

# The Reinvention of the Self

Elizabeth Gould overturned one of the central tenets of neuroscience. Now she's building on her discovery to show that poverty and stress may not just be symptoms of society, but bound to our anatomy.

by Jonah Lehrer

Professor Elizabeth Gould has a picture of a marmoset on her computer screen. Marmosets are a new world monkey, and Gould has a large colony living just down the hall. Although her primate population is barely three years old, Gould is clearly smitten, showing off these photographs like a proud parent. Marmosets are the ideal experimental animal: a primate brain trapped inside the body of a rat. They recognize themselves in the mirror, form elaborate dominance hierarchies and raise their young cooperatively. If you can look past their rodent-like stature and punkish pompadour, marmosets can seem disconcertingly human.

In her laboratory at Princeton University's Department of Psychology, Gould is determined to create a marmoset environment that takes full advantage of their innate intelligence. She doesn't believe in metal cages. "We are housing

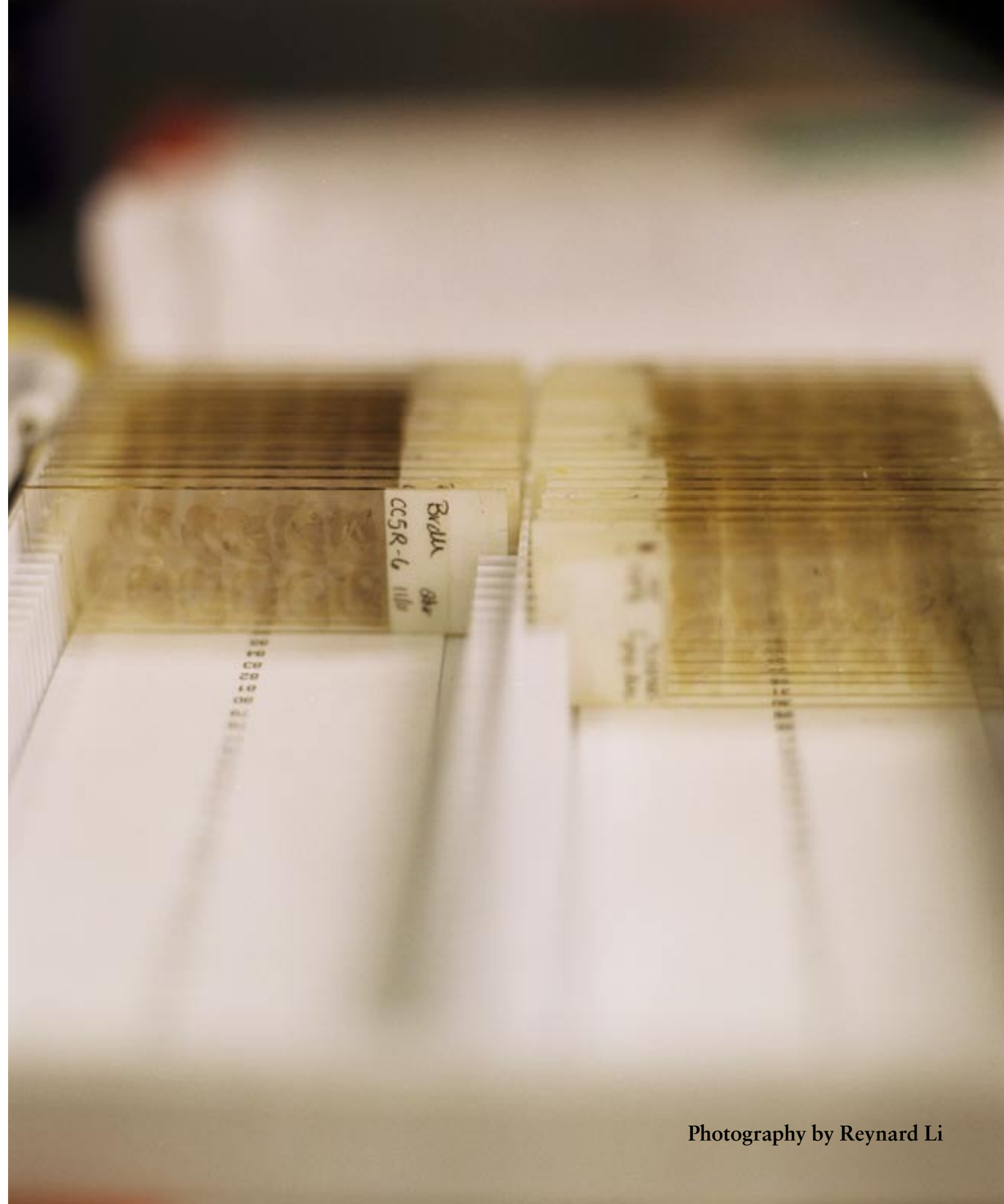
our marmosets in large, enriched enclosures," she says, "and with a variety of objects to support foraging. These are social animals, and it's important to let them be social. Basically, we want to bring our experimental conditions closer to the wild."

