fewer subjects and cuts down on expensive scanner time. But individual variations in the brain aren't hard to find for those who look.

Rees says his interest was piqued by studies finding that the size of the human primary visual cortex can vary up to threefold. He wondered whether that resulted in differences in vision, an idea his lab has been investigating with a combination of optical illusions and functional magnetic resonance imaging (fMRI). At the end of 2010, Rees's group reported online in *Nature Neuroscience* that people with a smaller visual cortex more strongly experience certain illusions in which the apparent size of an object depends on its visual context. The findings suggest to Rees that even something as basic as how we perceive the world around us varies from person to person in subtle ways that can be traced to variations in brain anatomy.

Richard Haier, a neuroscientist at the University of California, Irvine, is one of the few intrepid scientists who've waded into the potentially touchy realm of individual differences in the brain that influence intelligence. His work, beginning in the late 1980s, has identified a network of regions of parietal and frontal cortex whose anatomy and activity correlates with scores on tests of general intelligence. At the same time, Haier's work suggests that this network isn't identical in all individuals with similar intelligence scores. In other words, smart brains may be built in a variety of ways.

The largest study ever undertaken to look at individual wiring variations in the human brain is the Human Connectome Project, a 5-year, $38.5 million effort funded by the U.S. National Institute of Mental Health. Now in its third year, the project aims to enroll 1200 healthy adults for a battery of behavioral tests and brain scans, including diffusion imaging scans that show connections between regions of the brain. The overall goal is to investigate individual variations in brain structure and activity and how they may correlate with differences in memory, emotion, and other functions, says David Van Essen of Washington University in St. Louis, Missouri, who is one of the project's leaders.

The project will also examine heritability of brain characteristics by enrolling 300 pairs of twins, plus one or more nontwin siblings for each pair. Researchers will collect DNA for genotyping and possibly whole genome sequencing if the cost drops enough by the final year of the project, Van Essen says.

> "I'm confident we'll see interesting individual differences."
>
> —DAVID VAN ESSEN, WASHINGTON UNIVERSITY IN ST. LOUIS

Whether the differences in neural circuitry that make each person unique will be visible at the resolution of MRI scans is an open question. "It's sobering for sure that the resolution is only at the level of a millimeter or two, which means that each voxel contains literally hundreds of thousands of neurons or axons," Van Essen says. (A voxel is the smallest volume of brain tissue discernable in a brain scan.) "But I'm confident we'll see interesting individual differences."

Other researchers are working on far more detailed maps of neural circuitry. Sometimes called microconnectomics, these efforts employ recently developed methods in genetic engineering, automated microscopy, and image analysis to map out the synaptic connections of individual neurons. So far, the approach has been applied only to millimeter-size chunks of tissue in worms and mice, but some researchers see a microconnectome of the human brain as an ultimate if distant goal.

It's not clear what such a circuit diagram would reveal. Proponents think it would explain a great deal about how the brain works and about the nature of individual differences. Critics contend that deciphering brain function from a circuit diagram—no matter how detailed—is like trying to figure out what a computer does by studying its wiring diagram. In both cases, the circuitry may say something about what the machine is capable of, but it's the precise pattern of electricity coursing through it at a given time that determines what it's actually doing.

It seems far off, but there may yet come a day when brain scans and genetic tests can predict—with enough accuracy to matter in the real world—an individual's mental strengths and weaknesses, predisposition to psychiatric problems, or maybe even his favorite color. In the meantime, in the cafes and bars, there will be plenty to discuss.

–GREG MILLER

Can We Make Our Brains More Plastic?

Rewiring the brain is hard work, and as we age it gets even more difficult. A baby exposed to multiple languages can, without apparent effort, become fluently bilingual or even trilingual. Most adults have to work much harder to master new languages, and few are able to achieve the fluency of native speakers.

There are good reasons that our brains become less flexible as they mature: A developing brain gives up some of its plasticity in favor of efficiency and stability. "A fully plastic brain is not very helpful," says Gerd Kempermann, a neuroscientist at the Center for Regenerative Therapies Dresden and the German Center for Neurodegenerative Diseases. "It learns everything but remembers nothing." Too much plasticity may also play a role in some neurological disorders, including epilepsy and schizophrenia.

