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

## Chapter 5. THE MAPMAKERS

Although the content of consciousness depends in large measure on neuronal activity, awareness itself does not….
To me, it seems more and more reasonable to suggest that the mind may be a distinct and different essence.

*—Wilder Penfield, 1975*

Looking back on it, there had been hints for decades. At the end of the nineteenth century, long before Allen and Domitian and Big Boy had their cortices mapped, long before the brains of OCD patients changed in response to therapy, scholars generally agreed that the adult brain is not immutable. To the contrary: most believed that learning physically alters the brain. As neuronal pathways are repeatedly engaged, the psychologist William James argued in the nineteenth century, those pathways become deeper, wider, stronger, like ruts in a well-traveled country road. In the chapter on habit in his magisterial 1890 work *Principles of Psychology*, James had this to say:

*Plasticity, then, in the wide sense of the word, means the possession of a structure weak enough to yield to an influence, but strong enough not to yield all at once. Each relatively stable phase of equilibrium in such a structure is marked by what we may call a new set of habits. Organic matter, especially nervous tissue, seems endowed with a very extraordinary degree of plasticity of this sort; so that we may without hesitation lay down as our first proposition the following, that the phenomena of habit in living beings are due to the plasticity of the organic materials of which their bodies are composed.*

It was an idea that reflected the spirit of its age. With the scientific revolution of the eighteenth and nineteenth centuries, notions that had once existed solely as abstract hypotheses—electrons, atoms, species—were being shown to have a physical reality, a reality that could be quantified, measured, and probed. Now it was the mind's turn. Farewell to the airy notion that our habits, to take James's example, were patterns whose basis floated above the physical realm. Now theorists proposed that the experiences of our lives leave footprints in the sands of our brain like Friday's on Robinson Crusoe's island: physically real but impermanent, subject to vanishing with the next tide or to being overwritten by the next walk along the shore. Our habits, skills, and knowledge are expressions of something physical, James and others argued. And because that physical foundation can change, so, too, we can acquire new habits, new skills, new knowledge.

Experimentalists soon vindicated that theory. In the early twentieth century neuroanatomists began discovering something odd. They were investigating so-called movement maps of the brain, which show which spot in the motor cortex

corresponds to moving which part of the body. The maps, more often than not, turned out to vary among individual animals: electrical stimulation of a particular spot in the motor cortex of one monkey moved the creature's index finger, but stimulation of the same spot in another monkey moved the hand. You couldn't even think of drawing a tidy movement map for, say, the "typical" squirrel monkey. Sure, you could draw a map for this monkey. But it would be different from the map for that monkey.

In 1912 T. Graham Brown and Charles Sherrington, the British neurophysiologist we met in the last chapter, decided to see whether this variability in movement maps reflected mere experimental sloppiness or something real. In landmark but long-forgotten experiments, the duo methodically applied surface electrical stimulation to lab animals' motor cortices and observed which muscles responded. It was true: movement maps were as individual as fingerprints. Stimulating one animal's motor cortex here produced a twitch of a cheek muscle; stimulating another animal in the exact same spot twitched a different muscle. What was the basis for this variability? Unlike fingerprints, the scientists concluded, the cortical representations of movements are not inborn. Instead, they reflect the history of use of the motor system—the footprints in the sand. Enduring changes in the complex neural circuits of our cerebral cortex, they proposed, must be induced by our behaviors. To take a fictitious example, a monkey in the habit of holding its fruit with its thumb and pinky would have a movement map in which the spots of the cortex moving those two fingers lie close together. If the monkey switched to habitually using its thumb and forefinger, then the brain would eventually shift too, rezoning the motor cortex so that neurons moving the thumb lay beside those moving the forefinger, with the pinky representation shunted aside. Sherrington's and Brown's work provided the earliest empirical evidence that, as James had guessed, habits are behavioral expressions of plastic changes in the physical substrate of our minds.

And it launched what would be a blossoming of research into neuroplasticity. Three years after the work on monkeys' movement maps, a neurologist named S. Ivory Franz compared movement maps in the primary motor cortices of macaques. He, too, found high variability and concluded that the differences probably reflect the motor experiences and skills of the different monkeys. In 1917, Sherrington himself described "the excitable cortex of the chimpanzee, orang-utan and gorilla," documenting great variation in the movement areas of the cortex. The brain, he concluded, is "an enchanted loom, where millions of flashing shuttles weave a dissolving pattern, always a meaningful pattern, though never an abiding one."

In 1923 Karl Lashley, a former colleague of Franz, added his voice. His work was a departure from that of his predecessors, who compared one animal to another. Logically, the differences they discovered between movement maps need not have been the result of the animals' different life experiences; the idiosyncrasies might have been inborn. To rule out that explanation, Lashley derived four movement maps over the course of a month from the same adult rhesus monkey. If

differences in the maps reflect only inborn differences, then the map of that monkey's cortex today should be the same as its map last week. But it was not. Each time Lashley worked out the monkey's movement map, he found that it differed in detail from the previous one, and even more from maps derived earlier. There must be, he surmised, a general "plasticity of neural function" that allows the movement map in the motor cortex to change throughout life, remodeling itself continually to reflect its owner's motor experiences. Crucially, Lashley concluded that muscles that move more receive a greater cortical representation than muscles that move less. That bears repeating: the more a creature makes a movement, the larger the cortical area given over to that movement. Each time Friday walks his favorite route in the wet sands at the water's edge, he leaves new imprints, fresh and sharp. If he walks the same route, his footprints become ever deeper, while those on the route less traveled fade away, until they barely dimple the sands.

By the middle of the twentieth century, there was a compelling body of evidence that the cerebral cortex is dynamic, remodeled continually by experience. Thus when Donald Hebb postulated coincident-based synaptic plasticity in 1949 ("Neurons that fire together, wire together," as discussed in Chapter 3), he didn't regard his proposal as particularly revolutionary: the notion that coincident inputs strengthen synapses was, he thought, generally acknowledged. But there had always been voices of dissent over the notion of a plastic brain. In 1913 the great Spanish neuroanatomist Ramón y Cajal had argued that the pathways of the adult brain are "fixed, ended, immutable." Although he also posited that "absolutely new relations between previously nonconnected neurons are elicited by learning," by the 1950s the "immutable" paradigm had become the conventional wisdom in neuroscience. The theories and experimental findings of Sherrington, Franz, and Lashley were swept aside and largely forgotten. According to the prevailing camp at midcentury, the brain establishes virtually all of its connections in such primary systems as the visual cortex, auditory cortex, and somatosensory cortex in the first weeks of life. The groundbreaking work on the visual system by Hubel and Wiesel in the 1960s, as discussed in Chapter 3, seemed to establish once and for all the principle that, after a critical period early in life, experience can no longer change the brain much. The mature cortex is fixed and immutable. This became a tenet of neuroscience.

The few experiments that continued to mine the vein that Sherrington and his successors had opened therefore made all the impact of a whisper at a rock concert. Take the rats, for instance. Researchers reported in 1976 that the amount of auditory cortex given over to neurons that process a tone used in Pavlovian conditioning increases: the more the rat uses those neurons, the more space they occupy in the auditory cortex. Lashley would have been pleased. Or take the cats. In 1979, the neuroscientists John Kalaska and Bruce Pomeranz reported that denervation of the paws of kittens and adult cats causes the "paw cortex" in the brain to respond to stimulation of the felines' forearm instead, suggesting that the forearm representation creeps into the paw representation once paw neurons no

longer send signals to the cortex. (As you'll recall from Chapter 4, *representation* is the space in the cortex devoted to processing particular sensory inputs or movement outputs.) This was precisely what Tim Pons and his team had found in the Silver Spring monkeys: if an animal stops receiving sensory input from one part of its body, the area of somatosensory cortex that used to process that input remaps itself. Instead of wasting valuable processing space on the sounds of silence, the area starts listening to a part of the body that is still transmitting signals to headquarters. And don't forget the raccoons (though neuroscientists did). In 1982, after amputating a raccoon's fifth digit (pinky), Douglas Rasmusson found that its somatosensory cortex reorganized, reassigning the cortical region that used to handle incoming signals from the pinky to a part of the body (the fourth digit) that was still transmitting. Andrew Kelahan and Gernot Doetsch also found somatosensory reorganization in the cortices of raccoons after amputation of a digit.

