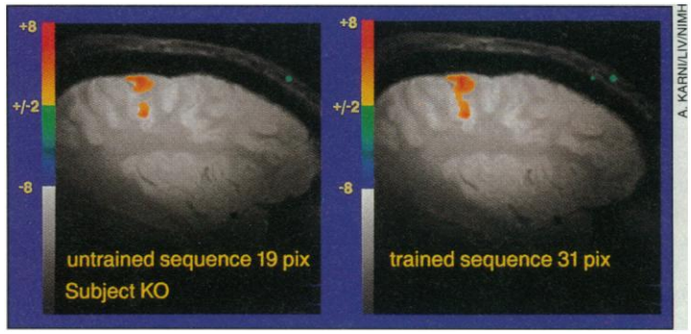
Watching the Brain Remake Itself

Researchers continue to identify new facets of the brain's malleability. Some of the latest faces of neurological change being investigated reflect learning, fear, and pain

Nothing is more constant about the nervous system than its ability to change. Neural plasticity, the capacity to remold connections within this system, is at the root of memory storage, for example. But plasticity is not limited to learning. It is also central to the nervous system's development, and to some of its responses to injury or disease.

Over the past decade, researchers have continued to find surprising new forms of change in the nervous system. And late last month in Miami, at the annual meeting of the Society for Neuroscience, neural plasticity appeared as a theme in many of the more than 730 posters and talks attended by nearly 18,000 neuroscientists, while the ever-changing winds of tropical storm Gordon howled outside.



Rehearsal time. These functional magnetic resonance images show that more neurons in the primary motor cortex are involved in performing a practiced task *(colored area, right)* than a fairly novel one *(left)*.

Finger-tapping finding

Neural plasticity must be a key element of the growing dexterity that accompanies the learning of a new physical skill. When you learn any new skill, from typing to roller-blading, you will be very clumsy at first and then gradually improve as your brain adapts and adjusts to meet the demands of the new activity.

Where do these changes occur? Until a decade or so ago, one of the the last places anyone would have looked would have been the primary motor cortex (M1), the part of the brain that directs body movements, or the primary sensory cortex, where sensations are registered. "The dogma was that these areas were hardwired," says Avi Karni of the National Institute of Mental Health (NIMH). But recent research in many labs suggests that both areas are surprisingly changeable. For instance, as a blind adult learns to use a forefinger to read Braille, the area representing that finger in the person's somatosensory cortex—the part of the brain that detects touch—expands into areas previously devoted to neighboring fingers. But many of the tasks we master don't involve a specific portion of the anatomy in this way—they instead are made up of multiple movements by many body parts. How does that type of learning change the brain?

At the Miami meeting, Karni and Leslie Ungerleider, who work together at NIMH, presented a tantalizing finding suggesting that more neurons become active in M1 during a well-learned task than during performance of a similar but relatively novel one. In their study six human volunteers learned to tap their fingers against their thumb in a certain sequence, such as 4-2-3-1-4, where 1 represents the index finger and 4 is the pinky. They practiced the sequence for 10 minutes every day, and over several weeks their speed more than doubled and their accuracy improved.

Periodically during the study, the volunteers performed the task while they underwent a brain scan using a technique called functional magnetic resonance imaging (fMRI), which indirectly measures regional brain activity by detecting blood oxygenation levels in the brain. For purposes of comparison during these tests, the subjects performed a similar but unrehearsed task: tapping their fingers in the reverse sequence, 4-1-3-2-4.

Both tasks use the same finger-to-thumb movements and even use each finger the same number of times. And during the brain scans, the subjects performed the rehearsed and unrehearsed sequences at the same speed, a slow and deliberate 2 taps per second, to make the execution of the two tasks as similar as possible. Given the parallelism, the researchers reasoned, any difference in brain activity would reflect a difference between rehearsal and relative novelty, rather than between physical demands.

At the first brain scan, before practice sessions began, both tasks activated similarly sized areas in the motor cortex. But by the fourth week of training, when the volunteers were showing greater proficiency on the rehearsed task, the fMRI images showed activity in a greater area of the motor cortex when the subject was performing the rehearsed sequence.

