

How Learning Preserves New Brain Cells

SCIENTIFIC AMERICAN

March 2009 \$5.99 www.SciAm.com



Detecting Secret
**NUCLEAR
TESTS**

page 70

Was Einstein Wrong?

Quantum weirdness
defies special relativity

**Nanotube
Radios** for
Microrobots

Fighting the
TB Pandemic

A Concise Guide to
Renewable Power



Saving NEW BRAIN CELLS

Fresh neurons arise in the adult brain every day. New research suggests that the cells ultimately help with learning complex tasks—and the more they are challenged, the more they flourish
BY TRACEY J. SHORS

If you watch TV, read magazines or surf the Web, you have probably encountered advertisements urging you to exercise your mind. Various brain fitness programs encourage people to stay mentally limber by giving their brain a daily workout—doing everything from memorizing lists and solving puzzles to estimating the number of trees in Central Park.

It sounds a bit gimmicky, but such programs may have a real basis in neurobiology. Recent work, albeit mostly in rats, indicates that learning enhances the survival of new neurons in the adult brain. And the more engaging and challenging the problem, the greater the number of neurons that stick around. These neurons are then presumably available to aid in situations that tax the mind. It seems, then, that a mental workout can buff up the brain, much as physical exercise builds up the body.

The findings may be particularly interesting to intellectual couch potatoes whose brains could benefit from a few cerebral sit-ups. More important, though, the results lend some support to the notion that people who are in the

early stages of Alzheimer's disease or who have other forms of dementia might slow their cognitive decline by keeping their minds actively engaged.

It's a New Neuron!

In the 1990s scientists rocked the field of neurobiology with the startling news that the mature mammalian brain is capable of sprouting new neurons. Biologists had long believed that this talent for neurogenesis was reserved for young, developing minds and was lost with age. But in the early part of the decade Elizabeth Gould, then at the Rockefeller University, demonstrated that new cells arise in the adult brain—particularly in a region called the hippocampus, which is involved in learning and memory. Similar reports soon followed in species from mice to marmosets, and by 1998 neuroscientists in the U.S. and Sweden had shown that neurogenesis also occurs in humans [see “New Nerve Cells for the Adult Brain,” by Gerd Kempermann and Fred H. Gage; *SCIENTIFIC AMERICAN*, May 1999].

KEY CONCEPTS

- Thousands of new cells are generated in the adult brain every day, particularly in the hippocampus, a structure involved in learning and memory.
- Within a couple of weeks, most of those newborn neurons will die, unless the animal is challenged to learn something new. Learning—especially that involving a great deal of effort—can keep these new neurons alive.
- Although the neurons do not seem to be necessary for most types of learning, they may play a role in predicting the future based on past experience. Enhancing neurogenesis might therefore help slow cognitive decline and keep healthy brains fit.

