, as well as others in which the subject might engage. Comparison tasks are more complex, requiring most high-level operations chosen because either they differ in some specific way from the target task or because they share important features with the target task, or both. The choice of comparison tasks is a major determinant of the ultimate perspicuity and value of a study: Careful choice of tasks can go far in disclosing the functional roles of one or a few brain regions, while inappropriate choice of tasks can result in a study that fails to answer any specific cognitive question.

4. Blocked Designs

The ability of fMRI to acquire data in brief time slices confers important advantages over other imaging methods, such as PET. Blocked designs are necessary in PET, and used to be common in fMRI, but are becoming less so. In blocked

designs, subjects perform one type of task for a period or ''block'' of time (in fMRI usually between 10-30 seconds, and in PET for several minutes), e.g., decide whether a scenario explained in a short paragraph is a crime. Then they switch to another type of task, e.g., decide whether the same scenario involves a male or a female actor. Blocked designs are relatively easy to analyze, for the data are averaged across blocks of the same task type, and subtracted from data averaged across blocks of a different task type. The resulting activation pattern can be compared with a control condition when the subject is either not doing the task or doing some other sort of task. The information one gains from such studies reflects aggregate differences in brain activity in different regions between the two task periods.

Blocked designs have some serious limitations, however. Some tasks are performed differently when one knows exactly what sort of task one has to perform, and the ability to distinguish between different trials is lost. Thus, certain kinds of information regarding differences in task or performance cannot be investigated by this method, such as differences between correct and error trials. In other words, blocked designs limit the specificity with which brain activation can be associated with particular cognitive processes.

5. Event-Related Designs

A marked improvement over the blocked design, called *event-related design*, takes advantage of the temporal resolution available with fMRI. Event-related designs are more powerful than blocked designs for exploring cognitive function, capturing more subtle differences in task performance, so it is now widely used. An event-related experimental design measures the BOLD signal synchronized on various events during a task such as presentation of the short paragraph to read and production of the response reporting whether it describes a crime or whether the actor is male or female. The signal is then averaged across many experimental trials so that the random fluctuations of the BOLD signal that are unrelated to the brain processes performing the task cancel out, leaving the systematic variation of the BOLD signal that is related to performance of the task. The fMRI response to an event starts after 1-2 seconds, peaks at 5-6 seconds, and returns to the starting level after 12-20 seconds. Although this is much slower than event-related EEG and MEG, it is still fast enough to provide useful information if the task events are designed properly.

Different types of trials (target, comparison, and baseline) can be randomly interleaved, and after the data are collected computers sort, align and average the BOLD signal for each type of trial. The location and timing of the BOLD signal occurring immediately before or after task events is contrasted across trial types to draw conclusions about the brain processes occurring during the tasks. This approach can reveal differences in brain activation related to, for example, the types of stimuli, whether or not the subject performed correctly, and the time taken to respond. Event-related designs are typically analyzed by correlating activation patterns with mathematical models of task performance that incorporate various task-related aspects of the experiment, such as stimulus onset, response timing, response type, etc. The models are based on functional decompositions; the validity of the results will depend on the accuracy of the models.

6. Multi-Voxel Pattern Analysis

The procedures described above emphasize the magnitude and timing of BOLD activation in particular parts of the brain, referred to as *regions of interest (ROI)*. More recently, an entirely different analysis approach has been devised that examines the pattern of activation across the voxels throughout a brain region or even the entire brain. This is known as *multi-voxel pattern analysis* (MVPA). This analysis includes the BOLD signal in all the voxels during the various conditions in the experimental trials. Particular statistical methods then use the information in all the voxels to discriminate between the task conditions. This approach provides greater sensitivity to detect BOLD pattern differences between testing conditions than the conventional ROI analyses. MVPA results are often offered in terms of ''brain reading'' whereby particular mental states or representational content is decoded from fMRI activity patterns.

D. HUMAN BRAIN MANIPULATION

This section explores different ways — temporary and permanent, planned and unplanned — whereby the human brain is manipulated. Subsection 1 examines how brain lesions have been used to study mechanisms of disease, as well as more generally how the brain works together as a whole. In particular, it focuses on surgically created lesions, some techniques that are obsolete and others that are still used today in the treatment of certain diseases. The next two subsections describe two techniques that researchers use to temporarily improve or disrupt brain function. Finally, we survey briefly the use of drugs to manipulate brain function.

