The Mind and the Brain: Neuroplasticity and the Power of Mental Force - Jeffrey M. Schwartz, Sharon Begley (2003)

Chapter 3. BIRTH OF A BRAIN

Martha Curtis was, if not a musical prodigy, then certainly musically gifted. She was playing the piano at age five and at nine took up the violin, eventually coaxing from the instrument passionate and even heartbreaking concertos. But something else made Martha stand out: she had begun suffering convulsions at age three and a half. Her doctors diagnosed her condition as epilepsy and started her on the standard medication prescribed to control the seizures. But the seizures only continued, and by the time she was eleven, they were sometimes leaving the little girl unconscious on the floor, terrifying her parents. Martha soldiered on, however, and won a place in the junior orchestra at Michigan's Interlochen Arts Camp, from whose academy she graduated as her class's salutatorian. But by the time she entered the Eastman School of Music in the mid-1970s, she was seizing on stage. As a twenty-something, while performing with various orchestras, Martha had seizures that punched through the pharmaceutical overlay of the drugs frequently and relentlessly.

In April 1990, she suffered four grand mal seizures, three while performing. Knowing that no orchestra would let her back on stage if she kept seizing, she sought help at the Cleveland Clinic. There, the neurologist Hans Luders took Martha off drugs and admitted her to an inpatient epilepsy unit, where electrodes could monitor her temporal lobes twenty-four hours a day. The electroencephalogram showed a constant storm of abnormal electrical activity emanating from Martha's right temporal lobe and spreading over her entire brain like a fast-moving squall—the hallmark of epilepsy. Surgery to remove the spawning ground of the storms, Luders told his patient, was the only option: the quantity of carbamazepine (Tegretol) needed to quiet the pathological electrical activity, Luders said, was already toxic. There was one problem, however. The right temporal lobe seems to be where the brain stores musical memories. Removing it might well eliminate Martha's epilepsy; it might also leave her unable to play the violin ever again. That was something she could hardly face. It was only because she had music in her life than she had been able to bear her illness. "I am alive today," she said in 2000, "because I had a violin."

Martha had surgery in January 1991. As soon as she left intensive care, she took up her violin and, fearing the worst, tried to play a Bach composition. She chose it because, before her surgery, she had found it one of the hardest pieces to play from memory. She nailed it. But although her musical ability seemed intact, her brain seemed to have been left too intact: the surgery had apparently not removed enough of her right temporal lobe (specifically, it had left behind too much of the hippocampus) : Martha's seizures persisted. She returned to Cleveland for a second operation. This surgery removed all the hippocampus and much of the amygdala, but the seizures continued, for they were originating from a specific tiny spot in the

amygdala. But still Martha could play. When she asked for a third surgery, her doctors warned that taking away so much of her right temporal lobe could prove catastrophic, leaving her paralyzed or even dead. But Martha had decided that she simply could not go on living with the unpredictable and debilitating seizures.

By the time she emerged from the third surgery, close to 50 percent of her right temporal lobe, including the entire hippocampus, was gone. So were her seizures. Her musical memory, however, was very much intact, allowing her to memorize complex pieces even better than before her surgeries, when the anticonvulsants left her in a mental fog. Her brain, doctors concluded, must have been damaged when she was still a toddler, probably by the measles she contracted at age three. Because Martha had begun learning music at such a young age, her brain, it seems, adapted to the damage, with the result that regions other than the abnormal right temporal lobe were drafted during childhood to support musical memory. Because the real estate that the brain usually zones for musical memory was essentially unusable, the brain—exploiting its youthful plasticity—picked up and moved its musical operations across the neural road.

At Johns Hopkins University Medical Center, surgeons challenged the adaptability of a child's brain even more. In 2000 a three-and-a-half-year-old girl named Alexandria Moody had arrived at the Baltimore hospital from her home in Indiana with her mother and stepfather, suffering from chronic seizures. Her physicians back home suspected the little girl was suffering from a brain aneurysm, but an MRI revealed something completely unexpected: the entire left hemisphere of Alex's brain had suffered severe developmental abnormalities. The seizures seemed to be emanating from there, concluded John Freeman, a specialist in pediatric epilepsy. He recommended a complete hemispherectomy—removal of the entire left side of the brain. The operation sounds radical, and it is. But starting in the mid-1980s it became the treatment of choice for children suffering from uncontrollable and often life-threatening seizures due to developmental abnormalities, stroke, or Rasmussen syndrome that do not respond to drugs. Although the brain's deep structures (the brainstem, thalamus, and basal ganglia) are left intact, patients almost always suffer some paralysis on the side of the body opposite the lost hemisphere. But the reward is generally worth the risk: in June 2001, Hopkins surgeons performed their one hundredth hemispherectomy.

The pediatric neurosurgeon Ben Carson performed the operation on Alexandria. Having done more than eighty hemispherectomies since 1985, he was optimistic. "If you see the patients who have had hemispherectomies, you're always amazed," he said. "Here they are, running, jumping, talking, doing well in school. They're able to live a normal life"—despite losing half their brain. What saves these children is their youth. "You can take out the right half of the brain or the left half," Carson said. "Plasticity works in both directions. The reason it works so well in very young patients is that their neurons haven't decided what they want to do when they grow up. They're not committed. So they can be recruited to do other things. Whereas if I had a hemispherectomy it would be devastating." The worst a child suffers from

losing half her brain, however, is some impairment of the peripheral vision and fine motor skills on one side of the body.

The brain of a child is almost miraculously resilient, or plastic: surgeons can remove the entire left hemisphere, and thus (supposedly) all of the brain's language regions, and the child still learns to talk, read, and write as long as the surgery is performed before age four or five. Although in most people the left cerebral hemisphere supports language, the brain, it seems, can roll with the punches (or the surgery) well enough to reassign language function to the right cerebral hemisphere, all the way over on the other side of the head. Therefore, if the brain suffers damage before age two, and loses the areas originally designated as language regions, it usually reorganizes itself to reassign those language functions to another area. By age four to six, a brain injury that wipes out the original language areas usually leaves the child with a profound learning deficit, although she will typically retain the language she had learned up to then. After six or seven, however, the brain is already becoming set in its ways, and loss of its language regions can leave a severe and lasting language deficit. If an adult suffers damage to the left perisylvian, the site of language areas in the brain, the result is typically (though as recent stroke research shows, not always) permanent *aphasia*, the inability to use or understand words. A preschooler can recover from the loss of half her brain, but a little lesion in the same hemisphere leaves an elderly stroke patient mute. So although the brain of a young child retains impressive plasticity, that malleability yields, within a few short years, to something like neural obstinacy: the brain balks at rearranging itself in the face of changed circumstances.

As far as scientists can tell, then, a young brain can usually compensate for injury to a particular region by shifting the function of the damaged region to an unaffected region. But this comes at a cost. The area to which an otherwise-lost function is shifted becomes neurologically crowded, says Jordan Grafman of the National Institute of Neurological Disorders and Stroke, part of the National Institutes of Health. As a result, when the brain tries to execute two tasks in adjacent regions it can cause a sort of traffic jam. Grafman offers the example of an adolescent boy whose brain had been injured years before in a freak childhood accident. His right parietal lobe, a structure that supports visual and spatial skills, suffered a lesion. Yet despite the injury, the boy developed normal visual and spatial skills. Oddly, however, he had great difficulty with math, which is normally a function of the left parietal lobe. Through brain imaging, researchers learned that functions ordinarily controlled by the (injured) right side of the brain had moved over to the left hemisphere. Spatial skills typically develop before math skills do. As a result, when it came time for the child to learn math, the region of his brain that would ordinarily be responsible for that function had already been taken, and there was little neural real estate left to support mathematical reasoning.

