# SYNAPTIC SELF

HOW OUR BRAINS BECOME WHO WE ARE

JOSEPH LeDOUX

VIKING

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CHAPTER TWO

# SEEKING THE SELF

KNOW THYSELF

—Oracle at Delphi

SELF-KNOWLEDGE IS A DANGEROUS THING.

—Lou Reed

Before we go looking for the essence of a person in the brain, it would help to have some conception of what we are seeking. There's certainly no shortage of opinion about what terms like *personality* or *the self* might mean. William James, for example, proposed: "*In its widest possible sense . . . a man's Self is the sum total of all that he CAN call his,* not only his body and his psychic powers, but his clothes and his house, his wife and children, his ancestors and friends, his reputation and works, his lands and horses, and yacht and bank-account. . . . If they wax and prosper, he feels triumphant; if they dwindle and die away, he feels cast down,—not necessarily in the same degree for each thing, but in much the same way for all."[1]

In fact, a whole area of psychology is devoted to the study of personality and the self.[2] And theologians, philosophers, novelists, and poets have also had much to say on the subject. While seemingly deep truths have sometimes emerged from these musings, it is not clear how, if at all, these insights might relate to the workings of the brain. After all, for many people, the brain and the self are quite different. I hope to show here that this is not the case. To do so, I first need to describe a way of thinking about the self that is compatible with current understanding of brain function.

## "SOUL SERENADE"[3]

A few months after starting this book, I attended a conference on the relation between the brain and the soul, sponsored by (fittingly enough) the Vatican.[4] The specific topic was "Neuroscience and Divine Action," and the theologians who organized this meeting were trying to reconceptualize Church teachings in a way that would make sense in light of current scientific understanding of how the world works. In particular, they were attempting to determine how it is possible for God to influence people's lives without violating the laws of physics. I can't present the full range of views expressed, but one that stood out was the notion that God *interacts* but doesn't *intervene.*

The basic idea goes something like this: In the beginning, God set the universe up in a certain way (that is, he created the laws of physics) and has subsequently left it alone, at least for the most part.[5] On a typical day, therefore, God doesn't control the position of stars and planets, move mountains, part seas, change weather conditions, or make people do things they wouldn't otherwise do (in other words, he doesn't usually intervene), but he does communicate with people (he interacts).

Our concern here is not with the theological arguments for and against a noninterventionist view of God but rather with the possibility (or impossibility) of a scientific view of interaction. Given that people live a physical existence in the physical world, and that God is not part of the physical world, the question is: How can God interact with people? If you believe in the existence of a nonmaterial soul, then all you need to assume is that when God was creating the universe, he worked out some way of interacting with the soul. Since both God and the soul are nonmaterial, that interaction would also be nonmaterial, and the laws of physics would therefore be unviolated when interactions occur.

Much to my surprise, however, many of the theologians attending this meeting didn't believe in a classic nonmaterial soul (this would probably be an even bigger surprise to the faithful they represent). Instead, they seemed to accept the principle that the mind is inexorably tied to the brain, and they consequently believed in a soul that is pretty much one and the same as the neurally mediated mind, a part of the physical world that must by its nature obey the laws of physics.

Theologians who link the soul to the physical world actually have history on their side. While many Christians today continue to believe in a soul that is separate from the body and that survives death, this idea didn't really be-

come prominent in Christianity until the Middle Ages. Early Christian teachings emphasized the resurrection of the body itself on Judgment Day rather than merely the survival of a nonmaterial soul. According to Mark 9:47, Jesus said, "It is better for you to get into the Kingdom of God with but one eye than to be thrown into Gehenna with both eyes." This lesson was apparently not meant symbolically but instead reflected the early Judaic notion that we take into the afterlife the bodily state with which we leave this life.[6] (This explains why Jews and Christians, and Muslims, have cemeteries on the western slopes of Mount Olive, facing the Eastern Gate of the Old City in Jerusalem: the closer their bodies are buried to the Eastern Gate, which is where the Final Judgment is expected, the sooner they will be raised.) Ancient Egyptians also seem to have believed that the body, and not just the spirit, carries on in some way after death. In the Tomb of Menena, for example, a foe of the royal family chiseled off their faces to ensure that they went into the next life physically challenged.[7]

If the soul is indeed physical in nature, part of the dilemma about how to sustain a belief in both physics and God would be solved (the part about how the soul meshes with the body). However, the thoroughly modern theologians would still be in a bit of a quantum pickle. If the soul is equivalent to the mind, and the mind depends on the functioning of the brain, how can God interact with people without physically affecting their neurons and, thus, intervening? And where is the soul hanging out while the body decays in the interim between death and Judgment Day? Not surprisingly, the Vatican conference ended inconclusively. No matter how all the pieces of the puzzle were moved around, they didn't fit together to make a coherent picture. As the philosopher David Hume said long ago, logic and reasoning (and presumably science) cannot explain the immortality of the soul.[8] Either you believe or you don't.

My reason for discussing this conference and the issues it raised is not so much to argue the point that it would be difficult, and maybe impossible, to find scientific solutions to theological riddles, but rather to demonstrate that a spiritual view of the self isn't (or doesn't have to be) *completely* incompatible with a biological one. Whatever else we are and aren't, much of what we are is accounted for by what goes on in our brains. Some theologians, as we've seen, have come to accept this. But even people who believe in an immaterial soul that survives death have acknowledged the fact that the normal functioning of the soul depends on the brain. Shakespeare embraced this notion when he called the brain the soul's frail dwelling.[9] A few minutes with my

mother, a devout Catholic with Alzheimer's disease, makes it painfully clear just how fragile the soul's dwelling is.

## THE LIMITS OF LOGIC

Theologians aren't the only ones who have concerned themselves with interactions between body and soul.[10] The question is also one of the major puzzles that has occupied philosophers through the ages. In the seventeenth century, the French mathematician René Descartes devised a way of thinking about body and soul that has shaped philosophical debate on this topic ever since.[11] Like the contemporary theologians described above, Descartes sought a means of reconciling science and faith. His solution was to propose that "the mental" and "the physical" were separate substances that met and interacted at a special place in the brain.

Historians seem to agree that the earliest Greek philosophers did not have clearly distinguished notions of body and soul.[12] Later, though, some philosophers came to view body and soul as separate. Plato, for example, believed that the intellectual essence of an individual—his psyche or soul—survives death.[13] In fact, Plato looked forward to death so that he could be free of his body and all its needs and passions and finally be capable of pure thought.[14] For Aristotle, in contrast, body and soul were so integrally related that they could not be separated, though they could be distinguished conceptually.[15] By the Middle Ages, philosophers adopted a combination of these notions, viewing body and soul as two unified 'substances' (like Aristotle) but regarding the soul as eternal (like Plato). Aquinas, for example, believed that the intellectual, nonmaterial qualities of mind gave the soul immortality, and that the body was resurrected and reunited with the soul on Judgment Day.[16]

This was the intellectual backdrop against which Descartes played his influential discussion of body and mind. Like Plato, he viewed the mental and physical as separate substances: "My soul, by which I am what I am . . . is entirely and absolutely distinct from my body, and can exist without it." In a fusion of faith and psychological theory, Descartes equated the soul with consciousness, and said only humans have conscious control of their behavior. Therefore, only human souls can gain or lose access to heaven by their actions. The behaviors of other animals were, in Descartes's scheme, reflexive or automatic, and carried out without thought. So, for Descartes, if it wasn't conscious, it wasn't mental. Descartes didn't exactly deny the existence of unconscious processes, but simply relegated them to the physical world, pro-

posing that they function in humans the way they do in mindless (soulless) animals.

But if 'the physical' and 'the mental' are completely different entities, how can the conscious soul (the mental) be responsible for the physical body? Descartes's solution was that the conscious soul substance can interact with the material body by means of a small region of the brain called the pineal gland. While most parts of the brain exist in duplicate, the pineal gland is singular and centrally located, which suggested to Descartes that it must be the seat of mind-body interaction—a place where commands from the soul can influence the body, and where information from the body (either about the outside world or the body itself) can enter the soul as perceptions, emotions, and knowledge.

In Descartes's scheme, the nonphysical soul substance actually served the dual function of communicating with the physical body as well as with God. This interplay between physical and nonphysical substances is precisely the kind of solution to the problem of how God interacts with people that the theologians at the Vatican conference were trying to move beyond. Our interest here, however, is not in the theological question (How does God interact with the soul?), but in the philosophical one (How does the mind interact with the body?). Descartes's framing of the philosophical question, and his particular answer to it (a mind-body interaction in the brain), set up the conundrum known as the mind-body problem, which philosophers have struggled with ever since.[17] I want to make two points about this subject that are relevant to the present discussion.

First, in equating the mind with consciousness, Descartes framed the mind-body problem in terms of the relation between consciousness and the brain. As such, the mind-body problem, in its traditional conception, concerns an *aspect* of the mind rather than the whole mind. Most of what the brain does is not, in fact, part of the traditional mind-body debate. Some contemporary philosophers take a broader view than Descartes and accept that certain nonconscious aspects of brain function also contribute to mental life.[18] However, they regard such nonconscious aspects as "easy problems" that are not really the concern of philosophy. As will become apparent later in this chapter, I believe that these implicit or unconscious aspects of the self also play an important role, in fact an essential one, in shaping who we are and explaining why we do what we do.

Second, it's important to distinguish the philosophical mind-body problem from the neuroscientific problem about how the brain creates the mind.

Philosophers, by definition, seek philosophical solutions to problems (including the mind-body problem) and discuss the possible relations, the logic, that might exist between fundamental substances in nature (matter and mind). Neuroscientists, by contrast, typically start with the assumption that the materialist view of the mind-body problem is correct (that the mind is a product of the brain), and then try to understand how the brain makes the mind possible.[19] In fact, many philosophers today accept some version of materialism, but even if the tides should shift in the coming years and dualism (the belief that mind and body are separate substances) should take over philosophy, neuroscientists will not be out of jobs. Brain researchers are, after all, studying the brain, not philosophy. This does not mean that the paths of the neuroscientist and philosopher never cross. They often do, and when they do, each group has sometimes been enlightened (and sometimes enraged) by the other.[20] But, ultimately, because philosophers and brain scientists are pursuing different concerns, progress in one field does not necessarily signal an advance or defeat in the other.

In spite of my own contention that consciousness is not the be-all and end-all of mind and behavior, I nevertheless have considerable sympathy for the belief that neuroscience will come to explain consciousness. Descartes was correct in thinking about unconscious mental processes in physical terms; he erred, however, in conceiving of consciousness as nonphysical. That the brain mechanisms underlying conscious experience haven't been figured out yet doesn't mean that they will remain obscure forever. In fact, recent research has begun to make some headway in understanding the brain mechanisms of consciousness, and we'll take a look at this work later in the book.

## OUR BODIES, OUR SELVES

Although the mind-body problem is the favorite topic of philosophers who work in the area called the philosophy of the mind, some of these philosophers have other things on their minds. One that is particularly relevant to us, and that is closely intertwined with the mind-body problem, is the issue of what constitutes a person. Is a person a body, a mind, a mind *in* a body? Does a person have to be human? Are all humans persons? Could a creature from another planet be a person? Can a human lose personhood as a result of brain damage, insanity, or moral transgressions? When during life does personhood start and stop? Is an embryo or an infant a person? What about someone who lingers for months in a coma from which he will, by medical prediction,

never recover? The latter questions have wide-ranging social and legal implications, but only if the former ones can be answered in some reasonable way. If we can't establish precisely what a person is, it matters little whether we are one or not. John Locke had something like this in mind when he said, hundreds of years ago, that *person* is a "forensic term, appropriating actions and their merit; and so belongs only to intelligent agents, capable of a law, and happiness and misery. . . . This personality extends itself beyond present existence to what is past, only by consciousness."[21]

Peter Strawson is perhaps the best-known modern philosopher in this area. His much-cited paper "Persons"[22] starts with Ludwig Wittgenstein's assertion that bodies are not in possession of the states of consciousness that come out of them: "The I occurs in philosophy through the fact that the 'world is my world.' The philosophical I is not the man, not the human body, or the human soul . . . but the metaphysical subject, the limit—not a part of the world." You'll probably be happy to know that Strawson, too, was puzzled by these words, which he called impressive but obscure.

Strawson was motivated by Wittgenstein's arcane statements to try to explain the idea of something that is both a subject of experiences (that is, is conscious) and is a part of the world (that is, is dependent on a body). He wanted to understand the relation between two questions: Why do we ascribe states of consciousness to our bodies, and why do we ascribe states of consciousness to anything at all? Descartes had raised the first when he said, "I am not lodged in my body like a pilot in a vessel," and Wittgenstein the second with his statement that "The thinking, presenting subject—there is no such thing."[23]

According to Strawson, because we can attribute our own states of consciousness to ourselves, others like us must also have similar states of consciousness. If we can figure out how to identify those who are like us, we can know to whom consciousness should be attributed—in other words, we can know who is a person. To do this, he distinguished between two kinds of statements: those that obviously can be applied to material bodies that also exhibit consciousness ("is in pain," "is thinking," "believes in God") and those that can be applied equally to material bodies that are conscious and that are not ("is heavy," "is tall," "is hard").

Like Locke and Strawson, many philosophers have taken the view that personhood is a characteristic of intelligent, conscious creatures, that consciousness is, in fact, the quality that defines personhood. But others demand more, in the form of a moral element. This was implicit in Locke, as well as in the

writings of Kant. Daniel Dennett combined the thought of Locke and Kant, and other philosophers, proposing that there are two interrelated notions of a person, one moral and one metaphysical.[24] The metaphysical person is a thinking, feeling, intelligent, conscious agent, while the moral person is one who is accountable for his actions. Dennett asks whether being a person in the metaphysical sense automatically makes one a person in a moral sense, or does it merely make a moral capacity possible. He goes on to list several conditions of personhood. A being is a person if it is rational, verbal, conscious, and, in fact, self-conscious, capable of being acted toward in a certain way, and capable of reciprocating when acted toward in this way. Dennett's list also borrowed from John Rawls, who argued, "To recognize another as a person one must respond to him and act towards him in certain ways,"[25] and from Thomas Nagel, who affirmed that "extremely hostile behavior towards another is compatible with treating him as a person."[26] But Dennett, in the end, concludes that these are necessary but not sufficient conditions for defining a person—that there is, fundamentally, no way to set a passing grade for personhood that is not arbitrary.

The concept of the self, which is of utmost importance to us here, is closely related to the philosophical notion of a person. Within philosophy, there has, in fact, been a growing interest in the self,[27] an outcome of which has been the emergence of distinctions between different aspects of the self.[28] One much-discussed distinction is between the minimum and the narrative self.[29] The former is an immediate consciousness of one's self, and the latter a coherent self-consciousness that extends with past and future stories that we tell about ourselves.[30] The narrative self bears some relation to the postmodern notion that the self is socially constructed.[31] While social construction is often viewed as diametrically opposed to a scientific view of man,[32] the two are not necessarily at odds with each other since brains, in the end, are responsible for both the behaviors that collectively constitute the social milieu, and for the reception by each individual of the information conveyed by this milieu.

In focusing on consciousness as the leading metaphysical feature of who we are, philosophers interested in the question of personhood and the self leave out much of who we are—all the nonconscious aspects. And in dividing the world into material objects and conscious selves or persons, as Strawson did, nonhuman animals are placed in a kind of ontological limbo, since a nonhuman animal cannot be a person.

Although other animals are not conscious in the human sense, they are not simply objects, like rocks or chairs. They are living creatures with nervous sys-

tems that make it possible for their bodies to interact with and change the material world in ways that rocks and chairs cannot. The concept of a person, a conscious self, while useful as a way of evaluating issues related to being human, is thus less valuable as a general-purpose concept for understanding existence in the context of our animal ancestry. And because we must pursue many aspects of how the brain works through studies of nonhuman organisms, we need a conception of who we are that recognizes the evolutionary roots of the human body, including the brain.

Though not as widely discussed as conscious aspects of the self, nonconscious aspects are nevertheless important. They are essential to the Buddhist attempt to eliminate the conscious self,[33] to ideas about multiple selves by William James and others,[34] as well as to notions of a primitive, nonconceptual,[35] or ecological[36] self that exists outside of conscious awareness. Once we accept that the self of a human can have conscious and nonconscious aspects, it becomes easy to see how other animals can be thought of as having selves, so long as we are careful about which aspects of the self we are ascribing to each species in question.

