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# Understanding The Brain



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# UNDERSTANDING THE BRAIN

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# Obama Seeking to Boost Study of Human Brain

By **JOHN MARKOFF**

*FEB. 17, 2013*

The Obama administration is planning a decade-long scientific effort to examine the workings of the human brain and build a comprehensive map of its activity, seeking to do for the brain what the Human Genome Project did for genetics.

The project, which the administration has been looking to unveil as early as March, will include federal agencies, private foundations and teams of neuroscientists and nanoscientists in a concerted effort to advance the knowledge of the brain's billions of neurons and gain greater insights into perception, actions and, ultimately, consciousness.

Scientists with the highest hopes for the project also see it as a way to develop the technology essential to understanding diseases like Alzheimer's and Parkinson's, as well as to find new therapies for a variety of mental illnesses.

Moreover, the project holds the potential of paving the way for advances in artificial intelligence.

The project, which could ultimately cost billions of dollars, is expected to be part of the president's budget proposal next month. And, four scientists and representatives of research institutions said they had participated in planning for what is being called the Brain Activity Map project.

The details are not final, and it is not clear how much federal money would be proposed or approved for the project in a time of fiscal constraint or how far the research would be able to get without significant federal financing.

In his State of the Union address, President Obama cited brain research as an example of how the government should "invest in the best ideas."

"Every dollar we invested to map the human genome returned \$140 to our economy — every dollar," he said. "Today our scientists are mapping the human brain to unlock the answers to Alzheimer's. They're developing drugs to regenerate damaged organs, devising new materials to make batteries 10 times more powerful. Now is not the time to gut these job-creating investments in science and innovation."

Story C. Landis, the director of the National Institute of Neurological Disorders and Stroke, said that when she heard Mr. Obama's speech, she thought he was referring to an

existing National Institutes of Health project to map the static human brain. “But he wasn’t,” she said. “He was referring to a new project to map the active human brain that the N.I.H. hopes to fund next year.”

Indeed, after the speech, Francis S. Collins, the director of the National Institutes of Health, may have inadvertently confirmed the plan when he wrote in a Twitter message: “Obama mentions the #NIH Brain Activity Map in #SOTU.”

A spokesman for the White House Office of Science and Technology Policy declined to comment about the project.

The initiative, if successful, could provide a lift for the economy. “The Human Genome Project was on the order of about \$300 million a year for a decade,” said George M. Church, a Harvard University molecular biologist who helped create that project and said he was helping to plan the Brain Activity Map project. “If you look at the total spending in neuroscience and nanoscience that might be relative to this today, we are already spending more than that. We probably won’t spend less money, but we will probably get a lot more bang for the buck.”

Scientists involved in the planning said they hoped that federal financing for the project would be more than \$300 million a year, which if approved by Congress would amount to at least \$3 billion over the 10 years.

The Human Genome Project cost \$3.8 billion. It was begun in 1990 and its goal, the mapping of the complete human genome, or all the genes in human DNA, was achieved ahead of schedule, in April 2003. A federal government study of the impact of the project indicated that it returned \$800 billion by 2010.

The advent of new technology that allows scientists to identify firing neurons in the brain has led to numerous brain research projects around the world. Yet the brain remains one of the greatest scientific mysteries.

Composed of roughly 100 billion neurons that each electrically “spike” in response to outside stimuli, as well as in vast ensembles based on conscious and unconscious activity, the human brain is so complex that scientists have not yet found a way to record the activity of more than a small number of neurons at once, and in most cases that is done invasively with physical probes.

But a group of nanotechnologists and neuroscientists say they believe that technologies are at hand to make it possible to observe and gain a more complete understanding of the brain, and to do it less intrusively.

In June in the journal *Neuron*, six leading scientists proposed pursuing a number of new approaches for mapping the brain.

One possibility is to build a complete model map of brain activity by creating fleets

of molecule-size machines to noninvasively act as sensors to measure and store brain activity at the cellular level. The proposal envisions using synthetic DNA as a storage mechanism for brain activity.

“Not least, we might expect novel understanding and therapies for diseases such as schizophrenia and autism,” wrote the scientists, who include Dr. Church; Ralph J. Greenspan, the associate director of the Kavli Institute for Brain and Mind at the University of California, San Diego; A. Paul Alivisatos, the director of the Lawrence Berkeley National Laboratory; Miyoung Chun, a molecular geneticist who is the vice president for science programs at the Kavli Foundation; Michael L. Roukes, a physicist at the California Institute of Technology; and Rafael Yuste, a neuroscientist at Columbia University.

The Obama initiative is markedly different from a recently announced European project that will invest 1 billion euros in a Swiss-led effort to build a silicon-based “brain.” The project seeks to construct a supercomputer simulation using the best research about the inner workings of the brain.

Critics, however, say the simulation will be built on knowledge that is still theoretical, incomplete or inaccurate.

The Obama proposal seems to have evolved in a manner similar to the Human Genome Project, scientists said. “The genome project arguably began in 1984, where there were a dozen of us who were kind of independently moving in that direction but didn’t really realize there were other people who were as weird as we were,” Dr. Church said.

However, a number of scientists said that mapping and understanding the human brain presented a drastically more significant challenge than mapping the genome.

“It’s different in that the nature of the question is a much more intricate question,” said Dr. Greenspan, who said he is involved in the brain project. “It was very easy to define what the genome project’s goal was. In this case, we have a more difficult and fascinating question of what are brainwide activity patterns and ultimately how do they make things happen?”

The initiative will be organized by the Office of Science and Technology Policy, according to scientists who have participated in planning meetings.

The National Institutes of Health, the Defense Advanced Research Projects Agency and the National Science Foundation will also participate in the project, the scientists said, as will private foundations like the Howard Hughes Medical Institute in Chevy Chase, Md., and the Allen Institute for Brain Science in Seattle.

A meeting held on Jan. 17 at the California Institute of Technology was attended by

the three government agencies, as well as neuroscientists, nanoscientists and representatives from Google, Microsoft and Qualcomm. According to a summary of the meeting, it was held to determine whether computing facilities existed to capture and analyze the vast amounts of data that would come from the project. The scientists and technologists concluded that they did.

They also said that a series of national brain “observatories” should be created as part of the project, like astronomical observatories.

# Obama to Unveil Initiative to Map the Human Brain

By **JOHN MARKOFF** and **JAMES GORMAN**

*APRIL 2, 2013*

President Obama on Tuesday will announce a broad new research initiative, starting with \$100 million in 2014, to invent and refine new technologies to understand the human brain, senior administration officials said Monday.

A senior administration scientist compared the new initiative to the Human Genome Project, in that it is directed at a problem that has seemed insoluble up to now: the recording and mapping of brain circuits in action in an effort to “show how millions of brain cells interact.”

It is different, however, in that it has, as yet, no clearly defined goals or endpoint. Coming up with those goals will be up to the scientists involved and may take more than year.

The effort will require the development of new tools not yet available to neuroscientists and, eventually, perhaps lead to progress in treating diseases like Alzheimer’s and epilepsy and traumatic brain injury. It will involve both government agencies and private institutions.

The initiative, which scientists involved in promoting the idea have been calling the Brain Activity Map project, will officially be known as Brain Research Through Advancing Innovative Neurotechnologies, or Brain for short; it has been designated a grand challenge of the 21<sup>st</sup> century by the Obama administration.

Three government agencies will be involved: the National Institutes of Health, the Defense Advanced Research Projects Agency and the National Science Foundation. A working group at the N.I.H., described by the officials as a “dream team,” and led by Cori Bargmann of Rockefeller University and William Newsome of Stanford University, will be charged with coming up with a plan, a time frame, specific goals and cost estimates for future budgets.

The initiative exists as part of a vast landscape of neuroscience research supported by billions of dollars in federal money. But Dr. Newsome said that he thought a small amount of money applied in the right way could nudge neuroscience in a new direction.



“The goal here is a whole new playing field, whole new ways of thinking,” he said. “We are really out to catalyze a paradigm shift.”

Brain researchers can now insert wires in the brain of animals, or sometimes human beings, to record the electrical activity of brain cells called neurons, as they communicate with each other. But, Dr. Newsome said, they can record at most hundreds at a time.

New technology would need to be developed to record thousands or hundreds of thousands of neurons at once. And, Dr. Newsome said, new theoretical approaches, new mathematics and new computer science are all needed to deal with the amount of data that will be garnered.

As part of the initiative, the president will require a study of the ethical implications of these sorts of advances in neuroscience.

While news of the announcement has been greeted with enthusiasm by many researchers in fields as diverse as neuroscience, nanotechnology and computer science, there are skeptics.

“The underlying assumptions about ‘mapping the entire brain’ are very controversial,” said Donald Stein, a neuroscientist at Emory University in Atlanta. He said changes in brain chemistry were “not likely to be able to be imaged by the current technologies that these people are proposing.”

Emphasizing the development of technologies first, he said, is not a good approach. “I think the monies could be better spent by first figuring out what needs to be measured and then figuring out the most appropriate means to measure them.” he said. “In my mind, the technology ought to follow the concepts rather than the other way around.”

However, supporters of the initiative argued that it could have a similar impact as the Sputnik satellite had in the 1950s, when the United States started a significant nationwide effort to invest in science and technology.

“This is a different time,” said Michael Roukes, a physicist at the California Institute of Technology. “It makes sense to have a brain activity map now because the maturation of an array of nanotechnologies can be brought to bear on the problem.”

While the dollar amount committed by the Obama administration does not match the level of spending on the Human Genome Project, scientists said that whatever was spent on the brain initiative would have a significant multiplier effect. The Salk Institute in La Jolla, Calif., is contributing money, said Terrence J. Sejnowski, head of the institute’s computational biology laboratory, adding that the project would have an impact at the neighboring University of California, San Diego, campus.

“One concrete example is that the chancellor has gotten excited about this and has decided that it is a great thing to invest in,” Dr. Sejnowski said. “That means hiring new

faculty and creating new space.”

The project grew out of an interdisciplinary meeting of neuroscientists and nanoscientists in London in September 2011. Miyoung Chun, a molecular biologist who is vice president of scientific programs at the Kavli Foundation, had organized the conference. Her foundation, she said, supports the idea that the next big scientific discoveries will come from interdisciplinary research.

“Federal funding is scarce these days, and I realized we need inspiring projects that can awake everyone’s imagination,” she said. “It occurred to me that this is a very inspiring idea.”

# Brains as Clear as Jell-O for Scientists to Explore

By **JAMES GORMAN**

*April 10, 2013*

The visible brain has arrived — the consistency of Jell-O, as transparent and colorful as a child’s model, but vastly more useful.

Scientists at Stanford University reported on Wednesday that they have made a whole mouse brain, and part of a human brain, transparent so that networks of neurons that receive and send information can be highlighted in stunning color and viewed in all their three-dimensional complexity without slicing up the organ.

Even more important, experts say, is that unlike earlier methods for making the tissue of brains and other organs transparent, the new process, called Clarity by its inventors, preserves the biochemistry of the brain so well that researchers can test it over and over again with chemicals that highlight specific structures and provide clues to past activity. The researchers say this process may help uncover the physical underpinnings of devastating mental disorders like schizophrenia, autism, post-traumatic stress disorder and others.

The work, reported on Wednesday in the journal *Nature*, is not part of the Obama administration’s recently announced initiative to probe the secrets of the brain, although the senior author on the paper, Dr. Karl Deisseroth at Stanford, was one of those involved in creating the initiative and is involved in planning its future.

Dr. Thomas Insel, director of the National Institute of Mental Health, which provided some of the financing for the research, described the new work as helping to build an anatomical “foundation” for the Obama initiative, which is meant to look at activity in the brain.

Dr. Insel added that the technique works in a human brain that has been in formalin, a preservative, for years, which means that long-saved human brains may be studied. “Frankly,” he said, “that is spectacular.”