But Gould is not a primatologist. She doesn't give her marmosets adorable names, or spend time cuddling with their young. In fact, these marmosets don't even know she exists: Gould prefers to observe them remotely, on a little video screen. Staring at the televised frenzy of this little marmoset world, it is poignant to know how their lives will end. Their brains will be cut into thousands of transparent slices. Their dissected neurons will be stained neon green and the density of their dendritic connections will be quantified under a powerful microscope. They will live on as data.

The naturalistic habitat that Gould has cre-

ated for these marmosets is essential to her studies, which involve understanding how the environment affects the brain. Eight years after Gould defied the entrenched dogma of her science and proved that the primate brain is always creating new neurons, she has gone on to demonstrate an even more startling fact: The structure of our brain, from the details of our dendrites to the density of our hippocampus, is incredibly influenced by our surroundings. Put a primate under stressful conditions, and its brain begins to starve. It stops creating new cells. The cells it already has retreat inwards. The mind is disfigured.

The social implications of this research are staggering. If boring environments, stressful noises, and the primate's particular slot in the dominance hierarchy all shape the architecture of the brain—and Gould's team has shown that they do—then the playing field isn't level.



Photography by Reynard Li



Poverty and stress aren't just an idea: they are an anatomy. Some brains never even have a chance.

Viewed through the magnified eyes of a confocal microscope, a newborn neuron looks fragile, almost lonely. Everything around it is connected to everything else, but the new cell is all alone, just a seed of soma and a thin stalk of axon desperately trying to plug itself into the network. If it doesn't, it will die. Staring at this tenuous neuron, it is hard to believe that so much depends upon its presence.

Dr. Gould insists on being called Liz. She wears faded jeans to work and ties back her long dark hair in a loose braid. She smiles easily, and intersperses discussions of marmoset families with stories about her own children. Gould doesn't talk about her research in listless sentences full of acronyms. Instead, she takes you through the experimental process, confessing all the difficulties and ambiguities along the way.

Gould's casual air conceals a necessary te-

lab studies the effect of two separate variables: stress and enriched environments. Chronic stress, predictably enough, decreases neurogenesis. As Christian Mirescu, one of Gould's post-docs, put it, "When a brain is worried, it's just thinking about survival. It isn't interested in investing in new cells for the future."

On the other hand, enriched animal environments—enclosures that simulate the complexity of a natural habitat—lead to dramatic increases in both neurogenesis and the density of neuronal dendrites, the branches that connect one neuron to another. Complex surroundings create a complex brain.

Gould's field is a new one. Only a decade ago, the idea that the primate brain is constantly creating new neurons, and that these new neurons are not only functional but responsive to changes in the environment, was unimaginable. Indeed, the fact that neurogenesis did not exist was one of modern neuro-

proof was limited, he persuasively defended the dogma. He even went so far as to construct a plausible evolutionary theory as to why neurons can't divide: Rakic imagined that at some point in our distant past, primates had traded the ability to give birth to new neurons for the ability to retain plasticity in our old neurons. According to Rakic, the "social and cognitive" behavior of primates required the absence of neurogenesis. His paper, with its thorough demonstration of what everyone already believed, seemed like the final word on the matter. No one bothered to verify his findings.

The genius of the scientific method, however, is that it accepts no permanent solution. Skepticism is its solvent, for every theory is imperfect. Scientific facts are meaningful precisely because they are ephemeral, because a new observation, a more honest observation, can always alter them. This is what happened to Rakic's theory of the fixed brain. It was, to use Karl Popper's verb, falsified.

Eight years after Gould defied the dogma of her field and proved that the primate brain creates new cells, she has gone on to demonstrate that the structure of the brain is incredibly influenced by one's surroundings.

The subject of stress has been the single continuous thread running through Gould's research career. From the brain's perspective, stress is primarily signaled by an increase in the bloodstream of a class of steroid called glucocorticoids, which put the body on a heightened state of alert. But glucocorticoids can have one nasty side-effect: They are toxic for the brain. When stress becomes chronic, neurons stop investing in themselves. Neurogenesis ceases. Dendrites disappear. The hippocampus, a part of the brain essential for learning and memory, begins withering away.

