American Handbook of Psychiatry

Perspectives in the Neurophysiological Study of Behavior and its Abnormalities

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e-Book 2015 International Psychotherapy Institute

From *American Handbook of Psychiatry: Volume 6* edited by Silvano Arieti

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PERSPECTIVES IN THE NEUROPHYSIOLOGICAL STUDY OF BEHAVIOR AND ITS ABNORMALITIES

The recent history of psychology has been characterized by alternate movements toward and away from biological explanations of behavior. The first rapprochement between psychology and biology dates with the work of Charles Darwin, in the middle of the nineteenth century. Darwin's discovery of a behavioral continuum between animals suggested to him that the behavior of man might profitably be studied by examining its analogues in lower forms. This notion stimulated the comparative study of behavior and led to the development of animal models that could be used in relating the nervous system to behavior. This new perspective brought about the divorce of psychology from metaphysics and theology, and the acceptance among psychologists of the idea, already established in neurology and psychiatry (see for example Meynert), that even the most complex behavioral processes have their bases in the nervous system. This acceptance was exemplified in American psychology by the publication of William James' *Principles of Psychology* in 1890. James' *Principles* generated a marvelous optimism about the capability of neurological science to relate brain mechanisms to behavior. But this optimism proved premature. During the first few decades of the twentieth century, studies of brain function failed to advance beyond a general localization of sensory and motor functions in various regions of the brain. The detailed mechanisms of behavior proved intractable to neural

analysis. As a result, psychology and the neurological sciences drifted apart. Even psychologists with strong neurological interests often abandoned biological perspectives for a psychology that was free of commitment to ill-defined notions of brain mechanisms. This separation was, and continues to be, healthy for psychology. It has permitted the development of coherent systems of behavioral description that are not contingent on vague parallels with neural mechanisms. Freed from artificial neurological constraints, psychology has been able to develop a rigorous behavioral tradition and to establish bridges with social psychology and sociology. A very special interest and excitement, however, continues to reside in the analysis of the biological mechanisms of behavior. This area has recently undergone remarkable developments that have infused new hope for relating neural mechanisms to behavior.

Major progress in understanding the neurophysiological basis of behavior has resulted from the development of techniques for studying individual nerve cells and from the selection of appropriate experimental systems for studying a variety of behavior. Specifically, advances have been made in three related and progressively more complex areas. (1) The functioning of the nerve cell and the process of synaptic transmission—the mechanism by which one neuron communicates with another —are beginning to be understood. (2) The study of the interconnections among populations of nerve cells has begun to yield significant findings. Particularly

good progress has been made in the sensory and motor systems where a beginning has been made in analyzing the cellular mechanisms of perception and motor coordination. (3) The application of cellular techniques to certain simple invertebrate animals, whose nervous systems are composed of relatively small numbers of cells, is making it possible to examine the total neural substratum of simple behavior. In these animals one can study not only the sensory information coming into the nervous system and the motor action coming out of it, but also the complete sequence of events that underlies a behavioral response.

These three developments provide a coherent framework of concepts and techniques that promises to clarify some basic relationships between brain functioning and behavior. While these concepts do not explain the complex behavior of man, they are beginning to prove useful in understanding certain elementary aspects of perception, motor coordination, and learning in animals.

In this chapter, I will try to summarize some of the main findings that have emerged from these three levels of investigation and to indicate the directions in which current research is going. I will particularly emphasize cellular studies both of sensory deprivation in newborn animals and of learning, two areas that are likely to provide useful and clinically interesting model systems of behavioral abnormalities. In being so selective, I hope to

cover in detail some areas that are of potential interest to students of psychiatry. Unfortunately, this means that I must here exclude from consideration other currently active areas of neurobiology.

The Cellular Biology of Neurons and Synapses

The properties of nerve cells that endow them with signaling capabilities stem from their ability to maintain a resting potential (membrane potential) that can be modulated by spike activity within the cell or by the synaptic activity of other cells. Until 1950, there were no satisfactory techniques for direct recording of the membrane potential maintained across the neuronal membrane or for the examination of the changes produced in it by synaptic activity and by spike generation. Technical advances made during World War II led to the development of the electronic instrumentation that could register and amplify small electrical signals recorded with minute high-resistance probes. This instrumentation led in turn to the development of the ultrafine glass microelectrode by Ralph Gerard and his colleagues. These could be filled with a concentrated potassium chloride solution and used to record directly the activity from central nerve cells and muscle fibers.

In the decade that followed World War II, microelectrode techniques were applied extensively to the study of nerve cells and to synaptic transmission, and they led to the development of a general model of neuronal

functioning that has provided the basis for much subsequent research. According to this model, all neurons, regardless of shape, size, location, and function, can be considered to have four functional components: (1) an input (receptor) component; (2) an integrative (spike-initiating) component; (3) a conductile (long-range signaling) component, and (4) an output (transmitter-releasing) component. The input component consists of the external subsynaptic membrane that contains the receptors and the ionic channels for generating two types of graded synaptic potentials, depolarizing excitatory postsynaptic potentials (EPSPs) and a hyperpolarizing inhibitory postsynaptic potential (IPSPs). Excitatory synaptic potentials reduce (depolarize) the membrane potential and, if sufficiently large, will bring the membrane potential of the integrative component to the threshold for spike generation. Inhibitory synaptic potentials tend to increase (hyperpolarize) the membrane potential and to keep the integrative component from reaching the threshold for spike generation. Thus, the integrative action of a neuron resides in adding the sum total of excitation and inhibition and deciding whether or not to discharge an action potential. This decision is made at a specific site within the neuron, the integrative component usually being located at the initial segment of the neuron. The threshold of the integrative component is exceeded and an action potential is initiated if the net depolarization produced by the excitatory synapses exceeds the net inhibition produced by the inhibitory synapses by a certain critical minimum.

Once initiated, the action potential propagates without decrement along the axon, the conductile or long-range signaling component of the neuron. At the terminal region of the axon, which abuts onto a specialized receptor site of the next cell, the action potential in the output component of the neuron leads to the release of the chemical transmitter substance. The transmitter substance diffuses across the small space (synaptic cleft) that separates the presynaptic and postsynaptic elements of the synapse, and it interacts with the receptor molecules in the external membrane of the postsynaptic cell. Depending on the nature of the transmitter and that of the receptor, the interaction leads to current flow in the postsynaptic cell, which alters its resting potential by producing either an inhibitory or an excitatory postsynaptic potential.

A large number of recent studies of central nerve cells in both invertebrates and vertebrates have shown that this model is quite general. The conclusion is that, although neurons differ in detail, most of them are surprisingly similar in their general electrophysiological properties.

These major insights derive largely from the work of Hodgkin, Huxley and Katz, (for review see) who developed the ionic hypothesis to explain how the electrical potential difference across the neuronal membrane (the resting potential) is generated, and how its sign is first quickly reduced and then reversed during the generation of the action potential. At rest, nerve cells

maintain a potential difference across their surface membranes of about —60 mV, with the inside negative in relation to the outside. Working on the giant axon of the squid, Hodgkin, Huxley and Katz demonstrated that this potential difference results from an unequal distribution of sodium, potassium, chloride, and organic anions across the semipermeable membrane of the nerve cell. This unequal distribution of ions leaves the inside of the nerve-cell membrane negatively charged in relation to the outside. The long-term distribution of ions is maintained by an active metabolic process, the "sodium-potassium pump," which keeps sodium concentration within the cell low and potassium concentration within the cell high by actively transporting sodium out of the cell and potassium into it. As a result of the constant activity of the sodium-potassium exchange mechanism, the potassium concentration inside nerve cells is about fifty times higher than that of the extracellular space and the sodium concentration is approximately ten times lower inside the cell than out. The resting-membrane potential results from the membrane's having a high leakiness (permeability) to potassium ions in its resting state and a relatively low permeability to sodium ions. Potassium is a positively charged ion. Because it is in high concentration inside the cell, it tends to be driven out under the influence of the concentration gradient, thereby making the cell membrane slightly more negative on the inside than the outside. The buildup of the negative charge on the inside of the cell tends to impede the further movement of the positively charged potassium ions. At

a certain potential, the force due to the electrical charge on the membrane becomes equal to the oppositely directed force due to the concentration gradient and no further net movement of potassium ions occurs. This potential is called the potassium-equilibrium potential and is usually about —70 mV. The value of the resting potential is close to the potassium-equilibrium potential. Small deviations of the resting potential from the potassium-equilibrium potential are usually due to the slight leakiness of the membrane to sodium and other ions.

