



THE MUTABLE BRAIN

SCORE ONE FOR BELIEVERS IN THE ADAGE “USE IT OR LOSE IT.” TARGETED MENTAL AND PHYSICAL EXERCISES SEEM TO IMPROVE THE BRAIN IN UNEXPECTED WAYS
BY MARGUERITE HOLLOWAY

“THE BRAIN WAS CONSTRUCTED TO CHANGE,” ASSERTS Michael M. Merzenich as he sits in a small conference room at the University of California at San Francisco Medical Center. The large windows to his left look out onto a hill thick with eucalyptus trees, their branches moving now this way, now that, in the morning’s wind. Merzenich’s observation—no longer so radical as it was when he and a handful of others put it forth in the 1980s—is that the brain does the same: it moves this way, then that, depending on how experience pushes it. This may seem an obvious idea: of course our brains revise themselves—we learn, after all. But Merzenich is talking about something bigger: this ability of the brain to reconfigure itself has more dramatic implications.

It is as if the brain is a vast floodplain. One year the water might run eastward in a series of small channels; the next it might cut a river deep through the center. A year later, and a map of the floodplain looks completely different: streams are meandering to the west. It is the same with a brain, the argument goes. Change the input—be it a behavior, a mental exercise, such as calculating a tip or playing a new board game, or a physical skill—

and the brain changes accordingly. Magnetic resonance imaging machines reveal the new map: different regions light up. And Merzenich and others who work in this field of neuroplasticity are not just talking about young brains, about the still developing infant or child brain, able to learn a first language and then a second in a single bound. These researchers are describing old brains, adult brains, your brain.

They are saying that the brain can be extensively remodeled throughout the course of one’s life, without drugs, without surgery. Regions of the brain can be taught to do different tasks if need be. If one area has dysfunction or damage, another can step in like an understudy and play the role. Such task shifting has been reported in stroke patients who have lost speech or motor ability, cerebral palsy patients, musicians or workers who can no longer move one finger at a time, and those with obsessive-compulsive disorder or reading disorders. **A series of intense mental and physical exercises have undone the effects of injury.**

The next step, Merzenich and colleagues say, is to expand and refine these treatments and to investigate exercise-based tasks that can ameliorate

THE HOMUNCULUS VIEW

CORTEX IS ORGANIZED into various regions, including the sensory cortex and the motor cortex. The classical homunculus diagram for each of these cortices shows the relative space—or map—that the brain uses for processing and responding to information from various parts of the body. New findings indicate that experience can revise such maps.



schizophrenia, Parkinson's disease, the memory loss of aging, autism and a host of other problems. "One of my dreams is to find all the ways that you can use the plasticity processes of the brain to drive correction," Merzenich muses. "My belief is that this sort of thing will be part of a normal future life. It will be understood that you have to exercise your brain and that there are specific things that you have to do."

To many people—those who meditate or practice biofeedback or undergo psychotherapy—this idea may seem intuitive: focus your effort in certain ways, and your brain, as glimpsed through your behavior, will alter. Within the neuroscience and medical communities, however, this idea and its potential clinical uses are new. "If you go back to the late 1970s and the 1980s, people thought of the brain as a hardwired black box," notes Thomas P. Sutula, director of the center for neuroscience at the University of Wisconsin–Madison. "This whole area is as close to a revolution in concept as you can imagine."

Yet it is a nascent revolution and one that is hard to get a handle on, perhaps in part because one of its leading figures is so difficult to pin down. Mention

Merzenich's name to a neuroscientist, and he or she will most likely celebrate his brilliance and the importance of talking with him in one breath and in the next add "if you can find him." People talk of being mesmerized by his vision during a presentation, only to wonder a few days later what the data were: "Where's the beef?" asks one scientist. "He is a phantom," jokes another. Some scientists are chary of Merzenich because he started a for-profit company to develop plasticity-based therapies and feel that he has rushed to market without adequate testing.

Beyond the controversy surrounding Merzenich lie the fundamental questions of this new field. Although researchers have laid the foundation for appreciating skill-based or experience-driven neuroplasticity, there are many unknowns. The limits of it, for one. No one knows just how plastic the adult brain is as opposed to the child's—except that it is less so. No one fully understands how plasticity operates at all its various levels, from electrical pulses and neurotransmitters on up to the synapses, networks and specialized regions of the brain. And no one knows how much one part of the brain may lose when it shouldered another's burden—what the "dark side," as some researchers put it, might entail.