The self, then, is a notion that can be conceived of along an evolutionary continuum. While only humans can have the unique aspects of the self made possible by the kind of brains that humans have, other animals have the kinds of selves made possible by their own brains. To the extent that many of the systems that function nonconsciously in the human brain function similarly in the brains of other animals, there is considerable overlap in the nonconscious aspects of the self between species. Obviously, the more similar the brains, the more the overlap.

The extent to which other animals have any kind of consciousness is, unfortunately, impossible to know. We can speculate, but because the human mind cannot become a cat, dog, bird, lizard, frog, or fish mind, we cannot know with certainty how such a question should be answered.[37] Descartes's greatest contribution was perhaps his conclusion that the only thing he could know with certainty was his own mind. So long as we are talking about other animals with brains like our own (that is, other humans), we can have some confidence that their mental states are like ours. But we cannot with any degree of certainty extrapolate from our own mental states to those of other species.

In spite of having gotten this far with some key concepts from philosophy, the fact is that philosophy will probably not give us the kind of foundation we need to pursue the relation between the self and the brain.[38] To state that a

mind, or a person, or a self is all physical, or all mental, or partly physical and partly mental, or something else altogether (like the product of socially constructed relations between people),[39] lays out the territory in a way that is useful for analyzing broad categories of experience within and between species, but does not tell us much about how to pursue mechanisms in the brain. If we are going to figure out how it is that our brains make us who we are, we need a way of linking a fairly detailed conception of who we are to neural functions. Psychology may be more relevant to that purpose.

## MIND SCIENCE

Psychology was actually a branch of philosophy until the late nineteenth century, when Wilhelm Wundt, a German physiologist, began doing experiments to understand the way the mind works rather than just speculating about it.[40] He and his followers, known as introspectionists, took the key steps required to convert psychology into an experimental science. Their main topic of investigation was conscious experience, which they explored by examining their own experiences, attempting to break them into essential, irreducible elements.

But early in the twentieth century, some psychologists began to argue that this was no way to conduct scientific research, since one's conscious experiences can only be known personally, and cannot be verified by others.[41] This idea caught on and eventually spawned behaviorism, which was based on the premise that a scientifically valid psychology had to focus on observable events (behavioral responses) rather than internal states.[42] Some of its adherents were methodological behaviorists, which meant they didn't necessarily reject the existence of consciousness, but simply believed it couldn't be studied. Radical behaviorists, in contrast, actually denied that consciousness existed. For them, mental states were illusions created by tendencies to act in one way or another. Philosophers like Gilbert Ryle adopted radical behaviorism as a resolution to the mind-body problem,[43] eliminating the mind entirely, leaving only the physical body to be explained in physical terms. Ryle called mental states "ghosts in the machine," after the "deus ex machina" of Greek tragedy, a god that was lowered onto the stage from above to solve the problems of mortals.

Toward the middle of the century, it dawned on some scientists that the operations (computations) performed by computers were not unlike what a human does when solving a problem.[44] This notion was embraced by some

farsighted psychologists like Jerry Bruner[45] and George Miller,[46] and the cognitive approach to psychology, which emphasized internal mechanisms that process information, was born.[47] This was an attractive alternative to mindless behaviorism, and eventually the cognitive movement dethroned behaviorism and brought the mind back to psychology.

The mind that returned, though, was not exactly the one that the behaviorists had disposed of. Behaviorists had objected to the emphasis of introspectionists on mental content (the experience of the color red, for example). Cognitive scientists, however, were studying mental *processes* rather than the content of consciousness. They were more concerned with how colors are detected and discriminated than in what it is like actually to experience them.

It is now widely recognized that we can have conscious access to the outcome of cognitive processes, but we are not usually aware of the processes that were involved in generating that content.[48] Our perceptions, memories, and thoughts generally work in happy ignorance of the processes that make them possible. For cognitive scientists, and in stark contrast to Descartes, mind and consciousness are not at all the same.

The cognitive movement had a tremendous impact on psychology, but its influence did not stop there. Information-processing concepts were also adopted by workers in linguistics, anthropology, and other social sciences, as well as mathematics and physics. And just as psychologists were conceiving of minds in terms of computer operations, computer scientists and mathematicians were pursuing the notion that computers might perform mindlike operations, an idea that led to the field of artificial intelligence (AI). Ultimately, cognitive science emerged as an interdisciplinary approach to understanding how the mind works. It came to be called "the new science of mind."[49]

The fact that cognitive processes are not dependent on consciousness (actually, consciousness depends on *unconscious* cognitive processes) means that the mental vs. physical dilemma does not have to be overcome in order to study the brain mechanisms of cognition. Indeed, many of the processes studied by cognitive scientists are also topics of research pursued by so-called cognitive neuroscientists. Led by breakthroughs in understanding the psychology of cognition, cognitive neuroscientists have been very successful in relating perception, attention, memory, and thinking to underlying mechanisms in the brain.[50]

Cognitive psychology, and its sister, cognitive neuroscience, would thus seem to be taking us ever closer toward psychological and neurobiological understandings of the self. However, this is not exactly the case. Though

we understand how specific cognitive processes work psychologically and neurologically, cognitive approaches fall short when it comes to explaining the self.

First of all, by its very definition, cognitive science is a science of only a part of the mind—the cognitive part—and not a science of the whole mind.[51] Traditionally, as we'll see in chapter 7, the mind has been viewed as a trilogy, consisting of cognition, affect (emotion), and conation (motivation).[52] The fact that emotion and motivation are not studied by cognitive science makes sense if cognitive science is regarded as a science of cognition, but is troubling if the field is supposed to be the science of mind. A mind without feelings and strivings (the kind of mind traditionally studied in cognitive science) might be able to solve certain problems given it by a cognitive psychologist, but it doesn't stack up well as the mental foundation of a self. The kind of mind modeled by cognitive science can, for example, play chess very well, and can even be programmed to cheat. But it is not plagued with guilt when it cheats, or distracted by love, anger, or fear. Neither is it self-motivated by a competitive streak, or by envy or compassion. If we are to understand how the mind, through the brain, makes us who we are, we need to consider the *whole* mind, not just the parts that subserve thinking.

A second shortcoming of cognitive science is that it has not grappled successfully with how various cognitive processes interact to form the mind. Considerable progress has been made in understanding how perception, memory, and thinking work, but not about how they work together. And in light of the tripartite nature of the mind, an understanding of the self is going to require that we not only figure out how various cognitive processes interact, but also that we include emotions and motivations in the mix and figure out how they interact with one another, as well as how they interact with cognitive processes. Our hopes, fears, and desires influence how we think, perceive, and remember. A science of mind needs to account for and understand these complex processes.

And, finally, cognitive science deals with the way the mind typically works in most of us, rather than the way it works uniquely in any one of us. While we all have basically the same mental processes mediated by the same brain mechanisms, the way these processes and mechanisms operate is determined by our particular genetic background and life experiences.

It would be hard to overstate the importance of cognitive science. It has been extremely successful as a research program, and has revolutionized the way we conceive of the mind. So when I single out the shortcomings of the

field, I do so not to condemn it, but instead to simply point out that it's incomplete when it comes to understanding what makes us who we are.

## THE PERSONALITY CONTEST

Psychology, as we know it today, is an imperfect marriage between two distinct approaches to the workings of the mind that emerged in the late nineteenth century.[53] One is the experimental approach, which emphasizes the way specific mental processes, like perception or memory, typically work. This is the approach that gave rise to cognitive psychology. The other approach is more concerned with how well-adjusted people are and how they might change their behavior to improve their psychological well-being. It focuses on individuals and their idiosyncratic traits, habits, feelings, and thoughts, rather than on the way things work in most people most of the time. The various forms of psychotherapy in use today are outgrowths of this approach, which has also been a fountainhead for theories of personality. This is the kind of psychology that is portrayed in films and novels and is what people usually have in mind when they think of what a psychologist is.

Ideas about personality are probably as ancient as ideas. Around 400 B.C., Hippocrates, for example, proposed that one's health and character were determined by the interaction among four bodily humors (blood, phlegm, black bile, and yellow bile), each of which, in turn, reflected four cosmic elements (earth, water, air, and fire).[54] Six hundred years later, Galen expanded the theory, proposing that excess in one or another humor gave people distinctive personalities. (Excess blood led to a sanguine, enthusiastic personality; too much black bile made one melancholic; abundance of yellow bile led to irritable or choleric temperament; and overproduction of phlegm gave rise to a slow, apathetic, or phlegmatic person.)[55]

Although views of personality, temperament, character, and the self continued to be developed over the centuries, modern approaches essentially began with Freud's psychoanalytic theory.[56] Subsequent theories have for the most part been variations on or reactions to Freud, and fall into several broad categories.[57] These include neo-Freudian psychodynamic theories, organismic or self theories, trait theories, behavioral or learning theories, and cognitive theories.

Personality theorists clearly have had valuable insights into the workings of the human mind, and have guided therapists in their efforts to help people adjust to life's challenges. But the various theories are often directly contra-

dictory.[58] There were feuds within psychoanalysis even in Freud's day (Jung, for example, broke away from strict Freudianism). Later, the neo-Freudians had disputes as well. For example, some maintained Freud's emphasis on repressed sexual urges as the root of anxiety, while others replaced sexuality with social and/or cultural factors as the core psychoanalytic concept. Psychoanalytic theory today is probably best viewed as a family of theories rather than a single well-defined view of how the mind works and how it breaks down in psychopathology.

But differences within psychoanalytic theory pale compared to differences between psychoanalytic and other personality theories. Some theories focus on psychopathology, while others are more concerned with the nature of the well-adjusted person. Unconscious motivation plays a key role in some theories, while others go in the opposite direction and focus almost exclusively on conscious strivings. Behavior is motivated in multiple ways in many theories, whereas in others, a single motive is emphasized (e.g., sexual gratification or self-actualization). Social considerations are important in some but are less crucial in others. Biological factors, especially genes, are believed to underlie stable personality traits over one's life span for some theorists, but others emphasize the role of learning and situational (especially social) factors in determining behavioral and mental states.

One possible explanation for the diversity of personality theories is that the topic is simply so difficult that no one has quite figured it out yet. Alternatively, there may have not been a clear winner in this personality contest not because the various theories proposed to date are all wrong, but because many are at least partly correct. If this is true—and I believe this is the case—then the best way to construct a view of the self might be not to pit the various theories against one another but rather to synthesize across them.

## A VIEW OF THE SELF

So far, I've used the terms *personality* and *the self* rather loosely. Now it's time to get more specific. From here on, when I use the term *the self* I am referring to the totality of the living organism. This notion subsumes the idea of personality[59] and is similar to what William James had in mind when he described the self as the sum total of who one is (see the opening paragraph of this chapter). But in order for this view of the self to be useful to our pursuit of how the brain makes the self possible, we need to refine it considerably.

In modern personality theory, as in philosophy, the notion of the self typ-

ically refers to the conscious self, in the sense of having self-knowledge, a self-concept, and self-esteem; of being self-aware, self-critical; of feeling self-important; and of striving toward self-actualization. Carl Rogers, a pioneer psychologist of the self, summed up this view, defining *the self* as "the organized, consistent conceptual gestalt composed of perceptions of the characteristics of the 'I' or 'me.'"[60] For Rogers, these perceptions are "available to awareness, though not necessarily in awareness." Modern self psychologists like Hazel Markus have a similar focus on self consciousness.[61] These psychologists do not deny that some aspects of mental life occur unconsciously, but instead minimize the importance of the unconscious components of the mind in favor of the notion of a self as an active agent in the control of mental states and behavior.

In spite of this long tradition of emphasis on the self as a conscious entity, the self that we are aware of, or can be aware of, is not the entirety of what the term *the self* refers to. The psychologist Ruth Munroe, for example, argues for a more fundamental view.[62] She points out that "a sense of self which *develops* in the course of living is too far confused with the truly necessary organismic self." Munroe is questioning whether the "sense of self" that develops over time is the whole self. In other words, she is arguing that the self that we are aware of and strive to improve, the self that we have a sense of, the self that many personality theorists have been enthralled with, is too narrow a view of what the self really is.

The existence of a self is a fundamental concomitant of being an animal. All animals, in other words, have a self, regardless of whether they have the capacity for self-awareness. As a result, the self consists of more than what self-aware organisms are consciously aware of. Indeed, recent research in social psychology has emphasized that many important aspects of human social behavior, including decision-making as well as the way we react to members of racial and ethnic groups, are mediated unconsciously.[63] These differences within organisms (conscious vs. unconscious aspects) and between organisms (creatures with and without consciousness) are not captured by an undifferentiated notion of the self, but can be accounted for by distinguishing between explicit and implicit aspects of the self.

Things we consciously know about who we are make up the *explicit* aspects of the self. These are what we refer to by the term *self-aware* and constitute what we call our self-concept; they are what the self psychologists are interested in. The *implicit* aspects of the self, by contrast, are all other aspects of who we are that are not immediately available to consciousness, either be-

cause they are by their nature inaccessible, or because they are accessible but not being accessed at the moment. All animals have implicit selves, but only animals that have the capacity for conscious self-awareness have explicit selves (this is why the existence of a personality in a pet does not necessarily mean that the pet is conscious in the human sense).

This view of the self contrasts with the idea of a person as elaborated by philosophers like Strawson, Dennett, and others. Only humans can be persons, but all animals can have selves, especially when we allow for the distinction between implicit and explicit selves. One might want to broaden the notion of a person to account for explicit and implicit aspects. This would solve one problem (the fact that there's more to a person than what that person is conscious of) but would leave another unaddressed (the relation between persons and other animals).

That explicit and implicit aspects of the self exist is not a particularly novel idea. It is closely related to Freud's partition of the mind into conscious, preconscious (accessible but not currently accessed), and unconscious (inaccessible) levels. However, Freud's terms carry much theoretical luggage that I want to leave behind.

The terms *implicit* and *explicit* are themselves not completely neutral. They are borrowed from the study of memory, where it is now widely recognized that the brain system involved in forming explicit, consciously accessible memories is distinct from a variety of other systems that are capable of learning and storing information implicitly, which is to say without conscious awareness.[64] Actually, since most brain systems are plastic, and work outside of consciousness, they can be thought of as implicit memory systems or, better yet, as systems that are able to store specific kinds of information implicitly. To the extent that our life's experiences contribute to who we are, implicit and explicit memory storage constitute key mechanisms through which the self is formed and maintained. Those aspects of the self that are learned and stored in explicit systems constitute the explicit aspects of the self. To be self-aware is to retrieve from long-term memory our understanding of who we are and place it in the forefront of thought. In contrast, those aspects of the self that are learned and stored in implicit systems make up the implicit aspects of the self. We use this information about our selves all the time, even though we may not be consciously aware of it. The way we characteristically walk and talk and even the way we think and feel all reflect the workings of systems that function on the basis of past experience, but their operation takes place outside of awareness. I will have much to say in later chapters about the workings of explicit and implicit memory functions of the brain.

The self is a unit, in the sense that organisms go to great pains to keep themselves alive and well. Physical damage to one's appearance is not taken lightly (remember the harm that face removal from the Egyptian tomb was meant to achieve), nor are insults to one's character. Both implicit and explicit systems are utilized to accomplish this unity in humans. But self-preservation is a universal motive, independent of whether the organism is aware that it is working toward this goal. A cockroach can scamper away when a human foot approaches without being explicitly aware of being in danger, the same way that a single-cell bacterium can detect and move away from harmful molecules in its chemical world.

The self is not static. It is added to and subtracted from by genetic maturation, learning, forgetting, stress, aging, and disease. This is true of both implicit and explicit aspects of the self, which may be influenced similarly or differently at any one point. For example, a mild compliment may only be registered and stored in explicit memory, but glowing praise, registered explicitly, might lead to the arousal of emotion systems that then also store aspects of the experience implicitly. On the other hand, stress is known to impair explicit memory while at the same time enhancing the implicit memory functions of emotion systems.[65]

As important as learning is, not all aspects of the self are learned. Some are due to our genetic heritage. All of the capacities that we have as *Homo sapiens,* including our capacities to learn and remember, are made possible by the genetic makeup of our species. What we place in our individual memory systems is a function of our unique experience, but the existence and basic mode of operation of these systems are due to our species's genes. At the same time, we each have a family genetic history that is a variation on the theme of being a human, and a personal set of genes that is a variation on our family's, and these variations also influence who we are.

