

1. INTRODUCTION



Santiago Ramon y Cajal playing chess (white) in 1898, at an age of about 46, while on vacation in Miraflores de la Sierra. This picture was taken by one of his children. Most neuroanatomists would agree that Ramon y Cajal stands out far before anyone else in their field and probably in the entire field of central nervous neurobiology. His two major contributions were (1) establishing beyond reasonable doubt that nerve cells act as independent units, and (2) using the Golgi method to map large parts of the brain and spinal cord, so demonstrating both the extreme complexity and extreme orderliness of the nervous system. For his work he, together with Golgi, received the Nobel Prize in 1906.

Intuition tells us that the brain is complicated. We do complicated things, in immense variety. We breathe, cough, sneeze, vomit, mate, swallow, and urinate; we add and subtract, speak, and even argue, write, sing, and compose quartets, poems, novels, and plays; we play baseball and musical instruments. We perceive and think. How could the organ responsible for doing all that not be complex?

We would expect an organ with such abilities to have a complex structure. At the very least, we would expect it to be made up of a large number of elements. That alone, however, is not enough to guarantee complexity. The brain contains 10^{12} (one million million) cells, an astronomical number by any standard. I do not know whether anyone has ever counted the cells in a human liver, but I would be surprised if it had fewer cells than our brain. Yet no one has ever argued that a liver is as complicated as a brain.

We can see better evidence for the brain's complexity in the interconnections between its cells. A typical nerve cell in the brain receives information from hundreds or thousands of other nerve cells and in turn transmits information to hundreds or thousands of other cells. The total number of interconnections in the brain should therefore be

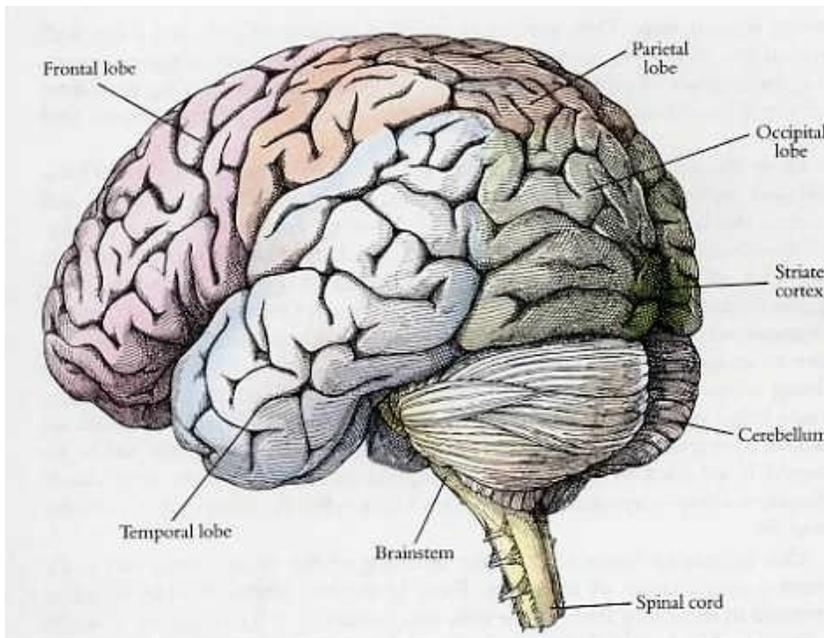
somewhere around 10^{14} to 10^{15} , a larger number, to be sure, but still not a reliable index of complexity. Anatomical complexity is a matter not just of numbers; more important is intricacy of organization, something that is hard to quantify. One can draw analogies between the brain and a gigantic pipe organ, printing press, telephone exchange, or large computer, but the usefulness of doing so is mainly in conveying the image of a large number of small parts arranged in precise order, whose functions, separately or together, the nonexpert does not grasp. In fact, such analogies work best if we happen not to have any idea how printing presses and telephone exchanges work. In the end, to get a feeling for what the brain is and how it is organized and handles information, there is no substitute for examining it, or parts of it, in detail. My hope in this book is to convey some flavor of the brain's structure and function by taking a close look at the part of it concerned with vision.

