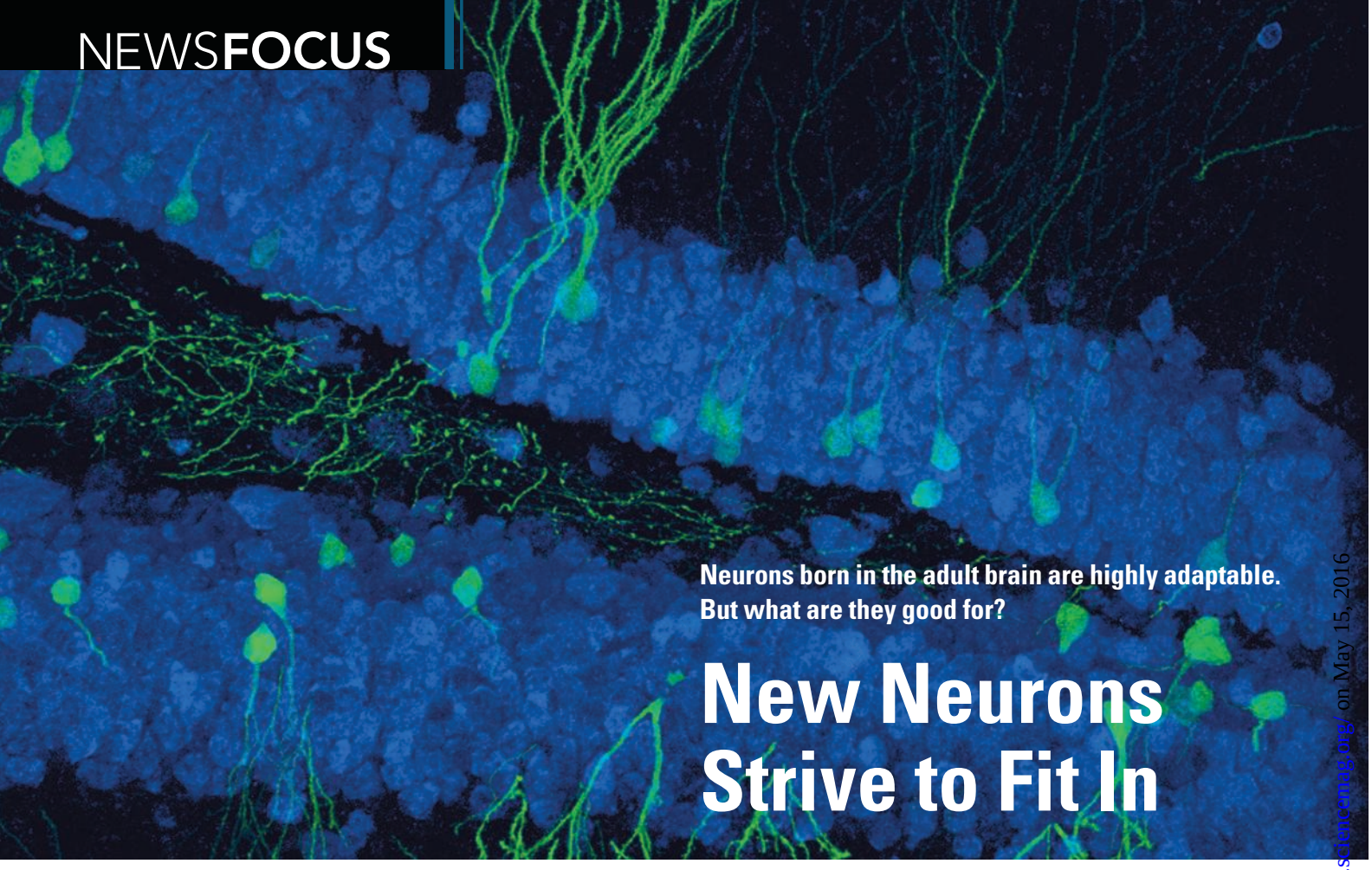

Neurons born in the adult brain are highly adaptable. But what are they good for?