The most well-articulated view of the role of genes in shaping behavioral and mental characteristics comes from biological trait theories of personality, which propose that one's enduring qualities are due to one's genetic background.[66] Considerable evidence has been amassed to support the view that some traits, such as the extent to which one is extroverted (gregarious) vs. introverted (shy, fearful, withdrawn), are highly influenced by one's genetic history. Nevertheless, there are two important caveats to genetic theory of personality.

First, genes have been found to account for only about 50 percent of a particular personality trait.[67] What this statement means is that genes account at most for half of a given trait, *not* that half of all of personality is accounted for

by genes. For some traits, genetic influence is far less and is often not measurable. Introversion is probably the trait with the strongest genetic influence.[68] Although many extremely shy, introverted children tend to become anxious, depressed adults,[69] some do just fine. Is this because the genetic influence in the latter group was temporary, or because the genetic tendency was squelched? The fact that when extreme introversion is caught early, it can be reversed to some extent by a supportive family environment suggests that genes do not fully dictate psychological destiny.[70] Life's experiences, in the form of learning and memory, shape how one's genotype is expressed. Even the most ardent proponents of genetic determination of behavior admit that genes and environment interact to shape trait expression. It's a matter of how much, not whether, both contribute.

The second caveat to the genetic account of personality stability comes from research showing that people are not always true to their so-called personality traits. One may be shy at work or in social groups, for example, but domineering at home. In fact, when psychologists have examined the consistency of behavior across situations, the results have not supported the view that people act consistently in different situations. Observations such as these suggest to Walter Mischel that behavioral and mental states are not dictated by constitutional factors but instead are situationally determined. Mischel argues that the ability to predict behavior depends upon knowing about a person's thoughts, motivations, and emotions relative to a particular set of circumstances.[71] He describes these as "if . . . then relations." "If" you are in situation A, "then" you do X, but "if" in situation B, "then" you do Y. According to Mischel, people don't possess stable personality traits over time, but stable "if . . . then" profiles.

As with most polarized arguments in psychology, there is truth in both the situational and the trait views. The stronger the genetic contribution to a particular characteristic, the more likely it will be expressed uniformly in different situations. At the same time, situations vary in the extent to which they dictate the way we act. A red traffic light will cause most people to stop, regardless of whether they are generally aggressive or timid, whereas a yellow light allows more latitude for tendencies like aggression or timidity to be expressed.[72] We'll visit questions about genetics and personality again in chapter 4, when we explore how the brain is built.

In proposing that the self exists, I run the risk of reifying something that is, ultimately, not real. Bob Dylan, for example, said, "I change during the course of a day. I wake and I'm one person, and when I go to sleep I know for

certain that I'm someone else. I don't know who I am most of the time. It doesn't even matter to me."[73] And, according to Philip Roth, "All I can tell you with certainty is that I, for one, have no self, and that I am unwilling or unable to perpetrate upon myself the joke of a self."[74] Mark Epstein, who has tried to integrate psychoanalysis and Buddhism, points out that the ego's image of itself (its object image) is always lacking as an account of the subject (the self), implying that much of the self is, in essence, implicit.[75] While the whole self is not usually encountered by the individual who possesses it (who *is* it), or by others, it nevertheless exists.

What then is it? In my view, the self is the totality of what an organism is physically, biologically, psychologically, socially, and culturally. Though it is a unit, it is not unitary. It includes things that we know and things that we do not know, things that others know about us that we do not realize. It includes features that we express and hide, and some that we simply don't call upon. It includes what we would like to be as well as what we hope we never become.

The fact that all aspects of the self are not usually manifest simultaneously, and that different aspects can even be contradictory, may seem to present a hopelessly complex problem. However, this simply means that different components of the self reflect the operation of different brain systems, which can be but are not always in sync. While explicit memory is mediated by a single system, there are a variety of different brain systems that store information implicitly, allowing for many aspects of the self to coexist. As William James said, "Neither threats nor pleadings can move a man unless they touch some one of his potential or actual selves."[76] In *Orlando,* Virginia Woolf pointed out, "A biography is considered complete if it merely accounts for six or seven selves, whereas a person may well have as many thousand."[77] Or as the painter Paul Klee expressed it, the self is a "dramatic ensemble."[78]

## THE SELF AND THE BRAIN

Theories of the self and personality are not usually framed in ways that are compatible with our understanding of brain function.[79] How, then, can we relate the complex constellation I've called the self to the systems and synapses of the brain?[80] The goal of the rest of the book is to answer this question. However, a brief preview is in order.

The self can be understood in terms of brain systems involved in learning and storing information, in explicit and implicit systems, about things that are significant in people's lives. The processing by these systems always occurs

in a physical and social context (a situation) and is performed by networks that function the way they do because of both genetic inheritance and past experiences. Put this way, in order to understand the self, we need to explain how brain systems underlying thinking, emotion, and motivation (the mental trilogy) develop under the influence of nature and nurture, and how these systems make it possible for us to attend to, perceive, learn about, and store and retrieve experiences. We especially need to explain how different systems interact with and influence one another. Without these interactions, and the mental integration they engender, each of us would simply be a collection of isolated mental functions rather than a coherent person.

The point, though, is not simply to state that learned and innate interactions between cognitive, emotional, and motivational processes make us who we are, but instead to explain ***how*** these interactions work. And the explanation that I will pursue in the remainder of this book involves neural, especially synaptic, mechanisms. I believe, in short, that an answer to the question of how our brains make us who we are can be found in synaptic processes that allow cooperative interactions to take place between the various brain systems that are involved in particular states and experiences, and for these interactions to be linked over time. It is probably not at all obvious what this statement means at this point in the book. Before it will begin to make sense, we need to cover more ground.

CHAPTER THREE

# THE MOST UNACCOUNTABLE OF MACHINERY

MY OWN BRAIN IS TO ME THE MOST UNACCOUNTABLE OF MACHINERY—ALWAYS BUZZING, HUMMING, SOARING ROARING DIVING, AND THEN BURIED IN MUD. AND WHY? WHAT'S THIS PASSION FOR?

—Virginia Woolf

Most of us are as mystified by our brains as Virginia Woolf, though perhaps less eloquent in our ignorance. Still, everyone has heard a few things about the wrinkled blob in the noggin—for instance, that we use only 10 percent of it. But who came up with this number? And why would we even have the rest if it weren't useful? Evolution doesn't usually make organs in such a way that they mostly go unused, just in case someone figures out one day what to do with the extra material. It's hard to imagine how 90 percent of the brain, lacking in value for most of us most of the time, could have ever come into existence. Researchers have been looking into what the brain does for many years now, and from what they have discovered, it doesn't seem that most of it is, in fact, resting idly.

People also tend to carry around with them one or both of two additional erroneous beliefs about the brain. The first is that functions of the brain, like perception, memory, or emotion, are located in specific areas. The other is that chemicals floating around in the brain determine our mental states. Unlike the 10 percent myth, these are actually part truths that, taken out of context, are patently false. We know, at least in a general sense, how the brain works, and it's not by islands of brain tissue or by isolated chemicals operat-

ing independently. Particular areas are important, but not on their own: they participate in functions by way of their synaptic connections with other areas. Chemicals are also important, but mainly because of their work at synapses within functional systems.

This chapter will give an account (albeit an abbreviated one) of this "most unaccountable of machinery," describing some basic facts that are necessary to understand the brain's synaptic systems. Although the discussion will have to get a bit technical along the way, this information is essential to my attempt to relate the self to synapses. Because I've kept things simple, those already in the know may wish to skip ahead. However, the novice will get a crash course on what neurons are, how synapses connect them together, and why synaptic connections are the key to brain function.

## BRAINS: SO DIFFERENT, YET ALL THE SAME

We mammals belong to the group of animals called vertebrates, a subphylum we share with other backboned creatures, including birds, reptiles, amphibians, and fish. Mammals and birds separately descended from reptiles millions of years ago. In spite of this common ancestry, the brains of reptiles, birds, and mammals look very different. Beneath these dissimilarities, though, there's a common plan that's rigorously adhered to.

Every vertebrate brain can be divided into three broad zones: the hindbrain, midbrain, and forebrain. In the early years of the twentieth century, neuroscientists discovered that damage to each zone had a different predictable consequence.[1] For example, in studies of cats, it was found that purposeful, voluntary behavior and problem-solving ability were impaired when the forebrain was damaged. Nevertheless, even with massive injuries to the forebrain, some semblance of normal coordinated behavior remained. Such compromised animals could orient toward a noise or withdraw their paw from heat, and could walk, eat, and groom. They could even display full-blown emotional responses, especially those typically expressed in anger or fear, if the hypothalamus, a small region situated at the base of the forebrain, was spared. When larger lesions were made that removed all of the forebrain, including the hypothalamus, only rudimentary responses remained. These animals, when challenged with intense stimulation, could hiss, bare their teeth, unsheathe their claws, or swipe a paw, but could not manage to put all of these behaviors together into a coordinated defense or attack response. When the midbrain was damaged, the animal was essentially comatose—

alive physically, but not behaviorally or psychologically. And when the hindbrain was destroyed, life itself ceased.

From these crude experiments, it was concluded that the hindbrain controls very basic functions, those necessary for staying alive; the midbrain is involved in maintaining wakefulness and coarse, isolated behavioral reactions; and the forebrain coordinates complex behavioral and mental processes. It should not be surprising, given these effects of brain damage, that the forebrain (necessary for thinking and problem-solving) is the region that differs the most between mammals and other vertebrates and the hindbrain (necessary for life) the least. Nevertheless, all three levels are represented in all vertebrates, and even the evolutionarily advanced forebrain is structured according to a common underlying organizational plan that is applicable to every vertebrate species.

For example, the human forebrain consists of several subdivisions,[2] one of which is the wrinkled outer layer, the neocortex. This is the part of the forebrain that makes possible many of our higher mental functions. The designation *neo* reflects the fact that this brain region was, for many years, believed to be evolutionarily new, having emerged when mammals evolved from reptiles.[3] Other vertebrates were thought to have a primordial or older cortex but not a mammalian or neocortex. This view began to change, though, in the late 1960s and early 1970s, when new techniques for studying the brain became available.[4] Based on the patterns of chemical staining and nerve connections discovered with these techniques, the organization of the brain came to be better appreciated, and researchers were able to use this information to find the equivalent (or at least the semblance) of a neocortex in both birds and reptiles, suggesting both that it wasn't so new after all and that it certainly wasn't unique to mammals. The reason this cortex had not been found in these animals earlier was because of its unusual location, buried beneath other brain areas, instead of resting on top, as it does in mammals.

While at the level of overall brain structure a similar organizational plan applies to many different animals, it is not the case that all brains are the same. A given brain area can vary enormously in size and complexity between different species, allowing some animals to do things that others cannot. In amphibians, for example, an area in the midbrain called the tectum is especially well developed, making it possible for most frogs to thrust their tongue into the flight path of an insect and capture it,[5] a feat most people can't accomplish. Bats and rats can hear things that we cannot, and bees use a magnetic sense, which we do not have, to guide their movements.[6] Different

species have been subjected to different evolutionary pressures, and their brains reflect their unique histories.[7]

The most obvious difference between the mammalian and other vertebrate brains is the extent to which the cortex has expanded. Although, as we have seen, reptiles and birds are now known to have some neocortex, the mammalian neocortex is far more elaborate than the equivalent areas in these other species.[8] And within mammals, there are distinctions as well: the neocortex is bigger and more differentiated in primates than in rodents, and in humans more so than in monkeys. These changes in cortical size and complexity are, however, superimposed on a basic neocortical plan. For example, in all mammals, processes related to sensation (vision, audition, touch) are represented in the rear and processes involved in controlling movement in the front of the cortex.

Within a given species, the similarities of cortical organization are striking. Early anatomists discovered that the major patterns of cortical wrinkles, which appear to be randomly arranged to the uninitiated eye, are amazingly consistent from person to person, and can be used as landmarks to identify various regions of the neocortex.[9] What's remarkable is that these purely structural parcels, defined by the wrinkles, turn out to correspond to functional divisions, areas that participate (by way of their synaptic connections with other cortical and/or subcortical areas) in different aspects of mental life and behavior.[10] For example, the area of the cortex involved in controlling precise movements of various body parts is located just in front of the central sulcus, one of the major wrinkles in the cortex, while touch, hearing, and visual areas are defined by their own wrinkles, as are areas involved in language comprehension and speaking. On careful examination, some variation in the organization of cortical or other brain areas is evident in different people, but the basic overall architectural plan of the brain is pretty much the same in any two individuals.

In spite of the tremendous similarity of our brains, we all act differently, have unique abilities, and have distinct preferences, desires, hopes, dreams, and fears. The key to individuality, therefore, is not to be found in the overall organization of the brain, but rather in the fine-tuning of the underlying networks. To understand the defining qualities of each person, we need to go beyond the superficial organization of the brain (its division into broad regions and areas within these) and turn to the microscopic structure and function of neural systems, and especially to the cells and synapses that constitute them.

## THE CELL WAR

All organs and tissues of the body are composed of cells. But unlike the cells in other body parts, brain cells, or neurons, directly communicate with one another. There's nothing magical about the process—neurons are simply built in a way that allows them to exchange information with one another in ways that other cells cannot.[11] Common patterns of communication between neurons ensure that all human brains work in basically the same way, whereas subtle differences in these patterns of communication give rise to the distinctive qualities that we each have.

The existence of cells in the brain and other parts of the body is taken for granted today, but this knowledge was only made possible by the further development of the microscope in the nineteenth century. Around 1837, Matthias Schleiden, a German botanist, first proposed that plants were made up of discrete units, or cells. The following year, his friend Theodor Schwann extended the notion to animals, and thereby brought botany and zoology together in a single theory, the so-called cell theory,[12] which argued that all living things are composed of cells.

Whether cell theory was applicable to the brain was a topic that was fiercely debated for decades. When early brain anatomists examined brain tissue under a microscope, they did see structures resembling cells. But unlike cells in other organs, brain cells had fine fibers extending out of them (fig. 3.1). Some scientists concluded that this meant that the brain was unique—not composed of discrete cells but instead made up of an entangled mesh or reticulum of continuously connected elements. Others, though, argued that the fundamentals of cell theory applied equally to the brain.

Two of the major figures in the debate were Santiago Ramón y Cajal of Spain and the Italian anatomist Camillo Golgi.[13] Golgi, working in his kitchen, invented methods for staining the brain that allowed better visualization of its microscopic anatomy. He favored the reticular theory. Ironically, on the basis of the methods pioneered by Golgi, Cajal argued forcefully for the application of the cell theory to the brain, and won many converts. One of these was Wilhelm Waldeyer, who in 1891 published a paper in which he suggested that brain cells be called neurons. In this paper, he also coined the phrase *the neuron doctrine* to account for the application of the cell theory to the brain. Cajal apparently considered the doctrine his, at least in spirit if not name, and was not happy to have had his thunder stolen by Waldeyer.[14] But the loss in stature, if any, was temporary. Every graduate student in

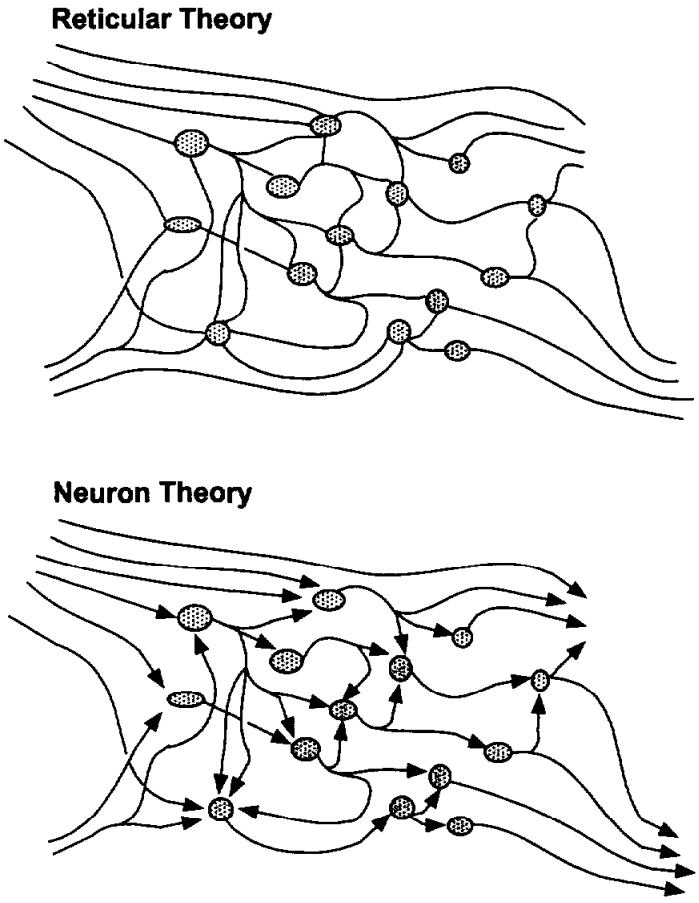


**FIGURE 3.1 RETICULAR VERSUS NEURON THEORY**

In the late nineteenth century, scientists fiercely debated the question of whether the brain was made up of a reticulum of continuously connected elements or, instead, of individual cells, neurons, that communicated with one another. By the beginning of the twentieth century, the so-called neuron doctrine had emerged as the prevailing view.

neuroscience today knows who Cajal was, whereas few have ever heard of Waldeyer.

