NEW FOR NEW NEURONS FOR MEMORIES

HOW DOES THE BRAIN FORM NEW MEMORIES WITHOUT EVER FILLING UP? SCIENTISTS TURN TO THE YOUNGEST NEURONS FOR ANSWERS

BY WILLIAM SKAGGS

Clusters of stem cells, similar to the one above, can give rise to new brain cells.
For many years scientists believed that you were born with all the neurons you would ever get. The evidence for this dogma seemed strong: neuroanatomists in the early 20th century had identified immature neurons under the microscope but only in the brains of mammalian embryos and fetuses, never after birth.

We now know that the truth is not quite so simple. By radioactively labeling DNA, researchers gradually began to find exceptions to the rule against new neurons in the adult brain. Today scientists have identified two small regions where neurogenesis, or the birth of new neurons, continues throughout life: the olfactory bulb and the hippocampus. The former area is part of the brain's odor-discrimination system, so neurons there likely participate in this process. But the hippocampus has a much broader function. It gives us memory.

The discovery of nascent neurons in the adult human hippocampus, first reported in 1998, came as a surprise to many in the field. Although sprouting new brain cells may sound useful, the costs are potentially high. After all, space within the skull is finite, and newcomers could disrupt the delicate neural networks that store knowledge.

Neuroscientists now suspect that neurons born in the hippocampus help the brain create and sift through the millions of memories we form over the course of a lifetime. If this is true, neurogenesis might solve a puzzle that has perplexed memory researchers for more than 60 years: how our brain keeps separate memories of similar events. These discoveries may ultimately reveal not only how we recall the episodes of our lives but also how we can preserve our brain's powerful record-keeping faculties despite the inevitable decline of aging.

**Making Memories**

In 1949 Canadian psychologist Donald O. Hebb proposed a theory of memory that would come to dominate the field. Hebb suggested that each neuron in the cerebral cortex, the brain's large outer layer essential to thought and intelligence, encodes some feature of the world and becomes active whenever that feature is present. He also noted that every brain cell is connected to many others by links called synapses. His idea was that we encode memories by creating alliances between groups of neurons. When two connected neurons are active at the same time, the synapses holding them together grow stronger. In other words, "cells that fire together wire together."

To understand how this works, imagine how a memory might map onto a set of interconnected neurons. Say you take a trip every summer. On one occasion, you pack your backpack for a journey to the mountains, including your favorite book. The

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**FAST FACTS**

**EXPANDING MEMORY'S STORES**

1. Neurogenesis, or the growth of new neurons, occurs in two regions of the adult brain: the hippocampus and the olfactory bulb.
2. Researchers suspect that the new brain cells in the hippocampus facilitate the storage and separation of memories.
3. Experimental evidence supports the idea that new neurons aid in creating memories, whereas older neurons help you recall earlier episodes.
features of the event—backpack, mountains, book—will each map onto separate neurons in the cortex. As you unpack the book at your alpine campsite one evening, those neurons fire together, bolstering the connections between the three elements and thereby storing the memory.

In reality, the brain uses far more than three neurons and their connections to encode memories, but the principle is the same. If any one of the neurons in the stored memory were to become active later, an electrical impulse would propagate to the other cells in that network. As a result, the neurons representing all three features would fire, encoding the full memory. This process, called pattern completion, is the way that memories are retrieved, according to Hebb's theory. It explains how merely glimpsing the backpack after the trip can conjure up mountain vistas in your mind's eye.

Yet this explanation of memory has a problem: What happens when features from different memories overlap? Suppose, for example, that on a second summer vacation you pack the same backpack, but this time with a newspaper for a trip to the beach. For this memory to be stored, neurons relevant to the backpack, beach and newspaper will need to connect. When you recall the episode, the attempt to perform pattern completion will activate the backpack neuron and send a burst of activity through both sets of connections. The memories of the two trips would become conflated. This phenomenon is known as interference. It is an inevitable consequence of Hebb's hypothesis and is not easy to fix.

Neuroscientists have spent decades devising ways around the interference problem. One simple solution is to minimize the number of shared features in the memories to be stored. The most straightforward way of doing that is to use features that are very specific. For example, instead of just storing the memory of a book in your backpack, you mentally classify it as a copy of James Joyce's *Ulysses* and the newspaper from the beach trip as the *New York Times*.

Yet this work-around has its drawbacks. The brain learns about the world by detecting patterns: consistent relations among sets of features. For example, you may come to appreciate sunblock after sustaining multiple burns on beach trips in which you neglected to pack...
Building Brain Cells

Researchers now suspect that newborn brain cells help to distinguish between memories whose features are stored in the cerebral cortex. This process could be the long-sought solution to a memory mystery.

Neurogenesis to the Rescue

Forty years after Hebb proposed his theory, three neuroscientists came up with an alternative approach. James L. McClelland and Randall C. O’Reilly, then at Carnegie Mellon University, and Bruce L. McNaughton, then at the University of Arizona, were pondering the two brain regions involved in memory—the cerebral cortex and the hippocampus—when it dawned on them that the brain might resolve the conflict between learning and memory by separating the two processes. They suggested that to prevent the interference problem, the cerebral cortex would help us forge connections and the hippocampus would focus on filing away distinct memories. They dubbed this hypothesis “complementary learning systems.”