Young brains are also relatively nimble at a form of neuroplasticity called *cross-modal reassignment*. This occurs when a brain region that ordinarily handles one form of sensory input does not receive the expected input. Rather than sit around

unused, it seems, that region becomes more receptive to receiving a different input, as a satellite dish receiving no signal when pointed in one direction shifts to catch signals from another direction. Such reassignment within the brain seems to explain the changes that occur in children who become blind at a very young age. The visual cortex no longer receives sensory input from the retina through the optic nerve, and as a result the somatosensory cortex, which receives tactile input, invades areas normally dedicated to processing visual input. People who have been blind from birth often have an exquisitely sensitive sense of touch, particularly if they learn to read Braille when still young. The feel of the raised dots is processed in the visual cortex.

Similarly, in children who are congenitally deaf, the brain seems to reassign its auditory cortex (which is receiving no auditory information) to process visual information instead. In one clear demonstration of this, scientists exposed subjects who had been deaf since birth to a flash of light in their peripheral vision: the auditory cortex experienced a wave of electrical activity, showing that it had been rewired for sight rather than sound. What seems to have happened is that, during gestation, a visual neuron from the retina took a wrong turn and found itself in the auditory cortex. Under normal circumstances, the connections that neuron formed with other neurons would wither away; retinal neurons just don't make connections in the auditory cortex. But in a deaf child auditory neurons are silent and so offer no competition for the wayward retinal neuron. Synapses made by the wayward neuron survive and actually come in handy: congenitally deaf people typically perform better on tests of peripheral vision than people with normal hearing, probably thanks to these extra visual synapses. And the deaf often use their auditory cortex to register sign language; people with normal hearing typically use the visual cortex.

Since the early 1990s, MIT researchers led by Mriganka Sur had been probing the limits of neuroplasticity in somewhat unheralded lab animals: newborn ferrets. In these animals as well as in humans, the optic and auditory nerves grow from the eye and the ear, respectively, through the brainstem and thalamus before reaching the visual or auditory cortex. In humans, as we'll discuss later, this basic wiring plan is present at birth; in ferrets, however, these connections reach the thalamic way station to the cortex only after birth. In their breakthrough experiment, the MIT scientists took advantage of this delay. They lesioned the normal inputs to the auditory thalamus on one side of the brain. With the competition out of the way, as it were, projections from the retina, arriving at the thalamus, grew into the auditory cortex. Now the auditory cortex on that side was receiving signals from the retina and only the retina.

The result: When the ferrets were shown flashes of light on the rewired side of their brain, they responded not as if they saw the light but as if they heard it. The retinal nerve had carried the signal to the auditory cortex. This part of the brain, normally dedicated to sensing sounds, had been rewired to respond to sight.

Whatever the zoning law that originally destined this patch of cortex to bloom into primary auditory cortex, on receiving input from the retina it was transformed into the animal's primary visual cortex. The result: when the ferrets were shown a flash of light, they saw it with their auditory cortex. And there was more. Just as in the visual cortex of normal ferrets, the "auditory" cortex of rewired ferrets contained neurons that specialized in inputs of different spatial orientations—vertical, horizontal, and everything in between. The ferrets consistently responded to a light stimulus presented to the rewired auditory cortex as if it were indeed a light signal, even though the retinal neurons carrying the input fed in to what is normally the turf of "auditory" cortex. This bears emphasizing. Whether the nerves run from the retina or from the cochlea, they carry signals in the same way, through electrical impulses that I'll discuss later. There is nothing inherently "sightlike" or "soundlike" in the signals. It was once considered a fundamental principle of brain organization that the way signals are perceived depends on which part of the brain processes them. In the rewired ferrets, retinal nerves carry signals to what had been auditory cortex. Yet the rewiring had given the auditory cortex a new identity, turning it into a de facto visual cortex. As Michael Merzenich of the University of California, San Francisco, commented, "The animals 'see' with what was their auditory cortex…. [I]n these rewired animals, the experience of sight appears to arise from visual inputs to the auditory cortex area." The findings reminded Merzenich of a comment William James once made: if we could tinker with the nerves so that exciting the ear activated the brain center concerned with vision, and vice versa, then we would "hear the lightning and see the thunder."

Before exploring further the neuroplasticity of the developing brain, let's review some basic neurobiology. First, some elementary anatomy: a neuron in the brain consists, typically, of a cell body called the *soma*—Greek for "body"—which measures 10 to 100 micrometers across (100 micrometers equals 0.1 millimeter). The soma contains all the little goodies that keep the cell metabolizing and synthesizing proteins and performing all the other housekeeping functions that cells of all kinds carry out. From the soma sprout numerous multibranched tentacles, called *dendrites*, like snakes from Medusa's head. The dendrites' chief function in life is to receive incoming electrochemical messages from other neurons and carry the messages to the cell they're part of. Dendrites are relatively thick where they emerge from the cell body but divide at dozens if not hundreds of branch points, becoming thinner and wispier each time. The number of dendrites varies tremendously, depending on the function of the cell.

Neurons also sprout from their soma a single *axon*, a long fiber that extends away from the cell body like a string from a balloon and whose job is to carry information to another neuron. This information takes the form of electrical currents. Where an axon from a transmitting neuron terminates on a receiving neuron, it develops special structures, including little holding tanks for neurochemicals. These vesicles release chemicals that transmit messages to the next cell in the circuit. In this way neurons transmit information along their axons and on to the next neuron. So,

again, dendrites receive, axons send. Axons can be as long as a meter, or as short as a few tenths of a millimeter, as are those that carry signals within a single part of the brain. Because these short-axon neurons link neurons locally, they are the most important players in the game of information processing: highly evolved animals have relatively more short-axon neurons than long-axon ones, reflecting their role in integrating and processing information. Exactly how many different types of neurons fill the brain remains an open question, although fifty seems to be a reasonable guess.

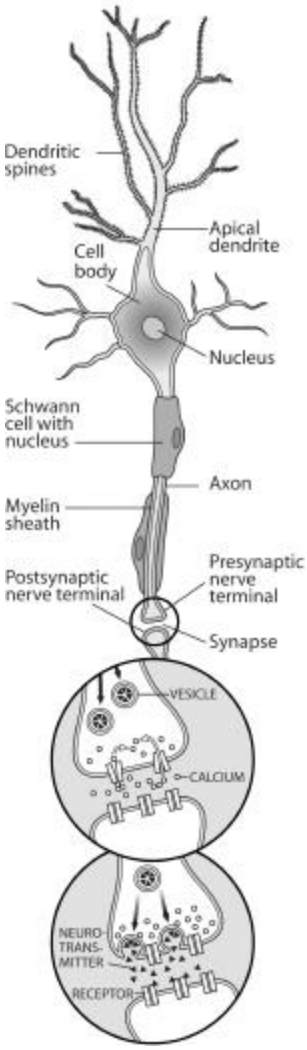

Figure 5: This neuron is typical of those that project from the cortex to the striatum. The inset shows the critical role that calcium ions play in triggering the release of neurotransmitter from vesicles in the presynaptic neuron into the synapse.