But it is a rare neuroscientist who pays much attention to raccoon experiments. No one exactly rewrote the textbooks on the basis of these rats, cats, or raccoons. Their brains were assumed to be too simple to serve as models for the human brain. As a result, neuroscientists largely ignored experiments that, in the late 1970s and early 1980s, began raising questions about the permanence of the brain's zoning maps, suggesting instead that the cortex is highly plastic and driven by experience. A loud silence greeted Patrick Wall's prescient suggestion of the physical basis for such rearrangements and expansions. In a 1977 paper in *Philosophical Transactions of the Royal Society of London (Biological Sciences)*, Wall wrote, "There are substantial numbers of nerve terminals which are normally ineffective…. If the normally functioning afferent nerve fibres are blocked or cut…large numbers of cells begin to respond to new inputs. The presence of ineffective synapses in the adult offers…a possible mechanism to explain plasticity of connections in adult brains." Little wonder scientists failed to pick up on Wall's suggestion of a mechanism for neural plasticity. After all, the phenomenon wasn't even supposed to exist.

What everyone "knew" to be true can still be seen in any lavishly illustrated brain book. There, in full-color diagrams, the structures of the brain are clearly mapped and labeled: areas that control language and areas that receive visual input, areas that process auditory input and areas that sense tactile stimulation of the left big toe or the right elbow. The thing resembles nothing so much as a zoning map produced by the most rigid of land-use boards. Every bit of real estate is assigned a function; and territory given the job of, say, processing sensations from the lower leg seem no more able to start recording feelings from the cheek than a plot of land zoned residential could suddenly become the site of a tractor factory. This view of the brain dates back to 1857, when the French neurosurgeon Paul Broca discovered that particular regions are specialized for particular functions. Throughout the nineteenth century neuroscientists had a field day demonstrating that different clusters of neurons located in well-defined places assumed specific functions. The

neuroanatomist who determined the function of a region first was often awarded (or claimed) pride of nomenclature: thus we now have Broca's region (speech), for instance, and Wernicke's region (language comprehension).

The discovery of links between structure and function gave rise to a view that became axiomatic: namely, that different parts of the brain are hard-wired for certain functions. Nowhere was this clearer than in every medical illustrator's favorite brain structure, the somatosensory cortex. A band that runs from about halfway along the top of the brain to just above each ear, the somatosensory cortex processes feelings picked up by peripheral nerves. Every surface of the body has a corresponding spot on this strip of cortical tissue, called a representation zone, as the Canadian neurosurgeon Wilder Penfield found in his experiments in the 1940s and 1950s, reviewed in Chapter 1. While patients were under local anesthesia for brain surgery, Penfield, who studied under Sherrington, stimulated spots on the surface of the exposed brain with a tiny electrode. Then he asked his conscious subjects what they felt. They didn't hesitate: depending on which spot Penfield's electrode tickled on the somatosensory strip, the patient would report feeling a sensation in the fingers, lips, feet, or other part of the body.

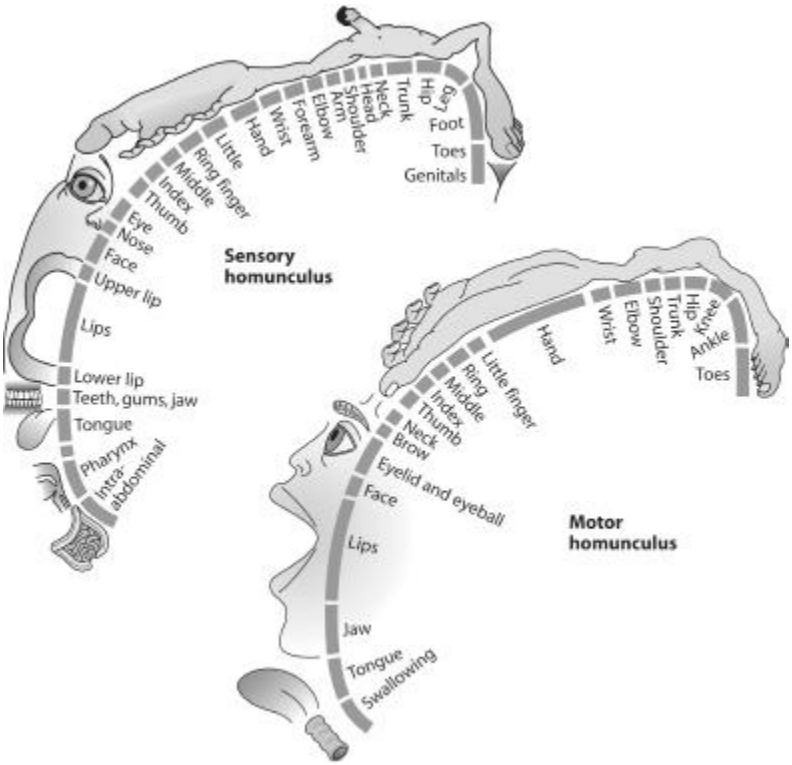


**Figure 6: A. The sensory homunculus depicts the location and amount of cortical space devoted to processing tactile signals from different places on the body. Sensitive regions such as the lips and genitals command a great deal of cortical space. B. The motor homunculus shows the amount of cortical space devoted to controlling the movement of different regions of the body. Muscles involved in speech and hand movements receive a great**

**deal of cortex, while less dextrous regions such as the shoulder receive very little.**

But it was an odd map. True, the part of the somatosensory cortex that registers sensation from the lips lies between the regions that register sensation from the forehead and the chin. So far, so good. The cortical representation of one finger is positioned relative to those of the other fingers, reflecting the arrangement of the fingers on the hand. Also good. But beyond these basics, the cortical representations of different regions of the body are arranged in a way that makes you suspect nature has a bizarre sense of humor. The somatosensory representation of the fingers, for instance, sits beside the face. The representation of the genitals lies below the feet. The reason for this arrangement remains lost in the mists of evolution. One intriguing hypothesis, however, is that it reflects the experience of the curled-up fetus: in utero, our arms are often bent so that our hands touch our cheeks, our legs curled up so that our feet touch our genitals. Perhaps months of simultaneous activation of these body parts, with the corresponding synchronous firing of cortical neurons, results in those cortical neurons' "being fooled" into thinking that these body parts are contiguous. It would be another example of coincident input's producing coherent structures during prenatal development, as discussed in Chapter 3.

The other oddity of the somatosensory cortex is easier to explain. The amount of cortical territory assigned to a given part of the body reflects not the size of that body part but its sensitivity. As a consequence, the somatosensory representation of the lips dwarfs the representation of the trunk or calves. The result is a homunculus with dinner-plate lips. Our little man also has monstrous hands and fingers: the touch-sensitive neurons on the tip of your index finger are fifteen times as dense as those on, for instance, your shin, so the homunculus's index finger receives more cortical real estate than a whole leg. The density of touch receptors on the tongue is also more than fifteen times as great as that of those on the back of your hand. Place the tip of your tongue under your front teeth and you'll feel the little ridges; but place the back of your hand against the teeth and all you're likely to feel is a dull edge.

The motor cortex, which controls the voluntary actions of muscles moving every part of the body, is also laid out like a homunculus. Here, the amount of neural territory assigned to moving such dexterous parts as the hands dwarfs the amount given to moving, say, the ears. The lips get more motor cortex than the leg; we are, after all, the ape that speaks. The torso is dwarfed by the representations of the face, tongue, and hands. The amount of motor cortex devoted to moving the thumb is as great as the amount zoned for moving the entire forearm: the former is capable of much finer movements than the latter. But the motor homunculus is as jumbled as his somatosensory brother. Penfield, again using mild electrical stimulation of the exposed brains of surgical patients, discovered that the motor cortex maps out a body plan as cartoonish as the somatosensory cortex does. The representation of the leg sits near the center of the motor cortex, at the crown of

the head; working outward, the arm (including hand and fingers), head, and face follow.

