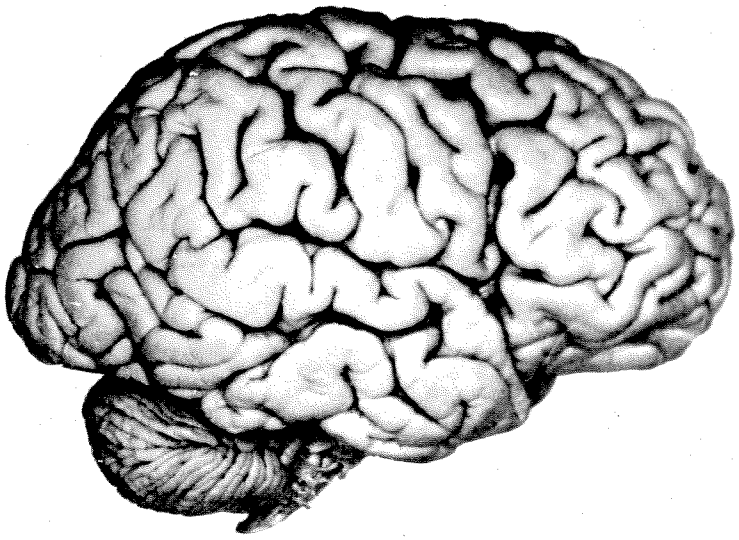
Insight into Sight

by David C. Van Essen



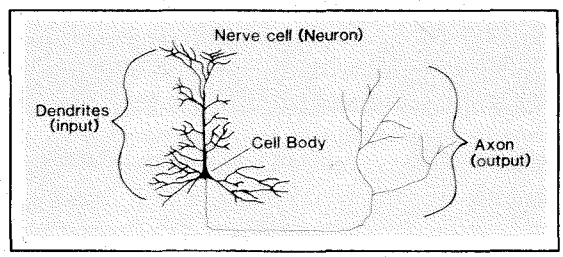
A view of the left hemisphere of the human brain as seen from the side. The cerebral cortex, with its numerous convolutions, is the dominant subdivision of the brain and is responsible for many of our higher mental functions.

WHAT HAPPENS within the brain as we look at the world around us? Is it possible to account for our visual perceptions in terms of the patterns of activity within the intricate living circuits of the brain? Scientists and philosophers alike have long been intrigued by such matters. In recent years research on the function of the visual system has clarified many basic issues and begun to provide coherent answers to these questions.

The impressive capacities of the human visual system are evident in many seemingly routine activities. For example, our ability to recognize a face in a photograph is based on the rapid and precise analysis of information about light intensity at many different points. The sequence of events in this analysis is of such bewildering complexity that it is profitable to begin with the consideration of much simpler examples. When we look at a single spot of light projected onto a screen, for instance, we can ask a number of basic but nonetheless useful questions: How is the light from the spot detected by the eye? How is the information encoded within the eye and sent back to the brain? To how many visual centers in the brain is it sent? How is it processed in each of those centers? Where does the actual percept of a spot arise? And how is the entire sequence different if the spot is projected onto a different part of the screen? By starting with relatively simple questions that build up in levels of complexity, we can make considerable progress toward fathoming many interesting aspects of brain function as it relates to vision.

It is useful at the outset to comment briefly on the raw materials used for processing information within the nervous system. The human brain weighs about five pounds and is made of rather soft and squishy biological materials. Superficially, it may not appear as imposing as one might expect for the most complicated device in the known universe. It is composed of an enormous number of fundamental subunits called nerve cells, or neurons. These are analogous to the transistors and other circuit elements that make up computers and other electronic devices. Each neuron has a cell body, which nourishes the cell and does various housekeeping chores, and it also has a collection of fine branches, which are used for making the connections that are essential for its role in processing information. One set of branches, called dendrites, are located close to the cell body and are used to receive input from other sources. Another branch, called the axon, provides the output of the cell. The axon starts as a single long fiber that travels anywhere from a fraction of an inch up to several feet before branching profusely to contact the dendrites at its target cells. At these contact points are exquisitely precise little devices called synapses, which allow for the transmission of information from the axon, or output side, of one cell to the dendrites, or input side, of the next cell.

