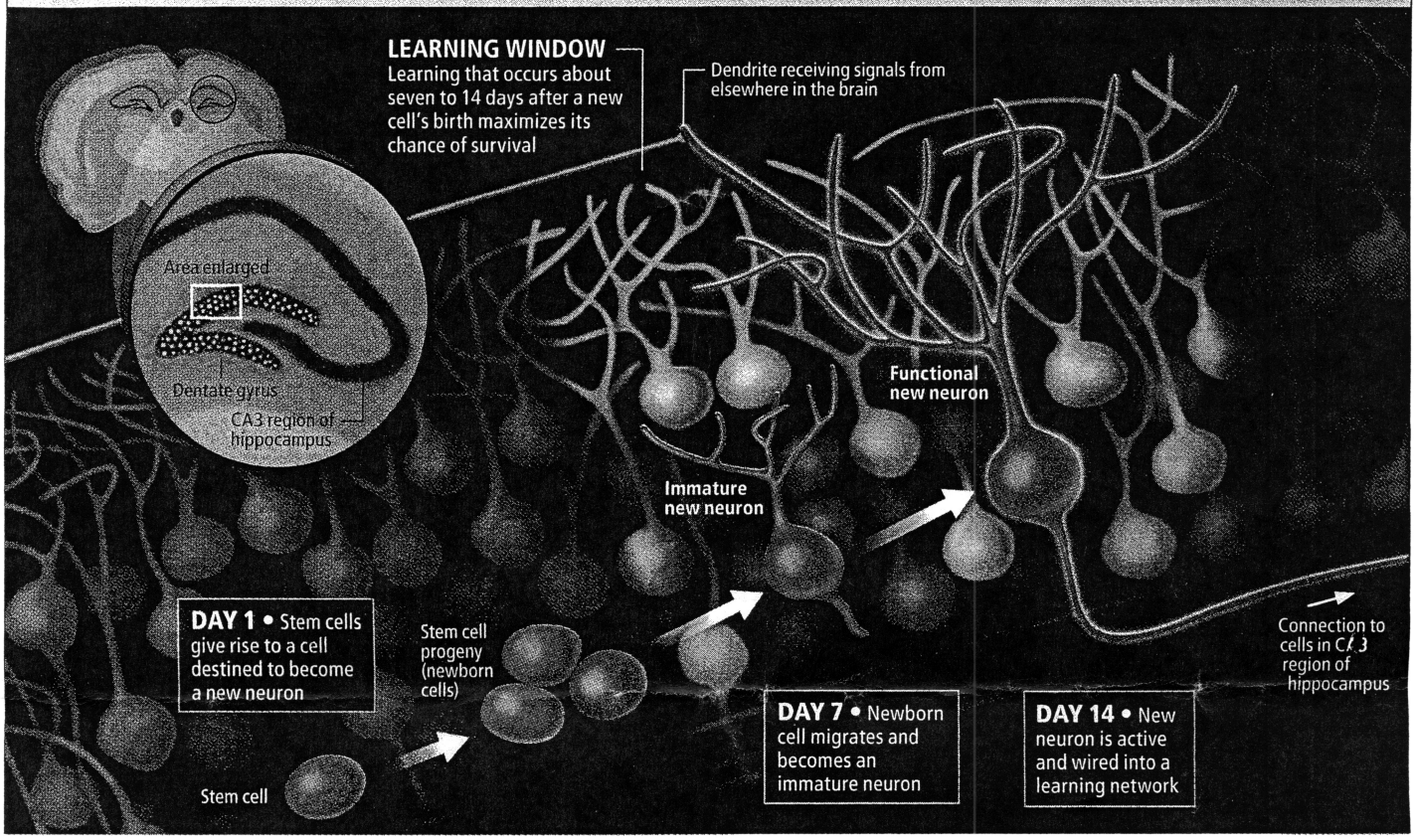
[HYPOTHESIS]

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.



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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?

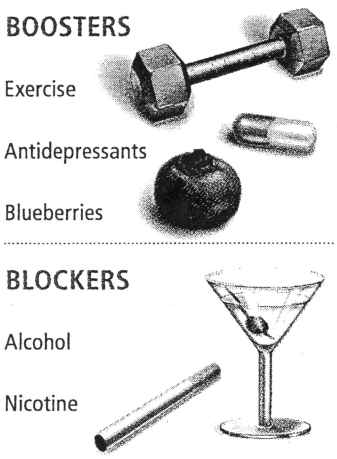
So thousands of new cells arise in the hippocampus every day, and if an animal is challenged to learn, these cells stay around. But what function do they perform? They cannot, of course, help with learning in real time as they arise. Much learning occurs almost instantaneously (over the course of seconds,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



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."

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

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.*

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