Despite their diversity of shape, size, types of connections, and neurochemical content, all neurons carry information in much the same way: they chatter away in electrochemical language. Information transmitted by one neuron and received by another takes the form of electrical signals generated by charged atoms, or *ions*—in

particular, positively charged sodium and potassium ions or negatively charged chloride ions. The flux of ions across the cell membrane of a neuron is meticulously regulated by membrane pumps to give the inside of the cell a net negative charge relative to its surroundings. Rapid changes in the flux of ions can generate a moving pulse of electric charge called an action potential. Like a bulge zipping down a jump rope, the action potential speeds down the axon at up to 200 miles an hour in vertebrates (though only 30 to 40 miles an hour in invertebrates). It is the physical embodiment of the information sent from one neuron to another.

At the end of the axon lies the synapse, which is actually just—well, almost nothing, actually. To be more precise, the *synapse* consists of the axon of a transmitting neuron (called the presynaptic neuron), the dendrite or soma of a receiving neuron (the postsynaptic neuron), and the gap one-millionth of a centimeter wide between them. The synaptic gap, first named by the physiologist Sir Charles Sherrington a century ago, is reminiscent of the almost-touch between the finger of God and the finger of Adam that Michelangelo painted on the ceiling of the Sistine Chapel. For in that achingly close encounter lies a world of potential—in the case of neurons, the potential to hand off the signals that find expression as thoughts, emotions, and sensory perceptions.

Neurons take E. M. Forster's dictum "Only connect" to extremes. The average brain neuron (insofar as there is such a beast) forms about 1,000 synaptic connections and receives even more. Many neurons receive as many as 10,000 inputs, and some cells of the cerebellum receive up to 100,000. When the pulse of charge arrives at the synapse, it stimulates the entry of calcium ions, which triggers the process by which those tiny vesicles in the presynaptic neuron release neurotransmitters. Since the discovery of the first neurotransmitter in 1921, their number has, as of this writing, topped sixty. Neurotransmitters come in a range of molecular types, from amino acid derivatives to gases like nitric oxide (NO). Because neurotransmitters are the language of neuronal communication in the brain, drugs for mental disorders ranging from depression to anxiety to OCD target them. Valium, for instance, facilitates the effects of the neurotransmitter gamma-aminobutyric acid (GABA).

Molecules of neurotransmitter diffuse across the synapse to the postsynaptic neuron. There, the molecules act as a little armada of space vehicles, docking with tailor-made receptors on the postsynaptic neuron as rovers dock with the mother ship. And, not to belabor the analogy, when the neurotransmitters dock, they unleash a flurry of activity inside the neuron not unlike that unleashed when space pods dock: cascades of very complex molecular interactions including ion fluxes that eventually make the postsynaptic neuron more electrically positive. Once the postsynaptic neuron crosses an electrical threshold, it fires an action potential of its own, shooting it off to the next neuron in the circuit. And the electrochemical activity that underlies the thoughts, emotions, and sensory processing within the brain keeps going.

Although this hurly-burly of electrochemical activity is often thought of as turning on activity in the brain (of being *excitatory*, in neuroparlance), in fact synaptic transmission can also be inhibitory. The preceding example describes an excitatory neuron, in which the released neurotransmitters bind to receptors on the postsynaptic neuron and cause it to become more positive. If it is sufficiently more positive, it fires its own action potential. Inhibitory neurons have an opposite effect. In this case, the flux of ions increases the negative charge across the membrane, thus decreasing the possibility that an action potential will be triggered. Synapses between such neurons are therefore called inhibitory.

One additional concept is necessary for any discussion of neuroplasticity, and this is the notion of altering the strength of synapses. At first blush it seems nonsensical to talk about changing the strength of what is, after all, only a gap. But by "altering synaptic strength," we mean making the postsynaptic cell more likely to initiate an action potential, and keep the information transmission going, than it was before. This, as far as neuroscientists can tell, is the basis not only of memory but also of the wiring together of millions of neurons into functional circuits. How might such functional circuits form? The electrical impulses that shoot down an axon cannot vary in amplitude; neurons either fire or don't fire (this is known as the all-or-none property of neurons). So if the incoming electrical signal is invariant, then the only plausible suspect for the focus of change induced by neural activity is the synapse.

In 1949, the Canadian psychologist Donald Hebb proposed that learning and memory are based on the strengthening of synapses that occurs when pre- and postsynaptic neurons are simultaneously active. Somehow, he suggested, either the presynaptic neuron or the postsynaptic neuron (or both) changes in such a way that the activation of one cell becomes more likely to cause the other to fire. Although the notion was plausible from the moment Hebb first advanced it, there was not exactly a rush to the lab bench to test it. Hebb, after all, was a mere psychologist, not a neuroscientist. (Hebb was also the first to float the concept, in the late 1940s, of an "enriched environment" as a cause of behavioral improvements—an idea that, in its 1990s incarnation, would launch a thousand *Baby Einstein* videos.) Eventually, however, neuroscientists amassed data showing that Hebb was on to something: electrically stimulating cortical cells to fire simultaneously strengthened their synaptic connections.

As you might guess, this kind of increased synaptic strength is a key to the formation of enduring neuronal circuits and has become known by the maxim "Cells that fire together, wire together." As best neuroscientists can determine, Hebbian plasticity begins with the release from presynaptic neurons of the neurotransmitter glutamate. The glutamate binds to two kinds of receptors on the postsynaptic neuron. One receptor notes that its own neuron, the postsynaptic one, is active; the other notes which presynaptic neurons are simultaneously active. The postsynaptic neuron therefore detects the simultaneous occurrence of presynaptic and postsynaptic activity. The ultimate result is that a particular action potential whizzing down the axon of a presynaptic neuron becomes more efficient at causing

the postsynaptic neuron to fire. When that happens, we say that there has been an increase in synaptic strength. The two neurons thus become locked in a physiological embrace, allowing the formation of functional circuits during gestation and childhood. The process is analogous to the way that traveling the same dirt road over and over leaves ruts that make it easier to stay in the track on subsequent trips. Similarly, stimulating the same chain of neurons over and over—as when a child memorizes what a cardinal looks like—increases the chances that the circuit will fire all the way through to completion, until the final action potential stimulates the neuron in the language centers and allows the kid to blurt out, "Cardinal!" As a result of Hebbian plasticity, the brain has learned that a crimson bird is called a cardinal. This same pathway crackles with electrical activity whenever you recall a cardinal, and the more you replay this memory, the greater the efficiency with which you can call it up. Changes in synaptic strength thus seem to underlie long-term memory, which must, by its very nature, reflect enduring (if not permanent) changes in the brain regions where memories are stored.

Altering connections in a way that strengthens the efficiency of a neuronal circuit over the long term was the first kind of neuroplasticity to be discovered. Plasticity must be a response to experience; after all, the only thing the brain can know and register about some perception is the pattern of neural activity it induces. This neural representation of the event somehow induces physical changes in the brain at the level of neurons and their synapses. These physical changes "allow the representation of the event to be stored and subsequently recalled," says Tim Bliss of the National Institute for Medical Research in Mill Hill, England. In a very real sense, these physical changes *are* the memory.

As much as any other neuroscientist, Dr. Eric Kandel of Columbia University has worked out the molecular changes that accompany Hebbian learning and the formation of memories. Kandel works with the unprepossessing creature called *Aplysia californica*, otherwise known as a sea snail, which resembles nothing so much as a crawling, bruise-colored blob with ears. *Aplysia*'s nerve cells are the largest (as far as scientists know) of any animal's; actually being able to see what you're investigating, without having to resort to stains and microscopes, makes the task of working out circuitry a lot simpler. So does having to keep track of a mere 20,000 nerve cells (compared to the 100 billion of the human brain).