Despite a contradictory experiment here and an iconoclast there, for decades it had been axiomatic that there was no plasticity in the somatosensory or motor cortex of the adult brain. The only form of plasticity allowed into the textbooks was that based on Hebbian remodeling, in which neurons that fire together wire together. Since Hebb's 1949 paper, many studies had demonstrated this limited kind of cortical plasticity, but plasticity in the sense of extensively rezoning the cortex, so that a region that originally performed one function switches to another, was unheard of.

This dogma had profound real-world consequences. It held that if the brain sustained injury through stroke or trauma to, say, a region responsible for moving the left arm, then other regions could not step up to the plate and pinch-hit. The function of the injured region would be lost forever. Observations that challenged this paradigm were conveniently explained away. Faced with the fact that stroke-related brain injury, for instance, is not always permanent—someone who suffers an infarct in the region of the right motor cortex responsible for moving the left leg might nevertheless regain some control of the left leg—the antiplasticity camp didn't budge. No, it isn't possible that another region of the motor cortex assumes control of the left leg in such cases, they argued. At best, lower and more primitive regions such as the basal ganglia, which encode grosser patterns of movement, might take over some of the functions of the injured region. But recovery from brain injury, held this camp, in no way undermined the paradigm that neural circuitry in the adult is fixed (except for memory and learning through Hebbian processes). The possibility that the adult brain might have the power to adapt or change as the result of experiences was dismissed. Sherrington's "enchanted loom" weaving a "dissolving pattern" seemed to be a whimsical illusion of a more naïve age.

As an undergraduate at Oregon's University of Portland in the early 1960s, Michael Merzenich was pretty sure he wanted to become a physician. But he stumbled onto a different vocation. A Portland alumnus had founded a scientific equipment company called Tektronix; over the years, the alum had contributed entire rooms full of gadgets and gizmos to support his alma mater. Because almost no one knew how to use it all, though, the stuff sat largely untouched. Almost on a lark, Merzenich and a friend decided to see what they could make of it. Even though they were "almost entirely ignorant about what we were doing," as Merzenich recalls, after a lot of fiddling around they actually managed to accomplish something: recording the electrical activity in the neurons of insects. A professor suggested that Mike call the med school; with luck, he might find someone who would take pity on him and his coconspirator and supervise their Tektronix exploits. Making a cold call, Merzenich suddenly had John Burkhardt on the line. President of the Physiological Society, Burkhardt was a lion of neuroscience. Surprised and impressed at what Merzenich had been able to accomplish, he decided to take the

young man under his wing. Eventually, Burkhardt made a few calls for Merzenich; without even applying, Merzenich found that both Harvard and Johns Hopkins University would be delighted to have him enroll in their graduate school. Merzenich headed for Hopkins, whose department had a strong reputation for research into awareness and perception. Although barely into his twenties, Merzenich already knew that his interest in neuroscience stemmed from more than a passionate desire to work out, say, the neuron-by-neuron circuit that enables a fly to move its right front leg. "I had been interested in philosophy," Merzenich says, "and I looked at neuroscience as a way to address questions of philosophy from a scientific perspective."

After finishing graduate school in 1968, Merzenich began a postdoctoral fellowship at the University of Wisconsin. There, he focused on how information from peripheral nerves is represented in the brain, and how that representation might change. In his experiment, he cut ("transected") the sensory nerves in one hand of each of six macaque monkeys. Later, after the tiny, peripheral nerve branches had atrophied, he surgically reconnected each severed nerve where it had been cut. The peripheral branches were left to grow back on their own. The result: skin "addresses" in the brain were shuffled like a deck in Vegas. What happened was that the branches of the sensory nerves grew back into the skin almost randomly, and not necessarily to their original sites, Merzenich reported in 1972. "They sort of meandered," he explains. The poor brain was hoodwinked. A nerve that used to carry information from, say, the tip of the forefinger had instead grown back to the middle segment of that finger. When a signal arrived in the brain via that nerve, the brain naturally figured it was hearing from the fingertip, when it fact the transmission came from a few millimeters away. Something similar happened at the other end, too: nerves from some skin surfaces took over the cortical representation zones originally occupied by others. As a result, a single skin surface (such as the tip of a finger) came to be represented across several small, separate patches in the cortex, rather than the usual continuous swatch, as its nerves grew back to different regions of the cortex. Normally, adjacent regions within a parcel of somatosensory cortex represent adjacent skin surfaces. But now the skin inputs to these adjacent cortical regions were all messed up.

But not necessarily forever. With enough use of their rewired hands, Merzenich's monkeys could achieve near-total correction of the scrambled brain addresses. The brain sorted out the new pattern of connections—okay, I keep receiving input from these two nerves at the same time; I'm going to guess that they come from adjacent areas of skin—and remade the somatosensory cortex accordingly. In other words, the brain registers which skin sites fire simultaneously. Through such coincident sensory ("afferent") input, the cortex creates functionally coherent receptive fields, a dramatic example of what has come to be called activity-dependent cortical reorganization.

"I knew it was astounding reorganization, but [back in the 1970s] I couldn't explain it," says Merzenich. "It was difficult to account for the emergence of such orderly

receptive fields when we shuffled the sensory input so drastically. Looking back on it, I realized that I had seen evidence of neuroplasticity. But I didn't know it at the time. I simply didn't know what I was seeing." Merzenich pauses. "And besides, in mainstream neuroscience, nobody would believe that plasticity was occurring on this scale." Although scientists in James's and Sherrington's day had debated and speculated about brain remodeling, by the time Merzenich got interested, the idea had pretty much been run out of town on a rail. Those tidy diagrams assigning one function to this patch of brain and another to that one—here some language comprehension, there some lip sensation—proved too compelling: neurons of the brain, held the dogma, figure out early what they're going to be and stick to it for life.

Merzenich wasn't persuaded. He determined to see just how extensively the cortex could reorganize after new patterns of input. What he needed were brains in which the somatosensory cortex is spread over a flat surface, rather than being plagued by fissures and sulci, simply so he could see the thing better. While at Wisconsin, he had struck up a friendship with Jon Kaas, also a postdoctoral fellow there. When Merzenich went off to the University of California, San Francisco (UCSF), in 1971, Kaas joined Vanderbilt University, where he was doing experiments with little New World primates called owl monkeys (*Aotus trivirgatus*); their somatosensory cortex was perfect for what Merzenich had in mind. The squirrel monkey (*Saimiri sciureus*), too, had an easy-to-map somatosensory cortex and would also prove popular in neuroplasticity investigations. In both species, the map of the hand takes up roughly eight to fourteen square millimeters of cortical real estate. Merzenich and Kaas began to investigate how surgically disconnecting sensory input alters animals' brains.

"We decided to re-do the experiment we had started together at Wisconsin," recalls Kaas, "in which we cut one of the monkey's peripheral nerves, let it grow back, and then examined the somatosensory cortex to see if there had been any changes." They started with what they figured would be the control experiment: severing the median nerve of an adult monkey's hand and not reconnecting it (left alone, severed nerves do not mend themselves). Once the monkeys had lived with their severed nerve for several months, Merzenich took a sabbatical from UCSF and joined Kaas at Vanderbilt. The next step was to probe how the surgery altered the animals' brains. To do that, they recorded the activity in hundreds of locations in the monkeys' somatosensory cortices. Thanks to new anesthetics, which did not render the cortex unresponsive as old barbiturates did, the team was able to put the animals under anesthesia but still get readings. "We were in the lab all the time," recalls Kaas.