Gould's insight was that understanding how stress damages the brain could illuminate the general mechanisms—especially neurogenesis—by which the brain is affected by its environmental conditions. For the last several years, she and her post-doc, Mirescu, have been depriving newborn rats of their mother for either 15 minutes or three hours a day. For an infant rat, there is nothing more stressful. Earlier studies had shown that even after these rats become adults, the effects of their developmental deprivation linger: They never learn how to deal with stress. "Normal rats can turn off their glucocorticoid system relatively quickly," Mirescu says. "They can recover from the stress response. But these deprived rats can't do that. It's as if they are missing the 'off' switch."

Gould and Mirescu's disruption led to a dramatic decrease in neurogenesis in their rats' adult brains. The temporary trauma of childhood lingered on as a permanent reduction in the number of new cells in the hippocampus. The rat might have forgotten its pain, but its brain never did. "This is a potentially very important topic," Gould says. "When you look at

naciousness: It is not easy to shift a paradigm. Four days after giving birth to her third child, Gould was back at work, lecturing to a room full of undergraduates. She has always worked long hours, and expects nothing less of her employees. (Saturdays in the Gould lab are indistinguishable from Mondays.) And even though her research has set off a frenzy of activity—neurogenesis is now one of the hottest topics in neuroscience—Gould has managed to remain at the cutting edge of the field she helped to invent.

For such a high-profile scientist, Gould's lab at Princeton is surprisingly small. Lavishly outfitted (she has her own \$400,000 confocal microscope and large marmoset colony) the lab consists of just two post-docs and two grad students. They are a close knit group, and work on overlapping problems. "When I first began at Princeton," Gould says, "I had tunnel vision. I was just so determined to answer my critics and prove that adult neurogenesis was real. But now I'm finally able to think about neurogenesis in a broader context. We are free to figure out what all these new cells actually do."

To understand how neurogenesis—the process of creating new brain cells—works, Gould's

science's founding principles. This theory, first articulated by Santiago Ramón y Cajal at the start of the 20th century, held that brain cells—unlike every other cell in our body—don't divide. They don't die, and they are never reborn. We emerge from the womb with the only brain we will ever have.

The most convincing modern defender of this theory was Pasko Rakic, the chairman of Yale University's neurobiology department and among the most respected neuroscientists of his generation. In the early 1980s, Rakic realized that neurogenesis had never been properly tested in primates. He set out to investigate. Rakic studied 12 rhesus monkeys, injecting them with radioactively-labeled thymidine which allowed him to trace the development of neurons in the brain. Rakic then killed the monkeys at various stages after the injection of the thymidine, and searched for any signs of new neurons. There were none.

"All neurons of the rhesus monkey brain are generated during pre-natal and early post-natal life," Rakic wrote in his 1985 paper, "Limits of Neurogenesis in Primates." "Not a single" new neuron "was observed in the brain of any adult animal." While Rakic admitted that his



For each deprivation and stress that inhibits the brain, Gould's teams are seeking a hopeful antidote. The brain, like skin, can repair itself: The scars of stress can literally be healed by learning new things.

all these different stress disorders, such as PTSD [post-traumatic stress disorder], what you realize is that some people are more vulnerable. They are at increased risk. This might be one of the reasons why."

Subsequent experiments have teased out a host of other ways stress can damage the developing brain. For example, if a pregnant rhesus monkey is forced to endure stressful conditions—like being startled by a blaring horn for 10 minutes a day—her children are born with reduced neurogenesis, even if they never

actually experience stress once born. This prenatal trauma, just like trauma endured in infancy, has life-long implications. The offspring of monkeys stressed during pregnancy have smaller hippocampi, suffer from elevated levels of glucocorticoids and display all the classical symptoms of anxiety. Being low in a dominance hierarchy also suppresses neurogenesis. So does living in a bare environment. As a general rule of thumb, a rough life—especially a rough start to life—strongly correlates with lower levels of fresh cells.

Gould's research inevitably conjures up comparisons to societal problems. And while Gould, like all rigorous bench scientists, prefers to focus on the strictly scientific aspects of her data—she is wary of having it twisted for political purposes—she is also acutely aware of the potential implications of her research.

"Poverty is stress," she says, with more than a little passion in her voice. "One thing that always strikes me is that when you ask Americans why the poor are poor, they always say it's because they don't work hard enough, or don't want to do better. They act like poverty is a character issue."

