

4

Methods of Cognitive Neuroscience

The frontiers of scientific discovery are defined as much by the tools available for observation as by conceptual innovation. In the 16th century the Earth was considered the center of the solar system. Simple observation verified it: The sun rose each morning in the east and slowly moved across the sky to set in the west. But the invention of the telescope in 1608 changed astronomers' observational methods. With this new tool, astronomers suddenly found galactic entities that they could track as these objects moved across the night sky. These observations rapidly exposed geocentric theories as painfully wrong. Indeed, within 5 years, Galileo spoke out for a heliocentric universe—a heretical claim that even the powerful Roman Catholic Church could not suppress in the face of new technology.

Theoretical breakthroughs in all scientific domains can be linked to the advent of new methods for observation. The invention of the bubble chamber allowed particle physicists to discover new and unexpected elementary particles such as *mesons*—discoveries that have totally transformed our understanding of the microscopic structure of matter. Gene cloning and sequencing techniques provided the tools for identifying new forms of proteins and for recognizing that these proteins formed previously unknown biological structures, such as the neurotransmitter receptor that binds with tetrahydrocannabinol (THC), the psychoactive ingredient in marijuana. Research in this area is now devoted to searching for endogenous substances that utilize these receptors rather than following the more traditional view that THC produces its effects by binding to receptors linked to known transmitters.

The emergence of cognitive neuroscience has been similarly fueled by new methods, some of which utilize high-technology tools unavailable to scientists of previous generations (Sejnowski & Churchland, 1989).

Positron emission tomography (PET), for instance, has enabled scientists to measure, albeit indirectly, activity in the human brain while people perform simple tasks such as reading or memory retrieval. Brain lesions can be localized with amazing precision owing to methods such as magnetic resonance imaging (MRI). High-speed computers allow investigators to construct elaborate models to simulate patterns of connections and processing. Powerful electron microscopes bring previously unseen neural elements into view.

The real power of these tools, however, is still constrained by the types of problems one chooses to investigate. The dominant theory at any point in time defines the research paradigms and shapes the questions to be explored. The telescope helped Galileo plot the position of the planets with respect to the sun. But without an appreciation of the forces of gravity, he would have been at a loss to provide a causal account of planetary revolution. In an analogous manner, the problems investigated with the new tools of neuroscience are shaped by contemporary ideas of how the brain works in perception.

thought, and action. Put simply, if well-formulated questions are not asked, even the most powerful tools will not provide a sensible answer.

In the preceding chapters we discussed some of the tools that neuroanatomists use to investigate the cellular and gross structures of the nervous system. In this chapter we turn to methods that form the core of cognitive neuroscience research. We focus on methods for study-

ing brain-behavior relationships that are employed by cognitive psychologists, computer modelers, neurophysiologists, and neurologists. Although each of the areas represented by these professionals has blossomed in its own way, the interdisciplinary nature of cognitive neuroscience has depended on the clever ways in which scientists have integrated paradigms across these areas. The chapter concludes with examples of this integration.

WHAT IS COGNITIVE PSYCHOLOGY?

It would be naive to suppose that people have only recently sought to relate behavior to brain function. What marks cognitive neuroscience as a new field for this endeavor is the advent of the paradigms developed in **cognitive psychology**, the study of mental activity as an information-processing problem. Cognitive psychology rests on the assumption that we do not directly perceive and act in the world. Rather, our perceptions, thoughts, and actions depend on internal transformations or computations. Information is obtained by sense organs, but our ability to comprehend that information, to recognize it as something that we have experienced before, and to choose an appropriate response depends on a complex interplay of processes.

As an introduction to the magic of the mind, see what sense you can make of the following passage:

ocacdrgi ot a schrehearc ta maccbriegd ineyurvts, ti edost'n rtaem ni awth rreod eht tteser ni a rwdo rea, eht ylon pirmtoatn gihtn si att het rifts nda satl ttelre eb tat het ghitr clepa, eht srte anc eb a oltla sesm dan ouy anc itlls arde ti owtuthi moprbel. ihst si cebusea eth nuamh nidm sedo otn arde yrvee telre yb stifle, tub eth rdow sa alohew.

Not much, eh? Now take another shot at it:

Aoccdrnig to a rscheearch at Cmabrigde Uinervtisy, it deosn't mtaer in waht oredr the ltteers in a wrod are, the olny iprmtoatnt tihng is taht the frist and lsat ltteer be at the rghit pclae. The rset can be a total mses and you can stil raed it wouhtit porblm. Tihs is bcuseae the huamn mnid deos not raed ervey lteter by istlef, but the wrod as a whole.

It is surprisingly easy to read the second passage, even though only a few words are correctly spelled. As long as the first and last letters of each word are in the correct position, we can accurately infer the correct spelling, especially when the surrounding context helps generate expectations for each word. Simple demon-

strations such as this help us discern the content of mental representations, and thus help us gain insight into how information is manipulated by the mind.

Mental Representations and Transformations

Two key concepts underlie the cognitive approach. The first idea, that information processing depends on internal representations, we usually take for granted. Consider the concept "ball." If we met someone from a planet composed of straight lines, we could try to convey what this concept means in many ways. We could draw a picture of a sphere, we could provide a verbal definition indicating that such a three-dimensional object is circular along any circumference, or we could write a mathematical definition. Each instance is an alternative form of representing the "circular" concept. Whether one form of representation is better than another depends on our visitor. To understand the picture, our visitor would need a visual system and the ability to comprehend the spatial arrangement of a curved drawing. To understand the mathematical definition, our visitor would have to comprehend geometric and algebraic relations. Assuming our visitor had these capabilities, the task would help dictate which representational format was most useful. For example, if we wanted to show that the ball rolls down a hill, a pictorial representation is likely to be much more useful than an algebraic formula.

The second critical notion of cognitive psychology is that mental representations undergo transformations. The need to transform mental representations is most obvious when we consider how sensory signals are connected with stored knowledge in memory. Perceptual representations must be translated into action representations if we wish to achieve a goal. Moreover, information processing is not simply a sequential process from sensation to perception to memory to action. Memory may alter how we perceive something, and the manner in which information is processed is

subject to attentional constraints. Cognitive psychology is all about how we manipulate representations.

Consider the categorization experiment, first introduced by Michael Posner (1986) at the University of Oregon, that is illustrated in Figure 4.1. Two letters are presented simultaneously in each trial. The subject's task is to evaluate whether they are both vowels, both consonants, or one vowel and one consonant. The subject presses one button if the letters are from the same category, and the other button if they are from different categories.

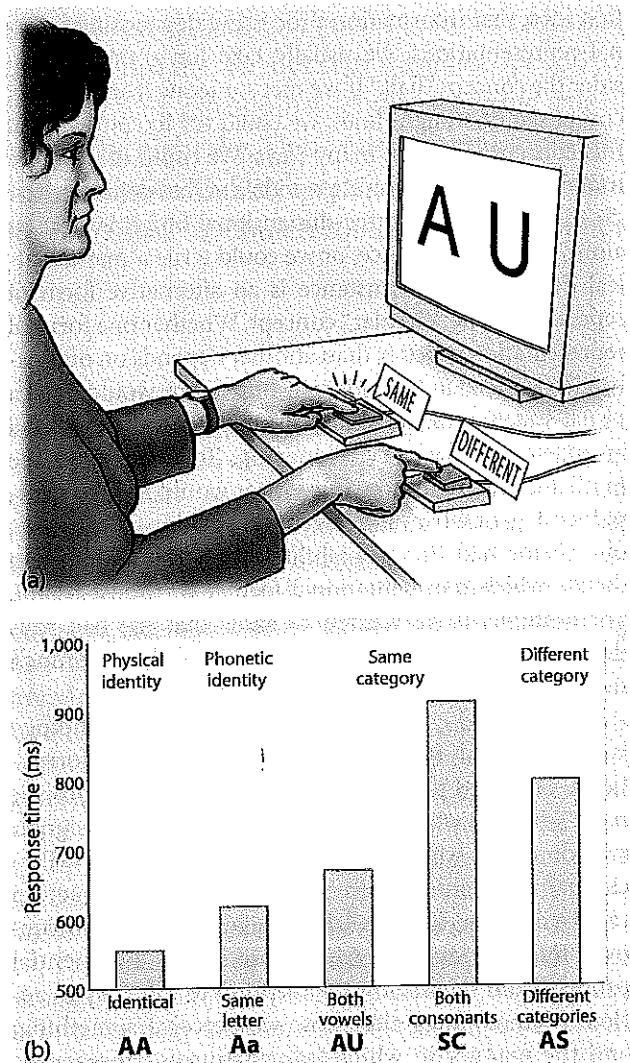
One version of this experiment includes five conditions. In the physical-identity condition, the two letters

are exactly the same. In the phonetic-identity condition, the two letters have the same identity, but one letter is a capital and the other is lowercase. There are two types of same-category conditions, conditions in which the two letters are different members of the same category. In one, both letters are vowels; in the other, both letters are consonants. Finally, in the different-category condition, the two letters are from different categories and can be either of the same type size or of different sizes. Note that the first four conditions—physical identity, phonetic identity, and the two same-category conditions—require the “same” response: On all three types of trials, the correct response is that the two letters are from the same category. Nonetheless, as Figure 4.1b shows, response latencies differ significantly. Subjects respond fastest to the physical-identity condition, next fastest to the phonetic-identity condition, and slowest to the same-category condition, especially when the two letters are both consonants.

The results of Posner's experiment suggest that we derive multiple representations of stimuli. One representation is based on the physical aspects of the stimulus. In this experiment, it is a visually derived representation of the shape presented on the screen. A second representation corresponds to the letter's identity. This representation reflects the fact that many stimuli can correspond to the same letter. For example, we can recognize that A, a, and *a* all represent the same letter. A third level of abstraction represents the category to which a letter belongs. At this level, the letters A and E activate our internal representation of the category “vowel.” Posner maintains that different response latencies reflect the degrees of processing required to do the letter-matching task. By this logic, we infer that physical representations are activated first, phonetic representations next, and category representations last.

This experiment provides a powerful demonstration that, even with simple stimuli, the mind derives multiple representations. Other manipulations with this task have explored how representations are transformed from one form to another. In a follow-up study, Posner and his colleagues used a sequential mode of presentation. Two letters were presented again, but a brief interval (referred to as the *stimulus onset asynchrony*, the time between the two stimuli) separated the presentations for the letters. As Figure 4.2 shows, the difference in response time to the physical-identity and phonetic-identity conditions was reduced as the stimulus onset asynchrony became longer. Hence, the internal representation of the first letter is transformed during the interval. The representation of the physical stimulus gives way to the more abstract representation of the letter's phonetic identity.

Figure 4.1 Letter-matching task. (a) In this version of the task, the subject responds “same” when both letters are either vowels or consonants and “different” when they are from different categories. (b) The reaction times vary for different conditions.



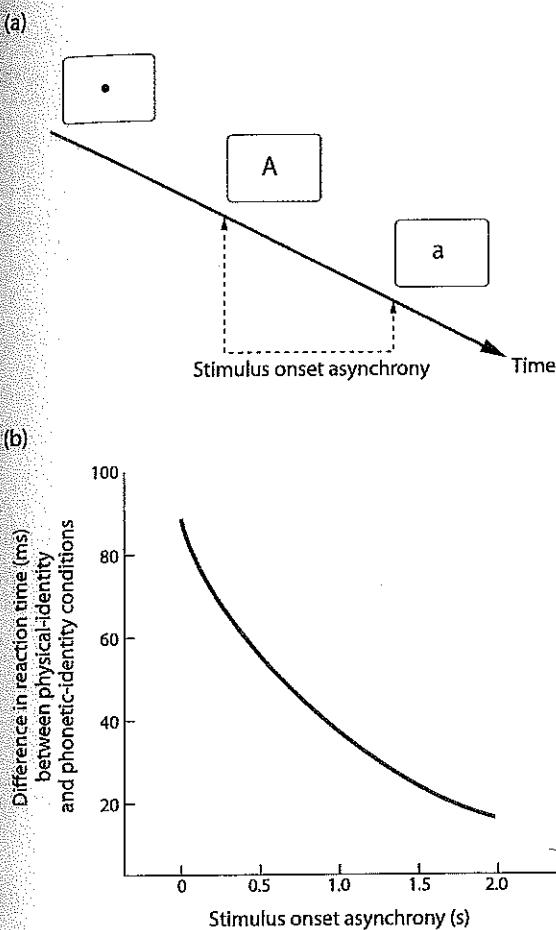


Figure 4.2 (a) The same letter-matching task as in Figure 4.1, except that an interval, defined as the stimulus onset asynchrony, separates the presentation of the two letters. (b) As this interval is lengthened, the difference in the reaction time to the physical-identity and phonetic-identity conditions becomes smaller, suggesting a transformation of the representation into a more abstract code.

As you may have experienced personally, experiments such as these elicit as many questions as answers. Why do subjects take longer to judge that two letters are consonants than they do to judge that two letters are vowels? Would the same advantage for identical stimuli exist if the letters were spoken? What about if one letter were visual and the other were auditory? Suppose that the task were to judge whether two letters were physically identical. Would manipulating the stimulus onset asynchrony affect reaction times in this version? Cognitive psychologists address these questions and then devise methods for inferring the mind's machinery from observable behaviors.

In the preceding example, the primary dependent variable was reaction time, the speed with which subjects make their judgments. Reaction time experiments utilize the chronometric methodology. *Chronometric* comes from the Greek words *chronos* ("time") and *metron* ("measure"). The chronometric study of the mind is essential for cognitive psychologists because mental events occur rapidly and efficiently. If we consider only whether a person is correct or incorrect on a task, we miss subtle differences in performance. Measuring reaction time permits a finer analysis of internal processes. In addition to measuring processing time as a dependent variable, chronometric manipulations can be applied to independent variables, as with the letter-matching experiment in which the stimulus onset asynchrony was varied.

Characterizing Mental Operations

Suppose you arrive at the grocery store and discover that you forgot to bring your shopping list. As you wander up and down the aisles, you gaze upon the thousands of items lining the shelves, hoping that they will help prompt your memory. Perhaps you cruise through the pet food section, but when you come to the dairy section you hesitate: Was there a carton of eggs in the refrigerator? Was the milk supply low? Were there any cheeses not covered by a 6-month rind of mold?

This memory retrieval task draws on a number of cognitive capabilities. A fundamental goal of cognitive psychology is to identify the different mental operations that are required to perform tasks such as these. Not only are cognitive psychologists interested in describing human performance—the observable behavior of humans and other animals—but also they seek to identify the internal processing that underlies this performance. A basic assumption of cognitive psychology is that tasks are composed of a set of mental operations. Mental operations involve taking a representation as an *input* and performing some sort of process on it, thus producing a new representation, or *output*. As such, mental operations are processes that generate, elaborate on, or manipulate mental representations. Cognitive psychologists design experiments to test hypotheses about mental operations.

Consider an experimental task introduced by Saul Sternberg (1975) when he was working at Bell Laboratories. The task bears some similarity to the problem faced by an absentminded shopper, except that in Sternberg's task, the difficulty is not so much in terms of forgetting items in memory, but rather in comparing sensory information with representations that are active

in memory. On each trial, the subject is first presented with a set of letters to memorize (Figure 4.3a). The memory set could consist of one, two, or four letters. Then a single letter is presented, and the subject must decide if this letter was part of the memorized set. The subject presses one button to indicate that the target was part of the memory set ("yes" response) and a second button to indicate that the target was not part of the set ("no" response). Once again the primary dependent variable is reaction time.

Sternberg postulated that, to respond on this task, the subject must engage in four primary mental operations (Figure 4.3b):

1. *Encode*. The subject must identify the visible target.
2. *Compare*. The subject must compare the mental representation of the target with the representations of the items in memory.
3. *Decide*. The subject must decide whether the target matches one of the memorized items.
4. *Respond*. The subject must respond appropriately for the decision made in Step 3.

Note that each of these operations is likely to be composed of additional operations. For example, responding might be subdivided into processes involved in selecting the appropriate finger and processes involved in activating the muscles that make the finger move. Nonetheless, by postulating a set of mental operations, we can devise experiments to explore how putative mental operations are carried out.

A basic question for Sternberg was how to characterize the efficiency of recognition memory. Assuming that all items in the memory set are actively represented, the recognition process might work in one of two different ways: A highly efficient system might compare a representation of the target with all of the items in the memory set simultaneously. On the other hand, the recognition operation might be limited in terms of how much information it can handle at any point in time. For example, it might require the input to be compared successively to each item in memory.

Sternberg realized that the reaction time data could distinguish between these two alternatives. If the comparison process can be simultaneous for all items—what is called a *parallel* process—then reaction time should be independent of the number of items in the memory set. But if the comparison process operates in a sequential, or *serial*, manner, then reaction time should slow down as the memory set becomes larger, because more time is required to compare an item with a large memory list than with a small memory list. Sternberg's

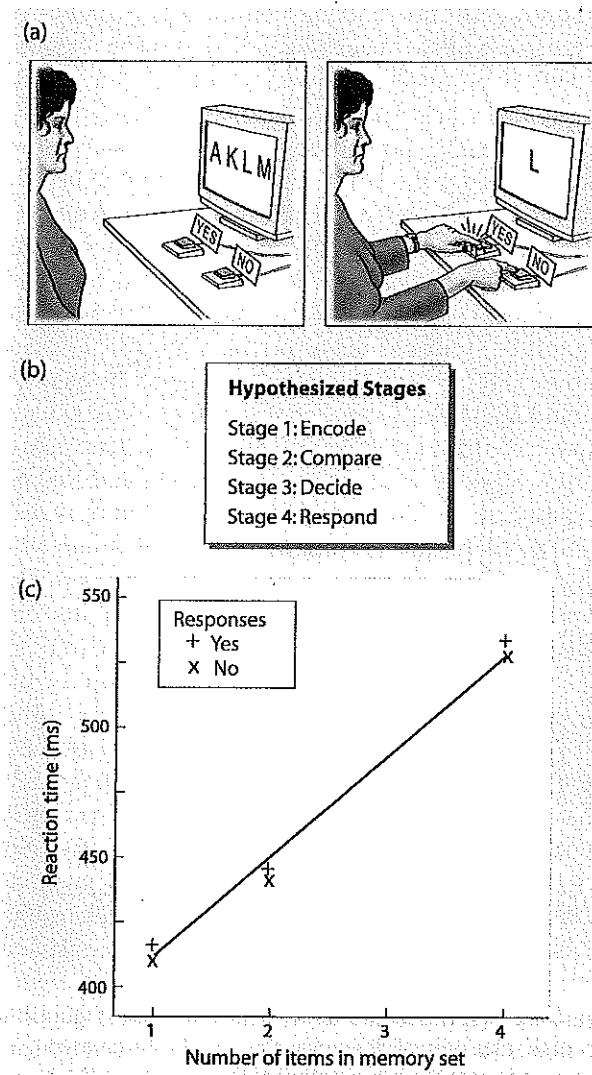


Figure 4.3 Memory comparison task. (a) The subject is shown a set of one, two, or four letters and is asked to memorize them. After a delay, a single probe letter appears, and the subject indicates whether that letter was a member of the memory set. (b) Performance of this task is hypothesized to require four different mental operations. (c) Reaction time increases with set size, indicating that the target letter must be compared with the memory set sequentially rather than in parallel.

results convincingly supported the serial hypothesis. In fact, reaction time increased in a constant, or linear, manner with set size, and the functions for the "yes" and "no" trials were essentially identical (Figure 4.3c).

The parallel, linear functions allowed Sternberg to make two inferences about the mental operations associated with this task. First, the linear increase in reaction time as the set size increased implied that the memory comparison operation took a fixed amount of internal

processing time. In the initial study, the slope of the function was approximately 40 ms per item, implying that it takes about 40 ms for each successive comparison of the target to the items in the memory set. This does not mean that this value represents a fixed property of memory comparison. It is likely to be affected by factors such as task difficulty (e.g., whether the nontarget items in the memory set are similar or dissimilar to the target item) and experience. Nonetheless, the experiment demonstrates how mental operations can be evaluated both qualitatively and quantitatively from simple behavioral tasks.

Second, the fact that the two functions were parallel implied that subjects compared all of the memory items to the target before responding. If subjects had terminated the comparison as soon as a match was found, then the slope of the "no" function should have been twice as steep as the slope of the "yes" function. This follows because in "no" trials, all of the items have to be checked. With "yes" trials, on average only half the items need to be checked before a match is found. The fact that the functions were parallel implies that comparisons were carried out on all items in what is called an *exhaustive search* (as opposed to a serial, self-terminating search). An exhaustive process seems illogical, though. Why continue to compare the target to the memory set after a match has been detected? One possible answer is that it is easier to store the result of each comparison for later evaluation than to monitor "online" the results of successive comparisons.

Although memory comparison appears to involve a serial process, much of the activity in our mind operates in parallel. A classic demonstration of parallel processing is the word superiority effect (Reicher, 1969). In this experiment, a stimulus is shown briefly and subjects are asked which of two target letters (e.g., A or E) was presented. The stimuli can be composed of words, nonsense letter strings, or letter strings in which every letter is an X except for the target letter (Figure 4.4). Brief presentation times are used so that errors will be observed, with the critical question centering on whether the context affects performance. *Word superiority effect* refers to the fact that subjects are most accurate when the stimuli are words. Somewhat counterintuitively, this finding suggests that we do not need to identify all of the letters of a word before we recognize the word. Rather, when we are reading a list of words, representations corresponding to the individual letters and to the entire word are activated in parallel for each item. Performance is facilitated because both representations can provide information as to whether the target letter is present. A word-level representation is not possible with nonsense

Does the stimulus contain an A or an E?

Condition	Stimulus	Accuracy
Word	RACK	90%
Nonsense string	KARC	80%
Xs	XAXX	80%

Figure 4.4 Word superiority effect. Subjects are more accurate in identifying the target vowel when it is embedded in a word. This result suggests that letter and word levels of representation are activated in parallel.

words and letter strings, and thus judgments must be based solely on letter-level representation.

Constraints on Information Processing

In the memory search experiment, information processing operates in a certain manner because the memory comparison process is limited. The subjects cannot compare the target item to all of the items in the memory set simultaneously. An important question is whether this limitation reflects properties that are specific to memory or a more general processing constraint. Perhaps the amount of internal processing that people can do at any one time is limited regardless of the task. An alternative explanation is that processing limitations are task specific. Processing constraints are defined only by the particular set of mental operations associated with a particular task. For example, although the comparison of a probe item to the memory set might require a serial operation, encoding might occur in parallel such that it would not matter whether the probe was presented by itself or among a noisy array of competing stimuli.

Exploring the limitations in task performance is a central concern for cognitive psychologists. Consider a simple color-naming task that was devised in the early 1930s by an aspiring doctoral student, J. R. Stroop (1935; for a review, see MacLeod, 1991), and that has become one of the most widely employed tasks in all of cognitive psychology. In this task, a list of words is presented and the subject is asked to name the color of each stimulus as fast as possible. As Figure 4.5 illustrates, it is

Color matches word	Color without word	Color doesn't match word
RED	XXXXX	GREEN
GREEN	XXXXX	BLUE
RED	XXXXX	RED
BLUE	XXXXX	BLUE
BLUE	XXXXX	GREEN
GREEN	XXXXX	RED
BLUE	XXXXX	GREEN
RED	XXXXX	BLUE

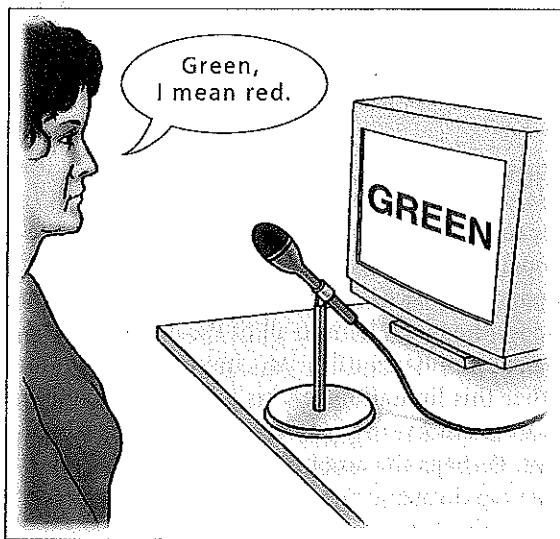


Figure 4.5 Stroop task. Time yourself as you work through each column, naming the color of the ink of each stimulus as fast as possible. Assuming that you do not squint to blur the words, it should be easy to read the first and second columns but quite difficult to read the third.

much easier to do this task when the words match the ink colors.

The Stroop effect powerfully demonstrates the multiplicity of mental representations. The stimuli in this task appear to activate at least two separable representations. One representation corresponds to the color of each stimulus; it is what allows the subject to perform the task. The second representation corresponds to the color concept associated with the words. The fact that

you are slower to name the colors when the ink color and words are mismatched indicates that this representation is activated even though it is irrelevant to the task. Indeed, the activation of a representation based on the words rather than the colors of the words appears to be automatic. The Stroop effect persists even after thousands of trials of practice, reflecting the fact that skilled readers have years of practice in analyzing letter strings for their symbolic meaning. On the other hand, the interference from the words is markedly reduced if the response requires a key press rather than a vocal response. Thus, the word-based representations are closely linked to the vocal response system and have little effect when the responses are produced manually.

Another method used to examine constraints on information processing involves dual tasks. For these studies, performance on a primary task alone is compared to performance when that task is carried out concurrently with a secondary task. The decrement in primary-task performance during the dual-task situation helps elucidate the limits of cognition. Sophisticated use of dual-task methodology also can identify the exact source of interference. For example, the Stroop effect is not reduced when the color-naming task is performed simultaneously with a secondary task in which the subject must judge the pitch of an auditory tone. However, if the auditory stimuli for the secondary task are a list of words and the subject must monitor this list for a particular target, the Stroop effect is attenuated. It appears that the verbal demands of the secondary task interfere with the automatic activation of the word-based representations in the Stroop task, thus leaving the color-based representations relatively free from interference.

The efficiency of our mental abilities and the way in which mental operations interact can change with experience. The beginning driver has her hands rigidly locked to the steering wheel; within a few months, though, she is unfazed to steer with her left hand while maintaining a conversation with a passenger and using her right hand to scan for a good radio station. Even more impressive is the fact that, with extensive practice, people can become proficient at simultaneously performing two tasks that were originally quite incompatible.

Elizabeth Spelke and her colleagues at Cornell University studied how well college students read for comprehension while taking dictation (Spelke et al., 1976). Prior to any training, their subjects could read about 400 words per minute when faced with difficult reading material such as modern short stories. As we would expect, this rate fell to 280 words per minute when the subjects were required to simultaneously take dictation,

and their comprehension of the stories was also impaired. Remarkably, after 85 hours of training spread over a 17-week period, the students' proficiency in reading while taking dictation was essentially as good as

when reading alone. The results offer an elixir for all college students. Imagine finishing the reading for an upcoming psychology examination while taking notes during a history lecture!

COMPUTER MODELING

The computer is a powerful metaphor for cognitive neuroscience. Both the brain and the computer chip are impressive processing machines, capable of representing and transforming large amounts of information. Although there are vast differences in how these machines process information, cognitive scientists use computers to simulate cognitive processes. To *simulate* is to imitate, to reproduce behavior in an alternative medium. The simulated cognitive processes are commonly referred to as *artificial intelligence*—artificial in the sense that they are artifacts, human creations—and intelligent in that the computers perform complex functions. Computer programs control robots on factory production lines, assist physicians in making differential diagnoses or in detecting breast cancer, and create models of the universe in the first nanoseconds after the big bang.

Many commercial computer applications are developed without reference to how brains think. More relevant to our present concerns are the efforts of cognitive scientists to create models of cognition (Rumelhart et al., 1986). In these investigations, simulations are designed to mimic behavior and the cognitive processes that support that behavior. The computer is given input and then must perform internal operations to create a behavior. By observing the behavior, the researcher can assess how well it matches behavior produced by a real mind. Of course, to get the computer to succeed, the modeler must specify how information is represented and transformed within the program. To do this, concrete hypotheses regarding the “mental” operations needed for the machine must be generated. As such, computer simulations provide a useful tool for testing theories of cognition. Successes and failures of models give valuable insights to the strengths and weaknesses of a theory.