*Mapping takes hours and hours, so we would start in the morning and not leave until two days later, once we had finished all the recordings—or else got too goofy to work. No one wanted to miss out on what we were finding. There was a feeling that you didn't know what would be seen next, and if you weren't right there you wouldn't believe it. I remember taking a candy break one midnight after a pretty*

*successful run, and eating a Payday. When I finally finished at 6 A.M. one day, I broke out a beer. It was called "Quitting Time."*

Their findings were worth more than a cheap beer, for what the researchers assumed would be the control experiment—preventing the cut nerve from reconnecting—turned out to be a neuroscience landmark. "Quite unexpectedly, the cortex that had received input from the severed nerve, and which should now have been silent, responded to stimulation of other parts of the hand," Kaas recalls. Within three weeks after they had severed the median nerve, which carries signals from the thumbward half of the monkey's palm and fingers, new inputs from the radial and ulnar nerves—which serve the pinky side and the back of the hand, respectively—had completely annexed the median nerve's cortical territory. After four and a half months, the new maps were as refined as the original: "A beautiful, complete topographic representation of the dorsal hairy fingers [and ulnar palm] emerges," Merzenich later wrote with his UCSF collaborator, William Jenkins, "almost equal in detail to the representation…that it supplanted." As the investigators put it in 1983, "These results are completely contrary to a view of sensory systems as consisting of a series of hardwired machines."

The result was greeted with outright hostility. Most of the neuroscience community regarded the finding as somewhere between unlikely and impossible. "Whenever I talked about the extended implications of this, people were very antagonistic," Merzenich recalls. "Hubel and Wiesel's work had shown just the opposite: that after a critical period early in life the brain does not change as a result of changes in sensory input." At scientific meetings, critics heaped scorn on the idea. The peer reviewers of the 1983 paper seemed astonished and doubted its validity. The prevailing view, that the adult brain is fixed and immutable, was so strong that Kaas and Merzenich's work didn't come close to toppling it. "No one had really thought about activity-dependent reorganization in adult animals until Merzenich and Kaas's work," says Terry Allard, who would later spend four years in Merzenich's lab. "Even after this work, it seemed like no one really wanted to."

Kaas found that out the hard way. In another study, he cut some of the retinal nerves in lab animals. After a while, the surviving nerves filled in the area in the visual cortex that the damaged nerves had once delivered inputs to ("so that there were no holes in the vision field," as Kaas puts it). He submitted a paper describing that result to the journal *Science.* An anonymous reviewer dismissed it out of hand, because "everyone knew" that the visual system was not plastic in the adult. Hubel and Wiesel had shown that. Kaas was incredulous. How can you say that, he asked, when the experiment had never been done until now?

Slicing up monkeys' nerves was a pretty drastic way of inducing neuroplasticity, of course. Might the brain manage the feat more, well, naturally? In 1987 Merzenich and Kaas found out. They conducted, in adult owl and squirrel monkeys, experiments resembling Graham Brown and Sherrington's of three-quarters of a century before: comparing cortical maps of the hand in monkeys of about the same

size and age. The representation of the hand in the primary somatosensory cortex, they found, varied in size by more than a factor of 2. Representations of individual fingers or segments of digits varied upward of threefold; representation of the back of the hand sometimes occupied half the hand-zone area and sometimes just a small percentage of it. Differences between individuals often swamped differences between species averages—not that averages were looking very meaningful at this point. The different maps, Merzenich suspected, likely reflected the unique life history of each animal. The way the monkey ordinarily used its hands and fingers left an imprint on its brain. As they said, "We propose that the differences in the details of cortical map structure are the consequence of individual differences in lifelong use of the hands."

In another tip of the hat to classic experiments, Merzenich and Kaas mapped the hand representations in the somatosensory cortices of monkeys two to four times. Between mappings, the monkeys lived their normal laboratory life. "Each time we did it the map was unequivocally different," says Merzenich.

*I realized that we had inadvertently repeated that 1923 experiment of Karl Lashley, from which he argued that if you make a map of the motor cortex it would be different every time. He believed that the motor cortex is dynamic, reflecting the movements of the body part each spot represents. We were mapping somatosensory cortex, of course, and he was mapping motor cortex. But the conclusion was the same: the cortex is not static, but dynamic. Each time we mapped it, it was different. So what, we asked, was driving this dynamism? It could only have been behavior.*

The brain's response to messages from its environment is shaped by its experiences—experiences not only during gestation and infancy, as most neuroscientists were prepared to accept, but by our experiences throughout life. The life we live, in other words, shapes the brain we develop. To Merzenich, the real significance of the findings was what they said about the origins of behavior and mental impairments. "This machine we call the brain is being modified throughout life," he mused almost twenty years later. "The potential for using this for good had been there for years. But it required a different mindset, one that did not view the brain as a machine with fixed parts and defined capacities, but instead as an organ with the capacity to change throughout life. I tried so hard to explain how this would relate to both normal and abnormal behavior. But there were very few takers. Few people grasped the implications." For a while, it appeared that the monkeys' brains were a lot more adaptable than the research community's.

In an effort to break through, Merzenich decided to pose what he calls "a greater challenge to the brain." Until now, he had typically altered sensory input by transecting a nerve; cutting the nerve to the palm, for example, resulted in an expansion of cortical areas dedicated to the hand's hairy surfaces. But critics suggested that the hairy surfaces might have been connected to the palm area of the cortex all along. According to this line of argument, there was no true cortical

remapping, in which neurons carrying signals from the back of the hand invaded the palm's representation zone after its own input was cut off. Instead, maybe back-of-hand neurons had always been present, though silent, in the palm-side representation and were merely being "unmasked" once input from the palm vanished. To (he hoped) overcome such objections, Merzenich and his UCSF team decided to go beyond nerve transection. They amputated a single finger in owl monkeys, removing all possibility of sensory input from the digit, by any route.

Two to eight months after the surgeries, the researchers anesthetized each animal and carefully recorded electrical activity in the somatosensory cortex. They found that the cortical representation of the hand had reorganized. Skin of the palm and of the still-intact fingers adjacent to the amputated finger had taken over the cortical representation of the missing finger, invading the "amputation zone." Put another way, in the monkey version of the somatosensory homunculus, the little guy had lost his middle finger but grown a larger second finger. When the researchers stimulated the monkeys' second digit, the region of the somatosensory cortex that registered sensation in that digit fired, as expected. But so did the representation of what had been the area for the amputated digit, they reported in 1984. When his second finger was touched, the monkey responded as if the scientists were touching his missing finger.

"The amputation work was regarded as the breakthrough experiment," says Ed Taub, now more than a decade past his Silver Spring monkey trials. "Until the mid-1980s, it was an axiom of science that there was little or no plasticity in the adult nervous system. For that reason Merzenich's data aroused a great deal of interest."

Interest, however, is one thing; acceptance is another. The existing paradigm, denying the possibility of such cortical reorganization, would not die easily. The cortical reorganization that Merzenich and his colleagues reported was taking place over only two millimeters of cortical space—the distance, in the owl monkey's brain, that neurons from the second digit had spread in the cortex after amputation of the third digit. Even when Merzenich performed two-digit amputations, to see whether the cortex could remodel over even greater distances, reorganization was confined to a region no larger than a few millimeters. To those reluctant to accept the implications, this degree of rewiring seemed insignificant, perhaps even an error of measurement.

In 1984 Terry Allard, with a fresh Ph.D. from the Massachusetts Institute of Technology, arrived as a postdoc in Merzenich's lab, where he teamed up with Sharon Clark, a talented microsurgeon. Their assignment was an experiment in artificial syndactyly. (*Syndactyly* is a birth defect in which the fingers are joined together, as if in a fist; in artificial syndactyly, two adjacent fingers are sewn together.) What inspired the experiment was a simple enough question: what creates separate representations, in the somatosensory cortex, of the five digits? Merzenich's team hypothesized that the distinct representations reflect differences in the timing of their sensory input: because fingers receive noncoincident sensory

stimulation, they develop discontinuous representations. If so, then surgically fusing the digits should eliminate separate representations. "I had basically no background in this," says Allard, "but Mike was very convincing. If the somatosensory map is truly activity-dependent, he convinced me, then artificial syndactyly should be reflected in a new cortical map."