There are approximately 100 billion nerve cells within the human brain. These cells typically have thousands of synaptic inputs and thousands of synaptic outputs, so there are on the order of 100 trillion synapses in the brain — truly a staggering number in comparison with the number of electrical connections in even the most powerful computer. Although the signals used by the brain are electrical in nature, their



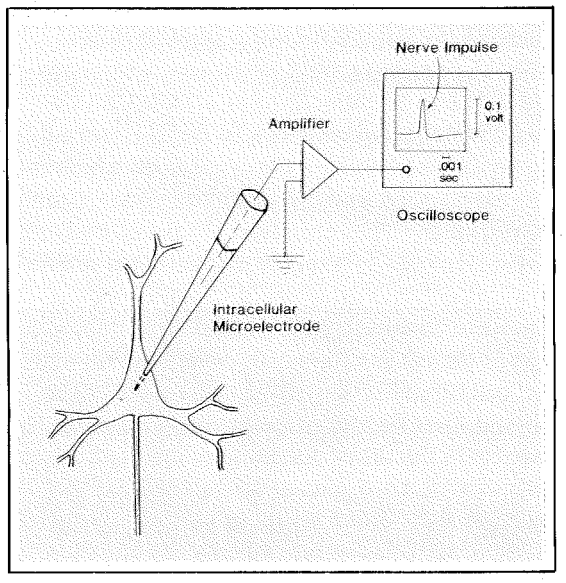
A typical nerve cell. The regions dealing with inputs and outputs are well separated from one another.

activity does not involve electrons flowing through wires. Rather, electrical potentials (voltages) are generated across an extremely thin sheet, the cell membrane, that separates the inside from the outside of the cell. We can record those signals with a microelectrode that is either inserted into the inside of the cell or placed just outside the cell membrane. The signals that are picked up by the microelectrode can be amplified and sent to an oscilloscope, a device that simply displays voltage as a function of time. A single nerve impulse is about 0.1 volt in amplitude and 0.001 second in duration. The size and shape of these impulses are constant; to transmit information, the cell changes the frequency at which the impulses are generated.

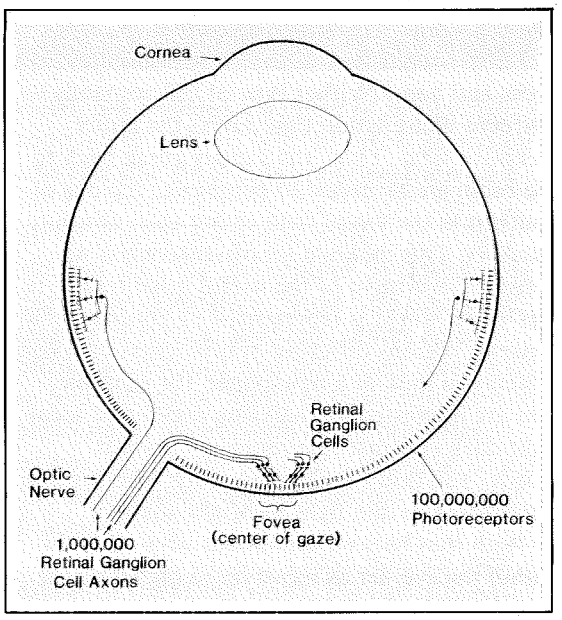
Visual signals enter the brain through the eye, which works very much like a camera, with an optical apparatus in front (the cornea and lens) and a sensory or receiving surface in back (the retina). An object in the external world is focused by means of the lens so that a sharp image is formed on the retina. In a microscope the retina reveals itself as a highly complicated sheet of tissue, only 0.01 inch thick but consisting of many layers of cells stacked together. When light reaches the retina, it is absorbed by specialized cells, called photoreceptors, which are densely packed together in a single layer. In each eye there are about 100 million photoreceptors of two basic types: rods, which are exquisitely sensitive to dim lights and are used for night vision, and cones, which are used for normal daytime vision. Cones come in three varieties that together provide the sense of color vision.