OVERVIEW/Remolding the Brain

- Contrary to long-held belief, the structure of the adult brain is not set in stone. More readily than was once thought, one region can step in and take over the function of another.
- Researchers are harnessing this neuroplasticity to treat people with reading disorders, stroke and forms of repetitive stress injury, among other conditions.
- Some scientists hope to use physical exercises and computer-based games to help individuals retrain their brains to overcome memory problems and various mental disorders.

Of Synapses and Sections

"'PLASTICITY' IS THE MOST abused word in neuroscience," declares Roger Nicoll, whose U.C.S.F. laboratory is just across town from Merzenich's. The term has come to describe virtually any change in the brain, from the chemical level to the formation of new neurons (a process called neurogenesis) to the remapping of larger regions. At its most basic, however, it is what Nicoll studies: the plasticity of the synapse, which is the place where neurons

communicate with one another by way of chemical signals, or neurotransmitters. Learning entails strengthening connections between neurons—by creating more connections between neurons as well as by enhancing their ability to communicate chemically. These changes link neurons in a chain that can be retraced to evoke a certain movement or feeling or thought, a phenomenon captured in the oft-quoted phrase “Neurons that fire together, wire together.” It is at the level of the synapse that neuroplasticity lives or dies.

Until the mid-1960s it was thought that adults could not form new synapses, that the connections between neurons were frozen into position once brain development stopped. Then studies began to suggest that this was not so. For instance, researchers Geoffrey Raisman and Pauline M. Field, then at Oxford University, demonstrated that there was synaptic plasticity in adults. Others, including Mark R. Rosenzweig of the University of California at Berkeley and William T. Greenough of the University of Illinois and their colleagues, made dramatic discoveries about how environment and experience affect the brain. Greenough, for example, demonstrated that both young and mature rats could establish new synapses if they were given challenging tasks or placed in “complex environments”—which, he points out, are simply very nice cages with nice toys, “certainly not as challenging intellectually as the environment in which they are normally found.” These synapses gave rise to enhanced memory and motor coordination.

These studies of exercise and what has come to be called enrichment (providing stimulation through toys or tasks) continue to flower and are being mined for their clinical applications. Stimulation and exercise speed recovery from brain injury in rats, and recent research has suggested that if mice carrying a Huntington’s gene are placed in a complex setting, the development of the disease is delayed. Greenough and other investigators have connected these effects not only to the creation of synapses but to the creation of blood vessels and of brain cells called astrocytes—which are important in mopping up excess materials, such as potassium, and in maintaining an optimal environment for neurons. The formation of myelin, a lipid sheath that covers nerve axons and is crucial for their survival and effectiveness, is also enhanced in these situations.

Appreciation for plasticity at a larger scale—at the level of an entire network of neurons or a region of the brain—came well after the recognition of synaptic plasticity. It was, however, an old suggestion. In the late 1800s and early 1900s several sci-

entists had proposed that the brain was plastic, shaped by experience. William James, for example, had posited that the brain is constantly changed by experience, and in the 1920s Karl Lashley found that the motor cortex of monkeys seemed to change every week. Similar work continued through the 1970s, but the findings of scientists who felt the adult brain was fixed and unchanging predominated: the brain changed massively only during infant development and early childhood, so-called critical stages. “The religion developed from the mainstream,” Merzenich notes, “and the mainstream thought that the brain was like a computer that established its critical functionality in critical periods.”

People THOUGHT of THE BRAIN as a hardwired BLACK BOX.

In the 1980s a series of experiments by Merzenich and his collaborators, including Jon Kaas of Vanderbilt University, revealed that an adult monkey’s motor cortex could undergo change. The cortex—the outer part of the brain where, in humans, regions for language and reasoning reside—is organized into areas for sensory, motor, auditory and other information. In one study the researchers am-

REMAPPING OF THE HAND

Immediately after nerve cut 22 days after cutting



IN A NOW CLASSIC monkey experiment, Michael M. Merzenich demonstrated the plasticity of the brain’s cortical maps. After he cut a nerve conveying information from a part of a finger or hand [shaded areas on left] to a specific patch of cortex, he found that the same cortical patch began responding to regions of the hand that it did not serve before [shaded areas on right]. What is more, the areas represented in that cortex expanded as time went by.

Constraint-induced movement therapy works on the principle that a person can be taught to use another part of his or her brain to take over the function of a damaged or dysfunctional area. By restraining his unimpaired arm, this patient forces his brain to relearn how to use the arm affected by stroke.

puted a monkey's finger and saw that the place in the motor cortex that had been activated by that finger was soon showing responses from neurons conveying information from an adjacent finger, indicating that the brain area originally devoted to the lost finger was now monitoring and processing information from the next one. Squatters had immediately laid claim to the abandoned site. "That was an awakening to me," Merzenich reflects.

