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

Chapter 6. SURVIVAL OF THE BUSIEST

What is it but a map of busy life, Its fluctuations, and its vast concerns?

—William Cowper, "The Task"

Laura Silverman started playing the piano at age six, and for thirteen years she practiced with a dedication that astonished her teachers. Every day after school, on weekends, and even during the muggy days of a Saint Louis summer Laura would settle in at the upright in the living room for at least a couple of hours. When an important recital loomed, soon after Laura turned eighteen, she stayed at the keyboard for eight hours a day, fanatically rehearsing Mozart's Twentieth Piano Concerto in D Minor, a piece renowned for its difficult arpeggios and a demanding andante movement that requires the fingers to fly over the keys in a blur. But suddenly, one afternoon, Laura's fingers not only failed to find the correct notes; they could barely reach the keyboard. If before they seemed possessed by the musical muse, now they seemed in the thrall of a darker demon. The thumb on her left hand drooped and refused to rise to the keyboard. Other fingers, on both hands, would rise unbidden when a neighboring digit reached for a note. Terrified, Laura canceled the concert and stayed away from the piano from May until August.

When she dared to try some scales after her three-month hiatus, the problem returned in force: her fingers still would not obey her mind's commands. She told her instructor what had happened, but he had never heard of such a bizarre condition and had no idea what to suggest, or even where Laura might seek help. Laura quit taking lessons. She tried to play on her own, but her fingers defied her mind's attempts to control them. At the typewriter, her fingers rebelled just as they did at the piano.

The following spring, Laura's mother saw an article about a famous hand doctor in Boston who specialized in working with musicians. Laura went to see him, only to be told, "I don't know what's wrong with your hand, but I suspect it's all in your head." He sent her to a psychiatrist, one who helped musicians overcome problems such as performance anxiety. Laura played the piano for him, but with only her right hand; by now, her left was musically useless. The psychiatrist dismissed her, saying she must have always had the problem. Laura visited several more doctors in and around Boston. Those who didn't say it was all in her head ventured that she might be suffering the beginnings of multiple sclerosis.

Desperate now, Laura tried alternative medicine…acupuncture…Alexander technique…yoga…breathing exercises. She was finishing her sophomore year in college; she would spend her junior year in Japan. After finishing her degree she entered Harvard graduate school to study comparative religion. By this time she could hardly take notes, and her condition only worsened as she pushed herself to

function despite it. Every once in a while she would try another doctor, with the same results: *It's all in your head*.

One, who asked her to go to his house to demonstrate how she played, or didn't play, the piano, finally offered a diagnosis no one else had. He told Laura, "You have focal hand dystonia." This usually painless condition, marked by a loss of control of individual finger movements, most often affects the third to fifth fingers (the middle finger to the pinky), and usually involves two or more adjacent fingers. It can strike pianists, flutists, guitarists, and other string players and is believed to reflect the brain's response to the many hours of daily practice that serious musicians engage in, often from a young age. "You can spend the rest of your life doing therapy," the doctor told Laura, "but there is no cure for what you have. Doctors are trying psychotherapy, biofeedback, prolonged rest, steroids, and even botulinum toxin for focal hand dystonia, but nothing works. I suggest you give up piano and start singing." Laura left his house devastated. That week, she faced final exams. As she filled out her blue book in religion class, she stopped halfway through, marched up to the professor, and said she had decided to drop out. She walked out of the exam room and was at Logan Airport the next morning awaiting a flight home—and throwing up in a garbage can. Although she soon reconsidered and returned to Harvard, when she began telling her professors about her disability many were incredulous. "I see you can still hold a book up," one shot back. Many assumed she was malingering. One blasted her for sloppy penmanship.

Laura got a job in New York with *Newsweek Japan* in May 1997 and started seeing a physical therapist every third week. The sessions consisted of typing without thumbs, or with only the forefinger, or very, very slowly. Although she saw no results for more than a year, in the summer of 1999 she began to regain control of her fingers and to type almost normally. She even bought a piano for her apartment. By the end of 1999, Laura had progressed: she could once again hold up her wrists and execute the proper keyboard fingering. "Bach is great because there are a lot of distinct finger movements on both hands, and a lot of mirroring, in which you play with the right and then the left hand," Laura says. "Speed is your enemy." Although the therapist didn't explain the underlying science to Laura, she was drawing on the latest findings in neuroplasticity: that coincident sensory input, such as touching the fingertips to piano keys, can alter the brain circuits responsible for moving those fingers.

Laura and other patients with focal hand dystonia illustrate, painfully, a route to cortical reorganization that is the polar opposite of the sensory input decrease caused by stroke or amputation: sensory input increase. In monkeys with deafferented arms and humans with amputations or strokes, cortical remapping follows a reduction of sensory input, as discussed in the previous chapter. As a result of the reduction of sensory input after such injuries, regions of the somatosensory cortex representing other parts of the body invade areas that represented the now-absent or sensory-deprived part of the body. But less than ten years after his work on amputee owl monkeys jump-started the field of

neuroplasticity, Michael Merzenich demonstrated another avenue to cortical reorganization: a concentrated dose of stimulation, analogous to what Laura got through constant piano practice. It is called either sensory input increase cortical reorganization or, preferably, *use-dependent cortical reorganization*.