New Neurons Strive to Fit In

IT'S NEVER EASY BEING THE NEW KID IN class. By the time you arrive on the scene, the social network is well-established. All the others know their places and have forged connections with one another. Act shy and you'll never fit in. You've got to be outgoing if you want to survive.

The cruel social dynamics of the schoolyard have a parallel in the daunting situation faced by newborn neurons in the mature brain. Now that the long-held dogma that the brains of adult mammals don't make new neurons has been refuted, neuroscientists are trying to figure out how adult-born neurons integrate into neural circuits that are already up and running. The picture of new neurons that's emerging is one of social gadflies rather than wallflowers.

Compared to older, established neurons, the newbies are hyperexcitable and adaptable. They act in many ways like neurons in the embryonic brain, readily making new synapses with other neurons and changing the strength of these connections. These characteristics seem to mesh well with the popular notion that new neurons play a role in the kinds of brain plasticity that underlie learning and memory. One recent study, for example, suggests that new neurons help adult mice learn novel odors.

"I think there's been huge progress" in understanding how new neurons mature and make working connections with other neurons, says Hongjun Song of Johns Hopkins University in Baltimore, Maryland.

Research on new neurons should ultimately reveal whether aberrations in adult neurogenesis—already described in disorders as diverse as epilepsy, depression, and drug addiction—are a cause or effect of such conditions. Such work also may have implications for future stem cell therapies for brain disorders.

Learning and memory

For decades, neuroscientists thought that the brain was one of the few mammalian organs that doesn't replenish its cells throughout life. This idea fell to pieces in the 1990s when researchers documented newborn neurons in the brains of adult mice and then in human brains. In particular, the hippocampus, a key memory center, proved to be a relative hot spot for neurogenesis in rodents and people. That finding, along with previous work demonstrating neurogenesis in the hippocampi of seed-caching birds and in regions of the songbird brain that are involved in song learning, suggested that new neurons might play a role in learning and memory (*Science*, 3 January 2003, p. 32).

That suggestion has been strengthened by several studies that demonstrated learning impairments in animals whose brains were treated with radiation to kill off dividing cells, or with cancer drugs that do the same. But although the low doses used in these experiments didn't make the animals overtly sick, the treatments may have had effects on the brain other than stopping neurogenesis—making it hard to know the true cause of the learning deficits. To clinch the case, researchers would like to find a way to stop neurogenesis cold without interfering with anything else. New genetic tricks may provide a way to do that.

In October 2005, Fred Gage, a neuroscientist at the Salk Institute for Biological Studies in La Jolla, California, and colleagues reported in *Nature* that Wnt proteins, key regulators of neural stem cells during development, also regulate neurogenesis in the adult hippocampus. When the researchers injected a virus carrying a gene that enhances Wnt activity into the hippocampi of mature mice, neurogenesis increased. A virus carrying another gene that reduces Wnt activity abolished neurogenesis almost completely.

Gage's team is now using this approach to investigate the link between neurogenesis and learning. At a satellite symposium at the annual meeting of the Society for Neuroscience last November in Washington, D.C., Gage's postdoc Sebastian Jessberger presented preliminary results from experiments in which he injected the virus that interferes

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Published by AAAS

Meet the new kids. Adult-born neurons (green) have to carve out a niche among more established cells (blue) in the mouse hippocampus.

with Wnt signaling into the hippocampi of adult rats. These rats performed much worse than untreated rats on a task that tested their recognition of an object they'd seen a week earlier, suggesting that neurogenesis indeed plays a role in long-term memory.

"This is a cleaner approach" to turning off neurogenesis than radiation or chemotherapy drugs, says Jeffrey Macklis, a neuroscientist at Harvard Medical School in Boston. Still, he and others caution that manipulating Wnt could have other effects on the adult brain.

Macklis, along with postdoc Sanjay Magavi and other colleagues, recently reported a different approach to investigating the role of new neurons. Rather than attempting to eliminate neurogenesis, the team studied the behavior of newborn neurons in the olfactory bulb of adult mice by examining the expression of so-called immediate early genes (IEGs), which increases in active neurons. It's very difficult to directly record the electrical activity of olfactory bulb neurons, Macklis says, but IEG expression is widely regarded as a reliable indicator of neural activity.