The change probably does not reflect the expansion of the area devoted to a particular body part, because the subjects perform the same component movements for both trained and untrained sequences. Instead, Ungerleider proposes, "perhaps practice results in a recruitment of neurons in M1 into a network that represents these motor sequences."

Other scientists agree. "With those built-in controls, you can't explain the data based on movement rate, and you can't explain it based on the types of movement that were done, so you have to explain it based on the repeated sequential use of body parts," says Brown University neuroscientist Jerome Sanes, who also studies human motor cortex. "What you may be seeing is the signature of how repeated sequential action modifies processing in local neural networks." And that, he says, is one more striking piece of evidence for the plasticity—and memory-storage potential—of the primary cortex.

Turning off fear

While researchers studying skill-learning focus on the motor cortex as a site of change, the locus of change in the brain for many other types of learning has yet to be pinpointed. One elusive quarry, which was the subject of several reports in Miami, is the brain area responsible for uncoupling fear from traumatic memories.

"Evolution has made our brains very proficient at making connections between environmental signals and dangerous situations," says Michael Davis of Yale University Medical School. "And when we realize that danger is no longer present, we learn to ignore those signals." Davis and others are trying to find the brain areas responsible for uncoupling fear from traumatic memories. The work is important because failure to dampen fearful associations when they are no longer relevant is at the root of many emotional disorders. A soldier in Vietnam, for example, may have learned all too well that the sound

of helicopters overhead signified danger. At home, helicopters are benign, yet for many veterans whirring rotor blades still unleash disabling terror.

The "on" switch responsible for forming these associations appears to be in a brain area called the amygdala. Rats conditioned to associate a particular stimulus such as a light or a tone with the mild pain of an electrical shock show fear of the stimulus after training—unless the amygdala has been removed. And some researchers speculated that if the amygdala contained the on switch, it must contain the "off" switch, too. But recent experiments by Davis and former graduate student William Falls cast doubt on that simple assumption.

Davis's group trains rats to expect an electrical shock to their feet when a light is turned on. After conditioning, whenever the light is on, the rats are jumpy and anxious—a state the researchers measure by testing how easily the rats are startled by a sudden noise. Next, the researchers introduce a "safety signal," in the form of a tone. When the tone accompanies the light, there are no shocks. The animals soon learn that the tone/light combination represents safety, and they remain calm.

To investigate whether the amygdala was involved in turning off the fear, Davis and Falls made use of a well-known, though slightly paradoxical phenomenon: Rats trained for many days to fear the light lose that fear when their amygdalas are removed, but can be retrained to fear the light, even in the amygdala's absence. The reason for this, says Davis, is not clear, but it may mean that other brain structures "learn" in parallel with the amygdala but don't express that learning until the amygdala is removed and the animal is retrained.

Davis and Falls trained a group of rats to fear the light and to recognize the tone as a safety signal. Then they removed the rats' amygdalas and retrained them to fear the light. Importantly, they did not repeat the training with the tone. To their surprise, the rats remembered that the tone means safety and relaxed when they heard it without having been retrained. That, says Davis, suggests that whatever is responsible for turning down fear must reside outside the amygdala, as that memory was retained even when the amygdala was removed.

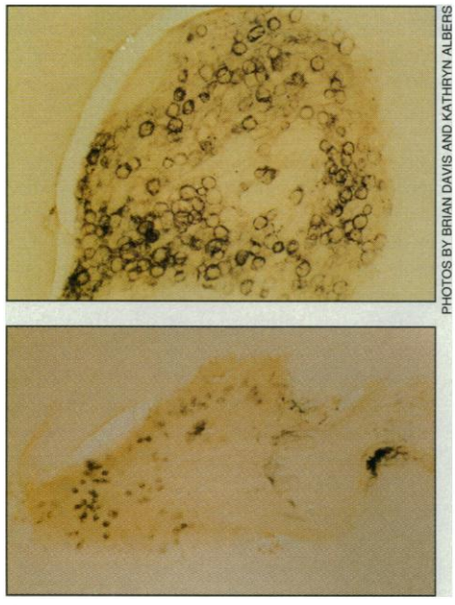
That finding is "very important," says Joseph LeDoux, who studies emotional memory at New York University. But he adds that it must be interpreted with caution. "I don't think we can dismiss the amygdala as being one place where the modulation might occur," he says, "but this result suggests there may be others as well."