An individual photoreceptor detects light and generates an electrical signal that indicates the amount of light absorbed at that particular spot on the retina. Each photoreceptor is pretty much oblivious to what is happening to its neighbors. This situation changes dramatically, however, by the time signals reach the output stage of the retina, which is a collection of cells called retinal ganglion cells. Each retinal ganglion cell sends a single axon across the surface of the retina and out to the brain through a bundle called the optic nerve. Since there are only one million retinal ganglion cells to handle the information coming from the 100 million photoreceptors, there must be a considerable convergence of information. This is handled in a clever fashion, by distributing retinal ganglion cells in a highly nonuniform manner. At the very back of the retina is a region called the fovea, which corresponds to the center of gaze. In this small region each photoreceptor has a direct linkage to a single retinal ganglion cell, so that resolution of fine detail is preserved. Off to the side of the retina, the information from literally hundreds or thousands of photoreceptors impinges onto each retinal ganglion cell. These cells in the periphery can detect the presence of light quite well but cannot tell exactly which photoreceptor was illuminated. Visual acuity, therefore, is much lower in the region of peripheral vision.

Retinal ganglion cells have another property that is even more important for understanding the kinds of transformations in information content that take place within the visual pathway. This feature was first discovered some 30 years ago by Stephen Kuffler, one of the founders of modern neurobiology, who studied the effects of different patterns of illumination on the retina. Kuffler found that the activity of



Technique for recording the electrical activity of nerve cells. In the diagram shown here, a glass tube drawn to an extremely fine tip and filled with a conducting solution is inserted into the cell. The amplifier strengthens the signal coming from the microelectrode and sends it to the oscilloscope, where it appears as a brief, stereotyped event.



A schematic cross section of the eye. The retina is a thin sheet containing several types of nerve cell. These include photoreceptors, which convert light energy into electrical signals, and retinal ganglion cells, which process the visual signals and transmit information to the brain via the optic nerve.

any given retinal ganglion cell could be influenced by illumination of a small region called the receptive field of the cell. The receptive field can be thought of as a region on the retina itself or, equivalently, as the corresponding region on the projection screen on which the eyes are focused and on which the visual stimuli are projected. The receptive field is not uniform in its organization, though, but rather is divided into concentric central and surround zones, which are antagonistic to one another. In one type of retinal ganglion cell, called an "on-center" cell, illumination of the center excites the cell and illumination of the surround inhibits its activity. In the other major type, the "off-center" cell, the arrangement is exactly the opposite, with light in the center inhibiting the cell and light in the surround exciting it. The most effective stimuli for on-center cells are spots and elongated slits of light, whereas the most effective stimuli for off-center cells are dark spots and bars. Neither type of cell responds to uniform illumination that covers the entire receptive field. Thus, the signals going back to the brain are arranged to emphasize regions of contrast in the visual field rather than absolute intensity. This makes a lot of sense when we consider that most of the useful information in our visual world is represented by contours that separate regions differing in brightness or color. When you look at a newspaper, for example, you are interested in analyzing regions of local light-dark contrast that represent printed words. You don't really care much whether you are reading in dim light or bright sunlight.

With that background about what goes on within the eye, let us move on to higher visual centers. The output from each retina goes by way of the two optic nerves to a juncture called the optic chiasm, right along the midline of the brain. At the optic chiasm an important redistribution of retinal ganglion cell axons takes place. Beyond the chiasm each hemisphere receives inputs from only the opposite half of the visual field, but it receives that information from both eyes. The retinal ganglion cell axons terminate in a relay structure named the lateral geniculate nucleus, which in turn sends its axons to the primary visual cortex. The primary visual cortex is the largest single subdivision of the cerebral cortex, which is itself the dominant structure of the brain.

