



Breaking down Scientific Barriers to the Study of Brain and Mind

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Science, New Series, Vol. 290, No. 5494. (Nov. 10, 2000), pp. 1113-1120.

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PATHWAYS OF DISCOVERY

Neuroscience: Breaking Down Scientific Barriers to the Study of Brain and Mind

Eric R. Kandel and Larry R. Squire

During the latter part of the 20th century, the study of the brain moved from a peripheral position within both the biological and psychological sciences to become an interdisciplinary field called neuroscience that now occupies a central position within each discipline. This realignment occurred because the biological study of the brain became incorporated into a common framework with cell and molecular biology on the one side and with psychology on the other. Within this new framework, the scope of neuroscience ranges from genes to cognition, from molecules to mind.

What led to the gradual incorporation of neuroscience into the central core of biology and to its alignment with psychology? From the perspective of biology at the beginning of the 20th century, the task of neuroscience—to understand how the brain develops and then functions to perceive, think, move, and remember—seemed impossibly difficult. In addition, an intellectual barrier separated neuroscience from biology, because the language of neuroscience was based more on neuroanatomy and electrophysiology than on the universal biological language of biochemistry. During the last 2 decades this barrier has been largely removed. A molecular neuroscience became established by focusing on simple systems where anatomy and physiology were tractable. As a result, neuroscience helped delineate a general plan for neural cell function in which the cells of the nervous system are understood to be governed by variations on universal biological themes.

From the perspective of psychology, a neural approach to mental processes seemed too reductionistic to do justice to the complexity of cognition. Substantial progress was required to demonstrate that some of these reductionist goals were achievable within a psychologically meaningful framework. The work of Vernon Mountcastle, David Hubel, Torsten

Wiesel, and Brenda Milner in the 1950s and 1960s, and the advent of brain imaging in the 1980s,

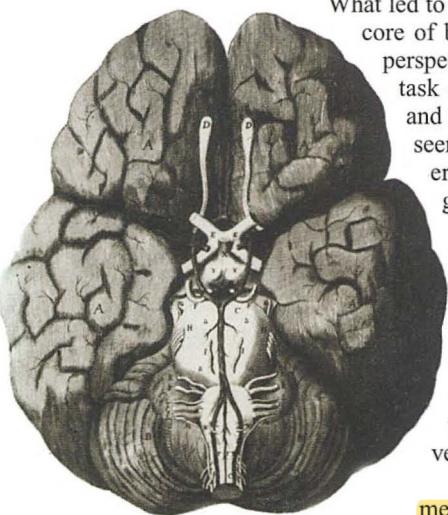
showed what could be achieved for sensory processing, perception, and memory. As a result of these advances, the view gradually developed that only by exploring the brain could psychologists fully satisfy their interest in the cognitive processes that intervene between stimulus and response.

Here, we consider several developments that have been particularly important for the maturation of neuroscience and for the restructuring of its relationship to biology and psychology.

The Emergence of a Cellular and Molecular Neuroscience

The modern cellular science of the nervous system was founded on two important advances: the neuron doctrine and the ionic hypothesis. The neuron doctrine was established by the brilliant Spanish anatomist Santiago Ramón y Cajal (1), who showed that the brain is composed of discrete cells, called neurons, and that these likely serve as elementary signaling units. Cajal also advanced the principle of connection specificity, the central tenet of which is that neurons form highly specific connections with one another and that these connections are invariant and defining for each species. Finally, Cajal developed the principle of dynamic polarization, according to which information flows in only one direction within a neuron, usually from the dendrites (the neuron's input component) down the axon shaft to the axon terminals (the output component). Although exceptions to this principle have emerged, it has proved extremely influential, because it tied structure to function and provided guidelines for constructing circuits from the images provided in histological sections of the brain.

BORDER ILLUSTRATIONS: MATT ZANG; THOMAS WILLIS, CEREBRAL ANATOMY, LONDON, 1664/LIBRARY OF MEDICINE



Artful brain. Gross anatomy made beautiful in a Christopher Wren illustration from a 1664 anatomy text.

JANUARY
"Science Wars"

FEBRUARY
Planetary Sciences

MARCH
Genomics

APRIL
Infectious Diseases

MAY
Materials Science

JUNE
Cloning and Stem Cells

JULY
Communications and Science

AUGUST
Quantum Physics

SEPTEMBER
The Cell Cycle

OCTOBER
Atmospheric Sciences

NOVEMBER
Neuroscience

DECEMBER
Astrophysics and Cosmology

A Timeline of Neuroscience

2nd Century

A.D.
Galen of Pergamum identifies the brain as the organ of the mind.

17th Century

The brain becomes accepted as the substrate of mental life rather than its ventricles, as early writers had proposed.

1664

Thomas Willis publishes *Cerebri anatome*, with illustrations of the brain by Christopher Wren. It is the most comprehensive treatise on brain anatomy and function published up to that time.

1791

Luigi Galvani reveals the electric nature of nervous action by stimulating nerves and muscles of frog legs.

1808

Franz Joseph Gall proposes that specific brain regions control specific functions.

1852

Hermann von Helmholtz measures the speed of a nerve impulse in the frog.

1879

Wilhelm Wundt establishes the first laboratory of experimental psychology in Leipzig, Germany.