The questions that I will be addressing can be simply stated. When we look at the outside world, the primary event is that light is focused on an array of 125 million receptors in the retina of each eye. The receptors, called rods and cones, are nerve cells specialized to emit electrical signals when light hits them. The task of the rest of the retina and of the brain proper is to make sense of these signals, to extract information that is biologically useful to us. The result is the scene as we perceive it, with all its intricacy of form, depth, movement, color, and texture. We want to know how the brain accomplishes this feat. Before I get your hopes and expectations too high I should warn you that we know only a small part of the answer. We do know a lot about the machinery of the visual system, and we have a fair idea how the brain sets about the task. What we know is enough to convince anyone that the brain, though complicated, works in a way that will probably someday be understood—and that the answers will not be so complicated that they can be understood only by people with degrees in computer science or particle physics.

Today we have a fairly satisfactory understanding of most organs of our body. We know reasonably well the functions of our bones, our digestive tubes, our kidneys and liver. Not that everything is known about any of these—but at least we have rough ideas: that digestive tubes deal with food, the heart pumps blood, bones support us, and some bones make blood. (It would be hard to imagine a time, even in the dark twelfth century, when it was not appreciated that bones are what make our consistency different from that of an earthworm, but we can easily forget that it took a genius like William Harvey to discover what the heart does.) What something is *for* is a question that applies only to biology, in the broad sense of the word "biology." We can ask meaningfully what a rib is for: it supports the chest and keeps it hollow. We can ask what a bridge is for: it lets humans cross a river—and humans, which are part of biology, invented the bridge. Purpose has no meaning outside of biology, so that I laugh when my son asks me, "Daddy, what's snow for?" How purpose comes into biology has to do with evolution, survival, sociobiology, selfish genes—any number of exalted topics that keep many people busy full time. Most things in anatomy—to return to solid ground—even such erstwhile mysterious structures as the thymus gland and the spleen, can now have quite reasonable functions assigned to them. When I was a medical student, the thymus and spleen were question marks. The brain is different. Even today large parts of it are question marks, not only in terms of how they work but also in terms of their biological purpose. A huge, rich subject, neuroanatomy consists largely of a sort of geography of

structures, whose functions are still a partial or complete mystery. Our ignorance of these regions is of course graded. For example, we know a fair amount about the region of brain called the motor cortex and have a rough idea of its function: it subserves voluntary movement; destroy it on one side and the hand and face and leg on the opposite side become clumsy and weak. Our knowledge of the motor cortex lies midway along a continuum of relative knowledge that ranges all the way from utter ignorance of the functions of some brain structures to incisive understanding of a few—like the understanding we have of the functions of a computer, printing press, internal combustion engine, or anything else we invented ourselves.

The visual pathway, in particular the *primary visual cortex*, or *striate cortex*, lies near the bone or heart end of this continuum. The visual cortex is perhaps the best-understood part of the brain today and is certainly the best-known part of the cerebral cortex. We know reasonably well what it is "for", which is to say that we know what its nerve cells are doing most of the time in a person's everyday life and roughly what it contributes to the analysis of the visual information. This state of knowledge is quite recent, and I can well remember, in the 1950s, looking at a microscopic slide of visual cortex, showing the millions of cells packed like eggs in a crate, and wondering what they all could conceivably be doing, and whether one would ever be able to find out.

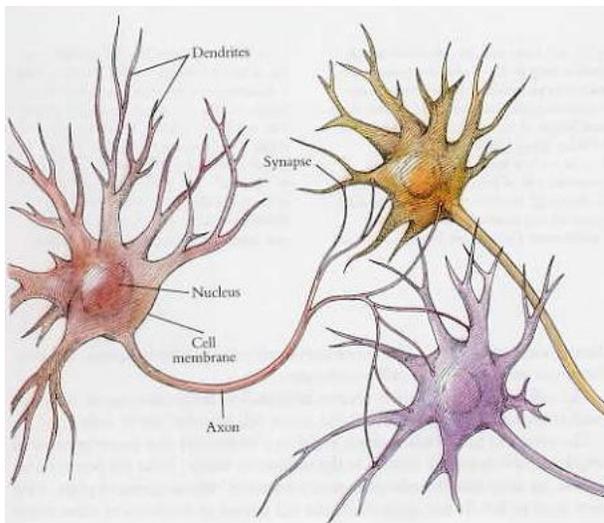


This view of a human brain seen from the left and slightly behind shows the cerebral cortex and cerebellum. A small part of the brainstem can be seen just in front of the cerebellum.