In certain situations, however, more plasticity could be helpful, making it easier for patients to recover after a stroke or spinal cord injury, for example. And it would be nice to effortlessly pick up the intricacies of Russian grammar. So, will we one day be able to turn on—and control—our brain plasticity at will?

Neuroscientists have begun to understand a few of the factors that govern the flexibility of certain parts of the maturing brain. By studying the development of sensory systems such as sight and hearing, they have uncovered a network of genes and proteins that influence so-called critical periods, windows of time in which the brain is primed for certain types of input. It is during these critical periods that the brain becomes wired for certain tasks, such as turning the signals received from the eyes into recognizable images, or distinguishing sounds present in spoken language. If a brain doesn't receive the right inputs during a critical period, it is extremely difficult to recover from the deficits that result. Children born with cataracts or a lazy eye will never see clearly unless the condition is corrected in the first years of life. Both mice and humans that lack adequate social contact as babies and juveniles have permanent behavioral and cognitive deficits.

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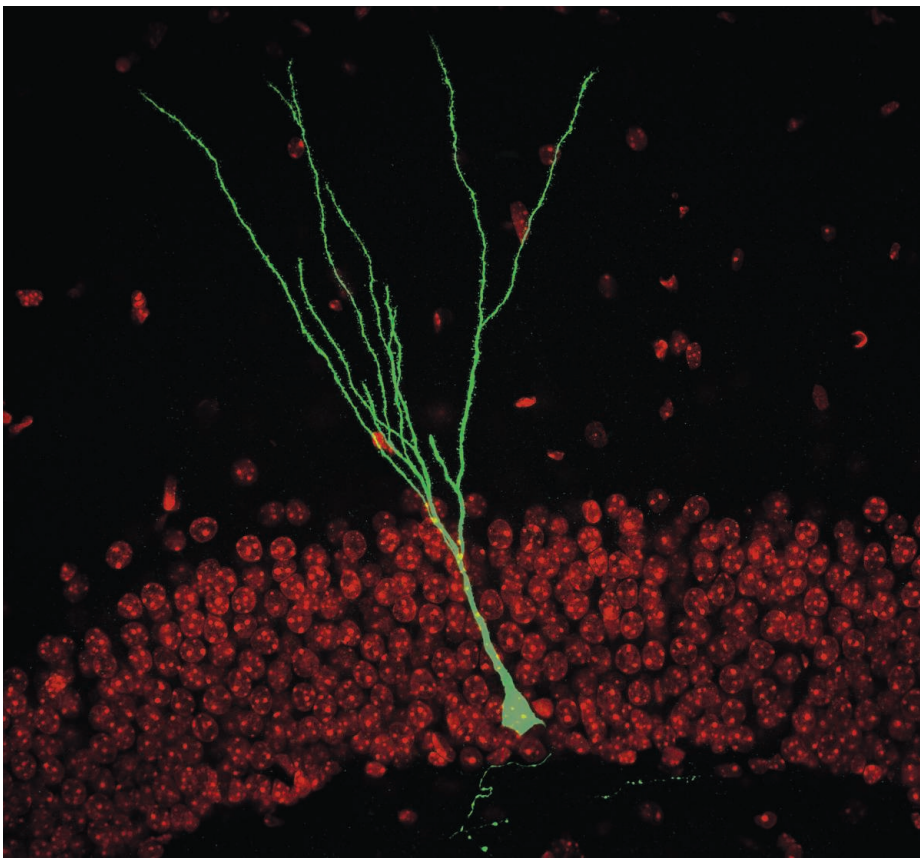

Plasticity potential. A newborn neuron in an adult mouse brain.

CREDIT: JASON SNYDER/FUNCTIONAL NEUROGENESIS

The critical periods that arise earliest in development govern senses such as sight, hearing, and balance. Later ones govern higher-order skills such as language acquisition and social interactions. Most critical periods occur during infancy and childhood, when the brain is still growing and producing new neurons. But more important than the new cells are the connections the neurons make with each other. Connections that receive reinforcement are strengthened and protected, for example, by the growth of myelin sheaths around axons. Connections that go unused are pruned back.