Cajal and his contemporary Charles Sherrington (2) further proposed that neurons contact one another only at specialized points called synapses, the sites where one neuron's processes contact and communicate with another neuron. We now know that at most synapses, there is a gap of 20 nm—the synaptic cleft—between the pre- and postsynaptic cell. In the 1930s, Otto Loewi, Henry Dale, and Wilhelm Feldberg established (at peripheral neuromuscular and autonomic synapses) that the signal that bridges the synaptic cleft is usually a small chemical, or neurotransmitter, which is released from the presynaptic terminal, diffuses across the gap, and binds to receptors on the postsynaptic target cell. Depending on the specific receptor, the postsynaptic cell can either be excited or inhibited. It took some time to establish that chemical transmission also occurs in the central nervous system, but by the 1950s the idea had become widely accepted.

Even early in the 20th century, it was already understood that nerve cells have an electrical potential, the resting membrane potential, across their membrane, and that signaling along the axon is conveyed by a propagated electrical signal, the action potential, which was thought to nullify the resting potential. In 1937 Alan Hodgkin discovered that the action potential gives rise to local current flow on its advancing edge and that this current depolarizes the adjacent region of the axonal membrane sufficiently to trigger a traveling wave of depolarization. In 1939 Hodgkin and Andrew Huxley made the surprising discovery that the action potential more than nullifies the resting potential—it reverses it. Then, in the late 1940s, Hodgkin, Huxley, and Bernard Katz explained the resting potential and the action potential in terms of the movement of specific ions—potassium (K^+), sodium (Na^+), and chloride (Cl^-)—through pores (ion channels) in the axonal membrane. This ionic hypothesis unified a large body of descriptive data and offered the first realistic promise that the nervous system could be understood in terms of physicochemical principles common to all of cell biology (3).

The next breakthrough came when Katz, Paul Fatt, and John Eccles showed that ion channels are also fundamental to signal transmission across the synapse. However, rather than being gated by voltage like the Na^+ and K^+ channels critical for action potentials, excitatory synaptic ion channels are gated chemically by ligands such as the transmitter acetylcholine. During the 1960s and 1970s, neuroscientists identified many amino acids, peptides, and other small molecules as chemical transmitters, including acetylcholine, glutamate, GABA, glycine, serotonin, dopamine, and norepinephrine. On the order of 100 chemical transmitters have been discovered to date. In the 1970s, some synapses were found to release a peptide cotransmitter that can modify the action of the classic, small-molecule transmitters. The discovery of chemical neurotransmission was followed by the remarkable discovery that transmission between neurons is sometimes electrical (4). Electrical synapses have smaller synaptic clefts, which are bridged by gap junctions and allow current to flow between neurons.

In the late 1960s information began to become available about the biophysical and biochemical structure of ionic

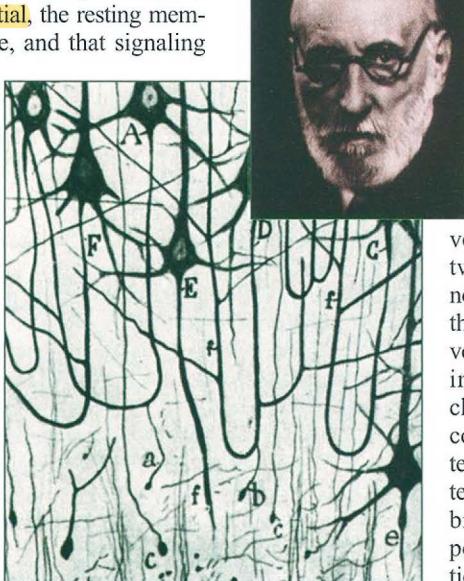
pores and the biophysical basis for their selectivity and gating—how they open and close. For example, transmitter binding sites and their ion channels were found to be embodied within different domains of multimeric proteins. Ion channel selectivity was found to depend on physical-chemical interaction between the channel and the ion, and channel gating was found to result from conformational changes within the channel (5).

The study of ion channels changed radically with the development of the patch-clamp method in 1976 by Erwin Neher and Bert Sakmann (6), which enabled measurement of the current flowing through a single ion channel. This powerful advance set the stage for the analysis of channels at the molecular level and for the analysis of functional and conformational change in a single membrane protein. When applied to non-neuronal cells, the method also revealed that all cells—even bacteria—express remarkably similar ion channels. Thus, neuronal signaling proved to be a special case of a signaling capability inherent in most cells.

The development of patch clamping coincided with the advent of molecular cloning, and these two methods brought neuroscientists new ideas based on the first reports of the amino acid sequences of ligand- and voltage-gated channels. One of the key insights to emerge from molecular cloning was that amino acid sequences contain clues about how receptor proteins and voltage-gated ion channel proteins are arranged across the cell membrane. The sequence data also often pointed to unexpected structural relationships (homologies) among proteins. These insights, in turn, revealed similarities between molecules found in quite different neuronal and non-neuronal contexts, suggesting that they may serve similar biological functions.

By the early 1980s, it became clear that synaptic actions were not always mediated directly by ion channels. Besides ionotropic receptors, in which ligand binding directly gates an ion channel, a second class of receptors, the metabotropic receptors, was discovered. Here the binding of the ligand initiates intracellular metabolic events and leads only indirectly, by way of “second messengers,” to the gating of ion channels (7).