Olfactory bulb neurons begin responding to odors about 2 weeks after they are born, the team reported in the 16 November *Journal of Neuroscience*. Even though the adult-born neurons are a tiny minority of neurons in the olfactory bulb, they responded to novel odors in larger numbers than did mature neurons. And this difference became even more pronounced with repeated exposures to a once-novel odor: The number of responsive adult-born neurons nearly doubled in a 7-week period, whereas the number of responsive mature neurons declined. The findings suggest that new neurons are essential for learning new odors, Macklis says: "We think it's the first direct evidence of a function of adult-born neurons."

"It's a great paper," says Gerd Kempermann, who studies adult neurogenesis at the Max Delbrück Center for Molecular Medicine in Berlin, Germany. The work shows that new neurons are integrated into the olfactory bulb in a meaningful way and may have a function distinct from that of older neurons, Kempermann says.

Additional evidence supports the learning connection. In 2004, a team led by Josef Bischofberger at Freiburg University in Germany reported in *Nature* that synapses formed by newborn neurons in the adult hippocampus are more malleable than those of more mature neurons. In experiments with slices of hippocampal tissue from adult rats, the team found that new neurons are more excitable than old neurons and can more readily strengthen or weaken their synaptic connections with other neurons—just the type of plasticity neuroscientists think underlies learning and memory.

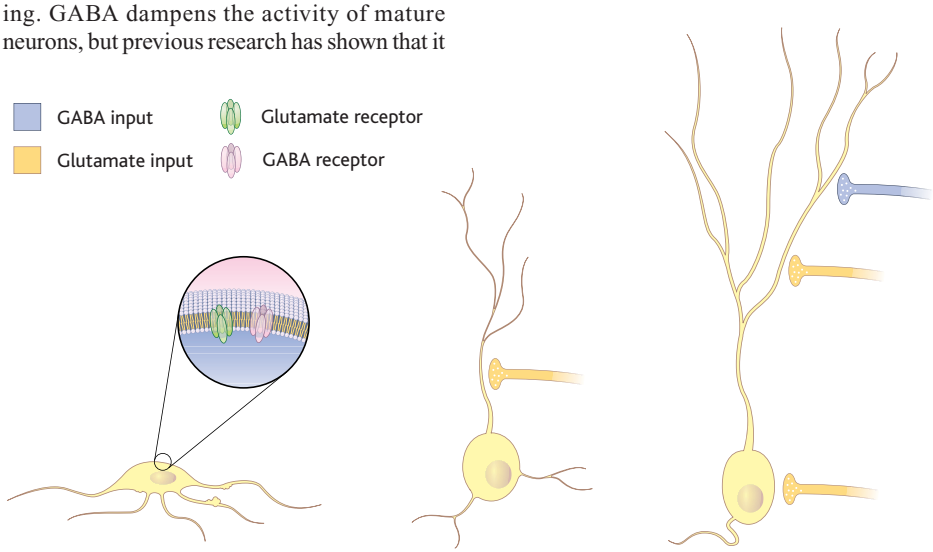
Only the active survive

At a symposium at the neuroscience meeting, Bischofberger and others presented additional details on the physiology of new neurons that suggest activity is a key to survival. Adult-born neurons that don't pick up on the buzz of electrical activity among their neighbors and add something useful to the conversation are less likely to integrate into the existing neural circuitry. And failure to fit in can be lethal to those new neurons, just as it can be in the developing brain, where neural activity helps weed out bad connections.

Song presented work, also published in the 2 February issue of *Nature*, suggesting that the neurotransmitter γ-aminobutyric acid (GABA) plays an important role in this selective weeding. GABA dampens the activity of mature neurons, but previous research has shown that it has the opposite effect on newborn embryonic neurons. Song's team found that GABA also excites new neurons in the hippocampuses of adult mice even before they've formed synapses with other neurons, presumably because receptors on the new cells' surface detect GABA that leaks out from the synaptic connections between older neurons. In essence, the newcomers eavesdrop on the conversations of their elders.