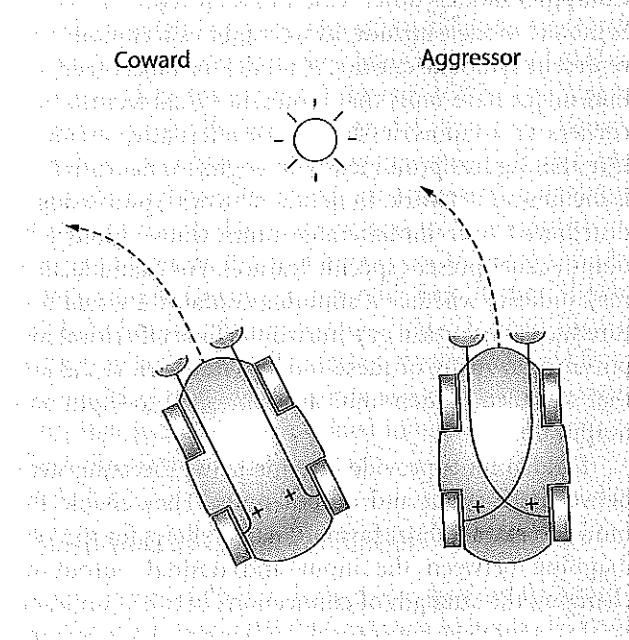
Models Are Explicit

Computer models of cognition are useful because they can be analyzed in detail. In creating a simulation, the researcher must be completely explicit; the way the computer represents and processes information must be totally specified. This does not mean that a computer's

operation is always completely predictable and that the outcome of a simulation is known in advance. Computer simulations can incorporate random events or be on such a large scale that analytic tools do not reveal the solution. But the internal operations, the way information is computed, must be determined. Computer simulations are especially helpful to cognitive neuroscientists in recognizing problems that the brain must solve to produce coherent behavior.

Braitenberg (1984) gave elegant examples of how modeling brings insights to information processing. Imagine observing the two creatures shown in Figure 4.6 as they move about a minimalist world consisting of a single heat source such as a sun. From the outside, the creatures look identical: They both have two sensors and

Figure 4.6 Two very simple vehicles, each equipped with two sensors that excite motors on the rear wheels. The wheel linked to the sensor closest to the sun will turn faster than the other wheel, thus causing the vehicle to turn. Simply changing the wiring scheme from uncrossed to crossed radically alters the behavior of the vehicles. The “coward” will always avoid the source, whereas the “aggressor” will relentlessly pursue it.



four wheels. Despite this similarity, their behavior is distinct: One creature moves away from the sun, and the other homes in on it. Why the difference? As outsiders with no access to the internal operations of these creatures, we might conjecture that they have had different experiences and so the same input activates different representations. Perhaps one was burned at an early age and fears the sun, and maybe the other likes the warmth.

As their internal wiring reveals, however, the behavioral differences depend on how the creatures are wired. The uncrossed connections make the creature on the left turn away from the sun; the crossed connections force the creature on the right to orient toward it. Thus, the two creatures' behavioral differences arise from a slight variation in how sensory information is mapped onto motor processes.

These creatures are exceedingly simple—and inflexible in their actions. At best, they offer only the crudest model of how an invertebrate might move in response to a phototropic sensor. The point of Braitenberg's example is not to model a behavior; rather, it represents how a single computational change—from crossed to uncrossed wiring—can yield a major behavioral change. When interpreting such a behavioral difference, we might postulate extensive internal operations and representations. When we look inside Braitenberg's models, however, we see that there is no difference in how the two models process information, but only a difference in their patterns of connectivity.

Representations in Computer Models

Computer models differ widely in their representations. Symbolic models include, as we might expect, units that represent symbolic entities. A model for object recognition might have units that represent visual features like corners or volumetric shapes. An alternative architecture that figures prominently in cognitive neuroscience is the **neural network**. In neural networks, processing is distributed over innumerable units whose input and output can represent specific features. For example, they may indicate whether a stimulus contains a visual feature such as a vertical or a horizontal line. Of critical importance in many of these models, however, is the fact that so-called hidden units are connected to input and output units.

Hidden units provide intermediate processing steps between the input and output units. They enable the model to extract the information that allows for the best mapping between the input and desired output by changing the strength of connections between units. To do this, a modeler must specify a *learning rule*, a quanti-

tative description of how processing within the model changes. With most learning rules, changes are large when the model performs poorly and small when the model performs well. Other learning algorithms are even simpler. For example, whenever two neighboring nodes are simultaneously active, the link between them is strengthened; if one is active when the other is silent, then the link between them is weakened.

Models can be very powerful for solving complex problems. Simulations cover the gamut of cognitive processes, including perception, memory, language, and motor control. One of the most appealing aspects of neural networks is that the architecture resembles, at least superficially, the nervous system. In these models, processing is distributed across many units, similar to the way that neural structures depend on the activity of many neurons. The contribution of any unit may be small in relation to the system's total output, but complex behaviors can be generated by the aggregate action of all units. In addition, the computations in these models are simulated to occur in parallel. The activation levels of the units in the network can be updated in a relatively continuous and simultaneous manner.

Computational models can vary widely in the level of explanation they seek to provide. Some models simulate behavior at the systems level, seeking to show how cognitive operations such as motion perception or skilled movements can be generated from a network of interconnected processing units. In other cases, the simulations operate at a cellular or even molecular level. For example, neural network models have been used to investigate how the variation in transmitter uptake is a function of dendrite geometry (Volfovsky et al., 1999). The amount of detail that must be incorporated into the model will be dictated to a large extent by the type of question being investigated. Many of these problems are difficult to evaluate without simulations, either experimentally because the available experimental methods are insufficient or mathematically because the solutions become too complicated given the many interactions of the processing elements.

An appealing aspect of neural network models, especially for people interested in cognitive neuroscience, is that "lesion" techniques demonstrate how a model's performance changes when its parts are altered. Unlike strictly serial computer models that collapse if a circuit is broken, neural network models degrade gracefully: The model may continue to perform appropriately after some units are removed, because each unit plays only a small part in the processing. Artificial lesioning is thus a fascinating way to test a model's validity. At the first level, a model is constructed to see if it adequately simu-

lates normal behavior. Then “lesions” can be made to see if the breakdown in the model’s performance resembles the behavioral deficits observed in neurological patients.

Models Lead to Testable Predictions

The contribution of computer modeling usually goes beyond the assessment of whether a model succeeds in mimicking a cognitive process. Models can generate novel predictions that can be tested with real brains. An example of the predictive power of computer modeling comes from the work of Szabolcs Kali of the Hungarian Academy of Sciences and Peter Dayan at the University College London (Kali & Dayan, 2004). Their computer models were designed to ask questions about how people store and retrieve information in memory about specific events—what is called *episodic memory* (see Chapter 8). Observations from the neurosciences suggest that the *formation* of episodic memories depends critically on the hippocampus and adjacent areas of the medial temporal lobe, whereas the *storage* of such memories involves the neocortex. Kali and Dayan used a computer model to explore a specific question: How is access to stored memories maintained in a system where the neocortical connections are ever changing (see the discussion on cortical plasticity in Chapter 3)? Does the maintenance of memories over time require the reactivation of hippocampal–neocortical connections, or can neocortical representations remain stable despite fluctuations and modifications over time?

The model architecture was based on anatomical facts regarding patterns of connectivity between the hippocampus and neocortex (Figure 4.7). The model was then trained on a set of patterns that represented distinct episodic memories. For example, one might correspond to the first time you visited the Pacific Ocean; another, to the lecture in which you first learned about the Stroop effect. Once the model had mastered the memory set by showing that it could correctly recall a full episode when given only partial information, it was tested on a consolidation task. Could old memories remain after the hippocampus was disconnected from the cortex if cortical units continued to follow their initial learning rules? In essence, this was a test of whether lesions to the hippocampus would disrupt long-term episodic memory. The results indicated that episodic memory became quite impaired when the hippocampus and cortex were disconnected. Thus, the model predicts that hippocampal *reactivation* is necessary for maintaining even well-consolidated episodic memories. In the model, this maintenance process requires a mechanism that keeps hippocampal and neocortical

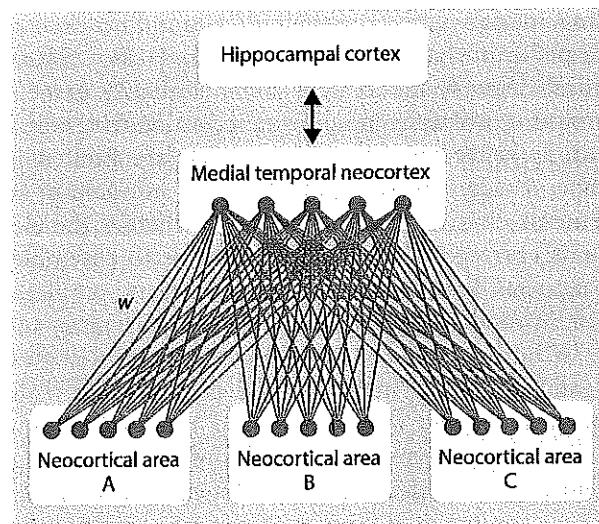


Figure 4.7 Computational model of episodic memory. “Neurons” (●) in neocortical areas A, B, and C are connected in a bidirectional manner to “neurons” in the medial temporal neocortex, which is itself connected bidirectionally to the hippocampus. Areas A, B, and C represent highly processed inputs (e.g., inputs from visual, auditory, or tactile domains). As the model learns, it extracts categories, trends, and correlations from the statistics of the inputs (or patterns of activations) and converts these to weights (w) that corresponds to the strengths of the connections. Prior to learning, the weights might be equal or set to random values. With learning, the weights become adjusted to reflect correlations between the processing units.

representations in register with one another, even as the neocortex undergoes subtle changes associated with daily learning.

This modeling project was initiated because research on people with lesions of the hippocampus had failed to provide a clear answer about the role of this structure in memory consolidation. The model, based on known principles of neuroanatomy and neurophysiology, could be used to test specific hypotheses concerning one type of memory, episodic memory, and to direct future research. Of course, the goal here is not to make a model that has perfect memory consolidation. Rather, it is to ask how human memory works. Thus, human experiments can be conducted to test predictions derived from the model, as well as to generate new empirical observations that must be incorporated into future versions of the computational model.

Limitations of Computer Models

Computer modeling is limited as a method for studying the operation of living nervous systems. For one

thing, models always require radical simplifications of the nervous system. Although the units in a typical neural network model bear some similarity to neurons—for example, nonlinear activation rules produce spikelike behavior—the models are limited in scope, usually consisting of just a few hundred or so elements, and it is not always clear whether the elements correspond to single neurons or to ensembles of neurons. Second, some requirements and problems arise in modeling work, particularly in learning, and are at odds with what we know occurs in biological organisms. Many network models require an “all-knowing” teacher who “knows” the right answer and can be used to correct the behavior of the internal elements. These models can also suffer *catastrophic interference*, the loss of old information when new material is presented.

Third, most modeling efforts are restricted to relatively narrow problems, such as demonstrating how the Stroop effect can be simulated by postulating separate

word name and word color representations under the control of a common attentional system. As such, they provide useful computational tests of the viability of a particular hypothesis but are typically less useful for generating new predictions. Moreover, as some critics have argued, unlike experimental work that, by its nature, is cumulative, modeling research tends to be conducted in isolation. There may be lots of ways to model a particular phenomenon, but less effort has been devoted to devising critical tests that pit one theory against another.

These limitations are by no means insurmountable, and we should expect the contribution of computer simulations to continue to grow in the cognitive neurosciences. Indeed, the trend in the field is for modeling work to be more constrained by neuroscience, with researchers replacing generic processing units with elements that embody the biophysics of the brain. In a reciprocal manner, computer simulations provide a useful way to develop theory, which may then aid researchers in designing experiments and interpreting results.

EXPERIMENTAL TECHNIQUES USED WITH ANIMALS

The use of animals for experimental procedures has played a critical role in the medical and biological sciences. Although many insights can be gleaned from careful observations of people with neurological disorders, as we will see throughout this book, such methods are, in essence, correlational. We can observe how behavior is disturbed following a neurological insult, but it can be difficult to pinpoint the exact cause of the disorder. For one thing, insults such as stroke or tumor tend to be quite large, with the damage extending across many neural structures. Moreover, damage in one part of the brain may disturb function in other parts of the brain that are spared. There is also increasing evidence that the brain is a plastic device: Neural function is constantly being reshaped by our experiences, and such reorganization can be quite remarkable following neurological damage.

The use of animals in scientific research allows researchers to adopt a more experimental approach. Because neural function depends on electrochemical processes, neurophysiologists have developed techniques that can be used to measure and manipulate neuronal activity. Some of these techniques measure and record cell activity, in either passive or in active conditions. Others manipulate activity by creating lesions through the destruction or temporary inactivation of targeted brain regions. Lesion studies in animals face the same limita-

tions associated with the study of human neurological dysfunction. However, modern techniques allow the researcher to be highly selective in creating these lesions, and the effects of the damage can be monitored carefully following the surgery.

Single-Cell Recording

The most important technological advance in **neurophysiology**—perhaps in all of neuroscience—was the development of methods to record the activity of single neurons in laboratory animals. With this method, the understanding of neural activity advanced a quantum leap. No longer did the neuroscientist have to be content with describing nervous system action in terms of functional regions. **Single-cell recording** enabled researchers to describe response characteristics of individual elements.

In single-cell recording, a thin electrode is inserted into an animal's brain. If the electrode is in the vicinity of a neuronal membrane, electrical changes can be measured (see Chapter 2). Although the surest way to guarantee that the electrode records the activity of a single cell is to record intracellularly, this technique is difficult, and penetrating the membrane frequently damages the cell. Thus, single-cell recording is typically done extracellularly. With this method, the electrode is situated on the outside of the neuron. The problem with this ap-

proach is that there is no guarantee that the changes in electrical potential at the electrode tip reflect the activity of a single neuron. It is more likely that the tip will record the activity of a small set of neurons. Computer algorithms are used to differentiate this pooled activity into the contributions from individual neurons.

Neurons are constantly active, even in the absence of stimulation or movement. This baseline activity varies widely from one brain area to another. For example, some cells within the basal ganglia have spontaneous firing rates of over 100 spikes/s, whereas cells in another basal ganglia region have a baseline rate of about 1 spike/s. These spontaneous firing levels fluctuate. The primary goal of single-cell recording experiments is to determine experimental manipulations that produce a consistent change in the response rate of an isolated cell. Does the cell increase its firing rate when the animal moves its arm? Is this change specific to movements in a particular direction? Does the firing rate for that movement depend on the outcome of the action (e.g., the food morsel to be reached)? As interesting, what makes the cell decrease its response rate?

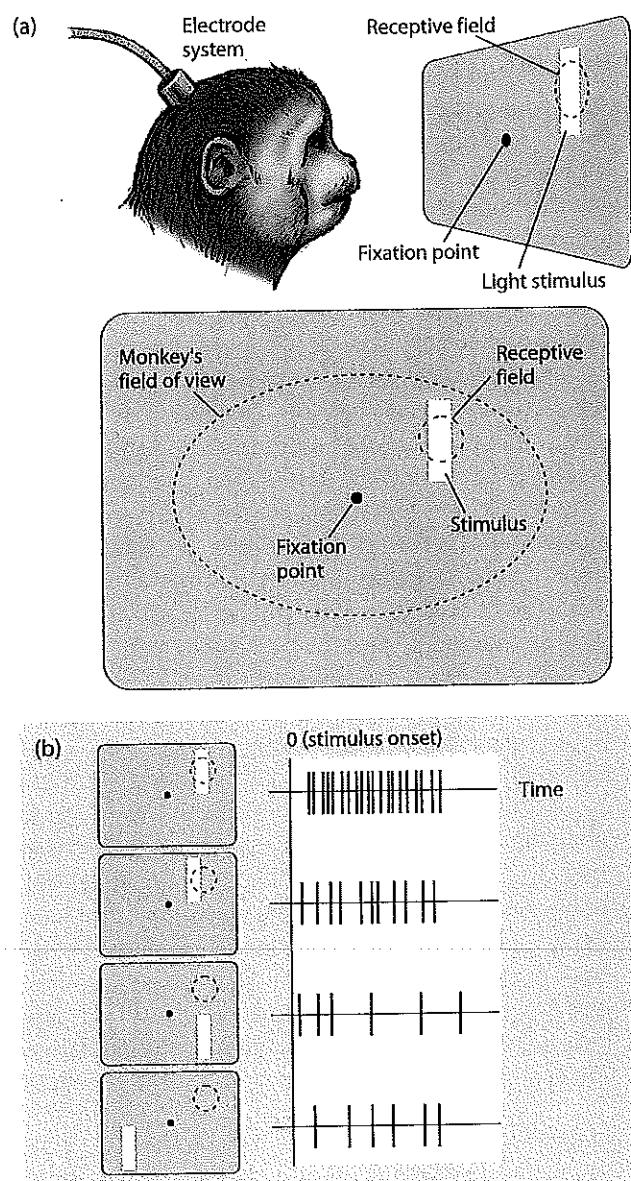
The neurophysiologist is interested in what causes change in the synaptic activity of a neuron. The experimenter seeks to determine the response characteristics of individual neurons by correlating their activity with a given stimulus pattern or behavior. The technique has been used in almost all regions of the brain in a wide range of nonhuman species. For sensory neurons, the experimenter might manipulate the type of stimulus presented to the animal. For motor neurons, recordings can be made as the animal performs a task or moves about the cage. Some of the most recent advances in neurophysiology have come about as researchers probe higher brain centers to examine changes in cellular activity related to goals, emotions, and rewards.

In the typical neurophysiological experiment, recordings are obtained from a series of cells in a targeted area of interest. In this manner, a functional map can describe similarities and differences between neurons in a specified cortical region. One area where the single-cell method has been used extensively is the study of the visual system of primates. In a typical experiment the researcher targets the electrode to a cortical area that contains cells thought to respond to visual stimulation. Once a cell has been identified, the researcher tries to characterize its response properties.

A single cell is not responsive to all visual stimuli. A number of stimulus parameters might correlate with the variation in the cell's firing rate; examples include the shape of the stimulus, its color, and whether or not it is moving (see Chapter 5). An important factor is the loca-

tion of the stimulus. As Figure 4.8 shows, all visually sensitive cells respond to stimuli in only a limited region of space. This region of space is referred to as that cell's **receptive field**. For example, some neurons respond when the stimulus is located in the lower left portion of

Figure 4.8 Electrophysiological methods are used to identify the response characteristics of cells in the visual cortex. (a) While the activity of a single cell is monitored, the monkey is required to maintain fixation, and stimuli are presented at various positions in its field of view. (b) The vertical lines to the right of each stimulus correspond to individual action potentials. The cell fires vigorously when the stimulus is presented in the upper right quadrant, thus defining the upper right as the receptive field for this cell.





THE COGNITIVE NEUROSCIENTIST'S TOOLKIT

The Ethics and Practice of Animal Research

Students on most university campuses are familiar with the annual protests during World Laboratory Animal Liberation Week by groups opposed to the use of animals for research purposes. These groups hand out inflammatory pamphlets graphically depicting how researchers callously exploit laboratory rats, cats, and especially monkeys in their pursuit of knowledge. Although many of the protests are peaceful and law-abiding, there have been numerous incidents of violence against people and property: Windows have been smashed, equipment destroyed, animals kidnapped, and professors harassed at their homes. The protesters argue that university administrators have become dependent on the money generated by public and private grants supporting "frivolous and unnecessary" research, and thus they are forced to resort to more dramatic measures to raise the public's consciousness.

In response, scientists have played offense, eager to educate the public about the importance of these forms of research. Almost all that we know about the structure and physiology of the nervous system has depended on invasive studies of animals. Human autopsies can provide only the crudest understanding of the anatomy of the nervous system. The fine structure that is revealed by sophisticated staining procedures is not possible unless the stains are injected into live animals and allowed to propagate along metabolically active tissue. All that we know about the operation of single neurons has been made possible only by the use of laboratory animals.

This basic research does not exist in a vacuum, sought after as part of an ephemeral quest for knowledge. Scientists and public policy makers have long recognized that advances in medicine depend on the ability to carry out both basic research and clinically inspired research. Human studies of brain metabolites may reveal that excessive dopamine levels are associated with schizophrenia, but animal research is essential for understanding where dopamine is produced and the metabolic processes that regulate the production and uptake of this transmitter. Only rarely have medical treatments been discovered in the absence of

animal models. In most cases, new medical treatments become available only after years of careful experimental work with animals, first involving years of basic research, then followed by the careful development of clinical measures involving animal studies.

The scientific research community has served as a visible target for animal rights groups. One reason has been a few well-publicized cases in which videotapes or photographs were used to demonstrate the extreme experimental manipulations being practiced on laboratory animals. Two of the more well-known cases involved monkeys. In one case the animals were subjected to severe blows to the head as part of a study of head trauma in car accidents. In the other case, the animals were in poor health after undergoing fetal surgery to destroy sensory fibers. The latter case resulted in the only recorded U.S. conviction of a scientist on animal cruelty charges.

Although abuses most certainly exist, research with laboratory animals is closely regulated by both research institutions and federal agencies. All research protocols must be approved by institutional animal care and use committees that include not only scientific peers but also lay members of the community. Three basic principles must be met for any research project to be certified (Rowan & Rollin, 1983). First, the goals of the research must be articulated clearly, showing that the studies are worthwhile and will advance our knowledge of the nervous system. Second, experiments must be conducted so as to minimize pain and distress through the use of anesthetics and analgesics. Any animals that show evidence of suffering must be humanely destroyed. Third, alternative methods that might yield similar knowledge must be considered.

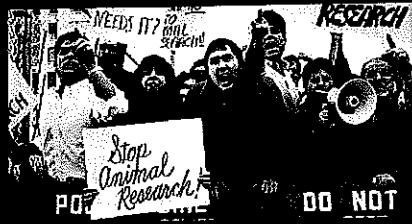
The evidence suggests that these codes are strictly followed. In almost all studies involving surgical procedures, animals are provided with anesthesia. The rare exceptions are those in which the focus is how the brain reacts to pain—an important problem faced by people recovering from surgery. The argument that computer models can serve as realistic substitutes for animal research is specious. Current models can simulate only the simplest of neural functions, and even these models are

useful only in terms of how well they converge with the results of studies on living organisms.

Nonetheless, it is important for the public to debate the fundamental question of whether it is ethical for humans to exploit other species for their own benefit. A researcher in 1898 was quoted as saying, "Animals have no more rights than inanimate objects, and it is no

worse from an ethical point of view to flay the forearm of an ape or lacerate the leg of a dog than to rip open the sleeve or rend a pair of pantaloons." It is clear that few would take this stance in our modern society. We must understand both the benefits and the costs of animal research in order to form educated opinions on these ethical matters.

Thanks to animal research, they'll be able to protest 20.8 years longer.



According to the U.S. Department of Health and Human Services, animal research has helped extend our life expectancy by 20.8 years. Of course, how you choose to spend those extra years is up to you.

Foundation for Biomedical Research

© Foundation for Biomedical Research, Inc., 2000. All rights reserved.

The morality of using animals for research purposes has been debated for centuries. People on both sides of the debate have recognized the importance of engaging the public—a point underscored by the fact that members of the U.S. Congress receive more letters on this issue than on any other.

the visible field. For other neurons, the stimulus may have to be in the upper left.

The sizes of the receptive fields of visual cells vary; they are smallest in primary visual cortex and become larger in association visual areas. Thus, a stimulus will cause a cell in primary visual cortex to increase its firing rate only when it is positioned in a very restricted region of the visible world. If the stimulus is moved outside this region of space, the cell will return to its spontaneous level of activity. In contrast, displacing a stimulus over a large distance may produce a similar increase in the firing rate of visually sensitive cells in the temporal lobe.

Neighboring cells have at least partially overlapping receptive fields. As a region of visually responsive cells is traversed, there is an orderly relation between the receptive-field properties of these cells and the external world. External space is represented in a continuous manner across the cortical surface: Neighboring cells have receptive fields of neighboring regions of external space (Figure 4.9). As such, cells form a topographic

representation, an orderly mapping between an external dimension such as spatial location and the neural representation of that dimension. In vision, topographic representations are referred to as **retinotopic**.

The retina is composed of a continuous sheet of photoreceptors, neurons that respond to visible light passing through the lens of the eye. Visual cells in subcortical and cortical areas maintain retinotopic information. Thus, if light falls on one spot of the retina, cells with receptive fields spanning this area are activated. If the light moves and falls on a different region of the retina, activity ceases in these cells and begins in other cells whose receptive fields encompass the new region of stimulation. In this manner, visual areas provide a representation of the location of the stimulus. Cell activity within a retinotopic map correlates with (i.e., predicts) the location of the stimulus.

There are other types of topographic maps. In Chapter 3 we reviewed the motor and somatosensory maps along the central sulcus that provide topo-

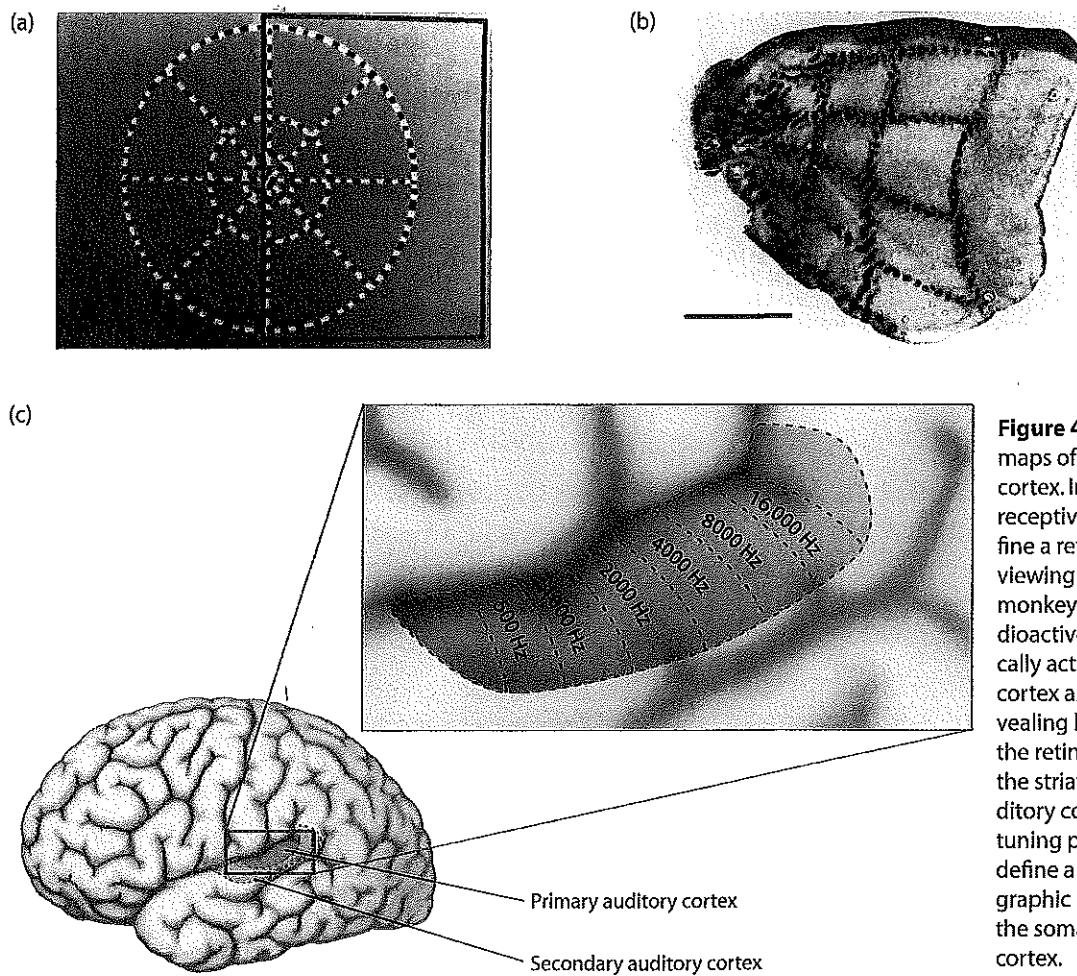


Figure 4.9 Topographic maps of the visual and auditory cortex. In the visual cortex the receptive fields of the cells define a retinotopic map. While viewing the stimulus (a), a monkey was injected with a radioactive agent. (b) Metabolically active cells in the visual cortex absorb the agent, revealing how the topography of the retina is preserved across the striate cortex. (c) In the auditory cortex, the frequency-tuning properties of the cells define a tonotopic map. Topographic maps are also seen in the somatosensory and motor cortex.

graphic representations of the body surface. In a similar sense, auditory areas in the subcortex and cortex contain tonotopic maps, in which the physical dimension reflected in neural organization is the sound frequency of a stimulus. With a tonotopic map, some cells are maximally activated by a 1000-Hz tone, and others by a 5000-Hz tone. In addition, neighboring cells tend to be tuned to similar frequencies. Thus, sound frequencies are reflected in cells that are activated upon the presentation of a sound. Tonotopic maps are sometimes referred to as *cochleotopic* because the cochlea, the sensory apparatus in the ear, contains hair cells tuned to distinct regions of the auditory spectrum.