The cerebral cortex is responsible in large part for a wide variety of different functions, including the senses of vision, hearing and touch, the control of voluntary movements, and the ability to reason, calculate, and use language and music. This rich diversity of functions is all the more impressive in view of the structural uniformity of the cortex. It is a sheet of gray matter about 0.1 inch thick that forms the outer wrapping of each hemisphere. Underneath the cortex is the white matter, composed of the axons of nerve cells whose cell bodies are in the gray matter of one region or another. The wrinkled appearance of the cortex is due to the numerous folds, or convolutions, that are characteristic of the brains of humans and other advanced mammals. These convolutions arise because the cortex is a sheet of limited thickness, which has increased rapidly in surface area during evolution and so has been crumpled or folded to get it to fit into a skull of limited dimensions.

An important principle of cortical organization is that it is divided into many functionally distinct subdivisions, or cortical areas. The total number of areas and their exact layout varies considerably in different species. In my own laboratory we have chosen to study the macaque monkey, a close relative of the common rhesus monkey, because of its superb visual system, very much like our own in many respects.

The task of identifying different cortical areas and determining their boundaries has been a major challenge to neuroscientists for more than a century. Fifteen years ago it was believed that there were only three or four cortical areas concerned with vision and even fewer areas concerned with other sensory modalities such as hearing and touch. This picture has now changed dramatically, thanks largely to the availability of new techniques for analyzing functional pathways within the brain. One especially important procedure involves the injection of special tracer substances into localized regions of the brain. One type of tracer is selectively transported from the cell bodies of neurons along their axons in the white matter to their synaptic terminations in various target areas. Another type of tracer is selectively transported in the reverse direction, from synaptic terminals back along the axons to the cell bodies, wherever they may be located. In either case, the final distribution of the tracers can be determined by appropriate treatment of histological sections cut through the brain.

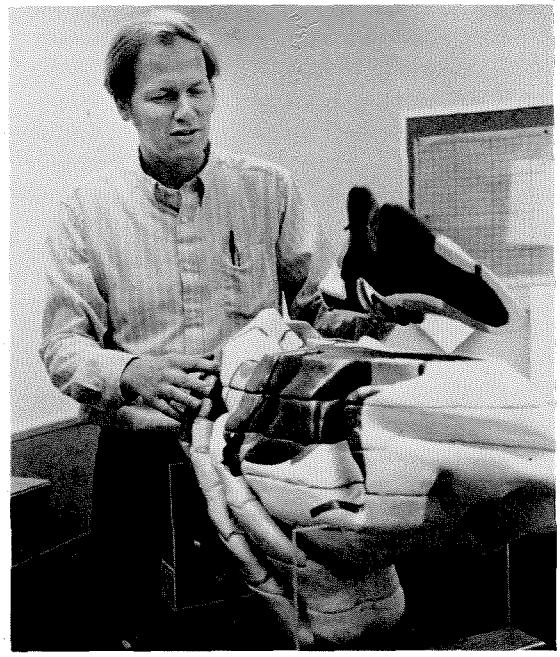
Using these techniques along with other complementary procedures, scientists have learned a great deal about cortical organization in recent years. In my own laboratory we have discovered the existence of four previously unidentified visual areas in the cortex of the macaque

monkey. Related discoveries in other laboratories have added to the number of identified cortical areas in the macaque as well as in a number of other laboratory animals.

One way of documenting the location of different cortical areas is to paint them in different colors on a scale model of the brain (right). This has the advantage of conveying the relationships that exist among areas in the intact brain. There are, however, problems with this format, particularly because it is difficult to see some of the smaller areas that lie within one or another of the deep cortical folds. In order to get around this difficulty we have developed a procedure for constructing unfolded, two-dimensional maps that accurately represent the surface of the cortex (below). One can see in this figure that the entire posterior half of the cortex is visual in function, while much smaller regions are devoted to the senses of hearing and touch and to the control of body movements. About 30 cortical areas have been identified to date, of which a dozen are visual in function. There are still a number of relatively uncharted regions in which we can anticipate that additional areas will be discovered.