How should we set about finding out? Our first thought might be that a detailed understanding of the connections, from the eye to the brain and within the brain, should be enough to allow us to deduce how it works. Unfortunately, that is only true to a limited extent. The regions of cortex at the back of the human brain were long known to be important for vision partly because around the turn of the century the eyes were discovered to make connections, through an intermediate way station, to this part of the

brain. But to deduce from the structure alone what the cells in the visual cortex are doing when an animal or person looks at the sky or a tree would require a knowledge of anatomy far exceeding what we possess even now. And we would have trouble even if we did have a complete circuit diagram, just as we would if we tried to understand a computer or radar set from their circuit diagrams alone—especially if we did not know what the computer or radar set was for.

Our increasing knowledge of the working of the visual cortex has come from a combination of strategies. Even in the late 1950s, the physiological method of recording from single cells was starting to tell us roughly what the cells were doing in the daily life of an animal, at a time when little progress was being made in the detailed wiring diagram. In the past few decades both fields, physiology and anatomy, have gone ahead in parallel, each borrowing techniques and using new information from the other. I have sometimes heard it said that the nervous system consists of huge numbers of random connections. Although its orderliness is indeed not always obvious, I nevertheless suspect that those who speak of random networks in the nervous system are not constrained by any previous exposure to neuroanatomy. Even a glance at a book such as Cajal's *Histologie du Systeme Nerveux* should be enough to convince anyone that the enormous complexity of the nervous system is almost always accompanied by a compelling degree of orderliness. When we look at the orderly arrays of cells in the brain, the impression is the same as when we look at a telephone exchange, a printing press, or the inside of a TV set—that the orderliness surely serves some purpose. When confronted with a human invention, we have little doubt that the whole machine and its separate parts have understandable functions. To understand them we need only read a set of instructions. In biology we develop a similar faith in the functional validity and even ultimately in the understandability of structures that were not invented, but were perfected through millions of years of evolution. The problem of the neurobiologist (to be sure, not the only problem) is to learn how the order and complexity relate to the function.



The principal parts of the nerve cell are the cell body containing the nucleus and other organelles; the single axon, which conveys impulses from the cell; and the dendrites, which receive impulses from other cells.

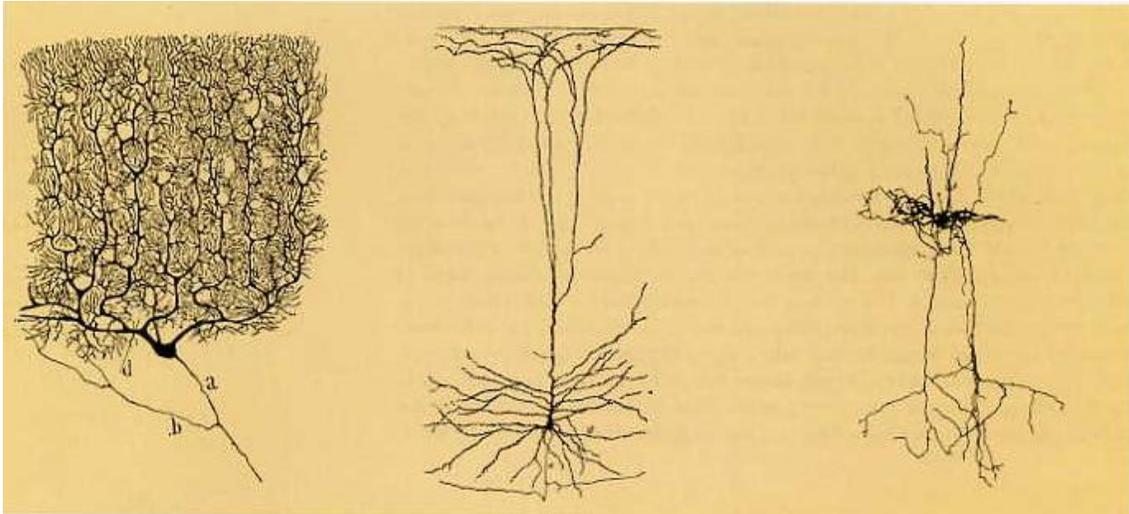
To begin, I want to give you a simplified view of what the nervous system is like—how it is built up, the way it works, and how we go about studying it. I will describe typical nerve cells and the structures that are built from them.

The main building blocks of the brain are the nerve cells. They are not the only cells in the nervous system: a list of all the elements that make up the brain would also include glial cells, which hold it together and probably also help nourish it and remove waste products; blood vessels and the cells that they are made of; various membranes that cover the brain; and I suppose even the skull, which houses and protects it. Here I will discuss only the nerve cells.

