STATES OF MIND

NEW DISCOVERIES ABOUT HOW OUR BRAINS MAKE US WHO WE ARE

Adapted from the original talks by

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John Wiley & Sons, Inc.
NEW YORK • CHICHESTER • WEINHEIM • BRISBANE
SINGAPORE • TORONTO

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Introduction

Every day, in the course of ordinary conversation, we use a very small word that we learn early in life. The word is *I*. We say things like "I think so" or "I don't remember" or "I have a headache." And then there's Mark Twain, who wrote, "I have a prodigious quantity of mind; it takes me as much as a week sometimes to make it up."

Beneath the wry joke, Twain was expressing an element of bemused wonder—or exasperation—that many of us might share. Human beings have always wondered, in some fashion, about the self, or consciousness, that seems to inhabit the body we identify as ours and that experiences the world "out there." Who (or what), exactly, is the ubiquitous "I" who so readily thinks, remembers, and feels pain? And where in relation to that "I" is the "mind" that can't be made up?

Although we generally manage to carry on without worrying too much about such philosophical conundrums, most of us, at some point in our lives, have been drawn—if not consumed—by the need to know who we are and to understand how we come by our identity and why we feel and behave the way we do. We question how much we owe to (or can blame on) the set of genes we inherited, to what extent we are the product of the circumstances in which we grew up, and how much is within our own control. When we say of a child, "She's got a temper, just like her dad!" are we reflecting on an innate, inherited characteristic, or on behavior learned from a parent?

Far from being academic, these questions and the answers we seek not only bear on the quality of our relationships with family and friends but also have implications for how we function as a society. To what extent is a bad temper, for example, or an inability to find joy in life, a function of will, and to what extent are they the products of the complex interaction between our genes and our environment? The two debates—over what has been called "the mind-body problem" and over "nature versus nurture"—have engaged philosophers and physicians for centuries.

On the mind-body front, the pendulum has swung first one way and then the other several times. Nearly eighteen hundred years ago, for instance, there was essentially no distinction between the mind and the body. The physician Galen of Pergamum ascribed not only physical health but also psychological temperament, or personality type, and emotional well-being to biological influences—varying concentrations of so-called bodily humors such as blood and phlegm. Galen's approach would be called "holistic" today, the idea being that physicians should attempt to treat the whole person. In the seventeenth century, with the advent of a philosophy known as dualism, this integration of mind and body was sundered. The tenets of dualism were crystallized by the French philosopher René Descartes, who argued that the mind was such an ephemeral phenomenon that it must exist utterly distinct from the obviously physical brain and body. In the nineteenth century, painstaking anatomists countered this notion by showing that disorders of the mind and the emotions arise from injury or other flaws in the physical structure of the brain.

In the past several decades, advances in neuroscience have renewed and clarified the integration of the brain and the mind. We now know, for example, that a number of mental problems,

such as obsessive-compulsive disorder and schizophrenia, are associated with structural abnormalities in the brain and are also responsive to treatment by drugs, allowing us to try to alleviate them with biological approaches. And today, although we have yet to unravel the mystery of consciousness, we know that it arises—somehow—from the activity of the 100 billion nerve cells that make up the human brain.

As many neuroscientists like to say, "Mind is what the brain does." We know that if the neurons in certain regions of brain tissue are damaged through accident or illness, we can lose large aspects of our "self"—the ability to make new memories, speak coherently, feel love, recognize faces, or comprehend what music is. By the same token, we also know that the brain is remarkably adaptable—or "plastic," as neuroscientists describe it—able to respond to virtually every experience by modifying its connections. Indeed, without this plasticity, we could learn nothing new. With it, adult victims of stroke, or young children who have had large portions of their brains removed to control dangerous epileptic seizures, can recover and thrive, because their energetic neurons reorganize themselves to take over missing functions.

Most neuroscientists now argue that the biological organ inside our skulls is both source and repository of our elusive identity and of all aspects of cognition and emotion. The balance of chemicals in our individual brains may predispose us to react to life's ups and downs with a characteristic tranquillity or agitation. Disturbances of that chemical balance can trigger mood disorders and mental illness. And burgeoning research into the connection between the brain and the body is reinforcing the idea that the influence flows in both directions—that is, our attitudes and emotions, once regarded as purely a function of "mind," can affect the health of the body, and vice versa. The

eight scientists who have contributed to this book are united in their belief that any approach to understanding the human mind must take into account both partners in the dance: It is impossible to separate the function of mind from that of the brain.