To test their guess, the scientists first had to determine the lay of the land in the brains of adult owl monkeys before their fingers were fused. After anesthetizing each monkey, Bill Jenkins exposed its cortex and then carefully moved the animal to a large camera stand so he could take a four- by five-inch Polaroid of the surface of its brain. He marked several hundred spots on the photo—the places where he would check for activity by positioning electrodes there. Then he gently brushed a spot on the animal's hand or fingers. Through the electrodes inserted into the marked spots, he determined which spot responded to the stimulus. "It was hugely time-consuming," Jenkins recalled. "Constructing a hand map would take, typically, eight hours. It would usually be me and a couple other people, me looking through the microscope and positioning the electrodes, and someone else defining the receptive fields based on the electrodes' response."

Once they had their baseline map, Sharon Clark split the skin of the ring finger and the middle finger of the owl monkeys and then sewed together the dorsal and ventral surfaces. Recalls Allard, "After that, the monkeys just lived their life in the cage. We didn't do anything additional to drive stimulation. But after two or three months, we found that the cortex had been remapped. The very first monkey we did, there was no question the brain had reorganized." Whereas before the surgery the monkeys' fingers transmitted nonsimultaneous signals to the cortex, with the result that the cortex devoted separate little islands to receive input from each separate finger, once the fingers began sending only joint messages (since whenever one finger touched an object, so did the other, as if they were a single digit), the brain reassessed the situation. It seemed to figure that it needed only a single receiver rather than two. What had been separate representations of the fingers became a single, continuous, overlapping representation, they reported in 1988. "We felt we had found the language of the somatosensory cortex, the input that determines how it is organized," says Allard. "We had a sense that we were part of something important, discovering an aspect of the brain that hadn't been recognized before—this whole dynamic aspect of the brain." Years later, researchers in New York would find that the same principle applied to people. Surgeons operated on two patients to separate their congenitally fused fingers. Before the surgery, the cortical map of their digits was shrunken and disorganized. But when the fused digits were separated, the brain quickly created separate receptive fields for the two digits.

Back at Vanderbilt, Kaas knew that no matter how many such breakthroughs were reported, mainstream neuroscience was not about to abandon Hubel and Wiesel's antiplasticity paradigm—at least not until someone challenged their findings head-on. So Kaas and his team turned their attention to the visual cortex of cats, the

very animals and the very system that the earlier scientists' Nobel-winning work had characterized as plastic only in infancy. "The organization of the visual cortex has been considered to be highly stable in adult mammals," Kaas's group declared, with some understatement. But when the researchers created small lesions in the cats' retinas, the representation of the retina in the visual cortex shifted. Cortical neurons that formerly received input from the now-lesioned regions did the equivalent of changing pen pals after the original correspondent stops writing. With no input arriving from the lesioned areas of the retina, the cortex began processing inputs from parts of the retina surrounding the lesions. The adult visual cortex seemed just as capable of reorganizing itself as other areas of the brain were.

There was entrenched opposition even to considering whether the cortical reorganization that Merzenich, Kaas, and their colleagues had found in owl monkeys might be applicable to cortical injuries in people—in particular, injuries from stroke. "The reason people were interested but not excited was that the results did not seem to have the potential for recovery of function, because the region involved was too small," recalls Taub. "Even if you extrapolated this to human beings, you were still talking about only 3 to 4 millimeters." Although Merzenich and Kaas were by now convinced that the brain is dynamic and adaptive, creating its maps of the body on the basis of the inputs it receives, and changing those maps as the input changes, critics still dismissed the extent of reorganization they were finding as simply too small to have any significance.

But then Pons and Mishkin got permission to experiment on four of the Silver Spring monkeys. Their 1991 discovery that the deafferentation zone—the part of the somatosensory cortex that originally processed signals from the entire upper limb—was not silent at all, but was instead receiving input from the macaques' faces, changed everything. Merzenich's amputation experiments had documented reorganization of the somatosensory cortex in adult owl monkeys of a millimeter or so; in the Silver Spring monkeys, cortical reorganization spanned a distance an order of magnitude greater, between one and two centimeters. And the reorganization was very complete: every single neuron from 124 recording sites tested in the deafferentation zone had a new connection. "This generated a great deal of excitement," says Taub. "It had the odor of being involved in recovery of function. With this result, it began to look like you could get cortical reorganization on a massive scale, and that might mean something."

At this point, however, there had never been a demonstration of cortical reorganization in people. That was about to change. As soon as the neurologist V. S. Ramachandran read the Silver Spring monkeys study, it "propelled me into a whole new direction of research," he recalled. "My God! Might this be an explanation for phantom limbs?" If touching the faces of the Silver Spring monkeys could excite the somatosensory cortex representation of what was once their arm, Ramachandran wondered, might his amputees' homunculi have been rearranged, too, in a way that would explain the phenomenon of phantom limbs? After all, in the human homunculus, the hand and arm are also near the face.

Although the term *phantom limb* had been around since just after the Civil War, when it was coined by Dr. Silas Weir Mitchell, it had remained a medical conundrum. In 1866 Mitchell had first published his description of it—under a pseudonym. Even when he went public with his finding in 1871, he eschewed the medical journals in favor of the pop magazine *Lippincott's Journal*, the better to insulate himself from the expected derision of colleagues. The phenomenon has struggled to earn respect, or even recognition of its physical reality. As recently as the 1980s researchers (in the *Canadian Journal of Psychiatry*) ascribed phantom limb to wish fulfillment. Just as one might imagine hearing the voice of a recently deceased loved one, went their reasoning, so might an amputee feel a recently lost limb.

Ramachandran immediately phoned colleagues in orthopedic surgery and asked whether they had any recent amputees. They did: Victor Quintero, seventeen, who a month before had lost his left arm just above the elbow in a car crash. Victor swore up and down that he could still feel the missing appendage. Ramachandran enlisted him for an experiment. With Victor sitting still with his eyes closed tight, Ramachandran lightly brushed the boy's left cheek with a cotton swab just as Pons's team had the Silver Spring monkeys. "Where do you feel that?" Ramachandran asked. On my left cheek, Victor answered—and the back of my missing hand. Stroking one spot on the cheek produced the sensation of his absent thumb's being touched. Touching the skin between his nose and mouth created the sensation that his phantom index finger was being brushed. The somatosensory remapping was so fine that when Ramachandran stroked a spot just below Victor's left nostril, the boy felt a tingling on his left pinky. And in perhaps the most peculiar result of somatosensory remapping, when Victor felt an itch in his spectral hand, scratching his lower face produced relief. (Victor was delighted at this, since now, whenever his missing fingers itched, he knew where to scratch.) In a final test, Ramachandran dribbled warm water down Victor's left cheek—and the young man, incredulous, felt a warm feeling in the ghost of his amputated hand. The feeling was so powerful that he actually double-checked that his arm was still gone.

There are some 4 million amputees in the United States. For nearly 70 percent of them their missing arms, hands, legs, or feet continue to experience all-too-real feelings of pressure, pain, warmth, cold, tingling, or other sensations—including Victor's itching. Human amputees, Ramachandran told a 1993 scientific meeting in Santa Fe, experienced cortical reorganization similar to that found in the Silver Spring monkeys: stimulation of the face produced an electrical response in both the somatosensory representation of the face and the amputation zone representing the now-missing arm, as if facial nerves had invaded that region. Brain neurons that originally received input from a limb, it seems, react much as the Silver Spring monkeys did to the decrease in sensory input: rewiring themselves to receive input from other sources. Phantom sensation arises from neuroplastic changes in the brain. Neurons in regions that originally fired in response to stimulation of a now-missing body part look for new work, as it were, and instead respond to peripheral

neurons that are still in the game. Just as people in Times Square on New Year's Eve push into any suddenly vacant spot, so surrounding neurons push into the otherwise-silent region of cortex. And also like the New Year revelers, neurons immediately adjacent to a cortical area are most likely to get first dibs at any vacancies.

