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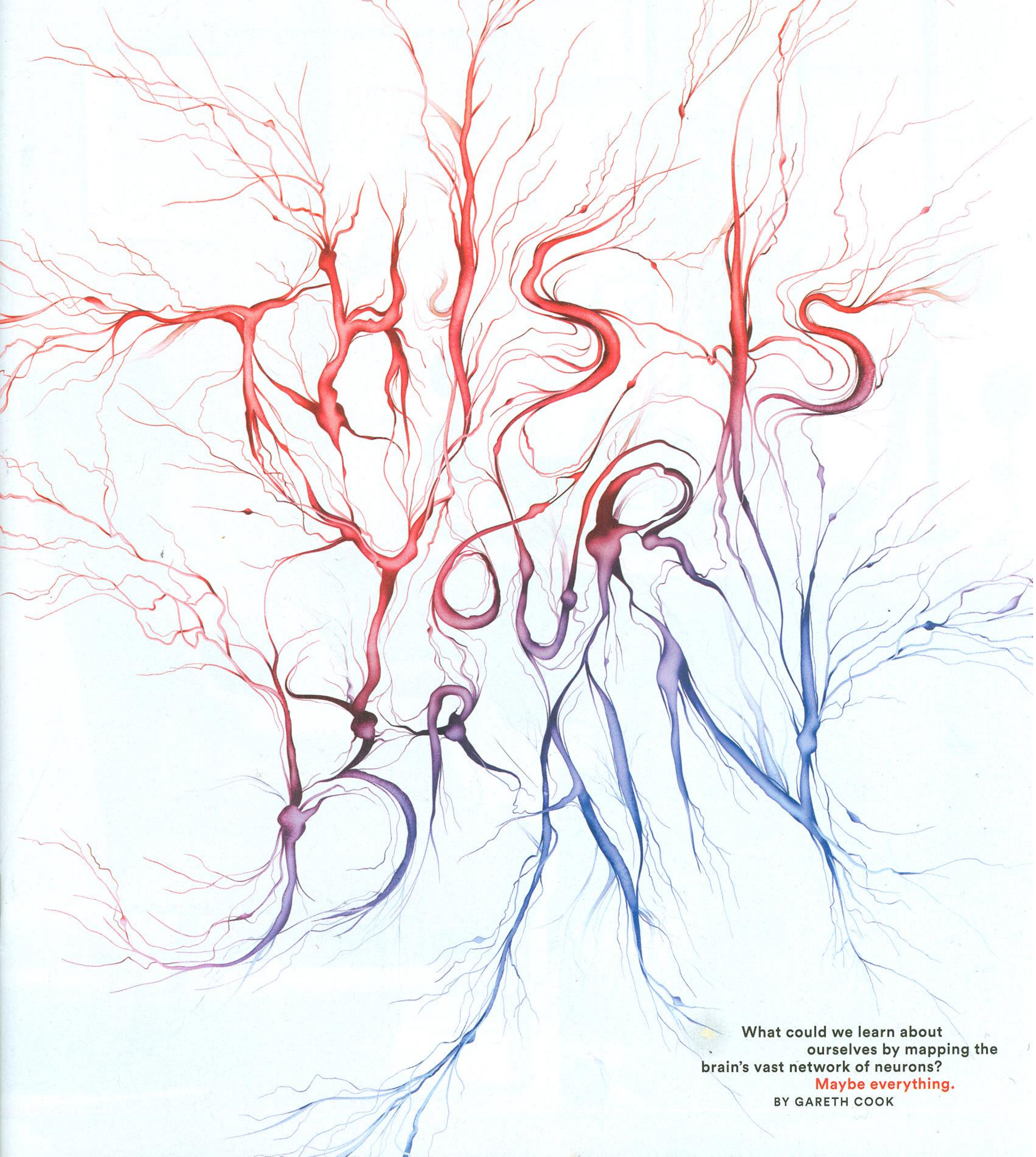


What could we learn about ourselves by mapping the brain's vast network of neurons? **Maybe everything.**

BY GARETH COOK

USING CROWDSOURCING AND ARTIFICIAL INTELLIGENCE, A PRINCETON NEUROSCIENTIST IS HOPING TO MAP THE INTRICATE WIRING OF THE HUMAN BRAIN. IF HE SUCCEEDS, COULD WE LIVE FOREVER AS DATA?

 PHOTO ILLUSTRATION BY DANNY JONES. ORIGINAL IMAGES FROM EYEWIRE.