It is equally impossible to separate the influences of our genes and our environment, although advocates of one side or the other in the debate over nature versus nurture have often tried to do just that. Proponents of eugenics, a term coined by Sir Francis Galton in the late nineteenth century, argued for the primacy of genetic inheritance and were in favor of improving the human race through selective breeding—an argument that was taken to its horrifying conclusion by Adolf Hitler in the mid-twentieth century. Those who argued for the primacy of nurture tended to proclaim that family and societal influences were fundamentally responsible for everything from general intelligence to mental stability.

Today, however, scientists have repeatedly shown that both influences are at work, especially when it comes to mental illness or substance abuse, as Steven Hyman points out in Chapter 1. The particular array of genes we were born with may make us susceptible to manic-depressive illness or alcoholism, for example, but an environmental trigger, or "second hit," must activate the genes in question in order to make us ill or alcoholic. So although we may not be able to modify our genetic inheritance, Hyman reminds us that the brain is phenomenally responsive to experience. If the brain can learn addiction, for example, it can also be taught to unlearn it.

Genes and environment are also at play in the development of our personality, or temperament. In Chapter 2, Jerome Kagan suggests that we come into the world with a brain chemistry that inclines us to be a bold, "I'll try anything once" sort of per-

son, or a timid watcher from the sidelines, or something in between. But nature is also responsive to nurture: Despite being born with a given temperamental tendency, Kagan notes, a fearless, outgoing child can be traumatized into becoming fearful and hesitant, while support and encouragement can help even the most fearful child grow up to be a poised and sociable adult.

The question of a temperamental predisposition, and its underlying physiology, is crucial to any discussion of the mood disorder known as manic-depressive illness (MDI). In Chapter 3, Kay Jamison describes the prevalence of MDI among gifted artists, writers, and musicians and notes that suicide rates among these individuals are well above those for the general population. In describing many studies that suggest that creativity and mood disorders are somehow related, she raises several questions: If the genes that predispose someone to MDI can be identified, should high-risk individuals undergo genetic testing and gene manipulation? By trying to eliminate the genetic roots of MDI in an effort to rid society of this devastating illness, what else do we risk losing?

Not everyone is subject to MDI's cycle of manic highs and depressive lows. More familiar—but just as dangerous—is the phenomenon that we call stress. As Bruce McEwen explains in Chapter 4, the demands of modern life can chronically overload the physiological "fight-or-flight" system that's designed to help protect us from danger. Chronic stress can not only accelerate a host of illnesses but can also cause damage in parts of the brain that are associated with memory—a direct instance of bodily ills affecting cognitive abilities.

The brain-body connection that links our emotions and our health hinges on certain key molecules that are highlighted in Chapter 5 by Esther Sternberg, who describes new findings that pinpoint the substances at work in the nervous and immune

systems. When emotional upsets cause blood levels of the stress hormone cortisol to rise, she explains, the immune system can be shut down, making us susceptible to infection. But too little cortisol can send the immune system out of control, turning the body's defenses against itself. Such findings, Sternberg suggests, make a strong case for the argument that classifying illnesses as either medical or psychiatric is an artificial distinction.

Given that emotions can affect our health so profoundly, it stands to reason that we would benefit from having a clearer idea of how emotions work. But what are emotions, anyway? We all "know"—until we're asked to define it. In Chapter 6, Joseph LeDoux explains his own definition and describes his pioneering research into the biology of one fundamental emotion: fear. Fear plays a crucial role in the formation of emotional memory, whose long-lasting covert effects influence our day-to-day reactions and decision-making ability. Indeed, in describing the workings of the body's fear system, LeDoux notes that its repercussions in memory provide a neurological basis for Freud's theories about the unconscious.

We tend to form indelible memories of events associated with strong emotions such as fear, but we also learn through repetition, a fact that Eric Kandel has put to use in his work on the molecular basis of memory of all kinds. As he explains in Chapter 7, by homing in on the genetic "switch" that triggers the formation of long-term memory from information held in short-term memory, we are gaining a greater understanding of how we remember, why we forget, and what we might someday be able to do about debilitating memory loss.

The formation of memory from what we learn and experience during the day appears to be one of the functions served by our nightly excursions into the surreal territory of dreams, as J. Allan Hobson explains in Chapter 8. As those who remember them

can attest, however, dreams are often extraordinarily bizarre. Hobson argues that these strange narratives may be merely the by-products of the brain's nighttime activity, created by the cortex in an effort to make sense of the spontaneous electric storm that takes place in the brain during sleep. Although these fanciful stories have always been a rich source of imagery and inspiration, Hobson discounts the idea of universal dream symbolism. Noting that our dreams are produced by our individual brains, which in turn are the products of a unique blend of heredity and environment, he suggests that dreams can offer each of us meaningful insights into our own psyches and concerns.