When the single-cell method was first introduced, neuroscientists were optimistic that the mysteries of brain function would be solved. All they needed was a catalog of contributions by different cells. Yet it soon became clear that, with neurons, the aggregate behavior of cells might be more than just the sum of its parts. The function of an area might be better understood by identification of the correlations in the firing patterns of groups of neurons rather than by identification of the response properties of each individual neuron. This idea has inspired single-cell physiologists to develop new techniques that allow recordings to be made in many neurons simultaneously—what is called **multiunit recording**.

Bruce McNaughton at the University of Arizona studied how the rat hippocampus represents spatial information by simultaneously recording from 150 cells (M. A. Wilson & McNaughton, 1994)! By looking at the pattern of activity over the group of neurons, the researchers were able to show how the rat coded spatial and episodic information differently. Today it is not uncommon to record from over 400 cells simultaneously (Lebedev & Nicolelis, 2006). As we will see in Chapter 7, multiunit recordings from motor areas of the brain are now being used to allow animals to control artificial limbs, a dramatic medical advance that may change the way rehabilitation programs are designed for paraplegics. For example, multiunit recordings can be obtained while people think about actions they would like to perform, and this information can be analyzed by computers to control robotic or artificial limbs.

Lesions

The brain is a complicated organ composed of many structures, including subcortical nuclei and distinct cortical areas. It seems evident that any task a person performs requires the successful operation of many brain

components. A long-standing method of the neurophysiologist has been to study how behavior is altered by selective removal of one or more of these parts. The logic of this approach is straightforward. If a neural structure contributes to a task, then rendering the structure dysfunctional should impair the performance of that task.

Humans obviously cannot be subjected to **brain lesions** as experimental procedures with the goal of understanding brain function (but see the section titled “Functional Neurosurgery” later in this chapter). Typically, human neuropsychology involves research with patients who have suffered naturally occurring lesions. But animal researchers have not been constrained in this way. They share a long tradition of studying brain function by comparing the effects of different brain lesions. In one classic example, Nobel laureate Charles Sherrington employed the lesion method at the start of the 20th century to investigate the importance of feedback in limb movement in the dog (see Chapter 7). By severing the nerve fibers carrying sensory information into the spinal cord, he observed that the animals stopped walking.

Lesioning a neural structure will eliminate that structure’s contribution. But the lesion also might force the animal to change its normal behavior and alter the function of intact structures. One cannot be confident that the effect of a lesion eliminates the contribution of only a single structure. The function of neural regions that are connected to the lesioned area might be altered, either because they are deprived of their normal neural input or because their axons fail to make normal synaptic connections. The lesion might also cause the animal to develop a compensatory strategy to minimize the consequences of the lesion. For example, when monkeys are deprived of sensory feedback to one arm, they stop using the limb. However, if the sensory feedback to the other arm is eliminated at a later date, the animals begin to use both limbs (Taub & Berman, 1968). The monkeys prefer to use a limb that has normal sensation, but the second surgery shows that they could indeed use the other limb.

With this methodology we should remember that a lesion may do more than eliminate the function provided by the lesioned structure. Nonetheless, the method has been critical for neurophysiologists. Over the years, lesioning techniques have been refined, allowing for much greater precision. Most lesions were originally made by the *aspiration* of neural tissue. In aspiration experiments, a suction device is used to remove the targeted structures. Another method was to apply electrical charges strong enough to destroy tissue. One problem with this method is the difficulty of being selective. Any

tissue within range of the voltage generated by the electrode tip will be destroyed. For example, a researcher might want to observe the effects of a lesion to a certain cortical area, but if the electrolytic lesion extends into underlying white matter, these fibers also will be destroyed. Therefore, a distant structure might be rendered dysfunctional because it is deprived of some input.

Newer methods allow for more control over the extent of lesions. Most notable are neurochemical lesions. Sometimes a drug will selectively destroy cells that use a certain transmitter. For instance, systemic injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) destroys dopaminergic cells in the substantia nigra, producing an animal version of Parkinson's disease (see Chapter 7). Other neurochemical lesions require application of the drug to the targeted region. Kainic acid is used in many studies because its toxic effects are limited to cell bodies. Application to an area will destroy the neurons whose cell bodies are near the site of the injection, but will spare any axonal fibers passing through this area.

Some researchers choose to make reversible lesions using chemicals that produce a transient disruption in nerve conductivity. As long as the drug is active, the exposed neurons do not function. When the drug wears off, function gradually returns. The appeal of this method is that each animal can serve as its own control. Performance can be compared during the "lesion" and "nonlesion" periods. In a different form of reversible lesion, neural tissue is cooled by the injection of a chemical that induces a low temperature. When the tissue is cooled, metabolic activity is disrupted, thereby creating a temporary lesion. When the coolant is removed, metabolic activities resume and the tissue becomes functional again.

Pharmacological manipulations also can be used to produce transient functional lesions. For example, the acetylcholine antagonist scopolamine produces temporary amnesia such that the recipient fails to remember much of what he or she was doing during the period when the drug was active. Because the low doses required to produce the amnesia have minimal adverse consequences, scopolamine provides a tool for studying the kinds of memory problems that plague patients who have hippocampal damage (Nissen et al., 1987). However, systemic administration of this drug produces widespread changes in brain function, thus limiting its utility as a model of hippocampal dysfunction.

Genetic Manipulations

The start of the 21st century witnessed the climax of one of the great scientific challenges: the mapping of the human genome. Scientists now have a complete

record of the genetic sequence on our chromosomes. At present, the utility of this knowledge is limited; we have only begun to understand how these genes code for all aspects of human structure and function. In essence, what we have is a map containing the secrets to many treasures: What causes people to grow old? Why are some people more susceptible to certain cancers than other people? What dictates whether embryonic tissue will become a skin cell or a brain cell? Deciphering this map is an imposing task that will take years of intensive study.

Genetic disorders are manifest in all aspects of life, including brain function. Certain diseases, such as Huntington's disease, are clearly heritable (see the section titled "Degenerative and Infectious Disorders" later in this chapter). Indeed, by analyzing individuals' genetic codes, scientists can now predict whether those individuals will develop this debilitating disorder. This diagnostic ability was made possible by analysis of the genetic code of individuals who developed Huntington's disease and that of relatives who remained disease free. In this particular disease, the differences were restricted to a single chromosomal abnormality. This discovery is also expected to lead to new treatments that will prevent the onset of Huntington's. Scientists hope to devise techniques to alter the aberrant genes, either by modifying them or by figuring out a way to prevent them from being expressed.

In a similar way, scientists have sought to understand other aspects of normal and abnormal brain function through the study of genetics. Behavioral geneticists have long known that many aspects of cognitive function are heritable. For example, controlling mating patterns on the basis of spatial-learning performance allows the development of "maze-bright" and "maze-dull" strains of rats. Rats that are quick to learn to navigate mazes are likely to have offspring with similar abilities, even if the offspring are raised by rats that are slow to navigate the same mazes. Such correlations also are observed across a range of human behaviors, including spatial reasoning, reading speed, and even preferences in watching television (Plomin et al., 1990). This should not be taken to mean that our intelligence or behavior is genetically determined. Maze-bright rats perform quite poorly if raised in an impoverished environment. The truth surely reflects complex interactions between the environment and genetics (see "The Cognitive Neuroscientist's Toolkit: Correlation and Causation," on p. 128).

To understand the genetic component of this equation, neuroscientists are now working with many species, seeking to identify the genetic mechanisms of both brain structure and function. Dramatic advances have been

made in studies with the fruit fly and mouse, two species with reproductive propensities that allow many generations to be spawned over a relatively short period of time. As with humans, the genome sequence for these species has been mapped out. More important, the functional role of many genes can be explored. A key methodology is to develop genetically altered animals, using what are referred to as **knockout procedures**. The term *knockout* comes from the fact that specific genes have been manipulated so that they are no longer present or expressed.

Scientists can then study the new species to explore the consequences of these changes. For example, *weaver* mice are a knockout strain in which Purkinje cells, the prominent cell type in the cerebellum, fail to develop. As the name implies, these mice exhibit coordination problems.

At an even more focal level, knockout procedures have been used to create strains that lack single types of postsynaptic receptors in specific brain regions while leaving intact other types of receptors. Susumu Tone-

gawa at the Massachusetts Institute of Technology (MIT) and his colleagues developed a mouse strain in which they altered cells within a subregion of the hippocampus that typically contain a receptor for *N*-methyl-D-aspartate, or NMDA (M. A. Wilson & Tonegawa, 1997; see Chapter 8). Knockout strains lacking the NMDA receptor in the hippocampus exhibit poor learning on a variety of memory tasks, providing a novel approach for linking memory with its molecular substrate (Figure 4.10). In a sense, this approach constitutes a lesion method, but at a microscopic level.

The New Genomics

Neurogenetic research is not limited to identifying the role of each gene individually; it is widely recognized that complex brain function and behavior arise from interactions between many genes and the environment. Using DNA arrays and knowledge gained from mapping of the human and mouse genomes, scientists can now

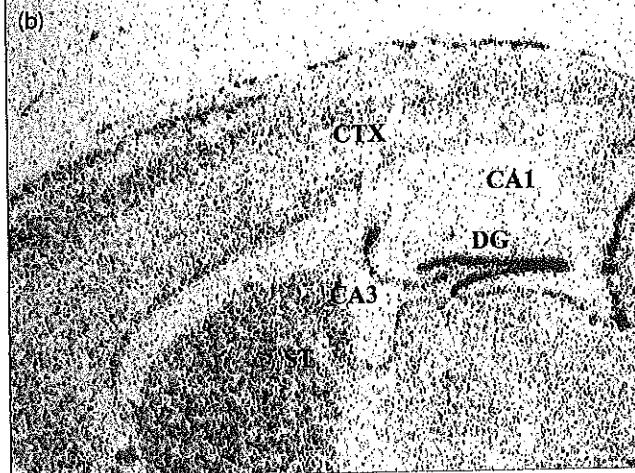
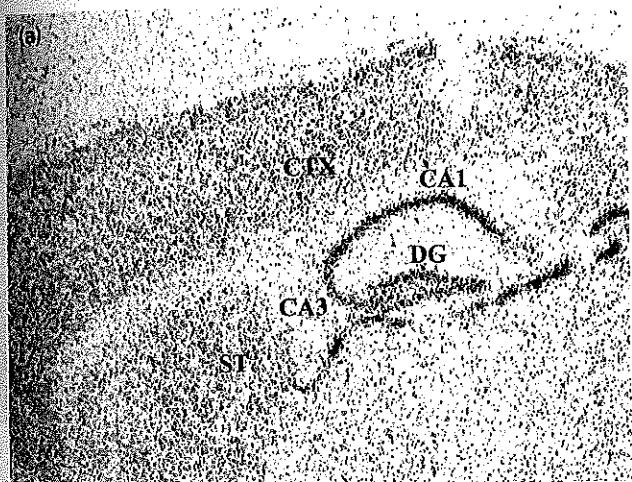
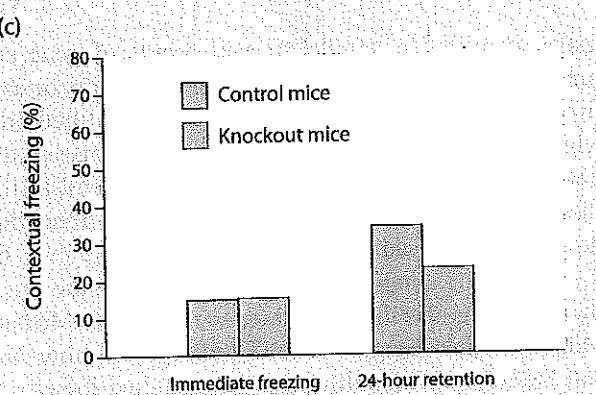


Figure 4.10 Brain slices through the hippocampus, showing the absence of a particular receptor in genetically altered mice. (a) Cells containing the gene associated with the receptor are stained in black. (b) The gene is absent in the CA1 region of the slice from the knockout mouse. (c) Fear conditioning is impaired in knockout mice. After receiving a shock, the mice freeze. When normal mice are placed in the same context 24 hours later, they show strong learning by the large increase in the percentage of freezing responses. This increase is reduced in the knockout mice. CTX = cortex; DG = dentate gyrus; ST = striatum.



THE COGNITIVE NEUROSCIENTIST'S TOOLKIT

Correlation and Causation: Brain Size and Posttraumatic Stress Disorder

The issue of causation is important to consider in any discussion of scientific observation. A recent study examining drinking habits and personal income found that self-reported drinkers earned about 10% more than self-reported abstainers, and that those who drank in bars earned an additional 7% more (Peters & Stringham, 2006). The research team offered the counterintuitive conclusion that the increase in alcohol consumption played a causative role in the higher income levels, at least in men. In their view, social drinking increases social networking and this networking has the benefit of increasing income. Although this causal chain is reasonable, there are certainly alternative ways to account for the relationship of drinking and income. For example, individuals who make a lot of money can afford to go to bars at night and spend their income on drinks! In elementary statistics we all learn to be wary about inferring causation from correlation, but the temptation can be strong.

The tendency to infer causation from correlation can be especially great when we're comparing the contribution of nature and nurture on brain and behavior. Consider the following results that have accumulated concerning the relationship of chronic stress and the hippocampus. From animal studies, we know that exposure to prolonged stress, and the resulting increase in glucocorticoid steroids, can cause atrophy in the hippocampus (Sapolsky et al., 1990). With the advent of

neuroimaging, we have also learned that people with chronic posttraumatic stress disorder (PTSD) have smaller hippocampi than individuals who do not suffer from PTSD (Bremner et al., 1997; M. B. Stein et al., 1997). Can we therefore conclude that the stress that we know is associated with PTSD results, over time, in a reduction in the hippocampal volume of people with PTSD? This certainly seems a reasonable way to deduce a causal chain of events between these observations.

However, it is also important to consider alternative explanations. For instance, the causal story may run in the opposite direction: Individuals with smaller hippocampi, perhaps due to genetic variation, may be more vulnerable to the effects of stress, and thus be at higher risk for developing PTSD. How might we contrast these different hypotheses? What study design could distinguish between two hypotheses—one that emphasizes environmental factors (e.g., PTSD, via chronic stress, causes reduction in size of the hippocampus) and one that emphasizes genetic factors (e.g., individuals with small hippocampi are at risk for developing PTSD)?

A favorite approach of behavioral geneticists in exploring questions like these is to study identical twins. Mark Gilbertson and his colleagues (2002) at the New Hampshire Veterans Administration Medical Center studied a cohort of 40 pairs of identical twins. Within each twin pair, one member had experienced

make quantitative parallel measurements of gene expression, observing how these change over time or as a function of environmental factors. These methods, which have been used to investigate gene changes in the developing brain (Reichert & Boyan, 1997) and in the diseased brain, can shed light on normal and abnormal development (Lockhart & Barlow, 2001).

Gene expression can also be used to study the genes that underlie specific behaviors. For instance, Michael Miles and his colleagues at the University of California, San Francisco (Thibault et al., 2000) studied the effects

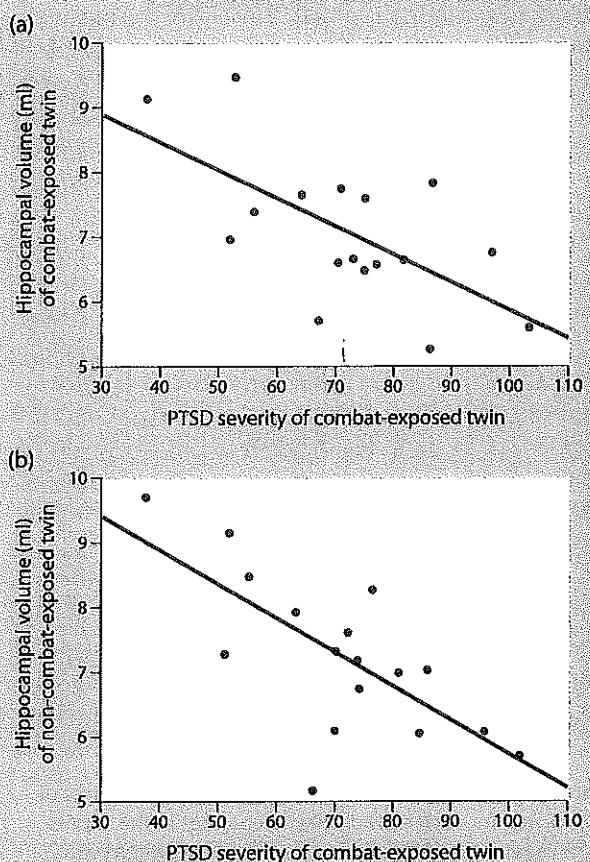
of alcohol on gene expression, asking how specific genes might be related to variations in alcohol tolerance and dependence (Figure 4.11 on p. 130). Similarly, Jorge Medina and his colleagues at the Universidad de Buenos Aires in Argentina (Igaz et al., 2004) used genomic methods to investigate memory consolidation and found that orchestrated, differential hippocampal gene expression is necessary for long-term memory consolidation.

Gene arrays and the new genomics provide great promise for detecting the polygenic influences on brain function and behavior.

severe trauma during a tour of duty in Vietnam. The other member of the pair had not seen active duty. In this way, each high-stress participant had a very well matched control, at least in terms of genetics: a twin brother.

Although all of the active-duty participants had experienced severe trauma during their time in Vietnam (one of the inclusion criteria for the study), not all of these individuals had developed PTSD. Thus, the experimenters could look at various factors associated with the onset of PTSD in a group of individuals with similar environmental experiences. Consistent with previous studies, anatomical MRIs showed that people with PTSD had smaller hippocampi than unrelated individuals without PTSD had. However, the same was also found for the twin brothers of the individuals with PTSD; that is, these individuals also had smaller hippocampi, even though they did not have PTSD and did not report having experienced unusual trauma in their lifetime. Moreover, the severity of the PTSD was negatively correlated with the size of the hippocampus in both the patient with PTSD [part (a) of the figure] and the matched twin control [part (b)]. Thus, the researchers concluded that small hippocampal size was a risk factor for developing PTSD and that PTSD alone did not cause the decreased hippocampal size.

This study serves as an example of the need for caution: We must be careful when making causal inferences based on correlational data. This study also provides an excellent example of how scientists are studying interactions between genes and the environment in influencing behavior and brain structure.



Correlations between hippocampal volume and posttrauma symptoms. Scatter plots illustrate the relationship of symptom severity in combat veterans with PTSD to (a) their own hippocampal volumes and (b) the hippocampal volumes of their identical twin brothers who were not exposed to combat. Symptom severity represents the total score received on the Clinician-Administered PTSD Scale (CAPS).

NEUROLOGY

Human pathology has long provided key insights into the relationship between brain and behavior. Observers of neurological dysfunction have certainly contributed much to our understanding of cognition—long before the advent of cognitive neuroscience. Discoveries concerning the contralateral wiring of sensory and motor systems were made by physicians in ancient societies attending to warriors with open head injuries. Postmortem studies by early neurologists, such as Broca and Wernicke, were instrumental in linking the left hemisphere with language

functions (see Chapter 1). Many other disorders of cognition were described in the first decades of the 20th century, paralleling the emergence of neurology as a specialty within medicine.

Even so, there is now an upsurge in testing neurological patients to elucidate issues related to normal and aberrant cognitive function. As with other subfields of cognitive neuroscience, this enthusiasm has been inspired partly by advances in the technologies for diagnosing neurological disorders. As important, studies of patients with brain damage have benefited from the

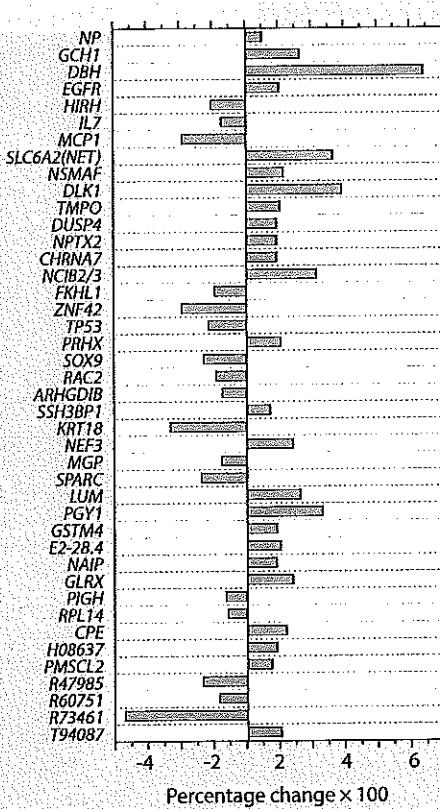


Figure 4.11 Effects of alcohol on gene expression. A set of genes (listed for each row) displayed changes in the expression of messenger RNA following 3 days of treatment with 100-mM ethanol. (The colors indicate groups of genes associated with different functions, such as metabolic processes or neural signaling.) For some genes, the change was an increase in RNA expression; for other genes, the change was a decrease in expression.

use of experimental tasks derived from research with healthy people.

Examples of the merging of cognitive psychology and neurology are presented at the end of this chapter; in this section we focus on the causes of neurological disorders and the tools that neurologists use to localize neural pathology. We also take a brief look at treatments for ameliorating neurological disorders.

We can best address basic research questions, such as those attempting to link cognitive processes to neural structures, by selecting patients with a single neurological disturbance whose pathology is well circumscribed. Patients who have suffered trauma or infections frequently have diffuse damage, rendering it difficult to associate the behavioral deficit with a structure. Nonetheless, extensive clinical and basic research studies have focused on patients with degenerative dis-

orders such as Alzheimer's disease, both to understand the disease processes and to characterize abnormal cognitive function.

Structural Imaging of Neurological Damage

Brain damage can result from vascular problems, tumors, degenerative disorders, and trauma. The first charge of neurologists is to make the appropriate diagnosis. They need to follow appropriate procedures, especially if a disorder is life-threatening, and to work toward stabilizing the patient's condition. Although diagnosis frequently can be made on the basis of a clinical examination, almost all hospitals in the Western world are equipped with tools that help neurologists visualize brain structure.

Computed tomography (CT or CAT scanning), introduced commercially in 1983, has been an extremely important medical tool for structural imaging of neurological damage in living people. This method is an advanced version of the conventional X-ray study; whereas the conventional X-ray study compresses three-dimensional objects into two dimensions, CT allows for the reconstruction of three-dimensional space from the compressed two-dimensional images. Figure 4.12a depicts the method, showing how X-ray beams are passed through the head and a two-dimensional image is generated by sophisticated computer software.

To undergo CT, a patient lies supine in a scanning machine. The machine has two main parts: an X-ray source and a set of radiation detectors. The source and detectors are located on opposite sides of the scanner. These sides can rotate, allowing the radiologist to project X-ray beams from all possible directions. Starting at one position, an X-ray beam passes through the head. Some radiation in the X-ray is absorbed by intervening tissue. The remainder passes through and is picked up by the radiation detectors located on the opposite side of the head. The X-ray source and detectors are then rotated and a new beam is projected. This process is repeated until X-rays have been projected over 180°. At this point, recordings made by the detectors are fed into a computer that reconstructs the images.

The key principle underlying CT is that the density of biological material varies and the absorption of X-ray radiation is correlated with tissue density. High-density material such as bone absorbs a lot of radiation. Low-density material such as air or blood absorbs little radiation. The absorption capacity of neural tissue lies between these extremes. Thus, the software for making CT scans actually provides an image of the differential absorption of intervening tis-

sue. The reconstructed images are usually contrast reversed: High-density regions show up as light colored, and low-density regions are dark.

Figure 4.12b shows a CT scan of a healthy individual. Most of the cortex and white matter appear as homogeneous gray areas. The typical spatial resolution for CT scanners is approximately 0.5 to 1.0 cm in all directions. Each point on the image reflects an average density of that point and the surrounding 1.0 mm of tissue. Thus, it is not possible to discriminate two objects that are closer than approximately 5 mm. Since the cortex is only 4 mm thick, it is very difficult to see the boundary between white and gray matter on a CT scan. The white and gray matter are also of very similar density, further limiting the ability of this technique to distinguish them. But larger structures can be easily identified. The surrounding skull and eye sockets appear white because of the high density of bone. The ventricles are black owing to the cerebrospinal fluid's low density.

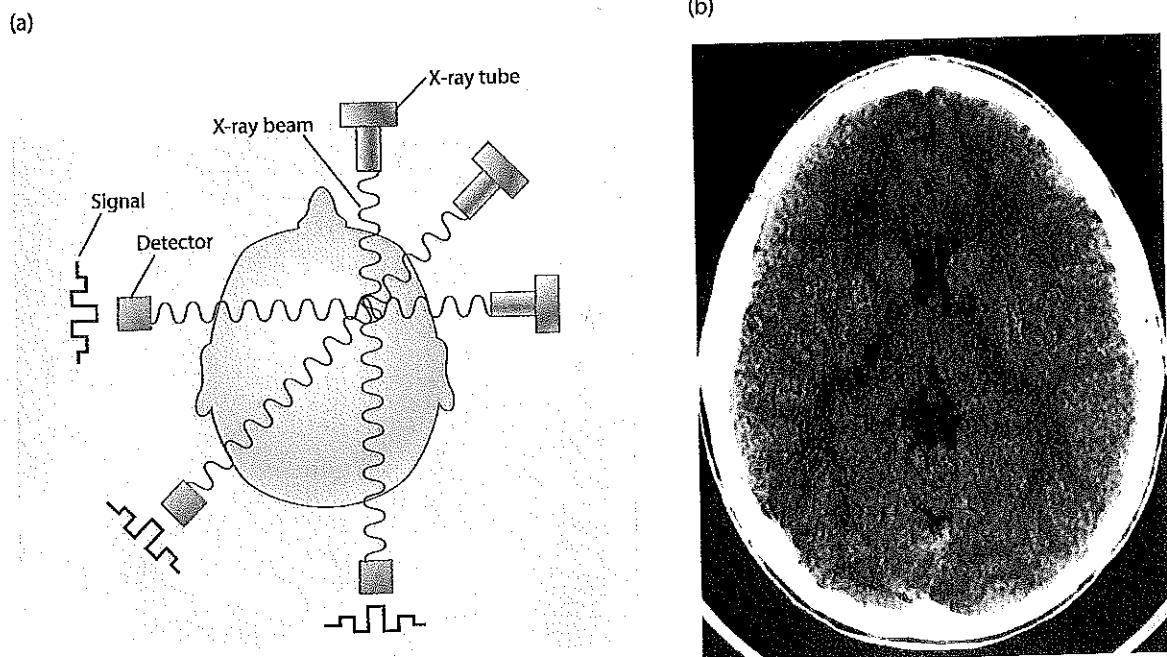
MAGNETIC RESONANCE IMAGING

Although CT machines are still widely used, many hospitals have now added a second important imaging tool,

the magnetic resonance imaging (MRI) scanner. In contrast to use of X-rays in CT, the MRI process exploits the magnetic properties of organic tissue. The number of the protons and neutrons in their nuclei makes certain atoms especially sensitized to magnetic forces. One such atom that is pervasive in the brain, and indeed in all organic tissue, is hydrogen. The protons that form the nucleus of the hydrogen atom are in constant motion, spinning about their principal axis. This motion creates a tiny magnetic field. In their normal state, the orientation of these protons is randomly distributed, unaffected by the weak magnetic field created by Earth's gravity (Figure 4.13).