1. Brain Damage

The brain can be damaged in many ways. A localized area of damage is referred to as a *lesion*. Brain lesions occur due to ''insults'' like stroke (blockage or bursting of blood vessels), tumors (cancerous growth of neurons, of glia, or of meninges), cysts (a cavity between the skull and brain formed by the meninges filled with cerebrospinal fluid or air), and traumatic injuries (like the tamping iron blown through Phineas Gage's head). Traumatic injuries can be very localized (such as penetrating gun shots) or diffuse (concussions). The recent wars in Iraq and Afghanistan have resulted in a large increase in patients with *closed head injuries* as a result of concussions suffered during explosions. Also, degenerative diseases such as Alzheimer's, Huntington's and Parkinson's result from loss of neurons in particular parts of the brain.

Historically, some of the first insights into brain function were obtained by correlating the site of the lesion with the type of changes of behavior. Often the location of the brain damage could not be determined until after death because the non-invasive imaging methods described above were not available. Nevertheless, particular patterns of symptoms were described. Neurologists and psychiatrists distinguish *positive symptoms* from *negative symptoms*. Positive symptoms are abnormal behaviors resulting from the brain damage. Examples include

abnormal movements such as the tremor and rigidity of Parkinson's disease or the hallucinations of psychosis. Negative symptoms are deficits of behavior resulting from the brain damage. Examples include blindness or paralysis consequent to a stroke damaging visual or motor cortex. Brain damage symptoms can be categorized as perceptual, motor, cognitive and mood. Damage to the primary sensory areas of the cerebral cortex and associated structures results in outright loss of sensation such as loss of hearing or vision. Damage to higher order sensory areas in the parietal and temporal lobes results in more complex perceptual disorders such as disorientation in space and lack of recognition of complex objects including speech.

Damage to the movement systems of the brain result in another pattern of symptoms. Neurologists distinguish *lower motor neuron* symptoms from *upper motor neuron* symptoms. Lower motor neuron signs include the weakness, atrophy, and reduced or absent reflexes consequent to damage to the spinal cord or neurons innervating the muscles (as in muscular dystrophy or Lou Gehrig's disease). Upper motor neuron signs occur in groups of muscles (like the side of the face or a whole arm) without atrophy and increased reflexes consequent to damage in the brain that removes control over the spinal cord. Damage to primary motor cortex and associated structures results in a pattern of symptoms, referred to as *hemiplegia*, that include loss of voluntary movement with changes in postural tone and reflexes on one side of the body (opposite the hemisphere with the lesion). Damage to higher order motor structures result in syndromes collectively referred to as *apraxia* that is inability to produce a movement that is not due to paralysis but instead seems to be a loss of a specific loss of skill. Various forms of apraxia occur depending on the particular site of the lesion. Examples include misuse of objects due to lack of recognition, difficulty with complex patterns or sequences of movements, inability to use objects for their intended purpose. Damage to the basal ganglia result in particular patterns of symptoms including tremors (involuntary oscillatory movements), athetosis (slow, writhing movements of fingers & hand), chorea (abrupt movements of limb and facial muscles), ballism (violent, flailing movements) and dystonia (persistent abnormal posture).

Damage to structures associated with the limbic system results in more complex patterns of symptoms including memory loss, mood changes including depression and anxiety, and poor judgment in decision-making. Post-traumatic stress disorder may arise from disordered functioning of parts of the limbic system. Also, research is suggesting that disordered functioning of parts of the limbic system and associated structures is a basis of criminal psychopathy.

We might think that a small lesion disrupts only one mental operation because of its location is restricted to a particular part of the brain. We would be wrong, however, because the brain is so massively interconnected that a particular symptom could arise following damage to different parts of the brain. Consider an automobile engine. Either allowing the spark plugs to decay or cutting the gas line will cause the car to stop running, but it doesn't mean that these two disrupted parts do the same thing — rather, their removal has similar consequences. On the other hand, damage at one location can have widespread consequences. In an automobile engine a dead battery will prevent the engine from starting, the radio from playing, and the doors from unlocking.

Obvious ethical considerations do not allow researchers to produce controlled lesions within the human brain; therefore, researchers study large groups of patients with similar patterns of brain damage and map the particular patient-to-patient variations onto a common brain to discover any correlation between damaged regions and the loss of a particular function.