Kwanghun Chung, the primary author on the paper, and Dr. Deisseroth worked with a team at Stanford for years to get the technique right. Dr. Deisseroth, known for developing another powerful technique, called optogenetics, that allows the use of light to switch specific brain activity on and off, said Clarity could have a broader impact than

optogenetics. “It’s really one of the most exciting things we’ve done,” he said, with potential applications in neuroscience and beyond.

“I think it’s great,” said Dr. Clay Reid, a senior investigator at the Allen Institute for Brain Science in Seattle, who was not involved in the work. “One of the very difficult challenges has been making the brain, which is opaque, clear enough so that you can see deep into it.” This technique, he said, makes brains “extremely clear” and preserves most of the brain chemistry. “It has it all,” he said.

In the mid-2000s, a team led by Dr. Jeff Lichtman at Harvard developed a process called Brainbow to breed mice that are genetically altered to make their brain neurons fluoresce in many different colors. The new technique would allow whole brains of those mice with their rainbow neurons to be preserved and studied.

“I’m quite excited to try this,” Dr. Lichtman said.

There are several ways to make tissue transparent. The key to the new technique is a substance called a hydrogel, a material that is mostly water held together by larger molecules to give it some solidity.

Dr. Chung said the hydrogel forms a kind of mesh that permeates the brain and connects to most of the molecules, but not to the lipids, which include fats and some other substances. The brain is then put in a soapy solution and an electric current is applied, which drives the solution through the brain, washing out the lipids. Once they are out, the brain is transparent, and its biochemistry is intact, so it may be infused with chemicals, like antibody molecules that also have a dye attached, that show fine details of its structure and previous activity.

Techniques like this, said Dr. Insel, “should give us a much more precise picture of what is happening in the brains of people who have schizophrenia, autism, post-traumatic stress disorder, bipolar disorder and depression.”

The tricky part was getting the right combination of temperature, electricity and solution. And it was very tricky indeed, said Dr. Chung. Over the course of years spent trying to make it work, he said, “I burned and melted more than a hundred brains.”

But with the paper’s publication, the recipe is now available to anyone who wants to use it, and, he said, “I think it will be relatively easy.”

The technique has its limits, of course. Dr. Chung said more work needed to be done before it could be applied to a whole human brain, because a human’s brain is so much larger than a mouse’s, and has more lipids.

Dr. Chung said he planned to start his own lab soon and to work on refining the technology. But he pointed out that it is already known that it works on all tissue, not just

brains, and can be used to look for structures other than nerve cells. On his laboratory bench, he said, "I have a transparent liver, lungs and heart."

Dr. Reid agreed that Clarity had applications in many fields. "It could permeate biology," he said.

# 3-D Map of Human Brain Gives Unprecedented Detail

By **JAMES GORMAN**

*June 20, 2013*

Researchers in Germany and Canada have produced a new map of the human brain — not the sort that shows every brain cell and its every connection or the kind that shows broad patterns of activity in brain regions, but a work of classic anatomy, done with high technology, that shows a three-dimensional reconstruction of a human brain in unprecedented detail.

The new map, called BigBrain, is 50 times as detailed as previous efforts and will be available to researchers everywhere, said Katrin Amunts of the Institute of Neuroscience and Medicine in Jülich, Germany, the lead author of a report on the project in the current issue of *Science*.

BigBrain depicts a specific human brain, that of a 65-year-old woman. It was preserved in paraffin after her death, sliced into 7,400 sections and photographed at a microscopic level just above that of viewing individual cells. Its portrait will serve, the researchers said, as an anatomical framework that other researchers can use as a reference, whether they are investigating large patterns of brain function or small details.

This kind of anatomical map is not what neuroscientists are pursuing in the new brain initiative from the Obama administration, nor does it show the expression of genes or connectivity that other projects are pursuing. But David Van Essen, a neuroscientist at Washington University in St. Louis and a principal investigator in the Human Connectome Project, which uses M.R.I. images of active human brains, described the work as a “technological tour de force,” adding that the three-dimensional reconstruction could help distinguish the many small areas of the brain with greater accuracy.

# The Map Makers: The Brain, in Exquisite Detail



Deanna Barch and her colleagues are trying to map connections in the human brain. The study is part of the Human Connectome Project. (Zach Wise for The New York Times)

**By JAMES GORMAN**

*January 6, 2014*

ST. LOUIS — Deanna Barch talks fast, as if she doesn't want to waste any time getting to the task at hand, which is substantial. She is one of the researchers here at Washington University working on the first interactive wiring diagram of the living, working human brain.

To build this diagram she and her colleagues are doing brain scans and cognitive, psychological, physical and genetic assessments of 1,200 volunteers. They are more than a third of the way through collecting information. Then comes the processing of data, incorporating it into a three-dimensional, interactive map of the healthy human brain showing structure and function, with detail to one and a half cubic millimeters, or less than 0.0001 cubic inches.

Dr. Barch is explaining the dimensions of the task, and the reasons for undertaking it, as she stands in a small room, where multiple monitors are set in front of a window that looks onto an adjoining room with an M.R.I. machine, in the psychology building. She asks a research assistant to bring up an image. “It’s all there,” she says, reassuring a reporter who has just emerged from the machine, and whose brain is on display.

And so it is, as far as the parts are concerned: cortex, amygdala, hippocampus and all the other regions and subregions, where memories, fear, speech and calculation occur. But this is just a first go-round. It is a static image, in black and white. There are hours of scans and tests yet to do, though the reporter is doing only a demonstration and not completing the full routine.

Each of the 1,200 subjects whose brain data will form the final database will spend a good 10 hours over two days being scanned and doing other tests. The scientists and technicians will then spend at least another 10 hours analyzing and storing each person’s data to build something that neuroscience does not yet have: a baseline database for structure and activity in a healthy brain that can be cross-referenced with personality traits, cognitive skills and genetics. And it will be online, in an interactive map available to all.

Dr. Helen Mayberg, a doctor and researcher at the Emory University School of Medicine, who has used M.R.I. research to guide her development of a treatment for depression with deep brain stimulation, a technique that involves surgery to implant a pacemaker-like device in the brain, is one of the many scientists who could use this sort of database to guide her research. With it, she said, she can ask, “how is this really critical node connected” to other parts of the brain, information that will inform future research and surgery.

The database and brain map are a part of the Human Connectome Project, a roughly \$40 million five-year effort supported by the National Institutes of Health. It consists of two consortiums: a collaboration among researchers at Harvard, Massachusetts General Hospital and the Laboratory of Neuro Imaging, which moved last year to the University of Southern California from U.C.L.A., to improve M.R.I. technology and the \$30 million project Dr. Barch is part of, involving Washington University, the University of Minnesota and the University of Oxford.

Dr. Barch is a psychologist by training and inclination who has concentrated on neuroscience because of the desire to understand severe mental illness. Her role in the project has been in putting together the battery of cognitive and psychological tests that go along with the scans, and overseeing their administration. This is the information that will give depth and significance to the images.



She said the central question the data might help answer was, “How do differences between you and me, and how our brains are wired up, relate to differences in our behaviors, our thoughts, our emotions, our feelings, our experiences?”

And, she added, “Does that help us understand how disorders of connectivity, or disorders of wiring, contribute to or cause neurological problems and psychiatric problems?”

The Human Connectome Project is one of a growing number of large, collaborative information-gathering efforts that signal a new level of excitement in neuroscience, as rapid technological advances seem to be bringing the dream of figuring out the human brain into the realm of reality.

## **Worldwide Study**

In Europe, the Human Brain Project has been promised \$1 billion for computer modeling of the human brain. In the United States last year, President Obama announced an initiative to push brain research forward by concentrating first on developing new technologies. This so-called Grand Challenge has been promised \$100 million of financing for the first year of what is anticipated to be a decade-long push. The money appears to be real, but it may come from existing budgets, and not from any increase for the federal agencies involved.

A vast amount of research is already going on — so much that the neuroscience landscape is almost as difficult to encompass as the brain itself. The National Institutes of Health alone spends \$5.5 billion a year on neuroscience, much of it directed toward research on diseases like Parkinson’s and Alzheimer’s.

A variety of private institutes emphasize basic research that may not have any immediate payoff. For instance, at the Allen Institute for Brain Science in Seattle, Janelia Farm in Virginia, part of the Howard Hughes Medical Institute, and at numerous universities, researchers are trying to understand how neurons compute — what the brains of mice, flies and human beings do with their information. The Allen Institute is now spending \$60 million a year and Janelia Farm about \$30 million a year on brain research. The Kavli Foundation has committed \$4 million a year for 10 years, and the Salk Institute in San Diego plans to spend a total of \$28 million on new neuroscience research. And there are others in the U.S. and abroad.

To be sure, this is not the first time such a focus has been placed on brain research. The 1990s were anointed the decade of the brain by President George H. W. Bush. Strides were made, but many aspects of the brain have remained mysterious.

There is, however, a good reason for the current excitement, and that is accelerating technological change that the most sanguine of brain mappers compare to the growing ability to sequence DNA that led to the Human Genome Project.

Optogenetics is one new technique that has been transformative. It uses light to turn on different parts of the brain in laboratory animals to open and shut modified genes. Powerful developments in microscopy made possible movies of brain activity in living animals. A modified rabies virus can target one brain cell and mark every other cell that is connected to it.

“There is an explosion of new techniques,” said Dr. R. Clay Reid, a senior investigator at the Allen Institute, who recently moved there from Harvard Medical School. “And the end isn’t really in sight,” said Dr. Reid, who is taking advantage of just about every new technology imaginable in his quest to decipher the part of the mouse brain devoted to vision.

## **Charting the Brain**

Of the many metaphors used for exploring and understanding the brain, mapping is probably the most durable, perhaps because maps are so familiar and understandable. “A century ago, brain maps were like 16<sup>th</sup>-century maps of the Earth’s surface,” said David Van Essen, who is in charge of the Connectome effort at Washington University, where Dr. Barch works. Much was unknown or mislabeled. “Now our characterizations are more like an 18<sup>th</sup>-century map.”

The continents, mountain ranges and rivers are getting more clearly defined. His hope, he said, is that the Human Connectome Project will be a step toward vaulting through the 19<sup>th</sup> and 20<sup>th</sup> centuries and reaching something more like Google Maps, which is interactive and has many layers.

Researchers may not be looking for the best sushi restaurants or how to get from one side of Los Angeles to the other while avoiding traffic, but they will eventually be looking for traffic flow, particularly popular routes for information, and matching traffic patterns to the tasks the brain is doing. They will also be asking how differences in the construction of the pathways that make up the brain’s roads relate to differences in behavior, intelligence, emotion and genetics.

The power of computers and mathematical tools devised for analyzing vast amounts of data made such maps possible. The gathering tool of choice at Washington University is an M.R.I. machine customized at the University of Minnesota.

An M.R.I. machine creates a magnetic field surrounding the body part to be scanned, and sends radio waves into the body. Unlike X-rays, which are known to pose

some dangers, M.R.I. scans are considered to be safe. It is one of the few methods of noninvasive scanning that can survey a whole human brain.

There are a variety of ways to gather and interpret information in an M.R.I. machine. And different types of scans can show both basic structure and activity. When a volunteer is trying to solve a memory problem, the hippocampus, the amygdala and the prefrontal cortex are all going to be involved. An M.R.I. machine can detect the direction of information flow, in a technique called diffusion imaging. In that kind of scan, the movement of water molecules shows not only activity, but which way the traffic is headed.

### **A Path to Research**

For Dr. Barch, 48, another kind of interest in the human brain put her on the path to Washington University. “I always knew I wanted to be a psychologist,” she said — specifically, a school psychologist. But as an undergraduate at Northwestern, she excelled in an abnormal psychology class, and the professor recruited her to do research.