One of the early and largely unrecognized soldiers in the neuron war was the young Sigmund Freud. After completing his medical training in Vienna, Freud accepted a position as a famulus, or research scholar, and studied the nervous system of fish and crayfish.[15] As early as 1883, long before the neuron doctrine was codified, he promoted the idea that nerve cells are physically separated from one another.[16] This concept later figured prominently in one of his earliest forays into psychological theory. In *Project for a Scientific Psychology,* written in 1895 but unpublished for many decades,[17] Freud stated that "the nervous system consists of distinct and similarly constructed neurones . . . which terminate upon one another." He introduced the term *con-*

*tact barriers* to describe the points where neurons abut, and suggested that interactions between neurons across contact barriers make possible memory, consciousness, and other facets of the mind. Although these notions were amazingly sophisticated for their time, Freud felt that progress in understanding the brain would be too slow for his taste and so abandoned a neural theory of the mind in favor of a purely psychological one.[18] The rest is history.

Two years after Freud wrote his *Project,* Sir Charles Sherrington proposed a different term for the connections between neurons.[19] Sherrington had been working on the reflex problem.[20] A reflex is the simplest kind of neural circuit that controls behavior. When your physician taps you on the knee, your leg jerks because the tap elicits sensations that are transmitted along *sensory* nerves that originate in your knee and travel to your spinal cord. The messages in the sensory nerves trigger activity in *motor* nerves that come out of the spinal cord and end in your leg muscles, leading to the jerk. Sherrington realized that the gap between the sensory and motor neurons had to be bridged somehow if information carried by the sensory nerves was to be transferred to the motor nerves. He was probably unaware of Freud's contact barriers, and chose to call the gaps synapses, derived from the Greek word meaning to clasp, connect, or join.[21] The notion of synapses as points of communication between cells is one to which we still adhere, and which is essential to our efforts to understand who we are in terms of brain mechanisms.

In 1906, Cajal and Golgi shared the Nobel Prize for their groundbreaking research on brain anatomy. Although the neuron doctrine had gained considerable support by then, Golgi clung bitterly to the reticular theory at the award ceremony.[22] Still, definitive proof that the nervous system is composed of cells did not come until many years later. With the invention of the electron microscope in the 1950s, scientists could finally examine the brain in sufficient resolution to see that the tiny fibers extending out of a neuron do not typically make direct physical contact with neighboring cells.[23] Indeed, they are separated by tiny spaces, synaptic spaces, across which the brain does its business.

## WHAT MAKES NEURONS SPECIAL?

By knowing the function performed by a few cells of most organs in the body, whether the liver, kidney, or gall bladder, you can deduce the organ's overall function.[24] This is not true of the brain, however, where cells participate in myriad activities, from seeing and hearing to thinking and feeling, from awareness of self to the incomprehension of infinity. The architecture of a

neuron helps us begin to understand why the brain is so multifunctional, while organs like the pancreas and spleen are not.

Neurons have two major parts. The first is the cell body (fig. 3.2), which is involved in important housekeeping functions, such as storing genetic material and making proteins and other molecules that are necessary for the cell's survival. The cell body does much the same work in neurons as it does in other cells. The major structural difference between neurons and other cells lies in the special appendages that neurons have—the nerves. These fibers, which extend out of the cell body, are what caused all the confusion in the nineteenth century about whether the brain was, like other organs, composed of discrete cells.

Nerve fibers are sort of like telephone wires. They allow neurons in one part of the brain to communicate with neurons in another. By way of these connections, communities of cells that work together to achieve a particular goal can be formed across space and time in the brain. This capacity underlies all of the brain's activities and is absent in other organs.

There are two varieties of nerve fibers, axons and dendrites (fig. 3.2). Axons are output channels, and dendrites are input channels. An axon carries messages to other cells. It can end nearby, allowing communication with its close neuronal neighbors, or it can stretch over very long distances, as much as several feet. If you are standing still and decide to take a step, the movement of your leg on the basis of your decision involves axons that originate in cell bodies located in the movement control regions in the frontal cortex (just behind your forehead) and that travel uninterrupted to the base of the spinal column (in the region of your lower back).

The end of the axon, called the terminal, is the point at which the sending neuron communicates with receiving neurons. Although terminals most of-

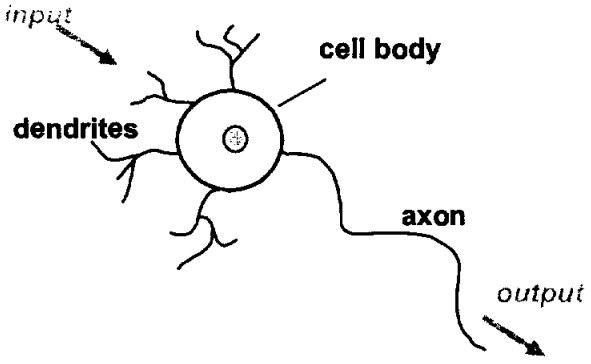


**FIGURE 3.2 COMPONENTS OF A NEURON**

All neurons contain three basic parts: a cell body and fibrous appendages called dendrites and axons.

ten form connections with dendrites, they can also contact cell bodies or other axons.[25] Dendrites, too, sometimes communicate between one another.[26] In order for the long axons descending from your frontal cortex to your spinal cord to cause your leg to move, the terminal has to contact dendrites of the receiving cells in the spinal cord. The axons of these receiving cells then extend out and terminate at muscles in your leg. The arrival of signals at the muscle leads to contraction, and thus movement.[27]

Many dendrites have little knobs called spines extending from them (fig. 3.3). These are readily seen when brain tissue is stained with the methods

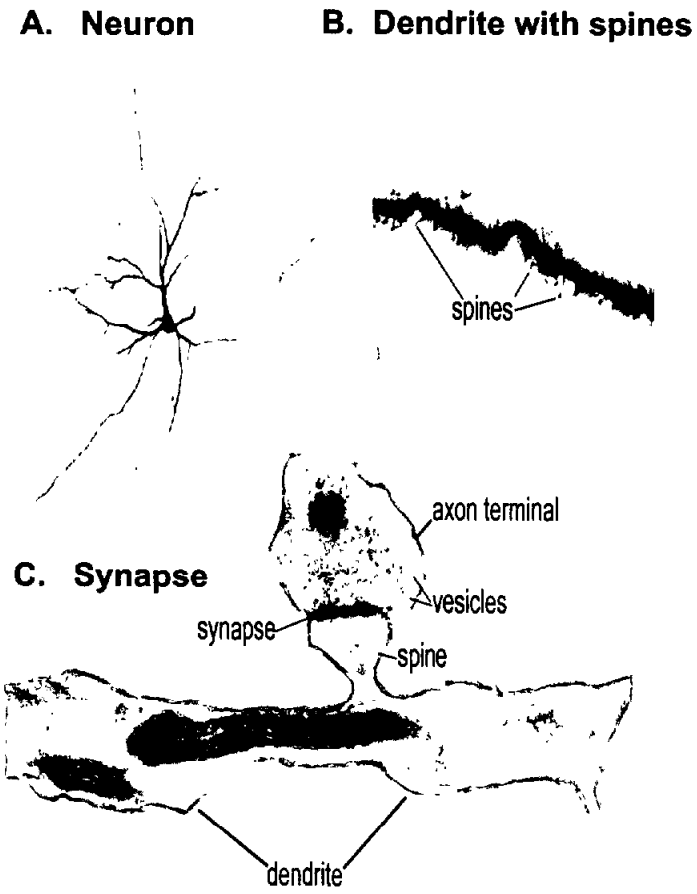


**FIGURE 3.3 WHAT A NEURON LOOKS LIKE**

*Upper left:* A single neuron and many of its dendrites. This neuron had been filled with a dye so that its shape can be seen. *Upper right:* A high magnification of a small piece of a dendrite showing the protrusion of the small spines from the dendritic shaft. Spines are often where axons from other neurons terminate and form synapses. *Bottom:* A highly magnified electron-microscopic picture of an axon terminal with vesicles forming a synapse with the spine of a dendrite. When an electrical charge travels down the axon to the terminal, neurotransmitter is released from the vesicles and drifts across the small synaptic space between the terminal and the spine. The neurotransmitter then binds to receptors on the spine and initiates electrical events in the receiving neuron.

developed by Golgi. Spines are especially important as receivers of messages from axons, and play a key role in brain development, as well as in learning and memory, as we will see later.

Most neurons have only one axon. However, each axon branches many times before it ends, allowing a single neuron to spawn many terminals. The result is that the messages sent out from one cell can affect many others. This is called divergence (fig. 3.4). At the same time, each neuron can receive inputs from numerous others. This is called convergence (fig. 3.4).

The point at which the sending and receiving elements of neurons meet is our star, the synapse. Because information usually flows across the synapse starting from the axon terminal, this side is said to be presynaptic, and the receiving side, often occupied by a dendritic spine, postsynaptic (fig. 3.5). As Sherrington noted, because a synapse is a space between the sending and receiving cells, something has to cross the synaptic space in order for the two cells to communicate.

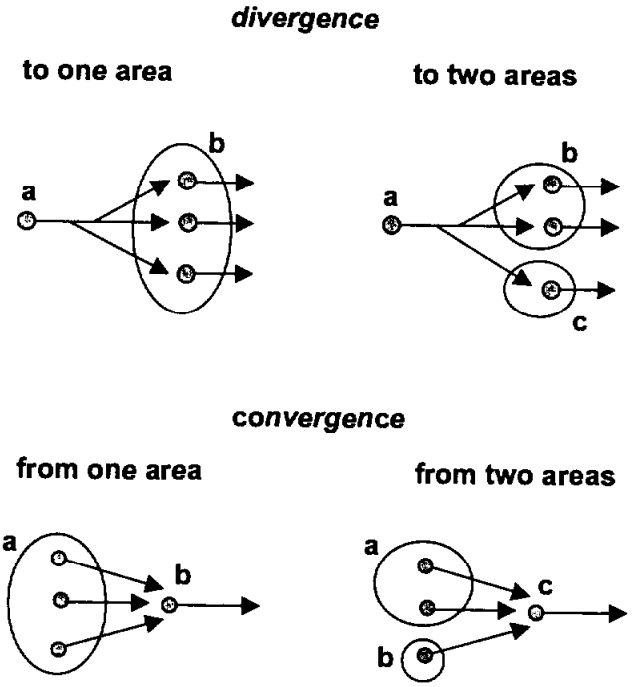


**FIGURE 3.4 DIVERGENCE AND CONVERGENCE**

Divergence exists when a neuron gives rise to axons that branch and terminate on multiple targets, whereas convergence exists when a single neuron receives inputs from multiple sources.

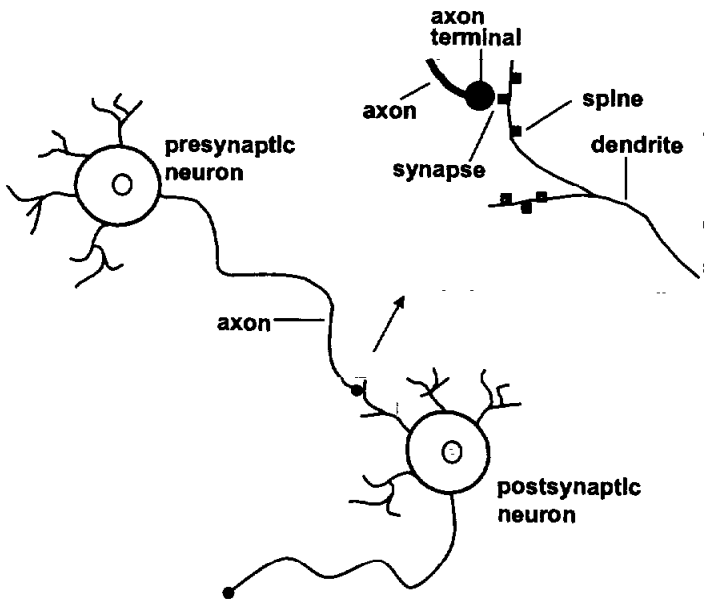


**FIGURE 3.5 PRESYNAPTIC AND POSTSYNAPTIC NEURONS**

This figure shows two neurons, one presynaptic to the other. The axon of the presynaptic neuron terminates at the dendrites of the postsynaptic neuron. Often, such terminations form synapses on the spines (small protrusions) on dendrites.

## GALVANIZED FROG LEGS

The question of how information is exchanged between neurons across the synaptic space is tied in closely with that of how information is transferred along a nerve fiber of a single neuron. Before we consider synaptic transmission, we therefore need to consider nerve conduction.

In the 1770s, Anton Mesmer, a Viennese physician, had been using iron magnets to treat a variety of physical and mental maladies, until he found he could have the same effect without the magnets when he looked into a patient's eyes and waved his hands over the afflicted body part.[28] This was the birth of mesmerization, or hypnosis. Mesmer believed that some mysterious, magnetically sensitive fluid was present throughout the universe, including the human body, and that he could help his patients by using his own animal magnetism to alter this fluid.[29] At the time, little was known about the physiology of the nervous system, and any theory, including one as wacky as animal magnetism, seemed possible.

A few years later, the Italian Luigi Galvani noticed that the amputated leg of a frog hung from an iron trellis with a brass hook twitched during a lightning storm.[30] He also found he could make a frog leg kick at any time he wished if he touched the nerves within the wound with one metal and the

foot with another. This was, in effect, the first battery. Galvani, in the tradition of Mesmer, concluded that the metals were conducting vital spirits from the frog. So-called animal electricity was an occult rather than a scientific phenomenon.[31]

Several decades later, Carlo Matteucci, another Italian, made the first measurements of genuine electrical activity in nerves.[32] In Germany, Johannes Müller and Emil Du Bois-Reymond, realizing the importance of this observation, began a research program that rescued electrical conduction in nerves from the world of mysticism and turned it into a thriving scientific research field.[33]

At the time, the assumption was that nerves conducted electricity like wires. But one of Du Bois-Reymond's students, Hermann von Helmholtz, did an experiment that suggested otherwise. He calculated the speed of electrical conduction in frog nerve fibers by measuring how much time elapsed before a given muscle twitched when nerves of different lengths were electrically stimulated. Although conduction time was fast—about 40 meters per second (roughly 40 mph)[34]—it wasn't as fast as electricity, which can under certain conditions flow through a wire at about the speed of light.

From these simple but informative experiments, it became clear that nerves do conduct electricity, but in a special way. Electricity does not flow passively through a nerve as it does through a wire. Rather, impulses conducted through nerves are *biologically* propagated, moved along by electrochemical reactions, a process that takes a lot longer than passive physical conduction.

The biologically propagated impulse in a nerve is called an action potential. This dramatic electrical event is normally initiated at the point where the axon emerges from the cell body. Once triggered, it travels like a rolling wave down the axon toward the terminal. The propagation occurs as a kind of neurodomino effect—an electrical change in one part of the axon membrane produces a similar change in adjacent parts, and so on, all the way down to the terminal. Action potentials can be triggered artificially by electrical stimulation, which makes them easy to study, but normally they occur in a cell when orders come from synaptic inputs.