The primary visual cortex (visual area 1, or V1 on the map) is a large area covering about one-sixth of the entire cerebral cortex, and it is the direct recipient of information relayed from the retina up through the lateral geniculate nucleus. This large sheet of cortex that makes up V1 in one hemisphere must process information from the entire opposite half of the visual field. (Its counterpart in the other hemisphere takes care of the remaining half of the visual field.) Within this sheet there is an orderly representation of the visual field, with the center of gaze represented at one end and the periphery of the visual field at the other. Neighboring points in the visual field are represented as neighboring points on the cortical surface. At a more detailed level scientists have found that the cortex can be subdivided on anatomical and physiological grounds into a large number of distinct modules, about one millimeter on a side. Within each of these modules there are approximately 100,000 nerve cells, each of them looking out at one tiny region of visual space. Together, the cells in that module carry out a first-order analysis of what things of visual interest are in that region.

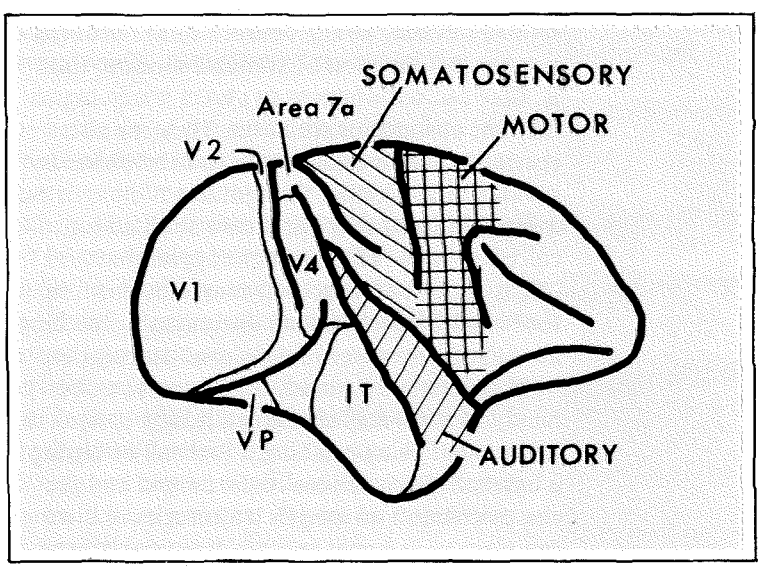
In order to ascertain the nature of this first-order analysis, we can study the responses of simple neurons to a variety of visual stimuli. This approach, pioneered for the visual cortex by Nobel laureates David Hubel and Torsten



The author with a scale model of a monkey's brain. The model is greatly enlarged from the original size of the brain, which is only a few inches long. Individual functional subdivisions of the cerebral cortex are indicated in various shades. The visual cortex is located at the rear of the brain, where the author's right hand is placed. In his left hand is a section through the top of the brain to show the white matter (painted black on the model).

Wiesel, has revealed a number of intriguing properties of cortical neurons. Most important is the fact that these cells are orientation selective: They insist not only that a light/dark contour be present in a certain place in the visual field, but also that this contour be elongated in a particular orientation. Some cells detect the presence of vertical contours, others detect horizontal contours, and still others detect various oblique angles. Many of these cells are also able to signal information about other basic features, such as the color of a stimulus, its size and distance away, and its direction and speed of motion.

After all the cells in V1 have finished their analysis of the visual world, the partially processed information is distributed to the numerous higher visual areas for additional rounds of



An unfolded, flattened map of the monkey's cerebral cortex. The various visual areas in the cortex denoted by V1, V2, etc., are illustrated in a drawing of the intact hemisphere (upper left) and again on the cortical map. Visual areas occupy about half of the entire cerebral cortex, whereas considerably smaller regions are devoted to other functional modalities of hearing, touch, and motor control. The largest area, V1, is separated from neighboring cortex on the map by a cut, or artificial discontinuity, introduced to minimize distortions in the representation of surface area.

analysis. In order to understand what occurs at these higher levels, it is first necessary to know which visual areas receive direct input from V1 and which receive their input indirectly, relayed through intermediate areas. It turns out that the pathways among cortical areas are quite complex, as each area has multiple sources of inputs and multiple outputs. Despite this complexity, we have recently found that there is a high degree of order within the system. Specifically, it is possible to arrange all of the visual areas into an overall hierarchical scheme, in which each area occupies a well-defined position in relation to other areas with which it is connected. This hierarchy is analogous to various schemes that are used to portray organizational relationships in certain human institutions, such as judicial and executive branches of government. In the visual pathway V1, not surprisingly, is at the bottom of the cortical hierarchy, and the visual areas in the temporal and parietal lobes are at the highest levels.