Most cells can generate a resting potential across their membranes. What differentiates excitable cells, such as nerve and muscle, from other cells is that the resting-membrane potential can be altered so as to serve as a signaling mechanism. When the membrane potential of a nerve cell is reduced by a certain critical amount, usually about 15 mV (from —60 mV to —45 mV) an all-or-none action potential is initiated. During the action potential there is a sudden reversal in the permeability characteristics of the nerve-cell membrane so that it suddenly becomes highly permeable to sodium. The resulting potential change is regenerative. Depolarization increases sodium permeability, which produces further depolarization, which increases sodium permeability even more. This explosive event abolishes and reverses the resting potential, ultimately driving the membrane potential to the sodium-equilibrium potential (about +60 mV). The sudden reversal of the membrane potential is, however, transient and self-limiting. The progressive

depolarization of the action potential leads to a shutting off (inactivation) of the enhanced sodium permeability. Concomitantly there is also a further increase in the already high permeability to potassium ions. These processes combine to bring the membrane potential back to the resting level.

The action potential, generated in the integrative component of the neuron, gives rise to the current flow necessary to depolarize and trigger an action potential in the next axon region, which in turn depolarizes the axon region ahead of it. In this way the action potential, once initiated, is assured faithful, undisturbed, all-or-none propagation without decrement along the whole length of the axon, the conductile element of the neuron. These several findings and their theoretical interpretation explain most of the major manifestations of electrical excitability of nerve and muscle. In all cases examined so far, the resting and action potentials have been found to be produced by a common mechanism, ions moving down their concentration gradient as a result of the selective permeability to one or more ion species.[1]

The pharmacologists Otto Loewi and Sir Henry Dales had previously shown that transmission at several peripheral synapses is chemical and involves the release of a transmitter substance such as acetylcholine or norepinephrine. In a major advance, Fatt and Katz utilized the peripheral neuromuscular junctions of frog and crab as model systems and applied the ionic hypothesis to synaptic transmission. They found that the transmitter

substance, released by the presynaptic terminals of a neuron, produces its action on the membrane potential of the post-synaptic cell by reacting with specific receptor molecules located on its external surface. This reaction leads to an increase in the permeability of the postsynaptic cell to certain ion species. By examining both excitatory and inhibitory junctions between nerve and muscle, Fatt and Katz found that the difference between synaptic inhibition and synaptic excitation depended upon which ionic permeabilities were increased. If the transmitter increased the permeability to sodium, the resulting action was invariably excitatory, even if other ionic permeabilities (e.g., potassium) were also increased. If the transmitter increased the permeability to potassium or chloride without altering sodium permeability, the resulting action was inhibitory. These differences in synaptic actions followed from the relationship of the threshold of the nerve cell (usually —45 mV) to the equilibrium potential of the ion whose permeability was increased. Any increase in the permeability to sodium would tend to depolarize the membrane beyond the threshold (—45 mV) in the direction of the sodium-equilibrium potential (+60 mV). By contrast, any increase in permeability to potassium or chloride would push the membrane potential away from the threshold voltage for spike generation toward the equilibrium potential for potassium (—70 mV) or chloride (—60 mV). Fatt and Katz thus showed that the difference between synaptic excitation and synaptic inhibition was in the relationship of the equilibrium potential of the specific ions involved to the

threshold potential of the cell.

Subsequent work by Katz and his colleagues del Castillo and Miledi and parallel morphological studies by de Robertis and Bennett and by Palade and Paley gave rise to the current morphological and functional view of how synaptic transmission at chemical synapses occurs. Synaptic transmission takes place only at certain morphologically specialized points in the nervous system, where the presynaptic neuron and the postsynaptic cell come into appropriate apposition. Here, the generation of an action potential in the presynaptic terminal leads to the release of a chemical transmitter substance. This transmitter substance is stored in packets or vesicles, each of which is thought to contain several thousand transmitter molecules. As the action potential invades the terminals, it gives rise not only to the usual influx of sodium ions but also to an influx of calcium ions from the extracellular space. The influx of calcium into the terminal region somehow increases the likelihood of transmitter packets combining with the cellular membrane. The fusion of the vesicle membrane with the inside surface of cell membrane is thought to be an essential step for an extrusion process known as exocytosis. Following membrane fusion the membranes open briefly to the extracellular space and the vesicles rapidly empty their contents into it. After the vesicle has extruded its contents, transmitter molecules diffuse across the synaptic cleft that separates the two cells, usually two hundred to three hundred A wide. The transmitter then interacts with specific receptors in the

postsynaptic cell to produce specific permeability changes that can be either inhibitory or excitatory.

In 1951, John C. Eccles took the bold step of applying the concepts that Hodgkin, Huxley, and Katz had developed in their study of resting and action potentials of the squid giant axon, and those that Fatt and Katz had developed from study of several neuromuscular junctions. He combined these separate conceptual schemes into a synthetic view of how central nerve cells function. This advance also required a well selected model system, and Eccles chose as his experimental object the large motor nerve cells (motor neurons) of the spinal cord. He found that the resting and action potentials of central nerve cells obeyed the predictions of the ionic hypothesis and that the function of central synapses could be explained by the Fatt and Katz model for peripheral synaptic transmission. In each case the electrical changes involved an increase in permeability to one or more ion species that then moved down their concentration gradients.

In 1953, Eccles summarized the ionic hypothesis and its applicability to central nerve cells in a book entitled *The Neurophysiological Basis of Mind.* This remarkable book pointed the study of mammalian neural science in a new direction. Its major message was twofold. First, Eccles emphasized that to understand the brain requires that it be studied in terms of individual nerve cells. There are no short cuts to studying this complex computing

system. Only by applying analytic techniques that can resolve neuronal processes on a unitary cellular level can one develop a useful, realistic, and synthetic understanding of how groups of cells and, ultimately, areas of the brain work. Second, Eccles emphasized, implicitly, something that is still not sufficiently appreciated, that studying the biophysical properties of nerve cells is necessary but insufficient for understanding how the brain works. To know how people perceive and think, feel and act, and how they relate to one another as human beings, it is essential to relate cellular function to behavior.

Within a few years of Eccles' pioneering work, cellular techniques were applied to a variety of brain structures, including the neocortex, hippocampus, thalamus, and the basal ganglia. This work moved surprisingly rapidly, in part because the model of neuron function derived from the study of spinal neurons proved to be general. As a result, it was possible to move slightly beyond studies of cellular properties and to describe a number of the key features of brain circuitry. Relating cellular function to behavior has proven more difficult and has occupied much of the attention of researchers for the last two decades. One step in this behavioral direction was accomplished between 1955 and 1965, and was characterized by brilliant growth in our understanding of sensory physiology and its relation to perception. Another step has come in the period since 1965 and derives from the development of invertebrate preparations in which elementary behaviors and their modifications can be examined.