It was a revelation to the neuroscientific community at large as well. "He was one of the first to do work showing that these [neural] maps moved, and I was stunned," recalls Bryan Kolb, a leading neuroplasticity researcher at the University of Lethbridge in Canada. "People thought there was a genetic blueprint of the brain and how things were organized. No one suspected that changes could have been detected at that gross a level."

The squatters had come from right next door, though, mere millimeters away. Then, in 1991, invaders were found to travel whole centimeters. The foundations for this discovery had been laid many years earlier when Edward Taub, now at the University of Alabama at Birmingham, severed some of the nerves of one arm in a few monkeys to see what happened to their brains as a result. Taub was forced to abandon his research on the Silver Spring monkeys, as they came to be known, because of a lawsuit by animal-rights activists. For a while, his investigations came to a halt.

Years later those same monkeys were examined

by Tim P. Pons of the Wake Forest University School of Medicine, Taub and other scientists, who found something remarkable. The area of the brain that had originally received information from the now useless arm was receiving information from the face. The changes extended across great distances. "There was huge reorganization in the cortex that no one thought possible," explains Ford Ebner of Vanderbilt University. "It was another milestone." The adult brain was clearly a dynamic and efficient landlord: no empty space went unused.

Musical Maps

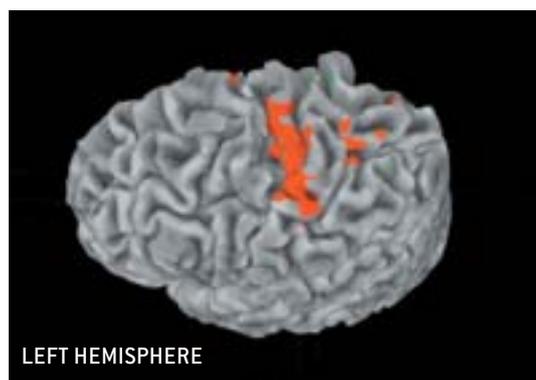
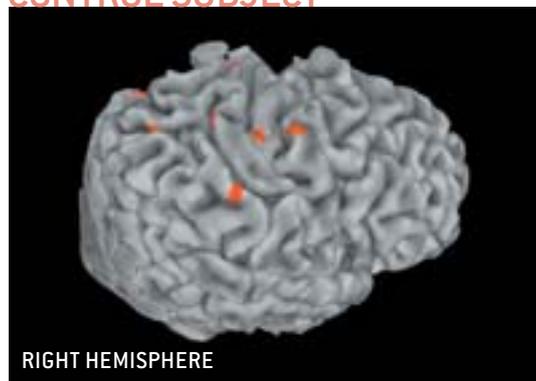
OVER THE PAST TWO DECADES, the research in monkeys has converged with evidence in humans, and cortical plasticity has become an accepted characteristic of the adult brain. In people who have lost a limb, studies show that the space that formerly deciphered information from that limb can serve the stump or the face. In string musicians, the area of the cortex governing the fingering hand is larger than that of the nonfingering hand, and the most-used fingers take the largest space. In Braille readers, the visual cortex becomes active as they touch their fingers to the bumps.

As all these data converged, Merzenich, Taub and others tried to figure out how to use them to benefit those with various injuries or disabilities. "We knew that the brains of children and adults are plastic throughout life," Merzenich says. "And that led us to a simple question: Can we drive changes in the brain at an older age that would be corrective?"

The strongest evidence so far that the brain can be healed by its own plasticity comes from work with stroke patients that Taub and his colleagues began in the 1980s. During earlier experiments, Taub had discovered that monkeys whose arm nerves had been severed could still move their arm if they were forced into doing so by an electric shock. It turns out that people who have lost motor function because of stroke can also learn to use their limb again. By restraining the good arm and having patients perform intensive motor tasks and training with the weak arm for many hours a day for two weeks, Taub and his co-workers—including Wolfgang Mitterer of the University of Jena and Thomas Elbert of the University of Konstanz, both in Germany—forced patients to get their seemingly dead limb to move again. Such treatment is called constraint-induced (CI) movement therapy. "The traditional wisdom in the field was that after one year, there was no recovery of function," Taub explains. Yet some patients—even those whose strokes occurred 20 or more years earlier—have been able to use their arms effectively again.



CONTROL SUBJECT



Active brain regions (red and yellow) can be seen in these fMRI images of a control subject's two hemispheres (left) and those of a stroke patient (right). When the control subject opens and closes his right hand, the left motor cortex lights up. After rehabilitation, a stroke patient with severe left hemisphere damage uses many areas of the cortex in both the right and left hemispheres to do the same, suggesting that the brain has reorganized to allow for this movement.