MIND GAMES

BY GARETH COOK

In 2005, Sebastian Seung suffered the academic equivalent of an existential crisis. More than a decade earlier, with a Ph.D. in theoretical physics from Harvard, Seung made a dramatic career switch into neuroscience, a gamble that seemed to be paying off. He had earned tenure from the Massachusetts Institute of Technology a year faster than the norm and was immediately named a full professor, an unusual move that reflected the sense that Seung was something of a superstar. His lab was underwritten with generous funding by the elite Howard Hughes Medical Institute. He was a popular teacher who traveled the world — Zurich; Seoul, South Korea; Palo Alto, Calif. — delivering lectures on his mathe-

Several distinct neurons in a mouse retina that have been mapped by volunteers playing a game developed by Sebastian Seung.

matical theories of how neurons might be wired together to form the engines of thought.

And yet Seung, a man so naturally exuberant that he was known for staging ad hoc dance performances with Harvard Square's street musicians, was growing increasingly depressed. He and his colleagues spent their days arguing over how the brain might function, but science offered no way to scan it for the answers. "It seemed like decades could go by," Seung told me recently, "and you would never know one way or another whether any of the theories were correct."

That November, Seung sought the advice of David Tank, a mentor he met at Bell Laboratories who was attending the annual meeting of the Society for Neuroscience, in Washington. Over lunch in the dowdy dining room of a nearby hotel, Tank advised a radical cure. A former colleague in Heidelberg, Germany, had just built a device that imaged brain tissue with enough resolution to make out the connections between individual neurons. But drawing even a tiny wiring diagram required herculean efforts, as people traced the course of neurons through thousands of blurry black-and-white images. What the field needed, Tank said, was a computer program that could trace them automatically — a way to map the brain's connections by the millions, opening a new area of scientific discovery. For Seung to tackle the problem, though, it would mean abandoning the work that had propelled him to the top of his discipline in favor of a highly speculative engineering project.

Back in Cambridge, Seung spoke with two of his graduate students, who, like everyone else in the lab, thought the idea was terrible. Over the next few weeks, as the three of them talked and argued, Seung became convinced that the Heidelberg project was bound to be more interesting, and ultimately less risky, than continuing with the theoretical work he had lost faith in. "Make sure your passports are ready," he said finally. "We are going to Germany next month."

Seung and his two students spent a good part of January 2006 in Germany, learning the finicky ways of high-resolution brain-image analysis from Winfried Denk, the scientist who built the device. The three returned to M.I.T. invigorated, but Seung's decision looked, for quite a while, like an act of career suicide. Colleagues at M.I.T. whispered that Seung had gone off the rails, and in the more snobbish circles of theoretical neuroscience, the engineering project was seen as, in Seung's words, "too blue-collar." In 2010, the Hughes institute pulled the money that funded his lab, and he had to scramble. When his wife went into labor with their daughter in the middle of the night, he was working on a grant application; he wound up staying awake for 36 hours straight.

'THINK OF WHAT WE COULD DO IF WE COULD CAPTURE EVEN A SMALL FRACTION OF THE MENTAL EFFORT THAT GOES INTO ANGRY BIRDS.'

("Science," Einstein once wrote, "is a wonderful thing if one does not have to earn one's living at it.") As the years passed, the advances out of the Seung lab were met with indifference, which was particularly hard on his graduate students. "Every time they had a success, they were depressed about it, because everyone else thought it was dumb," Seung said. "It killed me."

Last spring, eight years after he and his students packed a computer workstation into a piece of luggage and headed to Heidelberg, Seung published a paper in the prestigious journal Nature, demonstrating how the brain's neural connections can be mapped — and discoveries made — using an ingenious mix of artificial intelligence and a competitive online game. Seung has also become the leading proponent of a plan, which he described in a 2012 book, to create a wiring diagram of all 100 trillion connections between the neurons of the human brain, an unimaginably vast and complex network known as the connectome.

The race to map the connectome has hardly left the starting line, with only modest funding from the federal government and initial experiments confined to the brains of laboratory animals like fruit flies and mice. But it's an endeavor heavy with moral and philosophical implications, because to map a human connectome would be, Seung has argued, to capture a person's very essence: every memory, every skill, every passion. When the brain isn't wired properly, it can lead to disorders like autism and schizophrenia — "connectopathies" that could be revealed in the map, perhaps suggesting treatments. And if science were to gain the power to record and store connectomes, then it would be natural to speculate, as Seung and others have, that technology might some day enable a recording to play again, thereby reanimating a human consciousness. The mapping of connectomes, its most zealous proponents believe, would confer nothing less than immortality.