For more than a decade Merzenich had investigated cortical remapping through the scientific equivalent of brute force, transecting animals' nerves or amputating their fingers. The UCSF team was about to embark on something subtler. William Jenkins had joined Merzenich in January 1980 as a postdoctoral fellow. After spending his first years studying the auditory cortex, mapping which spots respond to which sound frequencies, in 1983 he read the landmark study in which Merzenich and Kaas showed that, after peripheral nerve cuts, the cortex reorganizes. "In that paper, Mike had used the term 'differential use,'" Jenkins recalls. "As a behaviorist, I was really struck by that, because until then only surgical interventions of one kind or another were producing the cortical remapping that Mike was reporting. I went to him and said this was a fascinating idea, with huge implications: if true, we should be able to drive competition for cortical space behaviorally, just as he and Kaas had done surgically." Merzenich agreed. "Cortical remodeling after injury, whether amputation, nerve transection, or lesion, is fascinating," he remembers thinking at the time, "but it's a sidelight to what I regarded as the real issue: how the brain remodels itself in response to behavioral demands." The experiments in which Sharon Clark created artificial syndactyly were an early shot in the battle to convince the neuroscience establishment that the brain creates representations of the body based on the input it receives. But that reflected a decrease in input, as two separate digits were reduced to one larger one. Would the brain also rezone itself to reflect additional input?

In 1985, a new postdoc arrived in Merzenich's lab. Randolph Nudo had been lured away from Florida State University, where he had completed his Ph.D., with the promise that Merzenich would extend his investigation of cortical reorganization from the somatosensory cortex to the motor cortex, Nudo's specialty. "I told Randy that this brain plasticity work Mike was doing was really exciting," recalls Bill Jenkins. "We were studying plasticity in the somatosensory regions, so I told him he should come out and do it for the motor cortex. 'You can own this,' I told him." But when Nudo arrived, it was not without qualms. "People who knew the motor cortex told me that was the last place they'd look for plasticity," Nudo recalls. "Everything in M1 [the primary motor cortex] was supposed to be hard-wired. It was the wrong place to look, they said. There's no question that when I joined Mike I was keeping an open mind, but I was definitely a skeptic."

Nudo came by his interest in wiring, plus some skills in electronics, honestly: he is the son of a TV repairman. He immediately put his talents to good use. In his initial experiment at UCSF, he compared the motor maps on the two sides of the brains of squirrel monkeys. The brain has a left and a right primary motor cortex, each controlling voluntary movements on the opposite side of the body. To map the motor cortex, Nudo inserted tiny stimulating electrodes into scores of locations in

that part of the brain and noted which muscles moved when a particular area fired. The motor cortex's representations of movements varied greatly between one monkey and the next, he found, as did the representations of the two hands: specific movements of the hand a monkey preferred to use for retrieving small objects took up more cortical area than maps of the same movements in the nonpreferred hand. Says Nudo, "The motor cortex controlling the preferred hand was bigger and more spatially complex. This suggested that the brain map was a function of the animal's experience, though at that point we had no way of telling whether it reflected recent experience or life experience." In a cart-before-the-horse move, it was only after Nudo had his results that he scoured the old literature to see whether anyone else had noticed such an asymmetry. That's when he discovered S. I. Franz's old paper, mentioned in the last chapter, which found an asymmetry in the movement maps incised in the right and left hemispheres of macaque monkeys. After another experiment, Nudo again discovered that someone else had beaten him to the punch. "It became a game," Nudo recalls. "Could I do anything original at all, or was I doomed to repeat what people had done 80 years ago?"

Nudo then launched an experiment that he would complete only after he had left UCSF: a study of the effects of motor skill learning on the motor cortex. It was the obvious next step, investigating whether everyday experiences, with no surgery to complicate the picture, would trigger reorganization of the motor cortex. To figure out how the monkeys' brains were zoned before training, Nudo needed to determine the so-called movement map of the hand in a monkey's motor cortex. He anesthetized the first of what would eventually be four squirrel monkeys. While monitoring the monkey's vital signs, Nudo spent some two hours preparing for the actual mapping: surgically photographing the brain's surface and setting up the electronics. He then inserted, one by one, tiny stimulating electrodes into the region of the brain that controls the voluntary movement of the forearm, wrist, and digits. The mapping itself, noting which spots in the motor cortex moved which fingers in which ways, took ten to fifteen hours. Often only one scientist—"Me," Nudo says—performed the mapping, once staying up forty-eight hours straight. (Because an animal's skull can't be repeatedly opened and closed, mapping sessions often take on this marathon nature.) "Apart from the exhaustion, the experiment was quite straightforward," he remembers. "We were surprised we could show anything with such a small number of monkeys, but we got clear results with only four."