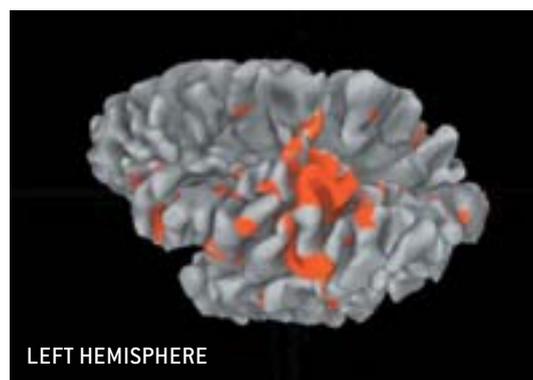
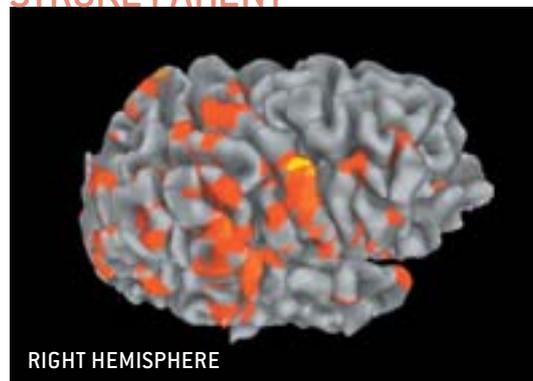
The recovery is reflected in the shifting maps of the subjects' brains. "The CI therapy had recruited large new areas of the cortex adjacent to the damaged area," Taub points out. Other groups have seen this as well, and CI therapy is now practiced in various institutions. A recent study by Daniel B. Hier of the University of Illinois at Chicago determined that cortical patterns in stroke patients also shift after another form of rehabilitation.

Although the practice is widespread in various forms, many experts are awaiting further study before they embrace it. To this end, the National Institutes of Health has funded a six-site clinical trial of CI therapy. It will be important to get replication, notes Jordan Grafman of the National Institute of Neurological Disorders and Stroke. Investigators need to know, he says, "whether CI therapy works for some kinds of patients and not others and when after injury it should be done. You need a lot of studies."

Taub, Elbert and their colleagues have begun to use CI therapy to treat children with cerebral palsy. They have also successfully rehabilitated stroke victims who have lost their ability to speak well. These aphasic patients have repeated certain sounds for hours a day. The "constraint" in this method does not entail any "restraint," as the motor therapy does. It is essentially just intensive practice of words and sounds.

Taub and others, including Merzenich and Nan-

STROKE PATIENT



cy Byl of U.C.S.F., have used similar therapy to help musicians and workers recover the use of individual fingers. Sometimes when people use a series of fingers over and over again in quick succession, the distinctions between regions in the cortex begin to blur. One finger's zone melds into another's. The result is focal-hand dystonia: try to raise one finger, and another or several inevitably come along, too. By using repetitive tasks that are very distinct for each finger, the researchers say they have been able to restore the original boundaries of the map.

Merzenich has also turned his attention to language disorders and dyslexia in children—as well as some adults—and it is this research that has earned him a degree of enmity and skepticism. In the mid-1990s he joined forces with Paula Tallal of Rutgers University to form Scientific Learning, a company that produces and sells a computer-based program called Fast ForWord. The idea the two had, based on insights from their independent research, was that by slowing down certain sounds—such as "ba" and "da"—children who were having trouble processing language could quickly begin to hear the distinct sounds, the "b" separated from the "ah." Over hundreds of repetitions—training during games that can last for 20 hours a week for months—these sounds could gradually be sped up and, in time, the child would learn to hear and process the sounds at normal speed. According to a recent paper in *Proceedings of the National Acade-*

my of Sciences by Merzenich, Tallal and a group of researchers, dyslexic children participating in Fast ForWord not only improved their reading skills, but their brains changed—different regions were processing language.

Although some researchers believe that this technique might well prove itself, they await independent reviews and replication before they are convinced. Guinevere F. Eden of Georgetown University Medical Center notes that there have been no controlled studies of reading improvements: the kids with reading problems who received the intervention have not been compared with another set of dyslexics who did not. “You would expect kids to be better on the second round of a task because they are always better on the second test—even if nontrained,” Eden observes, adding that computer-based games often increase players’ attention, so improvement might have more to do with attentiveness as opposed to language processing. And she worries that parents will develop hopes that won’t be realized or will spend too much money purchasing the software: “It is a very vulnerable group, and it is a pity that the system isn’t in place to protect them more.”