Their basic idea hinges on adding another set of neurons to the memory network formed in a Hebb-style trip to the beach. Each of these additional cells tags a small set of memories. Let’s say you embark on yet another trip with your trusty backpack. Instead of linking the features of all backpack vacations to one another, the brain allocates a single memory neuron for the latest adventure, and the trip’s salient features all link to it. That single memory cell would reside in your hippocampus, whereas the feature-related cells would dwell in the cerebral cortex. Moreover, the cells involved in memory in the hippocampus fire only in discrete groups because they inhibit or compete with one another. In consequence, only one memory can be active at a given time.

When McClelland and his colleagues advanced their theory, evidence for fledging neurons was still weak, but within a decade this had changed. In 2006 neuroscientists Fred H. Gage of the Salk Institute for Biological Studies, Gerd Kempermann, then at the Max Delbrück Center for Molecular Medicine in Berlin, and others recognized the potential importance of new neurons in the hippocampus. In two separate papers, they proposed that neurogenesis might be the brain’s way of continually expanding its stores of memory.

For one thing, they reasoned, the new cells can more easily connect to other neurons than older cells. A second clue is that young neurons have a more uncertain fate than older neurons do. Many of these new cells die in their youth, but their probability of survival improves when an individual is forced to learn unfamiliar tasks—a prime opportunity to form new memories. In fact, as Rutgers University neuroscientist Tracey J. Shors observed in 1999, the rate of neurogenesis can increase during learning exercises. Thus emerged a radical new idea in the science of memory. When the brain needs to create mental records, it might just grow more neurons.

sunblock. If these features are categorized so specifically that they rarely recur, the memories to which they belong will offer no basis for learning. The importance of sunscreen, for instance, applies to every sunny day—regardless of the beach you visit or brand of lotion.

These constraints seem to pit memory and learning against each other. Optimizing the brain for memory requires minimizing overlap, whereas learning depends on easy access to common elements so we can make associations.

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WILLIAM SKAGGS is a science writer and neuroscientist whose experimental work has focused on the role of the hippocampus in learning, memory and spatial navigation.
A radical new idea in the science of memory emerged: when the brain needs to create mental records, it might just grow new neurons.

The Brain Cell Bank

To test this idea, scientists set out to obliterate neurogenesis in rodents to see if its absence might reveal its function. They did so in inventive ways—manipulating the genes of mice and rats, exposing them to powerful x-rays and administering cell-destroying drugs. As predicted, studies have found that such meddling impairs the animals’ capacity to identify subtle differences between situations. Moreover, boosting neurogenesis appears to help them discriminate more deftly between very similar scenarios.

Neuroscientist Susumu Tonegawa of the Massachusetts Institute of Technology took these findings a step further in 2012. Tonegawa’s laboratory developed a genetically modified mouse in which old neurons were rendered inactive while new neurons remained functional. These mice then faced a series of new challenges, such as locating food pellets in a maze. The researchers found that the modified mice were better than the control mice at solving new puzzles but worse than the controls at recalling the solution to a maze from several weeks earlier. In other words, these neurons were temporarily tied to specific memories. The new cells offered an advantage in learning and recalling only recent concepts, whereas older cells aided the recollection of earlier episodes.

New brain cells may be equally significant in humans. In 2013 Jonas Frisén of the Karolinska Institute in Stockholm and his colleagues found that the rate of daily neurogenesis in humans—some 1,400 cells a day—is comparable to that of a mouse, which supports the idea that the findings in animal models could apply to people.

If neurogenesis does indeed supply the neurons needed for creating memories, studying the phenomenon could provide new approaches for understanding our powers of recollection. Studies of the maturing brain suggest dysfunction in the dentate gyrus—the part of the hippocampus where neurons are born—is associated with certain forms of cognitive decline. It is also well established that new nerve cells blossom rapidly in our early years but that this rate falls with age—although the exact cause is unclear. Harnessing the power of neurogenesis could therefore benefit burgeoning elderly populations.

For example, we already know of a few ways to boost the growth of new neurons. The techniques are familiar hallmarks of a healthy way of life. Both Gage and Kempermann have found that physical exercise and ongoing learning can increase neurogenesis. More recently, they have confirmed that combining cognitive challenges with physical activity can encourage neuronal growth in older rodent brains. Perhaps a regimen of regular exercise, coupled with learning a new skill, could yield comparable benefits in humans.

In the opposite direction, severe and continued stress, alcohol and some drugs may hinder neurogenesis. Although the precise mechanisms remain a mystery, these findings hint that making healthful choices could prolong and improve your brain’s memory-building abilities.

More invasive techniques could also apply. In 2011 a research group led by neuroscientist Paul W. Frankland of the University of Toronto found that deep-brain stimulation could improve neurogenesis and subsequent performance on a spatial memory task. Other methods might one day mimic the conditions of neurogenesis, such as using stem cells to replace hippocampal neurons lost to aging.

Although many details of the brain’s vast archival process are still unknown, even a glimpse of these intricate activities can reveal their extraordinary sophistication. In helping you store, save and recall a vast array of experiences, your brain’s newest neurons might be the glue that connects your present with your past. M

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