Kandel and his colleagues made their first breakthrough when they played Pavlov, and instead of using dogs used *Aplysia*. They sprayed one of the sea snail's sensitive spots with water—this stimulus makes the creature snap back inside its mantle—and simultaneously gave it an electric shock. The result was sensitization: *Aplysia* jerked back inside its mantle whenever the scientists jolted it ever so slightly. This, in the world of the sea snail, counts as learning: *Aplysia* is remembering that a touch is followed by a nasty shock and so scoots back inside its protective mantle when it experiences the touch. In much the same way, Pavlov's dogs learned to salivate at the sound of a bell because, during training, food had been paired with that sound.

After identifying the neural circuits underlying this and other simple behaviors, Kandel and a series of collaborators were able to determine how the circuits change as *Aplysia* learns to respond to the different stimuli. They found, for instance, that the sensitized neurons had undergone a long-lasting change: when excited (by the touch), they discharge more neurotransmitter than do neurons of *Aplysia* that have not undergone sensitization. They also found that after a period of stimulation, certain reflex actions can be enhanced for significant periods of time—hours or even days. These stimuli give rise to increased levels of a so-called secondary messenger molecule, called cyclic AMP (or cAMP to its friends). The rise in cAMP levels results in the activation of certain genes in the nucleus of the nerve cell; the gene activation leads to the synthesis of new proteins, some of which appear to play a role in establishing new synaptic connections. It is these connections, neuroscientists now agree, that are the basis for long-term memory. Experience, then, produces stable, observable changes in what passes for *Aplysia*'s brain, changes that mammals also undergo, as Kandel showed in the 1990s when he added mice to his menagerie of lab animals and replicated the work in rodents.

The molecular basis of memory and learning, the discovery of which earned Kandel a share of the 2000 Nobel Prize in physiology or medicine, stands as one of the best understood of the changes the brain undergoes. It is one of the mechanisms that underlie the plasticity of the developing brain. Changes in how an organism interacts with its environment result in changes in connectivity.

We've spent some time on synaptic efficiency, and the "cells that fire together, wire together" mantra, because similar phenomena seem to underlie the plasticity of the developing brain, the diminution of plasticity in the mature brain, and the possibility of directed or induced neuroplasticity in every brain. At the beginning of the 1990s, neuroscientists had only a general idea of how a few embryonic cells transform themselves into a brain, a spinal cord, and a skein of peripheral nerves, all hooked up in such a way as to form a sensing, thinking, feeling human being. Wiring up the circuits of neurons that support those tricks is, to put it mildly, a daunting task. Neurons must appear in the right place at the right time and in the right quantity, to be sure. But contrary to Woody Allen's conclusion that 90 percent of life is just showing up, for a neuron, showing up is just the start. The axons that shoot out of the neurons must also find their way to the correct target cells and make functional connections, and in the last few years researchers started to glimpse how the brain does it. The key finding is that the brain wires itself in response to signals it receives from its environment, a process very similar to that underlying neuroplasticity in the adult brain, too.

It has become a cliché to note that the human brain is, as far as we're aware, the most sophisticated and complex structure in the known universe. A newborn brain contains something on the order of 100,000,000,000—that's 100 billion—nerve cells. That is most of the neurons a brain will ever have. Although 100 billion is an impressive number, it alone cannot explain the complexity, or the power, of the brain that lets us see and hear, learn and remember, feel and think; after all, a

human liver probably contains 100 million liver cells, but if you collect 1,000 livers, you fall quite a few synapses short of a brain. The complexity of a brain, as distinct from a liver, derives chiefly from the connections that its neurons make. Neurons consist of that cell body we described, of course, but it is the neuron's accessories—axons and dendrites—that truly set a neuron apart from a liver cell.

Axons and dendrites enable neurons to wire up with a connectivity that computer designers can only fantasize about. Each of the 100 billion neurons connects to, typically, anywhere from about a few thousand to 100,000 other neurons. The best guess is that, at birth, each neuron makes an average of 2,500 of these specialized junctions, or synapses; reaches a connectivity peak of 15,000 synapses at age two or three; and then starts losing synapses in a process called pruning. If we take a conservative mean for the number of connections (1,000), then the adult brain boasts an estimated 100,000,000,000,000—100 trillion—synapses. Other estimates of the number of synapses in the adult brain go as high as 1,000 trillion.

Although it would be perfectly reasonable to posit that genes determine the brain's connections, just as a wiring diagram determines the connections on a silicon computer chip, that is a mathematical impossibility. As the Human Genome Project drew to a close in the early years of the new millennium, it became clear that humans have something like 35,000 different genes. About half of them seem to be active in the brain, where they are responsible for such tasks as synthesizing a neurotransmitter or a receptor. The brain, remember, has billions of nerve cells that make, altogether, trillions of connections. If each gene carried an instruction for a particular connection, we'd run out of instructions long before our brain reached the sophistication of, oh, a banana slug's. Call it the genetic shortfall: too many synapses, too few genes. Our DNA is simply too paltry to spell out the wiring diagram for the human brain.

Before we explore what makes up the shortfall, it's only fair to give genes their due by describing some aspects of brain development that they do deserve credit for. Since fetal brains follow almost identical developmental sequences and reach the same developmental milestones at about the same time, it's safe to say that the overall pattern of brain development is surely under genetic control (which is not to say that developmental neuroscientists have figured out how the genes do it). The brain starts down the developmental highway soon after a sperm fertilizes an egg. By the fourteenth day, what is now a ball of hundreds of cells folds in on itself, resembling a cleft in a plump chin: cells on the outer surface infold, until they arrive in the interior of the ball. As the ball of cells continues folding in, it simultaneously lengthens, forming a tube. One end will become the spinal cord; the other will develop into the brain. At about three weeks the embryo begins to produce neurons, reaching a peak of production in the seventh week and largely finishing by the eighteenth. Running the numbers shows what a prodigious feat neurogenesis is: since a newborn enters the world with 100 billion or so neurons in its brain, and since the lion's share of neurogenesis is completed just short of halfway through gestation, the fetal brain is producing something on the order of 500,000 neurons

every minute during the high-production phase, or 250,000 per minute averaged over the entire nine months in utero. More than 90 percent have formed midway through gestation. After nine months, the newborn's brain is a jungle of that estimated 100 billion nerve cells.

From stem cells on the walls of the brain-to-be's ventricles, immature neurons are born. Starting in the second trimester of pregnancy, these protoneurons immediately begin to migrate outward in a journey so challenging that it has been likened to a baby's crawling from New York to Seattle and winding up in the precise neighborhood, on the right street, at the correct house that he was destined for from the moment he left Manhattan. These baby neurons follow a sort of cerebral interstate, a structure of highways laid down by cells called *radial glia*. These cells form an intracranial road network complete with rest stops (for the glial cells also nourish the traveling neurons). Protoneurons destined for the cortex observe a first-to-go, first-to-stop rule: those that first leave the ventricular walls stop in the closest cortical layer. The second wave of émigrés continues on to the second-closest layer, and the subsequent waves migrate past each formative layer before stopping at an ever-more-distant layer, until all six cortical layers are populated. Once the immature neurons are in place, the radial glia vanish. How neurons realize that they have reached their final destination remains a mystery, too. But we do know that it is only when the immature neurons are in place that they become full-fledged neurons and put down roots, blossoming with dendrites and sprouting an axon by which they will communicate with, and form a circuit with, other neurons near and far.