The Neuronal Mechanisms of Sensation and Perception

Feature Abstraction and Binocular Interactions in the Visual System

In the decade 1955 to 1965, single cell techniques were applied with remarkable success to an examination of various stages in the visual and the somatosensory system. From this work it became clear that our brain "sees" the world around us not as a precise replication of reality but as an abstraction accomplished by neural transformations that occur at almost every stage in the hierarchy of relays in the sensory system, from the peripheral receptors onward. These insights stem primarily from the work on the somatosensory system by Vernon Mountcastle and his colleagues at Johns Hopkins, and from the work on the visual system by Stephen Kuffler, David Hubei, and Torsten Wiesel at Harvard. (For reviews see Hubei and Mountcastle.) I will consider here only the visual system.

As early as 1942, Wade H. Marshall and Samuel Talbott had used gross electrical recording techniques to show that the receptor sheet of the retina is represented in the visual cortex in an orderly, topographical manner and that by this means the brain achieves an anatomical representation of the external world. In 1953, Stephen Kuffler applied single cell recording techniques to the visual system and carried this analysis one step further. Kuffler examined the output of the retina, the retinal ganglion cells (whose axons form the optic nerve) to see what kind of transformation of neural information occurs within

the retina itself. The retina of mammals consists of receptors, the rods, and the cones. It ends on bipolar cells that in turn synapse on retinal ganglion cells. After forming the optic nerve, the medial (nasal) fibers from the retina cross in the optic chiasma to join the contralateral-optic tract and synapse in the contralateral geniculate. The fibers from the lateral (temporal) portion of the retina continue in the ipsilateral-optic tract and synapse in the ipsilateral lateral geniculate body. Neurons from the lateral geniculate body send axons to the striate visual cortex, area seventeen. Cells in this area project to the peristriate cortical regions, areas eighteen and nineteen. Cells from these two areas in turn project to the inferotemporal association cortex. The cells in the visual system are spontaneously active and fire occasional action potentials in the absence of visual stimulation. Kuffler found that the spontaneous activity of the retinal ganglion cells could be modulated by small spots of light projected onto the surface of the retina. He described the response characteristics of ganglion cells in terms of the *receptive field* properties of single cells. The receptive field of a cell (in the visual system) refers to the area of the retina that, upon stimulation with light, alters the firing pattern of a single cell. In anatomical terms, the receptive field of a retinal ganglion cell thus describes all the receptor and subsequent cells in the retina that converge upon and influence the firing pattern of a single ganglion cell. Kuffler discovered that the receptive fields of the retinal ganglion cells were round in shape and had distinct concentric excitatory and inhibitory zones. In

the region of the macula, where most of these studies were done, the size of the receptive fields was small, ranging from 4 to 8° of arc in diameter. On the basis of the architecture of their receptive field properties, Kuffler divided all cells into two groups. One class of cells had a central excitatory zone and a surrounding inhibitory region ("on" center cells) whereas the other class of cells had an inhibitory ("off") central region and an excitatory surround region (off center cells). For example, cells with an on center receptive field responded very briskly to small spots of light aimed at the center of the receptive field but were inhibited if light impinged on the annular surround region. The most effective excitatory stimulus for a cell with an on center receptive field was therefore a circular spot covering the entire central region of the field. As the stimulus was enlarged to include some of the annular surround region, the effectiveness of the stimulus was reduced because of the mutual antagonism between the center and the surround region. The most effective inhibitory stimulus was a doughnut of light on the surround region. By contrast, cells with an off center receptive field were inhibited by light on the central region and excited by light on the surround region. Kuffler thus found that as early in the visual pathway as the retinal ganglion cells a significant amount of abstraction of sensory input had already occurred. The retinal ganglion cells did not respond primarily to light intensity but to the contrast between light and dark.

This analysis was carried further by David Hubei and Torsten Wiesel,

who analyzed cells in the lateral geniculate and in the visual (striate) cortex (area seventeen). In the lateral geniculate cells, receptive field properties were very similar to the retinal ganglion cells. However, in the cortex Hubei and Wiesel found that the response properties of the cells were very much more complicated. Cortical cells could no longer be effectively stimulated by the circular-shaped stimuli that proved so effective in the retina and in the lateral geniculate. To be effective a stimulus had to have linear properties; the best stimuli were lines, bars, rectangles, or squares. On the basis of receptive field properties, Hubei and Wiesel grouped cortical cells into two classes: simple and complex. Cortical cells with simple receptive fields had discrete rectangular excitatory and inhibitory zones. A typical receptive field might have a central rectangular excitatory area with its long axis running from twelve to six o'clock, flanked on each side by similar shaped inhibitory areas. For this type of cortical cell, the most effective excitatory stimulus is a bar of light with a specific axis of orientation—in this case from twelve o'clock to six o'clock—projected on the central excitatory area of the receptive field. Since this rectangular zone is framed by two rectangular inhibitory areas the most effective stimulus for inhibition is one that stimulated one or both of the two flanking inhibitory zones. A horizontal or oblique bar of light would stimulate both excitatory and inhibitory areas and would therefore be relatively ineffective. Thus a stimulus that is highly effective if projected vertically onto a given area of retina so as to be on target for the excitatory zone would

become ineffective if held horizontally or obliquely. Other cells had similar receptive field shapes but different axes of orientation (vertical or oblique). For a cell with an oblique field the most effective stimulus would be a bar of light running from ten o'clock to four o'clock or from two o'clock to eight o'clock.

The most interesting feature of the simple cortical cells is that they are much more particular in their stimulus requirement than the retinal ganglion or the geniculate cells. For a stimulus to be effective for a retinal ganglion or a geniculate cell, it only has to have the proper shape, in general circular, and the proper retinal position so as to activate appropriate receptors in the retina. But in the cortex, in addition to shape (now generally rectangular) and retinal position, the effective stimulus has also to have a proper axis of orientation. Slight changes in the axis of orientation of the light-bar stimulus would make an effective stimulus ineffective. Thus the simple cortical cells not only have to represent all retinal positions and several shapes (lines, bars, rectangles) but also for each shape they have to represent all axes of orientation. These findings provide some insight as to why the visual cortex (or any cortex) needs so many cells for its normal functions. Cells are required to represent every retinal area in all axes of orientation so as to abstract the information presented to the cortex.

Another feature distinguishes striate cortical cells from geniculate cells.

Geniculate cells only respond to stimulation of one or the other eye. In area seventeen of the cortex one begins to find cells responding to both eyes. These cells provide the neural basis for binocular fusion, essential for the stereoscopic vision of higher animals.

Hubel and Wiesel suggested that the simplest explanation for the response properties of a cortical cell with a simple receptive field was that they received innervation from a set of geniculate cells that had appropriate on center and off center properties and appropriate retinal positions.

Hubel and Wiesel also found a group of cells in the striate cortex with complex receptive field properties. For these cells the effective stimuli were also linear and had to have a correct axis of orientation, but the receptive fields of these cells did not have clearly delineated excitatory and inhibitory zones so that the exact position of the stimulus within the receptor field was not important. For example, a cell might have a fairly large rectangular receptive field (10° by 15° of arc) and respond to a vertical bar oriented at twelve o'clock to six o'clock and placed anywhere in its field. But this cell would not respond if the bar were tilted obliquely or horizontally. Hubei and Wiesel suggested that the simplest explanation for the generation of a complex receptive field was that these cells received excitatory projections from a set of simple cortical cells with similar receptive field positions and identical axes of orientation. In support of this idea is the finding that the

visual cortex was organized into a series of narrow vertical columns, two cells to fifty cells wide, running from the surface of the cortex to the white matter. In a given column, cells had roughly similar receptive field positions and generally similar receptive field properties. Any one column contained both simple and complex cells and the properties of the simple cells in that column were such that they could account for the properties of the complex cells in the same column if one supposed that the simple cells of a column converged upon the complex ones. This finding not only provides some indirect support for the Hubei and Wiesel hierarchical scheme but also provides insight into the function of cortical columns. The columns seem to serve as elementary units of cortical organization designed both to bring cells together so that they can be appropriately interconnected and to generate from their interconnections the properties needed for cells with higher-order receptive fields.