Work by many pioneering neuroscientists established the basic principles of electrical propagation in axons, which became the foundation for much of what we now know about the working of neurons. A good deal of this research was performed using the giant axons of squids, the sheer size of which made it easier to investigate electrical conduction. Especially noteworthy were the studies performed in the 1940s by Alan Hodgkin and Andrew Hux-

ley in England. Building on Ohm's law of electricity (which states that voltage is equal to current times resistance), they characterized in precise mathematical form the basic features of electrical transmission in axons. The Hodgkin-Huxley equations are still used today to calculate current, voltage, and resistance in axons.

## SYNAPTIC CHATTER

The existence of electrical conduction in nerves suggested to late-nineteenth-century scientists that electrical impulses played a critical role in the normal functions performed by the brain. A key related question was whether electrical propagation was sufficient to explain how the brain worked. Sherrington's studies of reflexes determined that it was not.

Electrical impulses in sensory and motor nerves clearly seemed involved in reflexes: when sensory nerves detect a tap on your knee, they conduct electrical impulses that, in turn, lead to electrical impulses in motor nerves, and to the jerk. But how does the sensory nerve communicate with the motor neuron? Sherrington demonstrated that while electrical stimulation of a sensory nerve elicited an electrical response in the motor nerve, stimulation in the motor nerve did not evoke a response in the sensory nerve (fig. 3.6). He concluded that the junction between cells, the synapse, had a valvelike property—it only transmitted in one direction, from sensory to motor nerves.[35] This was particularly significant ammunition against the reticular theory, for if neurons were continuously connected and communicated only by electrical conduction, then motor nerves should have as sizable an effect on sensory nerves as the other way around. Neurons must therefore communicate with one another by some means other than mere electrical conduction.

Subsequent research revealed that the one-way conduction between neurons is due to the fact that synaptic transmission involves the release of chemicals from storage sites in the presynaptic axon terminal. These molecules are released when action potentials propagated from the cell body reach the terminal. The released chemicals then drift across the liquid-filled synaptic space[36] and come in contact with spines or other portions of the postsynaptic cell. Because the chemical storage sites usually are present in the presynaptic terminal and not in the postsynaptic dendrite, transmission only occurs in one direction. These chemicals are called neurotransmitters, since they allow neurons to communicate across the synaptic gap—they transmit between neurons.

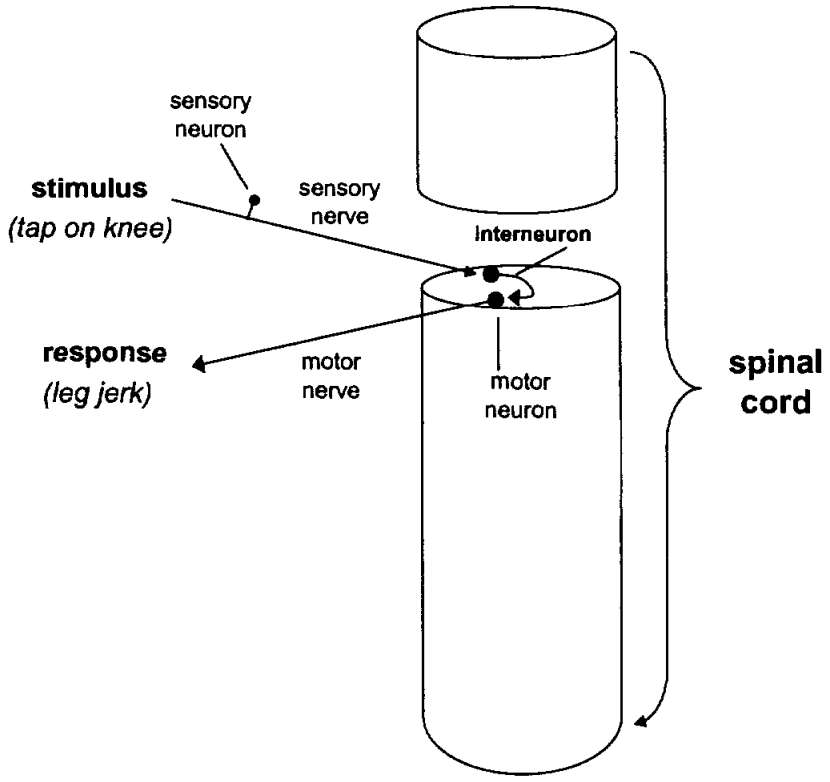


**FIGURE 3.6 A SPINAL REFLEX**

The basic elements of a spinal reflex include sensory neurons that receive messages about an external stimulus, motor neurons that initiate muscle movements, and interneurons in the spinal cord that link the sensory and motor neurons. Sherrington's studies of spinal reflexes led him to the conclusion that synaptic transmission is a one-way street.

The chemical nature of neuronal transmission was suspected from studies in the early 1900s showing that the effects of electrical stimulation of nerves could be mimicked or blocked by certain chemical agents. But it was an ingenious experiment by Otto Loewi in the 1920s that provided the ultimate proof.[37] He removed the hearts from two frogs, leaving the nerves connected to one heart but not the other, and infused each with a saltwater solution (similar to normal body fluid). He then electrically stimulated the nerves on one, which changed the beat rate of the heart (the heart is postsynaptic to these nerves). When he removed the solution from the stimulated heart and injected it into the other, the heartbeat changed in the unstimulated heart, much as if it had been stimulated, indicating that some chemical that had been released in the stimulated heart was transferred in the solution to the other.

While Loewi's experiments involved the connection between a nerve and a

muscle—the heart, in this case—essentially the same thing happens when the connection is between two neurons. That is, the arrival of the action potential in the presynaptic terminal leads to the release of neurotransmitter into the synaptic space.

The release of neurotransmitter molecules from the presynaptic terminal is a means, not an end. Its goal is to generate an electrical response in the postsynaptic cell. Although it is often the dendrites that are the postsynaptic beneficiaries of the chemical message, the electrical change produced in the dendrite has to be propagated to the cell body, and then to the axon, before an action potential can occur. This is so because the action potential is generated in the initial part of the axon where it connects with the cell body (fig. 3.7).

The arrival of transmitter from a single presynaptic terminal is typically not sufficient to produce an action potential in the postsynaptic cell (fig. 3.7). Only if the postsynaptic cell is bombarded with transmitter molecules from many presynaptic terminals at about the same time—within milliseconds—will an action potential result.[38]

A given postsynaptic cell is believed to receive relatively few synaptic contacts from any one presynaptic neuron. As a result, much of the convergence that drives a postsynaptic cell toward action potentials comes from the convergence of different presynaptic cells onto the postsynaptic neuron (that is, the near-simultaneous arrival of neurotransmitter from different presynaptic neurons). In order for the inputs to arrive in the postsynaptic cell body at about the same time, action potentials have to have been triggered in the various presynaptic cells at about the same time. The timing has to be adjusted for different lengths of axons, since, as Helmholtz demonstrated, the longer the axon, the longer it takes for the action potential to travel down it. Keeping time in the nervous system is a very complex job.

Once the postsynaptic cell generates an action potential, its role shifts from that of a receiver to a sender. It now becomes a presynaptic neuron that helps fire action potentials in other cells.

The full sequence of communication between neurons is thus usually electrical-chemical-electrical: *electrical* signals coming down axons get converted into *chemical* messages that help trigger *electrical* signals in the next cell. There are also synapses through which communication between presynaptic and postsynaptic sites is purely electrical,[39] but chemical transmission is the more prevalent form. Thus, much of what the brain does involves electrical-to-chemical-to-electrical coding of experience. As hard as it may be to imag-

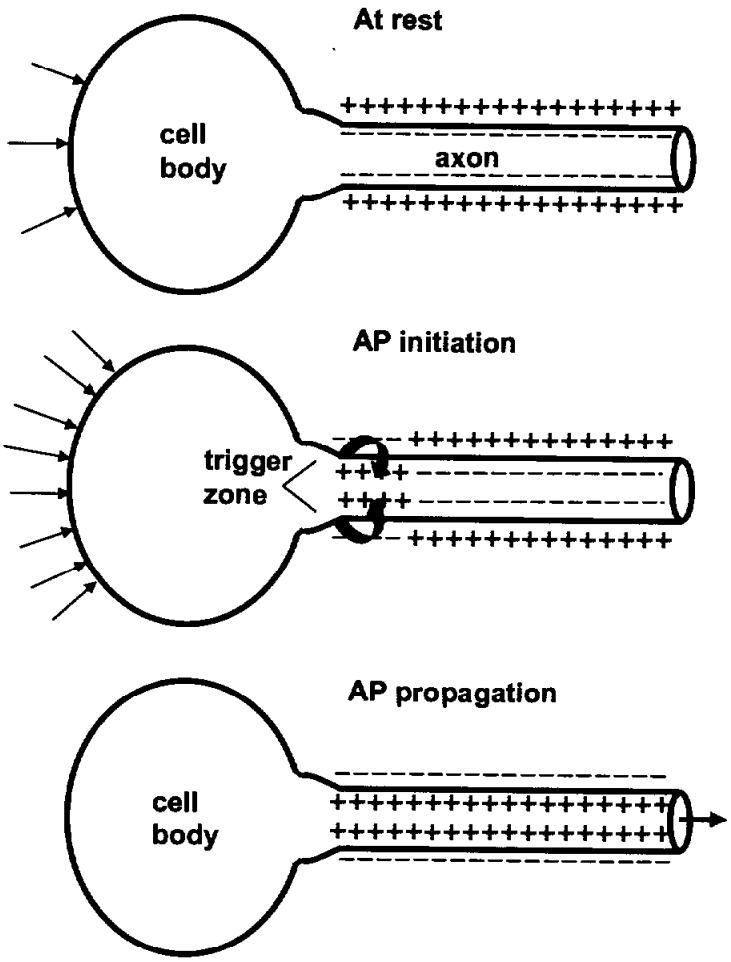


**FIGURE 3.7 ACTION POTENTIALS**

When a neuron is activated by other neurons, an action potential is initiated. This electrical storm begins at the trigger zone (the region where the axon joins with the cell body) and travels down the axon. *Top:* Neurons are "at rest" when they are not receiving sufficient inputs to alter their electrical properties. When at rest, the electrical charge of the inside of the axon is negative with respect to the outside (see the + and − signs along the axon). *Middle and bottom:* When enough inputs (arrows on left) converge at about the same time, an action potential is generated and propagated down the axon toward the terminal. The propagation process involves a wave of electrical change (inside becomes more positive at that spot) that moves step-by-step down the axon. When the terminal is reached, neurotransmitter is released into the synapse. Based on figure 2.6 in Guyton 1972.

ine, electrochemical conversations between neurons make possible all of the wondrous (and sometimes dreadful) accomplishments of human minds. Your very understanding that the brain works this way is itself an electrochemical event.

## FROM CELLS TO CIRCUITS AND SYSTEMS

Every human brain has billions of neurons that together make trillions of synaptic connections among one another. Chemicals are oozing and sparks flying constantly, during wakefulness and during sleep, during thoughtfulness and during boredom. At any one moment, billions of synapses are active.

Imagine a large cocktail party at which hundreds of people are standing around and chatting with one another. If you were to place a microphone in the chandelier at the center of the room high above the crowd, you probably wouldn't be able to make out what was being said, for the many unrelated conversations would blend together in the microphone. You'd learn more by listening in on small groups than by eavesdropping on the whole room at once. In the same vein, it's not particularly instructive to ask what all of the brain's billions of neurons and trillions of connections are up to collectively at any one time. Different groupings of cells are doing different things, so attempting to take a reading of them all together doesn't tell you much. It would be more informative to examine the operation of specific circuits or systems.

A *circuit* is a group of neurons that are linked together by synaptic connections. A *system* is a complex circuit that performs some specific function, like seeing or hearing, or detecting and responding to danger. Seeing, for example, involves the detection of light by circuits in the retina, which sends signals, by way of the optic nerve, to the visual thalamus, where the visual information is processed by circuits that relay their output to the visual cortex, where additional circuits engage in further processing, ultimately creating visual perceptions. The visual system, like other brain systems, can thus be thought of as a series of hierarchically arranged circuits linked together by synaptic connections to perform some function.

Synaptic interactions between two types of neurons, called projection neurons and interneurons, are key to understanding how circuits and systems function.[40] Projection neurons have relatively long axons that extend out of the area in which their cell bodies are located. In a hierarchical circuit, their main job is to turn on the next projection cell in the hierarchy (fig. 3.8). They do this by releasing a chemical transmitter that increases the likelihood that the postsynaptic cell, the next projection cell, will fire its own action potential. Projection cells tend to activate or excite postsynaptic cells.

Interneurons, also called local circuit cells, send their short axons to nearby neurons, often projection neurons, and are involved in information processing within a given level of a hierarchical circuit (fig. 3.8). One of their main

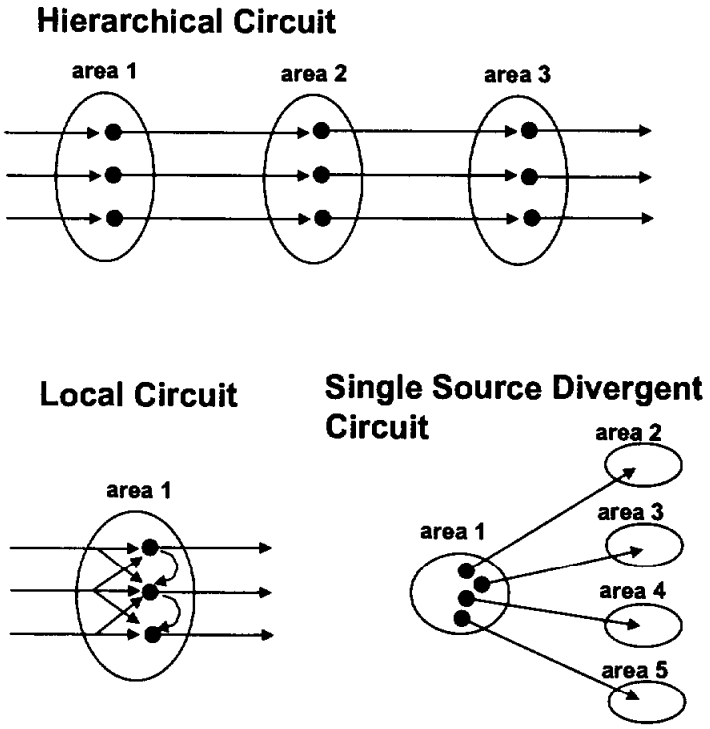


**FIGURE 3.8 THREE TYPES OF CIRCUITS**

Information is transmitted from area to area in sequence in hierarchical circuits. At each level of the hierarchy, though, processing is regulated by other kinds of circuits. Local circuit connections alter the processing at each hierarchical stage and also determine the ease with which activity in one area can influence the next. Single source divergent projections are typically made up of neurons located in one brain region that possess a particular chemical (typically, a neuromodulator like serotonin or dopamine—see text). These chemicals are then released at widespread areas and can influence processing by other circuits. Transfer of information from one level of a hierarchical circuit to another typically involves excitatory connections that are regulated by inhibitory local circuits, and both hierarchical and local circuit transmission is modulated by single source divergent connections. The terminology for these three circuit types is based on Bloom and Lazerson 1985.

jobs is to regulate the flow of synaptic traffic by controlling the activity of projection neurons. Inhibitory interneurons release a transmitter from their terminals that decreases the likelihood that the postsynaptic cell will fire an action potential. These neurons play an important role in counterbalancing the excitatory activity of projection cells.

Projection cells tend to be idle in the absence of inputs from other projection cells. Inhibitory interneurons, though, are often tonically active, which means they are firing all the time. Part of the reason why projection cells are inactive when not being stimulated is that they receive tonic inhibition from

interneurons. As a result, when excitatory inputs try to turn on a projection cell, preexisting inhibition of the projection cell has to be overcome. The balance between excitatory and inhibitory inputs to a neuron determines whether it will fire.