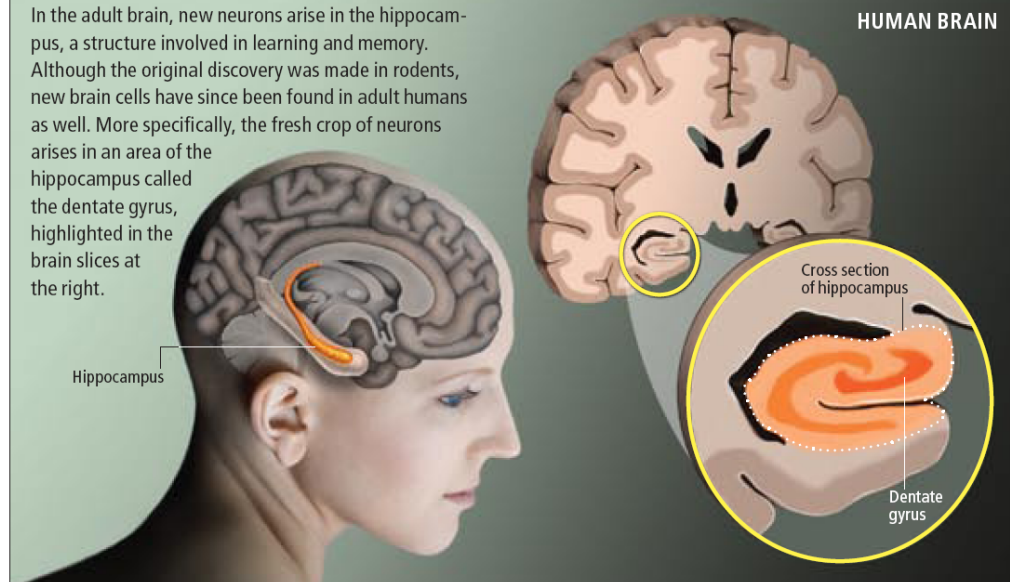
—The Editors

The tasks that rescue the most neurons are the ones that are hardest to learn.

[BASICS]

WHERE NEW NEURONS FORM

In the adult brain, new neurons arise in the hippocampus, a structure involved in learning and memory. Although the original discovery was made in rodents, new brain cells have since been found in adult humans as well. More specifically, the fresh crop of neurons arises in an area of the hippocampus called the dentate gyrus, highlighted in the brain slices at the right.



In rodents, studies of neurogenesis generally involve injecting the animals with a drug called BrdU (bromodeoxyuridine), which marks newly formed cells, making them stand out when viewed under a microscope. Those studies indicate that in rats, between 5,000 and 10,000 new neurons arise in the hippocampus every day. (Although the human hippocampus also welcomes new neurons, we do not know how many.)

The cells are not generated like clockwork, however. Instead their production can be influenced by a number of different environmental factors. For example, alcohol consumption has been shown to retard the generation of new brain cells. And their birth rate can be enhanced by exercise. Rats and mice that log time on a running wheel can kick out twice as many new cells as mice that lead a more sedentary life. Even eating blueberries seems to goose the generation of new neurons in the rat hippocampus.

Use It or Lose It

Exercise and other actions may help produce extra brain cells. But those new recruits do not necessarily stick around. Many if not most of them disappear within just a few weeks of arising. Of course, most cells in the body do not survive indefinitely. So the fact that these cells die is, in itself, not shocking. But their quick demise is a bit of a puzzler. Why would the brain go through the trouble of producing new cells only to have them disappear rapidly?

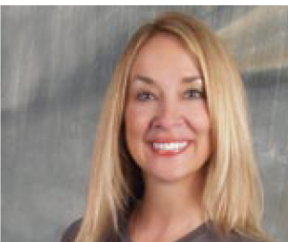
From our work in rats, the answer seems to be: they are made “just in case.” If the animals are cognitively challenged, the cells will linger. If not, they will fade away. Gould, who is now at Princeton University, and I made this discovery in 1999, when we performed a series of experiments looking at the effect of learning on the survival of newborn neurons in the hippocampus of rat brains.

The learning task we used, called trace eyeblink conditioning [see box on page 50], is in some ways similar to the experiments in which Pavlov’s dogs started to salivate when they heard a sound they associated with the arrival of dinner. In eyeblink conditioning, an animal hears a tone and then, some fixed time later (usually 500 milliseconds, or half a second), gets hit with a puff of air or a mild stimulation of the eyelid, which causes the animal to blink.

After enough trials—usually several hundred—the animal makes a mental connection between the tone and the eye stimulation: it learns to anticipate when the stimulus will arrive and to blink just before that happens. This “conditioned” response indicates that the animal has learned to associate the two events together in time. The rats’ accomplishment may sound trivial, but the setup provides a good way to measure “anticipatory learning” in animals—the ability to predict the future based on what has happened in the past.