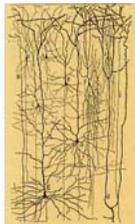
Many people think of nerves as analogous to thin, threadlike wires along which electrical signals run. But the nerve fiber is only one of many parts of the nerve cell, or *neuron*. The *cell body* has the usual globular shape we associate with most cells (see diagram on the next page) and contains a nucleus, mitochondria, and the other organelles that take care of the many housekeeping functions that cell biologists love to talk about. From the cell body comes the main cylinder-shaped, signal-transmitting nerve fiber, called the *axon*. Besides the axon, a number of other branching and tapering fibers come off the cell body: these are called *dendrites*. The entire nerve cell—the cell body, axon, and dendrites—is enclosed in the cell membrane.

The cell body and dendrites receive information from other nerve cells; the axon transmits information from the nerve cell to other nerve cells. The axon can be anywhere from less than a millimeter to a meter or more in length; the dendrites are mostly in the millimeter range. Near the point where it ends, an axon usually splits into many branches, whose terminal parts come very close to but do not quite touch the cell bodies or dendrites of other nerve cells. At these regions, called *synapses*, information is conveyed from one nerve cell, the *presynaptic* cell, to the next, the *postsynaptic* cell.

The signals in a nerve begin at a point on the axon close to where it joins the cell body; they travel along the axon away from the cell body, finally invading the terminal branches. At a terminal, the information is transferred across the synapse to the next cell or cells by a process called *chemical transmission*, which we take up in Chapter 2. Far from being all the same, nerve cells come in many different types. Although we see some overlap between types, on the whole the distinctiveness is what is impressive. No one knows how many types exist in the brain, but it is certainly over one hundred and could be over one thousand. No two nerve cells are identical. We can regard two cells of the same class as resembling each other about as closely as two oak or two maple trees do and regard two different classes as differing in much the same way as maples differ from oaks or even from dandelions. You should not view classes of cells as rigid divisions: whether you are a splitter or a lumper will determine whether you think of the retina and the cerebral cortex as each containing fifty types of cells or each half a dozen (see the examples on the next page).



Left: The cerebellar Purkinje cell, shown in a drawing by Santiago Ramon y Cajal, presents an extreme in neuronal specialization. The dense dendritic arborization is not bushlike in shape, but is flat, in the plane of the paper, like a cedar frond. Through the holelike spaces in this arborization pass millions of tiny axons, which run like telegraph wires perpendicular to the plane of the paper. The Purkinje cell's axon gives off a few initial branches close to the cell body and then descends to cell clusters deep in the cerebellum some centimeters away, where it breaks up into numerous terminal branches. At life size, the total height of the cell (cell body plus dendrites) is about 1 millimeter. *Middle:* Ramon y Cajal made this drawing of a pyramidal cell in the cerebral cortex stained. The cell body is the small black blob. *Right:* This drawing by Jennifer Lund shows a cortical cell that would be classed as "stellate". The dark blob in the center is the cell body. Both axons (fine) and dendrites (coarse) branch and extend up and down for distance of 1 millimeter.



This Golgi stain, in a drawing by Ramon y Cajal, shows a few cells in the upper layers of cerebral cortex in a one-month-old human baby. Only a tiny fraction of a percent of the cells in the area have stained.

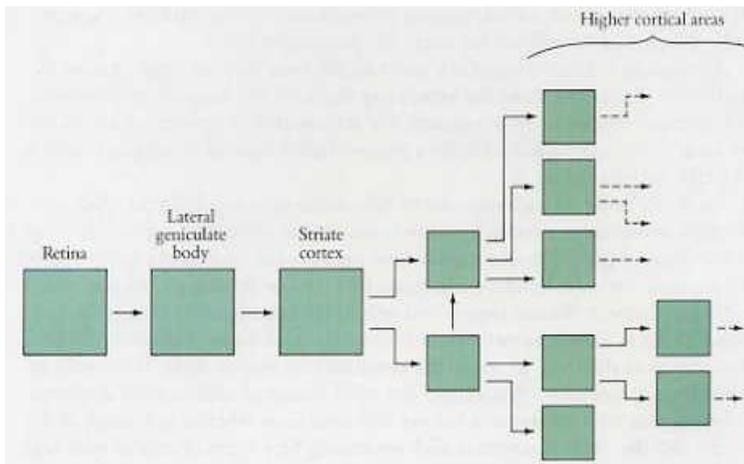
The connections within and between cells or groups of cells in the brain are usually not obvious, and it has taken centuries to work out the most prominent pathways. Because several bundles of fibers often streak through each other in dense meshworks, we need special methods to reveal each bundle separately. Any piece of brain we choose to examine can be packed to an incredible degree with cell bodies, dendrites, and axons, with little space between. As a result, methods of staining cells that can resolve and reveal the organization of a more loosely packed structure, such as the liver or kidney, produce only a dense black smear in the brain. But neuroanatomists have devised powerful new ways of revealing both the separate cells in a single structure and the connections between different structures.