Cells of area seventeen project to the peristriate cortex (areas eighteen and nineteen) and in these areas the visual message undergoes still further processing. Cells in areas eighteen and nineteen have more sophisticated properties than those of area seventeen. Hubei and Wiesel refer to these properties as hypercomplex. Cells with hypercomplex properties have even more specific stimulus requirements and some respond only to a highly selective geometrical form such as a corner: two lines that meet at 90° to each other. As the angle between the two lines is changed from 90 to 180°, the

stimulus becomes progressively less effective. As is area seventeen, areas eighteen and nineteen are organized into vertical columns that run from the surface of the cortex to the white matter. A given column contains cells with both complex and hypercomplex properties and, again, the properties of the complex cells are just what are needed to account for the hypercomplex ones, if one assumes that the hypercomplex cells receive their input from the complex cells in their own column. For example, in some columns the hypercomplex cells respond to a right angle whose base runs from three to nine o'clock. These columns contained complex cells that have two (but only two) types of axes of orientation. Some cells had an axis of orientation running from twelve to six o'clock whereas others had one running from three to nine o'clock.

From these studies Hubei and Wiesel have suggested a model for understanding how the cortex abstracts essential features from sensory stimuli. According to this scheme, the configuration of the effective stimulus that is necessary to excite (or inhibit) cells at various levels in the visual system varies. In the retina and in subsequent stages of the visual system, cells do not respond effectively to diffuse light but respond primarily to borders between light and darkness. Later in the system similar contrast detection is used in the analysis of lines. The hypercomplex cells respond primarily not to the linear properties of the stimulus but to changes in the direction of a line such as angles and corners. Thus hypercomplex cells may

be serving as angle and corner (curvature) detectors indicating changes in the direction of a line. In higher cortical areas the linear aspects of a stimulus may be analyzed by measuring changes in its contour much as the light intensity for stimulus is analyzed at lower levels by measuring contrast between light and dark.

The studies of Hubei and Wiesel also suggest a function for the regional subdivisions of the visual system: the retina, the lateral geniculate, striate cortex (area seventeen), and the peristriate cortex (areas eighteen and nineteen). Each of these areas accomplishes one or more specific transformations of neural activity, and in each the transformations seem to occur within specific columnar systems that abstract some new features of the stimulus. In area seventeen the quality that is abstracted is receptive field orientation whereas in areas eighteen and nineteen it is angle and contour detection. Hubei and Wiesel propose that complex and hypercomplex receptive fields are the early building blocks of perception.

What occurs at a more advanced relay stop, the inferotemporal cortex? The inferotemporal cortex receives afferent input from the peristriate areas eighteen and nineteen as well as from the pulvinar region of the thalamus. Both of these structures are known to respond to visual stimuli. The available behavioral data (see Gross) indicate that lesions of the inferotemporal cortex produce a severe impairment in the learning of visual discrimination, but do

not affect visual acuity. At Princeton Charles Gross has recently started to study the properties of neurons in the inferotemporal cortex of the monkey and found that they respond only to visual and not to other sensory stimulation. The receptive fields of units in the inferotemporal cortex were unusually large. Many were over 30° by 30° of arc in size. However, finding the effective stimulus for altering the spontaneous firing rate of these cells was very difficult, much more difficult than in the striate or peristriate cortex. Many cells showed a waning of response with repeated stimulation and it was often necessary to use stimuli separated by several seconds or more to get full recovery. Some of the cells encountered had the characteristics of the complex and hypercomplex units of the striate and peristriate cortex, but others had more unusual properties. By merely confining the stimulus to bars, edges, rectangles, and circles, Gross often was unable to describe the best stimulus for each unit. There were several cells that responded strongly to more complicated figures. Most striking were some units that responded weakly to dark rectangles but much better to a cutout of a monkey's hand: the more the stimulus resembled the hand, the more strongly the cell responded to it.

To summarize, the principle that emerges from the work of Kuffler, of Hubei and Wiesel, and of Gross is one of a series of hierarchical levels or stages in which cells, at each level, are converged upon by cells from the next lower levels. At each level cells abstract progressively more information,

about the visual dimension of the world and its meaning to the animal, than at the preceding level. From this work we can begin to get an idea of the perceptual meaning of neural activity in the visual system. A retinal ganglion surveys the activity of bipolar cells that survey a group of receptors. A train of action potentials in a retinal ganglion cell signals that a spot of light is shining upon a particular part of the retina. The geniculate cell surveys a group of retinal ganglion cells and activity in the geniculate cell signals much the same. A simple cortical cell surveys a population of geniculate cells and the firing of a single cell signals that a bar of light is shining in the retina. These cells no longer signal just position but also a new abstraction, the orientation of the stimulus with respect to vertical or horizontal axis. The complex cell surveys simple cells and their activity means a stimulus with an axis of orientation without specific commitment to positions within the receptive field. The hypercomplex cells survey the complex ones and the activity of hypercomplex cells means a change in the axis of orientation, an angle or corner. Out of these kinds of transformations the brain can abstract more complex geometrical shapes and in the inferotemporal cortex (where cells receive input from both hypercomplex cells and thalamic cells) the brain seems to begin to endow these shapes with further meaning. The most striking aspect of this hierarchical processing is feature detection. Successive hierarchies or neural transformation help to analyze two-dimensional retinal space so as to represent simple aspects of light contrast and shape.

But an unresolved question that is now receiving increasing attention is, how far can this hierarchy go? Is there a special super-complex cell or cell group on top of the hierarchical processing for each familiar face? Is there a group of cells that observes the hyper complex cells and makes one aware of the total pattern? And if so, is there a still higher group in the hierarchy that looks at combinations of complex patterns as these enter our awareness? There may indeed be other high-ordered cells combining the computational results of the inferotemporal—peristriate—striate cortices to produce even more elaborate abstractions. However, to discern the relatively simple features we have so far considered has already required an enormous amount of visual brain. It would appear curious to attribute progressively more important processing to a relatively smaller group of cells and ask them to do this incredibly complex abstraction. An alternative would be that at higher levels the mechanism of transformation changes, so that single units no longer serve to represent feature states (see Harmon). To represent a familiar face or a landscape may require simultaneous combined states of a very large number of cells in the inferotemporal—peristriate—striate cortices. At this higher level of representation many cells are likely to be involved and their simultaneous signals may serve as the feature detector. The states of the parts taken separately may not represent the whole; rather it is the relation among them that is important. Harmon makes an analogy with the individual silver halide grains of a photograph: these do not represent the photograph of a

face, but the ensemble of grains does. Thus a major question for future research in this area revolves around the “read out” of the abstracting process of the visual system. How do we ultimately perceive form? Is this information read out by a progressively smaller group of cells that sit progressively “higher” in a hierarchical system so that in the end one recognizes a face by the firing of a particular small set of feature detector cells that perceives as unique that particular face? Or does the hierarchical nature of the processing disappear and abstraction result from different combinations of neural populations firing in a certain temporal relation to each other? Recent work by Vernon Mountcastle and by W. A. Spencer indicates that in the somatosensory system the second process seems to be important for perception of tactile sensation. Mountcastle’s work has indicated the need to reconstruct the population activity of neurons to understand normal tactile sensation. Iwamura, Gardner and Spencer show how perceptual distortion, created by certain tactile illusions, can best be explained by changes in the contours and spatial gradients of the population of neurons activated by the tactile stimuli. My own guess is that work in the visual system will also tend to move in this direction now.

In the next two sections, I will restrict myself primarily to the early stages of visual transformation where detailed knowledge is available, and illustrate how this understanding about the lower stages of visual function can provide insights into how abnormal environmental experiences can

disturb the functioning of connections. But first let us briefly consider the formation of connections during embryonic development.