In parallel with this progress in understanding the anatomical organization of the visual cortex, we have also begun to make headway in analyzing the functions of some of the higher visual areas. The emphasis in my laboratory has been on understanding the way in which information about form, color, and motion in the visual world is processed. We have found that there appear to be two distinct functional streams within the visual cortex, one concerned specifically with motion analysis and the other concerned with both form and color.

The specialization for motion analysis is illustrated most clearly by considering area MT. This is a small visual area buried deep within one of the cortical fields; it was originally discovered by John Allman, associate professor of biology at Caltech, in a different species of monkey. Nearly all the neurons in MT are selective for the direction of stimulus motion; that is, they can tell whether an object is moving to the left, upward, or whatever. They are also specialized to determine how fast the object is moving, and whether the stimulus is close or far away. But these cells don't care at all about color or shape. These results suggest that area MT is concerned with analyzing movement in the visual field and telling the animal something about complex three-dimensional trajectories.

This capability would, of course, be quite handy to a monkey catching a falling banana or to a human being catching a football or hitting a baseball. Such actions require rapid and precise calculation of specific trajectories that we can react to in a split second. It is very convenient to have a system that can handle this without worrying for the moment about exactly what size or shape of object is approaching. The system for analyzing motion appears to start way down in the retina, involving a subset of retinal ganglion cells that are particularly sensitive to moving stimuli. These cells connect up to particular layers within the lateral geniculate nucleus. From there the information is transmitted to specific layers within V1 and then to MT. We are now interested in finding out what happens to these signals after they leave MT and reach still higher targets within the cortex.

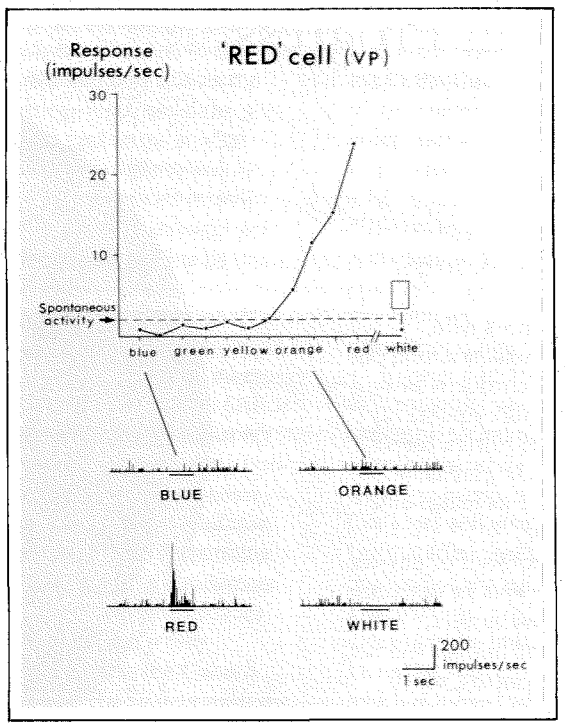
The cortex involved in analyzing form and color appears to be considerably more extensive than that for motion analysis. As was already pointed out, the output from V1 includes activity in a large number of cells that are responsive to local contours in the visual field, such as the margins of a face, or the eyes and nose within a face. We can imagine that the cells in area V1 look at these images in a piecemeal fashion, separately signaling a vertical contour here and a horizontal contour there, and so on. We know that subsequent stages take place in a number of areas, including areas V2, V4, VP, and the inferotemporal cortex (IT), whose locations are indicated on the cortical map. We do not yet know much about the nature of the higher level analysis that takes place in these areas; one attractive possibility, however, is that the piecemeal analysis carried out in V1 is reassembled in such a way that individual higher order neurons detect more complex patterns than just bars and edges. Neurons at intermediate levels, for example, might detect corners or contours with a particular curvature. Neurons at the highest levels might signal the presence of still more complex patterns, such as a nose, an entire face, or a tree. On the other hand, it may well be that complex features in the visual world can only be signaled by coordinated activity within an ensemble of neurons and not just by a single cell. Now that we know which visual areas to explore, it may be possible to resolve within the forseeable future which of these general schemes accounts for our ability to recognize an infinite variety of forms and patterns.