Gould's work implies that the symptoms of poverty are not simply states of mind; they actually warp the mind. Because neurons are designed to reflect their circumstances, not to rise above them, the monotonous stress of living in a slum literally limits the brain.

In 1989, Gould was a young post-doc working in the lab of Bruce McEwen at Rockefeller University, investigating the effect of stress hormones on rat brains. Chronic stress is devastating to neurons, and Gould's research focused on the death of cells in the hippocampus. (Rakic's declaration that there was no such thing as neurogenesis was still entrenched dogma.) While the idea was exciting—stress research was a booming field—the manual labor was brutal. She had to kill her rats at various time points, pluck the tiny brain out of its cranial casing, cut through the rubbery cortex, slice the hippocampus thinner than a piece of paper, and painstakingly count the dying neurons under a microscope. But while Gould was documenting the brain's degeneration, she happened upon something inexplicable: evidence that the brain also healed itself. "At first, I assumed I must be counting [the neurons] incorrectly," Gould said. "There were just too many cells."

Confused by this anomaly, Gould assumed she was making some simple experimental mistake. She went to the library, hoping to figure out what she was doing wrong. But then, looking through a dusty, 27-year-old science journal buried in the Rockefeller stacks—this was before the Internet—Gould found the explanation she needed, though not the one she was looking for.

Beginning in 1962, a researcher at MIT named Joseph Altman published several papers claiming that adult rats, cats, and guinea pigs all formed new neurons. Although Altman used the same technique that Rakic would later use in monkey brains—the injection of radioactive thymidine—his results were at first ridiculed, then ignored, and soon forgotten.

As a result, the field of neurogenesis vanished before it began. It would be another decade be-

fore Michael Kaplan, at the University of New Mexico, would use an electron microscope to image neurons giving birth. Kaplan discovered new neurons everywhere in the mammalian brain, including the cortex. Yet even with this visual evidence, science remained stubbornly devoted to its doctrine. Kaplan remembers Rakic telling him that "Those [cells] may look like neurons in New Mexico, but they don't in New Haven." Faced with this debilitating criticism, Kaplan, like Altman before him, abandoned the field of neurogenesis.

The Connecticut Mental Health Center is a drab brick building a mile from the Yale campus. After passing through a metal detector and walking by a few armed guards, a visitor enters a working mental institution. The cramped halls are an uneasy mixture of scientists, social workers and confined patients. The lights are bright and sterile.

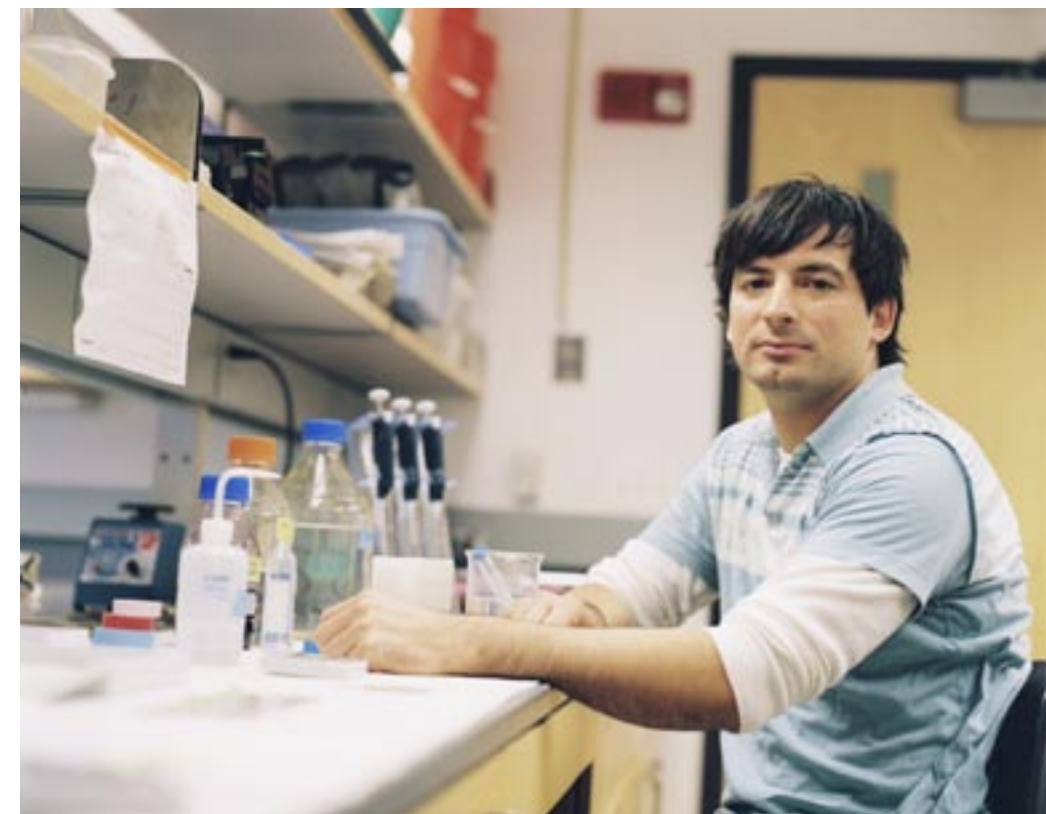
Ronald Duman, a professor of Psychiatry and Pharmacology at Yale, has a lab on the third floor, opposite a ward for the mentally ill. His lab is isolated from the rest of the building by a set of locked doors. There is the usual clutter of solutions (most of them just salt buffers), the haphazard stacks of science papers and the soothing hum of refrigerators set well below zero. It is here, in these rooms with a view of New Haven, that Duman is trying to completely change the science of depression and antidepressants.

