The Brain Remaps Its Own Contours

A striking body of recent work suggests that the adult brain can reorganize itself in areas that were long thought to be completely "hard-wired"

If you close one eye and stare at a point straight ahead of you, there is an area in your field of vision—about 15 degrees off center and the size of a fist held at arm's length—into which objects seem to disappear, swallowed up by the background scene. This is your open eye's "blind spot," which is caused by a patch of blood vessels in your retina that prevents a small part of the retina from responding to light. The brain automatically fills in the gap with whatever color or pattern surrounds the blind spot at that moment.

The existence of the blind spot has been a curiosity for centuries. But lately it has acquired a new scientific importance: It provides one example of a widespread phenomenon in the brain called "filling-in"—not only can your visual system fill in such gaps, it seems, your other senses can as well. And the discovery of this phenomenon is opening the eyes of neuroscientists, causing them to see the brain in a whole new light.

Only recently, most neuroscientists thought much of the brain—with the exception of certain specialized areas—was "hard-wired" from shortly after birth, with all the information-carrying pathways firmly and immutably formed. According to Rockefeller University neuroscientist Charles Gilbert, the brain was seen as "a set of fixed filters that just sort of handed the products of a fixed set of operations on to the next stage in the pathway." But the recent experiments on the filling-in phenomenon conjure up a radically different concept of the brain, as "a network that is continually remodeling itself," says Michael Merzenich, a neuroscientist at the University of California, San Francisco. And that in turn means that the brain can "learn" in areas where learning has never before been observed.

The notion of a "hard-wired" brain became widely accepted after the Nobel Prize–winning experiments of David Hubel and Torsten Wiesel at Harvard in the 1960s. Hubel and Wiesel, who were studying the visual cortex in cats, found patches of neurons called "ocular dominance columns," which respond preferentially to signals coming from either the right or the left eye. They found that sewing shut one of a newborn kitten's eyes stunted formation of the columns for that eye. What is more, after the passage of a critical period of development soon after birth, the layout of the columns in the brain became fixed—no longer changeable by experimental manipulations.

Hubel and Wiesel were studying the primary visual cortex, the place where visual information first enters the cerebral cortex. And that part of the brain is organized as a map of the visual world. Hubel and Wiesel's experiments suggested that visual experience in the first few weeks after birth puts the final touches on the map, which then is fixed for life.

Those conclusions for the primary visual cortex soon became generalized in the minds of many researchers to other areas of the primary cortex, where information from other senses is also recorded in the form of maps—areas such as the somatosensory cortex, the part of the brain that receives information about touch, where we have a map of all the skin surfaces of our body; the auditory cortex, which has a map based on frequencies of sound received by the cochlea of the ear; and the motor cortex, the part of the brain that triggers muscle movements, which has a "body plan" map somewhat similar to the somatosensory map.

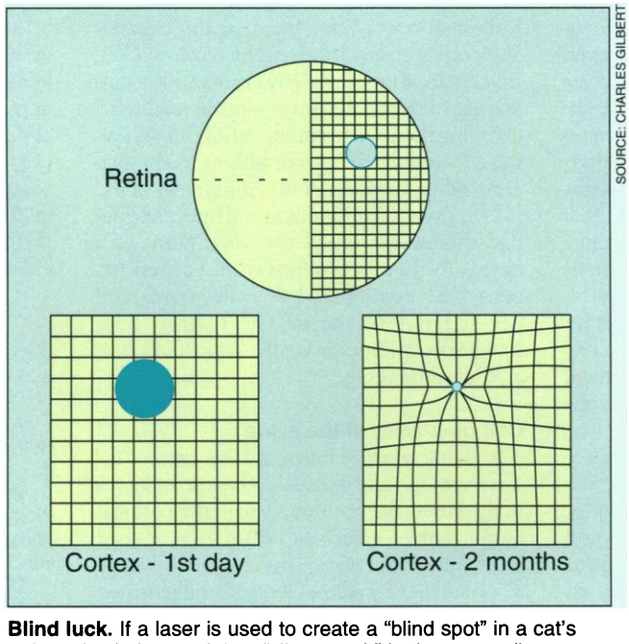
Throwing powerful shadows

Hubel and Wiesel's work suggested to most neuroscientists that all these maps behaved like the ocular dominance columns, taking form during critical periods and remaining fixed forever. "The unspoken assumption made by many in the field," says Gilbert, "was that all the plasticity necessary for learning happens in higher cortical areas, and that the topography of the primary areas was fixed" in the adult brain. Indeed, that view was so powerful that it overshadowed earlier observations hinting that some maps in the adult brain are capable of change.