The MRI machine creates a powerful magnetic field, measured in tesla units. Whereas gravitational forces on the Earth create a magnetic field of about 1/1000 tesla, the typical MRI scanner produces a magnetic field that ranges from 0.5 to 1.5 teslas. When a person is placed within the magnetic field of the MRI machine, a significant proportion of the protons become oriented in the direction parallel to the magnetic force. Radio waves are then passed through the magnetized regions, and as the protons absorb the energy in these waves, their orientation is perturbed in a predictable direction. When the

Figure 4.12 Computed tomography provides an important tool for imaging neurological pathology. (a) The CT process is based on the same principles as X-rays. An X-ray is projected through the head, and the recorded image provides a measurement of the density of the intervening tissue. By projection of the X-ray from multiple angles and with the use of computer algorithms, a three-dimensional image based on tissue density is obtained. (b) In this transverse CT image, the dark regions along the midline are the ventricles, the reservoirs of cerebrospinal fluid.



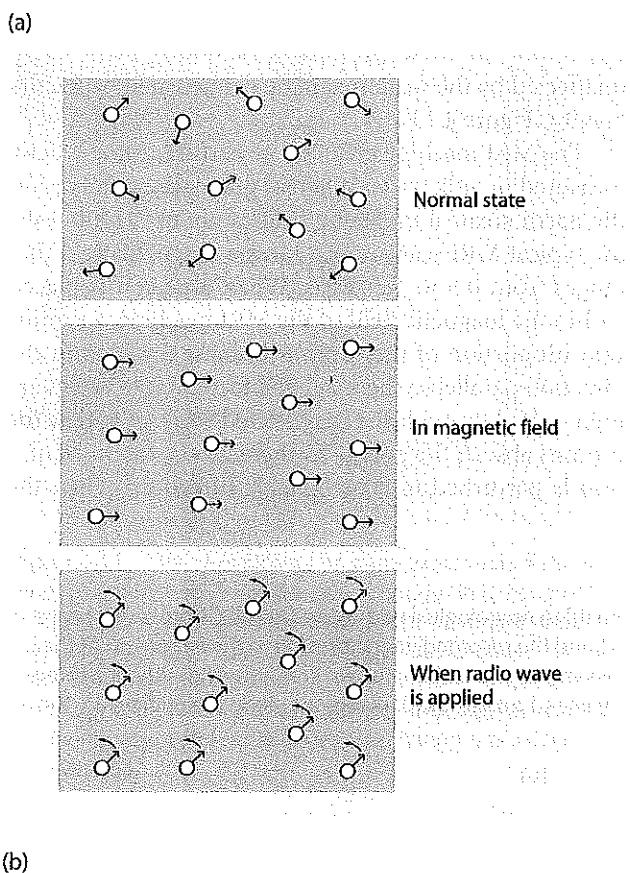
radio waves are turned off, the absorbed energy is dissipated and the protons rebound toward the orientation of the magnetic field. This synchronized rebound produces energy signals that are picked up by detectors surrounding the head. By systematically measuring the signals throughout the three-dimensional volume of the head, the MRI system can then construct an image re-

flecting the distribution of the protons and other magnetic agents in the tissue.

As Figure 4.13b shows, MRI scans provide a much clearer image of the brain than is possible with CT scans. This improvement reflects the fact that the density of protons is much greater in gray matter compared to white matter. With MRI, it is easy to see the individual sulci and gyri of the cerebral cortex. A sagittal section at the midline reveals the impressive size of the corpus callosum. The MRI scans can resolve structures that are less than 1 mm, allowing elegant views of small, subcortical structures such as the mammillary bodies or superior colliculus.

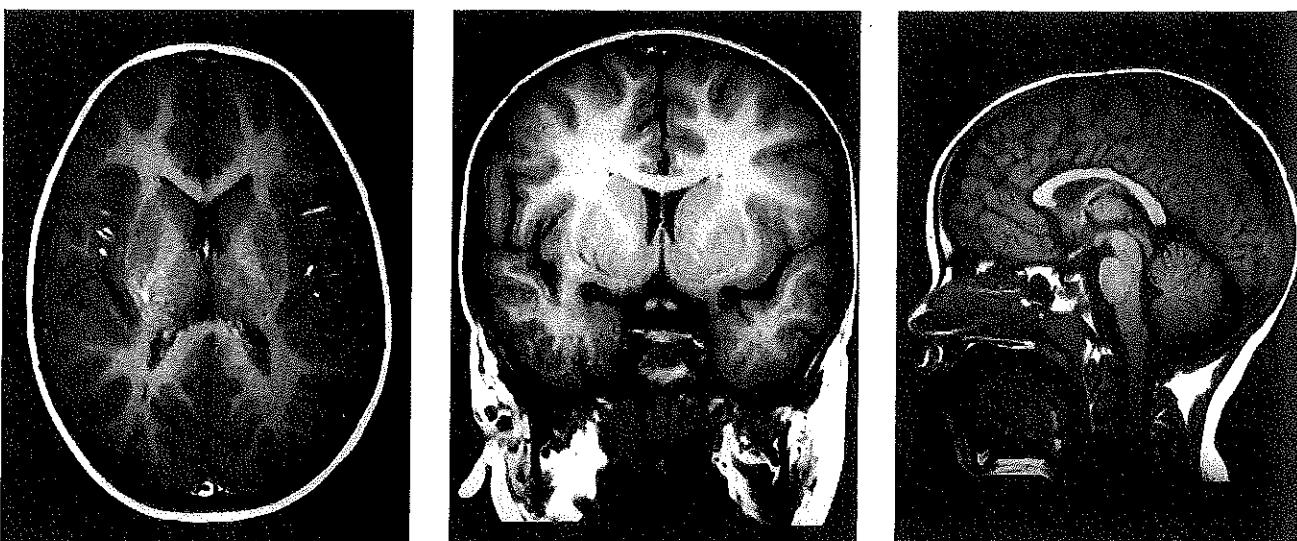
DIFFUSION TENSOR IMAGING

MRI scanners are now also used to study the microscopic anatomical structure of the axon tracts that form the white matter. This method is called **diffusion tensor imaging** (DTI; Figure 4.14). DTI is performed



(b)

Figure 4.13 Magnetic resonance imaging exploits the fact that many organic elements, such as hydrogen, are magnetic. (a) In their normal state, the orientation of these elements is random. When an external magnetic field is applied, the elements become aligned and can be perturbed in a systematic fashion by the introduction of radio waves. The MRI scanner measures the endogenous magnetic fields generated by these elements as they spin. The density of hydrogen atoms is different in white and gray matter, making it easy to visualize these regions. (b) Transverse, coronal, and sagittal images. Comparing the transverse slice in this figure with the CT image in Figure 4.12 reveals the finer resolution offered by MRI. Both images are from about the same level of the brain.



with an MRI scanner, but unlike traditional MRI scans, DTI measures the density and, more important, motion of the water contained in the axons. DTI utilizes the known diffusion characteristics of water to determine the boundaries that restrict water movement throughout the brain (Behrens et al., 2003). Free diffusion of water is *isotropic*; that is, it occurs equally in all directions. However, diffusion of water in the brain is *anisotropic*, or restricted, so it does not diffuse equally in all directions. The reason for this anisotropy is that the axon membranes restrict the diffusion of water; the probability of water moving in the direction of the axon is thus greater than the probability of water moving perpendicular to the axon (Le Bihan, 2003). The anisotropy is greatest in axons because myelin creates a lipid boundary, limiting the flow of water to a much greater extent than gray matter or cerebrospinal fluid does. In this way, the orientation of axon bundles within the white matter can be imaged (DaSilva et al., 2003).

MRI principles can be combined with what is known about the diffusion of water to determine the diffusion anisotropy for each region within the MRI scan. These regions are referred to as **voxels**, a term that captures the computer graphics idea of a pixel, but volumetrically. By introducing two large pulses to the magnetic field, we can make MRI signals sensitive to the diffusion of water (Le Bihan, 2003). The first pulse determines the initial position of the protons carried by water. The second pulse, introduced after a short delay,

detects how far the protons have moved in space in the specific direction that is being measured. It is standard to acquire DTI images in more than 30 directions.

The functional differences in diffusion anisotropy have been the subject of recent investigations. For instance, fractional anisotropy (a measure of the degree of anisotropy in white matter) in the temporoparietal region of the left hemisphere is significantly correlated with reading scores in adults with and without dyslexia. This correlation might reflect the differences in the strength of communication between visual, auditory, and language-processing areas in the brain (Klingberg et al., 2000).

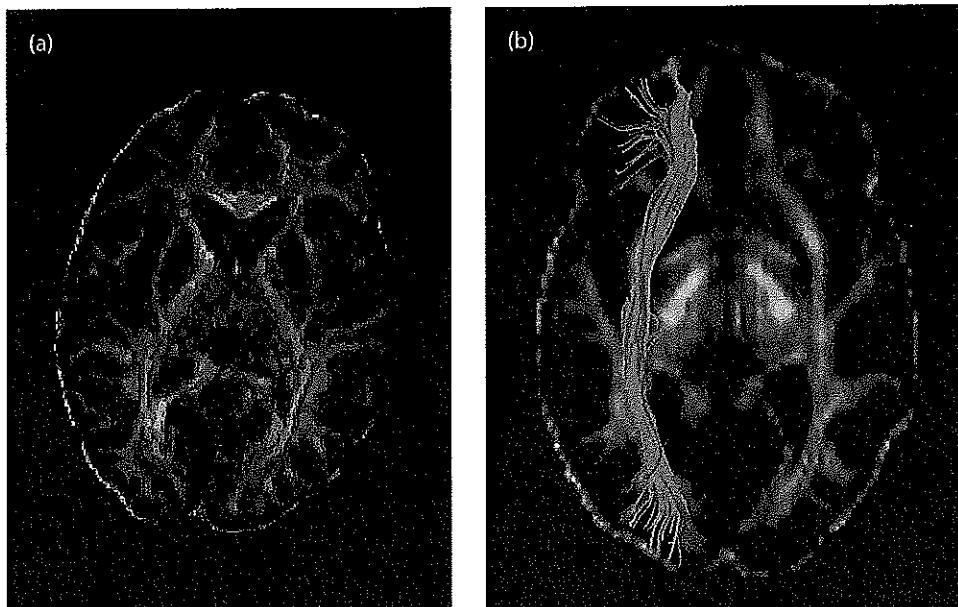
Causes of Neurological Disorders

Nature has sought to ensure that the brain remains healthy. Structurally, the skull provides a thick, protective encasement. The distribution of arteries is extensive and even redundant for much of the brain. Even so, the brain is subject to numerous disorders, and their rapid treatment is frequently essential to reduce the possibility of chronic, debilitating problems or death.

VASCULAR DISORDERS

As with all other tissue, neurons need a steady supply of oxygen and glucose. These substances are essential for the cells to produce energy and make transmitters for neural communication. The brain uses 20% of all the

Figure 4.14 Diffusion tensor imaging. (a) This axial slice of a human brain reveals the directionality and connectivity of the white matter. The colors correspond to the principal directions of the white matter tracts in each region. (b) DTI data can be analyzed to trace white matter connections in the brain. The tracks shown here form the inferior fronto-occipital fasciculus, which, as the name suggests, connects the visual cortex to the frontal lobe.



oxygen we breathe, an extraordinary amount considering that it accounts for only 2% of the total body mass. The continuous supply of oxygen is essential: A loss of oxygen for as little as 10 minutes can result in neural death. **Angiography** is an imaging method used to evaluate the circulatory system in the brain. As Figure 4.15 shows, this method helps us visualize the distribution of blood by highlighting major arteries and veins. A dye is injected into the vertebral or carotid artery, and then an X-ray study is conducted.

Oxygen and glucose are distributed to the brain from four primary arteries: the two internal carotid and two vertebral arteries. Each carotid artery branches into two major arteries—the anterior cerebral artery and the middle cerebral artery—as well as several smaller ones. Together, these arteries act as a network to supply the anterior and middle portions of the cortex with blood. The vertebral arteries join to form the basilar artery. Inferior branches from the basilar artery irrigate the cerebellum and posterior part of the brainstem. More superiorly, this system branches into two posterior cerebral arteries to provide blood to the occipital lobe and the medial temporal lobe. The major cerebral arteries partially overlap in their distribution, in areas referred to as *border zones* or *watershed areas*.

Cerebral vascular accidents, or strokes, occur when blood flow to the brain is suddenly disrupted. The most frequent cause of stroke is occlusion of the normal passage of blood by a foreign substance. Over years, arteriosclerosis, the buildup of fatty tissue, occurs in the heart. This tissue can break free, becoming an embolus

that is carried off in the bloodstream. An embolus that enters the cranium may easily pass through the large carotid or vertebral arteries. But as the arteries and capillaries reach the end of their distribution, their size decreases. Eventually, the embolus becomes stuck, or infarcted, blocking the flow of blood and depriving all downstream tissue of oxygen and glucose. Within a short period of time, this tissue will become dysfunctional. If the blood flow is not rapidly restored, the cells will die (Figure 4.16a).

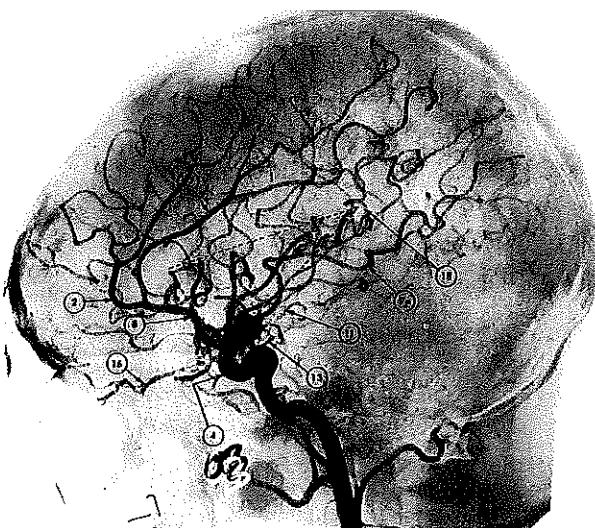
The onset of stroke can be quite varied, depending on the afflicted area. Sometimes the person may lose consciousness and die within minutes. In such cases the infarct is usually in the vicinity of the brainstem. When the infarct is cortical, the presenting symptoms may be striking, such as sudden loss of speech and comprehension. In other cases, the onset may be innocuous. The person may report a mild headache or be unable to use a hand in an appropriate manner. The vascular system is fairly consistent between individuals; thus, stroke of a particular artery typically leads to destruction of tissue in a consistent anatomical location. For example, occlusion of the posterior cerebral artery invariably leads to deficits in visual perception.

There are many other types of cerebral vascular disorders. Ischemia can be caused by partial occlusion of an artery or capillary due to an embolus, or it can arise from a sudden drop in blood pressure that prevents blood from reaching the brain. A sudden rise in blood pressure can lead to cerebral hemorrhage (Figure 4.16b), or bleeding over a wide area of the brain due to the breakage of blood vessels. Spasms in the vessels can result in irregular blood flow and have been associated with migraine headaches.

Other disorders are due to problems in arterial structures. Cerebral arteriosclerosis is a chronic condition in which cerebral blood vessels become narrow because of thickening and hardening of the arteries. The result can be persistent ischemia. More acute situations can arise if a person has an aneurysm (a weak spot or distention in a blood vessel). An aneurysm may suddenly expand or even burst, causing a rapid disruption of the blood circulation. Although some aneurysms appear to develop spontaneously, others can develop in people born with an arteriovenous malformation. An arteriovenous malformation that has remained innocuous for many years may suddenly weaken.

Cerebral vascular accidents require immediate attention. Often a neurological examination and CT can reveal the problem. Arteriovenous malformations or aneurysms, however, may require the more precise MRI or angiography. In these instances, surgery is frequently

Figure 4.15 The angiogram provides an image of the arteries in the brain.



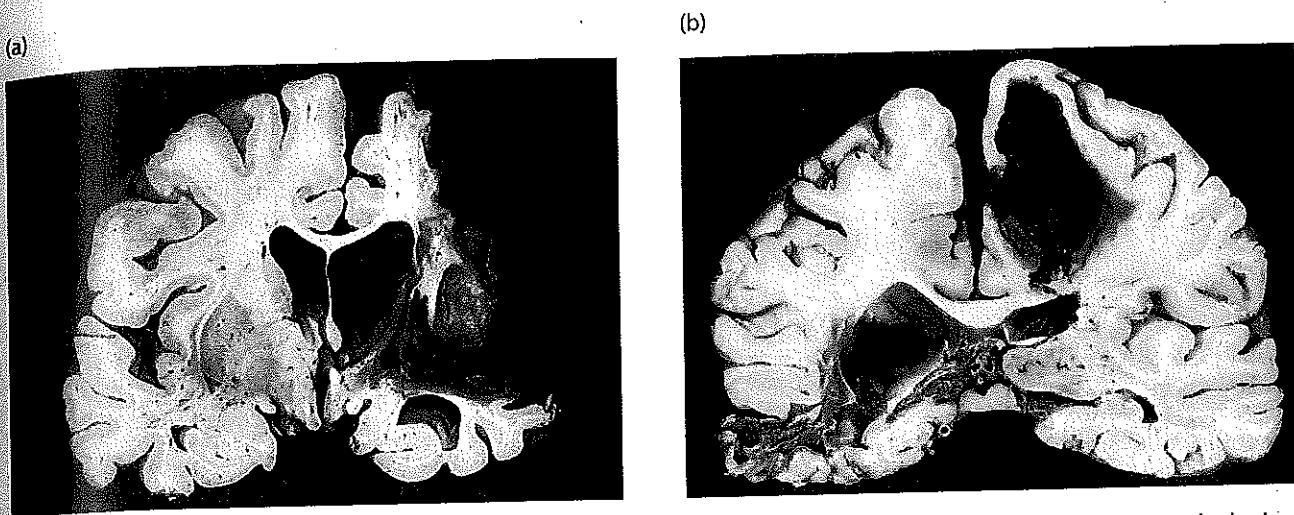


Figure 4.16 Vascular disorders. (a) Strokes occur when blood flow to the brain is disrupted. This brain is from a person who had an occlusion of the middle cerebral artery. The person survived the stroke. After death later, postmortem analysis showed that almost all of the tissue supplied by this artery had died and been absorbed. (b) This brain is from a person who died following a cerebral hemorrhage. The hemorrhage destroyed the dorsomedial region of the left hemisphere. The effects of a cerebrovascular accident 2 years prior to death can be seen in the temporal region of the right hemisphere.

required to prevent further bleeding. Occlusive strokes, on the other hand, do not generally require surgery. Either the occluded tissue is already completely infarcted, the clot is too small to remove, or the embolus has been absorbed into the surrounding tissue by the time of surgery. Such cases are usually treated by the administration of drugs to dissolve the clot and restore circulation prior to permanent tissue injury.

TUMORS

Brain lesions also can result from tumors. A *tumor*, or *neoplasm*, is a mass of tissue that grows abnormally and has no physiological function. Brain tumors are relatively common, with most originating in glial cells and other supporting white matter tissues. Tumors also can develop from gray matter or neurons, but these are much less common, particularly in adults. Tumors are classified as benign when they do not recur after removal and tend to remain in the area of their germination (although they can become quite large). Malignant, or cancerous, tumors are likely to recur after removal and are often distributed over a number of different areas. With brain tumors, the first concern is not usually whether the tumor is benign or malignant, but rather its location and prognosis. Concern is greatest when the tumor threatens critical neural structures. Neurons can be destroyed by an infiltrating tumor or become dysfunctional as a result of displacement by the tumor.

Three major types of brain tumors are distinguished according to where they originate:

1. *Gliomas* (Figure 4.17a) begin with the abnormal reproduction of glial cells. The rate of growth of different subtypes of gliomas can vary widely: Some escape detection for years; others expand rapidly and are malignant, with a poor prognosis because a lot of tissue is quickly disturbed.
2. *Meningiomas* (Figure 4.17b) originate in the meninges, the protective membrane that surrounds the brain. Although meningiomas do not invade the brain, they can create severe neurological problems by producing abnormal pressure.
3. *Metastatic tumors* (Figure 4.17c) originate in a non-cerebral structure such as the lungs, skin, or breasts. The malignant tissue invades the bloodstream or lymphatics and is ultimately carried to the brain. Metastatic tumors are commonly widely distributed, affecting many structures.

DEGENERATIVE AND INFECTIOUS DISORDERS

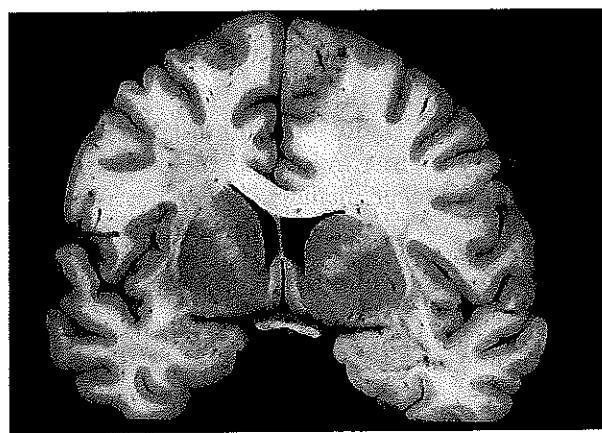
Many neurological disorders result from progressive disease. Table 4.1 lists some of the more prominent degenerative and infectious disorders. In later chapters we will review some of these disorders in detail, exploring the cognitive problems associated with them and how these problems relate to underlying neuropathologies.



(a)



(b)



(c)

Figure 4.17 Postmortem views of three types of brain tumors. (a) A malignant glioma infiltrated the white matter of the parietal lobe in the right hemisphere in this case. (b) Here a large meningioma led to massive compression of the right frontal lobe. This patient had been hospitalized at age 41 for psychotic behavior, quite likely due to the effects of this slow-growing tumor. The tumor was not detected until autopsy. (c) A metastatic tumor is seen here in the dorsomedial tip of the left hemisphere. This woman died 5 years after undergoing a mastectomy for breast cancer.

Table 4.1 Prominent Degenerative and Infectious Disorders of the Central Nervous System

Disorder	Type	Most Common Pathology
Alzheimer's disease	Degenerative	Tangles and plaques in limbic and temporo-parietal cortex
Parkinson's disease	Degenerative	Loss of dopaminergic neurons
Huntington's disease	Degenerative	Atrophy of interneurons in caudate and putamen nuclei of basal ganglia
Pick's disease	Degenerative	Frontotemporal atrophy
Progressive supranuclear palsy (PSP)	Degenerative	Atrophy of brainstem, including colliculus
Multiple sclerosis	Possibly infectious	Demyelination, especially of fibers near ventricles
AIDS dementia	Viral infection	Diffuse white matter lesions
Herpes simplex	Viral infection	Destruction of neurons in temporal and limbic regions
Korsakoff's syndrome	Nutritional deficiency	Destruction of neurons in diencephalon and temporal lobes

Here we focus on the etiology and clinical diagnosis of degenerative disorders.

Degenerative disorders have been associated with both genetic aberrations and environmental agents. A prime example of a degenerative disorder that is genetic in origin is Huntington's disease. The genetic link in degenerative disorders such as Parkinson's disease and Alzheimer's disease is weaker. Environmental factors are suspected to be important, perhaps in combination with genetic dispositions. The causes of Parkinson's disease are unknown, but it is suspected that the cell death in dopaminergic neurons may be accelerated by unknown toxins accumulating in the environment. Unlike many neurological disorders, there are no descriptions of people with parkinsonian symptoms in the pre-Industrial Age medical literature. The causes of Alzheimer's disease also remain a mystery, despite intense research efforts. The disease in about 5% of patients is clearly linked to a

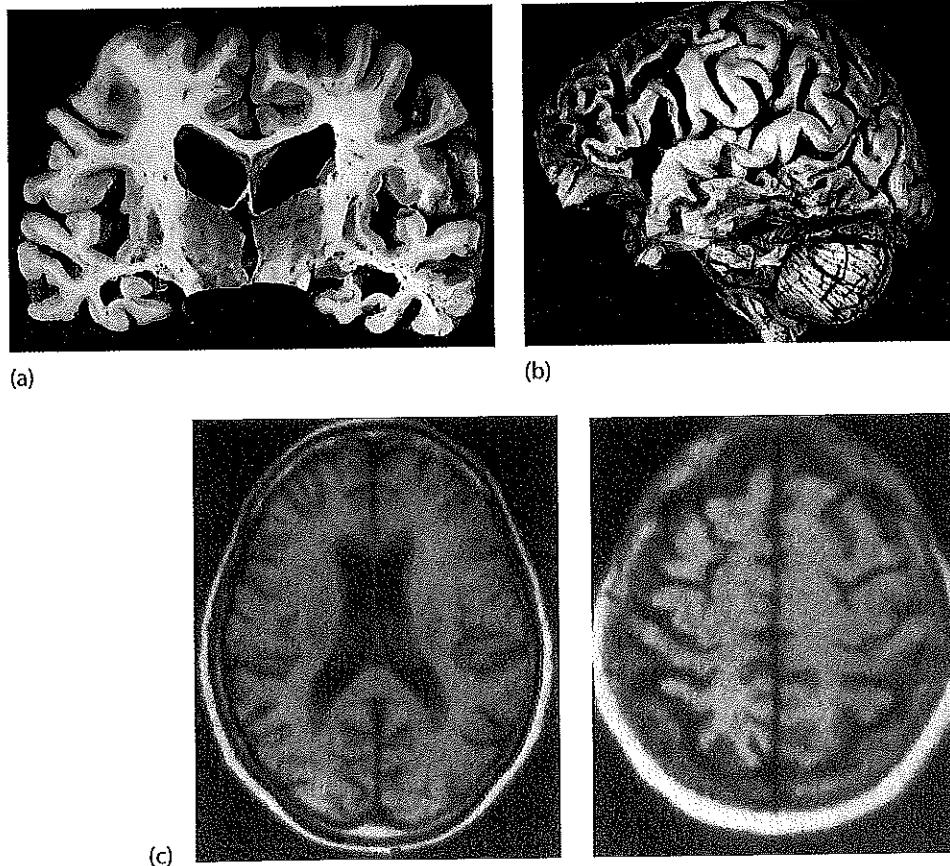
genetic deficiency; in the rest, there is no identifiable genetic component. Many hypotheses regarding the cause of Alzheimer's disease have been proposed. A leading hypothesis is that the production of amyloid, a ubiquitous protein in organic tissue, goes awry and leads to the characteristic plaques found in the brains of patients with the disease.

Progressive neurological disorders can also be caused by viruses. The human immunodeficiency virus (HIV) that causes acquired immunodeficiency syndrome (AIDS)-related dementia has a tendency to lodge in subcortical regions of the brain, producing diffuse lesions of the white matter by destroying axonal fibers. The herpes simplex virus, on the other hand, destroys neurons in cortical and limbic structures if it migrates to the brain. Viral infection is also suspected in multiple sclerosis, although evidence for such a link is indirect, coming from epidemiological studies. For example, the incidence of multiple sclerosis is highest in temperate climates, and a number of isolated tropical islands had not experienced multiple sclerosis until the population came in contact with Western visitors.

Degenerative and infectious disorders are usually characterized by a gradual onset of symptoms. Often the patient may not notice the deterioration of motor or cognitive abilities. Rather, the changes may be more apparent to a spouse or other family members. The neurological examination is especially critical for reliable diagnosis. The first signs of multiple sclerosis may be slight disturbances in sensation or double vision. The insidious onset of the memory problems associated with Alzheimer's disease may be difficult to detect, given our expectations of cognitive changes in normal aging. A patient developing Parkinson's disease may first note difficulty standing up or initiating movement. The experienced clinician will recognize the implications of these signs. CT and MRI may confirm a diagnosis, but usually the scans do not reveal any pathology in the early phases of these disorders. As the diseases progress, evidence of neural atrophy or degeneration becomes obvious (see Figure 4.18).

The pace of deterioration varies enormously, depending on the degenerative disorder. Whereas Huntington's disease invariably results in progressive deterioration and

Figure 4.18 Degenerative disorders of the brain. (a) This coronal section is from a patient with Alzheimer's disease who died at age 67, 8 years after the first reports of memory problems. Severe cortical atrophy is apparent; at death, her brain weighed only 750 g, less than half the weight of a normal brain. (b) In this brain from a patient who died of Pick's disease, the atrophy is limited to frontal and temporal lobe regions. (c) These transverse MRI scans from a patient with Alzheimer's disease show that atrophy has led to enlargement of the sulci and ventricles.



death within 5 to 15 years, demyelinating disorders such as multiple sclerosis may go into remission for many years. Part of this variation is due to differences in the underlying mechanisms producing the neural pathology. For example, in multiple sclerosis the disease process affects white matter, whereas Alzheimer's disease involves widespread atrophy of cell bodies. Another important factor affecting a patient's outcome is the use of medication to treat symptoms. Just 40 years ago, patients with Parkinson's disease were generally bedridden within a few years of diagnosis, and the disorder would be listed as the cause of death. With the introduction of drugs categorized as dopamine agonists, the symptoms are greatly minimized for many patients.