In recent years, evidence has mounted that the critical periods close not only because plasticity-driving signals decrease, but also because the brain begins to produce signals that limit new connections between cells. When scientists use genetic tricks to remove these brakes on brain plasticity in experimental mice, the critical periods last well into adulthood. That's encouraging to those who wish to improve plasticity in adult humans, says Carla Shatz, a neuroscientist at Stanford University in Palo Alto, California. Boosting the plasticity of an adult human brain may not require replacing a whole network of signals that turn on that flexibility, she suggests. "Just take away the brakes," she says, and the brain can perhaps recover its lost capabilities.

In lab animals, at least, that's possible: Researchers have bred mice that lack some of the various genes that act as plasticity brakes. When these so-called knockout mice lose sight in one of their eyes for a few days—the researchers suture it shut—their brains quickly compensate and reassign more area to the good eye, a process that resembles the plasticity seen in newborn brains. The mutant mice also recover from strokes better than control animals. And in several tests of neural function, they seem like supermice. On a rotarod, a kind of motor skills test for lab mice that resembles a log-rolling contest, the knockout animals "are like Olympians," Shatz says. She and her colleagues have done a range of behavioral tests on their knockout mice. So far, "they're really good at everything." That's certainly not the whole story, she adds: "There has to be some downside."

> "A fully plastic brain is not very helpful. It learns everything but remembers nothing."
>
> —GERD KEMPERMANN, CENTER FOR REGENERATIVE THERAPIES DRESDEN

One likely disadvantage is that too much rewiring can lead to short circuits—in a brain, that could mean seizures. Indeed, those same knockout mice respond to a smaller dose of seizure-inducing drugs than typical mice. In humans, the result of unleashing brain plasticity might be epilepsy. Shatz notes that unexplained epilepsy is much more common in childhood—when the brain is more plastic in many areas—and some epilepsy patients eventually outgrow their disease. A newborn "has to learn things fast or it's not going to survive. It's worth the risk of instability. But it's kind of dangerous to learn that fast. Once the organism has acquired fundamental experiences, you slow it down a bit and put on these brakes," Shatz says. Closing critical periods may also provide a firm foundation for further brain development, says Brigitte Röder, a neuropsychologist at the University of Hamburg in Germany. "If you're always shaking the basement, you can't build a taller house," she says. Takao Hensch, a neuroscientist at Boston Children's Hospital, notes that missing plasticity brakes are suspects not only in epilepsy but also in schizophrenia and Alzheimer's disease.

Some evidence suggests that the brain's plasticity can be augmented without the danger posed by completely removing the brakes. Michael Merzenich, a neuroscientist and professor emeritus at the University of California, San Francisco, explores how certain kinds of sensory signals—mainly sound and touch—can rewire adult brains. He and his colleagues have shown that specially designed computer games can improve performance on memory and other cognitive tasks in both children and older adults, even months after the training stops. Research led by Daphne Bavelier, a neuroscientist at the University of Geneva in Switzerland, has shown that playing action video games, such as Medal of Honor, can improve vision and several kinds of cognitive skills.

The success of those games might be linked to the brain's reward and attention systems, Hensch says. Several of the molecules identified as plasticity brakes involve these pathways. Two drugs that enhance attention, fluoxetine (better known as Prozac) and Aricept, can lengthen or even reopen critical periods in experimental mice. Both drugs are now in clinical trials for reversing the effects of lazy eye in childhood, and

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in one clinical trial fluoxetine helped stroke patients recover lost motor skills.

Fluoxetine also seems to influence another type of brain plasticity, the growth of new neurons throughout life in certain parts of the brain. Although most neurogenesis stops in childhood, two areas of the brain keep producing new neurons: the subventricular zone, which connects to the olfactory bulb; and the subgranular zone of the dentate gyrus, a part of the hippocampus. There are several ways to boost the production of new neurons in these regions; increased physical exercise and exposure to unfamiliar or complex environments are two clear neurogenesis enhancers. Fluoxetine and other antidepressants that act through the dopamine pathway also increase the neuronal birthrate and may keep the newborn neurons flexible longer.