Last year, Seung was lured away from M.I.T. to join the Princeton Neuroscience Institute and Princeton's Bezos Center for Neural Circuit Dynamics. These days, Seung, who is 48, has an office down the hall from his mentor Tank at the institute, a white building with strips of wraparound glazing that opened last year on the campus's forested southern fringe. Outside Seung's first-floor window are athletic fields, where afternoon pickup games of soccer occasionally lure him away. A few boxes lie around, half unpacked. Near a sycamore-veneer built-in desk designed by the building's architect sits a jumbo jar of mixed nuts from Costco, a habit he picked up from his father, a professor of philosophy at the University of Texas, Austin. With connectome mapping, Seung explained last month, it is possible to start answering questions that theorists have puzzled over for decades, including the ones that prompted him to put aside his own work in frustration. He is planning, among other things, to prove that he can find a specific memory in the brain of a mouse and show how neural connections sustain it. "I am going back to settle old scores," he said.

In 1946, the Argentine man of letters Jorge Luis Borges wrote a short story about an empire, unnamed, that set out to construct a perfect map of its territory. A series of maps were drawn, only to be put aside in favor of more ambitious maps. Eventually, Borges wrote, "the Cartographers Guilds struck a Map of the Empire whose size was that of the Empire, and which coincided point for point with it. The following Generations, who were not so fond of the Study of Cartography as their Forebears had been, saw that that vast map was Useless, and ... delivered it up to the Inclemencies of Sun and Winters."

With time, Borges's cautionary parable has become even more relevant for the would-be cartographers of the world, Seung among them. Technological progress has always brought novel ways of seeing the natural world and thus new ways of mapping it. The telescope was what allowed Galileo to sketch, in his book "The Starry Messenger," a first map of Jupiter's largest moons. The invention of the microscope, sometime in the late 16th century, led to Robert Hooke's famous depiction of a flea, its body armored and spiked, as well as the discovery of the cell, an alien world unto itself. Today the pace of invention and the raw power of technology are shocking: A Nobel Prize was awarded last fall for the creation of a microscope with a resolution so extreme that it seems to defy the physical constraints of light itself.

What has made the early 21st century a particularly giddy moment for scientific mapmakers, though, is the precipitous rise of information technology. Advances in computers have provided a cheap means to collect and analyze huge volumes of data, and Moore's Law, which predicts regular doublings in computing power, has shown little sign of flagging. Just as important is the fact that machines can now do the grunt work of research automatically, handling samples, measuring and recording data. Set up a robotic system, feed the data to the cloud and the map will practically draw itself. It's easy to forget Borges's caution: The question is not whether a map can be made, but what insights it will bring. Will future generations cherish a cartographer's work or shake their heads and deliver it up to the inclemencies?

The ur-map of this big science is the one produced by the Human Genome Project, a stem-to-stern accounting of the DNA that provides every cell's genetic instructions. The genome project was completed faster than anyone expected, thanks to Moore's Law, and has become an essential scientific tool. In its wake have come a proliferation of projects in the same vein — the proteome (proteins), the foldome (folding of proteins) — each promising a complete description of something or other. (One online listing includes the antiome: "The totality of people who object to the propagation of omes.") The Brain Initiative, the United States government's 12-year, $4.5 billion brain-mapping effort, is a conscious echo of the genome project, but neuroscientists find themselves in a far more tenuous position at the outset. The brain might be mapped in a host of ways, and the initiative is pursuing many at once. In fact, Seung and his colleagues, who are receiving some of the funding, are working at the margins of contemporary neuroscience. Much of the field's most exciting new technology has sought to track the brain's activity — like functional M.R.I., with its images of parts of the brain "lighting up" — while the connectome would map the brain's physical structure.


Seung discussing his mapping game, EyeWire, at Princeton.

To explain what he finds so compelling about the substance of the brain, Seung points to stories of near death. In May 1999, a young doctor named Anna Bagenholm was skiing down a ravine near the Arctic Circle in Norway when a rock snagged her skis, spinning her halfway around and knocking her onto her back. She sped headfirst down the slope, still on her skis, toward a stream covered with ice. It was a sunny day, unusually warm, and when she hit the ice, she went straight through. Rushing meltwater ballooned her clothes and dragged her farther under the ice. She found an air pocket, and her friends fought to free her, but the current was too strong and the ice too hard. They gripped her feet so they wouldn't lose her. Bagenholm's body went limp. Her heart stopped.