“When I graduated from college, I decided to become a case manager for the chronically mentally ill for a year to kind of suss out, ‘Do I want to do more clinical work or research?’ ” she said. “That was a great experience, but it really made me realize that research is the only way you’re going to have an impact on many lives, rather than sort of individual lives.”

She obtained her Ph.D. in clinical psychology at the University of Illinois at Urbana-Champaign. but then did postdoctoral study in cognitive neuroscience at the University of Pittsburgh and Carnegie Mellon University. Her years in graduate school in the 1990s coincided with the development and use of the so-called functional M.R.I., which can show not just static structure, but the brain in action.

“I got into the field when functional imaging was just at its very beginning, so I was able to learn on the ground floor,” she said.

She moved to Washington University after her postdoctoral research partly because of the number of people there working on imaging, including Dr. Marcus E. Raichle, a pioneer in developing ways of watching the brain at work.

As a professor at Washington University and a leader of one of five teams there working on the Human Connectome Project, Dr. Barch focuses her research on the way individual differences in the brains of healthy people are related to differences in personality or thinking.

For instance she said, people doing memory tasks in the M.R.I. machine may differ in competitiveness and commitment to doing well. That ought to show up in activity in

the parts of the brain that involve emotion, like the amygdala. However, she points out that the object of the Connectome Project is not to find the answers to these questions, but to provide the database for others to try to do so.

### **‘Pretty Close’**

The project at Washington University requires exhaustive scans of 1,200 healthy people, age 22 to 35, each of whom spends about four hours over two days lying in the noisy, claustrophobia-inducing cylinder of a customized M.R.I. machine. Sometimes they stare at one spot, curl their toes or move their fingers. They might play gambling games, or try memory tests that can flummox even the sharpest minds.

“In an ideal world, we would have enough tasks to activate every part of the brain,” she said. “We got pretty close. We’re not perfect, but pretty close.”

Over the two days, the research subjects spend another six hours taking other tests designed to measure intelligence, basic physical fitness, tasting ability and their emotional state.

The volunteers (and they are all volunteers, paid a flat \$400 for their time and effort) can also be seen in street clothes, doing a kind of race around two traffic cones in the sunlit corridor of the glass-walled psychology building, with data collected on how quickly they complete the course.

Or they can be glimpsed padding down a hallway in their stocking feet from the M.R.I. machine to an office where a technician dabs their tongues with a swab dipped in a mystery liquid, then asks them to identify the intensity and quality of the taste.

In the same office, they type in answers to cognitive tests, and to a psychological survey, for which they are left in solitude because of the personal nature of some of the questions: how they feel about life, how often they are sad. The results are confidential, as are all the test results.

So far almost 500 subjects have gone through the full range of tests, which amounts to about 5,000 hours of work for Dr. Barch and others in the program.

So far, data has been released for 238 subjects, and it is available to everyone for free through a web-based database and software program called Workbench.

The sharing of data is characteristic of most of the new brain research efforts, and particularly important to Dr. Barch.

“The amount of time and energy we’re spending collecting this data, there’s no possible way any one research group could ever use it to the extent that justifies the cost,” she said. “But letting everybody use it — great!”

## **The Elusive Brain**

No one expects the brain to yield its secrets quickly or easily. Neuroscientists are fond of deflecting hope even as they point to potential success. Science may come to understand neurons, brain regions, connections, make progress on Parkinson's, Alzheimer's or depression, and even decipher the code or codes the brain uses to send and store information. But, as any neuroscientist sooner or later cautions in discussing the prospects for breakthroughs, we are not going to "solve the brain" anytime soon — not going to explain consciousness, the self, the precise mechanisms that produce a poem.

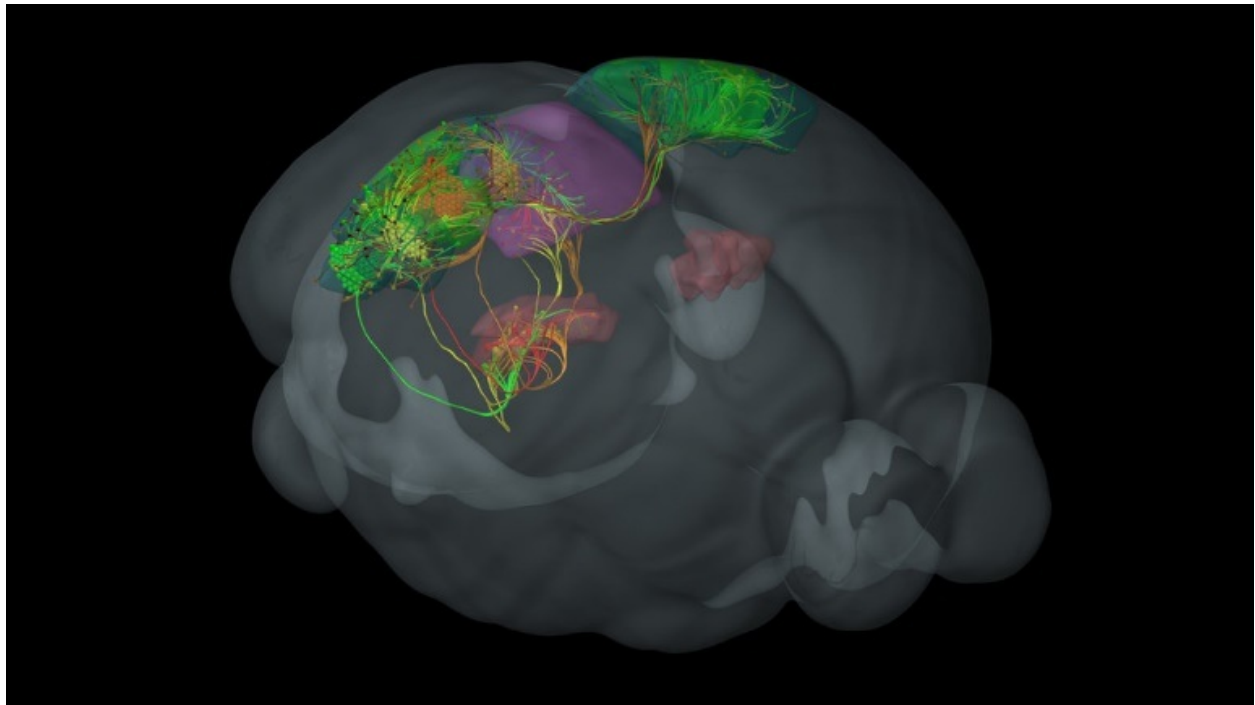
Perhaps the greatest challenge is that the brain functions and can be viewed at so many levels, from a detail of a synapse to brain regions trillions of times larger. There are electrical impulses to study, biochemistry, physical structure, networks at every level and between levels. And there are more than 40,000 scientists worldwide trying to figure it out.

This is not a case of an elephant examined by 40,000 blindfolded experts, each of whom comes to a different conclusion about what it is they are touching. Everyone knows the object of study is the brain. The difficulty of comprehending the brain may be more aptly compared to a poem by Wallace Stevens, "13 Ways of Looking at a Blackbird."

Each way of looking, not looking, or just being in the presence of the blackbird reveals something about it, but only something. Each way of looking at the brain reveals ever more astonishing secrets, but the full and complete picture of the human brain is still out of reach.

There is no need, no intention and perhaps no chance, of ever "solving" a poet's blackbird. It is hard to imagine a poet wanting such a thing. But science, by its nature, pursues synthesis, diagrams, maps — a grip on the mechanism of the thing. We may not solve the brain any time soon, but someday achieving such a solution, at least in scientific terms, is the fervent hope of neuroscience.

# The Map Makers: The Brain's Inner Language



Clay Reid and colleagues are going deep into the mouse brain to decipher the conversations and decisions of neurons. (Zach Wise for The New York Times)

**By JAMES GORMAN**

*February 24, 2014*

SEATTLE — When Clay Reid decided to leave his job as a professor at Harvard Medical School to become a senior investigator at the Allen Institute for Brain Science in Seattle in 2012, some of his colleagues congratulated him warmly and understood right away why he was making the move.

Others shook their heads. He was, after all, leaving one of the world's great universities to go to the academic equivalent of an Internet start-up, albeit an extremely well-financed, very ambitious one, created in 2003 by Paul Allen, a founder of Microsoft.

Still, "it wasn't a remotely hard decision," Dr. Reid said. He wanted to mount an all-out investigation of a part of the mouse brain. And although he was happy at Harvard, the Allen Institute offered not only great colleagues and deep pockets, but also an approach to science different from the classic university environment. The institute was already

mapping the mouse brain in fantastic detail, and specialized in the large-scale accumulation of information in atlases and databases available to all of science.

Now, it was expanding, and trying to merge its semi-industrial approach to data gathering with more traditional science driven by individual investigators, by hiring scientists like Christof Koch from the California Institute of Technology as chief scientific officer in 2011 and Dr. Reid. As a senior investigator, he would lead a group of about 100, and work with scientists, engineers and technicians in other groups.

Without the need to apply regularly for federal grants, Dr. Reid could concentrate on one piece of the puzzle of how the brain works. He would try to decode the workings of one part of the mouse brain, the million neurons in the visual cortex, from, as he puts it, “molecules to behavior.”

There are many ways to map the brain and many kinds of brains to map. Although the ultimate goal of most neuroscience is understanding how human brains work, many kinds of research can't be done on human beings, and the brains of mice and even flies share common processes with human brains.

The work of Dr. Reid, and scientists at Allen and elsewhere who share his approach, is part of a surge of activity in brain research as scientists try to build the tools and knowledge to explain — as well as can ever be explained — how brains and minds work. Besides the Obama administration's \$100 million Brain Initiative and the European Union's \$1 billion, decade-long Human Brain Project, there are numerous private and public research efforts in the United States and abroad, some focusing on the human brain, others like Dr. Reid's focusing on nonhumans.

While the Human Connectome Project, which is spread among several institutions, aims for an overall picture of the associations among parts of the human brain, other scientific teams have set their sights on drilling to deeper levels. For instance, the Connectome Project at Harvard is pursuing a structural map of the mouse brain at a level of magnification that shows packets of neurochemicals at the tips of brain cells.

At Janelia Farm, the Virginia research campus of the Howard Hughes Medical Institute, researchers are aiming for an understanding of the complete fly brain — a map of sorts, if a map can be taken to its imaginable limits, including structure, chemistry, genetics and activity.

“I personally am inspired by what they're doing at Janelia,” Dr. Reid said.

All these efforts start with maps and enrich them. If Dr. Reid is successful, he and his colleagues will add what you might call the code of a brain process, the language the neurons use to store, transmit and process information for this function.

Not that this would be any kind of final answer. In neuroscience, perhaps more than

in most other disciplines, every discovery leads to new questions.

“With the brain,” Dr. Reid said, “you can always go deeper.”

### **‘Psychoanalyst’s Kid Probes Brain!’**

Dr. Reid, 53, grew up in Boston, in a family with deep roots in medicine. His grandfather taught physiology at Harvard Medical School. “My parents were both psychoanalysts,” he said during an interview last fall, smiling as he imagined a headline for this article, “Psychoanalyst’s Kid Probes Brain!” Dr. Reid, he said, was not only smart and full of energy, but also “interested in asking questions that I think can get to the core of a problem.”

At Harvard, Dr. Reid worked on the Connectome Project to map the connections between neurons in the mouse brain. The Connectome Project aims at a detailed map, a wiring diagram at a level fantastically more detailed than the work being done to map the human brain with M.R.I. machines. But electron microscopes produce a static picture from tiny slices of preserved brain.

Dr. Reid began working on tying function to mapping. He and one of his graduate students, Davi Bock, now at Janelia Farm, linked studies of active mouse brains to the detailed structural images produced by electron microscopes.

Dr. Bock said he recalled Dr. Reid as having developed exactly the kind of intuition and “good lab hands” that Dr. Wiesel seemed to be encouraging. He and another graduate student were stumped by a technical problem involving a new technique for studying living brains, and Dr. Reid came by.