TRAUMA

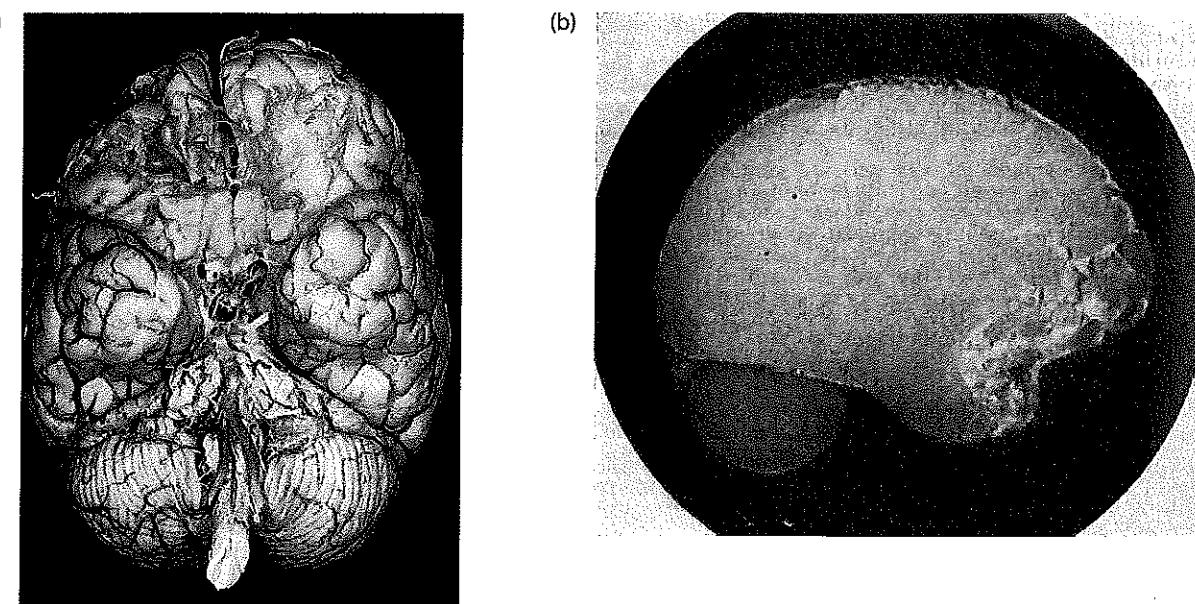
More than any natural cause, such as stroke or tumor, the reason that most patients arrive on a neurology ward is a traumatic event such as a car accident, a gunshot wound, or an ill-advised dive into a shallow swimming hole. The traumatic event can lead to a closed- or an open-head injury. In *closed* head injuries, the skull remains intact, but the brain is damaged by the mechanical forces generated by a blow to the head. The most

common cause of closed head injury is a car accident in which a person's head slams against the windshield. The damage may be at the site of the blow, for example, just below the forehead—damage referred to as a *coup*. In addition, reactive forces may bounce the brain against the skull on the opposite side of the head, resulting in a *countercoup*. Occipital deficits are sometimes observed in car accident victims who suffer a countercoup. Certain regions are especially sensitive to the effects of coups and countercoups. The inside surface of the skull is markedly jagged above the eye sockets; and, as Figure 4.19 shows, this rough surface can produce extensive tearing of brain tissue in the orbitofrontal region.

Open head injuries happen when the skull is penetrated by an object like a bullet or shrapnel. With these injuries, tissue may be directly damaged by the penetrating object. The impact of the object can also create reactive forces producing coup and countercoup.

Additional damage can follow a traumatic event as a result of vascular problems and increased risk of infection. Trauma can disrupt blood flow by severing vessels, or it can change intracranial pressure as a result of bleeding. Swelling after trauma might generate further brain damage, and seizures, common after trauma, can originate in scarred tissue.

Figure 4.19 Trauma can cause extensive destruction of neural tissue. Damage can arise from the collision of the brain with the solid internal surface of the skull, especially along the jagged surface over the orbital region. In addition, accelerative forces created by the impact can cause extensive shearing of dendritic arbors. (a) In this brain of a 54-year-old man who had sustained a severe head injury 24 years prior to death, tissue damage is evident in the orbitofrontal regions and was associated with intellectual deterioration subsequent to the injury. (b) The susceptibility of the orbitofrontal region to trauma was made clear by A. Holbourn of Oxford in 1943, who filled a skull with gelatin and then violently rotated the skull. Although most of the brain retains its smooth appearance, the orbitofrontal region has been chewed up.



Early work on localizing cognitive function often involved patients with traumatic injuries. The eminent British neurologist Sir Gordon Holmes (1919) provided some of the classic descriptions of cerebellar and occipital lobe function based on his observations of World War I soldiers who had open head injuries. Indeed, prior to the invention of CT, open head injuries offered the best way to localize brain damage while the patient was still alive. Note, however, that trauma patients frequently have multiple neuropsychological problems because the neurological damage is generally extensive and diffuse.

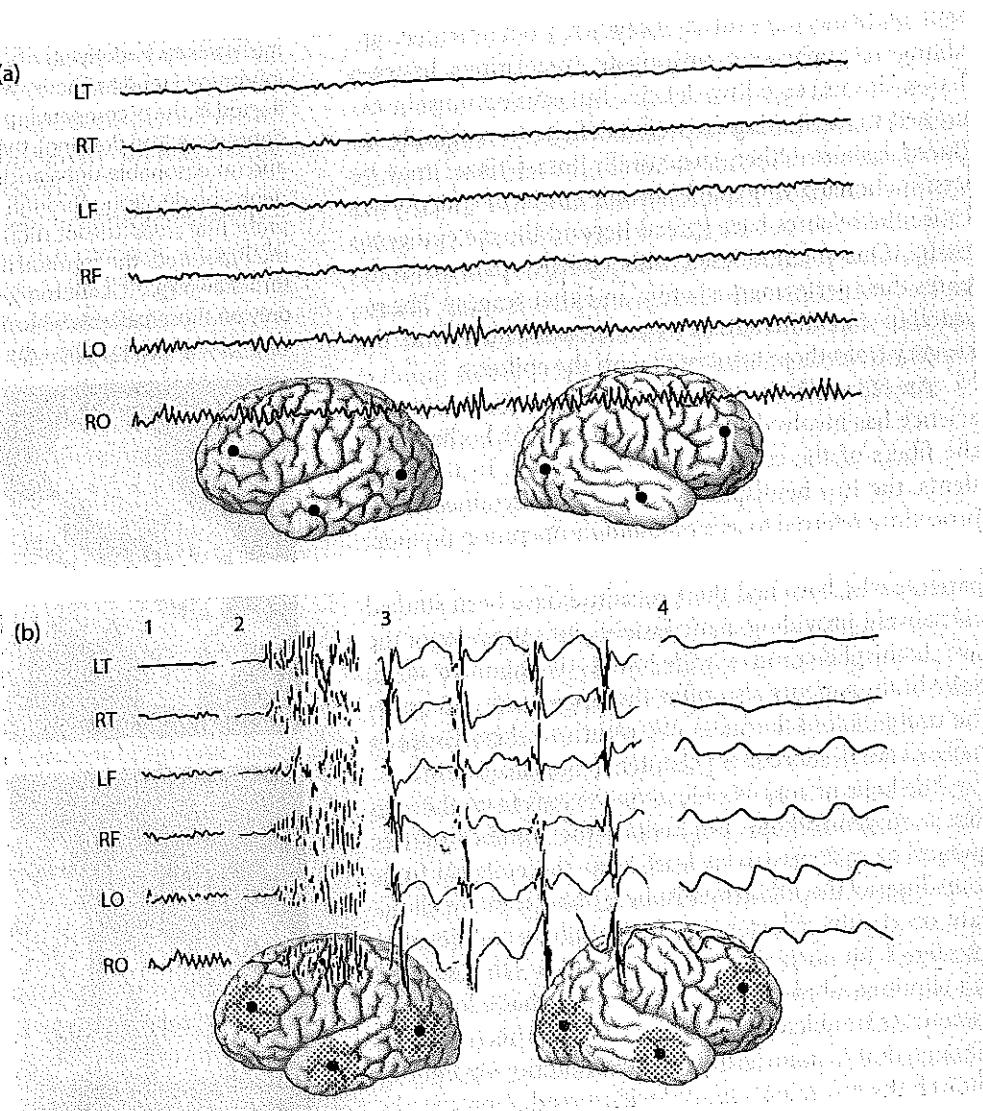
EPILEPSY

Epilepsy is a condition characterized by excessive and abnormally patterned activity in the brain. The cardinal symptom is a seizure, a transient loss of consciousness.

The extent of other disturbances varies. Some epileptics shake violently and lose their balance. For others, seizures may be perceptible only to the most attentive friends and family. Seizures are confirmed by electroencephalography (EEG) to record the patient's brain waves (see the section titled "Electrical and Magnetic Signals" later in this chapter). During the seizure, the EEG profile is marked by large-amplitude oscillations (Figure 4.20).

The frequency of seizures is also variable. The most severely affected patients can have hundreds of seizures each day, with each seizure disrupting function for a few minutes. Other epileptics suffer only an occasional seizure, but it may incapacitate the person for a couple of hours. Furthermore, simply having a seizure is not diagnostic of epilepsy. Although 0.5% of the general population has epilepsy, it is estimated that one in 20 people will have a seizure at some point during life. Often the

Figure 4.20 Electroencephalographic recordings from six electrodes, positioned over the frontal (F), temporal (T), and occipital (O) cortex on both the left (L) and the right (R) sides. **(a)** Activity during normal cerebral activity. **(b)** Activity during a grand mal seizure.



seizure is triggered by an acute event such as trauma, exposure to toxic chemicals, or high fever. Approximately 50% to 70% of epileptics respond well when treated with antiseizure medication. For the remaining patients, surgery may be an option if the disorder is chronic and severely debilitating.

Neuropsychologists are generally not interested in the cognitive deficits associated with epilepsy as they relate to normal function. Because the seizures disrupt neural activity across large sections of the brain, it is difficult to link behavioral deficits with structural abnormalities.

Functional Neurosurgery

Surgical interventions for treating neurological disorders provide a unique opportunity to investigate the link between brain and behavior. The best example comes from research involving patients who have undergone surgical treatment for the control of intractable epilepsy. The extent of tissue removal is always well documented, enabling researchers to investigate correlations between lesion site and cognitive deficits. But caution must be exercised in attributing cognitive deficits to surgically induced lesions. Other, structurally intact tissue may be dysfunctional owing to the chronic effects of epilepsy because the seizures have spread beyond the epileptogenic tissue. One method used with epilepsy patients compares their performance before and after surgery. The researcher can differentiate changes associated with the surgery from those associated with the epilepsy.

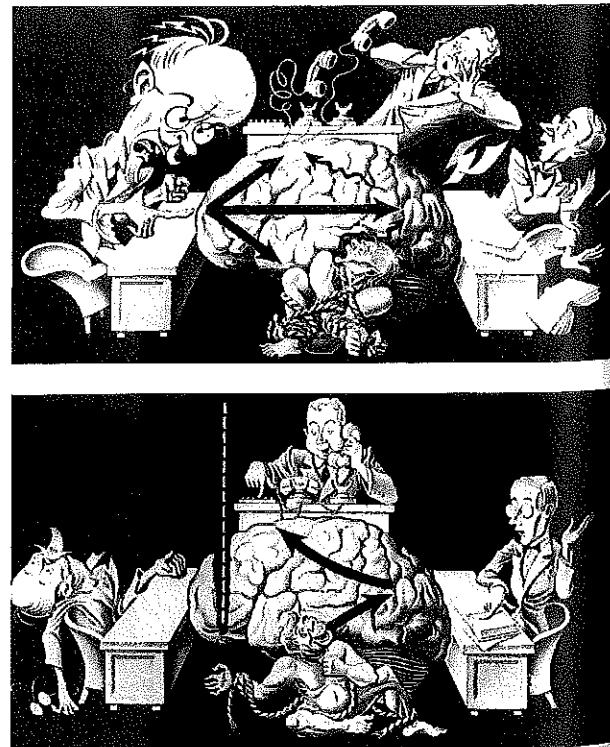
An especially fruitful paradigm for cognitive neuroscience has involved the study of patients who have had the fibers of the corpus callosum severed. In these patients, the two hemispheres have been disconnected—a procedure referred to as a *callosotomy* operation or, more informally, the *split-brain* procedure. The relatively few patients who have had this procedure have been studied extensively, providing many insights into the roles of the two hemispheres on a wide range of cognitive tasks. Split-brain patients also offer the opportunity to assess the unity of consciousness. We return to these issues in more detail in subsequent chapters (e.g., Chapter 11).

The logic of corpus callosotomy stems from the idea that a surgeon's knife can reduce the number or frequency of seizures (or at least keep the epilepsy from spreading to the other hemisphere) and thereby eliminate or greatly reduce physiological abnormalities that interfere with normal function. This idea—that surgery can eliminate abnormal brain function—has a long and sometimes troubled history in neurology. This reasoning motivated the notorious frontal lobotomy operation. Though the procedure enjoyed widespread popularity in

the middle of the 20th century as a treatment for depression, schizophrenia, and other psychiatric disorders, its theoretical motivation was weak—perhaps best captured in the *Life* magazine cartoon shown in Figure 4.21. A hyperactive superego, localized in the frontal lobes, was assumed to exert excessive control over posterior brain regions. Slicing the white matter in the frontal cortex (with crude techniques such as inserting an ice pick behind the eye sockets!) was thought to restore balance by reducing the connections between frontal and posterior brain regions.

In the preceding examples, neurosurgery was eliminative in nature, but it has also been used as an attempt to restore normal function. Examples are found in current treatments for Parkinson's disease, a movement disorder

Figure 4.21 *Life* magazine cartoon from 1947, sketching the mechanisms underlying the supposed benefits of the frontal lobotomy. Freudian theory was in its heyday at the time, as reflected in the accompanying caption, which read, "In agitated depression (top drawing), the superego becomes overbearing and unreasonable, unbalancing the whole mind. . . . The surgeon's blade, slicing through the connections between the prefrontal areas (the location of the superego) and the rest of the brain, frees the tortured mind from its tyrannical ruler (bottom drawing). . . . Lobotomy, however, should be performed only on those patients whose intelligence is sufficient to take control of behavior when the moral authority is gone."



resulting from basal ganglia dysfunction. Although the standard treatment is medication, the efficacy of the drugs can change over time and even produce debilitating side effects. Some patients who develop severe side effects are now treated surgically. One technique that has become widely used is **deep-brain stimulation (DBS)**, in which electrodes are implanted in the basal ganglia. These devices produce continuous electrical signals that trigger neural activity. Dramatic and sustained improvements are observed in many patients who undergo this procedure (Hamani et al., 2006; Krack et al., 1998). DBS is discussed in more detail in Chapter 7.

Another approach for treating severe Parkinson's disease is the use of fetal brain transplants. Neurochemically, Parkinson's disease results from a loss of cells in the substantia nigra, a nucleus that is the source of dopaminergic inputs to the basal ganglia and frontal cortex. To restore function to the basal ganglia, cells from aborted fetuses are placed in structures that receive inputs from the nigra. The fetal tissue is able to develop into dopamine-sensitive neurons (Kordower et al., 1995). In animals, fetal grafts have been placed in the spinal cord to promote reconnection of descending motor fibers following spinal resection.

A more dramatic development in clinical research—one that has garnered tremendous attention in public discussion—is the work on stem cells. The idea here is similar to that underlying neural transplants. However, the key difference is that, whereas transplants use tissue that is functionally similar to that of the targeted region, embryonic stem cells are immature cells from the developing embryo that have not yet differentiated and thus

have, in theory, limitless potential. That is, these cells have the potential of becoming a cell within any body system: circulatory, digestive, neural, or any other body part. Moreover, within these systems, stem cells can develop into specific cell types. The same stem cells could be used to create visual neurons, motor neurons, or cells in higher association areas.

The goal of stem cell research is to implant stem cells into a region where the adult cells have been damaged or atrophied and to create conditions such that the stem cells will mature, replacing and replenishing the damaged cells to restore function. For instance, someone who has had spinal cord injury could receive stem cell implants or injections in the damaged region. Over time, these neurons would mature into motor neurons, capable of conducting signals between the brain and periphery to allow the person to recover the ability to produce movement. The promise of stem cells is limitless. Researchers already envision a day in the not-too-distant future when stem cells might be used to reverse the effects of atrophic degenerative processes such as Alzheimer's disease.

We are still a long way from this goal, but major advances have occurred in the past decade. Recent studies have found that embryonic neural transplants can survive and even form synapses in an adult host's spinal cord (Fricker-Gates et al., 2002). The most successful growth appears to occur when neurological growth factors are present and the targeted area has not suffered a complete loss of cells. Possibly the remaining tissue helps provide signals for the development of pre- and postsynaptic circuits (Harel & Strittmatter, 2006).

CONVERGING METHODS

So far, we have taken a brief look at the basic methodologies of cognitive psychology, computer modeling, neurosciences, and neurology. Each discipline has unique methodologies for learning about the nature of the mind and the relation between brain and mind. But the real strength of cognitive neuroscience comes from the way in which these diverse methodologies are integrated, which is the subject of this final section.

Cognitive Deficits Following Brain Damage

Perhaps the best-established paradigm of cognitive neuroscience involves the effects of brain injury on behavior. For many centuries lesions have been studied extensively in animals and humans, and, as noted earlier in this chapter, the lesion model has laid an empirical founda-

tion for learning about brain organization. Fundamental concepts, such as the left hemisphere's dominant role in language or the dependence of visual functions on posterior cortical regions, were developed by observation of the effects of brain injury.

Two developments in the past 30 years have led to significant advances in the study of neurological patients. First, with neuroimaging methods such as CT and MRI, we can precisely localize brain injury *in vivo*. Second, the paradigms of cognitive psychology have provided the tools for making more sophisticated analyses of the behavioral deficits observed after brain injury. Early neuropsychological work focused on localizing complex tasks: language, vision, executive control, motor programming. The essence of the cognitive revolution has been that these complex tasks require

the integrative activity of many component operations. Cognitive neuropsychologists have extended this idea to research on brain-injured patients. Indeed, the excitement about neuropsychological research is not restricted to its potential to link mental activities to brain structures. Equally important, many researchers recognize that the study of dysfunctional behavior can help identify the component operations that underlie normal cognitive performance.

The logic of this approach is straightforward. If a behavior depends on processing within a certain brain structure, then damage to this structure should disrupt the behavior. As such, this approach assumes that brain injury is eliminative—that brain injury disturbs or eliminates the processing ability of the affected structure.

Consider the following example. Suppose that damage to brain region A results in impaired performance on task X. One conclusion is that region A contributes to the processing required for task X. For example, if task X is reading, we might conclude that region A is critical for reading. But from cognitive psychology we know that a complex task such as reading has many component operations: fonts must be perceived, letters and letter strings must activate representations of their corresponding meanings, and syntactic operations must link individual words into a coherent stream. By merely testing reading ability, we will not know which component operation or operations are impaired when there are lesions to region A. What the cognitive neuropsychologist wants to do is design tasks that diagnose the function of specific operations. If a reading problem stems from a general perceptual problem, then comparable deficits should be seen on a range of tests of visual perception. If the problem reflects the loss of semantic knowledge, then the deficit should be limited to tasks that require some form of object identification or recognition.

Associating neural structures with specific processing operations calls for appropriate control conditions. The most basic form of control is to compare the performance of a patient or group of patients with that of healthy subjects. Poorer performance by the patients might be taken as evidence that the affected brain regions are involved in the task. Thus, if we had a group of patients with lesions in the frontal cortex who showed impairment on our reading task, we might suppose that this region of the brain was critical for reading. Keep in mind, however, that brain injury can produce widespread changes in cognitive abilities. The frontal lobe patient not only might have trouble in reading but also might demonstrate impairment on just about any task, such as problem solving, memory, or motor planning. Thus, the challenge for the cogni-

tive neuroscientist is to determine whether the observed behavioral problem results from damage to a particular mental operation or is secondary to a more general disturbance. For example, many patients are depressed after a neurological disturbance such as a stroke, and depression is known to affect performance on a wide range of tasks.

SINGLE AND DOUBLE DISSOCIATIONS

Cognitive neuropsychologists typically design experiments that have at least two tasks: an experimental task and a control task. The best experiments are those in which the two tasks are similar in most respects but differ in requiring one hypothetical mental operation. Suppose a researcher is interested in the association between two aspects of memory. One aspect is knowledge about when we learned a particular fact or piece of information. For example, people who were alive in 1963 can recall not only that President Kennedy was killed in Dallas but also where they were when they first heard about the tragedy. A second aspect relates to the familiarity we have with that fact or piece of information. We recognize that our memory of Kennedy's death is not simply the result of that initial experience, but also a product of the countless news documentaries, books, and movies that have rehashed that event.

Our researcher hypothesizes that these two aspects of memory are separable. One way to test this hypothesis is to examine patients with memory disorders. For example, if the hypothesis is that familiarity is associated with the temporal lobe, then the researcher might test patients with temporal lobe lesions on two memory tests: one designed to look at memory of when information was acquired, and the second designed to look at familiarity. Patients with memory problems would be required to perform two tasks. For each task, the stimuli would be identical: a series of abstract drawings in which some items are shown once, others twice, and others three times. To test how well the patients remember when they learned something, the subjects would be presented with a pair of drawings and asked to judge which drawing was presented first—a test of temporal order. To test for familiarity, a frequency judgment task can be used. Here, the subjects would again be presented with a pair of drawings, but now they would have to decide which drawing they had seen more often. If temporal lobe lesions disrupt familiarity but not the ability to remember when something was learned, then the patients should demonstrate selective impairment on the frequency task. To detect the impairment, it would be necessary

to include a control group, such as people with no neurological problems.

Assuming the patients were selectively impaired on the frequency task, our researchers would have observed a **single dissociation** (Figure 4.22a). In single dissociations, two groups are tested on two tasks and a between-group difference is apparent in only one task. Two groups are necessary, so that the patients' performance can be compared with that of a control group. Two tasks are necessary to examine whether a deficit is specific to a particular task or reflects a more general impairment. Many conclusions in neuropsychology are based on single dissociations: Compared to control subjects, patients with hippocampal lesions cannot develop long-term memories even though their short-term memory is intact. Patients with Broca's aphasia have intact comprehension but struggle to speak fluently.

Single dissociations have unavoidable problems. In particular, the two tasks are assumed to be equally sensitive to differences between the control and experimental groups. However, often this is not the case. One task may be more sensitive than the other because of

differences in task difficulty or sensitivity problems in how the measurements are obtained. For example, the frequency judgment task might be more demanding than the temporal-order task, requiring a greater degree of concentration. If the brain injury produced a generalized problem in concentration, then the patients might have difficulty with this task, but the problem would not be due to a specific problem in memory for familiarity.

As an analogy, consider a comparison between two six-cylinder cars: one with an engine in mint condition, and a second that is running on only five cylinders. It might be difficult to tell the difference between the two cars when driving through the city because the speed must be kept low and frequent stops are necessary. But if the cars were taken out on the highway, it would quickly become apparent that one car drives rougher than the other. However, we would not want to conclude that this car has a selective deficit in highway driving. Rather, our city-driving test was not sufficiently sensitive to detect the persistent problem.

Double dissociations avoid these problems. In double dissociations, group 1 is impaired on task X and group 2 is impaired on task Y (Figure 4.22b). The two groups' performances can be compared to each other, or more commonly, the patient groups are compared with a control group that shows no impairment. With a double dissociation, it is no longer reasonable to argue that a difference in performance results merely from the unequal sensitivity of the two tasks. In our memory example, the claim that temporal lobe patients have a selective problem with familiarity would be greatly strengthened if it were shown that a second group of patients (e.g., frontal lobe patients) showed selective impairment on the temporal-order task. Double dissociations offer the strongest neuropsychological evidence that a patient or patient group has a selective deficit in a certain cognitive operation.

The inferential power of double dissociations has been exploited in many settings beyond the neuropsychology laboratory. Lesion studies in animals are most convincing when the conclusions are based on double dissociations. Cognitive research on healthy subjects has also benefited from the logic of double dissociations. Evidence of separable cognitive operations can be gained by demonstration that one task is affected by one type of manipulation, whereas a second task is selectively affected by a different manipulation. For example, in normal subjects the rate at which the stimuli appear might be found to affect performance on the temporal-order task, whereas the similarity between the stimuli affects familiarity performance. Here, the same subjects

Figure 4.22 Hypothetical series of results conforming to either a single (a) or a double (b) dissociation. With the single dissociation, the patient group shows impairment on one task and not on the other. With the double dissociation, one patient group shows impairment on one task and a second patient group shows impairment on the other task. Double dissociations provide much stronger evidence for a selective impairment.

(a) Single dissociation

Group	Tasks (% correct)	
	Recency memory	Familiarity memory
Temporal lobe damage	90	70
Controls	90	95

(b) Double dissociation

Group	Tasks (% correct)	
	Recency memory	Familiarity memory
Temporal lobe	90	70
Frontal lobe	60	95
Controls	90	95

serve as their own controls. The double dissociation arises because the two manipulations—rate and similarity—differentially affect performance on the two tasks. Such a result would suggest that the two tasks involve nonoverlapping component operations (Figure 4.23).

GROUPS VERSUS INDIVIDUALS

In many neuropsychological studies, groups are defined according to whether patients have a common neurological diagnosis (e.g., Alzheimer's disease) or have pathology in a common neural region (e.g., frontal strokes). Group studies have been criticized as inappropriate for human neuropsychology because of the variability among patients assigned to the same groups. No two strokes or tumors are exactly alike. In a similar sense, neurological and cognitive deficits found in degenerative diseases such as Alzheimer's disease vary from patient to patient. Human neuropsychology will never approximate the type of control that is possible in animal research, where the experimenter can dictate the size and location of the lesion. Even powerful MRI machines provide a relatively crude resolution compared to the histological procedures available to researchers working with animals, and some types of lesions go undetected with either CT or MRI. Given this anatomical variability, the utility of lumping patients into a single group has been questioned, as we should expect a similar lack of correspondence at the behavioral level. Instead, it has been argued that insights into cognitive processes can best be achieved by comprehensive documentation of the performance of individual patients and comparison across case studies (Caramazza, 1992).

In general, proponents of the case study approach want to use patient studies to develop models of cognitive architecture. Double dissociations are especially prominent. Individuals with unique deficits help isolate the component operations of a task. Yet the case study approach is more limited for linking neural structures to cognitive operations. Lesions from strokes or tumors encompass a wide area and affect several disparate structures. It is difficult to know which affected area correlates with a deficit. Group studies offer hope. Though the extent and location of damage may be heterogeneous, reconstruction software can identify regions of overlap, as Figure 4.24 shows. Despite individual differences that might occur because lesions extend into nonidentical regions, the common site of pathology might produce a consistent pattern of deficits on a task being studied.

The debate over group studies versus individual case studies reflects the difference between the root words in cognitive neuroscience and cognitive neuropsychology.

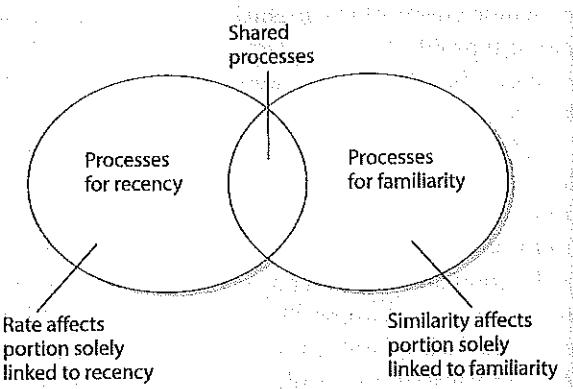


Figure 4.23 We can identify the mental operations required for a particular task by showing that different manipulations selectively influence different aspects of performance. In this example, it is hypothesized that recognition memory depends on both recency and familiarity, and that these two processes can be influenced by separate manipulations.