But in the mid-1980s came a finding too elegant to ignore, a finding that began to overturn the "hard-wired" view. Merzenich, with Jon Kaas of Vanderbilt University and other collaborators, severed a nerve from the palm of a monkey's hand to the brain and showed that, over a month or so, neurons in the cortex that had once received signals from that nerve changed their allegiance and began responding to sensations from the back of the hand. Their finding "brought everybody's attention to the idea that plasticity occurred in adult nervous systems," recalls John Donoghue of Brown University. The process Merzenich and his colleagues observed resembles the filling-in around the blind spot, but whereas filling-in of the visual blind spot had traditionally been attributed to higher brain functions (a subconscious assumption that whatever surrounded the spot must fill it as well), this filling-in was

NEUROSCIENCE COVERAGE

This week's *Science* carries two news stories of particular interest to neuroscientists: the one beginning on this page and one on research into spinal cord regeneration that begins on page 218. These stories are the News Department's contribution to an issue with a special concentration on neuroscience that also includes Perspectives and Reports on related subjects.



SOURCE: CHARLES GILBERT

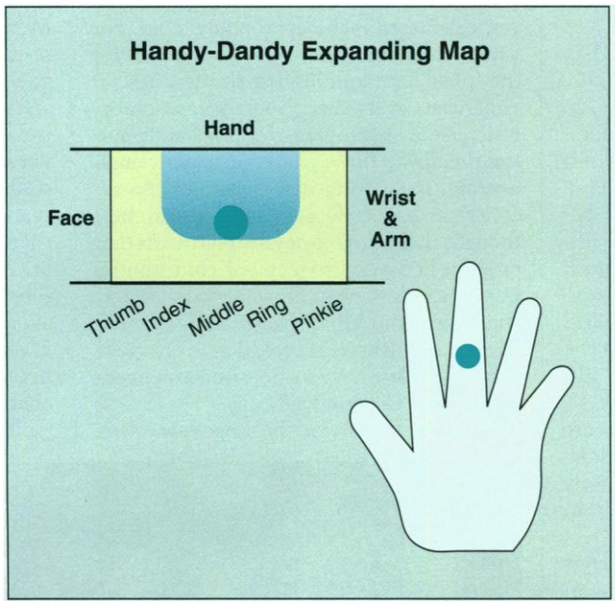
Blind luck. If a laser is used to create a "blind spot" in a cat's retinas *(top)*, the result is a "silent patch" in the cortex *(lower left)*, which fills in as neurons that lost their inputs begin responding to light from surrounding areas in the retina *(lower right)*.

clearly taking place in the primary cortex, where the sensory map is first laid out.

And that was just the first of a cascade of findings showing that filling-in happens throughout the cortex. For example, in the motor cortex, Donoghue and Jerome Sanes, also of Brown, showed that removing nerves that normally control the movement of a rat's whiskers causes the part of the cortex that used to control those whisker muscles to begin to take charge of other muscles instead.

Such findings were fascinating in themselves, but they left unanswered key questions that provided the framework for the next phase of the research. To name but one of these questions: Does filling-in happen through the formation of new neural connections—a rather radical concept when applied to the adult brain—or merely by unmasking existing, unused, connections? This and similar puzzles are only now beginning to be addressed, and out of that process have come further unexpected findings.

Some of the most surprising results come from recent experiments on the notorious Silver Spring monkeys. In the late 1970s, neuroscientist Ed Taub, then of the Institute for Behavioral Research, began studies on several macaque monkeys in which he destroyed the point where the sensory nerves from one arm enter the spinal column. Taub intended to use the monkeys for rehabilitation experiments, but they were confiscated in 1981 after a raid initiated by animal rights activists and kept alive for a decade. In 1987, Tim Pons and his colleagues at the National Institute of Mental Health began to test the brains of the monkeys for changes in their sensory maps.



Digital memory. Michael Merzenich showed that when a monkey is trained to repeatedly use its middle finger, the part of the brain dedicated to receiving primary inputs from that finger *(dark color)* expands *(light color)*.

Remapping—on a large scale

What they found was a neural reorganization that was astounding because of its scale. The region of the cortex that once would have responded to sensations from the affected arm and hand now responded to gentle touches—on the face! The face is adjacent to the hand in the somatosensory map, but nevertheless, the reorganization that had taken place covered an enormous area by the standards of the brain: more than 1 centimeter, or about one-third of the entire map. Those results were "totally unexpected," says Pons. "What we thought we would have is large zones of tissue [in the middle of the map] that were completely unresponsive to somatic stimulation. And that's not what happened at all."