“Clay got on this bench piled up with components,” Dr. Bock said. “He started plugging and unplugging different power cables. We just stood there watching him, and I was sure he was going to scramble everything.” But he didn’t. Whatever he did worked.

That was part of the fun of working in the lab, Dr. Bock said, “not that he got it right every time.” But his appreciation for Dr. Reid as a leader and mentor went beyond admiration for his “mad scientist lab hands.”

“He has a deep gut level enthusiasm for what’s beautiful and what’s profound in neuroscience, and he’s kind of relentless,” Dr. Bock said.

### **Showing a Mouse a Picture**

That instinct, enthusiasm and relentlessness will be necessary for his current pursuit. To crack the code of the brain, Dr. Reid said, two fundamental problems must be solved.

The first is: “How does the machine work, starting with its building blocks, cell types, going through their physiology and anatomy,” he said. That means knowing all the



different types of neurons in the mouse visual cortex and their function — information that science doesn't have yet.

It also means knowing what code is used to pass on information. When a mouse sees a picture, how is that picture encoded and passed from neuron to neuron? That is called neural computation.

“The other highly related problem is: How does that neural computation create behavior?” he said. How does the mouse brain decide on action based on that input?

He imagined the kind of experiment that would get at these deep questions. A mouse might be trained to participate in an experiment now done with primates in which an animal looks at an image. Later, seeing several different images in sequence, the animal presses a lever when the original one appears. Seeing the image, remembering it, recognizing it and pressing the lever might take as long as two seconds and involve activity in several parts of the brain.

Understanding those two seconds, Dr. Reid said, would mean knowing “literally what photons hit the retina, what information does the retina send to the thalamus and the cortex, what computations do the neurons in the cortex do and how do they do it, how does that level of processing get sent up to a memory center and hold the trace of that picture over one or two seconds.”

Then, when the same picture is seen a second time, “the hard part happens,” he said. “How does the decision get made to say, ‘That’s the one?’”

In pursuit of this level of understanding, Dr. Reid and others are gathering chemical, electrical, genetic and other information about what the structure of that part of the mouse brain is and what activity is going on.

They will develop electron micrographs that show every neuron and every connection in that part of a mouse brain. That is done on dead tissue. Then they will use several techniques to see what goes on in that part of the brain when a living animal reacts to different situations. “We can record the activity of every single cell in a volume of cortex, and capture the connections,” he said.

With chemicals added to the brain, the most advanced light microscopes can capture movies of neurons firing. Electrodes can record the electrical impulses. And mathematical analysis of all that may decipher the code in which information is moved around that part of the brain.

Dr. Reid says solving the first part of the problem — receiving and analyzing sensory information — might be done in 10 years. An engineer’s precise understanding of everything from photons to action could be more on the order of 20 to 30 years away, and not reachable through the work of the Allen Institute alone. But, he wrote in an email,

“the large-scale, coordinated efforts at the institute will get us there faster.” He is studying only one part of one animal’s brain, but, he said, the cortex — the part of the mammalian brain where all this calculation goes on — is something of a general purpose computer. So the rules for one process could explain other processes, like hearing. And the rules for decision-making could apply to many more complicated situations in more complicated brains. Perhaps the mouse visual cortex can be a kind of Rosetta stone for the brain’s code.

All research is a gamble, of course, and the Allen Institute’s collaborative approach, while gaining popularity in neuroscience, is not universally popular. Dr. Wiesel said it was “an important approach” that would “provide a lot of useful information.” But, he added, “it won’t necessarily create breakthroughs in our understanding of how the brain works.”

“I think the main advances are going to be made by individual scientists working in small groups,” he said.

Of course, in courting and absorbing researchers like Dr. Reid, the Allen Institute has been moving away from its broad data-gathering approach toward more focused work by individual investigators.

Dr. Bock, his former student, said his experience suggested that Dr. Reid had not only a passion and intensity for research, but a good eye for where science is headed as well.

“That’s what Clay does,” he said. “He is really good in that Wayne Gretzky way of skating to where the puck will be.”

# The Map Makers: Brain Control in a Flash of Light

By **JAMES GORMAN**

*April 21, 2014*

SAN DIEGO — Dr. Karl Deisseroth is having a very early breakfast before the day gets going at the annual meeting of the Society for Neuroscience. Thirty thousand people who study the brain are here at the Convention Center, a small city's worth of badge-wearing, networking, lecture-attending scientists.

For Dr. Deisseroth, though, this crowd is a bit like the gang at Cheers — everybody knows his name. He is a Stanford psychiatrist and a neuroscientist, and one of the people most responsible for the development of optogenetics, a technique that allows researchers to turn brain cells on and off with a combination of genetic manipulation and pulses of light.

He is also one of the developers of a new way to turn brains transparent, though he was away when some new twists on the technique were presented by his lab a day or two earlier.

“I had to fly home to take care of the kids,” he explained. He went home to Palo Alto to be with his four children, while his wife, Michelle Monje, a neurologist at Stanford, flew to the conference for a presentation from her lab. Now she was home and, here he was, back at the conference, looking a bit weary, eating eggs, sunny side up, and talking about the development of new technologies in science.

A year ago, President Obama announced an initiative to invest in new research to map brain activity, allocating \$100 million for the first year. The money is a drop in the bucket compared with the \$4.5 billion the National Institutes of Health spends annually on neuroscience, but it is intended to push the development of new techniques to investigate the brain and map its pathways, starting with the brains of small creatures like flies.

Cori Bargmann of Rockefeller University, who is a leader of a committee at the National Institutes of Health setting priorities for its piece of the brain initiative, said optogenetics was a great example of how technology could foster scientific progress.

“Optogenetics is the most revolutionary thing that has happened in neuroscience in the past couple of decades,” she said. “It is one of the advances that made it seem this is

the right time to do a brain initiative.”

Dr. Deisseroth, 42, who has won numerous prizes and received plenty of news media attention for his work on optogenetics, is quick to point out that there is no sole inventor for this technology.

“It’s not as if one person had a eureka moment,” he said. “The time had come, and it was a question of who had put the resources and effort and people” on the task, and who would get there first. But it was he and his colleagues, Edward Boyden and Feng Zhang, who took those previous discoveries and devised a practical way to turn neurons on and off with light.

Ehud Isacoff, of the University of California, Berkeley, who recently wrote about the development of the technique, said that Dr. Deisseroth “was incredibly important in getting all the parts to come together.”

The reason optogenetics has transformed neuroscience is that it allows scientists to go beyond observation. In neuroscience, as in all science, it is crucial to be able to make and test predictions.

“You want to be able to play the piano,” said Dr. Bargmann, paraphrasing Rafael Yuste, a Columbia University neuroscientist and one of the people who proposed creating a brain activity map. The tools of optogenetics are allowing scientists to perform the neuroscientific equivalent of “Chopsticks” in the brains of laboratory animals — to find and control, for example, neurons that control a kind of aggression in fruit flies.

The hope is that scientists can work their way up to the level of Chopin — and that this tool and others like it will uncover deep mechanisms of brain function that hold true not only for flies and mice, but for the ultimate neuroscientific puzzle, the human brain.

## **Discovering Psychiatry**

Karl Deisseroth was not always headed for a career in the laboratory, although his father, an oncologist, and his mother, who trained as a chemist, both exposed him to the world of science. “My first love was writing,” he said.

That was still the case in his first years at Harvard, when he took courses in creative writing and seriously considered pursuing a literary life. Eventually, however, interest in science took over. He majored in biochemistry and went on to Stanford for a medical degree and a Ph.D., expecting to become a neurosurgeon. In interviews at the San Diego meeting, and earlier at his Stanford lab, he explained what changed him.

Brain surgery “was the first clinical rotation I did; I was that certain that was what I wanted to do,” he said. But his next stop was psychiatry. “It was a completely transformative thing,” he said.

It was eye-opening, he said, “to sit and talk to a person whose reality is different from yours” — to be face to face with the effects of bipolar disorder, “exuberance, charisma, love of life, and yet, how destructive”; of depression, “crushing — it can’t be reasoned with”; of an eating disorder literally killing a young, intelligent person, “as if there’s a conceptual cancer in the brain.”

He saw patient after patient suffering terribly, with no cure in sight. “It was not as if we had the right tools or the right understanding.” But, he said, that such tools were desperately needed made it more interesting to him as a specialty. He stayed with psychiatry, but adjusted his research course, getting in on the ground floor in a new bioengineering department at Stanford. He is now a professor of both bioengineering and psychiatry.

With his own lab, in concert with other researchers, he began to pursue two projects. The one for which he was hired was low risk, involving stem cells and methods to enhance the growth of neurons. The second was the possibility of using light to control brain cells.

That was high risk, but not because it was an unknown idea; quite the opposite. Despite many barriers to success, it was a crowded field.

## **The Changeable Opsins**

At the heart of all optogenetics are proteins called opsins. They are found in human eyes, in microbes and other organisms. When light shines on an opsin, it absorbs a photon and changes.

When he came into the field, Dr. Deisseroth said, “Microbial opsins had been studied since the ’70s.” Thousands of papers had been published. So the basics of the chemicals were well known.

“People talked and thought about the possibility of putting them into neurons as a control tool, and everybody thought that it might work but it would be unlikely to be very effective, unlikely to work very well, because these opsins come from organisms that are very distant and separated from mammals evolutionarily,” he said.

The genes to make the opsins needed to be inserted into the neurons, and several more steps were necessary so the system would work.

By the early 2000s there had also been an improvement in engineering viruses that were effective in smuggling the opsin genes into nerve cells, but caused no harm. Research intensified.

“There were, to my knowledge, maybe six or seven people actually trying” to get this idea of light control of neurons to work, he said.

In 2005 Dr. Deisseroth; Dr. Boyden and Dr. Zhang, both of whom now have their own labs at M.I.T.; and Ernst Bamberg of the Max Planck Institute of Biophysics and Georg Nagel at the University of Würzburg published a paper showing that an opsin called channelrhodopsin-2 could be used to turn on mammalian neurons with blue light.

This was the breakthrough research, but it had antecedents. In 2002 Gero Miesenböck, now at Oxford, and Boris Zemelman, now at the University of Texas, proved that optogenetics could work. Both were then at Memorial Sloan-Kettering Cancer Center. They reported their success using opsins from the fruit fly to turn on mouse neurons that had been cultured in the lab.

Dr. Isacoff reviewed the development of optogenetics recently after the awarding of the 2013 European Brain Prize to six people, including Dr. Deisseroth and Dr. Boyden, for work on optogenetics. The other winners were Dr. Bamberg, Dr. Nagel, Dr. Miesenböck and Peter Hegemann at Humboldt University in Berlin. He wrote of Dr. Miesenböck's work, "If one had to identify the paper that launched the thousand ships of optogenetics, this is it."

But although this was a breakthrough and a proof that light could be used to control neurons, Dr. Miesenböck and Dr. Zemelman's work was not picked up as a tool by the neuroscience community because, Dr. Isacoff wrote, of the limited effectiveness of light in stimulating the neurons, and because it was hard to adapt to different biological systems.

Dr. Deisseroth's group, said Dr. Isacoff, turned instead to microbial opsins, building on the work of Dr. Bamberg, Dr. Nagel and Dr. Hegemann. They figured out how to get one of these opsins safely into mammalian neurons so that the neurons would respond strongly to light. That made all the difference.

"The methods that are widely used now are the ones that Karl developed," Dr. Bargmann said. "He flipped the switch that made them practical."

Shortly thereafter the lab of Stefan Herlitze of Ruhr University Bochum, in Germany, collaborating with Dr. Hegemann and Lynn Landmesser of Case Western Reserve University, reported a similar finding. Dr. Deisseroth pointed out, however, that the initial paper was just the beginning. It involved only cells in culture. Many questions remained. "How are you going to get the light deep into the brain?" he said. "How are you going to target these genes? Will it control behavior? Will you be able to turn on or off behaviors?"