The diagnosis of brain damage is often uncertain due to variability in the location, extent and duration of the lesion. To use stroke patients as an example, factors that can vary between patients include how long ago the stroke occurred, which artery within the brain was blocked, what areas were cut off from blood supply because of the blockage, and whether other arteries compensated to provide an alternative supply of blood to that particular region.

Brain damage can also have therapeutic effects. Neurosurgeons intentionally produce lesions to treat a variety of disorders. One obvious example is the treatment of epilepsy by removing the tissue sparking the seizure. Such treatments are not without negative side-effects.

For example, many years ago neurosurgeons removed parts of the medial temporal lobe including the hippocampus to eliminate seizures, but they stopped this treatment when it was discovered that it leaves the patient with profound *amnesia*, an inability to form new memories. More notorious and ineffective is the ''psycho-surgery'' known as the *frontal lobotomy*. This involved severing the connections between prefrontal cortex and the rest of the brain. It peaked in popularity in the mid-20th century as a treatment for disorders ranging from depression to schizophrenia because it seemed to reduce the negative symptoms of anxiety, severe depression, and manic-depressive psychosis. However, other normal functions were also often affected, such as empathy, performance of normal household and work duties, and sexual propriety. Consequently, this procedure is no longer performed except in very rare circumstances when all other treatment options have failed.

We cannot leave the topic of brain damage without calling attention to *brain plasticity*. The brain can repair itself, sometimes to an amazing extent. Through various mechanisms the brain adapts to certain kinds of insult. The discovery of brain plasticity has had many important therapeutic consequences. For example, amputees who have lost, say, an arm experience ''phantom limb'' pain — pain in the limb that is no longer there. Researchers have discovered that, in this phenomenon, the brain's map of the body changes after the limb is lost; neurons once devoted to the lost limb begin to respond to stimulation of neighboring parts of the body. As a result some patients who have lost an arm experience sensation on the arm when the face is touched.

This discovery has led to a potential therapy for phantom limb pain, providing patients the experience of seeing their missing limb as normal in a mirror. Also, if stroke patients who lose function of one limb are forced to use that limb, then they recover more function than they would otherwise. The recovery may not be complete, but it is more than it would have been without the challenging exercises. Finally, a neuroprosthetic treatment for profoundly deaf individuals uses a cochlear implant to pick up sounds and transmit electrical signals directly to the auditory nerve in the cochlea. Plasticity in the brain is believed to be crucial for patients to learn to make sense of the unusual sensory inputs.

2. Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a noninvasive method for either activating or inactivating fairly localized parts of the cerebral cortex. A person undergoing TMS has a figure-eight shaped device placed on their head, and when the device is pulsed, the brain stimulation occurs. To understand how it works, recall that every electrical field has an associated magnetic field and vice versa. TMS is accomplished when a very powerful magnetic field is generated by the figure-eight device located somewhere on the head; the electric field associated with this induced magnetic field passes through the scalp, skull, and dura mater to influence neural activity to some depth within the brain. The area of cerebral cortex affected is estimated at 1.0–1.5 cm^3.

Whether TMS activates or inhibits neurons varies for reasons that remain uncertain, but the influences of TMS can be vivid and reliable. For example, TMS over visual cortex elicits perception of light flashes. TMS over the hand representation in motor cortex elicits discrete twitches of the fingers. In addition, TMS targeted to other cortical areas can impair function, inducing temporary blindness or paralysis, loss of recognition of different letters, or an inability to read words. Thus, in some cases TMS is described as producing a temporary lesion. The variability of the effects of TMS is believed to be a result of the geometry of the cortex beneath the skull and the nature of the networks involved.

Originally, TMS was limited to single pulses of stimulation. Subsequently, the use of *repetitive TMS* (rTMS) was found to be safe when properly executed. Single pulse TMS has short-lasting effects, but rTMS can have much longer duration effects, lasting even beyond the end of the stimulation. In the clinic TMS has been used to assess the strength of connection between the primary motor cortex and the muscles to evaluate damage from insults such as stroke, multiple sclerosis, amyotrophic lateral sclerosis, and spinal cord injuries. Some investigators have reported modest therapeutic effects of rTMS in cases of major depression.