The case study method affords powerful insights into the functional components of cognition. For example, case studies have been essential for demonstrating that brain lesions can selectively disrupt restricted semantic classes. One patient studied by Alfonzo Caramazza and his colleagues at Johns Hopkins University showed a peculiar anomia, the inability to name things (Hart et al., 1985). For this patient, the problem was restricted to certain classes of objects. He was unable to generate the names of fruits and vegetables. In contrast, he showed no impairment when asked to name objects such as tools or furniture. If a study had been conducted with a group of patients with anomia, this patient's selective problem might have been attributed to normal between-subject variability. When he was treated as an isolated case, the problem stood out and inspired researchers to look for patients with similar problems, as well as patients with other category-specific anomias. This work has led to sophisticated models of the functional organization of semantic knowledge.

On the other hand, group studies have proved useful for relating cognitive processes to underlying brain structures (Robertson, Knight, et al., 1993). If a brain structure is hypothesized to perform a particular mental operation, then lesions to this structure should be associated with deficits on tasks that depend on the putative operation. This does not mean that all patients will be similarly affected. For some patients, the pathology may not be as extensive or encroach on the critical tissue. Moreover, as with healthy subjects, individuals will differ in how they perform a particular task, or they may have

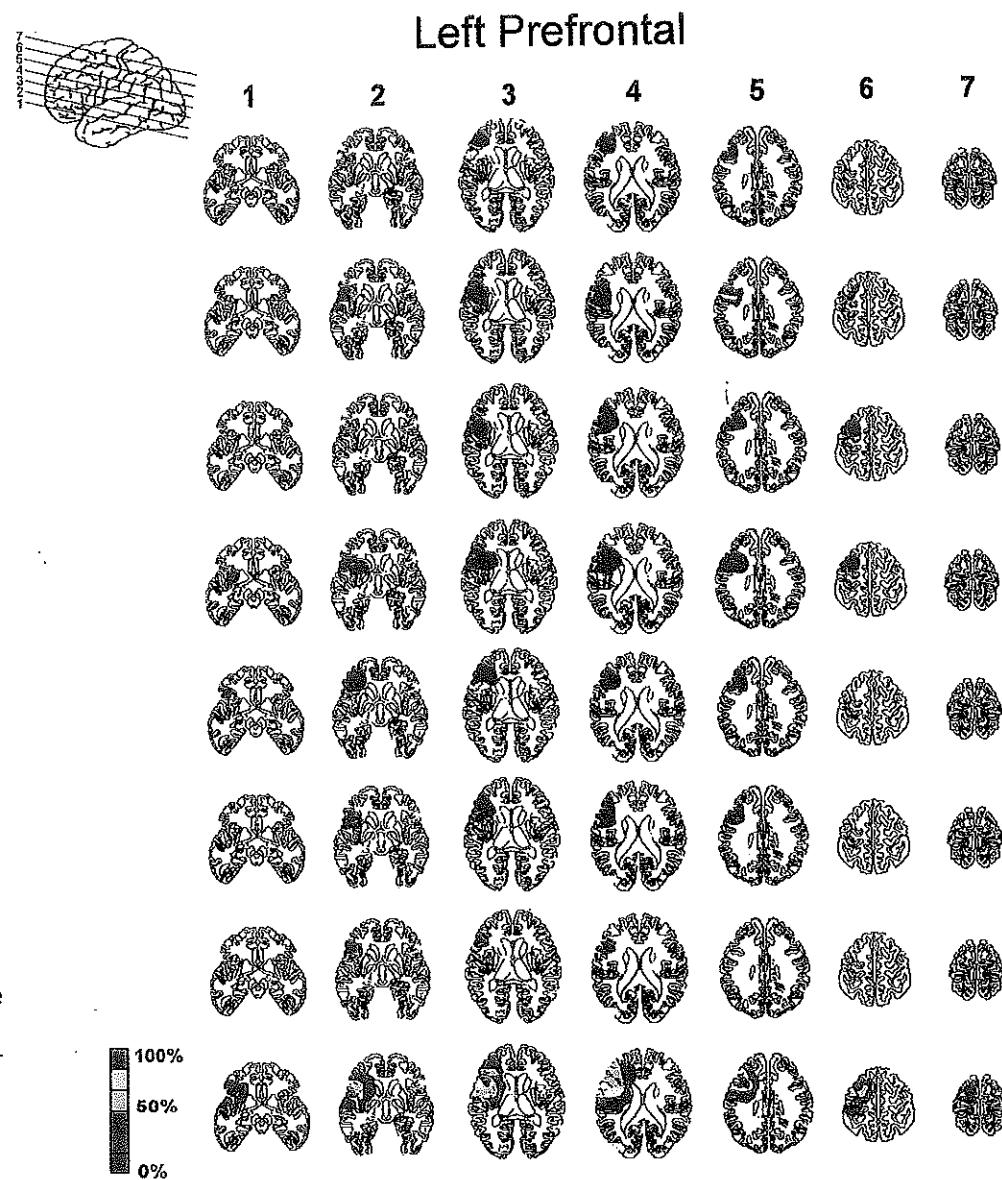


Figure 4.24 Drawing inferences from the study of humans with brain damage is difficult because naturally occurring brain lesions are never identical. Group studies can facilitate the functional analysis of brain structures by identifying regions of lesion overlap. Shown here are sketches of the extent of lesions in seven patients who had strokes in the frontal lobe of the left hemisphere. The individual patients are represented in each row, with the transverse slices going from inferior to superior (as the upper left diagram shows). The bottom row shows the extent of damage for the group in composite form.

developed idiosyncratic strategies. Nonetheless, group studies allow the researcher to look for similarities across patients with related lesions, as well as to make systematic comparisons between the effects of lesions centered in different brain structures.

Virtual Lesions: Transcranial Magnetic Stimulation

Lesion methods have been an important tool for both human and animal studies of the relationship between the brain and behavior. Observations of the performance of neurologically impaired individuals have tended to

serve as the starting point for many theories. Nonetheless, it is important to keep in mind that, with human studies, the experimenter is limited by the vagaries of nature (or the types of damage caused by military technology). Lesion studies in animals have the advantage that the experimenter can control the site and size of the damage. Here a specific hypothesis can be tested by comparison of the effects of lesions to one region versus another.

Transcranial magnetic stimulation (TMS) offers a methodology to noninvasively produce focal stimulation of the brain in humans. The TMS device consists of a tightly wrapped wire coil that is encased in an insulated sheath and connected to a source of powerful

electrical capacitors (Figure 4.25a and b). When triggered, the capacitors send a large electrical current through the coil, resulting in the generation of a magnetic field. When the coil is placed on the surface of the skull, the magnetic field passes through the skin and scalp and induces a physiological current that causes neurons to fire (Figure 4.26). The exact mechanism causing the neural discharge is not well understood. Perhaps the current leads to the generation of action potentials in the soma; alternatively, the current may directly stimulate axons. The area of neural activation will depend on the shape and positioning of the coil. With currently available coils, the primary activation can be restricted to an area of about 1.0 to 1.5 cm³, though there are also downstream effects (see Figure 4.25d).

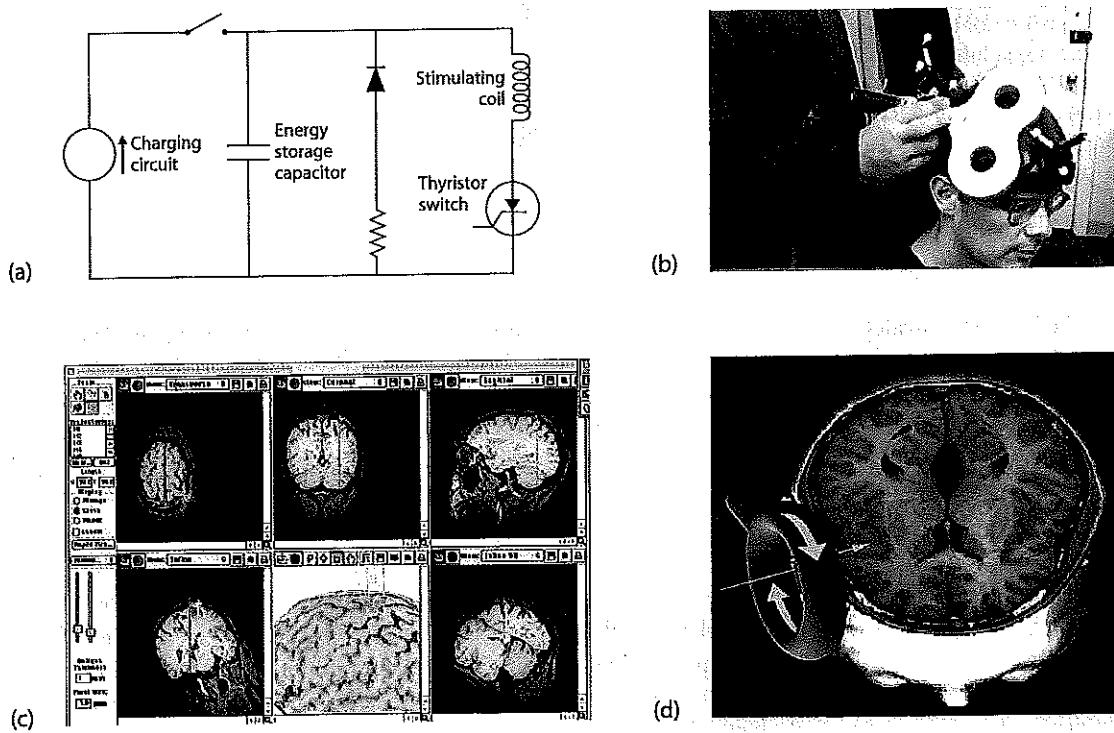
TMS has been used to explore the role of many different brain areas. When the coil is placed over the hand area of the motor cortex, stimulation will activate the muscles of the wrist and fingers. The sensation can be rather bizarre: The hand visibly twitches, yet the subject is aware that the movement is completely involuntary! Like many research tools, TMS was originally developed for clinical purposes. Direct stimulation of the motor

cortex provides a relatively simple way to assess the integrity of motor pathways because muscle activity in the periphery can be detected about 20 ms after stimulation.

The ability to probe the excitability of the motor cortex with TMS has been exploited in many basic research studies. Consider how we come to understand the gestures produced by another individual—for example, when someone waves at us as a greeting or throws a ball to another friend. Recognition of these gestures surely involves an analysis of the perceptual information. But comprehension may also require relating these perceptual patterns to our own ability to produce similar actions. Indeed, as TMS shows, the motor system is activated during passive observation of actions produced by other individuals. Although we can assume that the increased excitability of the motor cortex is related to our experimental manipulation, we cannot infer that this change is required for action comprehension. Such a claim of causality would require showing that lesions of the motor cortex impair comprehension.

A different use of TMS is to induce “virtual lesions” (Pascual-Leone et al., 1999). By stimulating the brain, the experimenter is disrupting normal activity in a se-

Figure 4.25 Transcranial magnetic stimulation. (a) This schematic shows the electrical circuit used to induce the TMS pulse. (b) Here the TMS coil is being applied by an experimenter. Both the coil and the subject have affixed to them a tracking device to monitor the head/coil position in real time. (c) The subject's MRI can be used along with the tracking system to display the cortical area being targeted. (d) The TMS pulse directly alters neural activity in a spherical area of approximately 1 cm³.



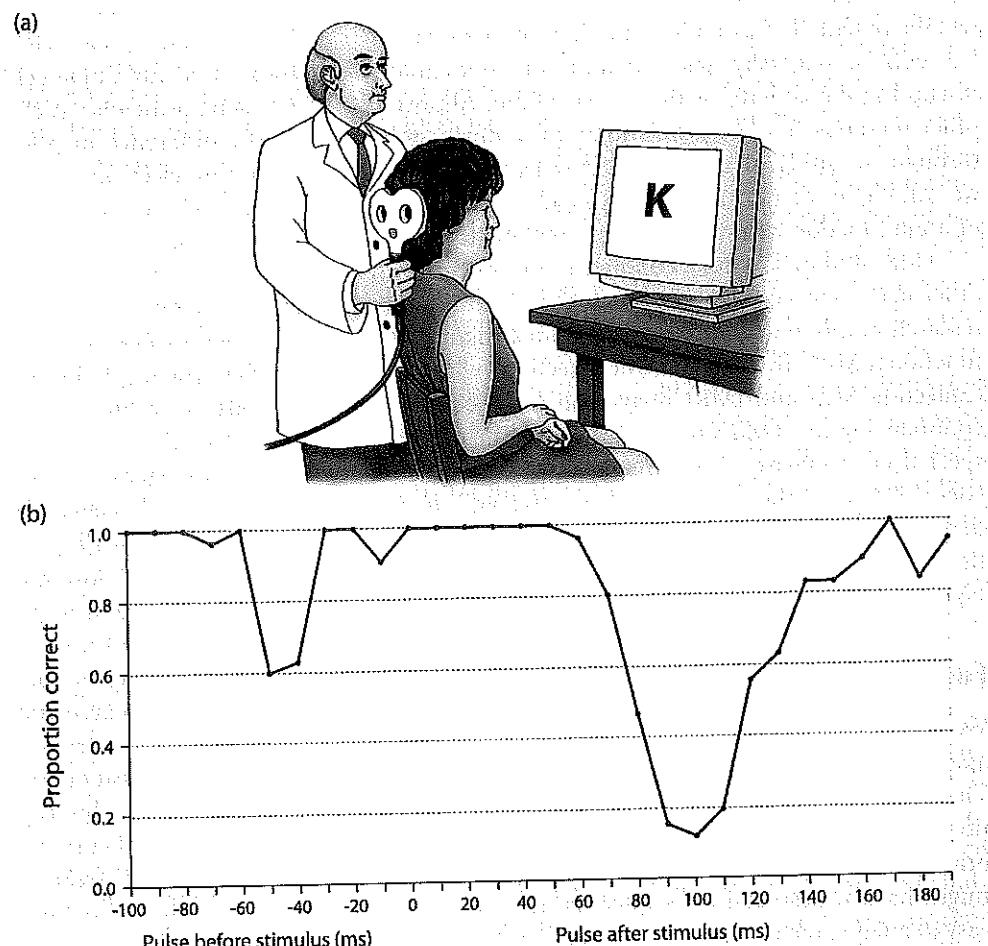


Figure 4.26 Transcranial magnetic stimulation over the occipital lobe. (a) The center of the figure-eight coil is placed over the targeted area. When a large electrical field is passed through the coil, a magnetic pulse is generated and passes through the skull. This pulse activates neurons in the underlying cortex. (b) The time between the onset of the letter stimulus and the pulse varies. When the pulse follows the stimulus by 70 to 130 ms, the subject fails to identify the stimulus on all trials. Note the failures when the pulse precedes the letter. These occur because the subject briefly blinks on some trials after the pulse.

lected region of the cortex. Similar to the logic in lesion studies, the consequences of the stimulation on behavior are used to shed light on the normal function of the disrupted tissue. What makes this method appealing is that the technique, when properly conducted, is safe and noninvasive, producing only a relatively brief alteration in neural activity. Thus, performance can be compared between stimulated and nonstimulated conditions in the same individual. This, of course, is not possible with brain-injured patients.

The virtual-lesion approach has been successfully employed with stimulation of various brain sites, even when the person is not aware of any effects from the stimulation. For example, stimulation over visual cortex can interfere with a person's ability to identify a letter (Corthout et al., 1999). The synchronized discharge of the underlying visual neurons interferes with their normal operation. The timing between the onset of the TMS pulse and the onset of the stimulus (e.g., presenta-

tion of a letter) can be manipulated to plot the time course of processing. In the letter identification task, the person will err only if the stimulation occurs between 70 and 170 ms after presentation of the letter. If the TMS is given before this interval, the neurons have time to recover; if the TMS is given after this interval, the visual neurons have already responded to the stimulus.

TMS has some notable limitations. As the previous example illustrated, the effects of TMS are generally quite brief. The method tends to work best with tasks in which the stimulation is closely linked to either stimulus events or movement. It remains to be seen if more complex tasks can be disrupted by brief volleys of externally induced stimulation. The fact that stimulation activates a restricted area of the cortex is both a plus and a minus. The experimenter can restrict stimulation to a specific area, especially if the coordinates are based on MRI scans. But TMS will be of limited value in exploring the function of cortical areas that are not on the superficial

surface of the brain. Despite these limitations, TMS offers the potential of providing the cognitive neuroscientist with a relatively safe method for momentarily disrupting the activity of the human brain. Almost all other methods rely on correlational procedures, either through the study of naturally occurring lesions or, as we will see in the next section, through the observation of brain function with various neuroimaging tools.

TMS studies are best conducted in concert with other neuroscience methods. Much of the cutting-edge research in this area combines data from structural and functional MRI (fMRI; see the next section) with TMS. Collecting MRI and fMRI images on a subject before commencing the TMS study, and feeding the data into specialized software programs, allows for real-time copositioning of the TMS stimulation area and the underlying anatomical region (MRI) with known functional activation (fMRI) in an individual subject (see Figure 4.25b and c).

Functional Imaging

We already mentioned that patient research rests on the assumption that brain injury is an eliminative process: The lesion is believed to disrupt certain mental operations while having little or no impact on others. But the brain is massively interconnected, so damage in one area might have widespread consequences. It is not always easy to analyze the function of a missing part by looking at the operation of the remaining system. For example, allowing the spark plugs to decay or cutting the line distributing the gas to the pistons will cause an automobile to stop running, but this does not mean that spark plugs and distributors do the same thing; rather, their removal has similar functional consequences.

Concerns such as these point to the need for methods that measure activity in the normal brain. Along this front have occurred remarkable technological breakthroughs during the past 25 years. Indeed, new tools and methods of analysis develop at such an astonishing pace that new journals and scientific organizations have been created for rapid dissemination of this information. In the following section we review some of the technologies that allow researchers to observe the electrical and metabolic activity of the healthy human brain *in vivo*.

ELECTRICAL AND MAGNETIC SIGNALS

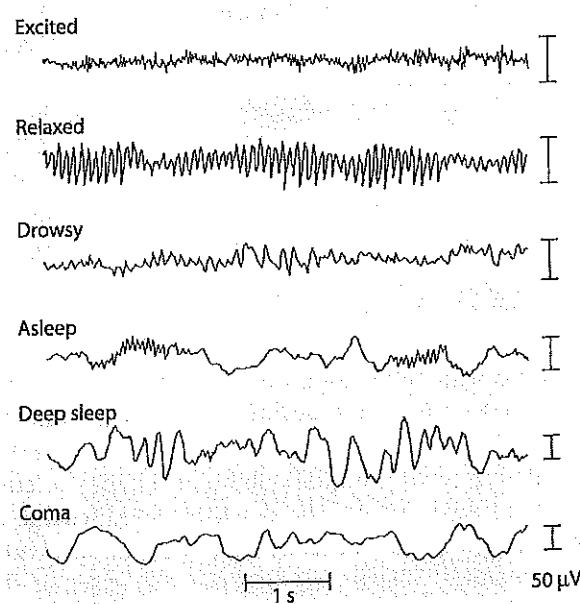
Neural activity is an electrochemical process. Although the electrical potential produced by a single neuron is minute, when large populations of neurons are active together, they produce electrical potentials large

enough to be measured by electrodes placed on the scalp. These surface electrodes are much larger than those used for single-cell recordings, they but involve the same principles: A change in voltage corresponding to the difference in potential between the signal at a recording electrode and the signal at a reference electrode is measured. This potential can be recorded at the scalp because the tissues of the brain, skull, and scalp passively conduct the electrical currents produced by synaptic activity. The record of the signals is referred to as an *electroencephalogram*.

Electroencephalography, or EEG, provides a continuous recording of overall brain activity and has proved to have many important clinical applications. The reasons stem from the fact that predictable EEG signatures are associated with different behavioral states (Figure 4.27). In deep sleep, for example, the EEG is characterized by slow, high-amplitude oscillations, presumably resulting from rhythmic changes in the activity states of large groups of neurons. In other phases of sleep and during various wakeful states, this pattern changes, but in a predictable manner.

Because the normal EEG patterns are well established and consistent among individuals, EEG recordings can detect abnormalities in brain function. As noted earlier, EEG provides valuable information in the assessment and treatment of epilepsy (see Figure 4.20b). Of the many forms of epileptic seizures, gener-

Figure 4.27 EEG profiles obtained during various states of consciousness.



alized seizures have no known locus of origin and appear bilaterally symmetrical in the EEG record. Focal seizures, in contrast, begin in a restricted area and spread throughout the brain. Focal seizures frequently provide the first hint of a neurological abnormality. They can result from congenital abnormalities such as a vascular malformation or can develop as a result of a local infection, enlargement of a tumor, or residual damage from a stroke or traumatic event. Surface EEG can only crudely localize focal seizures, because some electrodes detect the onset earlier and with higher amplitude than other electrodes.

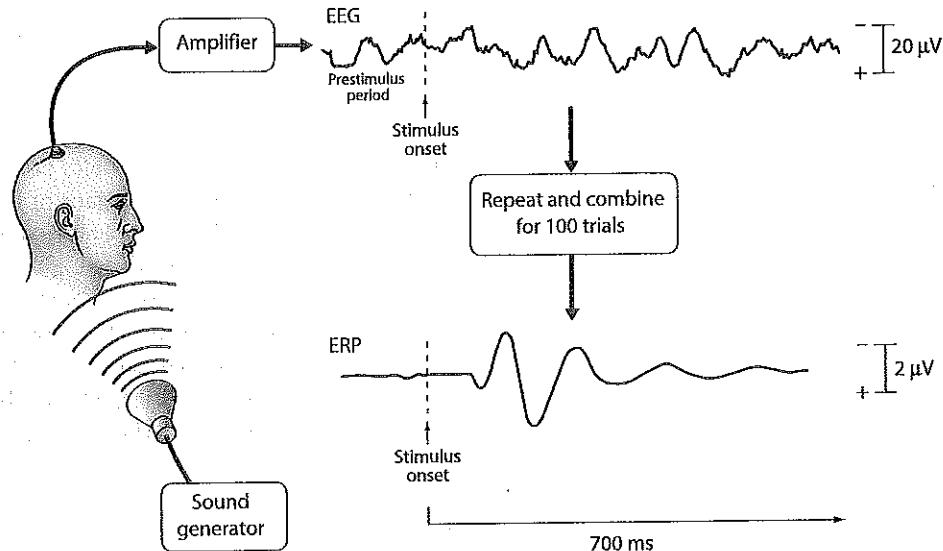
EEG is limited in providing insight to cognitive processes because the recording tends to reflect the brain's global electrical activity. A more powerful approach used by many cognitive neuroscientists focuses on how brain activity is modulated in response to a particular task. The method requires extracting an evoked response from the global EEG signal.

The logic of this approach is straightforward. EEG traces from a series of trials are averaged together by being aligned according to an external event, such as the onset of a stimulus or response. This alignment washes out variations in the brain's electrical activity that are unrelated to the events of interest. The evoked response, or **event-related potential (ERP)**, is a tiny signal embedded in the ongoing EEG. By averaging the traces, investigators can extract this signal, which reflects neural activity that is specifically related to sensory, motor, or cognitive events—hence the name *event-related potential* (Figure 4.28). A significant feature of evoked re-

sponses is that they provide a precise temporal record of underlying neural activity. The evoked response gives a picture of how neural activity changes over time as information is being processed in the human brain.

ERPs have proved to be an important tool for both clinicians and researchers. Sensory evoked responses offer a useful window for identifying the level of disturbance in patients with neurological disorders. For example, the visual evoked potential can be useful in the diagnosis of multiple sclerosis, a disorder that leads to demyelination. When demyelination occurs in the optic nerve, the early peaks of the visual evoked response are delayed in their time of appearance. Similarly, in the auditory system, tumors that compromise hearing by compressing or damaging auditory processing areas can be localized by the use of auditory evoked potentials (AEPs) because characteristic peaks and troughs in the AEP are known to arise from neuronal activity in anatomically defined areas of the ascending auditory system. The earliest of these AEPs indexes activity in the auditory nerve, occurring within just a few milliseconds of the sound. Within the first 20 to 30 ms, a series of responses indexes, in sequence, neural firing in the brainstem, midbrain, thalamus, and cortex (Figure 4.29). These stereotyped responses allow the neurologist to pinpoint the level at which the pathology has occurred. Thus, by looking at the sensory evoked responses in patients with hearing problems, the clinician can determine if the problem is due to poor sensory processing and, if so, at what level the deficit becomes apparent.

Figure 4.28 The relatively small electrical responses to specific events can be observed only if the EEG traces are averaged over a series of trials. The large background oscillations of the EEG trace make it impossible to detect the evoked response to the sensory stimulus from a single trial. Averaging across tens or hundreds of trials, however, removes the background EEG, leaving the event-related potential (ERP). Note the difference in scale between the EEG and ERP waveforms.



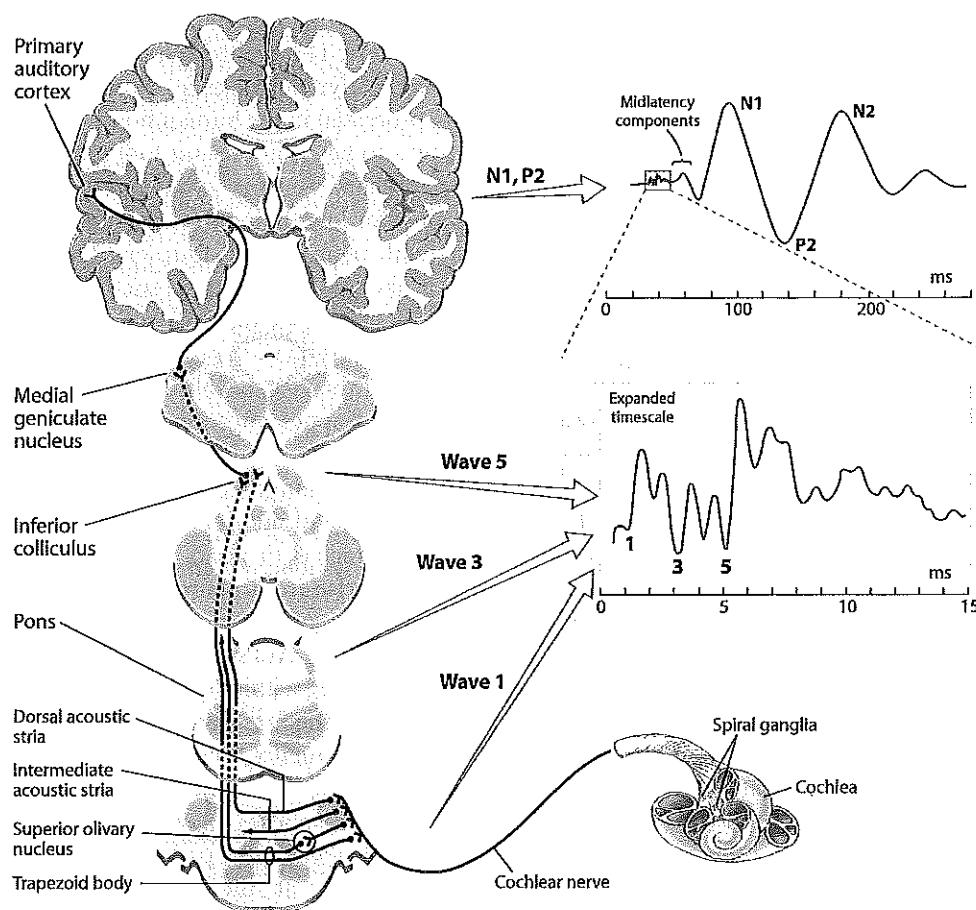


Figure 4.29 The evoked potential shows a series of positive (P) and negative (N) peaks at predictable points in time. In this auditory evoked potential, the early peaks are invariant and have been linked to neural activity in specific brain structures. Later peaks are task dependent, and localization of their source has been a subject of much investigation and debate.

In this example we specified the neural structures associated with the early components of the ERP. Note that these localization claims are based on indirect methods because the electrical recordings are made on the surface of the scalp. For early components related to the transmission of signals along the sensory pathways, the neural generators are inferred from the findings of other studies that used direct recording techniques, as well as considerations of the time required for peripheral pathways to transmit neural signals. This is not possible when we look at evoked responses generated by cortical structures. The auditory cortex relays its message to many cortical areas; all contribute to the measured evoked response. Thus, the problem of localization becomes much harder once we look at these latter components of the ERP.