Which part of the upper quadrant of the body invades the amputation zone therefore turns out to be somewhat random. After a hand is amputated, either the face or the trunk can invade its somatosensory representation. And because the representations of the feet and genitals abut, some people who have suffered the loss of a leg report feeling phantom sensations in the missing limb or limbs during sex: the somatosensory map of the leg, starved of sensation as a result of losing its original input, can be invaded by nerves from the genitals. Similarly, a man whose cancerous penis is amputated may, if his foot is stimulated, have sensations of a phantom penis. (This proximity may help explain why some people find feet erogenous: not merely because the foot unconsciously reminds some people of the penis, as Freud suggested, but also because the somatosensory representation of the foot lies beside the representation of the genitalia.)

The amputation zone, it appeared, was akin to the deafferentation zone in the brains of the Silver Spring monkeys. Monkeys, being somewhat less verbal than your typical amputee, had not been able to tell Pons that cortical remapping produced perceptual effects. Thus Ramachandran's was the first report of a living being's describing the effect of his own brain rewiring.

One of those attending the 1993 Santa Fe meeting at which Ramachandran presented his data was Edward Taub. Taub's rehabilitation into the world of science began in 1986, when Carl McFarland, chairman of the psychology department, recruited him to the University of Alabama, Birmingham (UAB). Taub started work in 1987. The city was trying to shake its history as a citadel of racism and turn itself into a research powerhouse. Taub had an office and a research home. He even had a salary. But he had no "real" money—no research grants. "When I came here I had zero, and not only did I have zero but I couldn't get anything," Taub recalls. "It wasn't the Silver Spring situation," as he calls it, but the sheer unacceptability of his views on neuroplasticity. Soon after he arrived in Birmingham he gave a presentation on the deafferentation data. After methodically describing how the monkeys would resume using their supposedly useless, deafferented arm if their good arm were constrained, he boldly suggested that a similar approach—constraining the movement of the unaffected arm of stroke patients—might restore the use of the affected arm. After all, there was little to lose. No physical or occupational therapy had really been effective in chronic stroke patients, those whose stroke was years in the past and who were thus past the point of spontaneous recovery.

That amounted to millions of people. Every year, at least 600,000 Americans suffer a stroke, which works out to one victim every fifty-two seconds. Of the 440,000

who do not die immediately, 300,000 are left seriously disabled. Thanks to the graying of America, the personal and social toll from stroke is on the increase, with the prevalence of cerebrovascular accident survivors—the technical term—projected to double by 2050. "I just laid it out, not being antagonistic, and of course I didn't know anything about the rehabilitation community," Taub recalls of that first presentation. "I was stepping on everyone's toes with this. The head of the rehabilitation center literally began to stammer, and his face became purple, and he said, 'Are you trying to tell me that a behavioral intervention has an ameliorative effect on a neurological injury of the central nervous system?!' I said, 'But, after all, what is physical therapy if not a behavioral intervention?' He went ballistic. You still have this orientation in the medical community that behavior isn't real."

Taub wasn't the only one whose work connecting plasticity to rehab fell on deaf ears. In 1981 Steve Wolf took up a suggestion Taub had made the year before (Taub himself was still unable to conduct research at this point). Wolf had twenty-five patients with brain damage, most due to stroke, wear a sling on their unaffected arm all their waking hours, except for a half-hour exercise period, for two weeks. He did nothing else. Consistent with Taub's findings on the deafferented monkeys, however, the patients' speed and strength of movement in the disabled arm showed significant improvement on lab motor function tests. Although the effect was small (mostly because Wolf did not use intensive training of the patients' disabled arms), it seemed worth following up. Yet for years no one did. At UCSF, Merzenich and Jenkins had had a similar inspiration. In 1987, they independently proposed that the plasticity of the cortex in response to sensory input, experience, and learning was relevant for stroke rehab. But no one beat down their doors to follow up on the suggestion. After all, "the rehab community was united in opposition to the idea that therapy after a stroke could reverse the neurological effects of the infarct," Taub recalls. "The official position of the American Stroke Association was that rehab for patients with chronic stroke only increases a patient's muscular strength and confidence."

Others were more open-minded. One was the behavioral neuroscientist Niels Birbaumer of Germany's University of Tübingen. At a 1991 presentation in Munich, he heard Taub propose adapting the therapy he had used on the Silver Spring monkeys—constraining their good arm, forcing them to use their "useless" one—to stroke patients. Birbaumer invited him to set up a stroke program in Germany. Taub arrived in Tübingen soon after the 1993 Santa Fe meeting and had lunch with the German psychologist Herta Flor. He told her about Ramachandran's study, describing Ramachandran's claim that touching the face of someone whose arm has been amputated can evoke the feeling that the missing arm is being touched, and suggested that it needed to be verified. Flor responded, "No problem—why don't we do it? I'll just call up my friend Thomas Elbert who has an MEG [*magnetoencephalograph*, which records magnetic changes in neurons that correspond to neuronal activation] and we'll run some patients." "I said, 'fine,'" recalls a still-startled Taub. And thus was born a collaboration that would influence

the entire landscape of neuroplasticity. As we learned in Chapter 4, by this time the deafferented Silver Spring monkey research had given rise to two parallel research tracks. One was large-scale cortical reorganization, which Pons and colleagues had put on the map with their experiment on the monkeys. The other was constraint-induced movement (CI) therapy, which as long ago as 1980 had been a glimmer in Taub's eye, but a glimmer extinguished by the debacle of Silver Spring.

As early as 1987 at least some of Taub's colleagues at Birmingham had come around to the notion that behavior can leave footprints on the brain, including the injured brain—well, they'd come around enough to collaborate with him. That year Taub and some UAB colleagues began a pilot experiment. They started working with four patients who were in the top quartile of stroke survivors in terms of ability to move their affected arm: they were able to extend their wrist a minimum of twenty degrees and to flex each finger a minimum of ten degrees. Restraining the intact arm of the Silver Spring monkeys or training the deafferented arm had induced the creatures to use that deafferented arm. Taub suspected that the same two procedures applied to a stroke patient would coax movement out of the affected one—especially training the affected arm. The same general techniques that accomplished that in the deafferented monkeys, Taub maintained, "should be equally applicable following other types of neurological injury, including stroke."

In constraint-induced movement therapy, stroke patients wear a sling on their good arm for approximately 90 percent of waking hours for fourteen straight days. On ten of those days, they receive six hours of therapy, using their seemingly useless arm: they eat lunch, throw a ball, play dominoes or cards or Chinese checkers, write, push a broom, and use standard rehab equipment called dexterity boards. "It is fairly contrary to what is typically done with stroke patients," says Taub, "which is to do some rehabilitation with the affected arm and then, after three or four months, train the unaffected arm to do the work of both arms." Instead, for an intense six hours daily, the patient works closely with therapists to master basic but crucial movements with the affected arm. Sitting across a pegboard from the rehab specialist, for instance, the patient grasps a peg and labors to put it into a hole. It is excruciating to watch, the patient struggling with an arm that seems deaf to the brain's commands to extend far enough to pick up the peg; to hold it tightly enough to keep it from falling back; to retract toward the target hole; and to aim precisely enough to get the peg in. The therapist offers encouragement at every step, tailoring the task to make it more attainable if a patient is failing, then more challenging once the patient makes progress. The reward for inserting a peg is, of course, doing it again—and again and again. If the patient cannot perform a movement at first, the therapist literally takes him by the hand, guiding the arm to the peg, to the hole—and always offering verbal kudos and encouragement for the slightest achievement. Taub explicitly told the patients, all of whose strokes were a year or more in the past, that they had the capacity for much greater use of their arm than they thought. He moved it for them and told them over and over that they would soon do the same.