Whenever a small pulse of current moved, for instance, a digit, Nudo noted the location of the cortical neurons causing the movement. In this way, he created a brain map of the neurons that controlled how a monkey moved its hands. Now he wanted to see whether that map could be rezoned. He placed, outside each monkey's cage, a series of four food wells, ranging in diameter from 25 to 9.5 millimeters. In the wells, he placed banana-flavored food pellets one at a time. Each subsequent well was smaller than its predecessor, and so progressively more

difficult to retrieve a food pellet from. To pick up the morsel, the monkey had to extend his arm fully, drop a finger or two into the shallow well, palpate the pellet at the bottom, remove it, grasp it, and get it to his mouth. For the three larger wells, the monkeys didn't have much of a problem getting the pellet. But the 9.5-millimeter well was a different story. At first, the creatures fumbled a lot and almost invariably couldn't quite grasp the pellet. But after a few hundred tries over the course of several days or (in the case of some slow learners) weeks, their performance became nearly flawless, and they were able to pick up their daily allotment of 600 or so tiny pellets fluidly, decisively, and confidently, as if they'd never known any other way to dine.

No wonder: the animals had a new brain to go with their new skill, as Nudo discovered when he went back in to their motor cortices and repeated the arduous brain mapping. What he found was that retrieving 600 pellets during two thirty-minute sessions every day for eleven to fifty days produced dramatic remodeling of the monkeys' motor cortices. The area that became active when a monkey moved his digits, wrist, and forearm had doubled, compared to the motor cortex representations in animals not trained to retrieve food pellets from annoyingly narrow food wells. The neurons controlling the busy fingers had undergone the neural equivalent of suburban sprawl, colonizing more space in the motor cortex, crowding out neurons that controlled some other part of the body (though with no obvious effect on other body parts). As a monkey mastered the smallest well, the area of activation expanded, and the representation in the motor cortex of some movements increased several-fold. In a related experiment, done to see whether the forearm representation could be selectively increased, one of the four monkeys was trained to turn a key-shaped bolt with a twisting movement of its arm. Sure enough, there was a marked expansion in the forearm area of the motor cortex. The motor cortex, concluded the researchers, "is alterable by use throughout the life of an animal." Much as during brain development in childhood, experience changes the connectivity of neurons in response to the circuits that are the most active. Learning a new skill strengthens billions of synaptic connections. "This dramatic brain remodeling almost certainly is the cortical part of the skill acquisition," Merzenich and colleagues concluded later that year. Sherrington and Lashley were undoubtedly smiling down from scientific heaven.

Even more remarkable was what happened after the researchers made small lesions in the monkeys' brains—this time, in the area of the somatosensory cortex that represented the tip of the finger used to palpate the pellet. At first the monkeys became real klutzes at retrieving the pellets from the cups, but after several days they got the hang of it again. You can guess the punchline: when the scientists mapped the somatosensory representation of the fingertip, they found that it had changed again, as alternative response zones emerged to do the job. Although the area of the brain that originally received sensory input from the fingertip had been knocked out of service, other regions took over that function because signals kept arriving from that fingertip. Similarly, when the researchers

destroyed the part of the motor cortex that controlled these deft finger movements, the monkeys were once again all thumbs. But after they practiced and practiced the move, the representation of that movement reemerged in areas of motor cortex that formerly represented movement of the hand or forelimb. "Functional recovery can be accounted for by the reemergence of the representation of functions critical for the behavior, in cortical zones that were concerned primarily with other…activities prior to the lesion," the scientists concluded.

Several years before Nudo focused on rezoning in the motor cortex, Merzenich had turned on other postdocs to the somatosensory cortex. The UCSF team trained lab animals in a behavior that, by driving sensory input, might change the representation of skin surfaces in the brain. To determine whether any change occurred, of course, the scientists first had to know how the monkeys' brains were wired at the start. Hands are so important to owl monkeys (as to humans) that a significant amount of the brain's real estate is devoted to them. To construct what they called a premap of the animals' cortex, Jenkins and Terry Allard labored for three days straight, in a tag-team approach, starting at 9 A.M. and working through the night. They took photographs of the monkey's exposed cortex, rushed off to the darkroom to develop them, and figured out what was what from vascular landmarks. One scientist sited the electrodes; one recorded activity in response to light brushes on the fingers. "We'd put three chairs together so one of us could sleep while the other worked," recalls Allard.

Then it was time to teach the old (or at least adult) owl monkeys new tricks. In what's fondly called the spinning disk experiment, Jenkins trained them to reach through the bars of their cage and keep a couple of digits in contact with wedge-shaped grooves in a four-inch disk that was spinning like an old LP. The monkeys had to modulate carefully the force they applied to the disk: too little, and their fingers would lose contact with the disk; too much and their fingers would ride along as if on a carousel. But if the animals did it just right, maintaining contact without getting taken for a ride, they were rewarded with a banana-flavored pellet. "I'd sit there for hours, hand-training a hungry monkey until he got it," says Jenkins. Then, some 500 times a day, the monkeys practiced the move; if successful, they got a pellet. "We made sure the monkeys were hungry, and put the disk near them," recalls Allard. "Once they had mastered the task and were performing it hundreds of times a day for several weeks, we went in to their brains. We found a fourfold increase in the area of the somatosensory cortex responding to signals from these fingers." This wasn't a response to something as traumatic as an amputation, a lesion, or a nerve transection, as the earlier work had been. The researchers didn't have to cut the animal to get a change in its brain: the rezoning was purely a response to purposeful behavior.