By the time a mountain-rescue team freed her, pulling her body through a hole they cut downstream, she had been under for more than an hour. At that point she was clinically dead. The rescue team began CPR, winched her up into a waiting helicopter and ferried her to Tromso University Hospital, a one-hour flight, her body still showing no signs of life. Her temperature measured 57 degrees. Doctors slowly warmed her, and suddenly her heart started. She spent a month in intensive care but recovered remarkably well. Months later, Bagenholm returned to work and was even skiing again.

What preserved Bagenholm's memories and abilities, over hours, in a state of clinical death? Scientists believe that every thought, every sensation, is a set of tiny electrical impulses coursing through the brain's interconnected neurons. But when a little girl learns a word, for example, her brain makes a record by altering the connections themselves. When she learns to ride a bike or sing "Happy Birthday," a new constellation of connections takes shape. As she grows, every memory — a friend's name, the feel of skis on virgin powder, a Beethoven sonata — is recorded this way. Taken together, these connections constitute her connectome, the brain's permanent record of her personality, talents, intelligence, memories: the sum of all that constitutes her "self." Even after the cold arrested Bagenholm's heart and hushed her crackling neuronal net to a whisper, the connectome endured.

What makes the connectome's relationship to our identity so difficult to understand, Seung told me, is that we associate our "self" with motion. We walk. We sing. We experience thoughts and feelings that bloom into consciousness and then fade. "Psyche" is derived from the Greek "to blow," evoking the vital breath that defines life. "It seems like a fallacy to talk about our self as some wiring diagram that doesn't change very quickly," Seung said. "The connectome is just meat, and people rebel at that."

Seung told me to imagine a river, the roiling waters of the Colorado. That, he said, is our experience from moment to moment. Over time, the water leaves its mark on the riverbed, widening bends, tracing patterns in the rock and soil. In a sense, the Grand Canyon is a memory of where the Colorado has been. And of course, that riverbed shapes the flow of the waters today. There are two selves then, river and riverbed. The river is all tumult and drama. The river demands attention. Yet it's the riverbed that Seung wants to know.

When Seung was just shy of his 5th birthday, his father took him to their local barbershop, a screen-door joint in Austin where the vending machine served Coke in bottles. While Seung's father was getting his hair cut, the barber stopped and pointed out an endearing scene: Little Sebastian was pretending to read the paper. "No," his father said, "I think he's really reading it." The barber went over to investigate, and sure enough, the boy was happy to explain what was happening that day in The Austin American-Statesman. Seung had taught himself to read, in part by asking his father to call out store names and street signs. At 5, he told his father — a man who escaped North Korea on his own as a teenager — that he would no longer be needing toys for Christmas.

Growing up, Seung's primary passions were soccer, mathematics and nonfiction (with an exception made for Greek myths). As a teenager, he was inspired by Carl Sagan's "Cosmos." He took graduate-level physics cours-

PHOTOGRAPH BY DOLLY FAIBYSHEV FOR THE NEW YORK TIMES es as a 17-year-old Harvard sophomore and went directly into Harvard's Ph.D. program in theoretical physics. During a 1989 summer internship at Bell Laboratories, though, Seung fell under the spell of a gregarious Israeli named Haim Sompolinsky, who introduced him to a problem in theoretical neuroscience: How can a network of neurons generate something like an "Aha!" moment, when learning leads to sudden understanding. This brought Seung to his own "Aha!" moment: At the fuzzy border between neuroscience and mathematics, he spied a new scientific terrain, thrilling and largely unexplored, giving him the same feeling physicists must have had when the atom first began to yield its secrets.

Seung became part of a cadre of physicists who deployed sophisticated mathematical techniques to develop an idea dating back as far as Plato and Aristotle, that meaning emerges from the links between things — in this case, the links between neurons. In the 19th century, William James and other psychologists articulated mental processes as associations; for example, seeing a Labrador retriever prompts thoughts of a childhood pet, which leads to musings about a friend who lived next door. As the century closed, the Spanish neuroscientist Santiago Ramón y Cajal was creating illustrations of neurons — long, slim stems and spectacular branches that connected to other neurons with long stems of their own — when people began to wonder whether they were seeing the physical pathways of thought itself.