The Development of Connections in the Visual System

Much of our understanding of the development of connections in the visual system derives from the experiments of Roger Sperry on the visual system of lower vertebrates: frogs, salamanders, and goldfish. These animals are useful objects for embryo-logical investigation because, unlike higher vertebrates, cold-blooded vertebrates have remarkable regenerative capacities, not only in their larval states but also as adults. Thus, for example, Sperry found that he could cut an optic nerve in the frog, thereby separating the eye from the brain, place the eye back in the socket and still have regeneration of the optic nerve occur. These regenerated animals have complete restoration of visual function. Despite the formation of a scar, the newly regenerating fibers seem to find their way back to appropriate cells in the brain and to establish the connection necessary for normal vision. Sperry studied this regenerative process further and found that outgoing fibers from the retina had multiple opportunities to make contact with a variety of nerve cells at various points as well as with the glial cells and capillaries that they encountered along their path. Despite these many opportunities for synapse formation the outgoing fibers connected only with the cells to which they were initially connected. Incorrect zones were consistently bypassed and left

empty. Only when an outgoing nerve fiber reached the part of the brain where it had originally made connection did synapse formation occur. This specificity in the regeneration experiments suggested to Sperry that the presynaptic terminal of the optic nerve fibers, and the specific neurons they innervate, must have a complementary specificity so that the appropriate pre- and postsynaptic elements of the synapse are attracted to each other and maintained (for an alternative view see Gaze and Keating). Sperry has done additional experiments that suggest that in lower vertebrates the development of appropriate synapses is due to a preprogrammed affinity between neurons that is fully present at birth. Synapse formation is not due to the pattern of impulses or to learning. For example, Sperry has cut the optic nerve in frogs, rotated the eye ball on its optic axis 180°, and found that regeneration still occurs. But now the animal's visual responses are inverted by 1800. When such an animal reaches for an object placed in its upper temporal visual field, it will invariably reach toward its lower nasal field. These maladaptive responses persist indefinitely without correction. These findings seem to indicate that despite their current inappropriateness the optic nerve fibers of the rotated eye grew back and remained connected to the central cells initially appropriate for the eye when it was still right side up. Failure to re-educate the visual system suggests that the neural connections in the optic system of lower vertebrates seem to be laid down in a preordained manner, early in development, and these connections cannot be

altered later even if they are nonadaptive. Jacobson has recently shown that retinal cells are specified to hook up to definite central areas (in the tectum) before the axons of the retinal ganglion cells even begin to grow out toward the tectum.

Impressed with the importance of the detailed wiring necessary for the response specificity that they found in cortical cells, Hubei and Wiesel addressed themselves to the development of connections in the mammalian visual system. They wanted to know whether hierarchical patterns of response to spots and bars of light that they found at different levels of the visual system in the adult animal were present at birth, prior to the animal's being exposed to pattern light. Hubei and Wiesel examined the major levels of the visual system in newborn kittens, and found that at each level the receptive field organization of the adult cat was present, at least to some degree. Although the results here are not completely clear, Hubei and Wiesel suggest that even in mammals the basic neuronal wiring necessary for complex perceptual behavior is built into the nervous system under genetic control. Newborn animals that have not been exposed to light show binocular interaction and some of their cells have specific axes of orientation.

These studies provided an interesting framework for examining two very different questions: (1) how is prewired neural architecture altered in early critical stages of development by abnormal sensory experiences and (2)

how is this prewired nervous system affected in the adult by normal learning experiences? As yet these questions have only been examined in a few model systems. For the first question we are fortunate, however, in having experiments in the visual system of the cat on which there is already much useful information.

The Effects of Light Deprivation on the Functional Interconnections of Cells in the Visual System

Several clinical studies (see Senden) suggest that people born with congenital cataracts that are not removed until maturity show permanent perceptual abnormalities. Such people may learn to recognize colors readily but show only the most rudimentary perception of visual pattern. Some require months to differentiate a square from a circle and have to count corners to distinguish a square from a triangle. Even after years of training they may never acquire the visual perception of people who have normal vision from infancy. Some of them may never learn to recognize people whom they see daily, on the basis of visual clues alone.

These experiments have been carried an important step further by the imaginative research on chimpanzees by Austin Riesen. Riesen found that at the age of four to seven months a normal chimpanzee has excellent visual perception and can readily learn to make selective responses to new visual stimuli. He will recognize those who care for him, welcoming their approach.

He will fear and avoid strangers. A chimpanzee that has been reared in darkness from birth to age four to seven months behaves completely differently. These animals have a great deal of difficulty in learning to discriminate even simple objects. Weeks after being returned to a normal environment they cannot discriminate between strangers and friends and show no sign of curiosity and fear.

Riesen then brought up chimpanzees in an unbroken field of light, without the contours of a normal visual environment, by enclosing their heads in translucent plastic domes. These animals were just as blind as the animals reared in darkness. Thus it is not the absence of light but the absence of visual patterns that produces such devastating defects in visual perception. What emerges from Riesen's study is that the development of normal visual perception, the mere ability to distinguish between objects in the visual world, requires a prolonged early period of exposure to patterned visual stimulation.

The cellular neuronal mechanism of this important paradigm has now been probed in a number of studies (see Hubei). In the first of these studies, Wiesel and Hubei examined the responses of newborn kittens who had one eyelid sutured closed so that the eye was not exposed to patterned vision. If the lid was kept closed for three months following birth, a naive animal became permanently blind in that eye. In the normal brain most cells in the

visual cortex respond to stimuli presented to either of the two eyes. In the cortex of a monocularly deprived animal, cells responded readily to appropriate stimuli presented to the normal eye, but no cell could be successfully stimulated from the eye that had been sutured closed. Closing the eyelid of an adult cat for a comparable period produced no effect.

The earlier experiments on newborn kittens suggested that the basic connections between the cells in the retina and the brain had been established at birth. Failure to find responses in the brain to stimulation of the eye deprived of patterned light suggests that something had happened in the visual system whereby previously interconnected neurons were now no longer in functional contact. This suggested to Hubei and Wiesel that, during this critical phase of development, immature synapses in the cortex need for their normal maintenance, stimulation via patterned light on the retina. Without exposure to patterned light the preexisting connections can be disrupted.

This theoretical notion has now been supported in a number of elegant experiments that involved more subtle alterations of the visual environment. In one of these, Hubei and Wiesel produced an artificial squint of the right eye by cutting an eye muscle, the right medial rectus, at the time of normal eye opening. These animals showed no behavioral defects three months later. When their visual cortices were examined, cells in the striate cortex still

responded normally to stimulation of each eye. Binocular interaction was, however, absent. Normally 80 percent of cells in the cortex respond to stimulation of homologus spots in each of the two retinas. In animals with squint, only 20 percent of cells could be influenced from both eyes. A similar result was obtained when an opaque contact lens was placed on each eye on alternate days. These experiments suggest that the integrity of certain striate cortical pathways may depend not only on patterned light but also on the normal, presumably synchronous, presentation of patterned light to both eyes. The integrity of the striate cortical pathways necessary for binocular interaction seems to depend on the synchronous interrelation between the activity of the two eyes.

These studies provide a superb paradigm for relating cellular neurophysiology to psychology. Innumerable clinical studies have illustrated the devastating effect of early social deprivation on the social, intellectual, and emotional development of children. This work has now been extended into an animal model by the Harlows who have documented the importance of maternal and peer interaction for the normal social and sexual development of infant monkeys. The Harlows have found that the first year of life is a critical period for simian social and sexual development. Isolation for more than six months during the first year has permanent and devastating effects. The studies of Hubei and Wiesel provide an extension of this approach to the cellular level. These studies begin to reveal the effect of the interaction

between developmental processes and environmental stimulation on the formation of connections during the early stages of maturation. Developmental processes carry the potentiality for forming completely correct connections between the eye and the brain. But this potentiality can be disrupted by abnormal environmental stimulation. During this critical phase a normal pattern of environmental stimulation is essential for the maintenance and further maturation of preexisting connections. By developing more extensive animal models, using other modalities and progressively more complex social deprivation, 011c may begin to get some clues into the nature of the cellular and perhaps even the molecular mechanisms that underlie the destructive influence of early childhood deprivation.