The map reorganizations discovered by Merzenich, Kaas, and their colleagues took place over less than 2 millimeters, and could be explained by the rerouting of information through known neural connections. But the reorganization in the Silver Spring monkeys, spanning more than a centimeter, couldn't be accounted for by the activation of any known pathways. "That put us in a whole new ballpark," says Pons. "One is almost forced to invoke [the growth of] new connections."

University of California (UC), San Diego, neuroscientist V.S. Ramachandran views

Recent results indicating that sensory maps can be redrawn in adult brains, says Michael Merzenich, suggest the brain is "a network that is continually remodeling itself."

new connections as an unlikely explanation, based on an intriguing experiment he performed on human subjects who had recently lost an arm. Ramachandran stroked various parts of their bodies with a Q-tip and found that several of the amputees, including one who had lost his arm only a month before, felt sensations in their missing hands when he stroked their faces. It would seem that these amputees had undergone map reorganizations comparable to those of the monkeys, but a month, Ramachandran argues, is too brief a period for new connections to have formed. Yet he and others acknowledge that there is little evidence for existing connections spanning such long distances, hence the mechanism of massive reorganizations of the somatosensory map remains a mystery. "One thing I would emphasize," says Pons, "is how much we still don't know."

That may be true, but parallel work being done on the visual system has revealed a type of neural connection that might provide the links needed to explain at least some types of plasticity; these links, first found in the visual cortex by Rockefeller's Gilbert, are now being found in other areas of the cortex as well. They are the so-called horizontal connections that link neurons of the cortex over distances of 6 to 8 millimeters. Gilbert proposes that these horizontal connections may act like backup communication lines, ready to reroute information to neurons from more distant sources should the main cables bringing information directly from the lower parts of the brain be silenced.

The concept of these long-distance horizontal linkers is consistent with data from experiments that build on observations of filling-in the blind spot. Both Kaas and Gilbert recently did independent studies of visual filling-in, using cats in which they had made small, matched, permanent blind spots on both retinas with a laser. Normally each neuron in the visual cortex responds to signals coming from a small part of the visual scene, called its "receptive field." Both groups found that within minutes of the laser lesions, cells in the part of the cortex covered by the blind spot began to expand their receptive fields until they were receiving signals from areas surrounding the blinded part of the retina—a result analogous to the one seen in the filling-in of the somatosensory map.

Floating icebergs of the brain

"The classical receptive field is the tip of a floating iceberg," says UC San Diego's Ramachandran. If the tip of the iceberg is cut off—by creating a blind spot that covers the receptive field—the iceberg can ride a bit higher in the water, exposing a new and broader receptive field. And such rapid expansion of receptive fields could only happen if there were an existing system of horizontal connections in place, ready to be activated when the main input is silenced.

But if the neurons in the brain are so readily capable of expanding their receptive fields, what keeps them operating along normal, circumscribed lines under ordinary circumstances? One possibility is that the strong signal coming directly along the sensory pathway to those neurons inhibits or outcompetes other, less direct, signals. Remove the direct

signal and the effect is cancelled—allowing weaker inputs to have their day.

Although the precise mechanisms of filling-in haven't yet been sorted out, it is clear that filling-in is a widespread phenomenon in the brain. And that, in turn, raises the question of what it is doing there. One obvious answer is that it can allow partial recovery after certain kinds of brain damage. For example, people with gaping holes in their visual fields caused by damage to retina or brain often don't notice, because of filling-in.

That's an interesting insight, but UC San Francisco's Merzenich says filling-in is only part of a much larger story. He characterizes filling-in as a "curious and bizarre phenomenon" that is most interesting for the light it may shed on a more important process: a continuous competitive give-and-take between neurons. In that give-and-take, filling-in is at one far end of the spectrum: If there is a silent spot in the cortex, there is no competition, and weaker connections will certainly fill it in. But in active parts of the brain, the same properties that lead to filling-in will lead to a more subtle plasticity—as conditions change, some connections are strengthened and others weakened, allowing parts of the brain that were formerly thought to be hardwired instead to adapt: in short, to learn.

The kind of competition Merzenich refers to is what lets our brain adapt every day in ways that improve performance. He offers as an example a recent experiment in which he and his colleagues used small vibrators to stimulate the middle finger of monkeys and asked the monkeys to make distinctions between the vibrational frequencies. At the same time, with electrodes implanted in the monkeys' brains, the researchers could monitor neurons in the monkeys' somatosensory cortex. What they found was that as the monkeys improved at the task, the region of the map corresponding to their middle fingers expanded. And Alvaro Pasqual-Leone, at the National Institutes of Health, recently found a similar map expansion in blind people who use one finger to read texts in Braille.