In just two weeks of constraint-induced movement therapy with training of the affected arm, Taub reported in 1993, patients regained significant use of a limb they thought would forever hang uselessly at their side. The patients outperformed control patients on such motor tasks as donning a sweater, unscrewing a jar cap, and picking up a bean on a spoon and lifting it to the mouth. The number of daily-living activities they could carry out one month after the start of therapy soared 97 percent. That was encouraging enough. Even more tantalizing was that these were patients who had long passed the period when the conventional rehab wisdom held that maximal recovery takes place. That, in fact, was why Taub chose to work with chronic stroke patients in the first place. According to the textbooks, whatever function a patient has regained one year after stroke is all he ever will: his range of motion will not improve for the rest of his life.

"It's true, spontaneous recovery of function usually stops between three and twelve months," Taub says. But his constraint-induced movement therapy picked up where spontaneous recovery stopped. "We got a large effect in the lab and a huge effect in the life situation," Taub says. Two years after treatment ended, the constraint patients were still outperforming controls, brushing their teeth, combing their hair, eating with a fork and spoon, picking up and drinking from a glass.

That fell short of winning over the establishment, however. Throughout 1992 and 1993, Taub recalls, he was rejected for funding by NIH "right and left" because his proposed stroke therapy was so beyond the pale. But as he and his colleagues ran more and more patients, and as other labs replicated their work, it became clear that his hunch, and his hope, were correct.

The Department of Veterans Affairs (Veterans Administration), which has a large population of elderly stroke survivors, finally awarded Taub a grant to extend his research beyond the top-functioning stroke patients to lower-functioning ones. In 1997 he found that patients in the top three quartiles exhibited significant improvement on standard tests of motor ability. The constraint-induced movement therapy worked for them, too, though not as well: the more-affected patients improved by a score of 1.7 on a scale of motor ability, compared to a change of 2.2 for higher-functioning patients. Patients who were functioning best before therapy retained most of their gains even two years afterward; second- and third-quartile patients lost a small fraction of their gains after two years, suggesting the need for what Taub calls "brush-up" training. But the point had been made. The therapy has restored function to patients who had their stroke as much as forty-five years before. "CI therapy appears to be applicable to at least 75 percent of the stroke population," concluded Taub.

The VA also supported an extension of Taub's work to stroke patients who had lost the use of a leg. In this case, constraining the unaffected limb isn't part of the therapy. Patients walk on a treadmill, wearing a body harness for support if necessary, to give them the confidence that they will not collapse as they try to use a leg that they had dismissed as hopelessly impaired. They walk up and down the

hall of the Birmingham VA hospital. They rise from a sitting position, climb steps, and do balance exercises. They work for seven hours a day for three weeks. In Taub's first group of sixteen stroke patients with lower-limb impairment, four had not been able to walk at all without support. Two of them learned to walk independently, if awkwardly. Two learned to walk again with only minimal assistance. Of the twelve less-impaired patients, all improved substantially.

What might be the basis for the improvement? In 1998 and 1999 two important studies on patients who underwent the arduous regimen of constraint-induced movement therapy began to provide the answers. In the first, Joachim Liepert and Cornelius Weiller of Friedrich-Schiller University in Jena, Germany, led an investigation of brain changes in six chronic stroke patients. They evaluated the patients before and after they were treated with fourteen days of CI therapy. All six showed significant improvement of motor function. Moreover, all six also showed "an increase of excitability of the neuronal networks in the damaged hemisphere," they found. "Following CI therapy, the formerly shrunken cortical representation of the affected limb was reversed…. [O]nly two weeks of CI therapy induced motor cortex changes up to seventeen years after the stroke." Taub's method of stroke rehabilitation had resulted in a clinically meaningful "recruitment of motor areas adjacent to the original location" involved in control of the limb.

In 1999, Taub and his German collaborators reported on four patients whose strokes had left the right arm extremely weak. The patients again underwent two weeks of CI therapy. All improved significantly. Then, three months later, the scientists recorded changes in the brain's electrical activity. In the most striking finding, when the patients moved their affected arm, the motor cortex on the same side crackled with activity. Ordinarily, the left motor cortex controls the right side of the body, and vice versa. But in these patients, the motor cortex on the same side as the affected arm "had been recruited to generate movements of [that] arm," Taub says. This suggests that the healthy side of the brain had been drafted into service by the patient's continued use of the affected arm. Normally, activity in one hemisphere suppresses the activity of the mirror-image region on the other side, apparently through the bundle of connecting nerves called the corpus callosum. But when activity in the original region is silenced, as by a stroke, that suppression is lifted. Something more than the absence of suppression was needed, however. The increase in the use of the affected arm had, through sustained and repeated movements, "induced expansion of the contralateral cortical area controlling movement of the…arm and recruitment of new ipsilateral area." Taub, adopting Mike Merzenich's term, called it *use-dependent cortical reorganization*. He suspected that it served as the neural basis for the permanent improvement in function of what had been thought a useless limb.

One of the patients Taub is proudest of is James Faust, who lives in Calera, Alabama. After a stroke damaged the left side of his cortex, Faust's right arm was so completely paralyzed that he even thought about asking a surgeon to cut off the useless appendage. But hearing about Taub's CI movement therapy, Faust enrolled.

After only a few weeks the change was astounding. One evening, when Faust and his wife were having dinner at a restaurant, she looked across the table at him. Her jaw dropped. James was holding a steak knife in his right hand and slicing away as if the stroke had never happened. That was all the encouragement he needed. From that evening on, he began using his right hand as much as he did before the stroke, even more so than he did with the at-home exercises Taub had prescribed: Faust had overcome the "learned nonuse" that Taub had first seen in his monkeys. Success bred success. The more Faust used his right arm and hand, the greater the cortical area the brain presumably devoted to their movement; the greater the cortical area devoted to their movement, the better they moved. Faust is now able to tie his shoes, shave, brush his teeth, and drive.

These two studies were the first to demonstrate a systematic change in brain function in stroke patients as a result of CI therapy. They documented that treatment produces a marked enhancement in the cortical areas that become active during movement of a muscle of an affected limb. Through CI therapy, the brain had recruited healthy motor cortex tissue in the cause of restoring movement to the stroke-affected hand. "Repetitive use of the affected limb induces an extremely large use-dependent cortical reorganization," says Taub. "The area that is responsible for producing movements of the affected arm almost doubles in size, and parts of the brain that are not normally involved, areas adjacent to the infarct, are recruited. You also get recruitment of parts of the brain that are not usually involved in generating movement in the affected arm—that is, areas on the other side of the brain."

The results Taub was obtaining with his stroke patients, corroborated in labs adopting his constraint-induced movement approach, made people more willing to accept such explanations of how and why that therapy worked at a neurological level. In 1999 his UAB team and Emory University received funding from the National Institutes of Health for a national clinical trial of constraint-induced movement therapy at six sites. It would be the first national clinical trial for stroke ever funded by NIH. Sadly, no previous therapy had achieved results sufficient to warrant one. The record of smaller clinical trials for ischemic stroke, as the UCLA neurologist Chelsea Kidwell put it in 2001, was "remarkably dismal."

In the spring of 2000, Taub and his colleagues reported on thirteen more stroke patients in what would be the definitive paper on the power of CI therapy. The thirteen had been living with their disabilities for between six months and seventeen years. They underwent twelve days of CI therapy. When it was over, the amount of motor cortex firing to move the disabled hand had almost doubled. Rehab, it seemed, had recruited new enlistees as effectively as anything the army has ever tried: huge numbers of previously uninvolved neurons were now devoted to moving the stroke-affected hand. Constraint-induced movement therapy had produced cortical remapping. And the improvements in function that accompanied these brain changes remained when the scientists tested the patients after four weeks, and again after six months. "This is the first time we have seen, in effect,

the re-wiring of the brain as a result of physical therapy after a stroke," said Dr. David Goode of Wake Forest University.