The cloning of metabotropic receptors revealed that many of them have seven membrane-spanning regions and are homologous to bacterial rhodopsin as well as to the photoreceptor pigment of organisms ranging from fruit flies to humans. Further, the recent cloning of receptors for the sense of smell (8) revealed that at least 1000 metabotropic receptors are expressed in the mammalian olfactory epithelium and that similar receptors are present in flies and worms. Thus, it was instantly understood that the class of receptors used for phototransduction, the initial step in visual perception, is also used for smell and aspects of taste, and that these receptors share key features with many other brain receptors that work through second-messenger signaling. These discoveries demonstrated the evolutionary conservation of receptors and

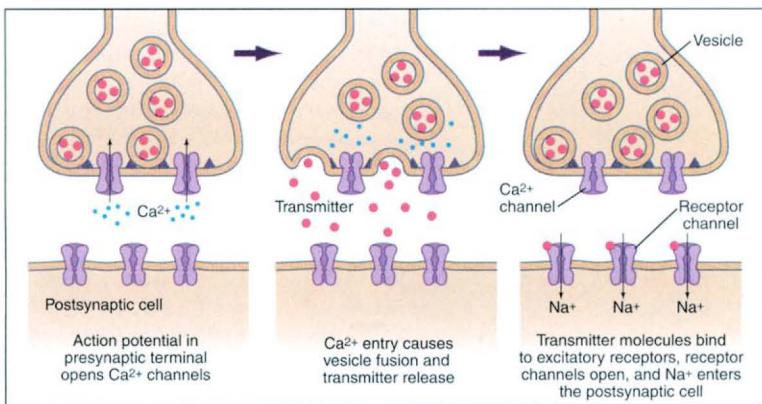


Seeing neurons. Anatomist Ramón y Cajal used Golgi's stain to examine individual nerve cells and their processes.

emphasized the wisdom of studying a wide variety of experimental systems—vertebrates, invertebrates, even single-celled organisms—to identify broad biological principles.

The seven transmembrane-spanning receptors activate ion channels indirectly through coupling proteins (G proteins). Some G proteins have been found to activate ion channels directly. However, the majority of G proteins activate membrane enzymes that alter the level of second messengers, such as cAMP, cGMP, or inositol triphosphate, which initiate complex intracellular events leading to the activation of protein kinases and phosphatases and then to the modulation of channel permeability, receptor sensitivity, and transmitter release. Neuroscientists now appreciate that many of these synaptic actions are mediated intracellularly by protein phosphorylation or dephosphorylation (9). Nerve cells use such covalent modifications to control protein activity reversibly and thereby to regulate function. Phosphorylation is also critical in other cells for the action of hormones and growth factors, and for many other processes.

Directly controlled synaptic actions are fast, lasting milliseconds, but second-messenger actions last seconds to minutes. An even slower synaptic action, lasting days or more, has been found to be important for long-term memory. In this case, protein kinases activated by second messengers translocate to the nucleus, where they phosphorylate transcription factors that alter gene expression, initiate growth of neuronal processes, and increase synaptic strength.



The synapse. A presynaptic neuron propagates a signal by releasing neurotransmitter molecules that diffuse across the synaptic cleft to bind to receptors on the postsynaptic cell.

Ionotropic and metabotropic receptors have helped to explain the postsynaptic side of synaptic transmission. In the 1950s and 1960s, Katz and his colleagues turned to the presynaptic terminals and discovered that chemical transmitters, such as acetylcholine, are released not as single molecules but as packets of about 5000 molecules called quanta (10). Each quantum is packaged in a synaptic vesicle and released by exocytosis at sites called active zones. The key signal that triggers this sequence is the influx of Ca^{2+} with the action potential.

In recent years, many proteins involved in transmitter release have been identified (11). Their functions range from targeting vesicles to active zones, tethering vesicles to the cell membrane, and fusing vesicles with the cell membrane so that their contents can be released by exocytosis. These molecular studies reflect another example of evolutionary conservation: The molecules used for vesicle fusion and exocytosis at nerve terminals are variants of those used for vesicle fusion and exocytosis in all cells.

A Mechanistic View of Brain Development

The discoveries of molecular neuroscience have dramatically improved the understanding of how the brain develops its complexity. The modern molecular era of developmental neuroscience began when Rita Levi-Montalcini and Stanley Cohen isolated nerve growth factor (NGF), the first peptide growth factor to be identified in the nervous system (12). They showed that injection of antibodies to NGF into newborn mice caused the death of neurons in sympathetic ganglia and also reduced the number of sensory ganglion cells. Thus, the survival of both sympathetic and sensory neurons depends on NGF. Indeed, many neurons depend for their survival on NGF or related molecules, which typically provide feedback signals to the neurons from their targets. Such signals are important for programmed cell death—apoptosis—a developmental strategy which has now proved to be of general importance, whereby many more cells are generated than eventually survive to become functional units with precise connectivity. In a major advance, genetic study of worms has revealed the *ced* genes and with them a universal cascade critical for apoptosis in which proteases—the caspases—are the final agents for cell death (13).

Cajal pointed out the extraordinary precision of neuronal connections. The first compelling insights into how neurons develop their precise connectivity came from Roger Sperry's studies of the visual system of frogs and salamanders beginning in the 1940s, which suggested that axon outgrowth is guided by molecular cues. Sperry's key finding was that when the nerves from the eye are cut, axons find their way back to their original targets. These seminal studies led Sperry in 1963 to formulate the chemoaffinity hypothesis (14), the idea that neurons form connections with their targets based on distinctive and matching molecular identities that they acquire early in development.

Stimulated by these early contributions, molecular biology has radically transformed the study of nervous system development from a descriptive to a mechanistic field. Three genetic systems, the worm *Caenorhabditis elegans*, the fruit fly *Drosophila melanogaster*, and the mouse, have been invaluable; some of the molecules for key developmental steps in the mouse were first characterized by genetic

screens in worms and flies. In some cases, identical molecules were found to play an equivalent role throughout phylogeny. The result of this work is that neuroscientists have achieved in broad outline an understanding of the molecular basis of nervous system development (15). A range of key molecules has been identified, including specific inducers, morphogens, and guidance molecules important for differentiation, process outgrowth, pathfinding, and synapse formation. For example, in the spinal cord, neurons achieve their identities and characteristic positions largely through two classes of inductive signaling molecules of the Hedgehog and bone morphogenic protein families. These two groups of molecules control neuronal differentiation in the ventral and dorsal halves of the spinal cord, respectively, and maintain this division of labor through most of the rostral-caudal length of the nervous system.