Those questions have now been answered through a great deal of work in Dr. Deisseroth's lab and in others'. Hundreds of papers have been published. Many researchers are using and developing techniques, which, Dr. Isacoff wrote, "have been

used to study brain waves, sleep, memory, hunger, addiction, aggression, courtship, sensory modalities, and motor behavior.”

### **And Now Clarity**

In 2013, while continuing the work on developing optogenetic techniques, the Deisseroth lab produced another technique that Dr. Deisseroth has high hopes for. He and Kwanghun Chung, now an assistant professor at M.I.T. with his own lab, managed to turn whole mouse brains transparent, with a method called Clarity.

This is not a technique for living brains. They infused mouse brain tissue with a hydrogel, a substance well known to chemists but not one previously used in neuroscience. The method leaves the brain tissue not only transparent, but also still available for biochemical tests.

The lab is now working on making a whole preserved human brain transparent; it was a presentation on this work that Dr. Deisseroth had missed during his shuttle parenting in San Diego.

The long-term goal of his work continues to be to find a way to help people with severe mental illness or brain diseases, and he has recently proposed ways that optogenetics, Clarity and other techniques may be turned to this aim.

He still treats patients. “I don’t think a day goes by that I’m not looking at results and thinking how to apply them clinically,” he said.

Optogenetics is a crucial tool in understanding function. Clarity, on the other hand, is an aid to anatomical studies, basic mapping of structure, which, he says, is as important to understand as activity.

“I’ve administered electroconvulsive therapy — I know we can administer this therapy and cause a general seizure,” he says, in which the activity of the whole brain is disrupted.

“Within a few minutes, the whole person comes back. Where does it come back from? From the structure,” he said.

# The Map Makers: Brain-Mapping Milestones

By **JAMES GORMAN**

*April 21, 2014*

As the Brain Initiative announced by President Obama a year ago continues to set priorities and gear up for what researchers hope will be a decade-long program to understand how the brain works, two projects independent of that effort reached milestones in their brain mapping work.

Both projects, one public and one private, are examples of the widespread effort in neuroscience to create databases and maps of brain structure and function that can serve as a foundation for research. While the Obama initiative is concentrating on the development of new tools, that research will build on and use the data being acquired in projects like these.

One group of 80 researchers, working as part of a consortium of institutions funded by the National Institute of Mental Health, reported that it had mapped the genetic activity of the human fetal brain. Among other initial findings, the map, the first installment of an atlas of the developing human brain called BrainSpan, confirmed the significance of areas thought to be important in the development of autism.

A group of 33 researchers, all but one at the Allen Institute for Brain Science, announced an atlas of the mouse brain showing the connections among 295 different regions.

Ed Lein, an investigator at Allen, was the senior author on the fetal brain paper. He said the research required making sections only 20 microns thick, up to 3,500 for each of four brains, two from fetuses at 15 weeks of development and two from about 21 weeks. The researchers measured the activity of 20,000 genes in 300 different brain structures.

One interesting finding, Dr. Lein said, was that “95 percent of the genome was used,” meaning almost all of the genes were active during brain development, significantly more than in adult brains. The team also found many differences from the mouse brain, underscoring the findings that, despite the many similarities in all mammalian brains, only so much can be extrapolated to humans from other animals.

The researchers also looked at genes that showed some association with autism in broad genome studies, and found that many of these genes were active during the



formation of a part of the brain called the neocortex, which is important for functions like conscious thought, supporting the idea that the characteristic problems of autism have their origin in early development.

The brains came from the Birth Defects Research Laboratory at the University of Washington and Advanced Bioscience Resources Inc. in Alameda, Calif., and all federal ethics guidelines for the use of human tissue were followed.

Hongkui Zeng was the primary author on the mouse paper, which described the completion of a “connectome” of the whole mouse brain, meaning a map of connections. There are, of course, many connectomes that can be mapped — between large brain regions, for example, or down to the level of the connections between each brain cell and its neighbors.

Dr. Zeng reported the completion of a “mesoscale” connectome, meaning it was in the middle, tracing the connections among 295 brain regions deemed important to map. The result is the Allen Mouse Brain Connectivity Atlas, and like the BrainSpan data and other atlases completed at the Allen Institute, it is all publicly available.

The atlas, like others that Allen has produced, is meant as a foundation for research, but Dr. Zeng said interesting patterns have already emerged. The researchers’ method, injecting tracers into brain regions and using light microscopy to track the connections, showed not only the direction of information flow, but also the intensity of the connections between regions.

The strength of the connections varied so much that some were a million times stronger than others, she said, with a small number of very strong connections and a “sea of weak connections.”

The role of these widely distributed weak connections, Dr. Zeng said, is not known. She said they could be involved in modulating brain activity, or perhaps in memory.

# The Map Makers: All Circuits Are Busy



Crowd-sourced science has exploded in recent years. An Internet game called Eyewire, from Sebastian Seung's lab at M.I.T., asks volunteers to trace the fine details of neurons. (Zach Wise for The New York Times)

**By JAMES GORMAN**

*May 26, 2014*

H. Sebastian Seung is a prophet of the connectome, the wiring diagram of the brain. In a popular book, debates and public talks he has argued that in that wiring lies each person's identity.

By wiring, Dr. Seung means the connections from one brain cell to another, seen at the level of the electron microscope. For a human, that would be 85 billion brain cells, with up to 10,000 connections for each one. The amount of information in the three-dimensional representation of the whole connectome at that level of detail would equal a zettabyte, a term only recently invented when the amount of digital data accumulating in the world required new words. It equals about a trillion gigabytes, or as one calculation framed it, 75 billion 16-gigabyte iPads.

Dr. Seung, who is in his late 40s and has just left the Massachusetts Institute of Technology for Princeton, is a visionary who projects that this ultimate map of the human

brain will be achieved in 20 to 30 years if computer technology continues to progress at its current pace.

He is also a realist. When he speaks publicly, he tells his audiences, “I am my connectome.” But he can be brutally frank about the limitations of neuroscience.

“We’ve failed to answer simple questions,” he said. “People want to know, ‘What is consciousness?’ And they think that neuroscience is up to understanding that. They want us to figure out schizophrenia and we can’t even figure out why this neuron responds to one direction and not the other.”

This mix of intoxicating ideas, and the profound difficulties of testing them, not only defines Dr. Seung’s career but the current state of neuroscience itself. He is one of the stars of the field, and yet his latest achievement, in a paper published this month, is not one that will set the world on fire. He and his M.I.T. colleagues have proposed an explanation of how a nerve cell in the mouse retina — the starburst amacrine cell — detects the direction of motion.

If he’s right, this is significant work. But it may not be what the public expects, and what they have been led to expect, from the current push to study the brain.

The excitement for neuroscience is everywhere. New institutes proliferate. Popular books on the brain come out so often it seems each of the 40,000 members of the Society for Neuroscience is writing one. About a year ago, President Obama created the Brain Initiative, with \$100 million in funding for the first year. The European Union has committed \$1 billion to the eyebrow-raising goal of recreating the workings of the human brain in a computer.

At the same time, the scientific work that makes it into the top journals, while deeply serious and perhaps of great significance, is technical and highly specific.

Dr. Seung is adept at conveying a sense of unlimited possibility, of a revolution in technology, of great things to come.

But his alter ego is in the lab, where research on the workings of the starburst amacrine cell better reflect what neuroscientists are trying to understand now.

There is a “huge gap,” Dr. Seung said, between “what the public wants us to know” and “what we actually know.” And in that gap lies the work to be done.

## **From Theory to the Lab**

Dr. Seung started out in physics, as did many other neuroscientists, particularly those interested in theory. He was always interested in the fundamental ideas in science, which meant physics to him, while growing up in Austin, the child of a philosopher and a musician.

At Harvard, he studied physics as an undergraduate and went on to get his Ph.D. in theoretical physics.

He went to Israel to do postdoctoral research in theoretical neuroscience, and worked at Bell Labs before he went to M.I.T. All the while, even in graduate school, his interest was turning to the deeper puzzles of biology and the mysteries of the brain. Around 2006, Dr. Seung turned his attention to the connectome. “One of the reasons I left physics was that I thought it couldn’t be tested conclusively,” he said. “It seemed like string theory was going to be impossible to test.”

Little did he know, he said, that “neuroscience would be the same.”

“One of the funny things about neuroscience is that it seems like we have so much data and yet we haven’t been able to test theories,” Dr. Seung said. “Theories and speculation can be around for half a century or a century without going beyond, without becoming real science.”

So he switched paths again, turning to experimental work, with the desire to ground theory in the actual, demonstrable workings of the brain. He decided, he said, to “change course and map out real neural networks” — the actual neurons themselves and how they are connected.

Now Dr. Seung is continuing that work at Princeton, commuting, for the time being, from Manhattan, where he lives with his wife and young daughter as they wait for work to be finished on their house.

## **A Slice of the Brain**

What Dr. Seung has concentrated on is not a human brain, not a mouse brain, but the mouse retina. Although the retina is part of the eye, it is also part of the central nervous system. It is composed of brain tissue, with neurons and synapses and, at least for vision, it is where the work of the brain begins, turning mere sensation into perceptions — size, distance, motion.

Winfried Denk, at the Max Planck Institute of Neurobiology, found in 2002 that the starburst amacrine cell was involved in detecting motion. The question was how. To answer that, Dr. Seung analyzed a small bit of connectome from a portion of the retina created by automated electron microscopy. In this process ultrathin slices of brain tissue are scanned by the microscope and the images are put together to form three-dimensional views of tiny chunks of the brain or retina. Jeff Lichtman at Harvard and Dr. Denk have developed such methods, and Dr. Seung has collaborated with both of them.

In the work on the starburst amacrine cell, he analyzed Dr. Denk’s 3-D connectome reconstructions. Part of the work was done by computer and part by humans, including

lab technicians. In this case, the public also participated, through an Internet game of sorts that Dr. Seung's group at M.I.T. developed, called Eyewire. Humans can still do some things better than computers, and one ability they have is pattern recognition. On Eyewire, volunteers examine the models online and trace the fine details of neurons.

Dr. Seung, Jinseop S. Kim, Matthew J. Greene and M.I.T. colleagues analyzed the structure of the starburst amacrine cell and its connections, considering previous work on physiology and the workings of neurons. From that, they proposed a mechanism for how the cell responds to motion in only one direction. It involves two other cells, bipolar cells that are excited by light and send impulses to the starburst cell.

If their analysis is right, the impulses from the bipolar cells have to reach the starburst cell simultaneously in order to make the starburst cell send out its own signal. Although one bipolar cell fires first as an object moves across the mouse's field of vision, and another fires second, the signal of the first is delayed along the way so that the signals from both bipolar cells arrive at the starburst amacrine cell at the same time. That simultaneous stimulation causes the starburst amacrine cell to send out its own signal, which carries the news that something is moving in a particular direction on to ganglion cells and then to the brain itself. This is a simplified analysis because in reality many pairs of bipolar cells are reporting to any given starburst amacrine cell.

The system is very similar to the motion detection circuit in the fruit fly that Dmitri B. Chklovskii and his colleagues at Janelia Farm reported on last summer. Dr. Chklovskii, who is about to move to the Simons Center for Data Analysis in New York, said of Dr. Seung's paper, "It validates our results with the fly." And it raises all sorts of questions about how evolution produced such similar systems in such different animals with such different brains and vision systems, he said.

Calling Dr. Seung's hypothesis "very bold," Dr. Chklovskii added: "There's not much wiggle room there. It's a very concise model, a very specific mechanism that can be tested with existing tools." If Dr. Seung is wrong, he will be clearly wrong.

If he is right, then his findings and Dr. Chklovskii's study are steps toward cracking the code of the brain — exactly how information is coded and travels through circuits of neurons to allow perceptions to be formed, actions to be taken and decisions to be made.