Song's team prevented GABA from exciting newborn neurons by injecting a short piece of RNA that blocked expression of a chloride channel on the neurons' surfaces. This changed the cells' physiology in a way that made GABA inhibitory, as it is in mature neurons. The altered neurons soon developed withered dendrites, the branches that receive inputs from other neurons. If they aren't excited by GABA, the new neurons can't integrate, Song says: "They don't have dendrites, they don't form synapses, and they die."

Another study presented at the symposium suggested that adult-born neurons compete to survive in their new environment—another parallel to brain development. Ayumu Tashiro, a postdoc working with Gage at the Salk Institute, described experiments on NMDA receptors, cell surface proteins sensitive to the neurotransmitter glutamate. Many experiments have implicated NMDA receptors in neuron survival in the developing brain. Tashiro used a combination of genetic manipulations to inactivate NMDA receptors in about 10% of new neurons in the hippocampi of adult mice. He also genetically labeled the cells so he could later determine how well they'd integrated into the hippocampus.

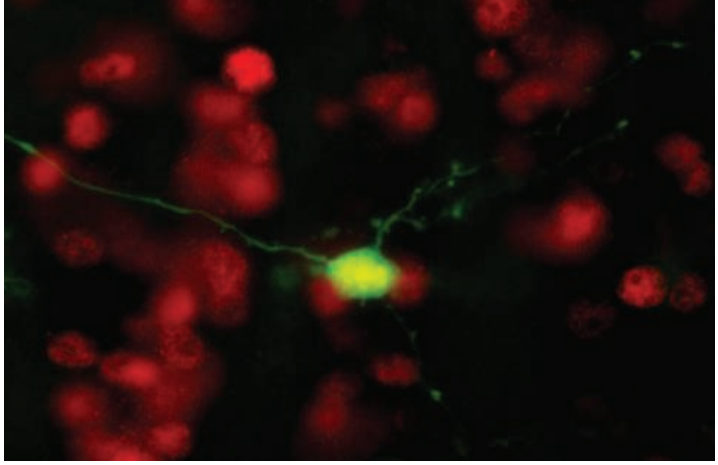


Growing up. Neurons born in the adult mouse hippocampus mature in about 4 weeks and go through a series of stages that mirrors the development of embryonic neurons (*left to right*). Although they initially respond to the neurotransmitters GABA and glutamate, only later do they form synapses with older neurons and produce spikes of electrical activity.

Not very well, it turns out. Many of the altered neurons appeared to be dying 2 to 3 weeks after they were born, Tashiro reported, suggesting that NMDA receptor activation, presumably via synaptic connections from more established neurons, is necessary for survival. Additional work indicated that it's not the overall amount of NMDA receptor activation that counts but the amount relative to other neurons. When Tashiro injected a drug that reduced NMDA receptor activity across the hippocampus, putting the altered new neurons on more equal footing, more of them survived. The bottom line seems to be that new neurons that get good connections survive, whereas those that don't perish—just as they do in the developing brain.

Another study that draws strong parallels to brain development comes from Alejandro

ILLUSTRATION: C. BICKEL/*SCIENCE*, ADAPTED FROM ESPÓSITO *ET AL.*, *JOURNAL OF NEUROSCIENCE* (2 NOVEMBER 2005)



Sniff, sniff. Adult-born neurons (green) in the olfactory bulbs of mice respond preferentially to novel odors.

Schinder and colleagues at the Fundación Instituto Leloir in Buenos Aires, Argentina. In the 2 November *Journal of Neuroscience*, the team painted a detailed picture of the maturation of adult-born hippocampal neurons. They monitored the movement and changing shapes of the neurons by labeling them with a fluorescent dye and examined how their electrical activity and responsiveness to different neurotransmitters shifted with time. "The [maturation] sequence is nearly identical" to what happens during embryonic development, Schinder says.