As you might expect, neurons having similar or related functions are often interconnected. Richly interconnected cells are often grouped together in the nervous system, for the obvious reason that short axons are more efficient: they are cheaper to

make, take up less room, and get their messages to their destinations faster. The brain therefore contains hundreds of aggregations of cells, which may take the form of balls or of stacks of layered plates. The cerebral cortex is an example of a single gigantic plate of cells, two millimeters thick and a square foot or so in area. Short connections can run between the neurons within a given structure, or large numbers of long fibers that form cables, or *tracts*, can run from one structure to another. The balls or plates are often connected in serial order as *pathways* (see the illustration on the next page).

A good example of such a serially connected system is the visual pathway. The retina of each eye consists of a plate having three layers of cells, one of which contains the light-sensitive receptor cells, or rods and cones. As we saw earlier, each eye contains over 125 million receptors. The two retinas send their output to two peanut-size nests of cells deep within the brain, *the lateral geniculate bodies*. These structures in turn send their fibers to the visual part of the cerebral cortex. More specifically, they go to the striate cortex, or primary visual cortex. From there, after being passed from layer to layer through several sets of synaptically connected cells, the information is sent to several neighboring higher visual areas; each of these sends its output to several others (see the illustration on the next page). Each of these cortical areas contains three or four synaptic stages, just as the retina did. The lobe of the brain farthest to the rear, the occipital lobe, contains at least a dozen of these visual areas (each about the size of a postage stamp), and many more seem to be housed in the parietal and temporal lobes just in front of that. Here, however, our knowledge of the path becomes vague.

Our main goal in this book will be to understand why all these chains of neuronal structures exist, how they work, and what they do. We want to know what kind of visual information travels along a trunk of fibers, and how the information is modified in each region—retina, lateral geniculate body, and the various levels of cortex. We attack the problem by using the microelectrode, the single most important tool in the modern era of neurophysiology. We insert the microelectrode (usually a fine insulated wire) into whatever structure we wish to study—for example, the lateral geniculate body—so that its tip comes close enough to a cell to pick up its electrical signals. We attempt to influence those signals by shining spots or patterns of light on the animal's retina.

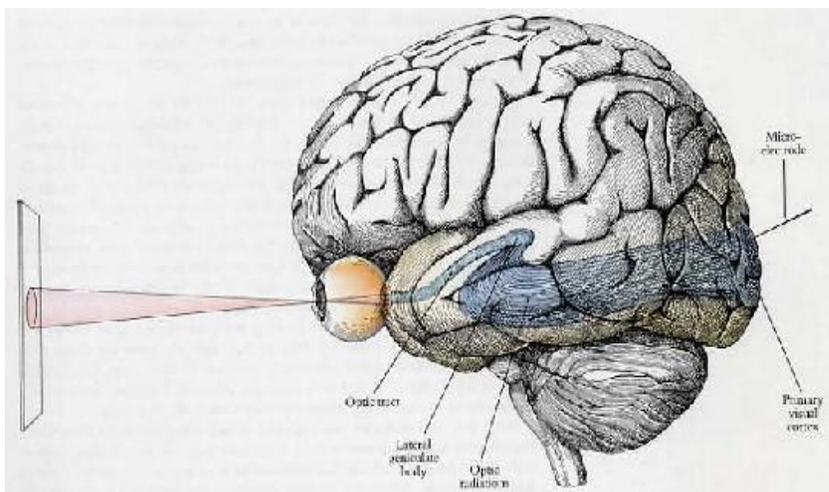


The visual pathway. Each structure, shown as a box, consists of millions of cells, aggregated into sheets. Each

receives inputs from one or more structures at lower levels in the path and each sends its output to several structures at higher levels. The path has been traced only for four or five stages beyond the primary visual cortex.