What this ongoing production of neurons means for the brain is unclear, however. Although the rate of adult neurogenesis in an individual's brain is correlated with certain kinds of learning, the connection is not straightforward.

Some evidence points to the idea that in the dentate gyrus, the new neurons may aid the brain in adjusting to new environments, perhaps by helping the brain detect unfamiliar aspects of an otherwise familiar setting. Kempermann has proposed that adult neurogenesis might be an adaptation that has helped certain animals—mice and humans, for example—to adapt to and thrive in a wide variety of unstable ecological niches.

The new neurons "are an extreme form of plasticity," says Fred Gage, a neuroscientist at the Salk Institute for Biological Studies in San Diego, California. He and his colleagues have found that the newborn cells seem to have their own critical period, lasting roughly 4 weeks, during which they are particularly excitable. (Recent studies suggest that fluoxetine might lengthen this period.) Gage speculates that the birth of neurons provides a continually fresh source of short-term critical periods for certain kinds of learning throughout life. The newborn neurons "are young kids that respond to everything," he says. By the time one set of neurons has grown up and settled down, there's another set of cells ready to take their place.

Determining how those new neurons interact with the circuits already in place might help scientists better understand how the circuits are wired in the first place—and how to safely and efficiently rewire when needed.

–GRETCHEN VOGEL

CREDIT: JASON SNYDER/FUNCTIONAL NEUROGENESIS

Brain Teasers

The brain poses many more than just the five quandaries we've highlighted on these pages. Delve into any one of them and you'll soon run into another. Remembering the past (p. 30), for example, is a significant part of human experience, which raises one of the slipperiest questions in all of science: What is the biological basis of consciousness? (See *Science*, 1 July 2005, p. 79.) The elusive nature of that problem has convinced some researchers to stick to memory. "It's as close to consciousness as I can get and still look myself in the mirror in the morning," quips Loren Frank, a neuroscientist at the University of California, San Francisco. Below are six more mysteries of the brain that any neuroscientist should be proud to tackle. **–GREG MILLER**

Star power. Researchers now realize that star-shaped astrocytes do more than just clean up after neurons. Recent studies find that they help shape synaptic connections in the developing brain, influence synaptic function throughout life, and may go haywire in a number of neuropsychiatric disorders. Given that astrocytes make up nearly half the cells in the human brain, we know too little about them.

Uncharted territories. What the heck does the habenula do? Or how about the retrosplenial cortex? Some brain regions get all the love from neuroimagers (yes, we're talking about you, anterior cingulate), while others get ignored. There's still much to learn about these rarely studied regions, their anatomical connections, and their contributions to cognition and behavior.

Snooze fest. Why we sleep isn't just a mystery of the brain, but considering that it's the brain that switches animals into slumber mode, the organ must be at the heart of it. Do animals sleep simply to conserve energy and stay out of trouble in the dangerous dark? Or is sleep necessary, as some newer research suggests, to reset the brain to meet the challenges of a brand-new day? And what, if anything, does dreaming accomplish?

What's the code? Asking how information is encoded in the nervous system may be one step shy of asking how the brain works. But getting a better handle on how neural firing patterns—or is it which neurons are doing the firing?—represent information is crucial for understanding everything we do, including perception, memory, and decision-making.

Getting reconnected. The inability of the central nervous system of adult mammals to regenerate after injury is a vexing puzzle. Research with rodents has led to a better understanding of the cellular signals that put the brakes on such repair. But translating that work to people with spinal injuries remains an elusive goal.

Feeling immune. Many immune system proteins take on different roles in the brain, and immune responses are known or suspected contributors to a number of brain disorders. Yet scientists have only scratched the surface of how the immune system and nervous system interact. Recent findings that the gut microbiota may act through the immune system to influence the brain and behavior add another intriguing twist.

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