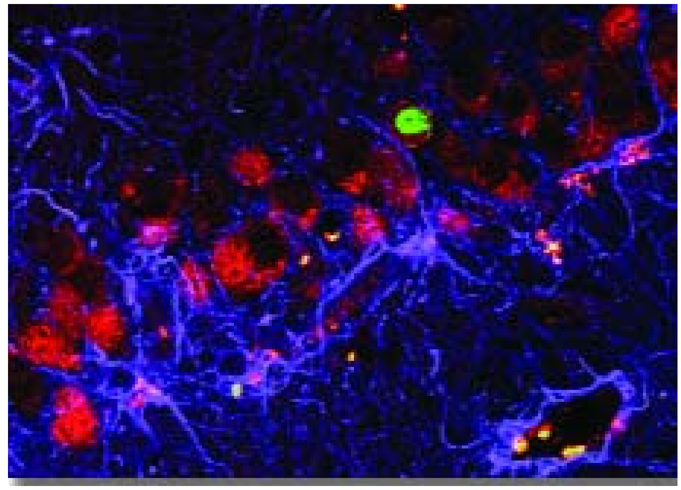
New Neurons Grow in Adult Brains

By James Adams

The longstanding belief that the adult brain does not produce new neurons is being challenged by current research. Adults may indeed be able to generate new neurons, in a process called neurogenesis, throughout life and at the rate of thousands per day. These findings could radically alter the way scientists look at the brain and could eventually lead to new methods of treating brain disease and injury.

In the most recent study, published in the October 15, 1999 issue of *Science*, researchers showed that new neurons are continually being added to the cerebral cortex of adult monkeys. The **cerebral cortex** is the largest and most complex region of the brain and is the seat of high-level decision-making, thinking, and personality.

The discovery, made by Elizabeth Gould and Charles Gross of Princeton's Department of Psychology, along with graduate student Alison Reeves and research staff member Michael Graziano, is likely to translate to humans. Monkeys and humans, as fellow primates, have fundamentally similar brains.



Using a green stain to identify new cells, scientists have discovered that brain cells can regenerate.
Photo courtesy of Dr. Gage - Salk Institute, Used by permission

Gould and Gross point out that it's not yet known what purpose the new cells serve in the cortex, but if the newly formed neurons are found to have a functional role, scientists may have to reexamine current theories about how the brain works. For instance, it's been known for some time that the adult brain displays a certain degree of plasticity, that is an ability to change, but traditional thought is that the brain handles processes like learning and memory by altering the nature of the connections, called synapses, between neurons. If new cells are being generated on a regular basis, a whole new level of complex it is opened up.

"We know that the brain is plastic and can change as a result of experience," says Allan Tobin, director of the Brain Research Institute at UCLA, "but what we don't know is whether these changes are mediated by presynaptic changes, post-synaptic changes, or now, by the generation of new cells."

If the results are confirmed in humans, they could have major implications for the treatment of neurodegenerative diseases like Parkinson's, Huntington's, or Alzheimer's disease. In these diseases, neurons either die or lose their normal function. When a critical number of cells have been lost, symptoms arise and continue to worsen as more and more neurons are effected. While practical applications are years away, physicians may one day find ways to influence the process of neurogenesis in order to generate more neurons in a particular region of the brain.

"With the idea that new cells themselves can be generated in the adult brain," says Tobin, "maybe you can find signals that will differentiate a whole cohort of cells to replace those that have died."

Finding New Neurons:

In order to test for the presence of new neurons in the adult brain, Gould and Gross injected rhesus monkeys with a chemical called BrdU. Cells that are dividing incorporate BrdU into their DNA and pass it on to the newly formed cells. At different time points after the injection, ranging from two hours to seven days, the researchers examined the cerebral cortex and found evidence of BrdU containing cells in three different regions. Because BrdU is only incorporated into the DNA of cells that are actively dividing, the cells with DNA containing the chemical had to have formed after the injection.

The researchers conducted additional experiments to determine that these newly formed cells had the characteristics of neurons. They were able to detect several different proteins in the cells that are found specifically in neurons. Also, they showed that the cells containing BrdU had the long extensions, called axons, characteristic of neurons. To do this Gould and Gross used a technique called fluorescent retrograde tracing. In this technique a chemical dye is applied to a small region of the brain, and the dye travels from the end of the axon back to the cell body, making the axon visible under a microscope.

According to Gould and Gross, the new cells appeared to originate in a region called the subventricular zone (svz) and **then migrated outward in a stream through the cerebral cortex to specific locations, where they differentiated into mature neurons** *[i.e. they migrate to where they are needed]*. The svz was previously identified by other researchers as a source of "neuronal stem cells" cells capable of dividing and differentiating into a variety of specialized brain cells.

The new cells were found in three of the four regions that were examined: the prefrontal region, the inferior temporal region, and the posterior parietal region. These three brain areas are involved in the complex cognitive tasks of decision making and short-term memory *[mind's eye*

(over)

process], recognition of objects and faces *[size, shape]*, and the representation of objects in space *[position-in-space, directionality]*, respectively. No new cells were found in the striate cortex, which is responsible for the initial, basic steps of visual processing.

The observation that ***new cells were found in regions important for cognitive functioning*** and not in an area involved in more rudimentary processing suggests that **neurogenesis may play a role in higher brain functions.** Gould and Gross speculate that **the new neurons could play a role in learning and memory by "marking the temporal dimension of memory"** and serving as **"a substrate for learning."** In a sense, **the new neurons may be time keepers, somehow helping keep memories in the right order and marking them in time.** They could also be serving as a blank slate, on which new memories could be written and new skills learned.

A Brief History:

"It's a surprise," says Tobin of UCLA, referring to the Gould and Gross experiments, "but it's a surprise that's been growing on us for the last couple of years."

In fact, evidence that neurogenesis occurs in the adult brains of some animals, such as rats and birds, has been around for many years. In 1965, Joseph Altman and his colleagues showed that new neurons were regularly produced by adult rats in the hippocampus, a region of the brain important for the early phases of learning and memory.

In the 1980's Fernando Nottebohm, of Rockefeller University, discovered that songbirds such as the canary, produced new neurons during the time they were learning new songs. This was particularly interesting work as it suggested that the production of new neurons was connected with a particular behavior. Nottebohm's continuing research has shown that birds add new neurons to their hippocampal complexes throughout their lives.

Studies of neurogenesis in primates during the 1980s turned up only negative results, and it was perhaps because of these results that the study of neurogenesis in higher mammals remained largely unexplored until now.

In any case, more recent evidence of neurogenesis has been found in the hippocampi of adult primates, including humans. In 1998, Fred Gage of the Salk Institute for Biological Studies in La Jolla, California, and Peter Eriksson at the Sahlgrenska University Hospital in Goteborg, Sweden, looked at hippocampal tissue from five patients that had died of cancer. These cancer patients had received an earlier injection of BrdU for diagnostic purposes (since BrdU labels dividing cells, it can also help in the detection of growing cancer cells). Gage and Eriksson found BrdU labeled neurons in the hippocampi of all five patients, who ranged in age from 57 to 72 years old.

Still, it was unclear whether neurogenesis occurs in the higher parts of the brain like the cerebral cortex. The newer structures, such as the cerebral cortex were still thought to lack the ability to grow new neurons.

That's where the new experiments by Gould and Gross come in. **By showing that neurogenesis occurs in the cerebral cortex of primates, they have shown that the brain is a much more dynamic organ than previously believed.** The next steps will include proving that similar results can be found in humans and discovering the functional role of the newly generated neurons.

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