For the last 40 years, medical science has operated on the understanding that depression is caused by a lack of serotonin, a neurotransmitter that plays a role in just about everything the mind does, thinks or feels. The theory is appealingly simple: sadness is simply a shortage of chemical happiness. The typical antidepressant—like Prozac or Zoloft—works by increasing the brain's access to serotonin. If depression is a hunger for neurotransmitter, then these little pills fill us up.

Unfortunately, the serotonergic hypothesis is mostly wrong. After all, within hours of swallowing an antidepressant, the brain is flushed with excess serotonin. Yet nothing happens; the patient is no less depressed. Weeks pass drearily by. Finally, after a month or two of this agony, the torpor begins to lift.

But why the delay? If depression is simply a lack of serotonin, shouldn't the effect of antidepressants be immediate? The paradox of the Prozac lag has been the guiding question of Dr. Ronald Duman's career. Duman likes to talk with his feet propped up on his desk. He speaks with the quiet confidence of someone whose ideas once seemed far-fetched but are finally being confirmed.

"Even as a graduate student," Duman says,



Elizabeth Gould's lab assistants in the department of psychology at Princeton. Opposite: Post-doc Benedetta Leuner. This page: Top, post-doc Christian Mirescu; bottom, grad student Genia Kozorovitskiy, who designed the enriched enclosures which fostered neurogenesis in the team's colony of marmosets.



“I was fascinated by how antidepressants work. I always thought that if I can just figure out their mechanism of action—and identify why there is this time-delay in their effect—then I will have had a productive career.”

When Duman began studying the molecular basis of antidepressants back in the early 90s, the first thing he realized was that the serotonin hypothesis made no sense. A competing theory, which was supposed to explain the Prozac lag, was that antidepressants increase the number of serotonin receptors. However, that theory was also disproved. “It quickly became clear that serotonin wasn’t the whole story,” Duman says. “Our working hypothesis at the time just wasn’t right.”

But if missing serotonin isn’t the underlying cause of depression, then how do antidepressants work? As millions will attest, Prozac does do something. Duman’s insight, which he began to test gradually, was that a range of antidepressants trigger a molecular pathway that has little, if anything, to do with serotonin. Instead, this chemical cascade leads to an increase in the production of a class of proteins known as trophic factors. Trophic factors make neurons grow. What water and sun do for trees, trophic factors do for brain cells. Depression was like an extended drought: It deprived neurons of the sustenance they need.

Duman’s discovery of a link between trophic factors and antidepressant treatments still left the essential question unanswered: What was causing depressed brains to stop producing trophic factors? Why was the brain hurting itself? It was at this point that Duman’s research intersected the work of Robert Sapolsky and Bruce McEwen (Gould’s advisor at Rockefeller), who were both studying the effects of stress on the mammalian brain. In an influential set of studies, Sapolsky and McEwen had shown that prolonged bouts of stress were devastating to neurons, especially in the hippocampus. In one particularly poignant experiment, male vervet monkeys bullied by their more dominant peers suffered serious and structural brain damage. Furthermore, this neural wound seemed to be caused by a decrease in the same trophic factors that Duman had been studying. From the perspective of the brain, stress and depression produced eerily similar symptoms. They shared a destructive anatomy.