The amount of inhibition affecting a cell can change from moment to moment, depending on other factors. For example, when projection cells in one area of a hierarchical circuit send enough convergent inputs at about the same time to activate projection cells in the next area, the level of inhibition in the second area usually goes up as well. This happens because the excitatory inputs to an area often activate interneurons as well as projection neurons. The momentary increase in excitatory inputs to interneurons leads to a momentary increase in their inhibitory behavior, which in turn produces a momentary inhibition of the projection neurons. So-called elicited inhibition contrasts with tonic inhibition. Because rapidly changing states of excitation and inhibition direct the flow of traffic through the brain, it's easy to understand how a breakdown in the flow of impulses could lead to neural gridlock.

Consider an example that will help illustrate how elicited and tonic inhibition regulate excitation. Imagine a circuit consisting of two projection neurons (A and B) linked together in a series (fig. 3.9). When A is active, B fires. If the job of the circuit were to make B fire action potentials as often as possible as long as A is active, these two neurons would be sufficient to do the job. But suppose its job instead is to take a barrage of action potentials in A and turn them into fewer action potentials in B, something that actually occurs quite often in the brain. This could be achieved by giving neuron B an inhibitory playmate (I). This local circuit neuron, like B, receives the output of A and then connects with B. So when A fires, it turns on B and I, and each produces an output. The output of B helps turn on the next cell in the circuit, while the output of I turns B off. As a result, B now produces fewer action potentials when it is fired by A.

Now suppose that the interneuron I is constantly inhibiting the projection cell B. With this tonic inhibition added in, it is going to be much harder for the input from A to trigger the projection cell. If we put more excitatory neurons in with A to drive B, and time arrival just so, the tonic inhibition can be overcome. The cell can now be continuously activated. But being stuck in fast-forward is not good for neurons, which can be damaged or even destroyed by unchecked excitation. Each burst of excitation thus needs to be countered with another round of inhibition. That's where elicited inhibition, like that described above, comes in. When an excitatory surge overcomes

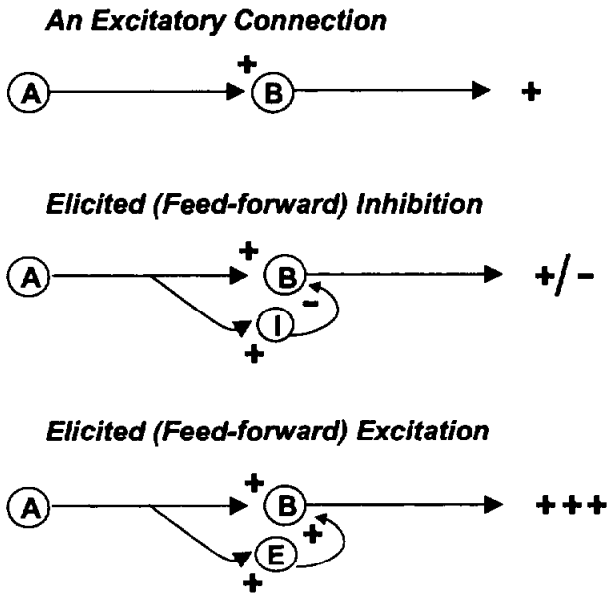


**FIGURE 3.9 EXCITATION AND INHIBITION IN CIRCUITS**

Excitation and inhibition are illustrated by way of an excitatory connection from A to B that is regulated by the inhibitory connection from I to B. The + and − signs to the right indicate the effect of the particular combination of connections. *Excitatory connection:* Activity in A leads to activity in B (+ on the right). *Feed-forward inhibition:* Activity in A leads to activity in B. A also activates I, which in turn inhibits B. B is thus first turned on by A (+ on right) but then turned off by I (− on right). The excitation of I by A thus gates or regulates the excitation of B by A. *Feed-forward excitation:* Activity in A leads to activity in B. Also activates E, which in turn further excites B. The excitation of B by A is thus amplified by E (+ + + on right).

tonic inhibition, elicited inhibition can rein in the excitation, resetting the circuit, preparing it for new inputs. There are many variations on this theme of tonic and elicited inhibition, but the scenario just described gives an idea of how inhibition in general works.

Inhibition is a very useful device in neural circuits. It adds tremendously to the specificity of information processing, filtering out random excitatory inputs, preventing them from triggering activity. Only if the excitatory inputs arrive simultaneously can they overcome the inhibition and elicit activity. And once activity is elicited, inhibition is important for keeping the excitation in check and resetting the circuit.

Although many local circuit cells are inhibitory, some are excitatory. Just as inhibitory interneurons can be thought of as filters, excitatory interneurons can be viewed as amplifiers. Again imagine a circuit consisting of neurons A

and B connected in series. As before, B is associated with an interneuron, but in this case it's an excitatory interneuron (E), and the axon of A branches and contacts both B and E (fig. 3.9). When A turns on B, the interneuron E is also activated, and its output causes further excitation of B. As a result, the output of B is amplified by an excitatory interneuron just as it was reduced by the inhibitory interneuron. But, as we've seen, all this excitation ultimately has to be regulated, both to maintain normal functions and to prevent injury.

## THE CHEMICAL BROTHERS

The job of a projection neuron, as we now know, is to turn on the next projection cell in the circuit. This means that action potentials in the axons of projection cells have to trigger the release of chemicals that cross the synapse and contribute to the firing of an action potential in the postsynaptic cell. Projection cells thus need to use a chemical neurotransmitter that has two properties. The transmitter first must be able to act quickly at postsynaptic sites—otherwise, our perceptions and other mental states could not keep up with rapidly changing events. And it must also be able to change the electrical state of the postsynaptic cell in such a way that the occurrence of an action potential is more likely to occur. Both requirements (speed and excitation) are fulfilled by the amino acid neurotransmitter glutamate, which is the main transmitter in projection neurons throughout the brain.

Glutamate actually has two roles in body function. In addition to serving as a neurotransmitter in the brain, it also plays a major part in basic life-sustaining metabolic processes that go on continuously throughout the body. For example, it is a building block in the construction of peptides and proteins, which are basic ingredients of living tissues. And, in the brain, it helps detoxify ammonia, which is a natural by-product of certain chemical reactions. Although glutamate is now known to be a ubiquitous excitatory transmitter in the brain, its role in transmission was for a long time hard to dissociate from its so-called metabolic functions.[41]

In contrast, inhibitory neurons, especially inhibitory interneurons, often release the amino acid GABA (short for gamma-aminobutyric acid) from the terminals of their short axons.[42] In contrast to glutamate, this inhibitory transmitter reduces the likelihood of an action potential being generated in the postsynaptic cell. By sending axons to nearby projection neurons, GABA interneurons thereby regulate the flow of traffic through a given area.

GABA actually was identified as a neurotransmitter long before glutamate.

Because it was well established that glutamate was one of the essential chemical components involved in the synthesis of GABA, its metabolic role in GABA production hampered the discovery that glutamate was itself a neurotransmitter.

Glutamate and GABA are together responsible for much of the neurotransmission business in the brain. If you understand the work done by these two chemicals, you will understand quite a lot about how synapses function. These and all other transmitters work by attaching to molecules called receptors on the postsynaptic cell. Receptors selectively recognize and bind (literally, hold on to) transmitter molecules. Glutamate receptors recognize and bind glutamate, but ignore GABA (fig. 3.10); GABA receptors are just as selective (fig. 3.10). How, then, does the binding of glutamate and GABA molecules to their receptor molecules lead to excitation and inhibition?

All cells in the body are completely enclosed by a membrane, which defines the boundary of an individual cell. The membrane is like a formfitting bag, a spandex suit, in which the cell is contained. In neurons, it covers the axons and dendrites as well as the cell body. The space outside the membrane between neurons is called the extracellular space. The fact that the extracellular space is filled with liquid has two important consequences.

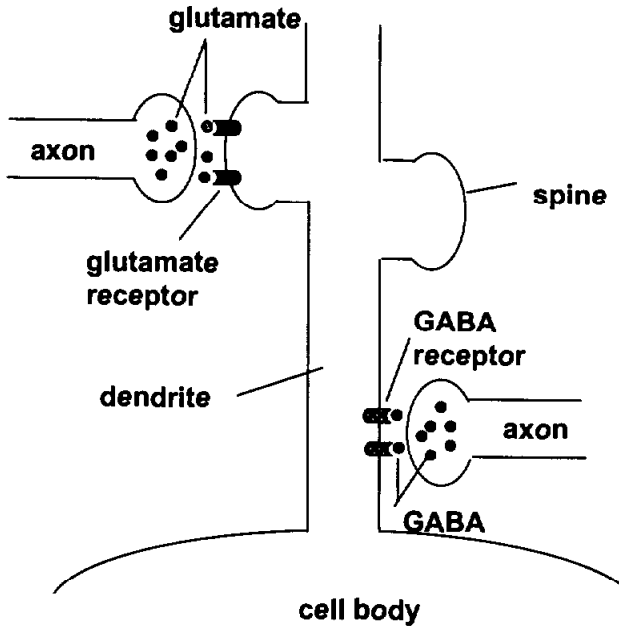


**FIGURE 3.10 GLUTAMATE AND GASA SYNAPSES**

The two major neurotransmitters are glutamate and GABA. These are released from different presynaptic neurons and bind to distinct postsynaptic receptors.

First of all, this liquid is a medium that allows transmitter molecules to cross the extracellular space between presynaptic and postsynaptic sites—the synapse. Transmitters do this by diffusing out from the terminal. The distance they have to travel is very small (it's measured in tiny units called angstroms, one of which equals one ten-millionth of a millimeter), making the postsynaptic site a close and easy target.

The second point is that extracellular liquid contains all sorts of chemicals, many with electric charges, that influence cellular function. The cell membrane keeps chemicals that are inside and outside the cell separate. At rest (when the cell is not being influenced by inputs), the chemical composition of the inside of the cell is more negatively charged than the fluid outside, due to the kinds of ions that are present on the other side of the cell membrane. Neuroscientists have measured the difference in electrical charge between the inside and outside of a nerve cell. In general, the inside of a neuron that is not being stimulated is about 60 millivolts (60 one-thousandths of a volt) more negative than the outside. In other words, the resting potential of the cell is about −60 mV.

For our purposes, the actual voltage is not that important. All we need to keep in mind is the fact that the membrane potential is fairly negative at rest. When a neuron is stimulated by excitatory inputs from other neurons, however, the membrane potential becomes more positive (see fig. 3.7). The reason for this is related to the way that glutamate works as a neurotransmitter.

Glutamate receptor molecules span the cell membrane, with part facing inside the cell and part facing outside. When glutamate (released from a presynaptic terminal) binds to the outside part of a postsynaptic receptor, a passage opens up through the receptor, allowing positively charged ions in the extracellular fluid to move inside the cell, which changes the chemical balance between outside and inside. If enough glutamate receptors are occupied on the postsynaptic cell at about the same time, and the voltage inside becomes sufficiently positive, then an action potential occurs.

In contrast, when GABA receptors are occupied, the inside of the cell becomes more negative (due to the influx of negative ions, especially chloride, through a passage in the GABA receptor). This makes it harder for glutamate released from other terminals to change the concentration of the positive ions in the postsynaptic cell sufficiently to trigger an action potential. Whether an action potential occurs, then, depends on the relation between glutamate (excitation) and GABA (inhibition). And since any one cell receives many excitatory and inhibitory inputs from many other cells, the likelihood of firing at

any one moment depends on the net balance between excitation and inhibition across all of the inputs at that particular time.

Glutamate receptors tend to be located out on the dendrites, especially in the spines, whereas GABA receptors tend to be found on the cell body, or on the part of dendrites close to the cell body. In order for glutamate-mediated excitation to reach the cell body to help trigger an action potential, it has to get past the GABA guard. Excitation coming down a dendrite and headed for the cell body can be extinguished by GABA.

Without GABA inhibition, neurons would send out action potentials continuously under the influence of glutamate, and would eventually literally fire themselves to death. This effect has been demonstrated in experiments where the action of GABA is blocked artificially, or where powerful doses of glutamate-related compounds, too strong to be inhibited by natural levels of GABA, are administered. Overactivity of glutamate, and the resulting injury to neurons, actually plays an important role in stroke and other vascular disorders of the brain, as well as in epilepsy and possibly Alzheimer's disease. Some people have experienced mild versions of glutamate toxicity after eating Chinese food. Monosodium glutamate (MSG), sometimes used as an additive in this cuisine, can increase the amount of glutamate in the body to the point of causing headaches, ringing ears, and other physical symptoms. Regulation of GABA inhibition is one of the ways that psychoactive drugs work. For instance, the antianxiety drug Valium works by enhancing GABA's natural ability to regulate glutamate. Excitatory inputs that would normally elicit anxiety by firing action potentials in fear circuits are less able to do so in the presence of Valium and related drugs.

## MOD SQUADS

Interactions between glutamate and GABA are key to understanding information processing by the brain, but these substances do not work alone or in isolation. For example, when receptors in the eye detect patterns of light, they send messages through the axons of the optic nerve to the brain. When the electrical signal reaches the axon terminal, glutamate is released. Whether the postsynaptic cell fires depends not only on the counterbalancing force of GABA inhibition, but also on other chemicals that are present at the time. These are called modulators.

Modulators are neurotransmitters in the sense that they provide a chemical link between the site from which they are released and the location of the

receptors upon which they act. But in contrast to glutamate and GABA, they are less directly involved in the transfer of information from point to point in hierarchical circuits. The way a modulator is distinguished from a transmitter is different for different kinds of modulators, as we'll see soon. And sometimes, the distinction is murky. But one important difference is related to their speed. Glutamate and GABA are fast-acting:[43] they cause an electrical change in the postsynaptic cell within milliseconds of being released from the presynaptic terminal, and their effect is over in a matter of milliseconds.[44] Modulators, on the other hand, have slower and longer-lasting effects.

We'll consider three classes of modulators: peptides, amines, and hormones. Each can have excitatory or inhibitory effects, depending on the specifics of their participation in functional circuits.

Peptides represent a large class of slow-acting modulatory substances found throughout the brain. They are made up of many amino acids, and are larger molecules than simple amino acids like glutamate or GABA. Because peptides are often present in the same axon terminal as glutamate or GABA (but in their own separate storage compartments), they are released with the fast transmitter when an action potential comes down the axon (fig. 3.11). But peptides bind to distinct postsynaptic receptors and can, as a result, augment or reduce the effect of the fast transmitter with which they are released. However, since peptides are slow to affect the postsynaptic site, and their effects are long-lasting, they tend to have more of an effect on subsequent squirts of fast

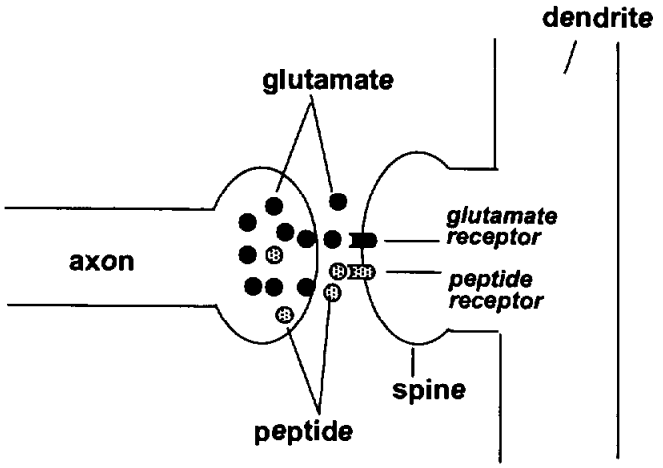


**FIGURE 3.11 GLUTAMATE AND PEPTIDE RELEASED FROM THE SAME TERMINAL**

Axon terminals sometimes release peptide transmitters along with glutamate (or GABA). In this case, different postsynaptic receptors bind the two kinds of molecules released from the same terminal.

transmitter. While glutamate and GABA can have slow effects as well as fast ones, depending on the receptors involved,[45] peptides typically only have slow modulatory actions. They can affect dramatically the ability of a cell to be fired by other inputs, but cannot do so with precise timing.

There are many, many peptides that participate in a wide variety of bodily functions. Our interest is in the neuroactive peptides, those that act in the nervous system. The best known of these are the opiates—endorphins and enkephalins. These are triggered by pain and stress and bind to their special receptors, altering pain sensations and mood. "Jogger's high" is said to be an opiate effect. Morphine generates its effects by binding to these receptors.