The process of neuronal pathfinding is mediated by both short-range and long-range cues. An axon's growth cone can encounter cell surface cues that either attract or

1891
Wilhelm von Waldeyer-Hartz introduces the term neuron.

1897
Charles Sherrington introduces the term synapse.

1898–1903
Edward Thorndike and Ivan Pavlov describe operant and classical conditioning, two fundamental types of learning.

1906
Santiago Ramón y Cajal summarizes compelling evidence for the neuron doctrine, that the nervous system is composed of discrete cells.

Alois Alzheimer describes the pathology of the neurodegenerative disease that comes to bear his name.

1914
Henry Dale demonstrates the physiological action of acetylcholine, which is later identified as a neurotransmitter.

1929
In a famous program of lesion experiments in rats, Karl Lashley attempts to localize memory in the brain.

Hans Berger uses human scalp electrodes to demonstrate electroencephalography.

1928–32
Edgar Adrian describes method for recording from single sensory and motor axons; H. Kefler Hartline applies this method to the recording of single-cell activity in the eye of the horseshoe crab.

1940s
Alan Hodgkin,
Andrew Huxley,
and Bernard Katz



explain electrical activity of neurons by concentration gradients of ions and movement of ions through pores.

1946
Kenneth Cole develops the voltage-clamp technique to measure current flow across the cell membrane.

1949
Donald Hebb introduces a synaptic learning rule, which becomes known as the Hebb rule.

1930s to 1950s
The chemical nature of synaptic transmission is established by Otto Loewi, Henry Dale, Wilhelm Feldberg, Stephen Kuffler, and Bernard Katz at peripheral synapses and is extended to the spinal cord by John Eccles and others.

Wilder Penfield and Theodore Rasmussen map the motor and sensory homunculus and illustrate localization of function in the human brain.

repel it. For example, ephrins are membrane-bound, are distributed in graded fashion in many regions of the nervous system, and can repel growing axons. Other cues, such as the netrins and the semaphorins, are secreted in diffusible form and act as long-range chemoattractants or chemorepellents. Growth cones can also react to the same cues differently at different developmental phases, for example, when crossing the midline or when switching from pathfinding to synapse formation. Finally, a large number of molecules are involved in synapse formation itself. Some, such as neuregulin, erbB kinases, agrin, and MuSK, organize the assembly of the postsynaptic machinery, whereas others, such as the laminins, help to organize the presynaptic differentiation of the active zone.

These molecular signals direct differentiation, migration, process outgrowth, and synapse formation in the absence of neural activity. Neural activity is needed, however, to refine the connections further so as to forge the adult pattern of connectivity (16). The neural activity may be generated spontaneously, especially early in development, but later depends importantly on sensory input. In this way, intrinsic activity or sensory and motor experience can help specify a precise set of functional connections.

The Impact of Neuroscience on Neurology and Psychiatry

Molecular neuroscience has also reaped substantial benefits for clinical medicine. To begin with, recent advances in the study of neural development have identified stem cells, both

embryonic and adult, which offer promise in cell replacement therapy in Parkinson's disease, demyelinating diseases, and other conditions. Similarly, new insights into axon guidance molecules offer hope for nerve regeneration after spinal cord injury. Finally, because most neurological diseases are associated with cell death, the discovery in worms of a universal genetic program for cell death opens up approaches for cell rescue based on, for example, inhibition of the caspase proteases.

With psychiatric disorders, progress has been slower for two reasons. First, diseases such as schizophrenia, depression, obsessive compulsive disorders, anxiety states, and drug abuse tend to be complex, polygenic disorders that are significantly modulated by environmental factors. Second, in contrast to neurological disorders, little is known about the anatomical substrates of most psychiatric diseases. Given the difficulty of penetrating the deep biology of mental illness, it is nevertheless remarkable how much progress has been made during the past 3 decades (19). Arvid Carlsson and Julius Axelrod carried out pioneering studies of biogenic amines, which laid the foundation for psychopharmacology, and Seymour Kety pioneered the genetic study of mental illness (20). Currently, new approaches to many conditions, such as sleep disorders, eating disorders, and drug abuse, are emerging as the result of insights into the cellular and molecular machinery that regulates specific behaviors (21).

Moreover, improvements in diagnosis, the better delineation of genetic contributions to psychiatric illness (based on twin and adoption studies as well as studies of affected families), and the discovery of specific medications for treating schizophrenia, depression, and anxiety states have transformed psychiatry into a therapeutically effective medical specialty that is now closely aligned with neuroscience.

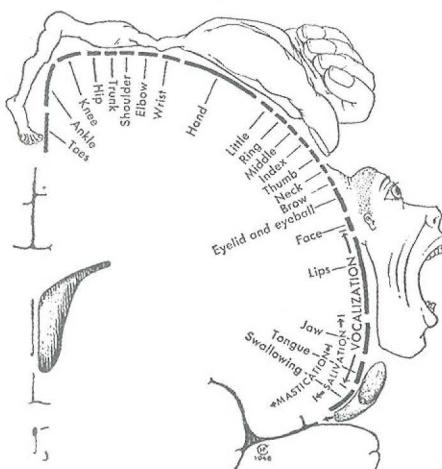
A New Alignment of Neuroscience and Psychological Science

The brain's computational power is conferred by interactions among billions of nerve cells, which are assembled into networks or circuits that carry out specific operations in support of behavior and cognition. Whereas the molecular machinery and electrical signaling properties of neurons are widely conserved across animal species, what distinguishes one

species from another, with respect to their cognitive abilities, is the number of neurons and the details of their connectivity.