Studies of sensory deprivation thus provide insight into the effect of normal and abnormal environmental stimuli on cellular functioning of the brain. They place Heinz Hartmann's concept of an average expectable environment in a cellular biological perspective. But so far we have only considered studies involving profound changes in an animal's perceptive environment. We are, however, all constantly exposed to less traumatic stimuli that nonetheless affect behavior for long periods of time. How are these changes accomplished? Do they leave an obvious imprint on the brain that can be examined on the cellular level?

To answer questions of this kind neural scientists are beginning to examine the neuronal mechanisms of simple types of learning. These are the best experimental models for environmentally produced alterations in behavior. We have seen in the previous section that one can use simple instances of sensory deprivation to develop model systems for studying the effects of social isolation and its consequences for the developing organism. In the next section we will consider the analysis of simple behaviors and their modifications so as to gain insight into the kinds of changes that may occur in the brain, as a result of day-to-day behavioral experiences. These studies are useful in understanding how the normal acquisition of behavioral patterns occurs. They may also soon provide some insight about the acquisition of abnormal behavior patterns.

Cellular Neurophysiological Studies of Behavioral Modifications

Like the study of perception, the neurophysiological study of learning requires a detailed knowledge of the total neural circuit that mediates the behavioral response being examined. This requirement is difficult to meet in the intact brain of a higher animal because it contains an enormous number of cells—a billion—forming an even larger number of interconnections. In addition, the behavior of vertebrates is often highly complex. A way around these problems is to study simple behaviors that are controlled by numerically reduced neural populations, such as isolated portions of the

vertebrate nervous system or invertebrate ganglia. Selecting an appropriately advantageous preparation for solving a particular problem is a common strategy in biology, but its application to psychology has not been fully explored. The most consistent progress comes from studies of two simple behavioral modifications, habituation and dishabituation, in two simple preparations: the spinal cord of the cat and the abdominal ganglion of the marine mollusk *Aplysia californica.*

Habituation, sometimes considered the most elementary form of learning, is a decrease in a behavioral response that occurs when an initially novel stimulus is presented repeatedly.

When a sudden noise is heard for the first time, one's attention is immediately drawn to it and a number of concomitant changes may occur—e.g., one's heart rate and respiratory rate may increase. However, if the same noise is repeated, one's attention and one's bodily responses gradually diminish. As a result of habituation one can become accustomed to initially distracting sounds and work effectively even in a noisy environment. One also becomes habituated to the clothes one wears and to one's own bodily sensations. These enter our awareness rarely, in special circumstances. In this sense habituation is learning to ignore recurrent external or internal stimuli that have lost novelty or meaning. Habituation develops not only in reflex response systems but in instinctive response systems as well. For example, a

fish will defend his territory against a nonspecific intruder. Upon repeated exposure to the intruder, however, the fish will gradually suppress his aggressive behavior, a maneuver permitting him to respond more effectively to other stimuli, such as sexual ones, that are more necessary for the survival of his species. Deliberate habituation of emotional responses to anxiety-provoking stimuli is used clinically as part of behavior therapy.

Besides being important in its own right, habituation is also frequently involved in more complex learning that consists not only in acquiring new responses but also in learning to reduce errors by eliminating incorrect responses to inappropriate stimuli. Once a response is habituated, two processes can lead to its restoration: (1) *spontaneous recovery* that occurs as a result of withholding the stimulus to which the animal has habituated, and (2) *dishabituation,* a restoration of the response that occurs as a result of changing the stimulus pattern, for example, by presenting another stronger stimulus to another pathway.

Habituation, recovery and dishabituation have been demonstrated for a wide variety of behavioral responses in all animals examined including man. Their general occurrence suggests that neuronal mechanisms underlying habituation may also prove to be quite general.

Flexion Withdrawal in the Cat

The first neural analysis of habituation was undertaken in the isolated spinal cord of the cat. The vertebrate spinal cord mediates the reflex responses underlying posture and locomotion. In the course of analyzing their neural mechanisms, Charles Sherrington found that certain reflex responses, such as the flexion withdrawal of a limb to stimulation of the skin, decreased with repeated stimulation and recovered only after many seconds of rest. Sherrington had the great insight to appreciate that neural reactions within the spinal cord differ from those in the peripheral nerves because of the numerous synaptic connections within the cord. He therefore attributed the decreased reflex responsiveness of the withdrawal reflex to a functional decrease (which he called “fatigue”) at the specific set of synapses through which the motor neuron was repeatedly activated. Thus, as early as 1906, Sherrington suggested that a change at central synapses could underlie response decrement.

Sherrington was able to show that the reflex decrement was central and not due to fatigue of the muscles or the sensory receptors, but he was not capable of testing his intriguing synaptic hypothesis because of the limitation of the neurophysiological techniques available to him. This problem was subsequently reinvestigated by Prosser and Hunter and more recently by Spencer, Thompson, and Neilson. They found that the habituated flexion withdrawal can be restored to full size (dishabituation) by applying a strong novel stimulus to another part of the skin. Indeed, Spencer et al. found that

dishabituation is not simply a transient abolition of habituation but an independent facilitatory process superimposed upon habituation. Spencer and his colleagues studied the features of spinal-reflex habituation in some detail and found that these resembled the habituation of more complex behavioral responses. They also began the cellular analysis of habituation. By recording intracellularly from motor neurons, they showed that response decrement did not involve a change in the properties of the motor neurons but only in the synaptic impingement upon them. However, the central synaptic pathways of the flexion withdrawal reflex in the cat are complex, involving many as yet unspecified connections through interneurons.

Gill Withdrawal in Aplysia

Further analysis of habituation required a still simpler system, one in which the behavioral response could be reduced to one or more monosynaptic systems. In search of such systems for behavioral studies, a number of investigators have been attracted to invertebrate preparations. These animals' nervous systems contain relatively few cells, a property that simplifies neuronal analysis of behavior. The nervous system of opisthobranch mollusks is particularly advantageous because it contains cells that are unusually large (almost 1 mm in diameter) and therefore easy to study with intracellular microelectrodes. The most detailed behavioral work has been carried out on a marine mollusk, *Aplysia.* The central nervous

system of *Aplysia* contains about twenty thousand cells. An individual ganglion such as the abdominal ganglion contains only about two thousand cells yet is capable of generating a number of biologically significant behaviors.

Working on *Aplysia,* Kupfermann and Kandel studied a defensive withdrawal response that is in some ways analogous to the flexion withdrawal response in the cat. *Aplysia* has a gill, an external respiratory organ, analogous to the lung in man. The gill is partially covered by the mantle shelf, which contains this animal's residual shell. When either the mantle shelf or the anal siphon or spout (a fleshy continuation of the mantle shelf) is touched, the siphon contracts and the gill withdraws into the cavity underneath the mantle shelf. The defensive purpose of this reflex is clear. It protects the gill, a vital and delicate organ, from possible damage. Gill withdrawal is thus analogous to the defensive flexion withdrawal of a limb in the cat, or the withdrawal of a man's hand from a hot or potentially damaging object. As is the case for these other defensive responses, the gill withdrawal response habituates when repeatedly elicited by a weak or non-noxious stimulus.

Habituation in vertebrates is characterized by nine parametric features. Seven of these features have been examined in the gill withdrawal response in *Aplysia* by Pinsker et al. and found to be similar to habituation in mammals.