To examine the connection between learning

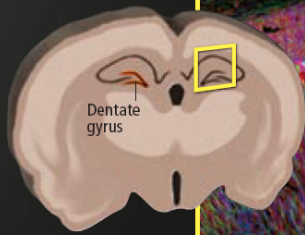
[THE AUTHOR]



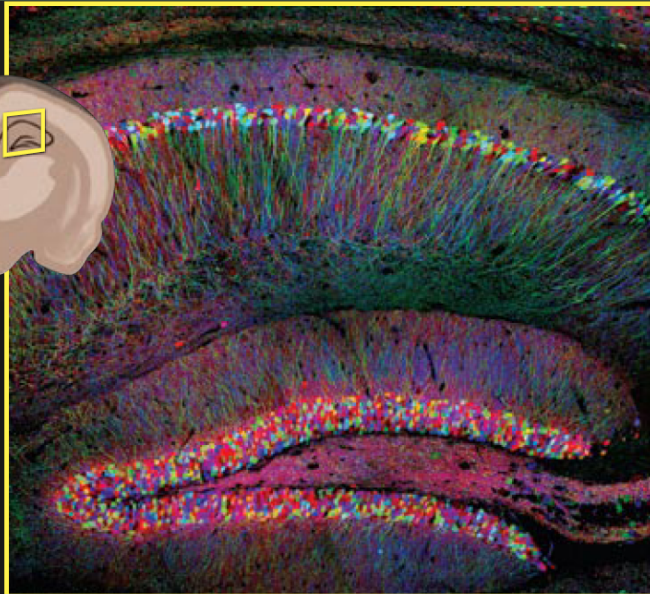
Tracey J. Shors, a professor in the department of psychology and the Center for Collaborative Neuroscience at Rutgers University, has had a long-standing interest in the neurobiology of learning and memory. Working with Elizabeth Gould of Princeton University, a discoverer of adult neurogenesis, Shors showed that learning enhances the survival of new neurons in the hippocampus and that these neural recruits seem to be involved in some aspects of learning. Some 10 years later Shors continues to ponder the question: “Neurogenesis: What’s learning got to do with it?”

COURTESY OF TRACEY J. SHORS (Shors); RUBBERBALL PRODUCTIONS/Getty Images (woman); JEN CHRISTIANSEN (illustrations)

RODENT BRAIN



The micrograph at the right shows the hippocampus of a "Brainbow" mouse, which was engineered to produce differently colored proteins in its neurons.

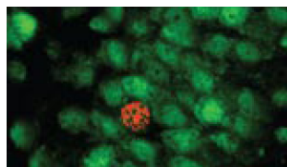


and neurogenesis, all the animals were injected with BrdU at the start of the experiments. One week later half the rats were recruited into the eyeblink training program; the others lounged in their home cages. After four or five days of training, we found that the rats that had learned to time their blink properly retained more BrdU-labeled neurons in the hippocampus than did the animals that had simply remained in their cages. We concluded that learning this task rescued cells that would otherwise have died. In the animals that received no training, very few of the newborn cells that had been labeled with BrdU at the start of the experiment could be seen at the end. And the better the animal learned, the more new neurons it retained. The same thing happens in animals that have learned to navigate a maze.

When we first started doing the eyeblink studies in the late 1990s, we examined the effects of training in animals that had learned well: in other words, rats that learned to blink within, say, 50 milliseconds of the eyelid stimulation—and did so in more than 60 percent of the trials. More recently, we asked whether animals that failed to learn—or that learned poorly—also retained new neurons after training. They did not. In studies published in 2007, rats that went through some 800 trials but never learned to anticipate the eyelid stimulation had just as few new neurons as the animals that never left their cages.

VIEWING NEW NEURONS

The chemical BrdU marks cells that are born after an animal has been exposed to the substance. The image below highlights one newborn cell—the BrdU shows up as red, and the green peeking through identifies the cell as a neuron. Mature neurons surround the new one.



We also conducted eyeblink experiments in which we limited the animals' opportunity to learn. This time we gave rats only one day—200 trials—to get it right. In this situation, some animals learned to anticipate the stimulus, and others did not. Again, the rats that learned retained more of the new neurons than the rats that did not, even though all went through the same training. These data imply that it is the process of learning—and not simply the exercise of training or exposure to a different cage or a different routine—that rescues new neurons from death.

No Pain, No Gain

Although learning must occur if newborn hippocampal neurons are to survive, not all types of learning work. For example, training an animal to swim over to a platform that is visible in a pool of water does not enhance cell survival. Nor does training an animal to recognize that two stimuli, such as a tone and an eyeblink stimulus, occur almost simultaneously.