Merzenich dismisses these criticisms, scoffing at the idea that the studies he is a party to—such as the recent one in *PNAS*—could be biased. And he says he has no regrets about forming Scientific Learning, except that the programs have not yet reached as many kids as he would have hoped. For some in the field, this business interest has tarnished Merzenich’s accomplishments; his research will always be colored by commercial interest. But others applaud it. “It is great to go sit in your lab, but better for people to act,” Sutula says. “You can make people’s lives better.”

And the company offered a practical solution for one of the principal problems of the field of applied neuroplasticity: the gulf between the neuroscience and the rehabilitation communities. “There is a lot of interesting knowledge about how to improve function in people,” Grafman notes. “But translating that into rehabilitation has been painful and slow.”

“It is very important that the research get carried out, and it is almost impossible to get funding to do this,” Taub agrees. To the rehabilitation community, several of these ideas “seem out of left

Reading program designed by Michael M. Merzenich and Paula Tallal seeks to rewire the brains of children with dyslexia or other problems. The controversial computer-based strategy, called Fast ForWord, has not been independently assessed so far, but the researchers say they have found significant improvement in children’s reading comprehension.



ELIZABETH DERAMUS

field,” he says. “Although from the point of view of neuroscience, it is absolutely straightforward.”

Limits of Plasticity

MERZENICH'S CURRENT preoccupation may seem even further afield. He is investigating whether training and games can reverse or ameliorate schizophrenia, autism and the memory loss that can accompany aging. As yet, there are no published data to turn to. And Merzenich is not forthcoming about his collaborators either. Although he granted a long interview and opened up his lab, Merzenich never responded to my requests for further information—despite his promises to provide names and despite myriad follow-up phone calls and e-mail messages.

But if his idea bears fruit, it will be stunning. Merzenich believes that the neurotransmitters that underlie memory can be bolstered during tasks performed while sitting at a computer. “Just as in kids that are having problems with learning and memory and whatever,” he argues, “the machinery is plastic. And you can almost certainly drive positive changes in the brains of elderly individuals by engaging that machine.” He says he can discuss results soon and that the same principle will apply—and is already working—for autistic patients and people with Parkinson's disease. “We are overwhelmingly dominated by thinking that we are going to fix everything in the brain by drug manipulation or by some change in the status of the physical structure of the brain, because it is deteriorating,” he asserts. “But a computer-directed exercise can be very efficient. Because it can pound your brain in a highly controlled way.” For example, patients could play a computer game in which they won money or overcame obstacles; the positive reward could trigger the release of, say, dopamine—a neurotransmitter associated with the experience of pleasure and one that is also progressively lost in certain illnesses, such as Parkinson's.

Researchers are waiting to see the beef. And to understand what the limits of plasticity are. “My fundamental concern about Mike's view is that he doesn't take the role of genes as seriously as the data suggest,” says Steven E. Hyman of Harvard University. “He is a brilliant zealot for plasticity—we need his voice. But ultimately I fear our brain may not turn out to be as plastic.” Others wonder what the costs might be—for instance, **could triggering plasticity at some point diminish the brain's ability to flourish later on?—and how drugs could be combined with an understanding of neuroplasticity to get fuller recovery.** “The sky's the limit, and we are trying to figure out the rules,” Kolb states.

In the meantime, evidence from other quarters seems to bolster Merzenich's fundamental belief that

healing plasticity can be driven by behavior. Jeffrey Schwartz of the University of California at Irvine has reported brain remapping in people with obsessive compulsive disorder who have undergone behavioral training. They have apparently remolded their brain to avoid certain patterns of thinking. Researchers at Laval University's Geriatric Research Unit in Quebec have suggested that exercise is protective against the development of Alzheimer's disease. A study last year in the *Journal of the American Medical Association* indicated that mental activity, such as reading the newspaper every day,

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could keep Alzheimer's at bay; a large-scale federal study came to the same conclusion.

And during the eight years after his riding accident, actor Christopher Reeve has apparently exercised himself out of paraplegia into a state where he can move his fingers and toes and push with his legs. His recovery marks the first time such extensive reconnection of the spinal cord to the brain has been recorded after such a long period. His brain lights up in unexpected places. “The nervous system is capable of doing all sorts of things,” declares Reeve's physician, John W. McDonald of the Washington University School of Medicine. As for fixing the brain, he says, “We just don't know yet which kinds of mental tasks can correct which problems.” Merzenich would probably say he knows—if you could get him on the phone. SA

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MORE TO EXPLORE

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