TMS has many limitations. First and most notable, perhaps, is that the electric field that activates neurons also activates the overlying muscles causing potentially uncomfortable contractions of scalp and facial muscles. Second, when TMS is done with longer trains of pulses, it can cause seizures. Third, although TMS is delivered to a particular location, its influence occurs through changes in brain circuitry of an unknown scale. To explore this, neuroscientists have developed procedures to obtain fMRI data (with an incredibly strong magnet) following TMS (with an incredibly strong magnetic field) to investigate how stimulation of one part of the cortex influences BOLD activation in other parts of the cortex. Ultimately, though, TMS cannot influence brain processes with the precision of localization that can be accomplished with invasive techniques.

3. Transcranial Direct Current Stimulation

Transcranial direct current stimulation (TDCS) is another noninvasive method for either activating or inactivating larger regions of the cerebral cortex. Whereas TMS involves pulses of rather intense stimulation, TDCS involves sustained weak

stimulation at levels corresponding to an automobile battery. A person undergoing TDCS has two small, wet sponges placed on the head, one over the brain region of interest and the other over a remote location like the shoulder, neck or cheek to complete the electrical circuit. Wires connect the sponges to the device that delivers the desired magnitude and duration of stimulation. The effects of the stimulation can vary according to whether the positive or negative pole of the device is connected to the sponge over the brain. It is thought that when the negative electrode (cathode) is located over the brain region, it hyperpolarizes neurons, making them less responsive. In contrast, when the positive electrode (anode) is located over the brain region, it depolarizes neurons, making them more responsive. TDCS seems to be less risky than TMS with few relatively minor side effects. TDCS has been shown to influence perception, attention, movement and decision-making. Importantly, TDCS often has prolonged effects after the stimulation period is finished. The general approach has been explored for over a century, but in the last several years interest has renewed for research and potential therapies.

4. Direct Brain Stimulation

Electrical stimulation to elicit responses has been used for decades to investigate brain function. For example, the function of different parts of the human cerebral cortex has been described in fascinating detail through discoveries that stimulating different parts elicits markedly different effects. Electrically stimulating the occipital lobe elicits punctate sensory experiences such as flashes of light, while stimulating parts of the temporal lobe elicits more complex perceptions like autobiographical memories. Meanwhile, stimulating the primary motor cortex in the frontal lobe elicits punctate movements like twitches of a finger, while stimulating the supplementary motor area elicits the feeling of willing a movement. Findings like these highlight the profound connection between brain function and our mental experiences. But for surgical treatment of epilepsy, electrical stimulation of the brain is essential to locate centers responsible for language (that should not be removed) and centers sparking the seizure (that should be removed).

Electrical stimulation of subcortical structures can also be very powerful. For example, stimulating around the amygdala elicits a phenomenon called *sham rage* in animals characterized by biting, clawing, hissing, arching the back and violently attacking vulnerable items in the environments. Meanwhile, stimulating in the base of the brain around a bundle of dopamine fibers passing to the limbic system is experienced as an incredibly potent reward that animals will work to earn to the exclusion of food and water. Both of these phenomena have been described in humans as well as animals.

Electrical stimulation of subcortical structures has also proven amazingly effective therapeutically. *Deep brain stimulation* (DBS) refers to electrical stimulation of structures deep in the brain to treat particular symptoms. This requires insertion of electrodes attached by a thin wire to a battery implanted near the collarbone. Supported by extensive anatomical and physiological testing in animal models, the therapeutic effect of DBS of a particular part of the basal ganglia for treating

Parkinson's disease was elucidated. DBS is now employed commonly in patients for whom the effectiveness of L-DOPA therapy (see below) has diminished. Subsequent research has reported beneficial effects of DBS of anterior cingulate cortex to treat major depression. Remarkably, the symptoms of the disease remit immediately after the stimulation is turned on, as long as the electrode is in the correct location — the tremor and rigidity of Parkinson's patients passes away, and the black cloud lifts from chronically depressed patients.

The previous examples have emphasized the specificity of effects of electrical stimulation of particular parts of the brain. The final example we will consider is referred to as *electroconvulsive therapy* because it involves effective stimulation of the whole brain. Complete seizures are induced in anesthetized patients to treat profound psychiatric disorders. Even though the mechanism of the therapeutic effect is not understood, electroconvulsive therapy may be effective for treating clinical depression in some individuals who have not responded to other treatments.