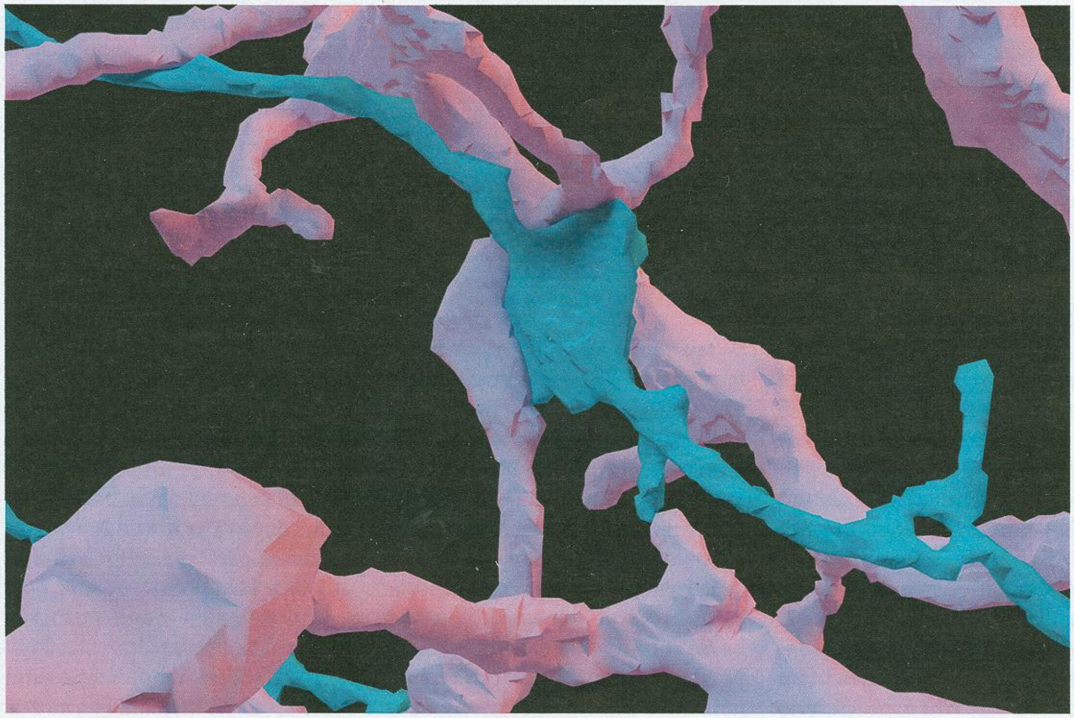
The next turn came in more recent decades as a cross-disciplinary group of researchers, including Seung, hit on a new way of thinking that is described as connectionism. The basic idea (which borrows from computer science) is that simple units, connected in the right way, can give rise to surprising abilities (memory, recognition, reasoning). In computer chips, transistors and other basic electronic components are wired together to make powerful processors. In the brain, neurons are wired together — and rewired. Every time a girl sees her dog (wagging tail, chocolate brown fur), a certain set of neurons fire; this churn of activity is like Seung's Colorado River. When these neurons fire together, the connections between them grow stronger, forming a memory — a part of Seung's riverbed, the connectome that shapes thought. The notion is deeply counterintuitive: It's natural to think of a network functioning as a river system does, a set of streams that can carry messages, but downright odd to suggest that there are parts of the riverbed that encode "Labrador retriever."

A typical human neuron has thousands of connections; a neuron can be as narrow as one ten-thousandth of a millimeter and yet stretch from one side of the head to the other. Only once have scientists ever managed to map the complete wiring diagram of an animal — a transparent worm called C. elegans, one millimeter long with just 302 neurons — and the work required a stunning display of resolve. Beginning in 1970 and led by the South African Nobel laureate Sydney Brenner, it involved painstakingly slicing the worm into thousands of sections, each one-thousandth the width of a human hair, to be photographed under an electron microscope.

That was the easy part. To pull a wiring diagram from the stack of images required identifying each neuron and then following it through the sections, a task akin to tracing the full length of every strand of pasta in a bowl of spaghetti and meatballs, using pens and thousands of blurry black-and-white photos. For C. elegans, this process alone consumed more than a dozen years. When Seung started, he estimated that it would take a single tracer roughly a million years to finish a cubic millimeter of human cortex — meaning that tracing an entire human brain would consume roughly one trillion years of labor. He would need a little help.

In 2012, Seung started EyeWire, an online game that challenges the public to trace neuronal wiring — now using computers, not pens — in the retina of a mouse's eye. Seung's artificial-intelligence algorithms process the raw images, then players earn points as they mark, paint-by-numbers style, the branches of a neuron through a three-dimensional cube. The game has attracted 165,000 players in 164 countries. In effect, Seung is employing artificial intelligence as a force multiplier for a global, all-volunteer army that has included Lorinda, a Missouri grandmother who also paints watercolors, and Iliyan (a.k.a. @crazyman4865), a high-school student in Bulgaria who once played for nearly 24 hours straight. Computers do what they can and then leave the rest to what remains the most potent pattern-recognition technology ever discovered: the human brain.

