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Long-Term Changes in Experience Cause Neurons to Sprout New Long-Lasting Connections

Howard Hughes Medical Institute researchers have discovered that neurons in the brains of mice sprout robust new connections when the animals are adjusting to new experiences. The new connections alter the circuitry of the brain by changing communication between neurons.

The researchers said their findings aid understanding of how procedural learning induces long-term rewiring of the brain. This type of learning is used in mastering skills such as riding a bicycle or typing on a computer.

"With novel sensory experience some populations of these new spines make connections that constitute beneficial new wiring"

— Karel Svoboda

Howard Hughes Medical Institute (HHMI) investigator Karel Svoboda and his colleagues reported their findings in the June 22, 2006, issue of the journal *Nature*. Other co-authors of the paper included Anthony Holtmaat and Linda Wilbrecht in Svoboda's laboratory at Cold Spring Harbor Laboratory; and Graham Knott and Egbert Welker at the University of Lausanne in Switzerland.

Svoboda is one of a handful of researchers in the world who are pioneering the development of new tools and techniques that permit scientists to observe the brain as it rewires over a period of weeks or months. This summer Svoboda will move to HHMI's Janelia Farm Research Campus where he will pursue neurobiology studies and projects in optics and microscopy.

In the studies reported in *Nature*, the researchers used mice that were genetically altered to produce a green fluorescent protein in specific neurons in the neocortex, which is a region of the brain that is known to adapt to new experiences. The researchers followed the growth of dendritic spines in the region of the neocortex that processes tactile information from the animals' whiskers. Sensory information from the whiskers is vitally important for mice

as they navigate their environment. Consequently, a significant portion of the mouse's brain is devoted to processing input from whiskers.

To monitor changes in neuronal structure visually, the researchers used a novel technique that Svoboda's team had developed earlier. The scientists employed laser-scanning microscopy aimed through a small glass window in the animals' skulls to image changes in fluorescence that revealed dendritic alterations present on the neurons.

In this most recent experiment, Svoboda's team was looking to see if persistent changes in connectivity occurred after a long-term change in experience. They focused on the formation of new long-lasting spines that indicate robust connections between a neuron's highly branched dendrites and nearby axons. Dendrites are the input side of neurons and axons the output side. Spines stipple the surface of dendrites, like twigs from a branch, and form the receiving ends of synapses, which are the junctions between neurons where neurotransmitters are released.

The researchers induced a long-term change in the sensory experience of mice by trimming the animals' whiskers, selectively cutting some but leaving neighboring whiskers, in a chessboard pattern. Over time, this selective grooming caused the animals' neurons to rewire themselves to adapt to loss of the whiskers - a strategy that reduces dependence on lost whiskers and enhances input from intact whiskers.

We knew from previous work that a subpopulation of dendritic spines appears and disappears over time, but we didn't know the biological meaning of this process, said Svoboda. In these experiments, we found that over about a month new spines appeared, and in particular a subset of these new spines stabilized to form new circuits, he said.

He said that the researchers were most excited to find that after this long-term change in experience there were many new spines that were large, robust and persistent, meaning that they remained over long periods of time. Under normal conditions, most new spines are faint and small, and disappear after a couple of days, said Svoboda. What we think they are doing is reaching out and probing for potential neuronal partners. And while most of them retract, with novel sensory experience some populations of these new spines make connections that constitute beneficial new wiring. So those spines gain bulk and are stabilized as persistent spines.

In addition to observing the gain and loss of persistent spines, the researchers also used electron microscopy to examine the new spines in more detail. That study showed that the new persistent spines participate in synapses, said Svoboda.

Svoboda said the discovery of experience-dependent, persistent-type dendritic spine growth has broader implications for understanding learning. We think these findings apply to understanding a form of implicit memory of training-based skills, he said. It's the kind of learning that you can't describe in words, like learning how to play the piano or to read Braille. It's in contrast

to explicit memory, which is used to remember facts.

Svoboda said the discovery suggests new ideas for future studies aimed at understanding the neuronal wiring process in greater detail. For example, he and his colleagues will study the rewiring of the animals' brain circuitry as trimmed whiskers regrow, to determine whether the rewiring can be 'undone' when conditions return to normal. The researchers also plan more detailed study of the circuitry itself, to understand the changes in the brain's wiring diagram caused by spine growth.