For this reason, ERPs are better suited to addressing questions about the time course of cognition than to elucidating the brain structures that produce the electrical events. For example, as we will see in Chapter 12, evoked responses can tell us when attention affects how a stimulus is processed. ERPs also provide physiological

indices of when a person decides to respond, or when an error is detected.

Nonetheless, researchers have made significant progress in developing analytic tools to localize the sources of ERPs recorded at the scalp. This localization problem has a long history: In the late 19th century, the German physicist Hermann von Helmholtz showed that an electrical event located within a spherical volume of homogeneously conducting material (approximated by the brain) produces one unique pattern of electrical activity on the surface of the sphere. This is called the *forward solution* (Figure 4.30a). However, Helmholtz also demonstrated that, given a particular pattern of electrical charge on the surface of the sphere, it is impossible to determine the distribution of charge within the sphere that caused it. This is called the *inverse problem* (Figure 4.30b). The problem arises because an infinite number of possible charge distributions in the sphere could lead to the same pattern on the surface. ERP researchers unfortunately face the inverse problem, given that all of their measurements are made at the scalp. The challenge is to determine what areas of the brain must

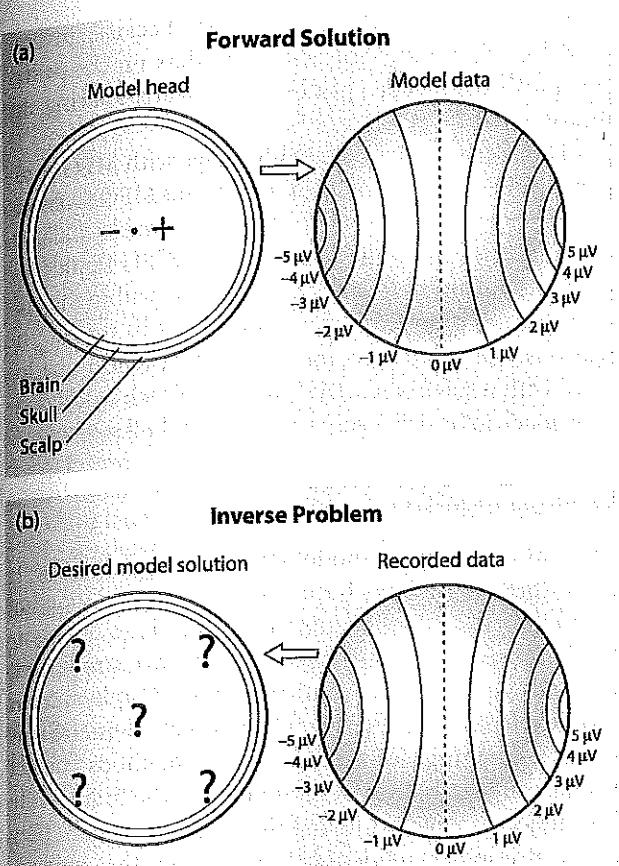


Figure 4.30 (a) In the forward solution, a model head is created that is based on known conductivities of various tissues of the brain, skull, and scalp. The pattern results from the location and orientation of a single dipolar charge, used to simulate an active neuronal population. The dipolar charge creates electrical currents that flow to the surface of the sphere, creating a distinct pattern of electrical voltages in the surface. (b) The inverse problem arises because a given pattern observed on the surface of the scalp can result from many possible locations of underlying neural generators.

have been active to produce the recorded pattern. In other words, where are the generators of a particular event in the ERP?

To solve this problem, researchers have turned to sophisticated modeling techniques. They have been able to do so by simplifying assumptions about the physics of the brain and head tissues, as well as the electrical nature of the active neurons. Of critical importance is the assumption that neural generators can be modeled as electrical dipoles, conductors with one positive end and one negative end, as shown in Figure 4.31. For example, the excitatory postsynaptic potential generated at the synapse of a cortical pyramidal cell can be viewed as a dipole.

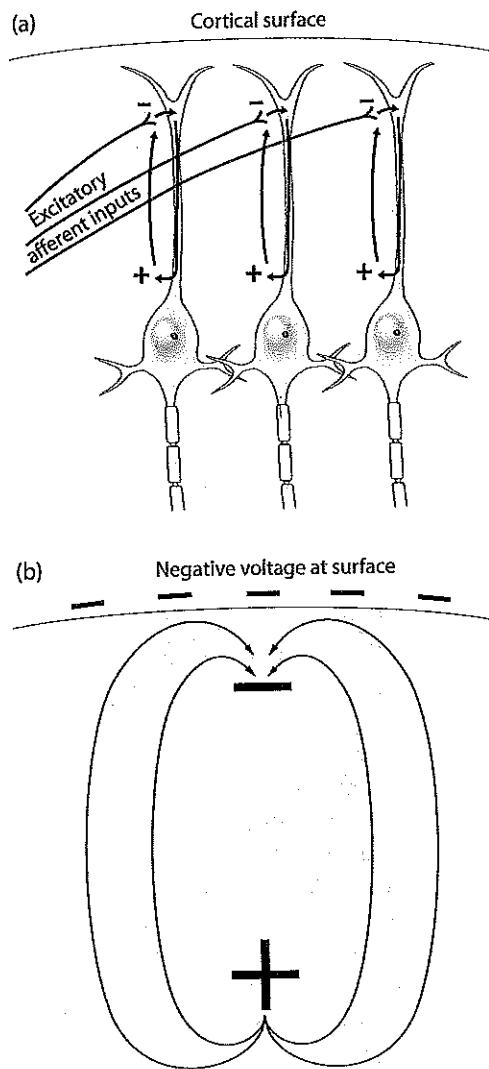


Figure 4.31 Inverse dipole modeling. (a) The long axes of these three cortical pyramidal neurons are perpendicular to the cortical surface (top of the figure). Each neuron is receiving an excitatory synaptic input at its apical dendrite. The postsynaptic potential that is created causes current to flow into the neuron near the cell body. This pattern of current flow produces an electrical field with one pole being the negative (-) electrical potential at the apical dendrite, and the other pole being the positive (+) electrical potential near the neuronal cell body. (b) The electrical fields of the pyramidal cells sum and can be represented by a single current dipole. In inverse dipole modeling, the source of the neural activity is estimated from the electrical activity that is recorded at the scalp.

Inverse dipole modeling is relatively straightforward. Using a high-speed computer, we create a model of a spherical head and place a dipole somewhere within the sphere. We then calculate the forward solution to determine the distribution of voltages that this dipole

would create on the surface of the sphere. Finally, we compare this predicted pattern to the data actually recorded. If the difference between the predicted and obtained results is small, then the model is supported; if the difference is large, then the model is rejected and we test another solution by shifting the location of the dipole. In this manner, the location of the dipole is moved about inside the sphere until the best match between predicted and actual results is obtained. In many cases, it is necessary to use more than one dipole to obtain a good match. But this should not be surprising: It is likely that ERPs are the result of processing in multiple brain areas.

Unfortunately, as more dipoles are added it becomes harder to identify a unique solution; the inverse problem returns. Various methods are employed to address this problem. Using anatomical MRI, investigators can study precise three-dimensional models of the head instead of generic spherical models. Alternatively, results from anatomically based neuroimaging techniques (see below) can be used to constrain the locations of the dipoles. In this way, the set of possible solutions can be made much smaller.

A technique related to the ERP method is **magnetoencephalography**, or MEG. In addition to the electrical events associated with synaptic activity, active neurons produce small magnetic fields. Just as with EEG, MEG traces can be averaged over a series of trials to obtain event-related fields (ERFs). MEG provides the same temporal resolution as with ERPs and has an advantage in terms of localizing the source of the signal. This advantage stems from the fact that, unlike electrical signals, magnetic fields are not distorted as they pass through the brain, skull, and scalp. Inverse modeling techniques similar to those used in EEG are necessary, but the solutions are more accurate.

Indeed, the reliability of spatial resolution with MEG has made it a useful tool in neurosurgery (Figure 4.32). Suppose that an MRI scan reveals a large tumor near the central sulcus. Such tumors present a surgical dilemma. If the tumor extends into the precentral sulcus, surgery might be avoided or delayed because the procedure is likely to damage motor cortex and leave the person with partial paralysis. However, if the tumor does not extend into the motor cortex, surgery is usually warranted. MEG provides a noninvasive procedure to identify somatosensory cortex. From the ERPs produced following repeated stimulation of the fingers, arm, and foot, inverse modeling techniques are used to determine if the underlying neural generators are anterior to the lesion. In the case shown in Figure 4.32, the surgeon can proceed to excise the tumor

without fear of producing paralysis because inverse modeling shows that the tumor borders on the posterior part of the postcentral sulcus, clearly sparing the motor cortex.

There is, however, one disadvantage with MEG compared to EEG, at least in its present form: MEG is able to detect current flow only if that flow is oriented parallel to the surface of the skull. Most cortical MEG signals are produced by intracellular current flowing within the apical dendrites of pyramidal neurons. For this reason, the neurons that can be recorded with MEG tend to be located within sulci, where the long axis of each apical dendrite tends to be oriented parallel to the skull surface.

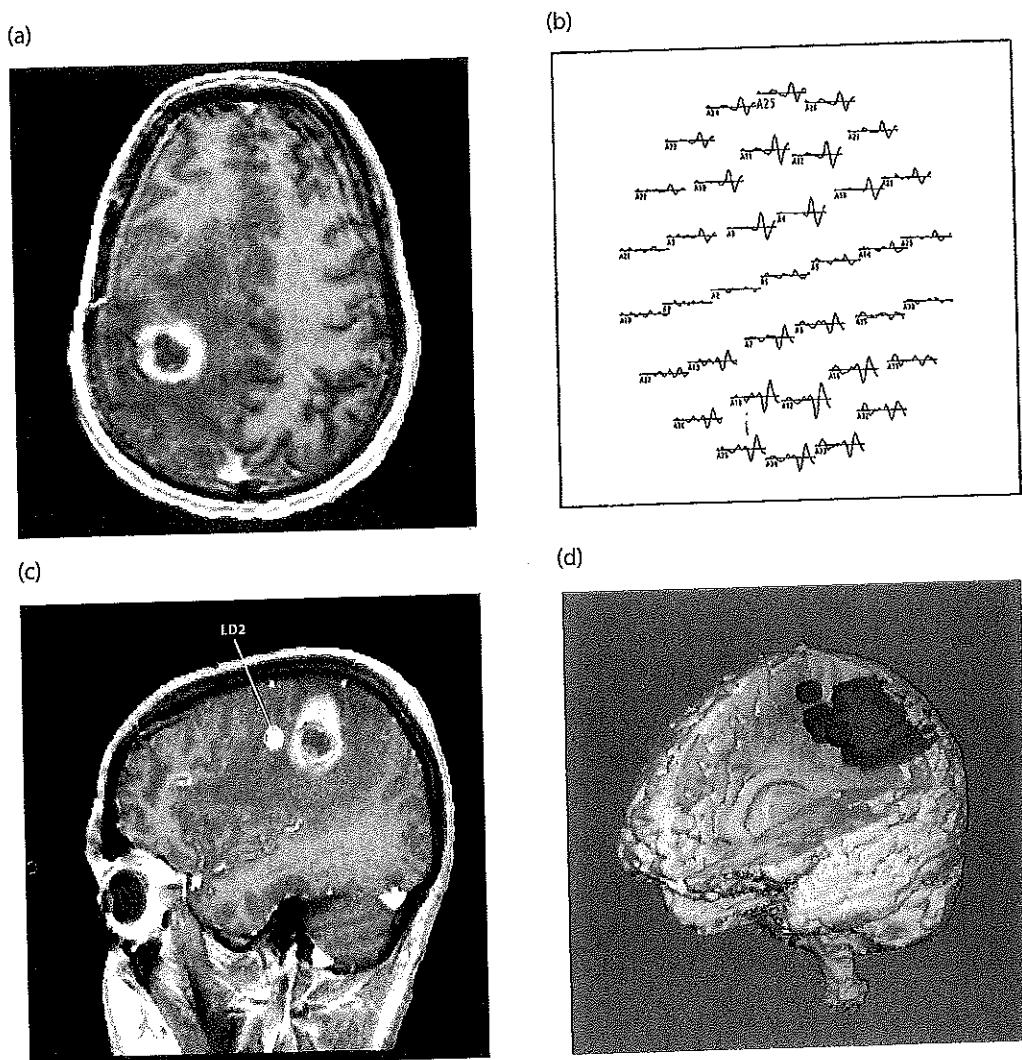
METABOLIC SIGNALS

The most exciting methodological advances for cognitive neuroscience have been provided by new imaging techniques that identify anatomical correlates of cognitive processes (Raichle, 1994). The two prominent methods are **positron emission tomography**, commonly referred to as PET, and **functional magnetic resonance imaging**, or fMRI. These methods detect changes in metabolism or blood flow in the brain while the subject is engaged in cognitive tasks. As such, they enable researchers to identify brain regions that are activated during these tasks, and to test hypotheses about functional anatomy.

Unlike EEG and MEG, PET and fMRI do not directly measure neural events. Rather, they measure metabolic changes correlated with neural activity. Neurons are no different from other cells of the human body. They require energy in the form of oxygen and glucose, both to sustain their cellular integrity and to perform their specialized functions. As with all other parts of the body, oxygen and glucose are distributed to the brain by the circulatory system. The brain is an extremely metabolically demanding organ. As noted previously, the central nervous system uses approximately 20% of all the oxygen we breathe. Yet the amount of blood supplied to the brain varies only a little between the time when the brain is most active and when it is quiet (perhaps because what we regard as active and quiet in relation to behavior does not correlate with active and quiet in the context of neural activity). Thus, the brain must regulate itself. When a brain area is active, more oxygen and glucose are made available by increased blood flow.

PET activation studies measure local variations in cerebral blood flow that are correlated with mental activity (Figure 4.33). To do this, a tracer must be introduced into the bloodstream. For PET, radioactive elements (isotopes) are used as tracers. Owing to their unstable

Figure 4.32 Magnetoencephalography as a noninvasive presurgical mapping procedure. (a) This MRI shows a large tumor in the vicinity of the central sulcus. (b) These event-related fields (ERFs) were produced following repeated tactile stimulation of the index finger. Each trace shows the magnetic signal recorded from an array of detectors placed over the scalp. (c) Inverse modeling showed that the dipole (indicated by LD2) producing the surface recordings in (b) was anterior to the lesion. (d) This three-dimensional reconstruction shows stimulation of the fingers and toes on the left side of the body in red and the tumor outlined in green.



state, these isotopes rapidly decay by emitting a positron from their atomic nucleus. When a positron collides with an electron, two photons, or gamma rays, are created. Not only do the two photons move at the speed of light, passing unimpeded through all tissue, but also they move in opposite directions. The PET scanner—essentially a gamma ray detector—can determine where the collision took place. Because these tracers are in the blood, a reconstructed image can show the distribution of blood flow: Where there is more blood flow, there will be more radiation.

The most common isotope used in cognitive studies is ^{15}O , an unstable form of oxygen with a half-life of 123 s. This isotope, in the form of water (H_2O), is injected in the bloodstream while a person is engaged in a cognitive task. Although all areas of the body will absorb some radioactive oxygen, the fundamental assumption

of PET is that there will be increased blood flow to the brain regions that have heightened neural activity. Thus, PET activation studies do not measure absolute metabolic activity, but rather relative activity. In the typical PET experiment, the injection is administered at least twice: during a control condition and during an experimental condition. The results are usually reported in terms of a change in **regional cerebral blood flow (rCBF)** between the two conditions.

Consider, for example, a PET study designed to identify brain areas involved in visual perception: In the experimental condition the subject views a circular checkerboard surrounding a small fixation point (to keep subjects from moving their eyes); in the control condition, only the fixation point is presented. With PET analysis, researchers subtract the radiation counts measured during the control condition from those

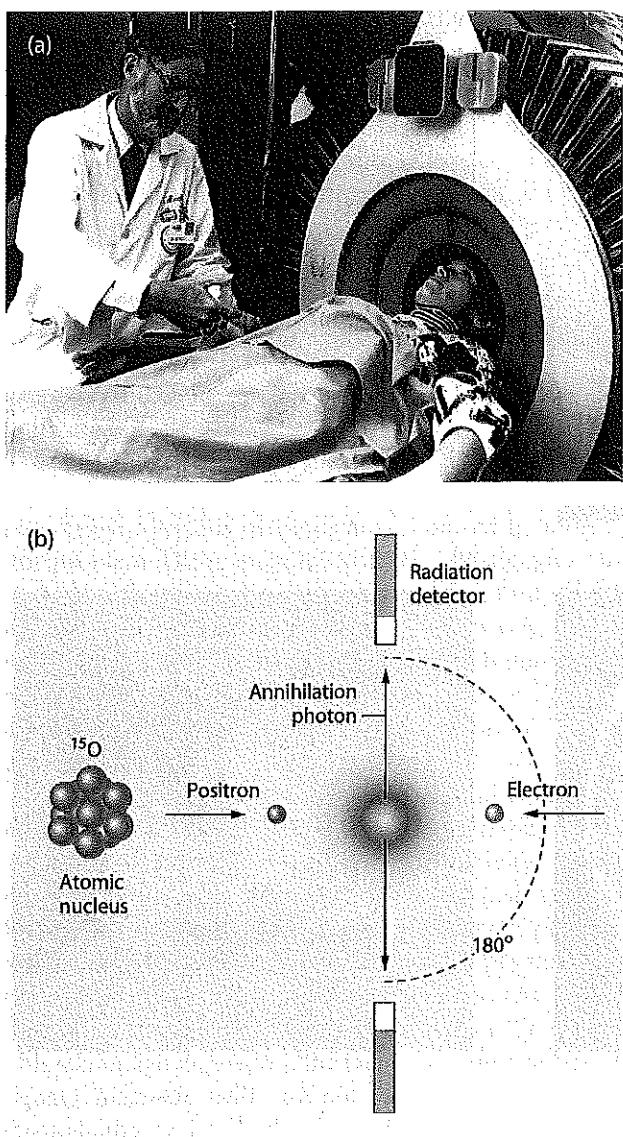


Figure 4.33 Positron emission tomography. (a) PET scanning allows metabolic activity to be measured in the human brain. (b) In the most common form of PET, water labeled with radioactive oxygen, ^{15}O , is injected into the subject. As positrons break off from this unstable isotope, they collide with electrons. A by-product of this collision is the generation of two gamma rays, or photons, that move in opposite directions. The PET scanner measures these photons and calculates their source. Regions of the brain that are most active will increase their demand for oxygen.

measured during the experimental condition. Areas that were more active when the subject was viewing the checkerboard stimulus will have higher counts, reflecting increased blood flow. This subtractive procedure ignores variations in absolute blood flow between the brain's areas. The difference image identifies areas that

show changes in metabolic activity as a function of the experimental manipulation.

PET scanners are capable of resolving metabolic activity to regions, or voxels, that are approximately 5 to 10 mm^3 in volume. Although this size includes thousands of neurons, it is sufficient to identify cortical and subcortical areas and can even show functional variation within a given cortical area. The panels in Figure 4.34 show a shift in activation within the visual cortex as the stimulus moves from being adjacent to the fixation point to more eccentric places.

As with PET, fMRI exploits the fact that local blood flow increases in active parts of the brain. The procedure is essentially identical to the one used in traditional MRI: Radio waves make the protons in hydrogen atoms oscillate, and a detector measures local energy fields that are emitted as the protons return to the orientation of the external magnetic field. With fMRI, however, imaging is focused on the magnetic properties of hemoglobin. Hemoglobin carries oxygen in the bloodstream, and when the oxygen is absorbed the hemoglobin becomes deoxygenated. Deoxygenated hemoglobin is more sensitive, or paramagnetic, than oxygenated hemoglobin. The fMRI detectors measure the ratio of oxygenated to deoxygenated hemoglobin. This ratio is referred to as the **blood oxygen level-dependent**, or **BOLD**, effect.

Intuitively, one would expect the proportion of deoxygenated tissue to be greater in active tissue, given the intensive metabolic costs associated with neural function. However, fMRI results are generally reported in terms of an increase in the ratio of oxygenated to deoxygenated hemoglobin. This change occurs because, as a brain area becomes active, the amount of blood being directed to that area increases. The neural tissue is unable to absorb all of the excess oxygen. The time course of this regulatory process is what is measured in fMRI studies. Although neural events occur on a scale measured in milliseconds, blood flow is modulated much more slowly, with the initial rise not evident for at least a couple of seconds and peaking 6 to 10 seconds later. This delay suggests that, right after a neural region is engaged, there should be a small drop in the ratio of oxygenated to deoxygenated hemoglobin. In fact, the newest generation of MRI scanners, reaching strengths of 4 teslas and above, are able to detect the initial drop (Figure 4.35). This decrease is small, representing no more than 1% of the total hemoglobin signal. The subsequent increase in the oxygenated blood can produce a signal as large as 5%. Continual measurement of the fMRI signal makes it possible to construct a map of changes in regional blood flow that are coupled with local neuronal activity.

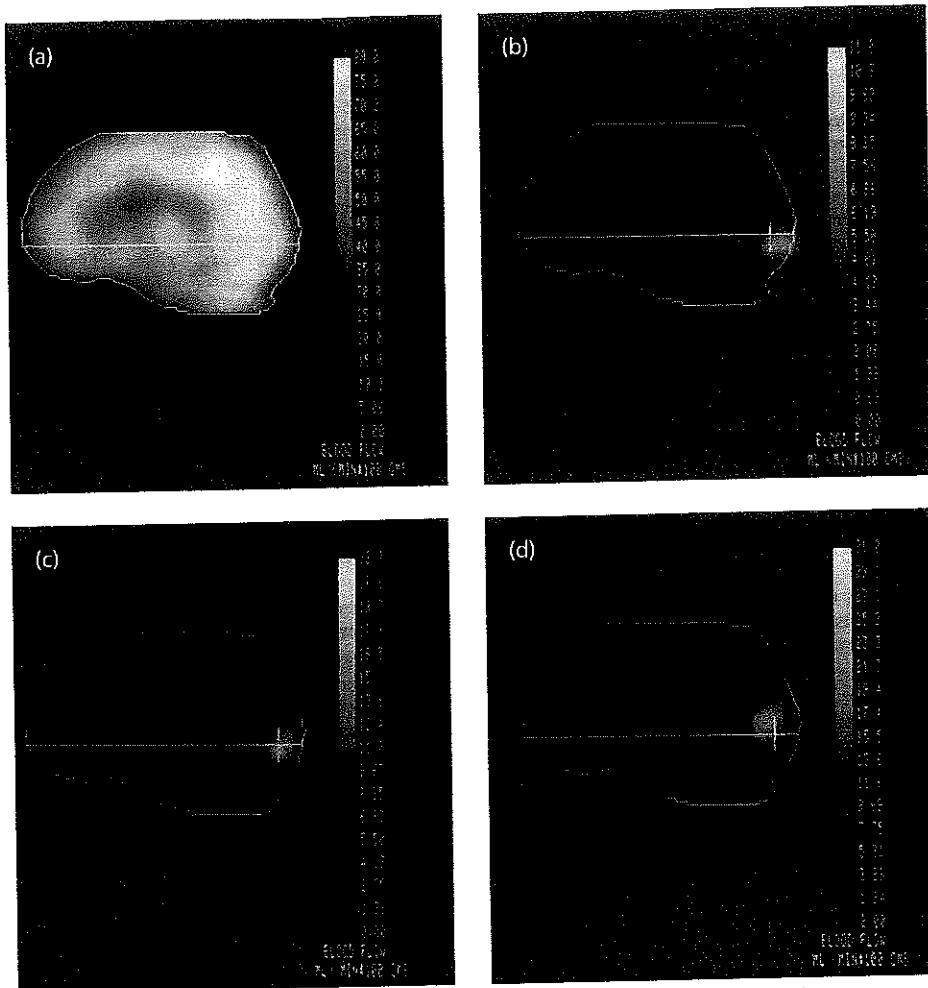
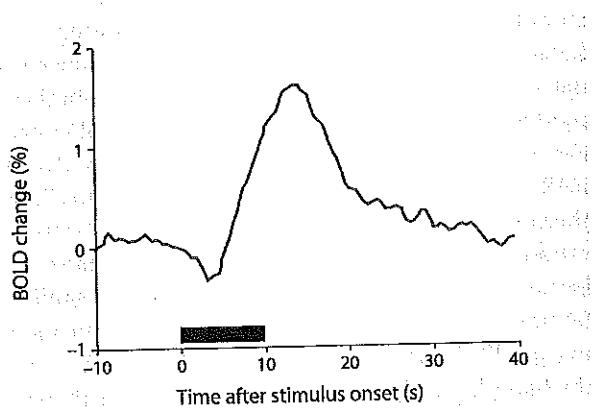


Figure 4.34 Measurements of cerebral blood flow using PET. (a) Blood flow when the subject fixated on a central spot. Activity in this baseline condition was subtracted from that in three other conditions in which the central spot was surrounded by a checkerboard in the center of view (b), more toward the periphery (c), or in the far periphery (d). A retinotopic map can be identified, with central vision represented more inferiorly than peripheral vision.

PET scanning provided a breakthrough for cognitive neuroscience, but fMRI has led to revolutionary changes. Only about a decade after the first fMRI papers appeared (in the early 1990s), fMRI imaging studies now fill the pages of neuroscience journals and proceedings of conferences. Functional MRI is popular for various reasons. For one thing, compared to PET, fMRI is a more practical option for most cognitive neuroscientists. MRI scanners are present in almost all hospitals in technologically advanced countries, and with modest hardware modifications most of them can be used for functional imaging. In contrast, PET scanners are available in only a handful of major medical facilities and require a large technical staff to run the scanner and the cyclotron used to produce the radioactive tracers.

In addition, important methodological advantages favor fMRI over PET. Because fMRI does not require the injection of radioactive tracers, the same individual can

Figure 4.35 Functional-MRI signal observed from visual cortex in the cat with a 4.7-tesla scanner. The black bar indicates the duration of a visual stimulus. Initially there is a dip in the blood oxygenation level-dependent (BOLD) signal, reflecting the depletion of oxygen from the activated cells. Over time, the BOLD signal increases, reflecting the increased hemodynamic response to the activated area. Scanners of this strength are now being used with human subjects.



be tested repeatedly, either in a single session or over multiple sessions. With these multiple observations it becomes possible to perform a complete statistical analysis on the data from a single subject. This advantage is important, given the individual differences in brain anatomy. With PET, computer algorithms must be used to average the data and superimpose them on a "standardized" brain because each person can be given only a limited number of injections. Even with the newest generation of high-resolution PET scanners, subjects can receive only 12 to 16 injections.

Spatial resolution is superior with fMRI compared to PET. Current fMRI scanners are able to resolve voxels of about 3 mm^3 . Moreover, the localization process is improved with fMRI because high-resolution anatomical images can be obtained when the subject is in the scanner. With PET, not only is anatomical precision compromised by averaging across individuals, but precise localization requires that structural MRIs be obtained from the subjects. Error will be introduced in the alignment of anatomical markers between the PET and MRI scans.

Functional MRI can also be used to improve temporal resolution. It takes time to collect sufficient "counts" of radioactivity in order to create images of adequate quality with PET. The subject must be engaged continually in a given experimental task for at least 40 s, and metabolic activity is averaged over this interval. The signal changes in fMRI also require averaging over successive observations, and many fMRI studies utilize a block design similar to that of PET in which activation is compared between experimental and control scanning phases (Figure 4.36).

However, the BOLD effect in fMRI can be time-locked to specific events to allow a picture of the time course of neural activity. This method is called *event-related fMRI* and follows the same logic as is used in ERP studies. The BOLD signal can be measured in response to single events, such as the presentation of a stimulus or the onset of a movement. Although metabolic changes to any single event are likely to be hard to detect among background fluctuations in the brain's hemodynamic response, a clear signal can be obtained by averaging over repetitions of these events. Event-related fMRI allows for improved experimental designs because the experimental and control trials can be presented in a random fashion. With this method, the researcher can be more confident that the subjects are in a similar attentional state during both types of trials, thus increasing the likelihood that the observed differences reflect the hypothesized processing demands rather than more generic factors, such as a change in overall arousal.