As all this research reaffirms, the fundamental characteristics of human consciousness and identity are that they are shaped and reshaped by a brain that is continually adapting to the world around us. Whether we're reading or walking, dreaming or talking, the particular impulses and pathways of the brain's billions of neurons are storing experience, learning and unlearning, and creating us anew in the process. Santiago Ramon y Cajal, the Spanish physician, anatomist, and Nobel laureate, captured the essence of the mysterious nature of the brain's workings when he described its collection of neurons as "the butterflies of the soul." Even as they rearrange themselves with breathtaking plasticity as we grow from infant to child to adult, something ineffable remains that makes us recognizable to ourselves and others from one day to the next throughout our lives.

1

Susceptibility and "Second Hits"

Steven Hyman

In the course of their lifetimes, as many as one in five Americans—regardless of age, race, or sex[1]—will be affected by a major mental illness. These disorders, which profoundly impair thinking, emotions, and behavior, are the product of structural or functional abnormalities in the brain—as real a biological malady as cancer or heart disease. In recent decades, neuroscience has made substantial progress in identifying some of the ways in which the brain's biology goes awry: imbalances in brain chemistry or circuit function, for example, or structural anomalies. But understanding how brain abnormalities arise remains a difficult challenge. Why does schizophrenia or manic-depressive illness strike some members of a family and not others? Can those who remain healthy be assured that their children will also be free of the disease? The short answer is, No one can say for certain, one way or the other. The most scientists can offer are statistical probabilities—a 3 percent chance, or a 14 percent chance, or a 50 percent chance that a child will become ill—depending largely on family history.

As Dr. Steven Hyman, director of the National Institute of Mental Health, explains in this chapter, the interplay of genes

and environment in the onset of mental illness is extremely complicated. Mental disorders are probably the product of the interaction between several genes that confer vulnerability to a given disease; the more genes are involved, the harder it is to detect any one of them and to unravel its precise role. Equally problematic is the task of identifying possible environmental "second hits"—nongenetic factors that convert a genetic susceptibility into full-blown illness. Is it something that occurs in the womb, the result of maternal malnutrition, or a bout with a virus? Or is the second hit a trauma that occurs at birth or in early childhood, when the brain is extremely malleable? Although scientists can explain many aspects of how the normal brain functions, much remains unknown. As a result, says Hyman, trying to understand what goes wrong in the brain to produce serious mental illness "may be the most difficult and complex activity that human beings have ever undertaken."[2]

As DAUNTING as the challenge is, there is no more compelling reason to attempt to understand the causes of mental illness than that these various afflictions exact an enormous human cost. The derangements of thought, emotion, and behavior that characterize mental disorders such as manic-depressive illness, depression, schizophrenia, and addiction are agonizing not only for the afflicted individuals but also for their family and friends. The torment of coping with a parent's hallucinations and emotional withdrawal, a sibling's psychotic rage, or a child's self-destructive behavior can exhaust families and leave lasting scars even on those who escape the illness itself. As one woman, who as a child watched both her older brother and her older sister succumb to schizophrenia, said, "They no longer inhabit my present life, but their illnesses haunt me like ghosts."[3]

Part of the torment for family members has long been the uncertainty of knowing whether they or their children might be subject to the same disorder or, in the case of parents of an affected child, whether they could have done something to prevent it. Although physicians as long ago as the mid-eighteenth century recognized mental disorders as illnesses,[4] they could offer little in the way of effective treatment. With no understanding of the causes of irrational or violent behavior, society was more likely to react with suspicion and fear than with compassion. To this day, many people living with the devastating hopelessness of clinical depression, for instance, are still ashamed to seek help. Families try to hide a loved one's schizophrenia or downplay delusional symptoms as mere "eccentricities."

Since the mid-1950s, however, progress in the fields of psychiatry, neuroscience, biology, and genetics has begun not only to remove the stigma that was once attached to these illnesses but also to help produce better treatments for those who are ill. Gradually, the public has come to recognize that mental disorders are the result of something gone wrong in a critical organ of the body: the brain. Thanks to modern brain-imaging techniques such as structural magnetic resonance imaging (MRI), positron-emission tomography (PET), and functional magnetic resonance imaging (fMRI), which reveal regions of the brain that are active under different circumstances, scientists have uncovered subtle and not so subtle abnormalities in brain structure and activity in patients suffering from various mental illnesses. In addition, many years of research have shown that these abnormalities have a strong hereditary component. That is, the risk of developing a mental illness increases significantly if a close family member is affected.

But how do genes cause a defect in the brain? And why does a given illness seem to skip around in a family, affecting one sister

but not another? Neuroscientists and geneticists have some answers, but by no means all. To appreciate the scope of the challenge these researchers face, we need first to appreciate the intricacy of the organ whose workings they are attempting to understand.