## **A Drive to Get Data**

That is, after all, why Dr. Seung "paused" in his theorizing to be able to put ideas to the test, another bold action. And the adjective is characteristic of his personality as well as his research. He has been called a "rock-star neuroscientist" in the news media, and he

takes easily to the stage. In addition to developing Eyewire, he dances and mugs shamelessly for the camera in videos to promote it.

Eve Marder, at Brandeis, whose work on a specific neural circuit in the crab has changed the understanding of how such circuits work, is a critic of some of the grander ideas of connectomics because, she says, knowing the wiring is never enough on its own, and only in some circumstances is the level of detail in an electron micrograph useful.

But she is an admirer of both Dr. Seung's theoretical work, and his move to the laboratory to get his hands dirty. "I really respect his decision," Dr. Marder said, "the fundamental drive to get the data."

His new boss feels the same way. David Tank, the head of the new Princeton Neuroscience Institute, recruited Dr. Seung, just as he years ago recruited him to work at Bell Labs.

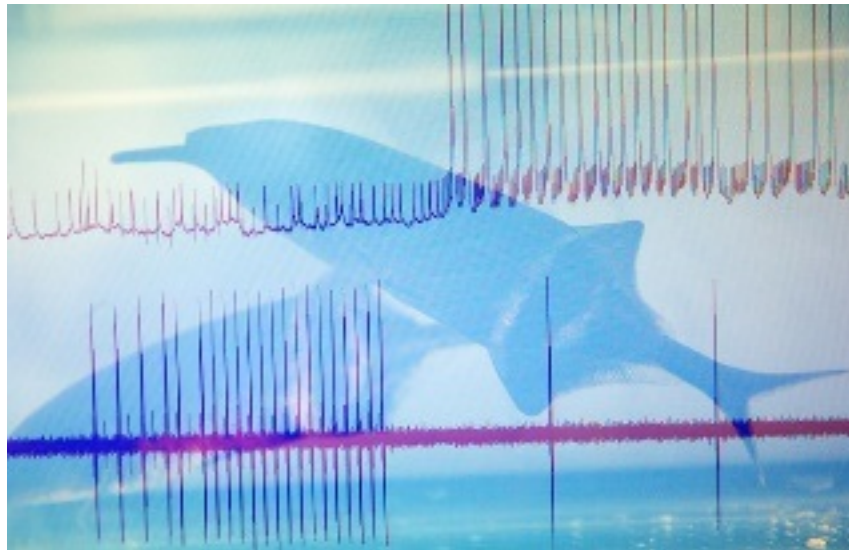
"He is an absolutely outstanding theorist," said Dr. Tank, who said Dr. Seung could have continued on that path for the rest of his career. Instead he has plunged into the work of trying to corral the vast amount of raw information that comes from techniques like electron microscopy.

"He focuses on what is the bottleneck in the whole process" of connectomics, which is finding a way to turn the vast amount of raw information that comes from electron microscopes into the structure of neurons and their connections, Dr. Tank said.

Dr. Seung, theorist, experimentalist, neuro-evangelist, dancer, debater, is dead serious about his research, but not so much about himself. Talking recently about his disappointment with theoretical science and his current mix of writing, theorizing and experimenting, he laughed.

"I'm worse than a theorist," he said. "I'm an intellectual."

# The Map Makers: Learning How Little We Know About the Brain



A double exposure of weakly electric fish with recordings of brain activity. (Béatrice de Géa for The New York Times)

By **JAMES GORMAN**

*November 10, 2014*

Research on the brain is surging. The United States and the European Union have launched new programs to better understand the brain. Scientists are mapping parts of mouse, fly and human brains at different levels of magnification. Technology for recording brain activity has been improving at a revolutionary pace.

The National Institutes of Health, which already spends \$4.5 billion a year on brain research, consulted the top neuroscientists in the country to frame its role in an initiative announced by President Obama last year to concentrate on developing a fundamental understanding of the brain.

Scientists have puzzled out profoundly important insights about how the brain works, like the way the mammalian brain navigates and remembers places, work that won the 2014 Nobel Prize in Physiology or Medicine for a British-American and two Norwegians.

Yet the growing body of data — maps, atlases and so-called connectomes that show linkages between cells and regions of the brain — represents a paradox of progress, with

the advances also highlighting great gaps in understanding.

So many large and small questions remain unanswered. How is information encoded and transferred from cell to cell or from network to network of cells? Science found a genetic code but there is no brain-wide neural code; no electrical or chemical alphabet exists that can be recombined to say “red” or “fear” or “wink” or “run.” And no one knows whether information is encoded differently in various parts of the brain.

Brain scientists may speculate on a grand scale, but they work on a small scale. Sebastian Seung at Princeton, author of “Connectome: How the Brain’s Wiring Makes Us Who We Are,” speaks in sweeping terms of how identity, personality, memory — all the things that define a human being — grow out of the way brain cells and regions are connected to each other. But in the lab, his most recent work involves the connections and structure of motion-detecting neurons in the retinas of mice.

Larry Abbott, 64, a former theoretical physicist who is now co-director, with Kenneth Miller, of the Center for Theoretical Neuroscience at Columbia University, is one of the field’s most prominent theorists, and the person whose name invariably comes up when discussions turn to brain theory.

Edvard Moser of the Norwegian University of Science and Technology, one of this year’s Nobel winners, described him as a “pioneer of computational neuroscience.” Mr. Abbott brought the mathematical skills of a physicist to the field, but he is able to plunge right into the difficulties of dealing with actual brain experiments, said Cori Bargmann of Rockefeller University, who helped lead the N.I.H. committee that set a plan for future neuroscience research.

“Larry is willing to deal with the messiness of real neuroscience data, and work with those limitations,” she said. “Theory is beautiful and internally consistent. Biology, not so much.” And, she added, he has helped lead a whole generation of theorists in that direction, which is of great value for neuroscience.

Dr. Abbott is unusual among his peers because he switched from physics to neuroscience later in his career. In the late 1980s, he was a full professor of physics at Brandeis University, where he also received his Ph.D. But at the time, a project to build the largest particle accelerator in the world in Texas was foundering, and he could see a long drought ahead in terms of advances in the field.

He was already considering a career switch when he stopped by the lab of a Brandeis colleague, Eve Marder, who was then, and still is, drawing secrets from a small network of neurons that controls a muscle in crabs.

She was not in her lab when Dr. Abbott came calling, but one of her graduate students showed him equipment that was recording the electrical activity of neurons and



translating it into clicks that could be heard over speakers each time a cell fired, or spiked. “You know what?” he said recently in his office at Columbia, “We wouldn’t be having this conversation if they didn’t have that audio monitor on. It was the sound of those spikes that entranced me.”

“I remember I walked out of the door and I kind of leaned up against the wall, in terror, saying, ‘I’m going to switch,’ ” he added. “I just knew that something had clicked in me. I’m going to switch fields, and I’m dead, because nobody knows me. I don’t know anything.”

Dr. Marder served as his guide to the new field, telling him what to read and answering his many questions. He was immediately accepted both in her lab and by other experimentalists, she said, “because he’s both wicked smart and humble.”

“He did something that was astonishing,” Dr. Marder said. “Six months in, he actually understood what people knew and what they didn’t know.”

Dr. Abbott recalled that it took a while for them to develop a productive collaboration. “Eve and I talked for a year and then finally started to understand each other,” he said.

Together, they invented something called the dynamic clamp technique, a way to link brain cells to a computer to manipulate their activity and test ideas about how cells and networks of cells work.

A decade ago, he moved from Brandeis to Columbia, which now has one of the biggest groups of theoretical neuroscientists in the world, he says, and which has a new university-wide focus on integrating brain science with other disciplines.

The university is now finishing the Jerome L. Greene Science Center, which will be home to the Mortimer B. Zuckerman Mind Brain Behavior Institute. The center for theoretical neuroscience will move to the new building.

Dr. Abbott collaborates with scientists at Columbia and elsewhere, trying to build computer models of how the brain might work. Single neurons, he said, are fairly well understood, as are small circuits of neurons.

The question now on his mind, and that of many neuroscientists, is how larger groups, thousands of neurons, work together — whether to produce an action, like reaching for a cup, or to perceive something, like a flower.

There are ways to record the electrical activity of neurons in a brain, and those methods are improving fast. But, he said, “If I give you a picture of a thousand neurons firing, it’s not going to tell you anything.”

Computer analysis helps to reduce and simplify such a picture but, he says, the goal is to discover the physiological mechanism in the data.

For example, he asks why does one pattern of neurons firing “make you jump off the couch and run out the door and others make you just sit there and do nothing?” It could be, Dr. Abbott says, that simultaneous firing of all the neurons causes you to take action. Or it could be that it is the number of neurons firing that prompts an action.

His tools are computers and equations, but he collaborates on all kinds of experimental work on neuroscientific problems in animals and humans. Some of his recent work was with Nate Sawtell, a fellow Columbia researcher, and Ann Kennedy a graduate student at the time in Dr. Sawtell’s lab, now doing post-doctoral research at Caltech. Their subject was the weakly electric fish.

Unlike electric eels and other fish that use shocks to stun prey, this fish generates a weak electric field to help it navigate and to locate insects and other prey. Over the years, researchers, notably Curtis Bell at the Oregon Health and Science University, have designed experiments to understand, up to a point, how its brain and electric-sensing organs work.

Dr. Abbott joined with Dr. Kennedy and Dr. Sawtell, the senior author on the paper that grew out of this work, and others in the lab to take this understanding a step further. The fish has two sensing systems. One is passive, picking up electric fields of other fish or prey. Another is active, sending out a pulse, for communication or as an electrical version of sonar. They knew the fish was able to cancel out its own pulse of electricity by creating what he called a “negative image.”

They wired the brain of a weakly electric fish and — through a combination of testing and developing mathematical models — found that a surprising group of neurons, called unipolar brush cells, were sending out a delayed copy of the command that another part of the brain was sending to its electric organ. The delayed signal went straight to the passive sensing system to cancel out the information from the electric pulse.

“The brain has to compute what’s self-generated versus what’s external,” said Dr. Sawtell.

This may not sound like a grand advance, but, Dr. Abbott said, “I think it’s pretty deep,” adding that it helps illuminate how a creature begins to draw a distinction between itself and the world. It is the very beginning of how a brain sorts a flood of data coming in from the outside world, and gives it meaning.

That is part of the brain’s job, after all — to build an image of the world from photons and electrons, light and dark, molecules and motion, and to connect it with what the fish, or the person, remembers, needs and wants.

“We’ve looked at the nervous system from the two ends in,” Dr. Abbott said, meaning sensations that flow into the brain and actions that are initiated there.

“Somewhere in the middle is really intelligence, right? That’s where the action is.”

In the brain, somehow, stored memories and desires like hunger or thirst are added to information about the world, and actions are the result. This is the case for all sorts of animals, not just humans. It is thinking, at the most basic level.

“And we have the tools to look there,” he said. “Whether we have the intelligence to figure it out, I view that, at least in part, as a theory problem.”

# Sebastian Seung's Quest to Map the Human Brain



The neuroscientist Sebastian Seung discusses his mapping game, EyeWire, at Princeton. (Dolly Faibyshev for The New York Times)

**By GARETH COOK**

*January 8, 2015*

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

mathematical 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. ("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 16<sup>th</sup> 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 21<sup>st</sup> 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.

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 5<sup>th</sup> 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 courses 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 19<sup>th</sup> 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.”

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. 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, steppingstones 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.”

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 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?”

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# The Brain's Empathy Gap: Can Mapping Neural Pathways Help Us Make Friends With Our Enemies?