Beginning in the 19th century there was great interest in how these cognitive abilities might be localized in the brain. One view, first championed by Franz Joseph Gall, was that the brain is composed of specialized parts and that aspects of perception, emotion, and language can be localized to anatomically distinct neural systems. Another view, championed by Jean-Pierre-Marie Flourens, was that cognitive functions are global properties arising from the integrated activity of the entire brain. In a sense, the history of neuroscience can be seen as a gradual ascendancy of the localizationist view.

To a large extent, the emergence of the localizationist view was built on a century-old legacy of psychological sci-



Little man inside. This 1950 homunculus summarized studies of the cerebral localization of motor function.

Next, consider the impact of molecular genetics. Huntington's disease is an autosomal dominant disease marked by progressive motor and cognitive impairment that ordinarily manifests itself in middle age. The major pathology is cell death in the basal ganglia. In 1993, the Huntington's Disease Collaborative Research Group isolated the gene responsible for the disease (17). It is marked by an extended series of trinucleotide CAG (cytosine, adenine, guanine) repeats, thereby placing Huntington's disease in a new class of neurological disorders—the trinucleotide repeat diseases—that now constitute the largest group of dominantly transmitted neurological diseases.

The molecular genetic analysis of more complex degenerative disorders has proceeded more slowly. Still, three genes associated with familial Alzheimer's disease—those that code for the amyloid precursor protein, presenilin 1, and presenilin 2—have been identified. Molecular genetic studies have also identified the first genes that modulate the severity

ence. When psychology emerged as an experimental science in the late 19th century, its founders, Gustav Fechner and Wilhelm Wundt, focused on psychophysics—the quantitative relationship between physical stimuli and subjective sensation. The success of this endeavor encouraged psychologists to study more complex behavior, which led to a rigorous, laboratory-based tradition termed behaviorism.

Led by John Watson and later by B. F. Skinner, behaviorists argued that psychology should be concerned only with observable stimuli and responses, not with unobservable processes that intervene between stimulus and response. This tradition yielded lawful principles of behavior and learning, but it proved limiting. In the 1960s, behaviorism gave way to a broader approach concerned with cognitive processes and internal representations. This new emphasis focused on precisely those aspects of mental life—from perception to action—that had long been of interest to neurologists and other students of the nervous system.

The first cellular studies of brain systems in the 1950s illustrated dramatically how much neuroscience derived from psychology and conversely how much psychology could, in turn, inform neuroscience. In using a cellular approach, neuroscientists relied on the rigorous experimental methods of psychophysics and behaviorism to explore how a sensory stimulus resulted in a neuronal response. In so doing, they found cellular support for localization of function: Different brain regions had different cellular response properties. Thus, it became possible in the study of behavior and cognition to move beyond description to an exploration of the mechanisms underlying the internal representation of the external world.

In the late 1950s and 1960s Mountcastle, Hubel, and Wiesel began using cellular approaches to analyze sensory processing in the cerebral cortex of cats and monkeys (22). Their work provided the most fundamental advance in understanding the organization of the brain since the work of Cajal at the turn of the century. The cellular physiological techniques revealed that the brain both filters and transforms sensory information on its way to and within the cortex, and that these transformations are critical for perception. Sensory systems analyze, decompose, and then restructure raw sensory information according to built-in connections and rules.

Mountcastle found that single nerve cells in the primary somatic sensory cortex respond to specific kinds of touch: Some respond to superficial touch and others to deep pressure, but cells almost never respond to both. The different cell types are segregated in vertical columns, which comprise thousands of neurons and extend about 2 mm from the cortical surface to the white matter below it. Mountcastle proposed that each column serves as an integrating unit, or logical module, and that these columns are the basic mode of cortical organization.

Single-cell recording was pioneered by Edgar Adrian and applied to the visual system of invertebrates by H. Keffer Hartline and to the visual system of mammals by Stephen Kuffler, the mentor of Hubel and Wiesel. In recordings from the retina, Kuffler discovered that, rather than signaling absolute levels of light, neurons signal contrast between spots of light and dark. In the visual cortex, Hubel and Wiesel found that most cells no longer respond to spots of light. For example, in area V1 at the occipital pole of the cortex, neurons respond to specific visual features such as lines or bars in a particular orientation. Moreover, cells with similar orientation preferences were found to group together in vertical columns similar to those that Mountcastle had found in somatosensory cortex. Indeed, an independent system of vertical columns—the ocular dominance columns—was found to segregate information arriving from

the two eyes. These results provided an entirely new view of the anatomical organization of the cerebral cortex.

Wiesel and Hubel also investigated the effects of early sensory deprivation on newborn animals. They found that visual deprivation in one eye profoundly alters the organization of ocular dominance columns (23). Columns receiving input from the closed eye shrink, and those receiving input from the open eye expand. These studies led to the discovery that eye closure alters the pattern of synchronous activity in the two eyes and that this neural activity is essential for fine-tuning synaptic connections during visual system development (16).

In the extrastriate cortex beyond area V1, continuing electrophysiological and anatomical studies have identified more than 30 distinct areas important for vision (24). Further, visual information was found to be analyzed by two parallel processing streams (25). The dorsal stream, concerned with where objects are located in space and how to reach objects, extends from area V1 to the parietal cortex. The ventral stream extends from area V1 to the inferior temporal cortex and is concerned with analyzing the visual form and quality of objects. Thus, even the apparently simple task of perceiving an object in space engages a disparate collection of specialized neural areas that represent different aspects of the visual information—what the object is, where it is located, and how to reach for it.