The reason these tasks fail to rescue new cells from death, we surmise, is that they do not require much thought. Swimming to a visible platform is something rats do readily. After all, they do not want to drown. And if eyelid stimulation overlaps in time with a tone, the animals do not need to form a memory trace of an event that happened in the past—the sound of the tone—to help them predict when the eyeblink stimulus will occur. They simply respond when they hear the sound.

We think that the tasks that rescue the most new neurons are the ones that are hardest to learn, requiring the most mental effort to master. To test this hypothesis, we took a task that is a bit of a no-brainer and made it a little more challenging. We started with the easy eyeblink task, in which the tone precedes but still overlaps in time with the eyelid stimulation. Learning that connection, as indicated above, does not typically rescue new neurons. Then we made this task more challenging by greatly extending the duration of the tone so that now the stimulus arrived toward the end of a very long sound.

Learning when to blink in this task is more difficult than in the easy test, because in this case blinking soon after the tone begins, like runners taking off after hearing the starting pistol, is not the correct response. The task is also more difficult than the standard, 500-millisecond trace test because the animal cannot use the

It appears there is a critical window of time in which learning can save new neurons.

end of the tone as a signal to “get ready.” Rather the rat must keep track of exactly when the tone started and estimate when the eyelid stimulation will occur—a real challenge for all animals, including humans. And we found that this challenge rescues as many, and sometimes more, new neurons than does the standard trace conditioning task.

Interestingly enough, among the animals that learned in our conditioning tasks those that were a bit slow—in that they required more trials to learn how to master a task—ended up with more new neurons than animals that learned fast. Thus, it seems that new neurons in the hippocampus respond best to learning that requires a concerted effort.

Timing Counts

Why effortful learning should be critical is not clear. One theory is that tasks requiring more thought—or taking longer periods of training to learn—activate more vigorously the networks of hippocampal nerve cells that include these newborn neurons, and that such activation is key. I tend to favor this hypothesis for a couple of reasons.

First, a number of investigators have demonstrated that tasks involving learning, such as the classical eye-blink conditioning test, generally increase the excitability of neurons in

the hippocampus, making them become much more active. Furthermore, this hippocampal hustle and bustle goes hand in hand with learning: the animals that show the most activation are the ones that best learn the task.

Next, it appears there is a critical window of time in which learning can save newborn neurons—in rodents, between about one week and two weeks after the cells arise. One recent study in rats reported, for instance, that learning can rescue cells when the cells are seven to 10 days old. Training that occurs after that time is too late: the neurons are already dying off. And training before that time is too early to help. This learning window corresponds to the period when these newborn cells, which start life unspecialized, begin to differentiate into neurons—sprouting signal-detecting dendrites (which receive impulses from other parts of the brain) and axons (which carry messages to a neighboring region of the hippocampus called CA3). Around this time they also begin to re-



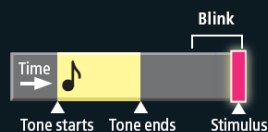
[LEARNING TESTS]

WHAT RAT STUDIES REVEALED

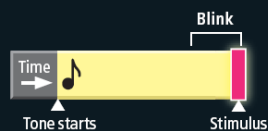
The author and her colleagues relied on “eyeblink conditioning” experiments to discover that working hard to learn something enhances the survival of new neurons. They began with a classical form of the experiment (*top*), in which an animal hears a tone that is followed half a second later by a stimulus that will make it blink. After several hundred trials, most animals learn to blink just before the stimulus arrives. Because the tone and the blink-inducing stimulus are separated in time, figuring out when to blink is difficult; this task rescues a large fraction of newborn neurons.

Rats master readily an easier version of the test—in which the blink stimulus overlaps with the tone (*middle*); this task does not enhance survival of new neurons. Making conditions more challenging—by having the rat wait much longer before the stimulus arrives (*bottom*)—rescues more neurons than even the classical approach does.