By **JENEEN INTERLANDI**

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Nyiregyhaza (pronounced NEAR-re-cha-za) is a medium-size city tucked into the northeastern corner of Hungary, about 60 miles from the Ukrainian border. It has a world-class zoo, several museums and universities and a new Lego Factory. It also has two Roma settlements, or “Gypsy ghettos.” The larger of these settlements is Gusev, a crumbling 19<sup>th</sup>-century military barracks separated from the city proper by a railway station and a partly defunct industrial zone. Gusev is home to more than 1,000 Roma. Its chief amenities include a small grocery store and a playground equipped with a lone seesaw and a swingless swing set. There’s also a freshly painted elementary school, where approximately 60 students are currently enrolled. Almost all those students are Roma and almost all of them live in Gusev.

Officially, most of the schools in Nyiregyhaza are integrated. Roma students have access to the same facilities as non-Roma students, and the ethnic balance of any given facility largely reflects the ethnic balance of the neighborhoods it serves. In practice, things are muddier. While many families in Gusev have been assigned to perfectly reputable schools, there is no busing program, and most schools are not within walking distance. For families living on just 60,000 forints (\$205) a month, the schools are also too expensive to reach by public transit. “Everything is fine on paper,” Adel Kegye, an attorney with the Chance for Children Foundation (C.F.C.F.), told me when I visited Hungary this past fall. “But in reality, they make it very hard for the Roma to go anywhere but the settlement school.”

In 2007, the municipality closed the Gusev school and began a busing program, as part of a larger effort to integrate the Roma into Hungarian society. But the program was short-lived, in part because of resistance from the community. Non-Roma children bullied, teased and ostracized Roma students, and non-Roma parents began pulling their children out of schools that took in too many Roma. In 2011, the busing program was discontinued and the settlement school was reopened under the direction of the Greek Catholic Church. That same year, C.F.C.F. filed a lawsuit charging the church and the



municipality with racial segregation. “The church has this totally modern school, with a brand-new swimming pool, right in the center of the city,” Kegye said. “Why can’t the kids from Gusev go to that school?”

Nyiregyhaza is by no means the only city to stand accused of such practices. C.F.C.F. has filed similar lawsuits throughout Hungary, and there are cases pending in Romania, the Czech Republic and elsewhere. But the Gusev case has attracted attention, in part because of the courtroom spectacle it has created. In 2013, Hungary’s minister of human resources, Zoltan Balog, testified on behalf of the Gusev school, claiming it offered Roma students a chance at social “catch-up” — the opportunity to develop the basic social and academic skills needed to join mainstream society. The school’s principal also took the stand, testifying that the Roma were infested with lice and that some had never used a fork. When asked by the presiding judge if room could be made for Roma children in the church’s other, nicer school, a priest replied that perhaps they could clear some space in the attic. When pressed, he said that mixing Roma children with non-Roma children would be “harmful” to the former. In February 2014, the court sided with C.F.C.F., ordering the Gusev school to stop accepting new students and ruling that it amounted to segregation. When I visited this fall, the Gusev school was appealing the judge’s decision, claiming it was better for the Roma to keep the school open. In the meantime, it had welcomed yet another incoming class.

Governments and nongovernmental organizations have spent decades perfecting the art of collective persuasion — getting people to do things that are good for them and for society. They have persuaded us to eat more vegetables and to wear our seatbelts, to walk for cures and to give to charity. What has not come so easily is persuading us to identify with — or even tolerate — people we perceive as outsiders. This is especially true when those outsiders form an entire community. A Facebook page devoted to individual portraits and the stories behind them might trigger an outpouring of donations for a “failing” public school in a blighted neighborhood. And the killing of a single unarmed black teenager might prompt thousands to protest in the streets. But social policies that address the problems behind individual fates — programs to combat poverty or racial bias in policing — remain as polarizing as ever.

While social and economic factors account for some of what divides us into warring camps, psychologists since Freud have suspected that something more fundamental is at work. In 1963, the Yale psychologist Stanley Milgram famously showed that average people were capable of inflicting grievous harm on one another — in this case, administering what they believed were powerful electric shocks — if they thought they were following the orders of a superior. A few years later, in an equally famous

experiment, the Stanford researcher Philip Zimbardo had subjects play prisoners and wardens and showed that context can be far more powerful than our own values and personality traits in determining how we treat other people. Together, the studies are perhaps the most emblematic of a generation of psychology research into the social cues that determine how one group treats another. What role does group identity play? Does authority make us passive or just reinforce our belief that we are right? How much of our empathy is innate and how much is instilled in us by our environment?

In the past two decades, with the advent of f.M.R.I. technology, neuroscientists also began to tackle such questions. Emile Bruneau, a cognitive neuroscientist at the Massachusetts Institute of Technology, has spent the past seven years studying intractable conflicts around the world. He has looked at Israelis and Palestinians in Israel and the West Bank, Mexican immigrants and Americans along the Arizona border and Democrats and Republicans across the United States. By supplementing psychological experiments with brain scans, he is trying to map when and how our ability to empathize with one another break down, in hopes of finding a way to build it back up.

This past fall, he traveled to Budapest. The struggle to integrate the Roma reminded Bruneau of the fierce opposition that greeted *Brown v. Board of Education*: In each case, the resistance to desegregation was forceful enough to trump national law. “I keep coming back to the same basic question,” he told me one evening at a restaurant along the Danube. “If we knew then what we know now, could we have done any better?”

In recent years, neuroscientists have begun to map empathy’s pathways in the brain. We know that the ability to identify other people’s thoughts and feelings as separate from our own (what psychologists refer to as having a “theory of mind”) is associated with a handful of interconnected brain regions known collectively as the “theory-of-mind network.” And we’ve begun to pin specific tasks — like identifying other people’s mental states, or making moral judgments about their actions — to specific parts of this network.

But the picture remains incomplete. We still need to map a host of other empathy-related tasks — like judging the reasonableness of people’s arguments and sympathizing with their mental and emotional states — to specific brain regions. And then we need to figure out how these neural flashes translate into actual behavior: Why does understanding what someone else feels not always translate to being concerned with their welfare? Why is empathizing across groups so much more difficult? And what, if anything, can be done to change that calculus?

So far, Bruneau says, the link between f.M.R.I. data and behavior has been tenuous. Many f.M.R.I. studies on empathy involve scanning subjects’ brains while they look at images of hands slammed in doors or of faces poked with needles. Scientists have shown

that the same brain regions light up when you watch such things happen to someone else as when you experience them or imagine them happening to you. “To me, that’s not empathy,” Bruneau says. “It’s what you do with that information that determines whether it’s empathy or not.” A psychopath might demonstrate the same neural flashes in response to the same painful images but experience glee instead of distress.

Similarly, stronger neural activity might correlate with how relevant a group or individual is to us, not what we feel for them. In a 2012 study, Bruneau showed that Arabs and Israelis displayed equal amounts of neural activity in their theory-of-mind regions when they read articles about their own group’s suffering as when they read about the other group’s suffering. But when they read about the suffering of South Americans — a group with whom they were not in direct conflict — their theory-of-mind regions quieted down. As far as the brain is concerned, he says, the opposite of love might not be hate but indifference.

In Hungary, Bruneau was trying to find a way to link what he observed in the field with what we know about how empathy works in our brains. “We must have learned something in the past 60 years,” he said. “I think we have an opportunity to put that knowledge to use now, to help the efforts underway here.”

At 42, Bruneau has a young face and a laid-back manner that betrays his self-described California hippie upbringing and that most likely served him well in his early career as a high-school biology teacher. His first formal experience in conflict resolution came when he was 24 and volunteering at a summer camp for Catholic and Protestant boys in Belfast. In an effort to build friendships between the two groups, the camp organizer, an American nonprofit, invited 250 children between the ages of 6 and 14 to bunk together for three weeks, all in the same large room. There were no planned activities or events. One volunteer was an artist who wanted to help the children design murals; another was a jazz musician who offered music therapy. But mainly the volunteer counselors, all in their early 20s, were left to improvise. “Everyone’s heart was in the right place,” Bruneau told me when I visited his office at M.I.T. this fall. “But nobody had any clue what they were doing.”

At first he thought things were going pretty well. Some Protestant boys built what seemed like genuine friendships with some Catholic boys. But on the last day of the program — after three weeks of nature walks, impromptu dialogues and trust-building exercises — a fight broke out between two participants that quickly devolved into a full-scale, 250-child brawl: Catholics against Protestants. Bruneau was startled. He knew the children to be both kind and empathetic toward one another. But those instincts were overridden by something much more powerful. He left Ireland wondering if peace-

building initiatives were doing more harm than good, and if there was any way to make them better.

He spent the next few years traveling. He had already been to South Africa for the fall of apartheid. Now he made his way to Sri Lanka, landing at the Colombo airport just hours before it was attacked by the Tamil Tigers, then spent the next several weeks trailing two journalist friends through the countryside as they interviewed people on both sides of the conflict. Here, as in Ireland, otherwise-reasonable people could not bring themselves to consider the opposing side's perspective, and as a result could not muster compassion for their suffering.

He returned to the States, settling in Ann Arbor, Mich., where he completed a Ph.D. in molecular biology. But he kept thinking about the conflicts he had witnessed, and about the failed peace-building initiatives. What struck him most were the similarities: the ideological motivations, the deep-rooted psychological biases and the careful way that people apportioned their empathy. The questions he most wanted to answer were not about the individual molecules he was studying in the lab but about how people interacted with others. So, with his Ph.D. complete, he abandoned molecular biology and talked his way into a cognitive neuroscience lab at M.I.T. "I wanted the research I was doing to match the stuff I was thinking about," he says. "And I just felt more and more that the most relevant level of analysis for generating social change was the psychological level."

He started looking into conflict-intervention programs and discovered that there were hundreds more like the one he volunteered for in Ireland, and that hardly any of them had been scientifically validated. No one was really checking to see if the programs accomplished their stated goals, or even if their stated goals were the best ones for achieving the desired outcomes. "They have all these very straightforward metrics like building trust, and building empathy, that sound totally reasonable," Bruneau says. "But it turns out that a lot of those common-sense approaches can be way off-base."

Increasing empathy seemed to be a key goal of every conflict-resolution program he looked at; he thought this reflected a misconception about the type of people who engage in political violence. "If Hollywood is to be believed, they're all sociopaths," he says. "But that's not the reality. Suicide bombers tend to be characterized by, if anything, very high levels of empathy. Wafa Idris, the first Palestinian woman suicide bomber, was a volunteer paramedic during the second Intifada."

Bruneau developed a theory to explain this paradox: When considering an enemy, the mind generates an "empathy gap." It mutes the empathy signal, and that muting prevents us from putting ourselves in the perceived enemy's shoes. He couldn't yet guess at the mechanism behind the phenomenon, but he hypothesized that it had nothing to do

with how empathetic a person was by nature. Even the most deeply empathetic people could mute their empathy signals under the right circumstances. And it was difficult to determine what role empathy played in group conflicts. Increasing empathy might be great at improving pro-social behavior among individuals, but if a program succeeded in boosting an individual's empathy for his or her own group, he reasoned, it might actually increase hostility toward the enemy.

To test these ideas in the lab, he divided a group of volunteers into two teams, each with its own colors and logo, and then pitted them against each other in an online game. Each participant read short anecdotes about the fortunes or misfortunes of other study participants, and rated how good or bad the anecdotes made them feel. With each anecdote, the team logo and colors of the person whose story it was appeared on the computer screen. Participants tended to feel much less empathy — less joy at the successes and less sorrow at the misfortunes — for members of the other team than for members of their own team or of a control group that hadn't been assigned to any team. And as Bruneau hypothesized, the width of this empathy gap did not correlate with a person's empathy rating on personality assessments; it was not wider in less empathetic people or narrower in more empathetic people.

What it did correlate with was the strength of a person's group identity. "The more an individual's team affiliation resonated for them, the less empathy they were likely to express for members of the rival team," he says. "Even in this contrived setting, something as inconsequential as a computer game was enough to generate a measurable gap."