Timing also seems to be under clear genetic control. For instance, the *sulci*—invaginations, or fissures—that divide one lobe of the brain from another emerge at what seem to be genetically programmed times: the central sulcus, dividing the frontal lobe from the parietal, appears around the twentieth week of gestation and is almost fully formed in the seventh month. At about the fifteenth week after conception a body map appears in the brainstem and then in the thalamus (a sort of relay station for incoming sensory input), whose neurons begin forming synapses in what will be the brain's somatosensory cortex. Only several weeks into the final trimester do thalamic axons begin to form synapses on cortical neurons that will be their (normally) permanent partners. In fact, it is the arrival of these thalamic axons that turns this strip of cortex into the somatosensory region. By the third trimester, if all is going as it should, most of the neurons have found their place, and, although the circuits are only rough approximations of what they will ultimately become, at least the brain's major structures have taken shape.

At birth, the spinal cord and brainstem are just about fully formed and functional. That works out well, since it is these structures that carry out such vital tasks as thermoregulation, heartbeat, and reflexes such as grasping, sucking, and startling. Soon after birth the cerebellum and midbrain become *myelinated* (encased in the fatty coating of myelin that enables them to carry electrical impulses efficiently); the thalamus, basal ganglia, and parts of the limbic system follow suit in the first

and second years after birth. Finally, the cerebral cortex, led by sensory areas, comes fully on line. At birth the somatosensory cortex, which processes the sense of touch, is a mess, with neurons from different points on the body converging in cortical regions that overlap so much that a newborn cannot tell where she is being touched. But through the experience of touch the somatosensory cortex develops into a precise "map," which means that one spot receives tactile stimuli from the lips and only the lips, and another receives tactile stimuli from the right knee and only the right knee, until every speck of skin is represented. This maturation proceeds from head to toe, with the mouth the first part of the body to become touch-sensitive. The rest of the cortex follows on the somatosensory toward maturity: motor regions first, followed by the parietal, temporal, and frontal association cortices (the seats of judgment, reason, attention, planning, and language, among other higher-order function), which are still forming in the late teens.

It is not merely gross anatomic structures of the brain that form during gestation and early childhood. Moving a few billion neurons to a particular site doesn't give you a working brain any more than throwing a few million integrated circuits into a plastic box gives you an iMac. All of those nerve cells need not only to find their way to the right location in the nascent brain but, crucially, to make the right connections once there, so that a taste detected on the tongue can make its way to the brainstem and from there to cortical regions that will identify it as, say, vanilla, or a tickle on the right cheek will be transformed into electrochemical signals that reach the part of the somatosensory cortex responsible for processing tactile sensations on that cheek.

Forming the right connections is no simple matter; that baby crawling from New York to a particular address in Seattle has it easy compared to what neurons face. Consider the challenge faced by neurons of the nascent visual system. Their goal is to form a functional pathway that goes like this: neural signals from the rods and cones of the eye's retina travel to retinal interneurons, which hand them off to retinal ganglion cells (which constitute the optic nerve) and then to a relay station called the *lateral geniculate* nucleus, where axons from the left eye alternate with axons from the right eye to form eye-specific layers. From there, the signal travels to cells in the primary visual cortex all the way in the back of the brain, where clusters of neurons receiving signals from the left eye form separate, alternating layers with clusters of neurons receiving input from the right eye. In order to effect this signal transfer properly, then, axons from the eye must grow to the correct spot in the lateral geniculate nucleus (LGN). Axons growing from the LGN must resist the urge to terminate in synapses in the auditory or sensory cortex (where they arrive first) and instead continue growing until they reach the appropriate target all the way back in the primary visual cortex. More than that, cells lying beside each other in the retina must extend their axons to neighboring neurons in the lateral geniculate, which must in turn extend their axons to neighboring cells in the visual cortex: for the ultimate goal is for each clump of a few hundred

neighboring neurons in the visual cortex to form synapses only with neurons responding to the same little region of the baby's visual field. How in the world do they do it?

The first part of the axon's journey—the extension of its tip in the right direction—is the easy part. That's because target neurons emit come-hither signals called *trophic factors*. These provide general directions that tell each growing axon from the retina to form a synapse with a particular target neuron in the visual cortex; which neurons emit trophic factors and which traveling axons respond to them seems to be under genetic control. Using a specialized tip called a *growth cone*, the axon is programmed to sniff out and grow toward molecules of specific trophic factors scattered along the predestined route, like Hansel and Gretel following the trail of crumbs through the forest path back to their cottage. Growth cones have what seem to be genetically encoded receptor molecules that make the axon elongate and migrate in the direction of attractant molecules. In this sense, target selection is preprogrammed, with genes directing axons and dendrites to grow to their approximate final destinations. At the same time neurons with which the axon is not destined to form a synapse release chemical signals that repel the axons. Between the attractants and repellents—which have been given names like *netrin* (from the Sanskrit *netra*, meaning "leader" or "guide") and *semaphorin (semaphor* is Greek for "signal")—the axon stays on track to its destination.

Once the axon has arrived in Seattle, to continue the analogy, it still has to find the right neighborhood and the right house that will be its ultimate cellular address. And this is anything but preprogrammed, for as we've seen humans simply don't have enough genes to specify every connection that the neurons in the brain must forge. To make up the genetic shortfall, it slowly dawned on neuroscientists in the 1980s, the brain must assemble itself into functional circuits through experience. Once the genes have run out, experience directs the axons to complete their journey.

The factor that provides the developing brain with the right connections is, ironically, an early profusion of wrong connections. The fetal brain is profligate in its overproduction of both neurons and synapses. Not all the axons trying to reach out and touch another will manage it; the failures die. About half the neurons that form in the fetal brain die before the baby is born: 200 billion neurons, give or take, are reduced to the 100 billion of a newborn as neurons that fail to form functional synapses vanish.

Synapses are pruned even more ruthlessly. Spinal cord synapses begin forming by the fifth week of embryogenesis, cortical synapses are forming at seven weeks, and *synaptogenesis* (synapse formation) continues through gestation and well into childhood. By one count, each cortical neuron forms, at the height of synaptogenesis, 15,000 connections: that works out to 1.8 million synapses per second from the second month in utero to the child's second birthday. Which synapses remain, and which wither away, depends on whether they carry any

traffic. If they do not, then like bus routes that attract no customers, they go out of business. By one estimate, approximately 20 billion synapses are pruned every day between childhood and early adolescence. It's survival of the busiest. Like a cable TV subscription canceled because nobody's watching, synaptic connections that aren't used weaken and vanish. Here is where the power of genes falls off rapidly: genes may lead neurons to make their initial, tentative connections and control the order in which different regions of the brain (and thus physical and mental capacities) come on line, but it's the environmental inputs acting on the plasticity of the young nervous system that truly determine the circuits that will power the brain. Thus, from the earliest stages of development, laying down brain circuits is an active rather than a passive process, directed by the interaction between experience and the environment. The basic principle is this: genetic signals play a large role in the initial structuring of the brain. The ultimate shape of the brain, however, is the outcome of an ongoing active process that occurs where lived experience meets both the inner and the outer environment. As we will see, as the prefrontal circuitry matures, volitional choice can become a critical element in shaping the architecture bequeathed by both genetic factors and environmental happenstance.