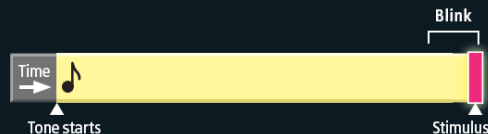
CLASSICAL “TRACE” CONDITIONING



DELAY CONDITIONING



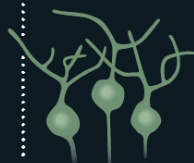
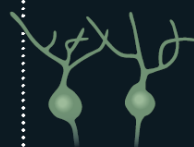
LONG-DELAY CONDITIONING



Difficulty



Neurons rescued

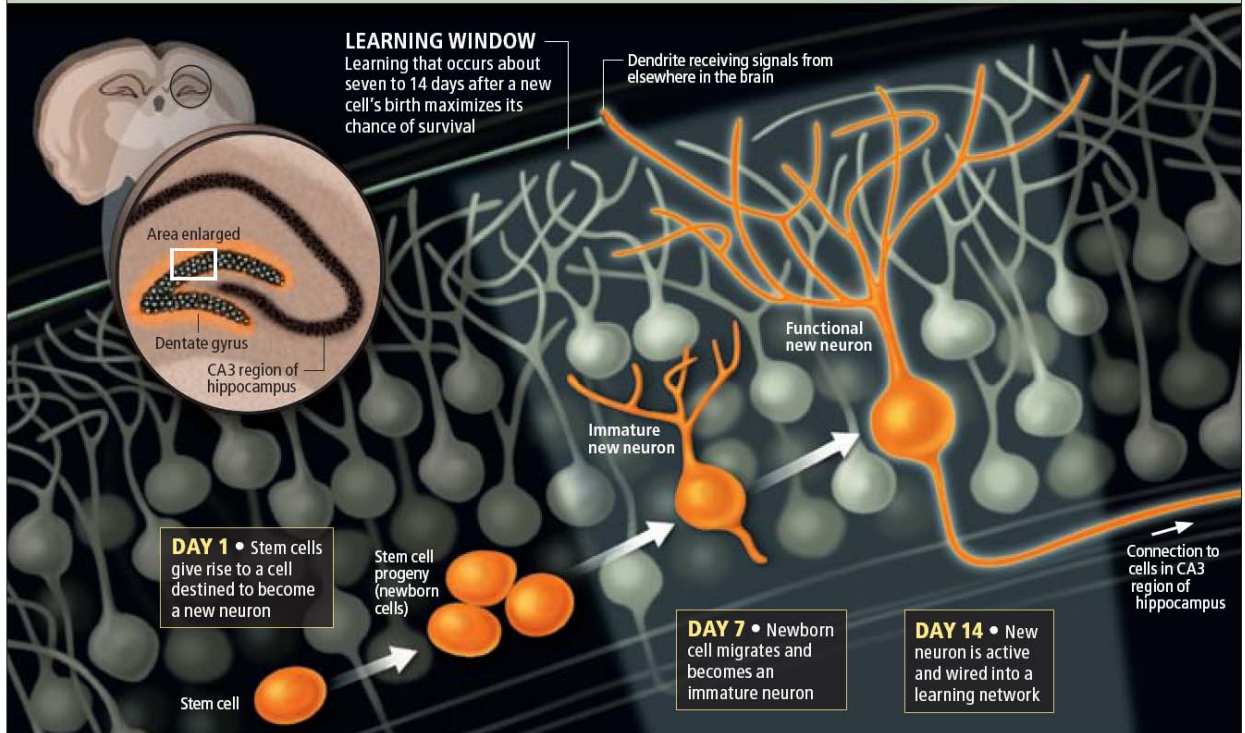


NIGEL CATTUN/Photo Researchers, Inc. (rat); JEN CHRISTIANSEN (illustrations)

HOW LEARNING HELPS TO SAVE NEW NEURONS

During their first week of life, newborn hippocampal cells migrate from the edge of the dentate gyrus in to a deeper area, where they mature and become wired into a network of neurons. Learning that occurs when the cells are between about one to two weeks old enhances their

survival—perhaps exerting this effect by stimulating existing neurons, which in turn release signals that foster maturation of young cells. In the absence of learning during the maturation period, most new hippocampal cells will die.



spond appropriately to certain neurotransmitters—the chemicals that carry communications between nerve cells.