Just as Duman was beginning to see the biochemical connections between trophic factors, stress, and depression, Gould was starting to document neurogenesis in the hippocampus of the primate brain. Reading Altman’s and Kaplan’s papers, Gould had realized that her neuron-counting wasn’t erroneous: She was just witnessing an ignored fact. The anomaly



had been suppressed. But the final piece of the puzzle came when Gould heard about the work of Fernando Nottebohm, who was, coincidentally, also at Rockefeller. Nottebohm, in a series of beautiful studies on birds, had showed that neurogenesis was essential to birdsong. To sing their complex melodies, male birds needed new brain cells. In fact, up to 1% of the neurons in the bird’s song center were created anew, every day.

Despite the elegance of Nottebohm’s data, his science was marginalized. Bird brains were seen as irrelevant to the mammalian brain. Avian neurogenesis was explained away as an exotic adaptation, a reflection of the fact that flight required a light cerebrum. In *The Structure of Scientific Revolutions*, the philosopher Thomas Kuhn wrote about how pre-paradigm-shift science excludes its contradictions: “Until

the scientist has learned to see nature in a different way, the new fact is not quite a scientific fact at all.” Evidence of neurogenesis was excluded from the world of “normal science.”

But Gould, motivated by the strangeness of her own observations, connected the dots. She realized that Altman, Kaplan and Nottebohm all had strong evidence for mammalian neurogenesis. Faced with this mass of ignored data, Gould began pursuing cell birth in the adult brain of rats.

She would spend the next eight years quantifying endless numbers of radioactive rat hippocampi. But the tedious manual labor paid off. Gould’s data would shift the paradigm. More than thirty years had passed since Altman first traced the ascent of new neurons in the adult brain, but neurogenesis had finally become a real science.

After her wearisome post-doc, during which her data was continually criticized, Gould was offered a job at Princeton. The very next year, in a series of landmark papers, Gould began documenting neurogenesis in primates, thus confronting Rakic’s data directly. She demonstrated that adult marmosets created new neurons in their brains, especially in the olfactory cortex and the hippocampus. The mind, far from being stagnant, is actually in a constant state of cellular upheaval. By 1999, even Rakic had admitted that neurogenesis is real. He published a paper in *Proceedings of the National Academy of Sciences* that reported seeing new neurons in the hippocampus of macaques, an old world primate. The textbooks were rewritten. The brain, Elizabeth Gould had now firmly established, is always giving birth. The self is continually reinventing itself.

Gould’s finding has led, via work Duman has done that builds on it, to a rash of R&D to stimulate neurogenesis in the brain. Duman had an epiphany reading Gould’s papers. He realized that stress and depression didn’t simply kill cells, they might also prevent new cells from being born. “I was reading these papers by McEwen and Gould,” Duman says, “and they were showing this relationship between stress and the adrenal hormones and neurogenesis. It just sort of all gradually came together.” Perhaps the time lag of antidepressants was simply the time it took for new cells to be created.

He immediately set to work to test this hypothesis. In December 2000, Duman’s lab published a paper in the *Journal of Neuroscience* demonstrating that antidepressants increased neurogenesis in the adult rat brain. In fact, the two most effective treatments they looked at—electroconvulsive therapy and fluoxetine, the chemical name for Prozac—increased neurogenesis in the hippocampus by 75% and 50%, respectively. Subsequent studies did this by increasing the exact same molecules, especially trophic factors, that are suppressed by stress.

Duman was surprised by his own data. Fluoxetine, after all, had been invented by accident. (It was originally studied as an antihistamine.) “The idea that Prozac triggers all these different trophic factors that ultimately lead to increased neurogenesis is just totally serendipitous,” Duman says. “Pure luck.”

But demonstrating a connection between antidepressants and increased neurogenesis was the easy part. It is much more difficult to prove that increased neurogenesis causes the relief provided by antidepressants, and is not just another of the drugs many side-effects. To answer this question, Duman partnered with the lab of René Hen at Columbia.

The research team, led by post-doc Luca Santarelli, effectively erased neurogenesis with low doses of radiation. All other cellular processes remained intact. If the relief from depression was due to changes in serotonin, then halting neurogenesis with radiation should have had no effect.

But it did. Hen and Duman’s data was unambiguous. If there is no increase in neurogenesis, then antidepressants don’t work in rodents. They stay “depressed.”