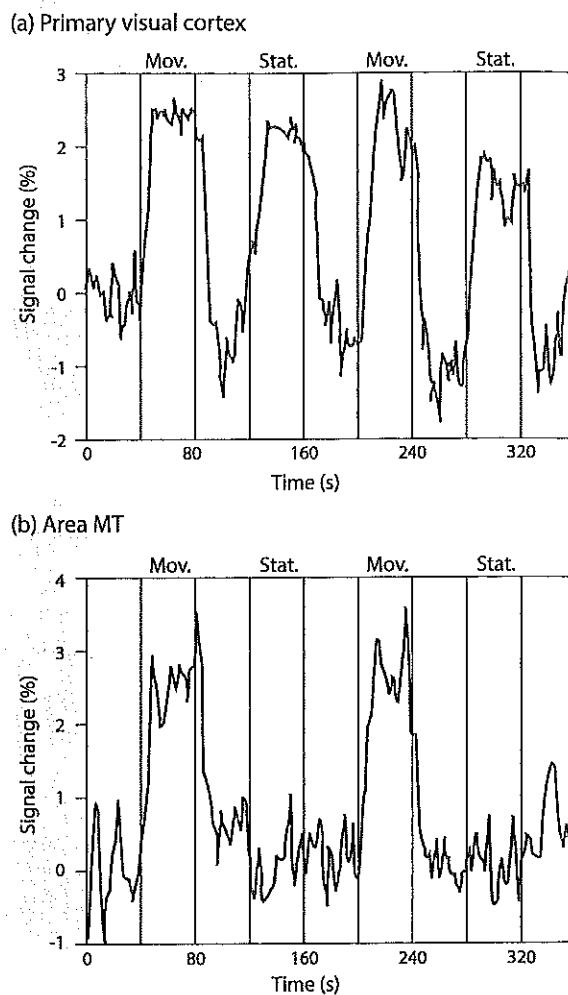


Figure 4.36 Functional MRI measures time-dependent fluctuations in oxygenation with excellent spatial resolution. The subject in this experiment viewed a field of randomly positioned white dots on a black background. The dots would either remain stationary or move along the radial axis. The 40-s intervals of stimulation (shaded background) alternated with 40-s intervals during which the screen was blank (white background). **(a)** Measurements from primary visual cortex (V1) showed consistent increases during the stimulation intervals compared to the blank intervals. **(b)** In area MT, a visual region associated with motion perception (see Chapter 5), the increase was observed only when the dots were moving.

A powerful advantage of event-related fMRI is that the experimenter can choose to combine the data in many different ways after the scanning is completed. As an example, consider memory failure. Most of us have experienced the frustration of being introduced to someone at a party and then being unable to remember the person's name just 2 minutes later. Is this because we

failed to listen carefully during the original introduction and thus the information never really entered memory? Or did the information enter our memory stores but, after 2 minutes of distraction, we are unable to access the information? The former would constitute a problem with memory encoding; the latter would reflect a problem with memory retrieval. Distinguishing between these two possibilities has proved very difficult, as witnessed by the thousands of articles on this topic that have appeared in cognitive psychology journals over the past 100 years.

Anthony Wagner and his colleagues at Harvard University used event-related fMRI to take a fresh look at the question of encoding versus retrieval (Wagner et al., 1998). They obtained fMRI scans while the subjects were studying a list of words, with one word appearing every 2 s. About 20 minutes after the scanning session was completed, the subjects were given a recognition memory test. On average, the subjects correctly recognized 88% of the words studied during the scanning session. The researchers then separated the trials on the basis of whether a word had been remembered or forgotten. If the memory failure was due to retrieval difficulties, no differences should be detected in the fMRI response to these two trials, since the scans were obtained only while the subjects were reading the words. However, if the memory failure was due to poor encoding, then one would expect to see a different fMRI pattern following presentation of the words that were later remembered compared to those that were forgotten. The results clearly favored the encoding-failure hypothesis (Figure 4.37). The BOLD signal recorded from two areas, the prefrontal cortex and the hippocampus, was stronger following the presentation of words that were later remembered. As we'll see in Chapter 8, these two areas of the brain play a critical role in memory formation. This type of study would not be possible with a block design method, because the signal is averaged over all of the events within each scanning phase.

The limitations of imaging techniques such as PET and fMRI must be kept in mind. The data sets from an imaging study are massive, and in many studies the contrast of experimental and control conditions produces a large set of activations. This should not be surprising, given what we know about the distributed nature of brain function; for example, asking someone to generate a verb associated with a noun (experimental task) likely requires many more cognitive operations than just saying the noun (control task).

The standard analytic procedure in imaging studies has been to generate maps of all the areas that show greater activity in the experimental condition. How-

ever, even if we discover that the metabolic activity in a particular area correlates with an experimental variation, we still need to make inferences about the area's functional contribution. Correlation does not imply causation. For example, an area may be activated during a task but not play a critical role in the task's performance. The area simply might be "listening" to other brain areas that provide the critical computations. New analytic methods are being developed that address these concerns. A starting point is to ask whether the activation changes in one brain area are related to activation changes in another brain area—that is, to look at what is called *functional connectivity* (Sun et al., 2004).

Using event-related designs, it is possible not only to measure changes in activity within brain regions, but also to ask if the changes in one area are correlated with changes in another area. In this manner, fMRI data can be used to describe networks associated with particular cognitive operations and the relationships between nodes within those networks.

Interpretation of the results from imaging studies is frequently guided by other methodologies. For example, single-cell recording studies of primates can be used to identify regions of interest in an fMRI study of humans. Or imaging studies can be used to isolate a component operation that is thought to be linked to a particular brain region because of the performance of patients with injuries to that area.

In turn, imaging studies can be used to generate hypotheses that are tested with alternative methodologies. For example, in one experiment fMRI was used to identify neural areas that become activated when people recognize objects through touch alone (Deibert et al., 1999; Figure 4.38a). Surprisingly, tactile object recognition led to pronounced activation of the visual cortex, even though the subjects' eyes were shut during the entire experiment. One possible reason for the pronounced activation is that the subjects identified the objects through touch and then generated visual images of them. Alternatively, the subjects might have constructed visual images during tactile exploration and then used the images to identify the objects.

A follow-up study with TMS was used to pit these hypotheses against one another (Zangaladze et al., 1999). TMS stimulation over the visual cortex impaired tactile object recognition. The disruption was observed only when the TMS pulses were delivered 180 ms after the hand touched the object; no effects were seen with earlier or later stimulation (Figure 4.38b). Thus, the results indicate that the visual representations generated during tactile exploration were essential for inferring

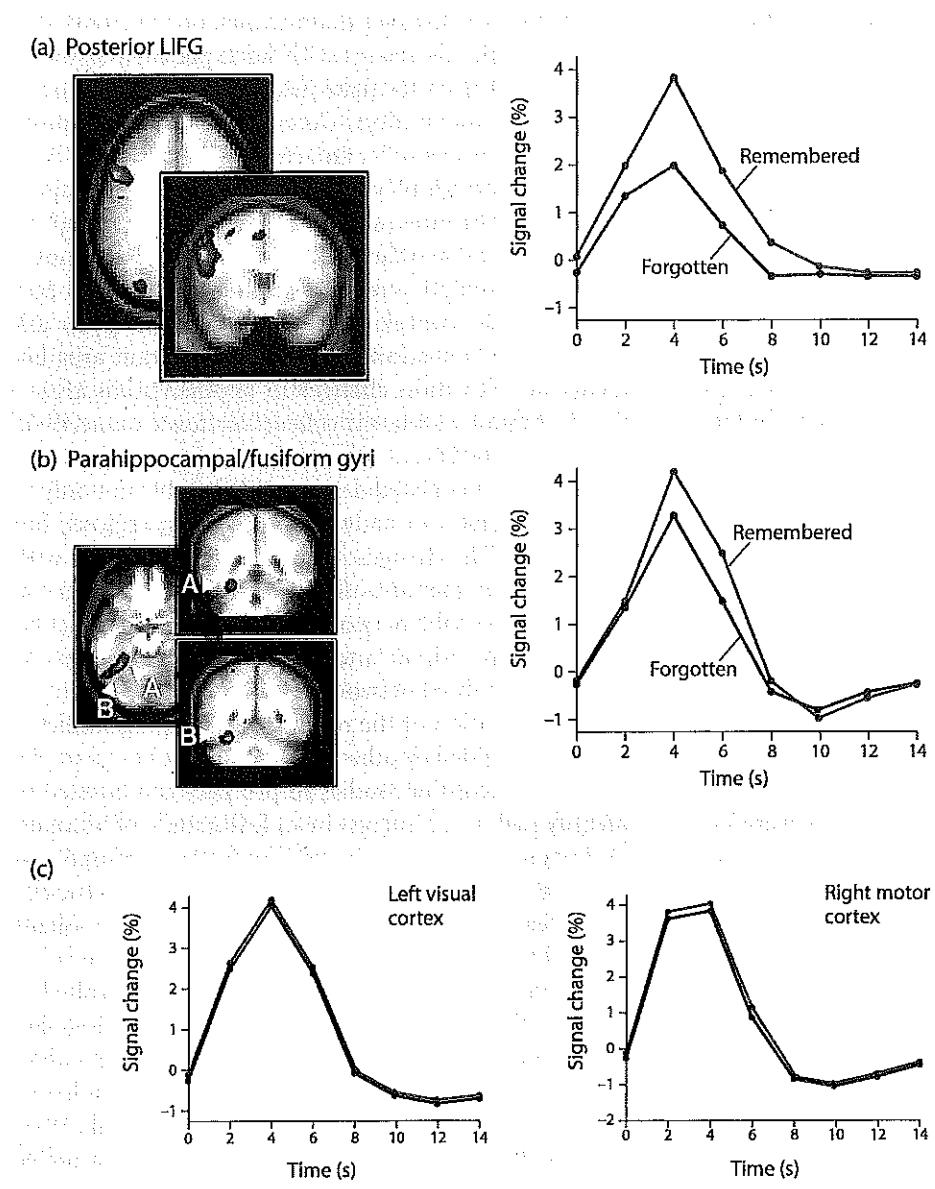


Figure 4.37 Use of event-related fMRI to identify areas associated with failures during memory encoding. Both the left inferior frontal gyrus (LIFG) (a) and the parahippocampal region (b) in the left hemisphere exhibit greater activity during encoding for words that are subsequently remembered compared to those that are forgotten. (A = parahippocampal region; B = fusiform gyrus.) (c) Activity over the left visual cortex and right motor cortex is identical following words that subsequently are either remembered or forgotten. These results demonstrate that the memory effect is specific to the frontal and hippocampal regions.

object shape from touch. These studies demonstrate how the combination of fMRI and TMS allows investigators to test causal accounts of neural function, as well as to make inferences about the time course of processing. Obtaining converging evidence from various methodologies enables us to make the strongest conclusions possible.

Another limitation of PET and fMRI is that both methods have poor temporal resolution in comparison to techniques such as single-cell recording or ERPs. PET is constrained by the decay rate of the radioactive agent. Even the fastest isotopes, such as ^{15}O , require measurements for 40 s to obtain stable radiation counts. Although

fMRI can operate much faster, the metabolic changes used to measure the BOLD response occur over many seconds. Thus, PET and fMRI cannot give a temporal picture of the “online” operation of mental operations. Researchers at the best-equipped centers frequently combine the temporal resolution of evoked potentials with the spatial resolution of fMRI for a better picture of the physiology and anatomy of cognition.

One of the most promising methodological developments in cognitive neuroscience is the combination of imaging, behavioral, and genetic techniques into single studies. This approach is widely employed in studies of psychiatric conditions known to have a genetic basis.

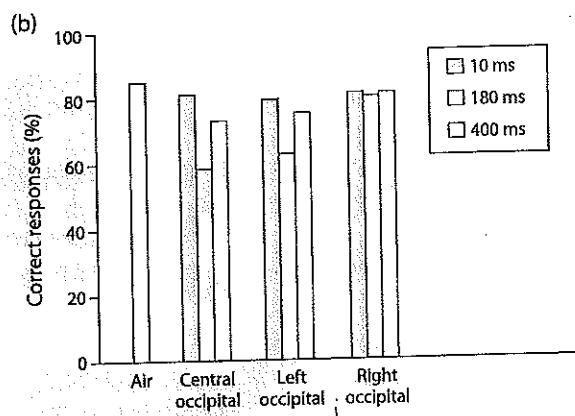
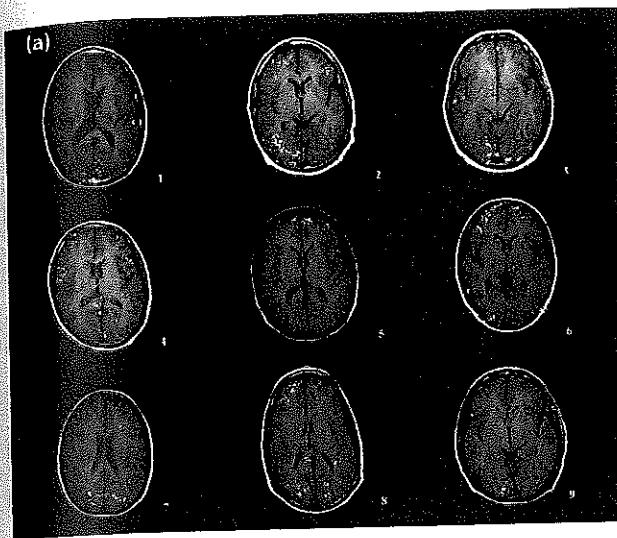


Figure 4.38 Combined use of fMRI and TMS to demonstrate the role of the visual cortex in tactile perception. **(a)** Functional MRI showing areas of activation in nine people during tactile exploration with the eyes closed. All of the subjects show some activation in striate and extrastriate cortex. **(b)** The results graphed here illustrate accuracy in making tactile orientation judgments when a textured object is vibrated against the right index finger. Performance is impaired when the TMS pulse is applied 180 ms after the vibration. This effect is observed only when the pulse is applied over the central occipital cortex or over the contralateral occipital lobe.

Daniel Weinberger and his colleagues at the National Institutes of Health have proposed that the efficacy of antipsychotic medications in treating schizophrenia varies as a function of how a particular gene is expressed, or what is called a *polymorphism* (Bertolino et al., 2004; Weickert et al., 2004). In particular, schizophrenics who express one allelic variant linked to the release of dopamine in prefrontal cortex showed changes in prefrontal activity during working memory tasks following the administration of an antipsychotic drug, as well as improved performance on the tasks. In contrast, schizophrenics with a different allele did not respond to the drugs.

The logic underlying these clinical studies can also be applied to ask how genetic differences within the normal population relate to individual variations in brain function and behavior. A common polymorphism in the human brain is related to the gene that codes for monoamine oxidase A (MAOA). Using a large sample of healthy individuals, Weinberger's group found that the low-expression variant was associated with increased tendency toward violent behavior, as well as hyperactivation of the amygdala when the subject was viewing emotionally arousing stimuli (Meyer-Lindenberg et al., 2006).

SUMMARY

Two goals have guided the overview of cognitive neuroscience methods presented in this chapter. The first was to provide a sense of the methodologies that come together to form an interdisciplinary field such as cognitive neuroscience (Figure 4.39). The practitioners of the neurosciences, cognitive psychology, and neurology differ not only in the tools they use but also in the questions they seek to answer. The neurologist may request a CT scan of an aged boxer to find out if the patient's confusional state is reflected in atrophy of the frontal lobes. The neuroscientist may want a blood sample from the patient to search for metabolic markers in-

dicating a reduction in a transmitter system. The cognitive psychologist may design a reaction time experiment to test whether a component of a decision-making model is selectively impaired. Cognitive neuroscience endeavors to answer these questions by taking advantage of the insights that each approach has to offer and using them together.

The second goal of this chapter was to introduce methods that we will encounter in subsequent chapters. These chapters focus on content domains such as perception, language, and memory, and on how the tools are being applied to understand the brain and behavior. Each chapter

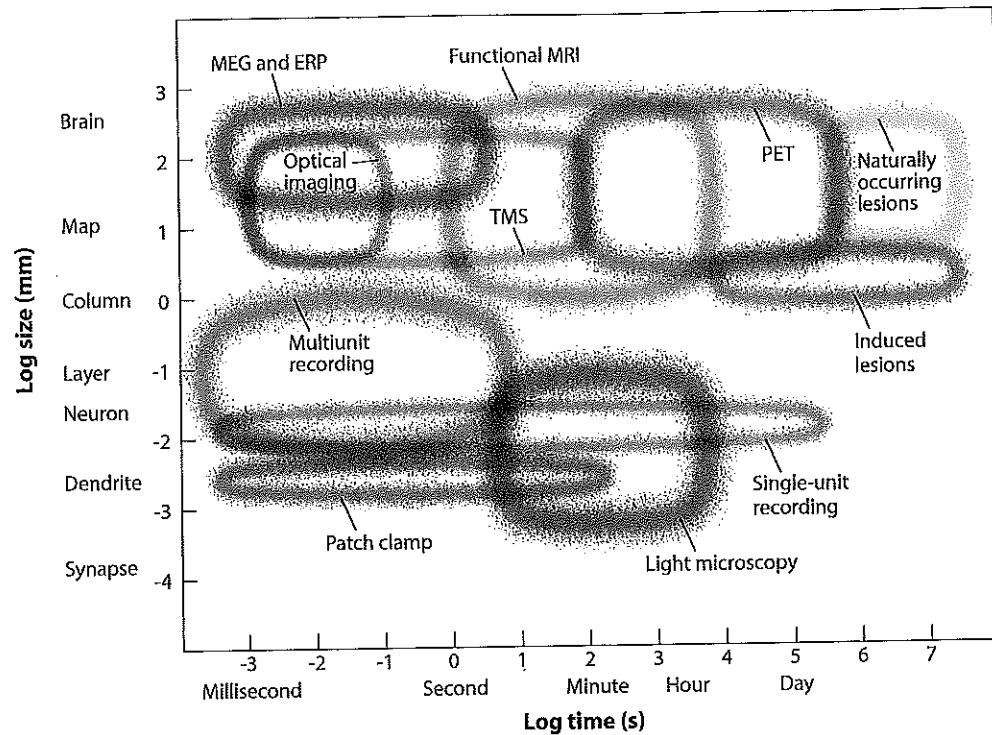


Figure 4.39 Spatial and temporal resolution of the prominent methods used in cognitive neuroscience. Temporal sensitivity, plotted on the x-axis, refers to the timescale over which a particular measurement is obtained. It can range from the millisecond activity of single cells to the behavioral changes observed over years in patients who have had strokes. Spatial sensitivity, plotted on the y-axis, refers to the localization capability of the methods. For example, real-time changes in the membrane potential of isolated dendritic regions can be detected with the patch clamp method, providing excellent temporal and spatial resolution. In contrast, naturally occurring lesions damage large regions of the cortex and are detectable with MRI.

draws on research that uses the diverse methods of cognitive neuroscience. Often the convergence of results yielded by different methodologies offers the most complete theories. A single method cannot bring about a complete understanding of the complex processes of cognition.

We have reviewed many methods, but the review is incomplete, in part because new methodologies for investigating the relation of the brain and behavior spring to life each year. Neuroscientists are continually refining techniques for measuring and manipulating neural processes at a finer and finer level. Patch clamp techniques isolate restricted regions on the neuron, enabling studies of the membrane changes that underlie the inflow of neurotransmitters. Laser surgery can be used to restrict lesions to just a few neurons in simple organisms, providing a means to study specific neural interactions. The use of genetic techniques such as knockout procedures has exploded in the past decade, promising to reveal the mechanisms involved in normal and pathological brain function.

Technological change is also the driving force in our understanding of the human mind. Our current imag-

ing tools are constantly being refined. Each year we witness the development of more sensitive equipment to measure the electrophysiological signals of the brain or the metabolic correlates of neural activity, and the mathematical tools for analyzing these data are constantly becoming more sophisticated. In addition, entire new classes of imaging techniques are just beginning to gain prominence.

In recent years we have seen the development of *optical imaging* (Gratton & Fabiani, 1998). With this type of imaging a short pulse of near-infrared light is projected at the head. The light diffuses through the tissues and scatters back. Sensors placed on the skull detect the photons of light as they exit the head. Brain areas that are active scatter the light more than areas that are inactive, allowing the measurement of neural activity. Noninvasive optical imaging offers excellent temporal resolution. Its spatial resolution is comparable to that of current high-field MRI systems, although the technique at present is limited to measuring structures near the cortical surface. Furthermore, the method is relatively inexpensive, and the tools are transportable. Whereas an MRI

system might cost \$5 million and require its own building, optical-imaging systems cost less than \$100,000 and can be used at the bedside.

We began this chapter by pointing out that paradigmatic changes in science are often fueled by technological developments. In a symbiotic way, the maturation of a scientific field such as cognitive neuroscience provides

a tremendous impetus for the development of new methods. The questions we ask are constrained by the available tools, but new research tools are promoted by the questions that we ask. It would be foolish to imagine that current methodologies will become the status quo for the field, which makes it an exciting time to study brain and behavior.

KEY TERMS

angiography	double dissociation	retinotopic
blood oxygenation level-dependent (BOLD)	electroencephalography (EEG)	simulation
brain lesion	event-related potential (ERP)	single-cell recording
cognitive psychology	functional magnetic resonance imaging (fMRI)	single dissociation
computed tomography (CT, CAT)	knockout procedure	transcranial magnetic stimulation (TMS)
deep-brain stimulation (DBS)	magnetic resonance imaging (MRI)	voxel
diffusion tensor imaging (DTI)		

TAKE-HOME MESSAGES

General

- Our tools for conducting research are only as good as the questions we ask with them.

Cognitive Psychology

- Cognitive psychology focuses on understanding how objects or ideas are represented in the brain and how these representations are manipulated.
- Fundamental goals of cognitive psychology include identifying the mental operations that are required to perform cognitive tasks and exploring the limitations in task performance.
- Computer models are used to simulate neural networks in order to ask questions about cognitive processes and to generate predictions that can be tested in future research.

Neuroscience Techniques and Tools

- Single-cell recording allows neurophysiologists to record from individual neurons in the animal brain in order to understand how increases and decreases in the activity of neurons correlate with stimulation of one of the senses or behavior.

- With multiunit recording, the activity of hundreds of cells can be recorded at the same time.
- Brain lesions, either naturally occurring (in humans) or experimentally derived (in animals), allow experimenters to test hypotheses concerning the functional role of the damaged brain region.
- Gene knockout technology allows scientists to explore the consequences of the lack of expression of a specific gene in order to determine its role in behavior.
- Computed tomography (CT or CAT) uses X-rays to image the structure of the brain.
- Magnetic resonance imaging (MRI) exploits the magnetic properties of the organic tissue of the brain in order to image its structure. The spatial resolution of MRI is superior to CT.
- Diffusion tensor imaging (DTI), performed with magnetic resonance scanners, is used to measure white matter pathways in the brain.
- Angiography is used to evaluate the circulatory system in the brain.

Neurological Disorders and Conditions

- Tumors can cause neurological symptoms either by damaging neural tissue or by producing abnormal pressure on spared cortex and cutting off its blood supply. There are three major types of brain tumors: Gliomas originate in glial cells; meningiomas originate in the meninges; and metastatic tumors originate in a noncerebral structures and are carried to the brain after invading the bloodstream.
- Degenerative disorders include Huntington's disease, Parkinson's disease, Alzheimer's disease, and AIDS-related dementia.
- Neurological trauma can result in damage at the site of the blow (coup) or at the site opposite the blow because of reactive forces (countercoup). Certain brain regions such as the orbitofrontal cortex are especially prone to damage from trauma.
- Epilepsy is characterized by excessive and abnormally patterned activity in the brain.

Treatment of Neurological Disorders

- Intractable epilepsy can be relieved by surgery to remove the focal region causing the epilepsy, or to disconnect the two hemispheres of the brain to limit the spread of the epilepsy via callosotomy.
- In deep-brain stimulation, electrodes are implanted in the brain to relieve conditions like Parkinson's disease.
- In fetal brain transplants, fetal neurological tissue is transplanted into an adult brain in order to replace neurons damaged by diseases like Parkinson's.
- In stem cell implantation, undifferentiated cells are implanted into the brain or spinal cord. The cells can differentiate into neurons, providing a mechanism to replace those that were damaged by trauma or disease—for instance, in spinal cord injury.

Neuroscience Tools

- Research involving patients with neurological disorders is used to examine structure–function relationships. Single and double dissociations can provide evidence that damage to a particular brain region may result in a selective deficit of a certain cognitive operation.

- Transcranial magnetic stimulation (TMS) utilizes magnetic pulses to transiently alter local brain physiology.
- Electroencephalography (EEG) measures the electrical activity of the brain. The EEG signal includes endogenous changes in electrical activity, as well as changes triggered by specific events (e.g., stimuli or movements).
- An event-related potential (ERP) is a change in electrical activity that is time-locked to specific events, such as the presentation of a stimulus or the onset of a response. When the events are repeated many times, the relatively small changes in neural activity triggered by these events can be observed by averaging of the EEG signals. In this manner, the background fluctuations in the EEG signal are removed, revealing the event-related signal with great temporal resolution.
- Magnetoencephalography (MEG) measures the magnetic signals generated by the brain. The electrical activity of neurons also produces small magnetic fields, which can be measured by sensitive magnetic detectors placed along the scalp, similar to the way EEG measures the surface electrical activity. MEG can be used in an event-related manner similar to ERPs, with similar temporal resolution. The spatial resolution can be superior because magnetic signals are minimally distorted by organic tissue such as the brain or skull.
- Positron emission tomography (PET) measures metabolic activity in the brain by monitoring the distribution of a radioactive tracer. The PET scanner measures the photons that are produced during decay of the tracer. A popular tracer is O¹⁵ because it decays rapidly and the distribution of oxygen increases to neural regions that are active.
- Functional magnetic resonance imaging (fMRI) utilizes MRI to track blood flow changes in the brain, which are thought to be correlated with local changes in neuronal activity.
- Powerful insights can be gained from experiments that combine methods such as genetic, behavioral, and neuroimaging techniques.

THOUGHT QUESTIONS

1. To a large extent, progress in all scientific fields depends on the development of new technologies and methodologies. What technological and methodological developments have advanced the field of cognitive neuroscience the most?
2. Cognitive neuroscience is an interdisciplinary field that incorporates aspects of neuroanatomy, neuro-

- physiology, neurology, cognitive psychology, and computer science. What do you consider the core feature of each discipline that allows it to contribute to cognitive neuroscience? What are the limits of each discipline in addressing questions related to the brain and mind?
3. Describe the requirements for establishing single and double dissociations, and explain why double dissociations provide stronger evidence for claims about the brain and behavior. Choose a task that interests you, and generate an example of each type of dissociation you might find if you were to study neurological patients whose ability to perform this task is impaired. Be sure to note what we learn about the brain and mind from these examples.
 4. A skeptic wrote in the *New York Times* science section in the spring of 2000 that, despite all of the excitement surrounding new imaging techniques like

PET and fMRI, these methods were unlikely to lead to profound insights into brain function. The author stressed that these tools were limited in terms of their resolution and were unlikely to provide more insight beyond simply showing which parts of the brain are activated during particular tasks. Describe explicitly the concerns that the writer was expressing, comparing these imaging tools to other methods that might not have similar problems. Discuss whether you share these concerns.

5. In anticipation of the next chapter, consider how you might study a problem such as color perception using the multidisciplinary techniques of cognitive neuroscience. Predict the questions that you might ask about this topic, and outline the types of studies that cognitive psychologists, neurophysiologists, and neurologists might consider.

SUGGESTED READING

- CHURCHLAND, P. S. (1986). *Neurophilosophy: Toward a unified science of the mind/brain*. Cambridge, MA: MIT Press.
- D'ESPOSITO, M., ZARAHN, E., & AGUIRRE, G. K. (1999). Event-related functional MRI: Implications for cognitive psychology. *Psychological Bulletin*, 125, 155–164.
- HILLYARD, S. A. (1993). Electrical and magnetic brain recordings: Contributions to cognitive neuroscience. *Current Opinion in Neurobiology*, 3, 710–717.
- HUETTEL, S., SONG, A. W., & McCARTHY, G. (2004). *Functional magnetic resonance imaging*. Sunderland, MA: Sinauer.
- KANDEL, E. R., SCHWARTZ, J. H., & JESSELL, T. M. (1995). *Essentials of neural science and behavior*. Norwalk, CT: Appleton and Lange.
- MORI, S. (2007). *Introduction to diffusion tensor imaging*. New York: Elsevier.
- POSNER, M. I., & RAICHLE, M. E. (1994). *Images of mind*. New York: Freeman.
- RAPP, B. (2001). *The handbook of cognitive neuropsychology: What deficits reveal about the human mind*. Philadelphia: Psychology Press.