Greg Recanzone had arrived as a graduate student in Merzenich's lab in 1984. Allard taught him how to train monkeys as well as how to carry out cortical cartography—to determine which minuscule spots in an animal's somatosensory cortex process sensory input from which spots on the animal's body. The first time

Recanzone went into the lab, Allard and Jenkins were running the final monkey in the spinning disk experiment. “Mike had a really small lab,” recalls Recanzone. “To get from A to B, you had to walk past other people. There was always someone working at a computer, making cortical recordings from an animal. Getting one little piece of equipment took an hour as you stopped and chatted, or looked at what people were doing. Bill had just finished the rotating disk experiment. The obvious question to ask next was, how do cortical changes relate to performance?”

In a landmark follow-up to the spinning-disk experiments, the UCSF researchers embarked on what they called flutter-vibration studies. “This was the first time we used psychophysical behavioral techniques to see whether a frequency discrimination ability gets better with practice,” explains Jenkins. They taught seven adult owl monkeys to discriminate among vibrational frequencies applied by a mechanical device to a single spot on one finger. The flutter vibration felt like the flapping wing of a bird. The frequency, but not the location, of the stimulus varied. To train the monkeys, Jenkins and Recanzone arrived early every morning for 200-plus days to run through the same drill: set up the equipment, retrieve a monkey from the basement room where the colony lived, put the animal in a booth for a couple of hours so it could practice the task, eat lunch, then repeat with a second monkey. “We put them in the apparatus every morning and adjusted the stimulation based on their performance,” recalls Jenkins. “We ran the animals seven days a week. Because we used food for a reward, we couldn’t skip any days, or they’d get out of practice.” Six of the seven trained monkeys got better at recognizing when the frequency changed. At first they could detect a change only when frequencies differed from a 20-hertz (twenty flutters per second) standard by at least 6 to 8 hertz. But over the course of training the monkeys learned to discriminate differences as small as 2 or 3 hertz.

Then the researchers compared the sensory representations of the trained hand of the monkey to those of the untrained hand, each in the opposite hemisphere of the cerebral cortex. On a photograph or computer image of each monkey’s cortex, they would carefully draw the receptive fields for the various skin surfaces. Bending over a light table and using colored pens, they meticulously mapped the cortical representation of fingers and hands in the somatosensory cortex of both hemispheres. The differences between the two sides of the brain were dramatic. “The cortical representations of the trained hands were substantially more complex in topographic detail than the representations of unstimulated hands,” concluded the team. The size of the cortical maps of the skin patches that had felt the flutter were up to three times larger than the maps of the analogous, unstimulated skin surfaces.

But there was a wild card. The use-dependent neuroplasticity that Recanzone and Jenkins found occurred only when the monkeys were attentive to frequency changes, as they would see in their next experiment. This time, they applied the flutter vibration to monkeys’ fingers but used sound to distract the animals. To make the distraction effective, the scientists rewarded the monkeys with a food

pellet whenever they correctly responded to a tone. The monkeys attending to the tones thus served as "passive controls" for the monkeys attending to skin vibrations: they felt the same flutters but were paying attention to sounds rather than tactile stimuli. The distracted monkeys had no meaningful brain changes. As it turns out, it's not the good vibrations: it's the attention that counts. If the monkeys' attention was focused elsewhere while they received the same tactile stimulation that had otherwise produced massive cortical remapping, no such reorganization occurred.

In a curtain raiser for experiments that would make Merzenich's name, Recanzone then switched to the primary auditory cortex, investigating whether that, too, exhibited plasticity. He trained adult owl monkeys for several weeks to discriminate small differences in the frequency of tones. The monkeys all became progressively better at the job. At the end of training, Recanzone recorded which clusters of neurons fired in response to different tones. Compared to that in control monkeys who were distracted by paying attention to tactile stimulation while hearing the same tones, in the trained monkeys the cortical area representing the behaviorally relevant frequencies had enlarged several-fold, he reported in 1993. This increase in cortical area was the only change that correlated with improved performance.

The emerging picture was dramatic: the brain's representations of the body, of movements, and of sounds are all shaped by experience. Our brain is marked by the life we lead and retains the footprints of the experiences we have had and the behaviors we have engaged in. "These idiosyncratic features of cortical representation," Merzenich said in a model of understatement, "have been largely ignored by cortical electrophysiologists." As early as 1990 Merzenich was floating a trial balloon: maybe, just maybe, the behaviorally based cortical reorganization he was documenting supported functional recovery after brain injury such as that caused by a stroke, which until then (and to some extent, even now) was attributed to entirely different causes. And maybe focal dystonias like the one that thwarted Laura Silverman reflect use-driven changes in cortical representations, degrading fine-grained cortical maps like the colors of a Mondrian bleeding into each other after a rain.