That result, says Brown's Donoghue, shows "you can adjust the organization of your system so it can operate more efficiently when the demand is put on a particular body part." If you need a sensitive touch, the brain expands the area focusing on that sensation. If you need a certain muscle group, as Donoghue and Sanes have observed in recent experiments with monkeys, the brain expands the part of the map devoted to those muscles. "Those adaptive changes, as far as the cortex is concerned, are learning," says Merzenich. And understanding how learning works is one of the ultimate aims of neuroscience—an aim that the latest findings on filling-in and on plasticity can only bring one step closer.

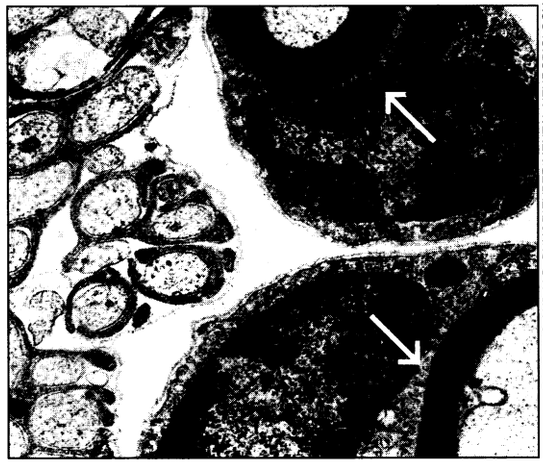
–Marcia Barinaga

SPINAL CORD INJURIES

New Optimism Blooms for Developing Treatments

A few weeks ago, the American Paralysis Association (APA) celebrated its 10th anniversary with a 2-day scientific meeting.* And yes, celebrated is the appropriate word. For while researchers have not found a cure for the spinal cord injuries that paralyze 10,000 Americans every year, progress in a number of diverse areas, ranging from drugs and physical therapy to tissue grafts and genetic engineering, is eliciting new optimism. As recently as a decade ago, most researchers thought that trying to devise treatments that promote recovery from spinal cord injuries was a hopeless task. Now, says Ira Black, chairman of the APA's science advisory council, "There has been a revolution in our views of recovery. We have a whole new armament of therapies to consider."

What accounts for the hopelessness researchers have long felt—and what makes spinal cord injuries so devastating—is the fact that in most mammals the cells of the central nervous system show little evidence of being able to regenerate themselves when they are damaged. That can mean paralysis when the spinal cord's axons, the long fibers that nerve cells send out, are damaged. Since the axons transmit electrical nerve signals from one cell to another, when they're destroyed, the cells can no longer communicate and the body loses all the functions the affected cells control, the ability to move the muscles of the leg, say, or to feel pain and other stimuli.



C.L. PAINO AND M.B. BUNGE/*EXPERIMENTAL NEUROBIOLOGY*

Insulating axons. Two myelinated axons *(arrows)* with their Schwann cells in a Schwann cell spinal graft.

But about 10 years ago, Albert Aguayo and his colleagues at McGill University in Montreal stunned the world of spinal cord research by showing that in the rat, axons could indeed regrow in the central nervous system. Of course, axon regeneration by itself is not enough to cure paralysis, since the nerves must also reconnect correctly to restore function, but the results provided a spark of hope in a depressed field. Since then, there has been an intensive effort to improve on Aguayo's effort by understanding what substances in the body inhibit or encourage axon regeneration. For example, the growing understanding of one protein in particular, nerve growth factor (NGF), has dramatically changed the field's thinking. But the use of molecular biology to produce NGF is only one among a variety of strategies designed to overcome—or prevent—the devastating changes in life that human beings experience after injuries to their spinal cords.

Molecular biology to the fore

One very promising cutting-edge approach exploits genetically modified cells that can produce healing proteins such as NGF on their own. Fred Gage of the University of California, San Diego, has engineered fibroblast cells to express nerve growth factor and other trophic factors. And in a recent experiment, he's transplanted a collagen gel suffused with such cells into rat spinal cords. The result: Axons grew into and out of the gel, apparently making correct contact with their target cells, Gage reports. Still to be determined, he cautions, is whether such nerve regeneration brings with it functional recovery. Other researchers, meanwhile, are working on a method that uses the herpes virus to integrate growth factor genes directly into damaged nerve cells.

Not all the effort in the molecular biology of spinal cord research is on growth factors. In fact, many feel that the work on so-called inhibitory proteins is the most exciting in the field. Many nerve cells are surrounded by a membranous layer of insulation known as the myelin sheath, and a few years ago, Martin Schwab and his colleagues at the University of Zurich, in Switzerland, discovered that two proteins, apparently present only in the myelin sheath in the mammalian

*"Recovery of Function: The Challenge of Spinal Cord Injury," 16 and 17 September, UMDNJ-Robert Wood Johnson Medical School, Piscataway, New Jersey.