These observations suggest that the new cells must be somewhat mature and wired into networks with other neurons in the brain before they can respond to learning. When learning is difficult, neurons throughout the hippocampus—including the new recruits—are fully engaged. And these recruits survive. But if the animal is not challenged, the new neurons lack the stimulation they need to survive and then simply fade away.

What Do They Do?

So thousands of new cells arise in the hippocampus every day, and if an animal is challenged to learn, these cells stay around. But what function do they perform? They cannot, of course, help with learning in real time as they arise. Much learning occurs almost instantaneously (over the course of seconds, if not less). Faced with a new task, the brain cannot

very well wait around a week or so for new neurons to be born, mature and hook up into functional networks before an animal can begin to learn. My colleagues and I suspected that the stockpiled cells influence some aspects of learning later on.

To test that idea, we decided to get rid of newborn brain cells. If these cells become important for learning, we reasoned, animals that lacked them would be less successful students. Of course, excising every single new cell from an animal's brain would be technically impossible. Instead we prevented the cells from being generated in the first place by treating rats for several weeks with a drug called MAM, which stops cells from dividing. Then the animals hit the classroom.

Rats treated with MAM, we found, were poor students in the standard, 500-millisecond trace eyeblink conditioning task. They had a difficult time learning to anticipate the stimulus. Yet the treated animals performed well on many other learning tasks that depend on the

WHAT HELPS, WHAT HURTS

Learning promotes the survival of new neurons but does not affect the number of cells produced. Other interventions, however, have been found to influence the generation of neurons in rodents.

BOOSTERS

Exercise



Antidepressants



Blueberries



BLOCKERS

Alcohol



Nicotine



Could neurogenesis somehow be exploited for preventing or treating disorders that bring about cognitive decline?

hippocampus, such as the Morris water maze. In this task, rats are dropped into a pool of opaque liquid through which they must swim until they find a submerged platform. The walls of the pool are marked with spatial cues that help the animals navigate. Rats bereft of recently born neurons caught on just as quickly as their untreated mates.

In our hands, animals that were treated with MAM also learned to remember the place in which an emotional experience occurred. For example, rats that received a mildly unpleasant stimulus to the foot when placed into a particular cage froze the moment they were put back there. This type of emotional learning, known as contextual fear conditioning, also depends on the hippocampus, but it did not give our treated animals any problems.

All told, the learning abilities of rats with few new neurons were relatively unimpaired. The animals did seem to have trouble learning more difficult associations, such as figuring out that a sound always precedes a stimulation to the eyelid by half a second. We surmise, therefore, that if the new neurons are necessary for learning at all, they come into play only in a select set of situations, apparently those involving some cognitive effort.

Biologically speaking, that kind of specialization makes sense: an animal would not want to rely on producing and developing an entire cohort of new neurons to respond to situations that will affect its immediate survival. So presumably the added cells, once they mature, are used to fine-tune or boost problem-solving skills that already exist. In the lingo of psychology, enhancement of such skills is called “learning to learn.”

What about My Brain?

All the studies discussed thus far were conducted in laboratory animals—either mice or rats. What would happen in humans who did not produce new neurons in the hippocampus? Modern medicine, sadly, provides us with a population of ready-made subjects: people who are undergoing systemic drug treatment (chemotherapy) for cancer. Like treatment with MAM, chemotherapy impairs the cell division required for generating new cells. It is perhaps no coincidence, then, that people who have had chemotherapy often complain that they have trouble learning and remembering things, a syndrome sometimes referred to colloquially as “chemobrain.”

In some ways, the observation fits our animal data. Like rodents who show very mild or limited cognitive impairment after MAM treatment, people undergoing chemotherapy function quite well under most circumstances. They get dressed, go to work, make meals, socialize with friends and family, and otherwise continue to live their lives. Which makes sense. Given the findings in laboratory animals, one would *not* expect profound or pervasive deficits in basic cognitive functions. Rather one would expect selective deficits in more difficult types of learning processes—the kinds of things everyone finds challenging, such as multitasking that calls for juggling multiple projects while trying to process new information.

To establish that neurogenesis plays a role in human learning, investigators need to develop noninvasive methods for detecting new neurons in the living brain, and they need to find reversible ways to prevent the cells’ maturation during the learning process. The former methods are

WHAT’S NEXT?