Merzenich's wasn't the only lab probing the power of neuroplasticity. In 1993, Alvaro Pascual-Leone, then at the National Institute of Neurological Disorders and Stroke, reported one of the earliest studies in human neuroplasticity. Are there people, he asked, who habitually experience powerful stimuli to a given portion of their bodies? The answer came almost immediately: the blind, who read Braille with their fingertips. Pascual-Leone therefore studied the somatosensory cortex of fifteen proficient Braille readers. He gave weak electrical shocks to the tip of the right forefinger (the "reading" finger) and then recorded which somatosensory regions fired in response. He compared the brain response to that when the left index finger—a nonreading finger—was stimulated. The area of the brain devoted to the reading finger of expert Braille readers was much larger than that of the nonreading finger, or of either index finger in nonreaders, Pascual-Leone found. It

was a clear case of sensory input increase, with the person paying close attention, leading to an expansion of the brain region devoted to processing that input.

At about the same time Edward Taub, although deep in his studies of how constraint-induced therapy might enable stroke patients to regain use of a limb, was also pursuing another goal: to determine how increases in sensory input affect the brain's organization. In the spring of 1995 Taub and his German collaborators had reported that arm amputation produces extensive reorganization in the somatosensory cortex. Soon after, Thomas Elbert of the University of Konstanz, who was about to embark on a major collaboration with Taub, joined Taub and his wife for dinner. Is there any normal human activity in which there is much more use of one hand than of the other hand? Taub asked. Elbert thought a bit and said, "Well, yes, pianists." But that wasn't right; pianists use both hands. But Taub's wife, Mildred Allen, a lyric soprano who had been a principal artist at the Metropolitan Opera in New York and a leading singer at the Santa Fe Opera, chimed in, "Oh, that's easy; use the left hand of string players." When a right-handed musician plays the violin, four digits of the left hand continuously finger the strings. (The left thumb grasps the neck of the violin, undergoing only small shifts of position and pressure.) The right, or bowing, hand, undertakes far fewer individual finger movements. Might this pattern leave a trace on the cerebral cortex?

The scientists recruited six violinists, two cellists, and one guitarist, all of whom had played the instrument for seven to seventeen years, as well as six nonmusicians who had no experience with stringed instruments. For the study, the volunteers sat quietly while a pneumatic stimulator applied light pressure to their fingers. A magnetoencephalograph positioned over their skulls recorded neuronal activity in the somatosensory cortex.

There was no difference between the string players and the nonmusicians in the representation of the digits of the right hand, the researchers reported in 1995. But there was a substantial cortical reorganization in the somatosensory map of the fingers of the left hand. The researchers concluded, "[T]he cortical territory occupied by the representation of the digits [of the left hand] increased in string players as compared with that in controls." The brain recordings showed that the increase in cortical representation of the fingering digits was greater in those who began to play before the age of twelve than in people who took up an instrument at a later age. When the results were published, the attendant publicity trumpeted that as the revelation—missing the point entirely, to Taub's frustration. The much greater discovery was the unmistakable evidence of cortical reorganization in all the string players. The surprise was not that the immature nervous system is plastic, as "everyone knew," says Taub, but that plasticity persists into adulthood. "Even if you take up the violin at 40, you still get use-dependent cortical reorganization," says Taub.

That same year Merzenich's lab reported, using their old reliable adult owl monkeys, that applying tactile stimuli to the fingers changes the maps of the hand

surface in the somatosensory cortex—a lab version of the real-world changes Taub and his team found in the string players. Despite dramatic results like these, even into the 1990s Merzenich still had not won over a lot of neuroscientists. When Xiaoqin Wang, then a graduate student at Johns Hopkins University, was weighing a postdoctoral fellowship in Merzenich's lab, he kept the idea from his thesis advisor. "His colleagues were very skeptical of the work Mike started," Wang recalls. He joined Merzenich's lab anyway and immediately set to work testing whether another nonsurgical, purely behavioral intervention would alter an animal's brain. Sure, Merzenich and Kaas had shown that lesions bring about a reorganization of the cortex. But "Mike's most important contribution was to argue that reorganization in the cortex is not solely a product of lesions," says Wang. "Brilliantly, he saw that the cortex adapts to its environment, and responds to a changing environment—including the behavioral environment."

Wang trained monkeys in a task that would finally shed light on what had gone wrong in the brains of people like Laura Silverman and other victims of focal hand dystonia. The monkeys placed one hand on a form-fitting handgrip containing two little metal bars. One bar, perpendicular to the fingertips, stimulated the tips of the second, third, and fourth fingers simultaneously. A second bar stimulated the same three fingers just above the knuckles. To make sure the monkeys were paying attention to the alternating stimuli (as we have seen, attention is a prerequisite for use-dependent brain changes), the scientists rewarded the animals for responding whenever two consecutive stimuli were applied by either bar. The monkeys underwent the behavioral training for some 500 trials day in and day out, for six and sometimes seven days a week. "I was supposed to go to my Hopkins graduation that May [of 1991], but I skipped it because I was training the monkeys," Wang recalls. "I didn't have the heart to leave in the middle."