Duman and Hen’s work was greeted, as expected, by a howl of criticism. Mice aren’t people. The experiment was flawed. The radiation wasn’t specific enough. Robert Sapolsky, whose work on stress paved the way for much of Duman’s own research, is one of the most incisive skeptics. He argues that neurogenesis researchers have no plausible model for how decreased neurogenesis might cause the symptoms of de-

Nevertheless, Duman’s research is completely changing the way neuroscience imagines depression. Several major drug companies and a host of startups are now frantically trying to invent the next generation of antidepressants (a \$12-billion-a-year business). Many expect these future drugs to selectively target the neurogenesis pathway. If these pills are successful, they will be definitive proof that antidepressants work by increasing neurogenesis. Depression is not simply the antagonist of happiness. Instead, despair might be caused by the loss of the brain’s essential plasticity. A person’s inability to change herself is what drags her down.

Scientists who pursue neurogenesis are audacious by definition—they have staked their career on a lark—and Dr. Jonas Frisén is no exception. He is probably the only person in Stockholm who wears a cowboy hat.

The theory that depression is caused by a lack of serotonin is mostly wrong; Yale’s Ronald Duman is showing that Prozac triggers neurogenesis.

pression. Why would having a handful fewer new cells in the hippocampus have such an effect? “The more expertise someone has about the hippocampus,” Sapolsky wrote in a review in *Biological Psychiatry*, “the less plausible they find this novel role.”

Duman himself is reluctant to discuss the clinical implications of his data. He imagines that neurogenesis in humans is just a single part of the antidepressant effect. “It’s a long way from looking at mice in cages to talking about depression in humans. All of these connections are very exciting, but we still don’t understand what’s actually going on inside the brain. We don’t know what the function of all these new cells is, and we have no idea how they might relate, if they do, to the mechanism of action of antidepressants in humans.”

“Super-exciting” is his favorite superlative. (He speaks English fluently, with a singsong Scandinavian accent.) Occasionally, Frisén gives his science papers titles lifted from Bob Dylan songs, as in his 2003 paper “Blood on the tracks: a simple twist of fate?” He thanks Dylan in the acknowledgments for “inspiration.”

Frisén has never known a brain that wasn’t filled with new cells. He became a neuroscientist after med school, just as neurogenesis was becoming a genuine fact. Although he is now a full professor in stem-cell research at the Karolinska Institute, the university in charge of administering the Nobel Prize for Medicine, Frisén began his career as a doctor. When he started medical school, he assumed he would become a brain surgeon, or perhaps a psychiatrist. That, after all, was how you healed the brain back



### 03.6 THE Y’S HAVE IT

— Been trying to conceive for a while? You’ll probably have a boy. And that’s no old wives’ tale: According to epidemiologist Luc Smits, of Maastricht University, a baby’s gender may be determined by how long it takes the mother to conceive. Women who take more than a year to become pregnant have boys 58% of the time. Why? It might be because boys swim faster. The Y-chromosome sperm, already swifter, swim better in the viscous cervical fluid that often makes conception difficult.



then: either with a scalpel or with words. The few drugs that worked on the mind—like antidepressants—performed their job mysteriously.

Frisén has helped to change that. He has pursued the neurogenesis hypothesis into the realm of clinical medicine, and his rise has been astonishingly swift. In 1998, only three years after becoming a doctor, Friséen was a tenured professor, in charge of a 15-person lab. He has a long list of influential papers to his name, published in frequently-cited journals like *Cell* and *Nature*.

Frisén first leapt to the attention of the neuroscience community in 1999, when his lab announced that they had identified stem cells in the brain. Stem cells are the source of neurogenesis: It is their mitotic divisions that create new neurons.

Subsequent experiments in Friséen's lab have explored exactly how these neural stem cells are regulated. His ambition is to decipher the complicated and convoluted cascade of proteins that connect the feeling of stress to a decrease in neurogenesis. Only then, Friséen says, "will we be able to create drugs that selectively target neurogenesis. And that is what everybody wants to do. Just think of all the things you can heal."

To achieve this, Friséen has founded a biotech firm, NeuroNova, dedicated to pursuing drugs which stimulate neurogenesis. When it launched, neurogenesis remained a controversial concept; founding an entire company on its therapeutic promise seemed like an imprudent gamble. In Friséen's case, the gamble is paying off.

The first disease NeuroNova targeted for treatment was Parkinson's Disease. Parkinson's is caused by the death of dopamine-producing neurons, and doctors have repeatedly tried to compensate for this selective cell death by surgically transplanting embryonic brain tissue into patients' brains, often with disappointing results. Friséen realized that the Parkinson's brain was capable, at least in theory, of healing itself. Driven by this radical hypothesis, NeuroNova began screening thousands of potential compounds for their effect on neurogenesis. Perhaps increased neurogenesis might compensate for the rapid death of dopamine neurons.