These features include: (1) response decrement, typically a negative exponential function of the number of stimulus presentations; (2) recovery with rest; (3) dishabituation; (4) habituation of the dishabituatory stimulus with repeated presentations; (5) greater habituation with weak rather than with strong stimuli; (6) greater habituation with short rather than long stimulus intervals, and (7) greater habituation with repeated periods of habituation and recovery.

The existence of this satisfactory fit between short-term habituation in *Aplysia* and in mammals made it interesting to analyze the neural circuitry of this behavior. This analysis was a prerequisite for examining the functional modifications in the neural circuit that produce the behavioral modifications.

To analyze this reflex, Kupfermann and Kandel developed a semi-intact preparation in which different neurons within the abdominal ganglion could be impaled with double-barrel microelectrodes for recording and direct stimulation and their function related to behavior. By firing different cells intracellularly and observing the movements of the external organs of the mantle cavity, Kupfermann, Carew and Kandel found ten motor cells that produced contractions of the gill, the siphon or the mantle shelf, the organs involved in the withdrawal response. Five of the ten motor cells produced movements limited to the gill. Four cells produced movement of the siphon and one cell produced movement of the gill, the siphon and the mantle shelf.

Thus the motor component of this reflex consists of individual elements with both a restricted and overlapping distribution. This motor organization is highly redundant as are other motor systems described in vertebrates and in invertebrates. These ten cells are unique individuals. They are so characteristic in their location, in their electrophysiological properties, and in their motor function that they can be repeatedly recognized and examined from animal to animal. These cells and others like them have been termed "identified" cells; they are often referred to by specific numbers and letters. Uniquely identified cells have not been found to control other behaviors in *Aplysia* as well as in other animals including some lower vertebrates.

Kupfermann and Kandel next analyzed the sensory component of the reflex. They mapped the tactile sensory receptive field of these motor cells and found that when the external organs of the mantle cavity were mechanically stimulated, causing the gill to withdraw, all five motor cells received large excitatory postsynaptic potentials producing a brisk repetitive spike discharge. The receptive field of these five motor cells involved the mantle shelf and siphon and was identical to that of the defensive withdrawal reflex. The excitatory input from this receptive field is in part monosynaptic and in part mediated by interneurons. Although the population of sensory neurons that mediate this reflex (consisting of about twenty-five sensory neurons and three different interneurons) is larger than the motor populations, it would appear that the sensory neurons and interneurons may

also be invariant. Byrne, Castellucci, and Kandel have found that at least some sensory cells have invariant receptive fields and make invariant central connections to both interneurons and motor neurons.

These findings, and similar ones emerging from the study of reflex systems in the leech and the crayfish, support Sperry's idea of the specificity of neuronal interconnections. In vertebrates this specificity can only be examined on the level of groups of cells. In invertebrates, where the resolution is greater because of the reduced number of cells and the ability to identify unique cells, one can ask exactly *how* unique are the neurons and how precise are the interconnections between neurons that mediate a given behavior. From the few studies available, it would appear that for simple behaviors the neural wiring is surprisingly precise and invariant. This finding raises an interesting paradox. Given this constancy of cells and interconnections, how does behavior become modified? How is one to reconcile this apparent invariance of the wiring with known malleability of behavior? Are there unspecified cells—learning cells—that are set aside as "blanks" only to be called upon by the learning process and to be superimposed on the basic wiring of the behavior? Do behavioral modifications involve the outgrowth of new cells or new connections, or do they involve some functional change in the properties of the preexisting neurons and their interconnections?

To examine this question, Kupfermann et al. studied the changes in the neural circuit that accompany habituation and dishabituation of the gill withdrawal reflex. They found that habituation, recovery, and dishabituation resulted from a functional change within the central nervous system. Thus, the excitatory postsynaptic potential, produced in the gill motor neurons by tactile stimulation of the skin, underwent characteristic changes that were causally related to habituation, to recovery, and to dishabituation. When a tactile stimulus was repeated so as to produce behavioral habituation, the excitatory postsynaptic potential in the gill motor neuron gradually decreased in size, and the amount and frequency of the evoked spike activity produced by the synaptic potential decreased correspondingly. With recovery of reflex responsiveness, produced either by rest or by a dishabituatory stimulus, there was an increase of the excitatory postsynaptic potential and a corresponding increase in spike activity.

In a more detailed examination of the mechanism underlying the change in the synaptic potential, Castellucci et al. radically simplified the sensory component of the reflex pathway and examined individual sensory elements in isolation. They recorded simultaneously from one of the sensory neurons and from a gill motor neuron so as to reduce the gill reflex to its most elementary monosynaptic components and examined each element in turn as well as the interaction between them. Stimulation of one of the mechanoreceptor sensory neurons produced fairly large elementary

excitatory synaptic potentials in the motor neuron. But repeated stimulation, at rates that produced habituation, led to a dramatic decrease in the amplitude of the excitatory postsynaptic potential; rest resulted in recovery. The synaptic potential produced by direct stimulation of the sensory neuron sometimes diminished so markedly that after a few stimuli it was barely visible. Similar changes have now been found in the connections between sensory neurons and several classes of interneurons. These data suggested that habituation is due to a change in excitatory synaptic efficacy of the central connections of the sensory neuron both to interneurons and motor neurons. This reduced synaptic effectiveness results from a decrease in the amount of transmitter released per unit impulse.

In the behavioral response of the intact animal, dishabituation occurs following the presentation of a strong stimulus to the animal's head or tail. On the cellular level, dishabituation is associated with a facilitation of the previously decreased effectiveness of the central excitatory synaptic connections of the sensory neurons. Thus, repetitive stimulation of tactile receptors of the siphon leads to habituation of the gill withdrawal reflex by producing a functional (plastic) decrease in the effectiveness of preexisting synapses made by branches of the sensory neurons (from the siphon) on the gill motor neurons and interneurons. Stimulation of the head leads to dishabituation of the gill withdrawal reflex by producing facilitation at the same set of synapses. Habituation is thus homosynaptic, involving a

functional change in the synapses of the stimulated (habituated) pathway. On the other hand, dishabituation is heterosynaptic, involving a functional change in synapses of the habituated pathway (from the siphon) as a result of activity in a parallel pathway (the sensory pathways from the head or the tail). Castellucci et al. have proposed a model that postulates that both habituation and dishabituation involve a common locus, a change in the synaptic terminals of the sensory neuron. These terminals are influenced by habituation and dishabituation so as to decrease or increase the amount of transmitter substance released per action potential.

An examination of the functional properties of the wiring diagram of a simple behavior undergoing habituation and dishabituation thus reveals that nonsynaptic properties of the neurons are not altered nor is there any fundamental change in their pattern of interconnections. No new connections appeared to be formed and no existing connections disappeared. What happened was that the functional effectiveness of certain connections was changed by the training procedure. The central synapses, made by various branches of the sensory neurons on the motor and the interneurons, are endowed with remarkable plastic properties, so that transmission across these synapses was greatly depressed during habituation and recovered only after a rest of many minutes. But functional effectiveness could be returned immediately as a result of the presentation of a dishabituatory stimulus. These results are therefore consistent with the idea that genetic and

developmental processes determine the properties of individual cells and the anatomical interconnections between cells. These processes leave unspecified, however, the degree of effectiveness of certain of these connections. Environmental factors, such as learning, produce their modifications in behavior by playing upon these "plastic" potentialities of neurons and their synapses.

Cellular studies thus lead one to think of three ontogenetic stages of synaptic modification. The first stage, synapse formation, occurs primarily in the developing organism and is under genetic control. The second stage, maintenance of newly developed synapses, occurs during the critical early period of development and requires an appropriate pattern of environmental stimulation. The third stage, the regulation of the transient and long-term effectiveness of synapses, occurs throughout later life, and is determined by day-to-day behavioral experience. One of the implications of this view is that the potentialities for all behaviors of which man is capable are actually built into his brain under genetic control. What learning does is to alter the effectiveness of certain anatomically preexisting pathways, thereby leading to the expression of new patterns of behavior.