It was the result that Taub had been working toward from his days with the Silver Spring monkeys and thus, for him, a personal vindication. It was, more than any other, the breakthrough that brought him in from the cold, and almost made up for his period in the wilderness, for the trial, for the fact that his name would forever be associated with the most notorious animal cruelty trial in the history of American research. Few people outside the animal rights community even remembered the Silver Spring monkeys. Those who did hardly cared. In November 2000, at the annual meeting of the Society for Neuroscience, Taub could mention before a roomful of reporters "some monkeys that lived for more than twelve years after deafferentation" without eliciting a single curious inquiry.

Cortical regions supporting sensory and motor functions are better understood, with their little homunculi, than are areas underlying memory and language, two functions whose loss after a stroke can be most devastating. It might seem almost natural, if the region of the motor cortex that once controlled the hand were damaged, for hand control to be taken up by the region that once controlled the shoulder. It's all motor cortex, after all, and therefore not so different from, say, one clothing boutique's blowing through a wall to annex the adjoining haberdashery. But can the same approach apply to higher-level functions? Taub was sure it could, probably through cortical reorganization like that in motor cortex. "If a stroke knocks out your Broca's region, I am suggesting, you can in effect grow a new Broca's region," he says. "That's the whole point. Functions are assigned in the brain in a very general way based on genetics, but they can be co-opted by new patterns of use. If you increase the use you create a competition for available cortical space, which is won by the function that is being most used. That's what we demonstrated in the motor cortex in stroke. So why shouldn't it be applicable in speech? It's just brain." Taub made good on this prediction in 2001, when a similar therapy was used successfully to treat patients who had been left aphasic—unable to speak—by a stroke.

Neurologists had debated for more than a century what lay behind spontaneous (that is, not in response to therapy) language recovery after stroke. One school held that unaffected language regions in the (otherwise damaged) left hemisphere begin playing a greater role. Another, more proplasticity school suspected that regions in the right hemisphere, which in most people are not specialized for language, suddenly undergo a midlife career change. In 1995 researchers led by Cornelius Weiller addressed this question. They studied six men whose devastating left-hemisphere stroke had largely destroyed their Wernicke's area. This region, lying near the junction of the left temporal and parietal lobes, is critical to understanding speech. The men had serious impairments in their ability to use and comprehend spoken words. Over time and with intensive therapy, however, all six largely regained their ability to speak and communicate. What happened? To find out, the researchers scanned the patients' brains with positron emission

tomography (PET) while they carried out two word exercises. The PET scans showed that regions in the right hemisphere, corresponding in position to the left cortex's Wernicke's area and other language centers, became active. Recovery, it seemed, had been accompanied by cortical reorganization. Right brain areas analogous to the left brain's damaged language zones had taken over their function.

The next year, Randy Buckner and colleagues in Saint Louis reported a similar finding. They studied a patient who had suffered a lesion to a small area in the left frontal lobe that plays a role in tasks like completing words from three-letter fragments. In normal subjects, turning letter strings such as *cou-* into words like *courage* activates this region. Although the patient was initially unable to master many language functions, within six months of his stroke and with no specific therapy he was performing at almost normal levels on this test. Brain scan results showed that, although the left frontal lobe region normally used to carry out this verbal task was quiet and dark (having been knocked out by the stroke), the mirror-image spot in the right frontal lobe was working away. As the investigators described it, "a pathway similar to that of normal subjects was activated except that, instead of left prefrontal cortex, [our patient] activated right prefrontal cortex." How could this be? Just as in the Weiller study, damage to the original language region in the left hemisphere apparently lifted the suppression of the corresponding region on the right, allowing it to step in and assume the functions of its impaired counterpart.

More support for the "It's all just brain" school of thinking emerged in 1996 from Mark Hallett's lab at NIH. They studied people who had been blind from an early age. In such patients, the primary visual cortex does not receive input from the expected sources, namely, the retina via the optic nerve. But it doesn't take this silence as a license to retire. Instead, Hallett found, reading Braille and performing other fine tactile discrimination tasks activate the visual cortex. But "reading" Braille, of course, means running fingers over raised dots, a task usually handled by the somatosensory cortex. From an early age, it seems, the visual cortex recognizes that it is not receiving signals from the eye. So it switches jobs, taking up tactile processing. The result is that a brain area usually dedicated to vision starts working on the sense of touch, a process that may explain the superior tactile sense of the congenitally blind. This is called *cross-modal functional plasticity*: brain areas that were thought to be genetically "hard-wired" for one function take on totally different functions.

Can such functionally significant brain reorganization be directly influenced by therapy? As we have seen, for people with OCD the answer is yes. The latest evidence, as mentioned, shows that therapy can help stroke patients regain not only the use of a limb, as Taub showed, but the use of language, too. In 1999, researchers in Germany led by Mariacristina Musso and Cornelius Weiller of Friedrich-Schiller University reported brain changes in four stroke patients suffering from aphasia as a result of lesions in Wernicke's area. They designed their study to

see whether brief intensive therapy can reorganize the brain and improve language comprehension. The patients had eleven short training sessions in which they had to point to a particular picture on the basis of an oral description, for instance, or indicate on the basis of a picture which of three oral sentences was accurate. The training was intended to stimulate the conscious processes that access linguistic knowledge. In twenty pilot patients, performance on a series of increasingly more complex commands, from "Pick up the yellow triangle" or "Pick up the white circle" (the patients had an array of tokens in front of them) to "Put the red circle on the green triangle" or "Put the white rectangle behind the yellow circle," improved significantly. PET scans on four of the patients provided systematic evidence of brain reorganization. A region of the right hemisphere, in a spot that was the mirror-image of the damaged Wernicke's region of the left, showed significantly increased activation, echoing the 1995 findings. But there was a critical difference. This study showed, for the first time, that the clinical recovery of language performance caused by the hard work of training is functionally related to brain reorganization. The increased activation in the right cortex, compensating for the functional loss of the left-brain homologues, reflected the training each stroke patient had. As with my OCD patients, it was yet more evidence that functional recovery reflects brain reorganization.

These stroke studies finally toppled the old dogma that when a stroke damages a neural network, function (whether speech- or movement-related) is lost because no other system in the brain knows how to perform the same job. The spontaneous recovery of such lost function, sometimes in only a few weeks, had always mystified neurologists. With the dawn of the new century it became clear that neuroplasticity, especially when nudged by effective therapy and mental effort, allows the brain to reassign tasks. The power of plasticity distinguishes the nervous system from every other system in the body. Although plasticity still seems to be greatest from infancy through early adolescence, it was now evident that the brain retains some plasticity throughout life, offering possibilities undreamed of just a few short years ago.

Now it is up to the rehabilitation community to use the findings for the good of millions of stroke patients. Some recover spontaneously, and some suffer damage so extensive that even intense therapy cannot reweave the torn threads in their neural tapestry. For the former, little or no therapy is necessary; for the latter, therapy that teaches how to compensate and cope is about all that one can hope for. But for a large middle group, therapy to induce directed neuroplasticity offers promise of independence and recovery.

Inducing neuroplasticity through a decrease in sensory input such as that after deafferentation, amputation, or stroke was the first challenge to the tenet that the adult human brain is incapable of reorganization. In fact, something close to the opposite is true. "I always think of the Balkans—all those countries that have come and gone and changed their boundaries over the 20th century," says Jordan Grafman of NIH. Through rehabilitation that exploits the vast potential of directed

neuroplasticity, stroke patients can now learn to perform actions and carry out tasks once lost to their brain injury. In many of these recoveries, functional reorganization is induced not only through the effort of repeated movement but also by sensory-input increase—something that, in many cases, is under the willful, conscious control of normal, healthy individuals. If the brain is like a map of lived experience, then the mind can, with directed effort, function as its own internally directed mapmaker. This is the subject to which we now turn.