The human brain is probably the most complex structure in the known universe. At birth, an infant's brain contains about 100 billion nerve cells, or neurons—a quantity that rivals the number of stars in our galaxy. But when we marvel at this complexity, we're not just talking about sheer number of cells. Rather, it's what these cells do. Unlike most other cells in the body—a muscle cell or a fat cell or a liver cell, for example—the neurons of the brain and the central nervous system carry on complex conversations with one another. Each of these billions of neurons makes, on average, several thousand contacts with other cells—and in some cases as many as 200,000. Consider the challenge of talking on the phone with 1,000 or 10,000 people at once and keeping all the conversations straight.

Yet whether we're awake or asleep, our brain cells are doing the neuronal equivalent of a mass phonathon, sending and receiving chemical messages triggered by electrical impulses. They do this by means of specialized appendages. Each nerve cell has a single long fiber called an axon for transmitting information and a fine filigree of fibers called dendrites for receiving information. [Figure 1] The length of a given neuron's axon varies. Some are quite short, but others may extend up to three feet, carrying an electrical impulse from, say, the base of the spine to the tip of the big toe. Three feet may not sound like much, until one imagines the nerve cell as a kite three feet across—with an axon tail that's forty miles long. Within the brain alone, given its billions of brain cells, there are probably about 3 million miles of axons.

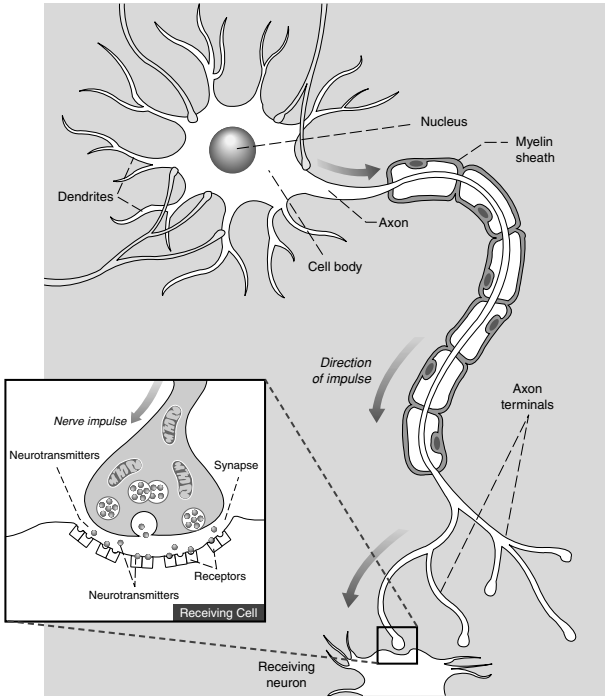

Figure 1 A nerve cell, or neuron, sends an electrical pulse down its myelin-insulated axon to the axon terminals. There chemicals called neurotransmitters are released to float across a small gap, the synapse, to the dendrites of the receiving neuron. If the sum of all incoming signals is sufficient, the receiving neuron will fire, sending an electrical pulse along its own axon to the next neuron in line. Altered from Kibiuk/Society for Neuroscience by Leigh Coriale Design and Illustration. Used with permission.

At its tip the axon splits into terminal regions—sometimes only a few, in other cases as many as several hundred. Each terminal converts the axon's electrical impulse into a chemical one, releasing molecules called neurotransmitters into the tiny gap, or synapse, between it and the receiving neuron. On the receiving end is a mass of fibers called dendrites that emanate from the cell body; each dendrite usually has many branches, each with

many receptive zones, allowing each neuron to receive messages from many others. The neurotransmitters—dopamine and serotonin are two of the more familiar ones—float across the synapse to be picked up by specialized receptors, each tuned to a specific neurotransmitter. Any single neuron might communicate using two or three different neurotransmitters, but some are amazingly multilingual; some neurons in the hypothalamus communicate using as many as eight different neurotransmitters. Moreover, researchers have recently discovered that a given neurotransmitter, rather than working in strict "lock and key" fashion with just one or two receptors as previously believed, may work with as many as several dozen or more. So far, for example, fourteen different receptors have been found for serotonin.[5] These myriad brain chemicals may excite or inhibit electrical activity in the next cell down the line, but some have effects far more complex and subtle. Since a given target cell is receiving tens of thousands of these messages at once, it must add them up, in effect. If the sum of the signals exceeds a certain threshold, the target cell will fire, sending electrical impulses along its own axon. At the same time, the incoming signal may trigger changes in the receiving cell itself.