Because the lateral geniculate body receives its main input from the retina, each cell in the geniculate will receive connections from rods and cones—not directly but by way of intermediate retinal cells. As you will see in Chapter 3, the population of rods and cones that feed into a given cell in the visual pathway are not scattered about all over the retina but are clustered into a small area. This area of the retina is called the *receptive field* of the cell. So our first step, in shining the light here and there on the retina, is to find the cell's receptive field. Once we have defined the receptive field's boundaries, we can begin to vary the shape, size, color, and rate of movement of the stimulus—to learn what kinds of visual stimuli cause the cell to respond best.

We do not have to shine our light directly into the retina. It is usually easier and more natural to project our stimuli onto a screen a few meters away from the animal. The eye then produces on the retina a well-focused image of the screen and the stimulus. We can now go ahead and determine the position, on the screen, of the receptive field's projection. If we wish, we can think of the receptive field as the part of the animal's visual world—in this case, the screen—that is seen by the cell we are recording from. We soon learn that cells can be choosy, and usually are. It may take some time and groping before we succeed in finding a stimulus that produces a really vigorous response from the cell. At first we may have difficulty even finding the receptive field on the screen, although at early stages, such as in the geniculate, we may locate it easily. Cells in the geniculate are choosy as to the size of a spot they will respond to or as to whether it is black on a white background or white on black. At higher levels in the brain, an edge (the line produced by a light-dark boundary) may be required to evoke a response from some cells, in which case the cells are likely to be fussy about the orientation of the edge—whether it is vertical, horizontal, or oblique. It may be important whether the stimulus is stationary or moves across the retina (or screen), or whether it is colored or white. If both eyes are looking at the screen, the exact screen distance may be crucial. Different cells, even within the same structure, may differ greatly in the stimuli to which they respond. We learn everything we can think to ask about a cell, and then move the electrode forward a fraction of a millimeter to the next cell, where we start testing all over again.



An experimental plan for recording from the visual pathway. The animal, usually a macaque monkey, faces a screen onto which we project a stimulus. We record by inserting a microelectrode into some part of the pathway, in this case, the primary visual cortex. (The brain in this diagram is from a human, but a monkey brain is very similar.)

From any one structure, we typically record from hundreds of cells, in experiments that take hours or days. Sooner or later we begin to form a general idea of what the cells in that structure have in common, and the ways in which they differ. Since each of these structures has millions of cells, we can sample only a small fraction of the population, but luckily there are not millions of kinds of cells, and sooner or later we stop finding new varieties. When we are satisfied, we take a deep breath and go on to the next level—going, for example, from the lateral geniculate body to the striate cortex—and there we repeat the whole procedure. The behavior of cells at the next stage will usually be more complicated than the behavior of cells at the previous level: the difference can be slight or it can be dramatic. By comparing successive levels, we begin to understand what each level is contributing to the analysis of our visual world—what operation each structure is performing on the information it receives so that it can extract from the environment information that is biologically useful to the animal.

By now, the striate cortex has been thoroughly studied in many laboratories. We have far less knowledge about the next cortical area, visual area 2, but there, too, we are beginning to get a fair understanding of what the cells are doing. The same is true of a third area, the middle temporal (MT) area, to which both the striate cortex and visual area 2 connect. From there on, however, our knowledge becomes rapidly more sketchy: in two or three regions we have only a vague idea of the kinds of information that are handled—things such as color or recognition of complex objects such as faces—and after that, for the dozen or so areas that we can be sure are primarily visual, we know practically nothing. But the strategy is clearly paying off, to judge from the rate at which our understanding is increasing. In the chapters to come, I will fill out some of the details of this picture for levels up to and including the striate cortex. In Chapter 2, I describe roughly how impulses and synapses work and give a few examples of neural pathways in order to illustrate some general principles of neuronal organization. From then on I will concentrate on vision, first on the anatomy and physiology of the retina, then on the physiology of the striate cortex and its anatomy. I next describe the remarkable geometric cortical patterns that result from the fact that cells with similar functions tend to aggregate together. Then will come several special topics: mechanisms for color perception and depth perception, the function of the fibers that connect the two hemispheres (the *corpus callosum*), and, finally, the influence of early experience on the visual system. Some parts of the story, such as the sections dealing with the nerve impulse and with color vision, will necessarily be slightly more technical than others. In those cases, I can only hope that you will adhere to the wise advice: "When in perplexity, read on!"