A cellular strategy can also be used to examine the biochemical mechanisms of behavioral modifications. Once the behavioral modification has been specified in cellular terms, it is possible to bring biochemical

techniques to bear on the further analysis of the molecular mechanisms. This has been undertaken on the gill withdrawal response by Schwartz, Castellucci, and Kandel. They have found that inhibition of protein synthesis for several hours does not interfere with either the acquisition or the retention of short-term habituation. This indicates that whatever the molecular mechanisms of short-term dishabituation and habituation may be, and we are still far from knowing them, they do not depend on the synthesis of new protein or on proteins that have remarkably fast turnover rates. This result is consistent with experiments on higher forms (see Chapter 4) that indicate new protein synthesis is not required for short-term learning.

The Mechanistic Relationships between Different Behavioral Modifications

Simple preparations are useful not only for examining the mechanisms of specific behavioral modification; they can also be used to examine the relationships between behavioral modifications. Previously these relationships could only be examined behaviorally, on a phenomenological level. I will consider here only two brief examples: (1) the relationship of habituation to dishabituation, and (2) the relationship of short-term to long-term behavioral modifications.

Pavlov, who discovered habituation, and many subsequent psychologists have thought that dishabituation is merely a removal of

habituation. As I have indicated above, the first new insight into this problem was provided by Spencer, Thompson, and Neilson. They suggested that dishabituation of the flexion withdrawal response is an independent facilitatory process superimposed on habituation. Carew, Castellucci, and Kandel have also examined these interrelationships, using the gill withdrawal reflex in *Aplysia.* They used two independent pathways (siphon and mantle shelf) to elicit gill withdrawal and found that habituation of one pathway does not generalize to the other pathway. If one pathway (siphon skin) is repeatedly stimulated so that reflex responsiveness to stimulation of that pathway is habituated, the reflex responsiveness of the other pathway (mantle shelf) is unaffected. Carew et al. then habituated one pathway but not the other and examined the effects of a common dishabituatory stimulus on the two pathways. They found that whereas habituation was limited only to the stimulated pathway, dishabituation was much more widespread, involving not only the habituated pathway but the non-habituated pathway as well. This evidence supports the work of Spencer, Thompson, and Neilson in showing that dishabituation is not merely the removal of habituation but is an independent superimposed excitatory process. Their findings and those of Carew, Castellucci, and Kandel indicate that dishabituation is a special case of sensitization, a form of behavioral arousal whereby a strong noxious stimulus can enhance a variety of reflex responses. Several investigators have now provided indirect evidence for the relation of dishabituation to sensitization

in higher forms, including man. These findings suggest that the independence of habituation and dishabituation and the relationship of dishabituation to sensitization may be quite general (see Groves and Thompson) .

Another problem that may soon be amenable to investigation in cellular terms is the relationship of short-term to long-term memory. One would like to know whether these are two separate phenomena or whether one is merely an extension of the other. Carew, Pinsker, and Kandel have begun to examine this question for habituation and for sensitization of the gill withdrawal reflex. Carew et al. found that if habituation training (ten trials a day) is repeated daily for four days, habituation of the reflex response builds up, so that it occurs more rapidly on each subsequent day. Thus on the fifth day, the mean duration of the reflex response was only twenty percent of its duration on day one. Habituation persists unchanged for a week and recovers only partially after three weeks. As is the case for complex behavioral modifications in vertebrates, massed habituation training (forty trials a day) was not as effective as spaced training (ten trials a day for four days). Thus habituation shows a sensitivity to the pattern of stimulation that resembles higher forms of learning. In a preliminary cellular analysis, Carew and Kandel have found that the acquisition of long-term habituation is associated with prolonged changes in synaptic transmission that qualitatively resemble those found in short-term habituation. This suggests that long-term memory may not be a qualitatively different phenomenon but merely a quantitative

extension of the short-term one. More extensive analyses are still required however to be certain of this point.

Recently, Pinsker, Carew and Kandel found that sensitization of the gill withdrawal reflex can also be prolonged. If an animal is given four highly noxious stimuli daily for four days, the duration or reflex withdrawal to a weak or moderate stimulus is enhanced for several weeks. Long-term sensitization of reflex responsiveness is of particular interest because of its resemblance to chronic anxiety states. In a neutral environment *Aplysia* learns to ignore a mild tactile stimulus, particularly when it is repeated daily —that is, it habituates to such a "nonthreatening" stimulus and tends not to respond to it even when it is presented many days later. However, an animal that is presented with noxious stimuli for several days no longer lives in a neutral environment but in a potentially hostile one. As a result, even mild tactile stimuli can no longer be ignored but bring forth a maximal defensive response.

Since these long-term behavioral modifications involve a reflex response whose neural circuitry is relatively well understood it may be possible to provide cellular explanations for the relation of short-term to long-term habituation and dishabituation and thereby to shed some light on the relation of short- to long-term memory. In analyzing long-term sensitization one might also be able to develop a model system for the cellular

studies of behavioral abnormalities. For example, it would be interesting to know whether other behavioral systems (heart rate, feeding, sexual behavior) are also affected by the sensitization procedure. What are the biochemical concomitants of sensitization? Can sensitization be reduced or abolished by drugs that can reduce anxiety in man? If so, what is the mechanism of action of these drugs?

Perspectives

In a jocular moment Sidney Brenner described the dictum of modern biology as: "think small and talk big." I'm afraid I've indulged in both in this chapter. Although cellular studies of perception and of simple behavioral modification span more than a decade of research, they represent but a small beginning. We are still far from understanding the neuronal mechanisms of perception, of long-term memory, and of higher learning. But within the last years progress has quickened perceptibly. As a result cellular approaches may soon be usefully applied to more complex learning processes and even to behavioral abnormalities.

I have here considered only studies that combine cellular neurophysiological and behavioral approaches. However, much will be learned in the future from combining behavioral and genetic techniques. Molecular biologists have been highly successful in dissecting the network of

cellular function in bacteria by using gene changes (mutations) in which one element is altered at a time. It thus seemed only natural to some molecular biologists that the network of the nervous system might also be successfully analyzed by the appropriate use of mutants. In an important series of studies, Seymour Benzer has begun to dissect the neural network underlying behavior in the fly *Drosophila* using behavioral mutants. Benzer now has mutants with a variety of behavioral abnormalities, including visual disturbances, abnormalities in circadian rhythm and sexual behavior; muscular dystrophies, and sudden cessation of development. He has found that mutations can alter behavior in a variety of ways using a variety of mechanisms. These can affect the development and function of sensory systems, motor systems, and central integrative systems. Mutations thus provide a powerful means for examining the component parts of a normal behavioral system. This approach promises to revolutionize behavioral genetics and in so doing will shed much light on the neural mechanism of behavior.

Looked at in the perspective of man's age-old search to understand himself and others, and of the relatively recent attempt of psychology and psychiatry to facilitate that search, one cannot help but view with optimism the accelerated progress in neural science. The long-sought merger between segments of psychology and neural science is becoming more of a reality. In this merger, neurobiology is likely to revitalize some segments of psychology

much as molecular biology revitalized cellular genetics. In turn, contact with psychology is likely to provide a humanizing perspective for neurophysiology. This cannot but be helpful. For neurophysiology has, until recently, tended to be fascinated and satisfied with what the neurologist Francis Walshe once called, "the bloodless dance of action potentials."

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Notes

1 In a few instances a small fraction of the total resting potential is maintained by an additional mechanism, the active, metabolically dependent extrusion of Na+ from the cell by an electrogenic Na-K+ pump (see Thomas).