Although the gross appearance and morphology of the brain change little after birth, neuroplasticity allows it to undergo immense changes at the cellular level, changes that underlie the unfolding cognitive and other capacities of a child. One of the starkest demonstrations of this has come from studies of speech perception. Newborns can hear all the sounds of the global Babel: the French *u* in *du*, the Spanish *n*, the English *th*. When one of the sounds stimulates hairs in the cochlea, the sound becomes translated into an electrical impulse that finds its way to the brain's auditory cortex. As a racer hands off the baton in a relay, each neuron between ear and cortex passes the electrical impulse to the neuron beyond. After enough repetitions of a sound, the synapses connecting all those neurons have been strengthened just as Hebb described. The result is that this precise neuronal pathway responds to *th*every time, culminating in the stimulation of a dedicated cluster of neurons in the auditory cortex that produces the subjective sense that you have heard the sound *th*. The result is that networks of cells become tuned to particular sounds in the language the newborn constantly hears.

Space in the auditory cortex is limited, of course. Once the Hebbian process has claimed circuits, they are hard-wired for that sound; so far, neuroscientists have not observed any situations in which the Hebbian process is reversed so that someone born into a sea of, say, Finnish loses the ability to hear Finnish's unique sounds. Although a growing appreciation of the plasticity of the adult brain has now overturned the idea that it is impossible to learn a second language and speak it without an accent after the age of twelve, without special interventions the auditory cortex is like development in a close-in suburb: it's all built up, and there are no empty lots that can be dedicated to hearing new sounds.

Patricia Kuhl, a leading authority in speech development, got a dramatic demonstration of this. In order to test Japanese adults and children on their ability to distinguish various phonemes, she made an audio disk with the various sounds and took it with her during a visit to the language lab of colleagues in Tokyo. Before testing any volunteers, she first wanted to demonstrate the disk to the Japanese scientists. As "rake, rake, rake" intoned through the high-end Yamaha speaker, her colleagues leaned forward expectantly for the sound change she had told them was coming. The disk segued into "lake, lake, lake," Kuhl had said—but the Japanese, all proficient at English, still leaned in expectantly. They literally could not hear any difference between the sound of *lake* and the sound of *rake*.

The difference lay in their brains. Children who grow up hearing the sounds of a language form dedicated circuits in their auditory cortex: the brains of the children Kuhl left behind in Seattle, where she is a professor at the University of Washington, had been molded by their auditory experience to discriminate *r* from *l*. When? The seven-month-old Japanese babies whom Kuhl tested had no trouble discriminating *r* from *l*. But ten-month-olds were as deaf to the difference as adults. When Kuhl did a similar test of Canadian babies raised in English-speaking homes, she got the same results: six-month-olds could distinguish Hindi speech sounds even though those sounds were not part of their auditory world; by twelve months they could not. Between six and twelve months, Kuhl concludes, babies' brains begin the "use it or lose it" process of pruning unused synapses. The auditory cortex loses its sensitivity to phonemes that it does not hear every day. This may be why children who do not learn a second language before puberty rarely learn to speak it like natives.

The reverse is true, too: connections that are used become stronger, even permanent elements of the neural circuitry. A newborn forms millions of connections every day. Everything he sees, hears, feels, tastes, and smells has the potential to shape the nascent circuits of his brain. The brain is literally wired by experience, with sights, sounds, feelings, and thoughts leaving a sort of neural trace on the circuits of the cortex so that future sights, sounds, feeling, thoughts, and other inputs and mental activity are experienced differently than they would otherwise be. In the case of Kuhl's young subjects, she speculates, the phonemes a child hears strengthen the auditory synapses dedicated to that sound; repeatedly hearing the sound broadens a child's perceptual category for that sound, crowding out sounds with a similar auditory profile, until the number of auditory neurons dedicated to those neighboring sounds eventually dwindles to literally zero.

Clearly, the hardware of the brain is far from fixed at birth. Instead, it is dynamic and malleable. As far back as the 1960s and 1970s, researchers were documenting that rats raised in a lab cage with wheels to run on and ladders to scamper up, as well as other rats to interact with, grew denser synaptic connections and thicker cortices than rats raised with neither playmates nor toys. The "enriched" environment was closer to the world a rat would experience in the wilds of New York City, for example. The cortical differences translated into functional

differences: rats with the thicker, more synaptically dense cortices mastered mazes and found hidden food more quickly than did rats from the poorer environments, who had thinner cortices.

From the moment a baby's rudimentary sensory systems are operational (which for hearing and tactile stimulation occurs before birth), experiences from the world beyond begin to impinge on the brain and cause brain neurons to fire. Let's return to the example of the visual system, which, when we left it, had axons from retinal neurons projecting into the nascent visual cortex. Alone among the senses, the visual system receives no stimulation until after birth. In the fourth week of gestation the eye begins to form. Synapses form first in the retina, then in subcortical visual areas, followed by the primary visual cortex, and, finally, higher visual centers in the temporal and parietal lobes. In the second trimester, the visual system experiences its growth spurt: between fourteen and twenty-eight weeks, all of the 100 million neurons of the primary visual cortex form. They start to make synapses in the fifth month and continue making them for another year at the staggering rate of 10 billion per day, until the visual cortex reaches its maximal density at eight months of age. At birth, a baby sees the world through a glass darkly. More synapses responsible for processing motion than for perceiving form have come on line, with the result that babies detect movement better than they do shape. The entire visual field, in fact, consists of no more than a narrow tunnel centered on the line of sight, and the baby's visual resolution is about one-fortieth that of a normal adult. Making the world look even odder (not that the baby has much to compare it to), newborns lack depth perception. They can see clearly only eight or so inches out. Normally, however, vision improves by leaps and bounds in the first few weeks, and by four months the baby can perceive stereoscopic depth. By six months, visual acuity has improved fivefold, and color vision, acuity, and volitional control of eye movements have all emerged. The tunnel of view expands, until by twelve months it is equivalent to an adult's. Around a child's first birthday, he sees the world almost as well as a normal adult.

The accurate wiring of the visual cortex that underlies the gradual improvement in vision occurs only if the baby receives normal visual stimuli. In other words, it is electrical activity generated by the very act of seeing that completes the wiring of the visual cortex. Again, although genes have played matchmaker between axons and neurons so that webs of neurons take shape, the number of human genes falls well short of the number needed to specify each synapse even within the visual cortex. Genes get the neurons to the right city and dispatch their axons to the general vicinity of neurons with which they will form synapses, but the baby's unique interaction with the environment has to take it from there. Scientists concluded in the 1990s that one of the main ways axons and dendrites make connections—and neurons therefore form circuits—is by firing electrical signals, almost at random, and then precisely honing the crude pattern to fit the demands of experience. "Even before the brain is exposed to the world, it is working to wire itself," says the neuroscientist Carla Shatz, one of the pioneers in the field of brain

development. She became a neuroscientist because, while she was in high school, her grandmother suffered a debilitating stroke that paralyzed one side of her body; Shatz vowed to join the search for how the nervous system works and settled on developmental neuroscience. "The adult pattern of connections emerges as axons remodel by the selective withdrawal and growth of different branches," she says. "Axons apparently grow to many different addresses within their target structures and then somehow eliminate addressing errors."