A Neuroscience of Cognition

The initial studies of the visual system were performed in anaesthetized cats, an experimental preparation far removed from the behaving and thinking human beings that are the focus of interest for cognitive psychologists. A pivotal advance occurred in the late 1960s when single-neuron recordings were obtained from awake, behaving monkeys that had been trained to perform sensory or motor tasks (26). With these methods, the response of neurons in the posterior parietal cortex to a visual stimulus was found to be enhanced when the animal moved its eyes to attend to the stimulus. This moved the neurophysiological study of single neurons beyond sensory processing and showed that reductionist approaches could be applied to higher order psychological processes such as selective attention.

It is possible to correlate neuronal firing with perception rather directly. Thus, building on earlier work by Mountcastle, a monkey's ability to discriminate motion was found to closely match the performance of individual neurons in area MT, a cortical area concerned with visual motion processing. Further, electrical microstimulation of small clusters of neurons in MT shifts the monkey's motion judgments toward the direction of motion that the stimulated neurons prefer (27). Thus, activity in area MT appears sufficient for the perception of motion and for initiating perceptual decisions.



Single-cell recording. Vernon Mountcastle, David Hubel, and Torsten Wiesel pioneered cellular studies of sensory cortex.

1950s
Karl von Frisch,
Konrad Lorenz,
and Niko Tinbergen
establish the
science of
ethology (animal
behavior in natural
contexts) and
lay the foundation
for neuroethology.

1955–60
Vernon Mount-
castle, David
Hubel, and
Torsten Wiesel
pioneer single-
cell recording
from mammalian
sensory cortex;
Nils-Ake Hillarp
introduces
fluorescent
microscopic
methods to study
cellular distribution
of biogenic
amines.

1956
Rita Levi-
Montalcini and
Stanley Cohen



isolate and purify
nerve growth
factor.

PATHWAYS OF DISCOVERY

These findings, based on recordings from small neuronal populations, have illuminated important issues in perception and action. They illustrate how retinal signals are remapped from retinotopic space into other coordinate frames that can guide behavior; how attention can modulate neuronal activity; and how meaning and context influence neuronal activity, so that the same retinal stimulus can lead to different neuronal responses depending on how the stimulus is perceived (28). This same kind of work (relating cellular activity directly to perception and action) is currently being applied to the so-called binding problem—how the multiple features of a stimulus object, which are represented by specialized and distributed neuronal groups, are synthesized into a signal that represents a single percept or action and to the fundamental question of what aspects of neuronal activity (e.g., firing rate or spike timing) constitute the neural codes of information processing (29).

Striking parallels to the organization and function of sensory cortices have been found in the cortical motor areas supporting voluntary movement. Thus, there are several cortical areas directed to the planning and execution of voluntary movement. Primary motor cortex has columnar organization, with neurons in each column governing movements of one or a few joints. Motor areas receive input from other cortical regions, and information moves through stages to the spinal cord, where the detailed circuitry that generates motor patterns is located (30).

Although studies of single cells have been enormously informative, the functioning brain consists of multiple brain systems and many neurons operating in concert. To monitor activity in large populations of neurons, multielectrode arrays as well as cellular and whole-brain imaging techniques are now being used. These approaches are being supplemented by studying the effect of selective brain lesions on behavior and by molecular methods, such as the delivery of markers or other molecules to specific neurons by viral transfection, which promise fine-resolution tracing of anatomical connections, activity-dependent labeling of neurons, and ways to transiently inactivate specific components of neural circuits.

Invasive molecular manipulations of this kind cannot be applied to humans. However, functional neuroimaging by positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) provides a way to monitor large neuronal populations in awake humans while they engage in cognitive tasks (31). PET involves measuring regional blood flow using $H_2^{15}O$ and allows for repeated measurements on the same individual. fMRI is based on the fact that neural activity changes local oxygen levels in tissue and that oxygenated and deoxygenated hemoglobin have different magnetic properties. It is now possible to image the second-by-second time course of the brain's response to single stimuli or single events with a spatial resolution in the millimeter

range. Recent success in obtaining fMRI images from awake monkeys, combined with single-cell recording, should extend the utility of functional neuroimaging by permitting parallel studies in humans and nonhuman primates.

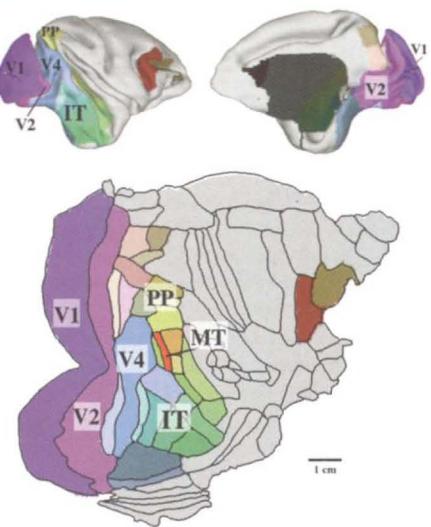
One example of how parallel studies of humans and non-human primates have advanced the understanding of brain systems and cognition is in the study of memory. The neuroscience of memory came into focus in the 1950s when the noted amnesic patient H.M. was first described (32). H.M. developed profound forgetfulness after sustaining a bilateral medial temporal lobe resection to relieve severe epilepsy. Yet he retained his intelligence, perceptual abilities, and personality. Brenda Milner's elegant studies of H.M. led to several important principles. First, acquiring new memories is a distinct cerebral function, separable from other perceptual and cognitive abilities. Second, because H.M. could retain a number or a visual image for a short time, the medial temporal lobes are not needed for immediate memory. Third, these structures are not the ultimate repository of memory, because H.M. retained his remote, childhood memories.

