

idea in [adult] cortex would have been that things are quite stable," he says. "If it's really true that synapses are turning over at the rate they suspect, it's remarkable."

Svoboda's group suggests that synaptic turnover serves an important purpose. When the researchers trimmed every other whisker on some mice—a manipulation shown previously to change which neurons in the barrel cortex respond to which whiskers—the daily turnover rate jumped to about 30%, which suggests that spine turnover is important for this rewiring.

The finding adds to evidence that plasticity in the adult brain may require re-running processes such as synapse formation that are common during development, says Kevin Fox, a neuroscientist at Cardiff University in the United Kingdom. "What you do in adults may be on a slower scale or lower key, but when you want to change the circuit, you basically repeat the program."

However, the Gan team's report suggests that the brain is far more stable. The researchers used a similar approach to study neurons in the visual cortex of young and old mice. In 1-month-old juveniles, about 73% of dendritic spines stayed put over a 1-month period. In 4-month-old adults, spines were even more stable: 96% remained in place for a month or more.

The two groups' strikingly different conclusions—20% daily turnover vs. 4% monthly turnover—may be partly the result of differences in their methods, says Stephen Smith, a neuroscientist at Stanford University. For example, barrel cortex and visual cortex may not be equally malleable in adults. Because a mouse is probably more likely to have a whisker chewed off than to suffer damage to its retina, one might expect to see more plasticity in barrel cortex, Smith says.

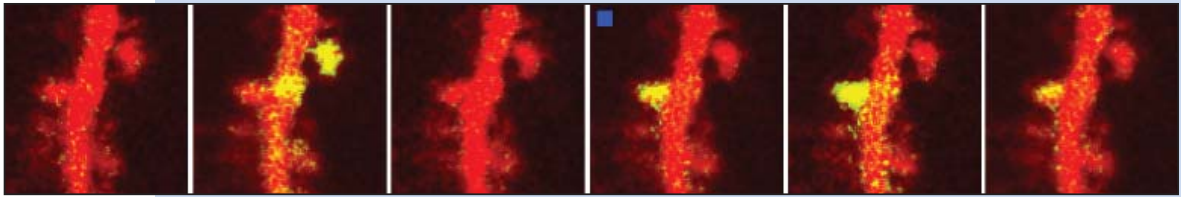
Another key difference may be the way the two groups defined a dendritic spine. Svoboda's group was fairly liberal, classify-

A Wish List for Learning About Learning

Given a magic lamp and an obliging genie, neuroscientists interested in the mechanisms of learning might ask for something like this: a way to visualize individual neurons—any ones they chose—in ultrafine detail, tracking minute changes in the cells' structure and electrical activity. Oh, and they'd want to do this in real time in unanesthetized animals—preferably humans.

Although they'll be kept waiting a while on some of these counts (the last one in particular), several techniques now in the pipeline could greatly expand scientists' ability to image neurons in living animals—particularly in rats and mice, whose brains are organized much like our own.

The degree to which learning in the mature brain depends on physically remodeling the contact points, or synapses, between neurons is a major question in neuroscience (see main text). Researchers have recently found anatomical signs of synapse formation in live mice, but it's difficult to tell whether these correspond to working synapses. Dyes that change color in response to voltage changes or changes in the concentration of calcium ions, both markers of neural activity, could help identify active synapses. Karel Svoboda of Cold Spring Harbor Laboratory in New York has been using such dyes in fruit flies. He and his team would like to use the dyes to follow up on their finding that neurons in the mouse cortex form new synapses with surprising ease. "We'd like to see synapses come online as they're made and see the synap-



Singing synapses. A fluorescent dye sensitive to changing calcium concentrations reveals active synapses.

tic strength," he says. The biggest obstacle is that many of the currently used dyes are toxic or work best at cool temperatures, forming useless clumps at mouse body temperature.

Kinks like this should be worked out in the next few years, but other techniques appear to be farther off. Take selective cell imaging: Researchers have engineered mice that express a fluorescent protein in some neurons, but so far they've had little control over which cells light up. Being able to pick and choose which neurons glow would help them focus on how different components of a given neural circuit respond as an animal learns. Alas, says Svoboda, "there are fundamental genetics problems" in doing this in mice, such as identifying promoters that will drive expression of fluorescent proteins in particular types of cells.

Another item on the wish list is a method that provides a deeper look into the brain, says Wenbiao Gan of New York University. Like Svoboda's group, his team has been using two-photon microscopy, a powerful technique that can peer about half a millimeter into the brain. That's enough to see most of the sheetlike cortex. But researchers would like to be able to trace important changes in deep brain structures, including the hippocampus, a region known to play a crucial role in memory formation.

Help may be on the way. Mark Schnitzer of Lucent Technologies' Bell Laboratories in Murray Hill, New Jersey, has recently developed a fiber-optic "microendoscope" for two-photon imaging that can reach anywhere in a rodent's brain.

One of researchers' deepest desires is to see into the unanesthetized brain. "The real question here is, 'How does the brain work?'" says Stephen Smith of Stanford University in California. And "anesthesia means the brain is not working, or at least it's not working normally." Hoping to break this barrier, Winfried Denk, a co-inventor of two-photon microscopy who is now at the Max Planck Institute for Medical Research in Heidelberg, Germany, has developed a miniature two-photon microscope that can be mounted on the head of an unanesthetized rat. Ultimately, Denk hopes to image activity in the cortical neurons of behaving animals, but he says the system isn't quite there yet.

As all these techniques evolve, they may bring about an optical revolution in neuroscience. And at the very least, they should generate loads of pretty pictures. **—G.M.**

ing all protrusions from the dendrite as spines. In doing so, the researchers included thin, transient structures called filopodia that lack the fully formed "head" of mature spines and are thought to represent tentative or immature connections between neurons. Gan's group excluded filopodia from its analysis. It's not clear that one method is better than the other, Smith says: "It's not a no-brainer to decide how you're going to classify things for

the purpose of this analysis."

Counting only protrusions that form functional synapses might be a reasonable solution, he says, and one that should be feasible in the not-too-distant future with the help of new fluorescent markers (see sidebar). In the meantime, both groups are working on additional experiments that they hope will settle the issue of how stable adult neurons really are. **—GREG MILLER**

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