"During early development, there's a critical period where neurons are capable of a greater degree of plasticity," says Linda Overstreet Wadiche, a neuroscientist at Oregon Health & Science University in Portland. Much of the new work is converging on the idea that adult-born neurons recapture this youthful flexibility, Wadiche says: "It's not just that [adult] neurogenesis is adding new cells; it's adding a new type of neuron."

Kempermann theorizes that new neurons optimize the hippocampus to process novel and complex stimuli. Based on his data, Macklis suspects a similar role for new neurons in the olfactory bulb. Both brain regions are ancient structures that help animals deal with novel and complex features of their surroundings, Macklis notes. New neurons may give these parts of the brain additional plasticity that couldn't be accomplished by tweaking existing synapses, as happens throughout the brain. "It makes sense evolutionarily that one would want to … allow whole new circuits to form by the integration of a steady stream of new neurons," Macklis says.

New neurons and disease

A better understanding of the physiology of new neurons in healthy brains should help researchers evaluate the role of adult neurogenesis in the diseased brain as well. An uptick in neurogenesis, perhaps as a compensatory response, has been proposed to accompany several types of brain injury, including stroke and neurodegenerative disorders such as Alzheimer's and Parkinson's disease. There's also evidence that depression reduces neurogenesis and that antidepressant drugs work by promoting it, at least in rodents (*Science*, 8 August 2003, p. 757). Yet little is known about whether newborn neurons in diseased brains successfully integrate into existing circuitry, let alone whether they could be exploited to restore the function of damaged circuits.

In some cases, they may even compound the problem. At the Society for Neuroscience meeting, Wadiche reported that epileptic seizures speed up the maturation of new neurons in adult mice, prompting the cells to form synapses more quickly than usual, and in some cases, to form inappropriate contacts with other neurons. It's a nice demonstration of how pathology can affect new neuron integration, says Song.

Figuring out what new neurons have to do to integrate into the adult brain could have important implications for researchers trying to maximize the brain's limited innate capacity to heal itself or design stem cell therapies for brain injury and disease. Based on what's known so far, however, it may be naïve to expect that just plopping some neural stem cells down will do the trick, says Macklis: "If we're going to repair neural circuits, we're going to have to very carefully activate new neurons so that they're incorporating into the existing circuits."

–GREG MILLER

SCIENTIFIC COMMUNITY

Scientists' Suicides Prompt Soul-Searching in China

A spate of deaths has raised questions about whether China's scientific community is piling too much stress on young researchers

BEIJING—Mao Guangjun seemed destined for scientific stardom. In September 2001, the 32-year-old theoretical physicist, just home after a postdoc stint in Japan, signed a 3-year contract as a full professor with the Institute of High Energy Physics (IHEP) of the Chinese Academy of Sciences (CAS) in Beijing. However, his personal and professional life soon soured, and in 2004, IHEP declined to renew his contract. He landed a position at another university but would never report for duty: On 14 September 2005, Mao, 36, jumped to his death from the fourth floor of his apartment complex.

Stress relief. Some young scientists need help to cope with increased pressures, says Li Daguang.

Although academic stresses weighed on Mao, family members and colleagues told *Science*, no one can say for certain whether those pressures caused him to take his own life; he did not leave a suicide note. But Mao's death and those of a handful of other young researchers in recent months have lifted the lid on simmering discontent among young scientists in China. Their concern is that some institutions, in pressing to gain on the West, are making life intolerable for vulnerable researchers. That's a hot topic these days on Web sites frequented by Chinese academics, including www.sohu.com, a Beijing-based information clearinghouse, www.xys.org, a U.S.-based site aiming to expose fraudulent academic behavior in China, and www.chinahexie.org, an information site run out of China's Guangdong Province. In the words of one anonymous researcher on China Hexie, "Mao Guangjun's death reflects the flaws of the current management system for Chinese intellectuals."

The wave of introspection has prompted some academics to question China's newfound obsession with a sacred cow of Western science, publish-or-perish. And the suicides have

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Greg Miller (February 17, 2006)
Science **311** (5763), 938-940. [doi: 10.1126/science.311.5763.938]