The results so far have exceeded everyone's expectations. In November 2005, NeuroNova announced that one of their leading drug candidates—clandestinely called sNN0031—restored normal bodily movement in rodent models of Parkinson's. Rats that were barely able to walk had their symptoms erased after only five weeks of treatment. Furthermore, initial results suggest that the drug worked by rapidly increas-

ing neurogenesis, thus restoring normal dopamine signaling in the rat brain. "The results really are spectacular," Friséen says.

The next step is to begin testing in primate models of Parkinson's, beginning early this year. If the drug doesn't produce toxic side effects—and that's unlikely, since it is already approved as a human treatment for an unrelated condition—human clinical trials are expected to begin shortly thereafter.

Neurogenesis is an optimistic idea. Though Gould's lab has thoroughly demonstrated the long-term consequences of deprivation and stress, the brain, like skin, can heal itself, as Gould is now beginning to document, finding hopeful antidotes to neurogenesis-inhibiting injuries. "My hunch is that a lot of these abnormalities [caused by stress] can be fixed in adulthood," she says. "I think that there's a lot of evidence for the resiliency of the brain."

On a cellular level, the scars of stress can literally be healed by learning new things. Genia Kozorovitskiy, an effusive graduate student who began working with Gould as a Princeton undergrad, has studied the effects of various environments on their colony of marmosets. As predicted, putting marmosets in a plain cage—the kind typically used in science labs—led to plain-looking brains. The primates suffered from reduced neurogenesis and their neurons had fewer interconnections.

However, if these same marmosets were transferred to an enriched enclosure—complete with branches, hidden food, and a rotation of toys—their adult brains began to recover rapidly. In under four weeks, the brains of the deprived marmosets underwent radical renovations at the cellular level. Their neurons demonstrated significant increases in the density of their connections and amount of proteins in their synapses.

The realization that typical laboratory conditions are debilitating for animals has been one of the accidental discoveries of the neurogenesis field. Nottebohm, for example, only witnessed neurogenesis in birds because he studied them in their actual habitat. Had he kept his finches and canaries in metal cages, depriving them of their natural social context, he would never have observed such an abundance of new cells. The birds would have been too stressed to sing. As Nottebohm has said, "Take nature away and all your insight is in a biological vacuum."

Gould has also become concerned about the details of experimental design. She now stresses the importance, for both rodents and primates,

of living in a naturalistic setting. An artificial cage creates artificial data.

(Precisely how artificial prior data from studies on brains of animals kept in un-naturalistic settings remains to be determined. Gould said that studying neurogenesis had led her to "reflect much more on the question of experimental design. This really should be a concern for all neuroscientists.")

The mind is like a muscle: it swells with exercise. Gould's and Kozorovitskiy's work reminds us not only how easy it is to hurt a brain, but how little it takes for that brain to heal. Give a primate just a few extra playthings, and its neurons are capable of escaping the downward cycle of stress.

When Gould first presented at the Society of Neuroscience's annual meeting, there was no such thing as the field whose birth she was there to announce; she was filed away in the "spinal cord rejuvenation" section. Today, she is almost frightened that her field has grown so big: "I do get worried sometimes that neurogenesis has gotten overblown. The science of it still isn't clear. But at the same time I understand why there is so much enthusiasm for the idea. It's a new way of looking at a lot of old problems."

Neurogenesis is a field that doubts itself. Because it has been scorned from the start, its proponents talk most emphatically about what they don't know, about all the essential questions that remain unanswered. Their modesty is accurate: The purpose of all of our new cells remains obscure. No one knows how experiments done in rodents will relate to humans, or whether neurogenesis is just a small part of our mind's essential plasticity.

Nevertheless, it is startling how much has been accomplished since Liz Gould, confused by her counting, went to the library in search of an answer. In 1989, no one would have dared to imagine that the environment we live in can profoundly influence the actual structure of our brain, or that childhood stress might have permanent neurological effects. No scientist could have guessed that Prozac modulates cellular division, or that a Swedish start-up would one day get a rodent brain to repair itself. If neurogenesis has taught us anything, it is that these extraordinary new facts aren't simply answers to an old set of questions. The paradigm has shifted: what Gould and others are working on now is a whole new list of mysteries. And like the newborn neurons in our brain, these scientists are only beginning. ∞

Opposite: Psychiatrist **Ronald Duman** in his office at the Connecticut Mental Health Center, near Yale.