Plasticity and Learning

The brain's wiring and communication system is not only stunningly complex but is also constantly changing in response to the environment. Indeed, scientists have been excited by recent findings on the degree to which neurons in many parts of the brain continue to undergo structural change not just through childhood and adolescence, as was once believed, but throughout life. The good news for those of us who are well past young

adulthood is that mental exercise, like physical exercise, may keep the brain supple and fit into our eighth and ninth decades. New experiences, at whatever age, can cause the brain to physically alter its synapses—a characteristic known as plasticity. Indeed, those who compare the human brain to a digital computer do the brain a major disservice. No digital computer comes equipped with an army of lilliputian technicians who climb around and rewire the machine in response to every environmental stimulus.

A key function of some of this rewiring of the brain is learning. Most of us, for example, if prompted with a date like 1776, can probably dredge up "Declaration of Independence!" Some of us, if asked the date of the Norman Conquest, can instantly reply, "1066." These facts were drummed into us somehow by our elementary-school teachers, and we've carried them around for decades. Now, how is that possible? And how is it possible that someone who hasn't been on a bicycle in years can get on one today and still know how to ride? How are "Norman Conquest—1066" and "how to ride a bike" stored?

When we learn facts about the world, or when our bodies learn how to ride a bike or play tennis, our brain is literally remodeling synaptic connections to store the information. This process may involve adding or pruning synapses, strengthening or weakening existing ones. Investigators using techniques such as PET and fMRI have seen wholesale changes in the pattern of brain activity in people who are trained to perform new motor tasks.

If all this remodeling occurs in response to the environment, or "nurture," where does "nature" come in? It turns out that in order to understand how this neuronal transformation occurs—and it occurs all the time as we go about our daily lives—we have to adjust our focus from the level of neurons down to the

level of genes. Within each neuron, as with all other cells in the body, is a nucleus that contains an individual's genetic material. Genes determine not only how the brain is built. They also supply the recipes for how its architecture can get rearranged throughout life.

Humans have about 80,000 genes, divided among the 23 pairs of chromosomes. (A full set of chromosomes, all of our inheritable traits, is called the genome.) Chromosomes are long molecules of deoxyribonucleic acid, or DNA, the famous double helix; DNA encodes the information to construct a human being in a simple alphabet made up of molecules known as nucleotide bases, whose names are abbreviated as T, C, G, and A.

Each gene, on average, is several thousand nucleotide bases long and contains the information to make a single protein. Indeed, that is the major function of genes: to instruct the cell in the manufacture of proteins. Proteins, in turn, are critical building blocks of cells. Receptors for the various neurotransmitters are proteins. Some neurotransmitters themselves are small proteins. Enzymes, the molecules that control all the chemical reactions in cells, are proteins. Proteins called growth factors cause nerve cells to grow and sprout dendrites; other proteins work to shrink them. Thus is the very nature of each type of cell in the body determined by its repertoire of proteins.

Given that every cell in your body has the same complement of 80,000 genes, which can make more than 80,000 proteins (because some genes make more than one protein), a fundamental problem during development is to make only the right proteins for the right cells. The cells that produce our hair and fingernails, for example, are expected to produce keratin but not hemoglobin, which is the job of cells in the bone marrow. And we'd prefer that the cells in the midbrain not produce keratin to

make fingernails when they should be producing the enzymes to make the neurotransmitter dopamine.

How do the cells know what to do? Through a precise system involving specific sequences of DNA and special controlling proteins, the cells are told which genes can be on and which should be off in any given cell. This is how we get a muscle cell instead of a nerve cell, for example.

During gestation, fetal brain cells multiply rapidly as the brain and the spinal cord assemble themselves. Fascinating research suggests that the fetal brain pulls itself up by its own bootstraps, in effect. Well before there's even a brain as such, these cells begin firing, generating pulsing waves of electrical activity that physically shapes the connections of the brain even as it is still growing.[6] Following orders from perhaps 50,000 genes—more than half the human genome—neural cells begin to lay the brain's foundations, making a kind of "best guess" as to what will ultimately be needed. In the process, they migrate to distant locations to put in place the connections that will link one part of the brain to another. The cerebral cortex, for example, is a structure that comes late in the development of the human brain. The billions of cells that will ultimately mold this outer rind of the cerebrum must somehow push through dense clumps of cells that are already formed[7]—a migratory mass journey akin to having everyone on the West Coast decide to move across the continent.

All this electrical pulsing and neuronal travel are dictated by the genes, which spell out the brain's basic wiring scheme on a kind of macro level, for example, linking the retina to a relay station in the thalamus and the thalamus to the visual cortex. Despite all the information carried in our DNA, however, there's still not enough to produce the final working circuit dia-

gram of our brains. What fine-tunes the precise synaptic connections that nerve cells make with one another is activity produced by the environment.