That "somehow" remains a holy grail of developmental neuroscience. Axons seem to be fairly promiscuous in their choice of target neurons: any will do. But then competition among inputs sorts out the axons, leading to areas with specific functions. An early clue to how they manage this feat came in the 1970s. David Hubel and Torsten Wiesel, working at Harvard, hit on the simple experiment of depriving newborn cats of visual input by sewing shut one of their eyes. After even a week of sightlessness, axons from the lateral geniculate nucleus representing the closed eye occupied a much smaller area of the cortex than did axons representing the normal eye. Then the scientists opened the eye that had been sewed shut, so that both eyes would deliver (it was thought) equal stimuli to the brain. They recorded from neurons in the primary visual cortex of the kittens, who by this time were at least four months old. Despite the fact that both eyes were open, virtually all of the visual cortex received input only from the eye that had been open since the kitten's birth. Neurons from the eye that had been sewed shut formed few functional connections; it was as if the synapses had melted away from disuse. If kittens do not receive visual input between thirty and eighty days after birth (a window of time now known as the critical period), it is too late: the unused eye is blind forever. The development of visual function in the cortex depends on visual inputs; visual deprivation early in life changes the cortex, Hubel and Wiesel found. Their work won them the 1981 Nobel Prize in physiology or medicine.

Extra activity—the opposite of deprivation—also changes the cortex, found the Harvard team. Brain regions stimulated by a kitten's normal, open eye invaded and colonized regions that should have handled input from its closed eye. As a result, input from the normal eye reached a disproportionately large number of neurons in the visual cortex. Rather than the eyes' having equal representation, most of the cortical cells received input only from the normal eye. This eye was now driving cells usually devoted to the shut eye. Yet this was not the case when the scientists recorded from cells in the retina or the lateral geniculate nucleus. That is, areas that should respond to stimulus of the normal eye did so, and areas that should respond to stimulus of the once-closed eye did not. Apparently, the majority of the changes induced by depriving the brain of visual input occurred in the cortex, not earlier in the visual pathway. This discovery suggested that if axons are carrying abnormally high electrical traffic, they take over more space in the visual cortex.

Other experiences produce even curiouser changes in the cortex. Neurons in the visual cortex turn out to be specialists. Some respond best to the sight of an edge oriented vertically, others to an edge oriented horizontally. There are roughly equal

numbers of cells that respond to each orientation. But if the world of a newborn cat is skewed so that it sees only vertical lines, then in time most of its neurons will respond only to vertical edges. When a kitten is reared in a room painted with vertical stripes, very few of its direction-sensitive neurons turn out to specialize in horizontal stripes, but there is a profusion of vertical specialists. The animal literally cannot see horizontal lines but perceives vertical ones with great acuity. Human brains bear similar marks of early visual experience: a 1973 study found that Canadian Indians, growing up in teepees, had better visual acuity for diagonal orientations than people reared in the modern Western standard of horizontal ceiling joints and vertical wall joints.

The key role that experience plays in wiring the human brain shows up most clearly when sensory stimuli are completely absent. In a human version of the kitten's sewn-shut eyelids, babies are sometimes born with a cataract—an opaque lens—in one eye or both. This congenital defect strikes about 1 baby in 10,000 in the United States. If both eyes suffer cataracts, the brain never develops the ability to see normally. If only one eye has a cataract, vision in the affected eye never develops, as a result of active suppression by the normal eye, explains Ruxandra Sireteanu of the Max-Planck Institute for Brain Research in Frankfurt: "The two eyes compete for a glimpse of the outer world. If left untreated, vision in the affected eye, and the ability to use both eyes for binocular vision, will be permanently lost. It is not actually the eye that suffers, but the brain." In this case acuity, the size of the field of vision, and the ability (or, rather, inability) to see stereoscopically remain stuck at the level of a newborn. Without normal visual input, the developing brain fails to establish the amazing network of connections that allow it to receive, process, and interpret electrical signals triggered by the fall of light on the retina.

Nowadays, doctors realize that removing the affected lens and replacing it with a clear, artificial one (the same sort of cataract surgery performed on elderly people) allows the brain to receive clear, sharp signals. What had remained unknown until recently, however, was how much visual input was required for the repaired eye to begin seeing. Was it hundreds of hours? Or mere seconds? In a 1999 study, researchers at the Hospital for Sick Children in Toronto went a long way toward finding an answer. They studied twenty-eight babies who had been born with dense cataracts: sixteen of the babies suffered cataracts in one eye, twelve had them in both. Between one week and nine months of age the babies underwent surgery to remove the cataracts; they had therefore been deprived of normal visual input for that length of time. Within days or weeks of surgery, the babies were fitted with contact lenses so that, for the first time in their lives, "visual input was focused on the retina." To test the babies' eyesight, the researchers showed them black-and-white vertical stripes on a gray background. By varying the spacing between the stripes, and using infants' well-established propensity to pay attention to novel objects, the researchers were able to measure the babies' visual resolution. Although the initial acuity of the treated eye or eyes was significantly worse than that of babies born with normal vision, it improved after as little as a single hour of

this exposure. "It appears that lack of visual exposure maintains the visual cortex of infants at the newborn level," says Sireteanu. "But even a one-hour exposure to the visual world sets the stage for rapid visual improvements."

Other sensory systems are similarly dependent on environmental input to finish the neuronal wiring that remains to be done once genetic instructions are exhausted. Auditory neurons first appear at three weeks after conception, and auditory centers in the brainstem emerge by thirteen weeks. In experiments with lab animals, removing the cochlea of one ear soon after birth reduces the number as well as the size of auditory neurons in the brainstem. Since these neurons receive no input, they essentially fold their tents and go out of business. But that kind of brain change can apparently be reversed, again through sensory input. In congenitally deaf children given cochlear implants, which bypass the damaged sensory hair cells of the inner ear and carry acoustical signals directly to the cortex, the sudden onset of sound after weeks or months of silence leads to nearly (depending on the age at which the implants are given) perfect speaking and hearing, as well as normal language development.

A 1999 experiment with kittens revealed the neurological basis for the rapid improvement. Researchers led by Rainer Klinke at the Physiologisches Institut of Frankfurt, Germany, tested the effects of the cochlear implants on a group of three- to four-month-old kittens that were deaf at birth. Brain imaging had already shown that the unstimulated auditory nervous system in the deaf kittens was not developing as it does in normal cats. But after the implants, the cats began to respond to sounds in the same way as cats born with normal hearing. Their auditory cortex changed, too: within a short time the size of the region of auditory cortex that responded to sound increased, the amplitude of the electrical signals in the auditory cortex soared, and measures of information processing within the cortex (called *long-latency neural responses*) increased. The experiment offers some explanation for the fact that cochlear implants in children born deaf prove quite successful. "It is quite likely that a similar 'awakening' of the visual cortex takes place in congenitally blind infants newly exposed to visual information after cataract removal and the fitting of an artificial lens," says Sireteanu.

A child need not suffer a congenital defect to demonstrate the power of sensory experience to wire the brain. Consider the somatosensory cortex. As mentioned, during fetal development it forms a rudimentary "map" of the body, so that the area receiving signals from the right hand abuts the area that receives signals from the right arm, which in turn abuts the area that receives signals from the right shoulder—you get the idea. But even at birth the somatosensory cortex has a long way to go. It is only through the experience of sensation that the map becomes precise. What seems to happen is that a baby is touched on, say, the back of her right hand. The neurons that run from that spot into the brain therefore fire together. But a neuron from the right wrist that took a wrong turn and wound up in the hand area of the somatosensory cortex is out of step. It does not fire in synchrony with the others (since touching the back of a hand does not stimulate

the wrist). The tentative synapse it formed in the somatosensory cortex therefore weakens and eventually disappears. The region of the somatosensory cortex that receives inputs from the back of the right hand now receives inputs only from the back of the right hand. As similar mismappings are corrected through experience and the application of the "neurons that fire together wire together" rule, a once-ambiguous map becomes sharp and precise.