The monoamines, another class of modulators, include substances like serotonin, dopamine, epinephrine, and norepinephrine. Unlike most other transmitters and modulators, the cells that produce monoamines are found in only a few areas, mostly in the brain stem,[46] but the axons of these cells extend to widespread areas throughout the brain (figs. 3.8 and 3.12). In this way, a small number of highly localized neurons making monoamines can influence cells in many other locations. Monoamines achieve their effects by facilitating or inhibiting the actions of glutamate or GABA (and the peptides that are released with them). Because the axons are so widely distributed, monoamines have relatively nonspecific effects. They are thus not involved in precise representation of stimuli in specific circuits. Instead, monoamines produce global state changes in many brain areas simultaneously, such as the high degree of arousal occurring throughout the brain when we encounter a sudden danger or the low degree of arousal required when we are going to sleep.

Many drugs used in the treatment of psychiatric disorders work by altering monoamines. Prozac, for example, prevents the removal of serotonin from the synaptic space. Normally, as part of the process by which transmitter action is regulated, neurotransmitters are sucked back into the terminals that release them. By preventing the removal of serotonin, allowing more to stay around longer, Prozac amplifies its effects. One theory holds that there is a deficiency of serotonin in depressed or anxious brains, which Prozac helps correct.[47] The exact means by which the increase in serotonin levels relieves anxiety or depression is not known.

Antidepressant drugs (like monoamine oxidase inhibitors and tricyclic antidepressants) and antipsychotics (like chlorpromazine or phenothiazine) also work by altering monoamine levels. Amines are also targets of recreational drugs: cocaine and amphetamine affect norepinephrine and dopamine levels, while LSD acts on serotonin receptors.

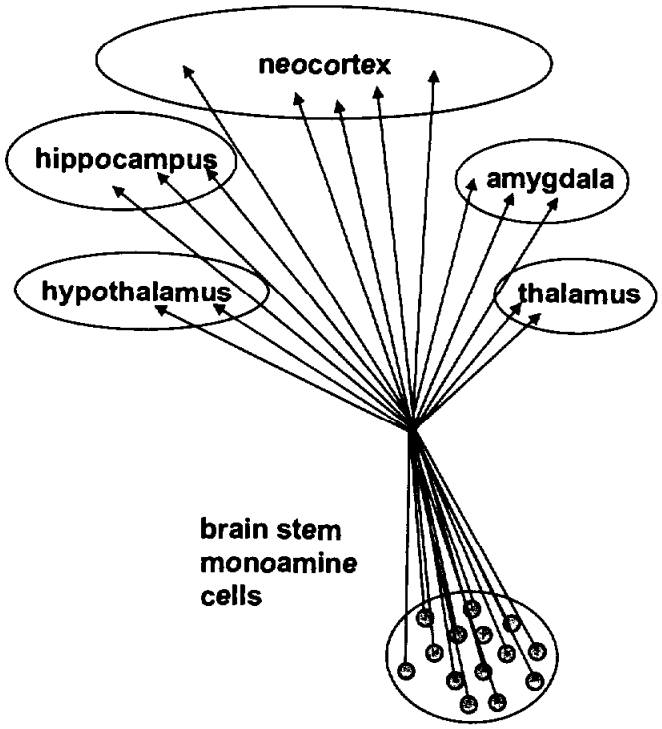


**FIGURE 3.12 DIFFUSE PROJECTION OF BRAIN STEM MONOAMINE CELLS TO FOREBRAIN AREAS**

Monoamine neuromodulators are made in discrete areas of the brain stem, but because of their diffuse connections, they can simultaneously modulate transmission in widespread areas of the brain.

Another monoamine is acetylcholine, which functions as a fast transmitter when it works with one receptor and as a modulator with a different receptor.[48] Disruption of acetylcholine in the neocortex is believed to play a role in Alzheimer's disease,[49] and many drugs that have been tested as treatments for Alzheimer's alter acetylcholine function.[50] Acetylcholine is also a very important transmitter in the body, involved with nerves such as those that control muscle movements and heart rhythm. Nerve gas works by disrupting acetylcholine transmission at muscles, especially muscles required for normal breathing. Many insecticides have similar effects in bugs.

Hormones are the last class of modulators we will consider (fig. 3.13). Typically, they are released from bodily organs (like the adrenal, pituitary, or sex glands) into the bloodstream where they travel to the brain. There they can, like other modulators, alter the efficacy of glutamate or GABA transmission by binding to specific receptors on cells. For example, cortisol, a steroid hormone released from the adrenal gland during stress, is known to alter informa-

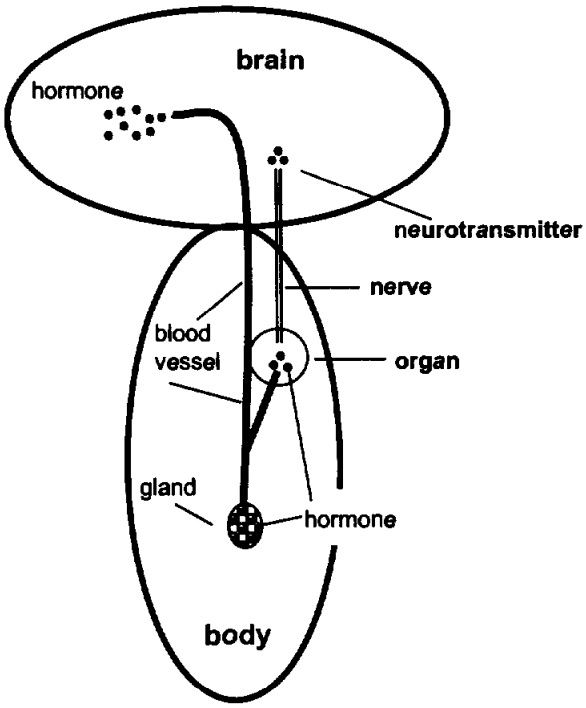


**FIGURE 3.13 HOW HORMONES REACH THE BRAIN**

Hormones released from glands in the body travel in the bloodstream and either can influence the brain directly or can influence the brain indirectly by acting in body organs that send nerves into the brain.

tion transmission in a variety of circuits involved in memory and emotional processes,[51] in part by altering the ability of GABA to inhibit glutamate.[52] Sex hormones, such as testosterone and estrogen, also can have profound effects on neural transmission and other brain functions. The mood-altering effects of monthly variation in estrogen levels in females are widely discussed, and estrogen replacement therapy during and after menopause is believed to counter some of the effects of aging on brain functions.[53] Because hormones reach the brain through the bloodstream, they can influence many regions simultaneously. However, since only certain areas, and only certain circuits in those areas, possess the relevant receptors, considerable specificity can be achieved by hormonal modulation.

## GOLGI AND THE GAP

As important as chemical synaptic transmission is in the brain, another form, called electrical transmission, also occurs. Although the extent to which electrical synapses operate is not known, it is becoming more and more ap-

parent that they are significant forces for us to deal with as we conceive brain function.

In order for two neurons to communicate electrically, their membranes have to fuse in such a way as to allow the direct flow of electricity from one to the other. These points of fusion are called gap junctions. Recent studies have shown that in some brain areas, like the hippocampus, a region important for the formation of explicit memories, GABA (inhibitory) cells are linked together, or electrically coupled, by gap junctions.[54] In this way, when GABA cells are activated, excitation can spread between them in such a way as to activate many of the interconnected cells at once. The cells then fire together, in synchrony, and thereby can regulate activity of projection cells throughout the region.

The existence of gap junctions gives partial vindication to Golgi's reticular theory of the brain, in the sense that some neurons can communicate directly by way of physical fusion. Much remains to be learned about them, and their contribution to synaptic transmission needs to be better integrated with our knowledge of chemical transmission.

## CIRCUITS IN ACTION

The same basic transmitters, modulators, and hormones can be involved in very different functions. Our abilities to see, hear, remember, fear danger, and desire happiness all involve excitatory (glutamate) synaptic transmission regulated by inhibitory (GABA) synapses and modulated by peptides, amines, and hormones. What makes a sound different from a sight, a memory different from a perception, a fear different from a desire is not so much the chemistry involved but instead the specific circuits in which the chemicals act. As a way of illustrating how glutamate, GABA, and modulators work, let us consider their role in the detection of danger by the amygdala.

The amygdala detects danger by virtue of its position in a synaptically connected system. In its simplest form, this system can be described in terms of a three-level excitatory chain of cells that releases glutamate—projection cells in sensory systems activate projection cells in the amygdala, which activate projection cells in motor control areas (fig. 3.14). This scheme leaves much out, but we'll have the opportunity to embellish it later.

Amygdala cells receive inputs from the sensory world constantly, but they ignore the majority of them. In fact, they tend to be quiescent most of the time. They do get worked up, though, when the right kind of stimulus is present—one that signifies danger or some other biologically significant event.

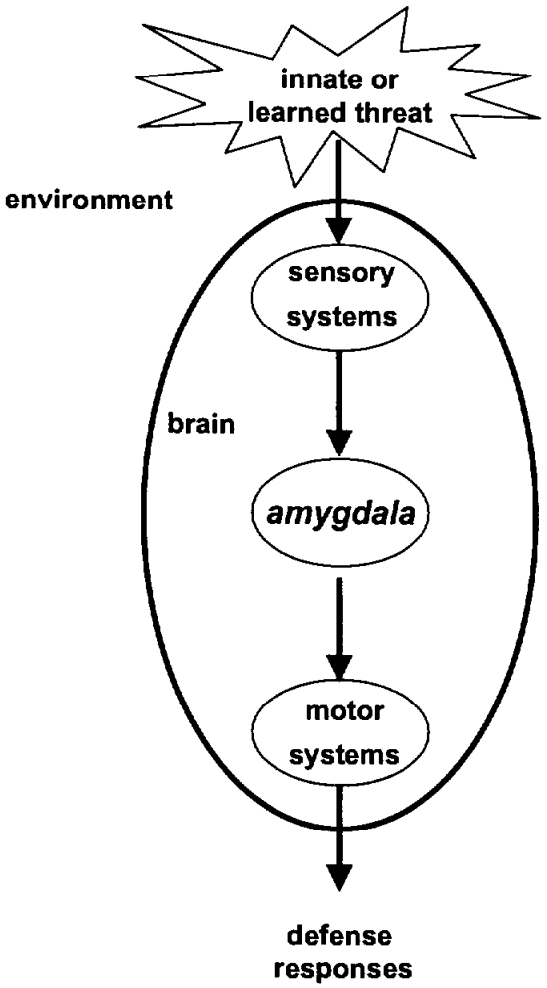


**FIGURE 3.14 INPUT AND OUTPUT CONNECTION OF THE AMYGDALA IN FEAR**

The amygdala is able to serve as an interface between threatening stimuli in the environment and defense responses because it is connected with sensory processing systems on the one hand and with motor control regions on the other.

This has been shown to be true in studies of both lower animals[55] and humans.[56] So what keeps a projection cell in the amygdala from firing in response to meaningless stimuli? The answer, as you've probably guessed, is GABA.[57]

As we've seen, the resting membrane potential of cells in many brain areas is about −60 mV. In the amygdala, however, some cells can be as negative as −80 mV,[58] due to sustained or tonic inhibition by GABA. With GABA receptors on amygdala projection cells occupied and passing chloride, the inside of the cells becomes more negative, which means it takes extra excitation to turn the amygdala on. As a result, not any old stimulus will do the trick. The stimulus has to have special qualities that allow it to overcome the tonic inhibition produced by GABA.

Stimuli that are inherently dangerous (the sight or smell of a predator) or unpleasant (intense stimuli, like loud noises or stimuli that cause pain) are able to overcome the tonic inhibition, as are stimuli that have emotional resonance acquired through past learning. Thus, an otherwise meaningless sound of modest intensity that previously occurred in association with pain has the same effect as a natural (innate) form of danger.[59] Both innate (hardwired) and learned danger signals cause amygdala cells to fire rapidly for a sustained period, and are thus able to overcome the GABA guard.

Even after fear-arousing stimuli get past tonic inhibition and cause amygdala cells to fire, however, they are still subject to GABA control. The inputs to the amygdala activate GABA cells as well as projection neurons.[60] As a result, as the inputs become more active, the elicited inhibition in the amygdala builds up, which in turn begins to shut down the activity of amygdala cells.[61]

If the ability of GABA to keep meaningless stimuli from turning on the amygdala is compromised for some reason (either because the projection cells come to fire more easily or because the GABA cells fire less easily), stimuli that are not dangerous come to be responded to as though they were. This may occur in certain fear and anxiety disorders. By the same logic, things that make projection cells fire less readily or that make GABA cells fire more readily should reduce fear and anxiety. Indeed, one of the most popular medications ever invented for the treatment of anxiety is Valium, which works by facilitating GABA transmission. Although drugs taken orally reach many sites in the brain, it is likely that at least some of their effects on fear and anxiety are achieved by enhancing inhibition in the amygdala, and thereby making it harder for external or internal stimuli to elicit fear responses by activating amygdala circuits.

The amygdala also receives modulatory inputs of various types. For example, serotonin fibers terminate there, and when the amount of serotonin rises in the amygdala the activity of excitatory projection cells is inhibited.[62] The inhibition in this case is not due to the fact that serotonin directly affects projection cells, but rather that serotonin excites GABA cells, and thus increases the degree to which they inhibit projection neurons.

Drugs like Prozac work by increasing the amount of serotonin available at synapses. By enhancing serotonin transmission at GABA synapses in the amygdala, and thereby reducing the activity of projection neurons, Prozac may, like Valium, help control anxiety by reducing the ability of inputs to the amygdala to activate fear circuits.

The amygdala is also the target of many hormones. One of these is cortisol, which is released from the adrenal cortex during fear-arousing and other-

wise stressful events.[63] The facilitation of GABA inhibition of amygdala projection cells by serotonin is modulated by cortisol.[64] Serotonin's ability to facilitate inhibition by exciting GABA cells thus depends on the binding of cortisol to receptors located on amygdala neurons. Cortisol is elevated in a variety of psychiatric disorders,[65] and cortisol increases the intensity of fear reactions.[66] Drugs like Prozac may reduce exaggerated fear and anxiety in psychiatric disorders by enhancing the ability of serotonin to facilitate GABA inhibition in the presence of elevated cortisol.

The fear system thus nicely illustrates the basic elements of neural transmission in the brain and its regulation by modulatory chemicals. We will build upon these points at various times in later chapters.

## ARE SYNAPSES ENOUGH?

My emphasis on the importance of synapses in brain function is not intended to minimize the role of other factors. For example, the rate at which a cell fires spontaneously is a function of certain electrical and chemical characteristics of the cell.[67] These are called intrinsic properties to distinguish them from extrinsic influences from other cells mediated by synaptic transmission and modulation. A cell's intrinsic properties, which may have a strong genetic component, will greatly influence everything that cell does, including its participation in synaptic transmission. But because psychological and behavioral functions are mediated by aggregates of cells joined by synapses and working together rather than by individual neurons in isolation, the contribution of the intrinsic properties of a cell to mental life or behavior occurs only by way of the role of that cell in circuits. While synapses themselves don't account for everything the brain does, they do participate crucially in every act or thought that we have, and in every emotion we express and experience. Synapses are ultimately the key to the brain's many functions, and thus to the self.

80. For other views of the self and the brain, see the list of citations below. For the most part, these have tended to emphasize the conscious aspects of the self. My view, in contrast, includes unconscious as well as conscious aspects. Others that include a role for unconscious aspects of the self include Antonio Damasio (Damasio 1999) and Michael Gazzaniga (Gazzaniga 1985, 1992, 1998; Gazzaniga is working on a book, *The Last to Know,* which emphasizes unconscious processing in the construction of consciousness). For ideas about the brain and the conscious self, see: Popper and Eccles 1977; Stuss 1991; Sperry 1984; Gazzaniga 1985, 1992, 1998; Brothers 1997; Arbib 1999; Llinas 2000; Damasio 2000; Feinberg 2000.