5. Pharmacological Manipulation

You learned in Chapter 7 how signaling between neurons involves the release of and response to neurotransmitter molecules at synapses. The synaptic transmission occurs through several steps, or can be manipulated pharmacologically. In this section we review some of the possible ways in which brain, and thus behavior, can be affected by drug use. It should be emphasized, however, that at present the complex web of relationships between drugs-brain-behavior remain in many ways unknown. While many of these mysteries may one day be solved, it may take considerable time. This is why, for instance, some large pharmaceutical companies have reduced their present investments in mind-altering drugs. Recognizing current limitations, drugs nevertheless play an important role in modifying brain function.

Drugs that facilitate or impede neurotransmission can improve or impair perception, movement, memory and mood. Drugs that influence mental processes are called *psychoactive drugs*. Humans have used such drugs for centuries, e.g., caffeine, cocaine, and cannabis. Modern neuroscience has provided many other psychoactive drugs motivated by the prevailing view that psychiatric disorders arise from improper functioning of specific brain neurotransmitter systems. We should also appreciate that other drugs can influence the brain by promoting birth of new neurons and influencing the expression of genes.

Drugs that affect the brain have been categorized as follows:

- *Anesthetics* or hypnotics are given to create a reversible loss of sensation, commonly for the purpose of a surgical procedure. Whereas local anesthetics, like lidocaine, prevent sensation from a limited part of the body, general anesthetics eliminate consciousness. One kind of general anesthetic is a gas that has its effects as long as it is inhaled. Other general anesthetics, exemplified by Propofol, are given intravenously to induce anesthesia quickly.
- *Antidepressants* and *anxiolytics* (anti-anxiety) are prescribed to treat depression and anxiety. Exemplified by Prozac, this group includes drugs that reduce

the reuptake of serotonin into the synapse, thus called *selective serotonin reuptake inhibitors* (SSRIs).

- *Antipsychotics* are prescribed to treat psychotic disorders such as schizophrenia. Exemplified by Haldol, one type of antipsychotic blocks the effect of dopamine at the synapse. A common side-effect of Haldol is impaired production of movements due to the blockage of dopamine in the basal ganglia. Exemplified by Clozapine, atypical antipsychotics influence serotonin as well as dopamine neurotransmission.
- Drugs to treat cognitive disorders are diverse. *Methylphenidate* and *Adderall* are prescribed to treat ADHD. *Modafinil* is prescribed to treat narcolepsy and has been suggested to be helpful for ADHD. Antidementia drugs such as acetylcholinesterase inhibitors are prescribed to treat the symptoms of Alzheimer's disease. Some of these and related drugs have been suggested as cognitive enhancing agents.
- The major drug to treat movement disorders such as Parkinson's disease is L-DOPA, a substance that will cross the blood-brain barrier and become converted into dopamine.
- *Analgesics* are prescribed to treat pain. Exemplified by morphine, these drugs bind to particular neurotransmitter receptors called endorphine.
- *Antiepileptic* drugs are given to prevent various forms of seizures. Exemplified by phenytoin, some of these drugs impede the propogation of nerve impulses. Others, such as benzodiazepines, enhance the GABA inhibition in the brain.
- Recreational psychoactive drugs are used to change perception and mood for entertainment or, perhaps, enlightenment. Why such drugs should results in such experiences is not clear at all. *Psychostimulants*, exemplified by cocaine, amphetamine and Ecstasy inhibit the reuptake and enhance the release of norepinephrine, dopamine and serotonin. Narcotics, exemplified by heroin, produce a sense of euphoria by activating the natural opiate receptors in the brain. *Psychedelics*, exemplified by LSD and mescaline, seem to affect serotonin neurotransmission. The effective compound in cannabis, referred to as THC, is an agonist for a specific second-messenger synaptic system that ultimately inhibits release of certain neurotransmitters. Alcohol affects brain processes in a variety of complex ways. Nicotine in the brain seems to regulate the release of numerous other neurotransmitters.

An important aspect of psychoactive drugs is their addictive properties. Addiction will be considered in detail in Chapter 18, but let's preview what is understood about some of the basic mechanisms. Cocaine, for example, activates dopamine receptors leading to a sense of satisfaction. However, later the dopamine system rebounds leading to a sense of dissatisfaction worse than before the cocaine was taken. Consuming more cocaine leads to a weaker sense of satisfaction because the dopamine system develops a tolerance for the drug; in other words, progressively more must be consumed each time to achieve equivalent senses of satisfaction. However, the rebound leading to dissatisfaction occurs after each consumption, so the downward spiral into addiction proceeds.

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