After four to six weeks of training the monkeys, Wang mapped their brains. To produce a map with the necessary high resolution, he recorded with microelectrodes from 300 locations, each just a few micrometers apart in the somatosensory cortex. The goal was to see which clutches of neurons fired in response to a light touch on a finger. Since both monkey and human fingers usually feel stimuli nonsimultaneously (we tend not to move our fingers as one, unless we are waving bye-bye to a toddler), the intense synchronous input across the monkeys' digits was expected to produce changes in the brain. And it did. "Individual fingers were no longer differentiated," says Wang. The normal segregation of fingers in primary somatosensory cortex "was completely broken down." In control animals whose fingers had been stimulated asynchronously, the brain represented each finger discretely. But when digits were stimulated synchronously, their representation in the brain fused, much as had happened to Laura Silverman: a single region of somatosensory cortex responded to the touch of two or even three fingers. Simultaneous stimulation, whether by bars in a lab or by too many andante movements, fools the brain's primary somatosensory cortex into thinking that different fingertips are part of a single unit. This discovery strongly

reinforced Merzenich's findings nearly a decade earlier that fusing fingers to create syndactyly breaks down the discrete representations of fingers, and that separating long-fused digits reseparates the fused representation in the somatosensory cortex. It all flows from the basic Hebbian principle: Cells that fire together wire together. In this way our brain, it seems, contains the spatial-memory traces of the timing of the signals it receives and uses temporal coincidence to create and maintain its representations of the body.

The motor cortex, you'll recall, is arranged like a little homunculus. But it is hardly a static layout. From day to day and even moment to moment, the motor cortex map changes, reflecting the kinds of movements it controls. Complex movements result in outputs from the motor cortex that strengthen some synapses and weaken others, producing enduring changes in synaptic strength that result in those things we call motor skills. Learning to ride a bicycle is possible, in all likelihood, not merely because of something called muscle memory but also because of motor-cortex memory.

In 1995, Alvaro Pascual-Leone, following up on his Braille study, conducted an experiment that, to me, has not received nearly the attention it deserves. This one modest study serves as the bridge between the experiments on humans and monkeys showing that changes in sensory input change the brain, on the one hand, and my discovery that OCD patients can, by changing the way they think about their thoughts, also change their brain. What Pascual-Leone did was have one group of volunteers practice a five-finger piano exercise, and a comparable group merely think about practicing it. They focused on each finger movement in turn, essentially playing the simple piece in their heads, one note at a time. Actual physical practice produced changes in each volunteer's motor cortex, as expected. But so did mere mental rehearsal, and to the same degree as that brought about by physical practice. Motor circuits become active during pure mental imagery. Like actual, physical movements, imagined movements trigger synaptic change at the cortical level. Merely *thinking about* moving produced brain changes comparable to those triggered by actually moving.

These were the opening shots in what would be a revolution in our understanding of the origins of human disabilities as diverse as focal hand dystonia, dyslexia, and cerebral palsy. Merzenich firmly believed that the focus of the previous two decades—attributing neurological illness (especially developmental abnormalities) primarily to molecular, genetic, or physical defects—had missed the boat. Instead, he suspected, it is the brain's essential capacity for change—neuroplasticity—that leaves the brain vulnerable to such disabilities. But if that is true, Merzenich persisted, surely the reverse would hold as well: if neuroplasticity opens the door to disabilities, then maybe it can be harnessed to reverse them, too—just as it reversed the "errors" caused by the ministroke in the food-pellet-retrieving monkeys. Just as a few thousand practice trials at retrieving pellets resulted in a new brain that supported a new skill in the monkeys, so, too, might several thousand "trials" consisting of hearing spoken language imperfectly, or playing the

same piano notes over and over, result in a new brain—and possibly a new impairment—in people. The brain changes causing these impairments could become so severe that Merzenich coined a term to capture their magnitude: *learning-based representational catastrophe*, as he characterized it to a scientific meeting in the late fall of 2000.

If an increased cortical representation of the fingering hand of string players, and a strengthening of motor circuits in the brains of people (and lab animals) learning a motor skill, is the positive side of use-dependent cortical reorganization, then focal hand dystonia is the dark side. In fact, Laura's doctors were not far off when they said that her condition was all in her head. "The musician loses control over one or more of the digits of one hand, and that usually terminates his or her professional career," says Taub. A pianist, or a typist, loses the ability to make rapidly successive movements with two (usually adjacent) fingers: when the index finger rises, for instance, the middle finger follows uncontrollably. "There is a fusion of the representation of the fingers in the dystonic hand," says Taub. "We think it has something to do with simultaneous excitation of the fingers, typically from playing rapid passages forcefully."