It subsequently became clear that only one kind of memory, declarative memory, is impaired in H.M. and other amnesic patients. Thus, memory is not a unitary faculty of the mind but is composed of multiple systems that have different logic and neuroanatomy (33). The major distinction is between our capacity for conscious, declarative memory about facts and events and a collection of unconscious, non-declarative memory abilities, such as skill and habit learning and simple forms of conditioning and sensitization. In these cases, experience modifies performance without requiring any conscious memory content or even the experience that memory is being used.

An animal model of human amnesia in the nonhuman primate was achieved in the early 1980s, leading ultimately to the identification of the medial temporal lobe structures that support declarative memory—the hippocampus and the adjacent entorhinal, perirhinal, and parahippocampal cortices (34). The hippocampus has been an especially active target of study, in part because this was one of the structures damaged in patient H.M. and also because of the early discovery of hippocampal place cells, which signal the location of an animal in space (35). This work led to the idea that, once learning occurs, the hippocampus and other medial temporal lobe structures permit the transition to long-term memory, perhaps by binding the separate cortical regions that together store memory for a whole event. Thus, long-term memory is thought to be stored in the same distributed set of cortical structures that perceive, process, and analyze what is to be remembered, and aggregate changes in large assemblies of cortical neurons are the substrate of long-term memory. The frontal lobes are also thought to influence what is selected for storage, the ability to hold information in mind for the short term, and the ability later on to retrieve it (36).

Whereas declarative memory is tied to a particular brain system, nondeclarative memory refers to a collection of learned abilities with different brain substrates. For example, many kinds of motor learning depend on the cerebellum, emotional learning and the modulation of memory strength by emotion depend on the amygdala, and habit learning depends on the basal ganglia (37). These forms of nondeclarative memory, which provide for myriad unconscious ways of responding to the world, are evolutionarily ancient and observable in simple invertebrates such as *Aplysia* and *Drosophila*. By virtue of the unconscious status of these forms of memory, they create some of the

1957
Brenda Milner
describes pa-



Big picture. Brain maps, like this one of the macaque visual system, reveal multiple brain regions working together as a functional system.

tient H.M. and discovers the importance of the medial temporal lobe for memory.

1958
Arvid Carlsson
finds dopamine
to be a transmitter
in the brain and
proposes that
it has a role in
extrapyramidal
disorders
such as
Parkinson's
disease.

1960s
Simple invertebrate systems,
including *Aplysia*
(below),



Drosophila,
and *C. elegans*,
are introduced
to analyze
elementary
aspects of be-
havior and learn-
ing at the
cellular and
molecular
level.

mystery of human experience. For here arise the dispositions, habits, attitudes, and preferences that are inaccessible to conscious recollection, yet are shaped by past events, influence our behavior and our mental life, and are a fundamental part of who we are.

Bridging Cognitive Neuroscience and Molecular Biology in the Study of Memory Storage

The removal of scientific barriers at the two poles of the biological sciences—in the cell and molecular biology of nerve cells on the one hand, and in the biology of cognitive processes on the other—has raised the question: Can one anticipate an even broader unification, one that ranges from molecules to mind? A beginning of just such a synthesis may be apparent in the study of synaptic plasticity and memory storage.

For all of its diversity, one can view neuroscience as being concerned with two great themes—the brain's "hard wiring" and its capacity for plasticity. The former refers to how connections develop between cells, how cells function and communicate, and how an organism's inborn functions are organized—its sleep-wake cycles, hunger and thirst, and its ability to perceive the world. Thus, through evolution the nervous system has inherited many adaptations that are too important to be left to the vagaries of individual experience. In contrast, the capacity for plasticity refers to the fact that nervous systems can adapt or change as the result of the experiences that occur during an individual lifetime. Experience can modify the nervous system, and as a result organisms can learn and remember.

The precision of neural connections possess deep problems for the plasticity of behavior. How does one reconcile the precision and specificity of the brain's wiring with the known capability of humans and animals to acquire new knowledge? And how is knowledge, once acquired, retained as long-term memory? A key insight about synaptic transmission is that the precise connections between neurons are not fixed but are modifiable by experience. Beginning in 1970, studies in invertebrates such as *Aplysia* showed that simple forms of learning—habituation, sensitization, and classical conditioning—result in functional and structural changes at synapses between the neurons that mediate the behavior being modified. These changes can persist for days or weeks and parallel the time course of the memory process (38). These cell biological studies have been complemented by genetic studies in *Drosophila*. As a result, studies in *Aplysia* and *Drosophila* have identified a number of proteins important for memory (39).

In his now-famous book, *The Organization of Behavior*, Donald Hebb proposed in 1949 that the synaptic strength between two neurons should increase when the neurons exhibit coincident activity (40). In 1973, a long-lasting synaptic plasticity of this kind was discovered in the hippocampus (a key structure for declarative memory) (41). In response to a burst of high-frequency stimuli, the major synaptic pathways in the hippocampus undergo a long-term change, known as long-term potentiation or LTP. The advent in the 1990s of the ability to genetically modify mice made it possible to relate specific genes both to synaptic plasticity and to intact animal behavior, including memory. These techniques now allow one to delete specific genes in specific

brain regions and also to turn genes on and off. Such genetic and pharmacological experiments in intact animals suggest that interference with LTP at a specific synapse—the Schaffer collateral-CA1 synapse—commonly impairs memory for space and objects. Conversely, enhancing LTP at the same synapse can enhance memory in these same declarative memory tasks. The findings emerging from these new methods (42) complement those in *Aplysia* and *Drosophila* and reinforce one of Cajal's most prescient ideas: Even though the anatomical connections between neurons develop according to a definite plan, their strength and effectiveness are not predetermined and can be altered by experience.