Ultimately, Seung still hopes that artificial intelligence will be able to handle the entire job. But in the meantime, he is working to recruit more help. In August, South Korea's largest telecom company announced a partnership with EyeWire, running nationwide ads to bring in more players. In the next few years, Seung hopes to go bigger by enticing a company to turn EyeWire into a game with characters and a story line that people play purely for fun. "Think of what we could do," Seung said, "if we could capture even a small fraction of the mental effort that goes into Angry Birds."



Two neurons, mapped by EyeWire players, making contact at a synapse.

The Janelia Research Campus features a serpentine "landscape building" constructed into the side of a hill northwest of Washington. The facility, funded by the Howard Hughes Medical Institute, is nearly 1,000 feet long, and most of the exterior walls are glass, the unusual design a result of a "view preservation" stricture put in place in perpetuity by the previous owners of the land. From the top of the hill, you can see little sign of the $500 million building, except for a pair of humming silver exhaust silos and a modest glass entryway, all rising inexplicably from a field of wild grasses where plovers have begun to nest.

Over the summer, I went to Janelia to meet Seung, who wore a gray polo shirt, blue shorts and a pair of Crocs.

 PHOTO ILLUSTRATION BY DANNY JONES. ORIGINAL IMAGES FROM EYEWIRE.

He was there to talk about possible collaborations and learn about the technology that others in the field are developing. Inside, he introduced me to Harald Hess, an acknowledged genius at creating new scientific tools. (Hess helped build a prototype in his living room of the extreme-resolution microscope — the one that earned a longtime colleague a Nobel this year.) Hess led us down a wide, arcing service corridor, the ceiling hung with exposed pipes, the wall lined with pallets of fruit-fly food. He unlocked a door and then ushered Seung into a room with white plastic curtains hanging from the 20-foot ceilings. He parted one with a *kshreeek* of releasing Velcro and said, "This is our 'act of God'-proof room."

The room contained a pair of hulking beige devices, labeled "MERLIN" in black letters — each part of a new brain-imaging system. The system combines slicing and imaging: An electron microscope takes a picture of the brain sample from above, then a beam of ions moves across the top, vaporizing material and revealing the next layer of brain tissue for the microscope. It is, however, a "temperature-sensitive beast," said Shan Xu, a scientist at Janelia. If the room warms by even a fraction of a degree, the metal can expand imperceptibly, skewing the ion beam, wrecking the sample and forcing the team to start over. Xu was once within days of completing a monthslong run when a July heat wave caused the air-conditioning to hiccup. All the work was lost. Xu has since designed elaborate fail-safes, including a system that can (and does) wake him up in the middle of the night; Janelia has also invested several hundred thousand dollars in backup climate control. "We've learned more about utilities than you would ever want to know," Hess said.

Here at Janelia, connectome science will face its most demanding test. Gerry Rubin, Janelia's director, said his team hopes to have a complete catalog of high-resolution images of the fruit-fly brain in a year or two and a completely traced wiring diagram within a decade. Rubin is a veteran of genome mapping and saw how technological advances enabled a project that critics originally derided as prohibitively difficult and expensive. He is betting that the story of the connectome will follow the same arc. Ken Hayworth, a scientist in Hess's lab, is developing a way to cleanly cut larger brains into cubes; he calls it "the hot knife." In other labs, Jeff Lichtman of Harvard and Clay Reid of the Allen Institute for Brain Science are building their own ultrafast imaging systems. Denk, Seung's longtime collaborator in Heidelberg, is working on a new device to slice and image a mouse's entire brain, a volume orders of magnitude larger than what has been tried to date. Seung, meanwhile, is improving his tracing software and setting up new experiments — with his mentor Tank and Richard Axel, a Nobel laureate at Columbia — to find memories in the connectome. Still, Rubin admitted, "if we can't do the fly in 10 years, there is no prayer for the field."

At the end of a long day, Seung and I sat on a pair of blue bar stools, sharing some peanuts and sipping on beers at Janelia's in-house watering hole. Seung was feeling daunted. Even at Janelia, which plans to spend roughly $50 million and has some of the best tool-builders on the planet, the connectome of a fruit fly looks to be a decade away. A fruit fly! Will he live to see the first human connectome? "It could be possible," he said, "if we assume that I exercise and eat right."