In 1990 Merzenich's group was already suggesting, on the basis of their monkey findings, that focal hand dystonia reflects brain plasticity. In the early 1990s Merzenich hooked up with Nancy Byl, director of the graduate program in physical therapy at UCSF, for a study in which they simulated writer's cramp in two adult owl monkeys by training them to grasp a handgrip that repeatedly opened and closed, moving their fingers about a quarter-inch each time, up to 3,000 times during a one- or two-hour daily training session. To keep the monkeys focused on the task, Byl rewarded them with food pellets for holding onto the hand grip. After three months of this for one monkey and six months for the other, the animals could no longer move their fingers individually. In the brain, the receptive field of fingers' sensory neurons had grown ten- or twentyfold, often extending over multiple fingers. "Rapid, repetitive, highly stereotypic movements applied in a learning context can actively degrade cortical representations of sensory information guiding fine motor hand movements," Byl told the 1999 meeting of the Society for Neuroscience. "Near-simultaneous, coincident, repetitive inputs to the skin, muscles, joints and tendons of the hand may cause the primary sensory cortex in the brain to lose its ability to differentiate between stimuli received from various parts of the hand." A patient with focal hand dystonia may feel a touch of her fingertip as a touch of another finger. She may have trouble identifying objects by feel. Fishing keys out from the bottom of a bag becomes hopeless.

If focal hand dystonia arises from highly attended, repetitive, simultaneous sensory input to several fingers, then the logical treatment is obvious. Correcting the problem, Merzenich believed, "requires a re-differentiation…of these cortical representations," through highly attended, repetitive, nonsimultaneous movements. In early 1999 Byl and colleagues therefore launched small-scale studies based on this premise, with the goal that patients with focal hand dystonia would remap their

own somatosensory cortex. They had the patients carry out tasks that demand acute sensory discrimination, such as reading Braille or playing dominoes blindfolded, all the while focusing their attention like a laser beam on the task. Byl encouraged them to use mental imagery and mentally to practice using the disabled hand and fingers; just as Pascual-Leone found that mentally practicing a piano exercise produces brain changes comparable to those produced by actually hitting the ivories, so patients with focal hand dystonia, she suspected, might break apart the merged representation of their fingers by imagining moving each finger individually. It would be wrong to minimize the challenge of this therapy, however. Merzenich's findings suggest that lab animals need something like 10,000 to 100,000 repetitions to degrade the initial representation of a body part; Byl therefore suspects that people require a comparable number of repetitions of a therapeutic exercise to restore normal representation. Her early findings look encouraging. In 2000, she reported an 85 to 98 percent improvement in fine motor skills in three musicians with focal hand dystonia after they took part in her "sensorimotor retraining program." Two of three returned to performing. The implication? In at least some patients with focal hand dystonia, the degraded cortical representation can be repaired.

In 1998, after confirming that in focal hand dystonia the somatosensory representations of the affected digits are fused, Taub and Elbert's team in Germany also developed a therapy based on the finding. To come up with an appropriate therapy, a grad student, Victor Candia, applied Taub's constraint-induced approach to restrain the movement of one or more less-dystonic fingers. The researchers recruited professional musicians with focal hand dystonia: five pianists (all soloists except one chamber music player) and two guitarists. Despite their disability, five of the musicians were still concertizing, masking their dystonia in some cases through atypical fingerings that avoided the dystonic finger. Taub and his colleagues thought they could do better. The scientists therefore restrained one or more of the healthy, less-dystonic fingers. The subject then used his dystonic finger to perform instrumental exercises, under a therapist's supervision, for one and a half to two and a half hours each day for eight straight days, followed by home exercises of one hour or more a day. The exercises consisted of sequential movements of two or three digits, including the dystonic one, followed by a brief rest and then another sequence. If the subject's ring finger was dystonic, for instance, and the pinky had been compensating for its neighbor's impairment, then the researchers restrained the pinky and had the patient run through the exercise index-middle-ring-middle-index. In simple terms, this separate stimulation teaches the brain that the ring finger is a separate entity, distinct from its digital neighbors. All five pianists were successfully treated, though one who did not keep up his exercises regressed. Two resumed concertizing without resorting to the fingering tricks they had used before. Four of the original seven played as well as they had before the dystonia struck. "Our suspicion was that we were breaking apart the fusion of the brain's representation of three and sometimes four fingers," says Taub.

The plasticity of the motor cortex might even underlie something so common, unremarkable, and seemingly inevitable as the tentative gait that many elderly people adopt. With age, walking becomes more fraught with the risk of a spill, so many people begin to walk in an ever-more constrained way. Old people become erect and stiff, or stooped, using shorter steps and a slower pace. As a result, they get less "practice" at confident striding—bad idea. Because they no longer walk normally and instead "overpractice" a rigid and shuffling gait, the motor-cortex representation of fluid movement degrades, just as in monkeys that stop practicing retrieving little pellets from wells. The result: we burn a trace of the old-folks' walk into our brain, eventually losing the ability to walk as we once did. It is the sadder facet of the neural traces burned into our brain at the beginning of life. There is, though, a bright side: there is every reason to believe that practicing normal movements with careful guided exercise may help prevent, or even reverse, the maladaptive changes.