Combined behavioral and molecular genetic studies in *Drosophila*, *Aplysia*, and mouse suggest that, despite their different logic and neuroanatomy, declarative and nondeclarative forms of memory share some common cellular and molecular features. In both systems, memory storage depends on a short-term process lasting minutes and a long-term process lasting days or longer. Short-term memory involves covalent modifications of preexisting proteins, leading to the strengthening of preexisting synaptic connections. Long-term memory involves altered gene expression, protein synthesis, and the growth of new synaptic connections. In addition, a number of key signaling molecules involved in converting transient short-term plasticity to persistent long-term memory appear to be shared by both declarative and nondeclarative memory. A striking feature of neural plasticity is that long-term memory involves structural and functional change (38, 43). This has been shown most directly in invertebrates and is likely to apply to vertebrates as well, including primates.

It had been widely believed that the sensory and motor cortices mature early in life and thereafter have a fixed organization and connectivity. However, it is now clear that these cortices can be reshaped by experience (44). In one ex-

periment, monkeys learned to discriminate between two vibrating stimuli applied to one finger. After several thousand trials, the cortical representation of the trained finger became more than twice as large as the corresponding areas for other fingers. Similarly, in a neuroimaging study of right-handed string musicians the cortical representations of the fingers of the left hand (whose fingers are manipulated individually and are engaged in skillful playing) were larger than in nonmusicians. Thus, improved finger skills even involve changes in how sensory cortex represents the fingers. Because all organisms experience a different sensory environment, each brain is modified differently. This gradual creation of unique brain architecture provides a biological basis for individuality.

Coda

Physicists and chemists have often distinguished their disciplines from the field of biology, emphasizing that biology was overly descriptive, atheoretical, and lacked the coherence of the physical sciences. This is no longer quite true. In the 20th century, biology matured and became a coherent discipline as a result of the substantial achievements of molecular biology. In the second half of the century, neuroscience emerged as a discipline that concerns itself with

1962–63
Brain anatomy in rodents is found to be altered by experience; first evidence for role of protein synthesis in memory formation.

1963
Roger Sperry proposes a precise system of chemical matching between pre- and postsynaptic neuronal partners (the chemoaffinity hypothesis).

1966–69
Ed Evarts and Robert Wurtz develop methods for studying movement and perception with single-cell recordings from awake, behaving monkeys.

1970
Synaptic changes are related to learning and memory storage in *Aplysia*.

Mid-1970s
Paul Greengard shows that many neurotransmitters work by means of protein phosphorylation.

1973
Timothy Bliss and Terje Lomo discover long-term potentiation, a candidate synaptic mechanism for long-term mammalian memory.

1976
Erwin Neher and Bert Sakmann develop the patch-clamp technique for recording the activity of single ion channels.

Late 1970s
Neuroimaging by positron emission tomography is developed.

1980s
Experimental evidence becomes available for the divisibility of memory into multiple systems; an animal model of human amnesia is developed.



Real-time brain. Imaging methods can reveal those brain areas that are active during specific cognitive tasks.

PATHWAYS OF DISCOVERY

1986
H. Robert Horvitz discovers the *ced* genes, which are critical for programmed cell death.

Patient R.B. establishes the importance of the hippocampus for human memory.

1990
Seiji Ogawa and colleagues develop functional magnetic resonance imaging.

Mario Capecchi and Oliver Smythies develop gene knockout technology, which is soon applied to neuroscience.

1991
Linda Buck and Richard Axel discover that the olfactory receptor family consists of over 1000 different genes. The anatomical components of the medial temporal lobe memory system are identified.

1993
The Huntington's Disease Collaborative Research Group identifies the gene responsible for Huntington's disease.

1990s
Neural development is transformed from a descriptive to a molecular discipline by Gerald Fischbach, Jack McMahan, Tom Jessell, and Corey Goodman; neuroimaging is applied to problems of human cognition, including perception, attention, and memory.

Reinhard Jahn, James Rothman, Richard Scheller, and Thomas Sudhof delineate molecules critical for exocytosis.

1998
First 3D structure of an ion channel is revealed by Rod MacKinnon.

both biology and psychology and that is beginning to achieve a similar coherence. As a result, fascinating insights into the biology of cells, and remarkable principles of evolutionary conservation, are emerging from the study of nerve cells. Similarly, entirely new insights into the nature of mental processes (perception, memory, and cognition) are emerging from the study of neurons, circuits, and brain systems, and computational studies are providing models that can guide experimental work. Despite this remarkable progress, the neuroscience of higher cognitive processes is only beginning. For neuroscience to address the most challenging problems confronting the behavioral and biological sciences, we will need to continue to search for new molecular and cellular approaches and use them in conjunction with systems neuroscience and psychological science. In this way, we will best be able to relate molecular events and specific changes within neuronal circuits to mental processes such as perception, memory, thought, and possibly consciousness itself.

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45. The work of E.R.K. is supported by NIMH, the G. Harold and Leila Y. Mathers Foundation, the Lieber Center for Research on Schizophrenia, and the Howard Hughes Medical Institute. The work of L.R.S. is supported by the Medical Research Service of the Department of Veterans Affairs, NIMH, and the Metropolitan Life Foundation. We thank Thomas Jessell and Thomas Albright for their helpful comments on the manuscript.

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