That the newborn brain needs stimulation in order to form the correct wiring pattern is uncontested. A bitter and somewhat politicized dispute has arisen, however, over the meaning of *stimulation*. To many neuroscientists, it means nothing more than what a baby with functioning senses would receive from being alive and awake in the everyday world: sights, sounds, tastes, touches, and smells. Numerous observations have documented that babies who are severely neglected, and who do little but lie in their crib for the first year or more of life, develop abnormally: few can walk by the age of three, and some cannot sit up at twenty-one months. Whether more stimulation, especially cognitive stimulation, would produce even better wiring is hotly contested. Selling desperate parents video tapes that promise to turn their not-yet-crawling baby into a junior Einstein, persuading them to fill the house with the strains of Mozart, admonishing them that a family meal without a math lesson using forks and spoons is a missed opportunity—such gambits have given "stimulation" a bad name. It is clear that some amount of stimulation is crucial to the development of the human brain. But in all likelihood, it's enough for the baby to explore the environment actively and interact with parents, to play peekaboo and hide-and-seek, to listen to and participate in conversations.

The great wave of synaptic sprouting and pruning was supposed to wash over the brain in infancy and toddlerhood, finishing in the first few years of life. But in the late 1990s scientists at several institutions, including here at UCLA, rocked the world of neuroscience with the discovery that a second wave of synaptic sprouting occurs just before puberty. In 1999, neuroscientists led by Elizabeth Sowell of UCLA's Lab of Neuro Imaging MRI compared the brains of twelve- to sixteen-year-olds to those of twenty-somethings. They found that the frontal lobes, responsible for such "executive" functions as self-control, judgment, emotional regulation, organization, and planning, undergo noticeable change during late adolescence: they start growing at ten to twelve years (with girls' growth spurt generally occuring a little earlier than boys'), much as they did during fetal development. And in another surprising echo of infancy, the frontal lobes then shrink in people's twenties as extraneous branchings are pruned back into efficient, well-organized circuitry. No sooner have teens made their peace (sort of) with the changes that puberty inflicts on the body than their brain changes on them, too, reprising a dance of the neurons very much like the one that restructured the brain during infancy. Contrary to the notion that the brain has fully matured by the age of eight or twelve, with the truly crucial wiring complete as early as three, it turns out that the brain is an ongoing construction site. "Maturation does not stop at age 10, but

continues into the teen years and even the 20s," says Jay Giedd of the National Institute of Mental Health, whose MRI scans of 145 healthy four- to twenty-one-year-olds also found that the gray matter in the frontal lobes increased through age eleven or twelve. "What is most surprising is that you get a second wave of overproduction of gray matter, something that was thought to happen only in the first 18 months of life. Then there is a noticeable decline. It looks like there is a second wave of creation of gray matter at puberty, probably related to new connections and branches, followed by pruning."

Again as during fetal development, synapses that underlie cognitive and other abilities stick around if they're used but wither if they're not. The systematic elimination of unused synapses, and thus unused circuits, presumably results in greater efficiency for the neural networks that are stimulated—the networks that support, in other words, behaviors in which the adolescent is actively engaged. Just as early childhood seems to be a time of exquisite sensitivity to the environment (remember the babies who dedicate auditory circuits only to the sounds of their native language, eliminating those for phonemes that they do not hear), so may adolescence. The teen years are, then, a second chance to consolidate circuits that are used and prune back those that are not—to hard-wire an ability to hit a curve ball, juggle numbers mentally, or turn musical notation into finger movements almost unconsciously. Says Giedd, "Teens have the power to determine their own brain development, to determine which connections survive and which don't, [by] whether they do art, or music, or sports, or videogames."

This second wave of synaptogenesis is not confined to the frontal lobes. When the UCLA team scanned the brains of nineteen normal children and adolescents, ages seven and sixteen, they found that the parietal lobes (which integrate information from far-flung neighborhoods of the brain, such as auditory, tactile, and visual signals) are still maturing through the midteens. The long nerve fibers called white matter are probably still being sheathed in myelin, the fatty substance that lets nerves transmit signals faster and more efficiently. As a result, circuits that make sense of disparate information are works in progress through age sixteen or so. The parietal lobes reach their gray matter peak at age ten (in girls) or twelve (in boys) and are then pruned. But the temporal lobes, seats of language as well as emotional control, do not reach their gray matter maximum until age sixteen, Giedd finds. Only then do they undergo pruning. The teen brain, it seems, reprises one of the most momentous acts of infancy, the overproduction and then pruning of neuronal branches. "The brain," says Sowell, "undergoes dynamic changes much later than we originally thought."

The wiring up of the brain during gestation, infancy, and childhood—and, we now know, adolescence—is almost as wondrous as the formation of a living, breathing, sensing, moving, behaving organism from a single fertilized ovum. The plasticity of the young brain is based on the overabundance of synapses, which allows only those that are used to become part of enduring circuits that underlie thinking,

feeling, responding, and behaving. But does the dance of the neurons eventually end?

The great Spanish neuroanatomist Santiago Ramon y Cajal concluded his 1913 treatise "Degeneration and Regeneration of the Nervous System" with this declaration: "In adult centres the nerve paths are something fixed, ended, immutable. Everything may die, nothing may be regenerated." Cajal based his pessimistic conclusion on his meticulous studies of brain anatomy after injury, and his gloomy sentiment remained neuroscience dogma for almost a century. "We are still taught that the fully mature brain lacks the intrinsic mechanisms needed to replenish neurons and reestablish neuronal networks after acute injury or in response to the insidious loss of neurons seen in neurodegenerative diseases," noted the neurologists Daniel Lowenstein and Jack Parent in 1999.

This doctrine of the adult hard-wired brain, of the loss of neuroplasticity with the end of childhood, had profound ramifications. It implied that rehabilitation for adults who had suffered brain damage was useless. It suggested that cognitive rehab in psychiatry was a misbegotten dream. But the doctrine, as was becoming apparent even as Lowenstein and Parent wrote, was wrong. Years after birth, even well into adolescence, the human brain is still forming the circuits that will determine how we react to stress, how we think, even how we see and hear. The fact that (even) adults are able to learn and that learning reflects changes in synapses tells us that the brain retains some of its early dynamism and malleability throughout life. The adult has the ability not only to repair damaged regions but also to grow new neurons. Even the adult brain is surprisingly plastic. Thus the power of willful activity to shape the brain remains the working principle not only of early brain development, but also of brain function as an ongoing, living process.

Even as I recorded changes in the brains of my OCD patients after mindfulness-based cognitive-behavioral therapy, a decades-long dogma was beginning to fall. Contrary to Cajal and virtually every neuroscientist since, the adult brain can change. It can grow new cells. It can change the function of old ones. It can rezone an area that originally executed one function and assign it another. It can, in short, change the circuitry that weaves neurons into the networks that allow us to see and hear, into the networks that remember, feel, suffer, think, imagine, and dream.