Years ago, Seung officiated at his best friend's wedding, and during the invocation he told the gathering, "My father says that success is never achieved in just one generation." As he has grown older and had a child of his own, he has felt his perspective shift. When Seung was in his 20s, science for him was solving puzzles, an extension of the math problems he did for fun as a child alone in his room on Saturdays after soccer. Now he finds great satisfaction in encouraging younger scientists, in helping them avoid dead ends that he has already explored. He wants to do something that will allow the community to progress, to build "strong foundations, stepping-stones that the next generation can be sure of."

The grounds of Janelia have a monastic feel, and while talking with Seung, I couldn't help thinking of the people who built Europe's great cathedrals — the carpenters and masons who labored knowing that the work would not be completed until after their deaths. From the bar, we could see through a glass wall to a patio lined with smooth river rocks and a fieldstone wall. A spare shrub garden was set with a trickling stainless-steel fountain, illuminated by a bank of sapphire lights. "I don't know how much I'll accomplish in my lifetime," Seung said. "But the brain is mysterious, and I want to spend my life in the presence of mystery. It's as simple as that."

As connectomics has gained traction, though, there are the first hints that it may be of interest to more than just monkish academics. In September, at a Brain Initiative conference in the Eisenhower building on the White House grounds, it was announced that Google had started its own connectome project. Tom Dean, a Google research scientist and the former chairman of the Brown University computer-science department, told me he has been assembling a team to improve the artificial intelligence: four engineers in Mountain View, Calif., and a group based in Seattle. To begin, Dean said, Google will be working most closely with the Allen Institute, which is trying to understand how the brain of a mouse processes images from the eye. Yet Dean said they also want to serve as a clearinghouse for Seung and others, applying different variations of artificial intelligence to brain imagery coming out of different labs, to see what works best. Eventually, Dean said, he hopes for a Google Earth of the brain, weaving together many different kinds of maps, across many scales, allowing scientists to behold an entire brain and then zoom in to see the firing of a single neuron, "like lightning in a thunderstorm."

'THE BRAIN IS MYSTERIOUS, AND I WANT TO SPEND MY LIFE IN THE PRESENCE OF MYSTERY.'

It's possible now to see a virtuous cycle that could build the connectome. The artificial intelligence used at Google, and in EyeWire, is known as deep learning because it takes its central principles from the way networks of neurons function. Over the last few years, deep learning has become a precious commercial tool, bringing unexpected leaps in image and voice recognition, and now it is being deployed to map the brain. This could, in the coming decades, lead to more insights about neural networks, improving deep learning itself — the premise of a new project funded by Iarpa, a blue-sky research arm of the American intelligence community, and perhaps one reason for Google's interest. Better deep learning, in turn, could be used to accelerate the mapping and understanding of the brain, and so on.

Even so, the shadow of Borges remains. The first connectome project began in the 1960s with the same intuition that later drove Seung: Sydney Brenner wanted a way to understand how behavior emerges from a biological system and thought that having a complete map of an animal's nervous system would be essential. Brenner settled on the worm C. elegans for simplicity's sake; it is small and prospers in a laboratory dish. The results were published in 1986 at book length, taking over the entirety of Philosophical Transactions of the Royal Society of London, science's oldest journal, the outlet for a young Isaac Newton. Biologists were electrified and still sometimes refer to that 340-page edition of the journal as "the book."

Yet nearly three decades later, Brenner's diagram continues to mystify. Scientists know roughly what individual neurons in C. elegans do and can say, for example, which neurons fire to send the worm wriggling forward or backward. But more complex questions remain unanswered. How does the worm remember? What is constant in the minds of worms? What makes each one individual? In part, these disappointments were a problem of technology, which has made connectome mapping so onerous that until recently nobody considered doing more. In science, it is a great accomplishment to make the first map, but far more *(Continued on Page 50)*

SEUNG
(Continued from Page 31)

useful to have 10, or a million, that can be compared with one another. "C. elegans was a classic case of being too far ahead of your time," says Gerry Rubin of Janelia.

The difficulties of interpreting the worm connectome can also be attributed to the fact that it has been particularly difficult to see the worm's wiring in action, to measure the activity of the worm's neurons. Without enough activity data, a wiring diagram is fundamentally inscrutable — a problem akin to trying to read the hieroglyphs of ancient Egypt before the Rosetta Stone, with its parallel text in ancient Greek. A connectome is not an answer, but a clue, like a hieroglyphic stele pulled up from the sand, promising insight into an empire but sadly lacking a key.