The Role of the Environment

Even at the earliest stages of development—a one- or two-celled embryo—genes aren't working in a vacuum. They're getting environmental information—a changing supply not only of nutrients but also of instructions—from the cytoplasm of the cell, and from the womb, the uterus. Maternal malnutrition, infections, or drug abuse, for instance, can intrude on the finely orchestrated dance between genes and environment. Indeed, insults to the developing fetal brain are thought to contribute to some forms of epilepsy, mental retardation, autism, and schizophrenia.[8]

Assuming that all goes well in the prenatal environment, a baby comes into the world with its full complement of 100 billion neurons and the appropriate initial connections. But the brain is far from a finished product at this stage. Environmental stimulation continues to be vitally important in the period immediately after birth, and for the first several years of life, in refining and strengthening the still-unfinished blueprint that the genes have laid out. For the human visual system, for example, those environmental experiences consist of visual information. In the case of the development of the emotional circuitry of the brain, we can speculate that early experiences of fear or nurturing will fine-tune certain emotional connections throughout life.

The visual system has been well studied and serves as a dramatic example of the way the environment affects brain wiring.

We know this partly as a result of some tragic "experiments of nature" and partly because of the pioneering animal studies of David Hubel and Torsten Weisel in the 1960s. Occasionally a child will be born with a congenital cataract, a clouding of the lens in one eye that blocks light. If this cataract is removed, the eye will be perfectly normal. But if the cataract is not removed until after the age of three, the child will be blind in that eye, even though the eye itself is optically restored to normal. That is because the wiring of the visual system, the wiring of the connections of the retina to the thalamus and the thalamus to the cerebral cortex, are remodeled by use—by neural firing that causes the release of neurotransmitters.

The first three years of life are a so-called critical period of plasticity for the visual system, a time when these brain circuits have an enhanced ability to respond to environmental information. In order to stabilize synaptic connections in the visual system so that they're retained long-term, the brain needs visual input—light impinging on the retina and activating the release of neurotransmitters, especially a neurotransmitter called glutamate. This activity not only paints a picture of the visual world; it also has an influence on the strength and vitality of the connections in the areas of the brain that are responsible for processing vision. So, in the case of a cataract, if one waits too long beyond the critical period to remove the cataract, the connections from the good eye, which have been stimulated by visual input, literally outcompete the neurons from the blinded eye. They take over nearly all connections to the visual cortex.

We know about critical periods and plasticity in the visual system best of all, but we also know something about it in other primary sensory systems, systems of touch and vibration, and we know a bit about it in the formation of our ability to process and speak language. For instance, we've learned that the age at

which you learn a second language determines whether you learn it with or without an accent. Henry Kissinger speaks with a very heavy German accent, but his brother, who is somewhat younger, speaks accentless English. Presumably, when the family immigrated to the United States, Henry had already passed the age of enhanced plasticity for certain motor aspects of learning a language, and his brother had not.

Turning Genes On and Off

How does a stimulus such as light change the way the neurons physically connect to one another? By activating genes, which direct the synthesis of proteins, which, in turn, build or prune synapses. This process of synaptic remodeling occurs not only during brain development but with all learning that produces a long-term memory. Similar processes in different regions of the brain also underlie many responses to psychotropic drugs, brain injury, and illness.

The idea that neural communication itself, drugs, or other stimuli can actually turn genes on or off may seem strange initially, but there is actually an ordinary example from outside the brain that illustrates this phenomenon: the pursuit of physical fitness. Let's say you decide to start working out at the gym; your goal is to build some muscle and get stronger. You begin lifting weights, and after the first workout the major result is that your arms ache for several days. This is because you've stressed the muscle fibers in your arms. But if you lift enough weight, hit the gym enough times a week, and keep at it long enough, eventually you'll have bigger muscles. How does that happen?

The exercise is a kind of stress to the muscle cells. The cell membrane sends a signal to the nucleus of the muscle cell and

turns on genes that make muscle proteins; these proteins are needed to respond to the stress caused by the muscles' having to lift unaccustomed weight. Properly carried out, with rest periods for recovery, the repeated stress leads to a stable adaptation to this state of affairs, resulting in increased muscle mass.

As you might expect, such processes are much more complicated in the brain, and produce complex and subtle results, but the principle is the same. Just as muscle cells respond and adapt to signals from the environment, so do brain cells, although in the case of brain cells the signals are mediated by the action of neurotransmitters or, sometimes, by drugs. When neurotransmitters bind with their specific receptor on the outside surface of a cell, a cascade of information flows across the cell membrane into the cell and even to the cell nucleus, with its cache of genes. As described above, each gene has regions containing the information to produce a protein as well as regions that control whether that necessary series of events will occur. (Gene "expression" is the term for the activation of a gene so that the information in its protein coding regions will be "read out," in effect.) So information coming from the environment—information carried by neurotransmitters and then receptors and then all of the intervening signaling steps—can chemically modify some of these control proteins, turning the genes on and off.