LeDoux and graduate student Maria Morgan reported work on a part of the brain that might be responsible for flipping that off switch: a part of the prefrontal cortex called the infralimbic cortex. Morgan trained rats to associate a tone with a shock, then once the rats were trained, turned on the tone with no shocks and measured how long it took the rats to lose their fear of the tone. Rats with a damaged infralimbic cortex continued to be fearful long after normal rats had relaxed, suggesting the infralimbic cortex is involved in extinguishing the fear.

But even if the infralimbic cortex does turn off fear, the mechanism by which this occurs is still not known. Neural outputs from the infralimbic cortex lead not only to the amygdala, but to many other structures—such as the brain stem and hypothalamus—which also get input from the amygdala. Davis suspects that it is one of these sites where the fears are actually turned off, but, says LeDoux, "it will be complicated figuring it out in a system that is [so] redundantly wired."

Painful plasticity

The nervous system, of course, is not limited to the brain—and neither is plasticity. Indeed, some of the biggest changes in the adult nervous system occur in peripheral nerves that relay signals between the brain and the rest of the body. Neurons in injured peripheral nerves, for example, sometimes form completely new—and inappropriate—synapses. These connections may cause an intractable pain syndrome called sympathetically maintained pain.



PHOTOS BY BRIAN DAVIS AND KATHRYN ALBERS

Crossed wires. In transgenic mice making excess nerve growth factor, an enzyme made by sympathetic neurons surrounds sensory neurons, indicating inappropriate connections *(dark circles, top)*. In normal mice, that enzyme, tyrosine hydroxylise, is less evident *(bottom)*.

The problem arises when nerve cells known as sympathetic neurons, which normally control involuntary functions such as sweating and heart rate, form synapses onto the sensory neurons that carry pain signals back to the brain. Once these normally distinct wires have been crossed, normal activity in the sympathetic neurons can cause pain. Worse yet, the pain is untouched by normal painkillers; drugs that suppress sympathetic activity have sporadic success.

A better understanding of what causes sympathetic neurons to make these inappropriate connections might help researchers develop better treatments. And that goal may be a step closer, thanks to a serendipitous discovery by Brian Davis and Kathryn Albers of the University of Kentucky and their colleagues, who reported in Miami that nerve growth factor (NGF) seems to cause the painful connections to form.

NGF is a protein that nurtures sympathetic and sensory neurons during embryonic development and after nerve injury. Davis and Albers set out to study the role of NGF in development by creating transgenic mice that make excess amounts of NGF in their skin. "It wasn't our intent to look at pain," says Davis. But Davis and Albers quickly realized that the mice were overly sensitive to painful stimuli.

That was puzzling. But then they sent the mice to David Katz at Case Western Reserve University in Cleveland to examine their sensory nervous systems, and they got part of the answer. "He called me and said, 'Brian, I see the strangest thing,' " Davis recalls. "The sympathetic nervous system in our animals had grown and formed synaptic contact with sensory neurons." Those connections suggested that the mice were suffering from sympathetically maintained pain. And that means NGF may be a key factor in causing the syndrome, Davis says. "It's been known since 1987 that when you crush peripheral nerve, NGF production increases dramatically," he points out. NGF is also known to encourage the growth of sympathetic neurons, and in this case may be causing them to form synapses where they don't belong.

Davis says the ideal way to treat sympathetically maintained pain would be to selectively destroy the abnormal connections. He and Albers plan to try to do this using a new NGF-neutralizing compound under development at Hoffmann-LaRoche. Such an approach just might work, because "the sympathetic nervous system, unlike some of the sensory systems, requires NGF throughout life," says Stanford University neuroscientist Eric Shooter, who studies NGF. "I could imagine that if you knocked out that source of NGF, you could reverse that phenomenon." If that reversal in direction can be achieved, it will be yet another change in what is proving to be a remarkably malleable nervous system.

–Marcia Barinaga