### CHAPTER THREE THE MOST UNACCOUNTABLE OF MACHINERY

1. For a summary, see LeDoux 1987.
2. The divisions of the forebrain include: the thalamus, hypothalamus, basal ganglia, limbic system, old cortex, and neocortex.
3. Ariëns Kappers 1909; Papez 1937; MacLean 1949; MacLean 1952; Nauta and Karten 1970.
4. Nauta and Karten 1970; Northcutt and Kaas 1995; Karten and Shimizu 1991.
5. Lettvin et al. 1959; Camhi 1984.
6. Camhi 1984; Suga 1990; Gould 1982.
7. For an alternative view that emphasizes evolutionary pressures on the whole brain rather than on specific systems, see Finlay and Darlington 1995.
8. Killackey 1990; Preuss 1995.
9. Brodmann 1909; Economo and Koskinas 1925; Campbell 1905.
10. Gazzaniga et al. 1996; Feinberg and Farah 1998; Ramachandran and Blakeslee 1998.
11. Nonneuronal cells communicate with each other but not the way neurons do. The electrochemical process of synaptic transmission is unique to nervous tissue.
12. Cell theory discussion based on Shepherd 1998, Jacobson 1993, and Microsoft Encarta 2000.
13. Based on chapter 3 in Shepherd 1988.
14. Shepherd 1988, p. 41.
15. Jones 1961, p. 32.
16. Jones 1961, p. 34.
17. Freud 1887–1902.
18. Jones 1961, Freud's biographer, says that though Freud dropped the anatomical terms, the principles that guided his psychological theories were underneath it all based on his early training in anatomy and physiology.
19. Sherrington 1897.
20. For a summary of Sherrington's early work on reflexes, see Sherrington 1906.
21. Shepherd 1988, p. 65.
22. Shepherd 1988, p. 42.
23. Rozental et al. 2000.
24. Kuffler and Nicholls 1976.
25. Zigmond et al. 1999; Kandel et al. 2000.
26. Chen et al. 2000.
27. Muscles don't have dendrites, but have their own special kind of receptive area that is contacted by the axon terminal.

28. Based on Winson 1985.
29. Boring 1950.
30. Boring 1950.
31. Gregory 1981.
32. Shepherd 1988.
33. Shepherd 1988.
34. Shepherd 1988.
35. From Jacobson 1993.
36. The space between neurons is filled with fluids that are in essence part of a vast continuous sea of liquid in which all the neurons of the nervous system are bathed. This sea is made up of so-called cerebrospinal fluid, and it occupies the so-called extracellular space.
37. Based on Kuffler and Nicholls 1976.
38. In fact, the postsynaptic cell has to receive convergent inputs within a matter of milliseconds, otherwise the inputs will not sum together and will not produce an action potential. Since the inputs are added up in the cell body, they can arrive from many different dendrites, as long as they produce electrical responses that reach the cell body at about the same time.
39. Electrical transmission is made possible by the existence of special contacts between cells called gap junctions (Rozental et al. 2000). These are actually physical contacts and are exceptions to the notion promoted by the neuron theory that cells are physically separate. These turn out to be important in synchronizing hippocampal GABA cells (Fukuda and Kosaka 2000).
40. Based on Bloom and Laserson 1985.
41. Cooper et al. 1978.
42. GABA cells sometimes have long axons and communicate between brain regions, but mostly they have short axons that end on nearby cells.
43. But even the time-course distinction between fast transmitters and modulators can be blurred. Most transmitters work with a variety of receptors. GABA, for example, has A and B receptors. While the A receptor mediates the fast effects we've been talking about, when GABA binds to B receptors its action is slower and more prolonged. Glutamate, too, has some late, longer-lasting effects when it binds to some of its receptors. Another fast transmitter is acetylcholine. When it binds to its nicotinic receptor, it does its fast transmitter thing, but when it binds to its muscarinic receptor, it works slowly. So it is often best to think of transmitters and receptors together when drawing conclusions about the kind of transmission involved.
44. Shepherd 1998.
45. See note 43 above.
46. The main exception involves the cholinergic neurons of the basal forebrain, which complement the brain stem cholinergic systems.
47. This will be discussed in chapter 10.
48. Shepherd 1998; Cooper et al. 1978.
49. Selkoe and Kosik 1983.
50. Babic 1999; Yamada et al. 1999.
51. This will be discussed in detail in later chapters, especially chapters 8 and 10.

52. Stutzmann et al. 1998; Stutzmann and LeDoux 1999.
53. Gibbs 2000; Dell and Stewart 2000.
54. See note 39.
55. Quirk et al. 1995; Rolls 1999; Ono and Nishijo 1992; Collins and Pare 2000; Maren 2000.
56. Breiter et al. 1996; Morris et al. 1996; Morris et al. 1998; Whalen et al. 1998; LaBar et al. 1998.
57. Li et al. 1996; Lang and Pare 1997; Collins and Pare 1999.
58. Chapman et al. 1990; Weisskopf and LeDoux 1999.
59. Quirk et al. 1995; Collins and Pare 2000; Maren 2000.
60. Woodson et al. 2000; Szinyei et al. 2000; Smith et al. 2000.
61. Li et al. 1996; Collins and Pare 1999.
62. Stutzmann et al. 1998; Stutzmann and LeDoux 1999.
63. McEwen and Sapolsky 1995.
64. Stutzmann et al. 1998.
65. Bogerts et al. 1993; Convit et al. 1995; de Leon et al. 1988; Fukuzako et al. 1996; Sheline et al. 1996; Starkman et al. 1992; Yehuda et al. 2000; Coplan et al. 1998; Young et al. 1994.
66. Corodimas et al. 1994; Conrad et al. 1999; Makino et al. 1994; Shors et al. 1992.
67. Llinas 1988.

### CHAPTER FOUR BUILDING THE BRAIN

1. This section on early development is based on Purves et al. 1996.
2. Nottebohm 1989; Gould et al. 1997; Gould et al. 1999; Fuchs and Gould 2000.
3. Rodier 2000.
4. Chan and Jan 1999; Reichert and Simeone 1999.
5. Schlaggar and O'Leary 1991.
6. Rakic 1995.
7. Schlaggar and O'Leary 1991; Shatz 1992; Rakic 1992.
8. Miyashita-Lin et al. 1999.
9. Based on Raper and Tessier-Lavigne 1998.
10. Terman and Kolodkin 1999.
11. Edelman 1987; Changeux and Danchin 1976.
12. Jerne 1967; see also Gazzaniga 1992.
13. Changeux and Dehaene 1989.
14. Edelman 1987.
15. Edelman 1987.
16. Based on text from the home page of the Neuroscience Institute, of which Gerald Edelman is the director (*www.nsi.edu*), and from a summary of Edelman's views by Flanagan 1994.
17. Changeux and Danchin 1976; Innocenti 1991.
18. For a summary, see Oppenheim 1998.
19. For review of regressive events, see O'Leary 1992.
20. Rakic et al. 1986.

21. Bourgeois et al. 1994.
22. Quartz and Sejnowski 1997.
23. Huttenlocher 1979.
24. See Quartz and Sejnowski 1997 and Katz and Shatz 1996. For one thing, it is very difficult to measure accurately the density of synapses in a brain region given that the region itself is changing size over time. Also, unless the synapse changes are related to specific cell types, it is hard to know what the implications would be. Finally, the relation of structural measures (like the number of synapses) to functional ones (is the synapse working?) is hard to assess. In early development, synapses are functional before they have the "look" of synapses, and these would go uncounted.
25. O'Leary 1992.
26. For further discussion, see Quartz and Sejnowski 1997.
27. Hubel and Wiesel 1962; Hubel and Wiesel 1963; Hubel and Wiesel 1965; Hubel and Wiesel 1972.
28. Apologies to visual scientists for this simplistic description of visual pathways.
29. For a summary see: Katz and Shatz 1996; Shatz 1996; Stryker 1991.
30. Antonini and Stryker 1993.
31. The experiment actually involved the injection of the tracer into cells in the visual thalamus area called the lateral geniculate nucleus. In this region, cells are organized in layers devoted to one eye or the other. By recording the action potentials elicited by stimulation of one eye, it is possible to find the layers and then to inject a cell in that layer with the chemical.
32. Actually, the tracer is actively transported to the terminal by natural processes that go on in the cell all the time. These are taking things made by the cell body and shipping them throughout the cell.
33. Quartz and Sejnowski 1997.
34. Neville 1990.
35. Neville and Lawson 1987.
36. Based on Katz and Shatz 1996.
37. Rakic 1977; Horton and Hocking 1996.
38. Galli and Maffei 1988; Wong et al. 1993.
39. Even when endogenous activity is blocked, the clusters develop if the nerves headed for the brain from the two eyes are electrically stimulated separately. This kind of stimulation simultaneously activates many fibers from a given eye to the brain, tricking the brain into thinking that it received lots of activity at the same time from one eye (see Stryker and Harris 1986; Crair 1998).
40. Chiaia et al. 1992.
41. Crair 1999.
42. Hebb 1949.
43. This phrase comes from Carla Shatz.
44. Katz and Shatz 1996; Shatz 1992; Shatz 1996; Stryker 1991; Purves 1994.
45. However, recall that cortical cells initially receive inputs from both eyes. So the cortical cell will actually receive correlated input from each eye, but at different times. How then can one eye come to dominate? Although each cell gets inputs from both eyes, the two eyes never quite have equal inputs, leading one eye to dominate slightly.

Hebbian plasticity builds upon this preexisting bias, wiring the connection between the cortical cell and its more efficient inputs. While Hebbian plasticity may be enough to wire up a particular cell, more is needed to establish the cell-specific clusters, the so-called ocular dominance columns, in the cortex. Ken Miller of UCSF has some interesting proposals on this; see Miller 1994 and Wimbauer et al. 1997. As a result, one eye or the other will come to be more efficient in driving a cortical cell. Miller's work on this was pointed out to me by Tony Movshon of NYU. Hebbian plasticity thus takes care of the problem of how inputs from one eye come to control an individual cell, but leaves open the question of how cells that are responsive to one eye come to cluster together. For this, it is generally assumed that there are factors that allow presynaptic inputs that are nearby and that are active at the same time to link up.

46. Glanzman et al. 1990; Martin and Kandel 1996.
47. Tsien 2000; Bliss and Collingridge 1993; Purves et al. 1996; Brown et al. 1988.
48. Katz and Shatz 1996.
49. Katz and Shatz 1996; Johnson 1998; Schuman 1999.
50. Oppenheim 1998.
51. Lorenz and Tinbergen 1938; Lorenz 1950; Tinbergen 1951.
52. Lehrman 1953.
53. Terrace 1984.
54. Terrace 1984.
55. Watson 1925; Skinner 1938; Hull 1943.
56. Chomsky 1957.
57. Gardner 1987.
58. Keil 1999.
59. Garcia and Koelling 1966.
60. For discussion, see chapters by H. S. Terrace, P. P. G. Bateson, and J. L. Gould and P. Marler in the book edited by Marler and Terrace 1984.
61. Pinker 1994.
62. Pinker 1997.
63. Pinker 1997.
64. Bickerton 1980.
65. Elman et al. 1997; Quartz and Sejnowski 1997.
66. See Gopnik 1997; Korenberg et al. 2000; Ridley 1999.
67. Pinker 1994; Gopnik 1997; Korenberg et al. 2000; Bickerton 1980; Ridley 1999.
68. Ekman 1999.
69. Cosmides and Tooby 1999; Barkow et al. 1992.
70. Cosmides and Tooby 1999; Barkow et al. 1992; Spelke 1994; Carey and Spelke 1994; Povinelli and Preuss 1995.
71. Cosmides and Tooby 1999; Barkow et al. 1992.
72. Gould 1997.
73. Gould 1991.
74. Gould quoted in Gazzaniga 1992.
75. Premack 1985.
76. Pinker 1997; Pinker and Bloom 1990; Cosmides and Tooby 1999.
77. Rose and Rose 2000.

78. For example, see Edwards and Pap 1959.
79. Spelke 1994; Carey and Spelke 1994; Marcus 1999; Pinker 1994, 1997; Piattelli-Palmarini 1989.
80. Wexler 1999.
81. Fodor 1983; Gazzaniga 1992; Tooby and Cosmides 2000; Mody et al. 1997; Denenberg 1999.
82. Keil 1999.
83. There is also a domain-independent learning system in the brain (the explicit or declarative memory system). However, this system is involved in recording facts and experiences independent of rewards and punishment, and though it might be thought of as a universal learning system, it does not appear to play an essential role in the kinds of learned behaviors that the behaviorists studied.
84. Elman et al. 1997.
85. Quartz and Sejnowski 1997.
86. Barton 1997.
87. Brothers 1997.
88. Barton 1997.
89. Neisser 1998.
90. Alcock 1998.
91. Arnold 1980.
92. Alcock 1998; Wimer and Wimer 1985.
93. Described in Alcock 1998; based on Holden 1980.
94. Tellegen et al. 1988.
95. Described in Harris 1998. Harris also argues that genetic influences are underestimated by heritability scores, noting that the correlation between parents and children on personality traits is sufficiently weak that genes they share might fully account for any similarities that exist.
96. Gardner 1998.
97. For summary, see Schuster and Ashburn 1992; Jacobson 1993.
98. For summary, see Jacobson 1993.
99. Harris 1998; Gardner 1998.
100. See Hall et al. 1998.
101. See Bruer 1999.
102. Mooney 1999; Gould and Marler 1984; Doupe and Kuhl 1999; Bottejer and Johnson 1997; Singh et al. 2000; Jarvis et al. 1998.
103. Elman et al. 1997.
104. Bruer 1999.
105. See Tallal 2000; Tallal et al. 1998.
106. Bruer 1999.
107. Gopnik et al. 1999.

### CHAPTER FIVE ADVENTURES IN TIME

1. Bartlett 1932; Schacter 1999.
2. Each time the brain learns something, it is changed.

3. Semon 1904; Schacter 1982.
4. Lashley 1929.
5. Lashley 1950.
6. Scoville and Milner 1957.
7. Scoville and Milner 1957; Milner 1962; Milner 1965; Milner 1967; Milner 1972.
8. Squire 1987; Cohen and Eichenbaum 1993.
9. Scoville and Milner 1957.
10. MacLean 1949; MacLean 1952; MacLean 1970.
11. Milner 1962; Corkin 1968.
12. Cohen 1980; Cohen and Squire 1980; Cohen and Corkin 1981.
13. Warrington and Weiskrantz 1973; Graf et al. 1984.
14. Weiskrantz and Warrington 1979.
15. Cohen and Squire 1980.
16. Schacter and Graf 1986.
17. The parahippocampal region consists of the entorhinal cortex, perirhinal cortex, and the parahippocampal cortex, as defined by Witter et al. 1989.
18. See Amaral et al. 1987; Suzuki and Amaral 1994; Witter et al. 1989; Burwell et al. 1995; Van Hoesen and Pandya 1975.
19. Entorhinal cortex, perirhinal cortex, and parahippocampal cortex are included in the parahippocampal region, as defined by Witter et al. 1989.
20. Jones and Powell 1970; Damasio 1989.
21. Mesulam et al. 1977.
22. This section is based on Squire and Kandel 1999.
23. The reason ECT produces memory disturbance is related to the fact that the conversion of short- to long-term memory is disturbed. For discussion, see Squire 1987.
24. McClelland et al. 1995.
25. Winson 1985; Buzsaki 1989; McNaughton 1998; Wilson and McNaughton 1994.
26. Wilson and McNaughton 1994; Nadasdy et al. 1999; Poe et al. 2000; Louie and Wilson 2001.
27. Nadel and Moscovitch 1997.
28. For discussion, see Nadel and Moscovitch 1997; Knowlton and Fanselow 1998.
29. Bontempi et al. 1999.
30. See Tulving 1983.
31. Vargha-Khadem et al. 1997.
32. Squire and Zola 1998.
33. Milner 1970.
34. For summary, see Mishkin and Murray 1994; Murray and Richmond 2001; Squire and Zola 1996, 1998.
35. Eichenbaum et al. 1994.
36. Section title adapted from Nadel and Willner 1980.
37. O'Keefe and Nadel 1978.
38. Olton et al. 1979.
39. O'Keefe and Nadel 1978.
40. Ranck 1973.
41. Muller et al. 1999.

# WORKS CITED

ALL SOURCES CITED IN THE CHAPTER NOTES ARE INCLUDED HERE, BUT IN ABBREVIATED FORM. FOR FULL BIBLIOGRAPHIC CITATIONS, PLEASE SEE WWW.CNS.NYU.EDU/HOME/LEDOUX/SYNSELF/WORKSCITED


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