

Tracking the Changing Brain

Elly Nedivi's lab is hunting for genes that let the mind adapt to experience

by Courtney Humphries

We often hear debates about nature versus nurture—whether it's our genes or our environment that controls how we think and behave. In reality, the two are interconnected. “The effect of the environment goes back to the genes,” says Elly Nedivi, the Fred and Carole Middleton Assistant Professor of Brain and Cognitive Sciences at MIT. “It's continuous. Every day, every thing you see, every stimulus turns on genes in your brain.” Likewise, the brain is not simply hardwired according to a genetic program. Instead, our brains are programmed to be flexible, to learn from experience. If our brains could not adapt, we could not learn, form memories, or survive changing conditions.

Nedivi hunts for the genetic roots of adaptability in the brain. She investigates genes in the adult brain that respond to the environment, an ability that scientists call “plasticity.”

In the brain, “activity is the driving force of plasticity,” Nedivi says. The brain changes in response to experience. Whether you are listening to a lecture, practicing a dance move, or watching a movie, your experiences eventually translate into electrical signals in individual nerve cells. So on the level of a cell, Nedivi says, “activity means electric impulses.”

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More than a decade ago, Nedivi and her colleagues embarked on a large-scale screen to identify genes in the brain that respond to electrical activity. By comparing the genes expressed in cells that were electrically activated to genes expressed in nonactivated cells, her team came up with a list of about 360 different genes that are sensitive to activity levels and might hold the key to the brain's plasticity. Some of them were known genes, but others were completely unknown. Making sense of such a large roster of genes, which she calls candidate plasticity genes (CPGs), seemed daunting, like trying to learn something about the social lives of a group of people from a list of names. “It's clear that plasticity is not the work of one individual gene, but lots of them working together,” she says. “We wanted to take a few examples and show that they teach us something.”

Call and response

The first unknown gene they chose to study, which they called CPG2, turned out to encode a protein that helps control how nerve cells receive incoming signals. About 85 percent of the nerve cells in the brain respond to a chemical signal called glutamate. Glutamate is a message sent from one cell to another; in order for the message to be received, it must stick to specialized receptors on a cell's outer surface. One way to change the strength of the signal is for a broadcasting cell to send more glutamate. But scientists have hypothesized that the receiving cell might be able to change how well it “listens” to incoming signals. Nedivi's team found that CPG2 does just that. It allows the receiving nerve cell to pull glutamate receptors in from the surface, making it less responsive to outside signals. “It's a rapid response mechanism,” Nedivi says, one that does not change the cell permanently, but allows it some flexibility in how it communicates with its neighbors.

The second gene Nedivi's lab chose to study, CPG15, encodes a chemical signal that travels between cells. Her team found that when a nerve cell releases CPG15, it causes nearby cells to grow more branches. Nerve cells with more branches form more points of connection, called synapses, with surrounding cells. So CPG15 is a way for cells to make their neighbors more communicative. Unlike CPG2, it works on a longer time scale by actually changing the structure of the brain's circuitry. From just these two examples, Nedivi says, it's apparent that “the brain really has multiple levels that it can adjust.” Some are quick and short-lived, others take time and persist for years.

Back in time

Nedivi went into the project hoping to find clues to plasticity in the adult brain, but she was surprised to see that many of the candidate plasticity genes are also expressed during development, when the brain and its major circuitry are being formed. These genes seem to play different roles in development than they will later adopt in the adult.

For example, Nedivi's team found that CPG15, which acts in the adult as a growth signal, helps cells in the developing brain survive. The brain begins with an overabundance of neurons, the majority of which will eventually die. What might seem like a wasteful process actually helps the brain eliminate bad connections and control the size and shape of its structures. For instance, the human cerebral cortex first balloons out with

new cells, after which the middle cells die off to separate the two hemispheres. Experiments in Nedivi's lab found that CPG15 is being expressed early in development, where it tells certain cells of the brain not to die off. Using mice, "we found we could affect the size of the brain by changing its expression," she says. "The more that is expressed, the bigger their brains."

The study shows how the brain makes use of the same genes for different purposes. "We're not only learning a lot about how synapses work but about how the brain gets built, how connections are formed in the first place," she says.

Change made visible

The traditional view of the brain is that all of its cells and connections are formed when it develops, and in adulthood there is just a small amount of tinkering at the synapses. But many of the known genes that Nedivi uncovered in her initial screen are involved in determining a cell's structure, suggesting that cells may actively change shape in adulthood.

To investigate how much structural change really happens in the adult brain, she has recently teamed up with Peter So, professor of mechanical and biological engineering and an expert in high-tech imaging. They devised a technique that

literally provides them a window into the adult brain. The researchers implanted small windows into the scalps of living mice, allowing them to peer into their brains using a powerful microscope to produce detailed, three-dimensional pictures of how neurons move and change shape over time. They were able to see the tree-like branches of neurons grow, retract, and redirect themselves.

The result of this study, published in the December 27 Public Library of Science Biology, demonstrates vividly that "the adult brain does have some capacity for structural change," Nedivi says. They now have a powerful tool to investigate how genetic or environmental manipulations alter the ability of the brain to change.

Ultimately, the goal of Nedivi's studies is to gain a better understanding of how the brain is designed to adapt. By learning as much as possible about the cellular events that underlie this ability, researchers can also learn more about how it goes awry and develop better therapies for neurological disorders. Nedivi will be speaking about her research in a talk entitled "Genes that Change Your Mind," at the MIT Life Sciences Conference, March 14-15, 2006 (see <http://ilp-www.mit.edu/events/lifesciences2006>).



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