Much remains to be discovered about how learning affects the survival of new neurons in the hippocampus. First, we would like to determine the molecular mechanisms by which cognitive challenges save new cells. Which neurotransmitters are involved? Which receptor proteins? And when exactly do those mechanisms operate? Does learning help new neurons to become integrated into neuronal networks, or does it promote the survival of those that are already connected? Further, how do neurons produced in the mature brain contribute to the ability to gain knowledge?

Those kinds of studies are being done in animals. But we would also like to understand more about neurogenesis in humans—both in healthy individuals and in people with diseases such as Alzheimer’s.

To do that, we will need noninvasive ways to monitor the birth and death of newborn neurons in the human brain. Armed with that ability, we could begin to address some interesting issues, such as how much neurogenesis goes on in a healthy human brain versus a brain afflicted by Alzheimer’s. Ultimately, we could also examine whether an intervention such as gene therapy could increase the numbers of new neurons generated in the human hippocampus—and whether particular brain-exercising activities would help keep those new neurons around.

—T.S.



being developed, and the latter are likely to be some time off.

Suppose, for the moment, though, that having a ready supply of new neurons on tap does help to keep the human brain intellectually limber. Could neurogenesis, then, somehow be exploited for preventing or treating disorders that bring about cognitive decline?

Consider the case of Alzheimer's, in which degeneration of hippocampal neurons leads to a progressive loss of memory and of learning ability. People with Alzheimer's do continue to produce new neurons, but it seems that many of the cells do not survive to become fully mature. Perhaps the process of neurogenesis and neuronal maturation is impaired in these individuals. Or perhaps the new cells do not survive because the disease hampers the ability to learn.

Yet some findings offer hope, at least for those in the early stages of dementia. As mentioned earlier, studies in healthy animals and people suggest that simple actions such as aerobic exercise can boost the production of new neurons. In addition, antidepressants have been found to be powerful modulators of neurogenesis. And a study in 2007 found that chronic treatment with antidepressants increases daily living and global functioning in patients with Alzheimer's—a hint, at least, that such therapy might promote production and survival of new neurons in patients.

Anecdotal accounts suggest that effortful learning may also help some patients. I recently presented our animal data at a meeting about Alzheimer's and other forms of dementia. The clinicians in the audience were intrigued by our findings indicating that efforts to learn something difficult help to preserve freshly minted nerve cells. They report having seen benefits from such exertions in their patients. And they note that patients who can fully engage themselves in cognitively demanding activities may be able to delay the progression of this mind-robbing disease.

That said, it would be foolish to think that cognitive engagement combined with antidepressants or physical activity could completely reverse the damage done by a disease such as Alzheimer's, which kills many more brain cells than just new ones. It could be, though, that such activities might slow the rate of cognitive decline—in people grappling with degenerative diseases and, perhaps, in all our brains as we grow older.

They say you can't teach an old dog new tricks, and certainly as adults, many of us find it painful to learn something completely new. But if we want to keep our brains in shape, it probably would not hurt to learn a new language, take up tap dancing, or tackle some fast gaming after your Wii Fit workout—and it might even help. ■

THE MORE CHALLENGING a cognitive task is, the more new neurons it is likely to rescue, if findings from rodents hold true in humans.

➔ MORE TO EXPLORE

Learning Enhances Adult Neurogenesis in the Hippocampal Formation. Elizabeth Gould, Anna Beylin, Patima Tanapat, Alison Reeves and Tracey J. Shors in *Nature Neuroscience*, Vol. 2, No. 3, pages 260–265; March 1999.

Neurogenesis in the Adult Is Involved in the Formation of Trace Memories. Tracey J. Shors, George Miesegages, Anna Beylin, Mingrui Zhao, Tracy Rydel and Elizabeth Gould in *Nature*, Vol. 410, pages 372–376; March 15, 2001.

Neurogenesis, Learning and Associative Strength. Jaylyn Waddell and Tracey J. Shors in *European Journal of Neuroscience*, Vol. 27, No. 11, pages 3020–3028; June 2008.