In 2000, President Bill Clinton and Prime Minister Tony Blair of Britain held a news conference to announce a complete draft of the human genome, which Clinton called the "most wondrous map ever produced by humankind." The map has indeed proved full of wonder — modern biology would be impossible without it — but in the years since, it has also become clear how incomplete the cartography is. The genome project identified roughly 20,000 genes, but cells also use a system of switches that turn genes off and on, and this system, called epigenetics, determines what work a cell can do and shapes what diseases a person might be prone to. Recent estimates put the number of switches in the hundreds of thousands, perhaps a million. An international consortium is now trying to map the epigenome, and no one can say when it will be finished.

Eve Marder, a prominent neuroscientist at Brandeis University, cautions against expecting too much from the connectome. She studies neurons that control the stomachs of crabs and lobsters. In these relatively simple systems of 30 or so neurons, she has shown that neuromodulators — signaling chemicals that wash across regions of the brain, omitted from Seung's static map — can fundamentally change how a circuit functions. If this is true for the stomach of a crustacean, the mind reels to consider what may be happening in the brain of a mouse, not to mention a human.

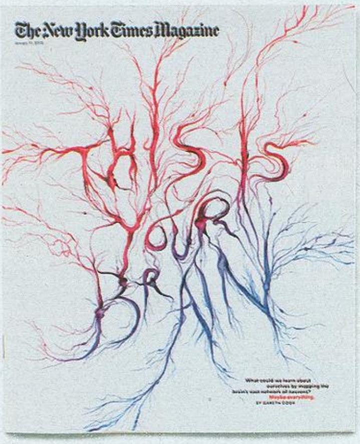
The history of science is a narrative full of characters convinced that they had found the path to understanding everything, only to have the universe unveil a Sisyphean twist. Physicists sought matter's basic building blocks and discovered atoms, but then found that atoms had their own building blocks, which had their own pieces, which has brought us, today, to string theory, the discipline's equivalent of a land war in Asia. After the genome delivered up the text of humanity's genetic code, biologists realized that our genetic machinery is so filled with feedback, and layers built on layers, that their work had only begun. Critics of Seung's vision therefore see it as naïve, a faith that he can crest the mountain in front of him and not find more imposing peaks beyond. "If we want to understand the brain," Marder says, "the connectome is absolutely necessary and completely insufficient."

Seung agrees but has never seen that as an argument for abandoning the enterprise. Science progresses when its practitioners find answers — this is the way of glory — but also when they make something that future generations rely on, even if they take it for granted. That, for Seung, would be more than good enough. "Necessary," he said, "is still a pretty strong word, right?" ◆

SEBASTIAN SEUNG'S QUEST TO MAP THE BRAIN

Reductionism is the favored path to understanding the brain these days, but what the computer model of the brain cannot explain is the connection between sensation and perception. For example, how is it that we understand that a tree we have never seen before is a tree? That we can use previous input to shape new stimuli is, to my mind, evidence that our memory works nothing like digital memory. That memory and recognition is widely distributed in the brain and not confined to one small series of connections is reason enough for me to question Seung's view of how the brain operates.

DAVID UNDERWOOD, *posted on nytimes.com*



The important part of Seung's work is not a complete map of the connectome. It is the frame of reference that he employs to relate any description of any neural circuitry to any type of mental activity, whether it be perception, the evocation of wonder or self-discovery. Seung obviously knows that his work will not yield a complete "circuit description" of the human brain, and probably doesn't care. His most important contribution will be the way circuit diagrams can be used to explain elements of human mental activity in a nontrivializing manner. He can let someone else worry about describing everything or downloading brains onto powerful computers. The trajectory of Seung's work is what is most important. **KENNETH MOSELLE,** *Victoria, British Columbia, posted on nytimes.com*

THE SEARCH FOR PETR KHOKHLOV

Through this detailed, careful account, we begin to see larger stories playing out: the Russian Federation in the disorder of decline, the longing of ordinary people for "stability" at any cost and the chaos sown by Russia's neo-imperialist ambitions, all set against the backdrop of Ukraine's failure to pull its rival ethnic groups together. And in the midst of all these larger forces and events, there are young men and women striving to do the right thing. **T.L. MORAN,** *Idaho, posted on nytimes.com*

NEXT YEAR IN HAVANA

It's been more than 50 years since the U.S. set up an embargo on trade with Cuba. Looking at those beautiful pictures, I realized that Cuba today looks very similar to how it looked a half-century ago. There are robust opportunities for the United States and Cuba to improve their economies and