Of Mendel and Multiple Genes

So far, we have been describing how our genes are turned on in the right cells at the right time during development and in response to particular environmental stimuli. But we must also address the fact that the versions of each of the genes we inherit from our parents may be subtly different from one individual to

another. These differences—a variation in perhaps one or two nucleotide bases in one version of a given gene versus another version of the same gene—contribute to the rich diversity of our species. However, these differences also mean that some of us are more vulnerable than others to illness, including mental illness.

In his original genetic analysis, the Austrian monk Gregor Mendel focused on the traits of pea plants that were each determined by variations in a single gene. Mendel found, for instance, that variation in one gene determined whether a pea plant was short or tall; in another, whether it had yellow peas or green peas; and in yet another, whether the peas were wrinkled or smooth, and so on. Important traits that can be attributed to one gene are thus called mendelian traits.

A number of serious human diseases are mendelian. A single defective gene, for example, can produce cystic fibrosis; another gene variant results in sickle-cell anemia. Among brain diseases, Huntington's disease—which produces abnormal involuntary movements, emotional disturbance, and progressive dementia—is caused by a single abnormal gene, which has recently been identified. The finding of this gene and its protein should begin to provide important clues for appropriate therapy.

When it comes to mental disorders, however, nothing is that simple. We've long known that disorders such as schizophrenia, manic-depressive illness, and major depression tend to run in families, as does alcoholism. Pinpointing whether this susceptibility is the result of shared genes or shared environmental stresses has been difficult, but over the years studies involving identical and fraternal twins have helped us determine the relative contribution made by genes and environment to these disorders.

Identical twins come from the same fertilized egg and share 100 percent of their genes. Fraternal twins, on the other hand,

come from two different fertilized eggs and thus, on average, share only 50 percent of their genes, as would any biological siblings. To evaluate the contribution made by heredity, the rate of a given disorder in identical twins is compared with the rate in fraternal twins. If identical twins are significantly more likely to share a disorder, then heredity is probably an important factor. For instance, in manic-depressive illness, if one identical twin is affected, the other has a 60 to 80 percent chance of also having the disorder. A fraternal twin of a manic-depressive individual, by contrast, has only an 8 percent chance of having the disorder. Similarly, the identical twin of someone who has schizophrenia has a 46 percent chance of being affected, whereas a fraternal twin has only a 14 percent chance of being affected.[9]

Adoption studies are also useful in weighing the relative roles of genes and environment. That is, we can ask whether children who were adopted early in life have more in common with their biological or with their adoptive parents. For example, one might have believed that family experiences create the lion's share of vulnerability to alcoholism. However, adoption studies in three Scandinavian countries showed that genes, more than familial environment, influence the risk of someone's becoming an alcoholic. In these studies, adopted sons whose biological fathers were alcoholic were more likely to be alcoholic themselves than were those whose adoptive fathers were alcoholic and whose biological fathers were not. In families where the genetic dice are loaded, so to speak, these genes appear to increase the risk of alcoholism nine- to tenfold over the ordinary sporadic incidence of alcoholism.

Since even identical twins do not always share a disorder, however, scientists cannot emphasize enough that the environment's role in determining whether susceptibility is converted into illness is critical. This complex interaction between

multiple genes and multiple environmental factors—the so-called second hits—explains why some families may have several members who are affected with a given disorder, why one child and not another becomes ill, and why the disorder may skip generations.

The idea of second hits is perhaps most familiar in the context of cancer. People who have genes that make them susceptible to cancer may never get it. But if they smoke, that might be an environmental second hit that converts genetic vulnerability into disease. Other people, with different genes, may smoke with impunity—although they may contract a different malady, such as emphysema or heart disease. We also have to keep in mind that a second hit can occur by pure random chance during pregnancy. Building the brain is a very complicated process, and even identical twins manifest many developmental differences. The key thing to remember, though, is that the brain of someone who has a disorder like schizophrenia or depression is functionally and often anatomically different.

The Mechanism of Addiction

We can get a sense of how functional changes in the brain create particular disorders if we look at how drugs of abuse modify the brain to produce addiction. Someone who is ill with alcoholism, for instance, may be past the stage of denial, may fully realize that he is losing a job, friends and family, and his health, may feel terrible and not even enjoy drinking anymore—yet, despite all of these negative consequences, he is unable to control his use of alcohol. In people who are vulnerable to addiction because of genetic or environmental factors, drugs or alcohol alters

the way the brain functions, commandeering, in effect, their motivational control.

The key mechanism of addiction resides in a particular chemical system of the brain, involving the neurotransmitter dopamine. There are several dopamine systems in the brain, and they have many jobs. The one that relates to addiction operates between certain areas of the midbrain and the limbic system; it is therefore associated with emotional behavior.