Tinnitus, or ringing in the ears, is characterized by the perception of auditory signals in the absence of any internal or external source of sound. It strikes an estimated 35 percent of the population at some point in life. In about 1 percent, the condition is severe enough, and maddening enough, to interfere with daily life. The source of the problem had remained a mystery for centuries: half of the investigators interested in tinnitus thought the central nervous system was involved, and half didn't. Taub and Thomas Elbert were squarely in the first camp, suspecting that tinnitus reflects cortical reorganization that is the a result of sensory input increase. Taub and Elbert again teamed up, this time with Werner Mühlnickel, a grad student. They compared ten subjects with tinnitus (in the range of 2,000 to 8,000 hertz) to fifteen without it. To the healthy subjects, they played four sets of pure tones, of 1,000, 2,000, 4,000, and 8,000 hertz. The tinnitus subjects heard the tone that matched their tinnitus frequency (determined by having subjects move a cursor on a computer screen that varied the tone of the sound output, until they reached the one that they always heard), and then the three standard tones (usually 1,000, 2,000, and 8,000 hertz). Usually, sound frequencies are represented in the auditory cortex according to a logarithmic scale: the lowest frequencies are near the surface of the brain, and higher frequencies are toward the interior. But in tinnitus sufferers, the scientists reported in 1998, the tinnitus tone had invaded neighboring regions. "The tonotopic map was normal except at this frequency, where there was a huge distortion, with more area given over to the tinnitus tone," says Taub. "Not only do you get cortical reorganization, but the strength of tinnitus is related to the amount of cortical reorganization." Increased sensory input to the auditory cortex at a particular frequency had apparently produced use-dependent cortical reorganization. And that suggests a therapy for what had been an untreatable syndrome: if patients attend to and discriminate acoustic stimuli that are near the frequency of the tinnitus tone, that might drive cortical reorganization of the nontinnitus frequencies into the cortical representation of the tinnitus tone. That should reduce the tinnitus representation, diminishing the sense that this tone is always sounding.

It is worth pausing here to address what neuroplasticity is not: just a fancy name for learning and the formation of memories. This not-infrequent criticism of the excitement surrounding the neuroplasticity of the adult brain is reminiscent of the old joke about how new ideas are first dismissed as wrong, and then, when finally accepted, as unimportant. In the case of neuroplasticity, the criticism goes something like this: the idea that the adult brain can rewire itself in some way, and that this rewiring changes how we process information, is no more than a truism. If by neuroplasticity you mean the ability of the brain to form new synapses, then this point is valid: the discovery of the molecular basis of memory shows that the brain undergoes continuous physical change. But the neuroplasticity I'm talking about extends beyond the formation of a synapse here, the withering away of a synapse there. It refers to the wholesale remapping of neural real estate. It refers to regions of the brain's motor cortex that used to control the movement of the elbow and shoulder, after training, being rewired to control the movement of the right hand. It refers to what happens when a region of the somatosensory cortex that used to register when the left arm was touched, for example, is invaded by the part of the somatosensory cortex that registers when the chin is gently brushed. It refers to visual cortex that has been reprogrammed to receive and process tactile inputs. It is the neural version of suburban sprawl: real estate that used to serve one purpose being developed for another. Use-induced cortical reorganization, says Taub, "involves alterations different from mere learning and memory. Rather than producing just increased synaptic strength at certain junctions, which is believed to underlie learning, some unknown mechanism is instead producing wholesale topographic reorganization." And more: we are seeing evidence of the brain's ability to remake itself throughout adult life, not only in response to outside stimuli but even in response to directed mental effort. We are seeing, in short, the brain's potential to correct its own flaws and enhance its own capacities.

The existence, and importance, of brain plasticity are no longer in doubt. "Some of the most remarkable observations made in recent neuroscience history have been on the capacity of…the cerebral cortex to reorganize [itself] in the face of reduced or enhanced afferent input," declared Edward Jones of the University of California, Davis, Center for Neuroscience, in 2000. What had been learned from the many experiments in which afferent input to the brain increased? Cortical representations are not immutable; they are, to the contrary, dynamic, continuously modified by the lives we lead. Our brains allocate space to body parts that are used in activities that we perform most often—the thumb of a videogame addict, the index finger of a Braille reader. But although experience molds the brain, it molds only an attending brain. "Passive, unattended, or little-attended exercises are of limited value for driving" neuroplasticity, Merzenich and Jenkins concluded. "Plastic changes in brain representations are generated only when behaviors are specifically attended." And therein lies the key. Physical changes in the brain depend for their creation on a mental state in the mind—the state called attention. Paying attention matters. It matters not only for the size of the brain's representation of this or that

part of the body’s surface, of this or that muscle. It matters for the dynamic structure of the very circuits of the brain and for the brain’s ability to remake itself.

This would be the next frontier for neuroplasticity, harnessing the transforming power of mind to reshape the brain.