Our sense of color has always been a source of fascination to vision researchers. This is partly because color greatly enriches and enhances the beauty of our visual world, and partly because of the availability of optical methods that give the experimentalist precise control over the spectral composition of stim-

uli. It has been known since the 19th century that color is encoded within the eye by three types of photoreceptors. One type, the blue cone, absorbs light preferentially at short wavelengths; another, the green cone, is most sensitive at intermediate wavelengths; and the third, the red cone, is most sensitive at long wavelengths. Each type of cone absorbs light over a large portion of the spectrum, though, and our ability to distinguish subtle differences in hue is dependent on making comparisons among the degree of activation of each cone type. Such comparisons begin within the retina itself and are continued up at the level of the visual cortex. We have found that in the various areas concerned with form and pattern vision (specifically areas V2, V4, and VP), a majority of neurons are also selective for the color of visual stimuli (right). Thus, form and color appear to be processed together in the same visual areas and sometimes within the same neurons, whereas motion, as already discussed, is largely segregated into a separate functional stream.

An interesting complexity in our sense of color vision has been pointed out by Edwin Land, inventor of the Polaroid Land camera. Last year in his Lauritsen lecture here at Caltech, Land demonstrated the remarkable ability of the human visual system to compensate for large changes in illumination and in the spectral content of the light coming to our eyes. Such compensatory interactions are important in our everyday ability to recognize the colors of natural objects despite the differences in illumination between, say, yellowish candlelight versus bluish fluorescent lights. The same phenomenon can be demonstrated by viewing a richly colored scene with and without color filters in front of the eyes. A yellow banana, for example, seen behind a red filter is still interpreted as yellow in its reddish surroundings, even though the light coming from it is distinctly orange when viewed in isolation. Although our ability to compensate for these changes in illumination is by no means perfect, it's still an impressive accomplishment. Preliminary studies from other laboratories suggest that this compensation may take place at high levels of the visual pathway. Further studies are needed to determine whether this actually does occur, and, if so, what happens in terms of the specific neural circuitry.

To summarize, we have seen that it is possible to take a particular sensory system within the brain and follow the kinds of transformations that occur as we go through many successive stages of processing. In the future it will be possible to delve even farther into the system and understand a great deal more about the basic principles of visual perception. Eventually these studies on animal models will help us to understand the operation of the cerebral cortex in the human brain. We are still not in a position to accurately determine the precise localizations of what may be a very large number of functional subdivisions in the human brain, as is now possible for the brains of other species. But we can expect that such discoveries will be aided by the recent development of powerful, noninvasive techniques for detecting activity in specific regions of the human brain.



Properties of a red-sensitive neuron in visual area VP. Below are histograms showing the response of the neuron to lights of different colors projected onto a screen facing the animal. The light was flashed on during the one-second period indicated by the horizontal bar. Only the red light provoked a large response from the cell, as indicated by the sharp peak in the histogram, which is a plot of instantaneous frequency of nerve impulses in the cell. Blue light and white light actually depressed the spontaneous background activity of the cell, and orange light produced only a weak response. The graph at the top shows the average response of the cell to these and other colored stimuli.

Here at Caltech we have more than a dozen research groups studying various aspects of the structure, function, chemistry, and development of the brain. These studies are carried out at several levels, from that of the molecular constituents of the brain, to assemblies of cells, to the behavior of the entire organism. The rewards of these diverse and complementary approaches will be more than purely intellectual in nature. Much of what we have learned and will yet learn will also have direct relevance to the ability to diagnose, understand, and treat a variety of diseases and disorders of the nervous system. As basic scientists we cannot say with certainty exactly which disease will be cured at which particular time, or which therapeutic product will be developed. Sooner or later, though, we can be confident of great progress that will have practical impact on improving and enriching our own lives. □