One way of characterizing the job of this dopamine circuit is that it's a reward system. It says, in effect, "That was good, let's do it again, and let's remember exactly how we did it." This reward circuit is so useful that it has been preserved throughout evolution; as a result, we can study it in animal models. Certainly things like sexual reproduction have to be sufficiently rewarding, or nature's experiment with the mechanism would have been a bust.

But even though something like sexual attraction may be hardwired, this circuit also has to be able to learn in order to discover what things in the world are good for the organism. From animal experiments, we've learned that discovery of a highly palatable new food, for example, triggers the release of dopamine in the brain. The pleasant taste was rewarding, and the dopamine circuit makes sure the brain makes a note of it and will remember how to do it again.

Addictive drugs, it turns out, are molecular mimics: They masquerade as neurotransmitters. Coca, or cocaine, in particular, looks enough like dopamine chemically to interfere with the way the brain ordinarily handles the real thing. Normally, dopamine is reabsorbed shortly after its release into the synaptic gap between neurons by the neuron that released it. But cocaine resembles dopamine enough to fool the protein transporters

that take up dopamine. The transporters bind cocaine instead, the removal mechanism gets clogged, and dopamine builds up in the synaptic gap. This excess of dopamine makes the cocaine user feel euphoric and extremely alert.

But the price the drug user may pay is a terrible one: addiction. Just as lifting sufficient weight often enough creates adaptations in muscle cells, taking cocaine long enough creates adaptations in the nerve cells. How do they adapt? Dopamine changes the expression of genes in these nerve cells. The activated genes make proteins, which in turn start pruning some connections and strengthening others. As neurons alter their connections in various regions of the brain, the nature of the neural communication between regions is changed.

Moreover, since the drugs have led to a flood of dopamine, the neurons in the brain that normally produce dopamine decrease production for a time. Then, when the cocaine stops coming at the end of a binge, the natural release of dopamine, which is already low, results in sudden deprivation and causes circuits to malfunction. Instead of euphoria, the addict now feels depressionlike symptoms, an inability to take pleasure in the world. This kind of response drives the cycle of renewed drug taking.

Even as drugs directly affect molecules and cells, they also affect certain aspects of learning. Because the dopamine reward circuit teaches the brain, "That was good, let's do it again, and let's remember exactly how we did it," the addict has learned to associate places where he used drugs, and friends with whom he used drugs, with the drug-induced euphoria. Even after addicts have been detoxified, and some of the brain adaptations have been reversed—just as some months after you've stopped lifting weights the muscles shrink—other important changes in the brain don't revert, including this deeply etched learning. This is

the root cause of relapses: When people who have been addicted to drugs see the friends with whom they once used drugs, or pass the alley where they used to shoot up, for example, they can suffer intense waves of desire for the drug.

If cocaine takes such advantage of the brain's pleasure and reward system, how is it that not everyone who tries the drug becomes addicted? Cocaine, like all drugs, has side effects. Thus, for some people it can have effects in other circuits in addition to the dopamine reward circuit. Given their particular genetic makeup and predisposition, these people might feel agitated and anxious to such an extent that the unpleasantness outweighs any pleasure they experience. They may therefore be resistant based partly on their own genetic makeup. Or they may, because of environmental factors such as upbringing, recognize the drug's potential for harm and simply decide not to touch it. People who get snared by drugs may not have these kinds of warning signals.

The critical point to remember in all of this is that in the dance of life, genes and environment are absolutely inextricable partners. On the one hand, genes supply the rough blueprint for the brain. Then stimulation from the environment, whether it's light impinging on the retina or a mother's voice on the auditory nerve, turns genes on and off, fine-tuning those brain structures both before and after birth. Genetic predispositions determine, to some extent, which features of the environment an individual responds to, even at an extremely young age. This give-and-take determines our genetic vulnerability to mental disorders or addiction, and whether that vulnerability will lead to illness.

When someone becomes ill, he and his loved ones want first to have the illness identified and then to know whether it can be treated. But the next question is often "How did I get this

disease in the first place?" Patients instinctively understand that knowing something about the causes of disease leads to better treatment as well as prevention and perhaps a cure. As researchers learn more about the many forms of mental illness, it becomes easier to test ideas for treatment, which in turn leads to a more sophisticated understanding of the disease itself. Given the breathtaking complexity of the genes/environment dance, mental disorders are considerably more difficult to fathom than sickle-cell anemia and Huntington's disease. The challenges are indeed daunting, but with modern tools and research skills, they are not insurmountable. The search for susceptibility genes in mental disorders will be exciting. Finding them will be life-changing for many.