In some ways the finding was not a surprise. Evidence of the empathy gap abounds: in political discourse, across daily headlines, even in the simple act of watching a movie. "People will cry for the suffering of one main character," Bruneau pointed out. "But then cheer for the slaughter of dozens of others." The observation reminded me of watching "Captain Phillips" in a packed theater at Lincoln Center, of how much people applauded when the Somali pirates — whose lives back home had been portrayed as dire — were killed. They were the bad guys. Never mind that they had barely reached manhood or that their families were desperate and starving. Never mind that some were reluctant to turn to piracy in the first place.

Back in 2010, while studying Israelis and Arabs living in the Boston area, Bruneau happened upon some unexpected data. Participants in the study read short letters about the Middle East published in local newspapers and rated how reasonable they thought each opinion was, while Bruneau scanned their brains. He'd noticed that a common sticking point in regional dialogues was that each side found the other ignorant or

irrational or both. Bruneau wanted to see if those perceptions could be traced to a specific part of the theory-of-mind network.

For the most part, the results were as expected. Israeli subjects were more likely to harbor anti-Arab biases and to rate Arab perspectives as unreasonable, and vice versa. And in both groups, a small region of the brain, the medial precuneus, which may be associated with the theory-of-mind network, responded more strongly when the subject was reading letters written by members of the other group. But for three subjects, the psychological and neurological tests contradicted each other. The psychological tests indicated that they held the same types of anti-Arab biases as the other Israeli subjects, but their brain scans, and their reasonableness ratings, indicated that they were able to identify with the Arab perspective nonetheless. All three of these outliers, it turned out, were Israeli peace activists. In a scatter plot of the study's results, in which blue dots represented the Israeli subjects and red dots represented the Palestinian ones, the peace activists stood out: three specks of blue in a quadrant of red.

The sample size was too small to make any broad inferences, but it set Bruneau on a quest of sorts. In Budapest, whenever he found himself chatting with Roma activists who were not themselves Roma, he would ask them why they wanted to help. He had a hunch that if he put any of these “non-Roma Roma” in the scanner, and then compared their results with those of other Hungarians, they, too, would end up as blue dots in a sea of red. He reasoned that something somewhere in their lives had overridden their implicit biases and moved them to behave with greater empathy toward the minority group. He wanted to know what that something was. “If we could figure out how it happens,” he said, “maybe we could harness it somehow.”

Bruneau is the first to admit that this is no simple task. For all the progress that has been made in neuroscience, he says, the human brain is still an enigma. He likens the brain to a human riding an elephant: The human rider is the part we can consciously access and control, and the elephant is the subliminal rest. “We know next to nothing about how the elephant works, or how to actually steer it,” he says. “But it exerts enormous influence on our behavior.”

Psychologists have developed a battery of tests to help them glimpse this elephant. The implicit association test, or I.A.T. (sometimes referred to as the “racist test” in popular culture), evaluates subconscious biases by measuring how long it takes a person to match certain words to certain images on a computer screen. Other tests have been designed to measure dehumanization, by gauging the extent to which we attribute higher-order, human-specific emotions to groups other than our own, or how evolved we deem a given racial group to be. They're crude tests, to be sure, especially for a scientist trained

in the precision of molecular biology. But Bruneau consoles himself with the trade-off. “The answers you get with psychology may be less final, and less satisfying in a way,” he says. “But the questions you get to ask are so much bigger.”

In Budapest, Bruneau planned to measure anti-Roma biases in a group of schoolteachers, and then to see how well those biases correlated to their treatment of Roma students and their support for Roma integration. The goal was to help NGOs and school administrators design more successful integration programs — programs that didn’t trigger political backlash or waves of white flight. “The idea is to intervene at the psychological level before we intervene at the societal level,” he said. “And then to see if doing that improves the success rate of various integration programs.”

Anna Kende, a social psychologist at Eotvos Lorand University in Budapest, is not as optimistic as Bruneau about the potential of psychological interventions to improve the Roma situation. “I appreciate his approach,” she told me. “But the problem is very complex.” Part of it has to do with the Roma themselves, she says. For three generations now, their communities have been blighted by unemployment and the poverty that comes with it. And their psyches have been frayed by that experience. Kende’s research suggests that children living in settlements understand social mobility and the mechanisms behind it: to have a nice life, you have to study hard so you can get a good job and buy a house. But they also understand that those paths are closed to them. When she asked students how they would afford a nice house and a family, many said they would have accidents and collect insurance money, or win at poker.

The Roma who do escape the settlements often shed their ethnic identities — either deliberately or by default. “So for example, the dominant group may accept a Roma who comes from the settlement and somehow makes it into college,” Kende says. “But it’s not, ‘Oh, now this changes my perception of Roma.’ It’s, ‘Oh, well that person is not really Roma.’ And then what you have left is, the word ‘Roma’ becomes shorthand for ‘dirty, lazy, thief.’” Those norms are so pervasive, she said, that the Roma themselves have adopted them. This was plain to see in the settlements I visited, where residents talked openly about expelling the lazy and the criminal alike. “We cannot protect people just because they are Roma,” one settlement dweller told me. “We have to throw out the bad elements.”

Marianna Pongo, who is Roma and grew up in Gusev, told me that at least some of the blame for the failure of Nyiregyhaza’s busing program lay with the Roma themselves. “They have behavioral problems,” she said one afternoon, as we sat in her kitchen over coffee and homemade cinnamon cookies. “The bus driver tried disciplining the kids at one point, because they were running around on the bus and he couldn’t drive. And when

the kids got off the bus, they told their parents that the driver hit them. So the parents basically attacked the driver.” At another school, there were so many fights between kids from the two Roma settlements that a security guard had to be hired to maintain order. “I’m all for integration,” she said. “But I think it needs to be pointed out that some of the Roma act in ways that don’t help.”

Kende was not the only one feeling pessimistic. The Decade of Roma Inclusion — a multicountry initiative begun in 2005, as former Soviet-bloc countries like Hungary prepared for admission to the European Union — was drawing to a close, and the numbers were as dismal as they were at the start. According to the United Nations Development Program, about 90 percent of Europe’s 11 million or so Roma were still living below the poverty line; about 45 percent of Roma live in households that lack basic amenities like indoor toilets and electricity. In Hungary, Roma unemployment is estimated at 70 percent, or 10 times the national average. Worst of all, though, were the education statistics. Access to education was the initiative’s centerpiece, and desegregation programs received the most funding. Only one out of two Roma children attends preschool or kindergarten.

True, the decade was not a complete loss. Anti-discrimination laws were enacted, several high-profile court cases were won — including two in the European Court of Human Rights — and there were enough small-scale successes to suggest that desegregation was possible, even if systemwide gains remained elusive. But those gains had yet to be translated into meaningful change. “There are islands of fantastic integration,” Andras Ujlaky, executive director of the European Roma Rights Center, told me in a separate conversation. “But you can count them on one hand. And nobody seems to want to replicate them.”

A few days into our trip, Bruneau and I had lunch with two NGO workers — one Roma and one ethnic Hungarian — who were intrigued by but a bit skeptical of Bruneau’s plans. “So you’ll do this study,” said Gabor Daroczi, the executive director of Romaversitas Foundation, an NGO that offers scholarships and mentorships to help individual Roma students go to college. “And at the end you’ll have a nice research summary. What are the plans to do with the findings?” Bruneau explained that the pilot study was not an end in itself, and that the next step would be to develop actual psychological interventions, and then to test them to see which were most effective.

Daroczi sighed. He told me later that his doubts had much less to do with Bruneau’s project than with the state of Hungarian society. More and more, his country reminded him of George Orwell’s “1984.” The government made big statements and sweeping gestures in one direction but then almost immediately reversed itself. Any criticism was



rejected wholesale. “Sometimes I think that even the very best research will only make things worse,” he said. “You may provide concrete evidence of racism, but being told by outsiders that they are racist and need to change will only inspire a fuller rejection of outsiders.”

Kornelia Magyar, director of the Hungarian Progressive Institute, thought the experiments sounded promising. She believed that racial prejudice was thwarting efforts to assimilate the Roma, and thought studies that exposed it could only help their cause. But she, too, was concerned about what the next steps might be. “Once you measure it,” she asked, “How do you change it?”

Bruneau said he thought the answer to that question might lie with non-Roma activists like her. And then he asked a question: What made her, an educated white woman, take up the Roma cause? This gave Magyar pause. After a brief silence, she explained that she grew up in a city close to the Austrian border and that she always felt like an outsider when her family would cross over to go shopping. Daroczi couldn’t help interjecting; after the fall of communism, he said, Hungarians crossed the border in droves, mostly to purchase basic goods. “It was written in Hungarian on the walls of the shops, ‘Hungarians: don’t steal!’” he said.

“It felt shameful,” Magyar added, nodding. “I think that really affected me.” Bruneau lit up at the anecdote; it was very similar to the stories he’d collected from other non-Roma activists. He told Magyar and Daroczi about the brain scans of the Israeli peace activists — the blue dots in a sea of red — and about his desire to somehow array the power of their experiences toward intervention efforts.

“Yes, but even that is tricky,” Magyar said. The way a person related her own experiences to the experiences of others was complicated, she said. “Sometimes those same experiences trigger the exact opposite reaction.”

In Gusev, the problems of integration seemed larger and more complex than any one scientific theory or NGO could address. With the lawsuit still pending against the school in Gusev, C.F.C.F. had been helping families transfer out individually. I joined Nikolett Suha, then an attorney with the organization, one afternoon in October, to meet a young woman named H., whose child, N., was a student at the segregated school. (H., fearing retaliation, asked that she and her child be identified by only their initials.) It was N.’s first year there. At first, H. was thrilled to accept the incentives the church offered to encourage enrollment: vouchers for the general store and at least some school supplies. But the five weeks since school started had brought a series of calamities for her child. N. came home with lice more than once and was pummeled in the schoolyard by an older

student — an 11-year-old who was twice N.'s size — for reasons that H. had not been able to determine.

And if all of that were not enough, a rumor was circulating in Gusev that one of the fourth graders at the school had hepatitis, and that all students in that grade had been given shots to keep them from catching it. Some parents were angry that they hadn't been told about the shots. Others were angry that only the fourth graders supposedly received them. What about the other students, they wondered. Weren't they also at risk?

H. was hoping that the C.F.C.F. attorneys could get N. into the elementary school closest to Gusev. It was just 15 minutes away on foot and adjacent to a brand-new playground. But she was also very worried about cooperating with them. Earlier that week, H. said, the principal called her into the office and screamed at her, in front of some of the other parents. She accused H. of hitting a student who bullied her child. H. insisted that this wasn't true, that she had only scolded the student for picking on N. But the principal said that there were witnesses, and that the police would be notified. "I think she's offended that I want to move N. out of the school," H. told Suha.

H.'s husband had only recently received a workfare contract — an assignment collecting garbage around Gusev — after a long stretch of unemployment. Work-for-welfare programs, which are mandated by the federal government and administered by the municipalities, are a main source of employment for Gusev's residents, and the assignments were tough to come by. If word got back to the municipality that she had been involved in a police incident at the school, H. worried, her husband's contract might be revoked.

For two nights after the confrontation, H. said, she paced the family home. On the third day, she sent her husband to the school to find out if the police had been called. The principal told him no, they hadn't, and the next day gave her blessing for N.'s transfer. This provided only meager relief to H. Principals, it seemed, were as fickle as everyone else who held sway over the lives in Gusev. If they swung one way with such little prompting, couldn't they just as easily swing the other? (According to C.F.C.F, H. has since been charged in criminal court with hitting the student.)

H.'s worries were not new to Suha. On each of her visits to settlement families, she confronted similar anxieties. "She's very courageous," Suha said as we walked from H.'s house, through Gusev and out the south entrance, then made our way over to the prospective school. "Some of the mothers want to transfer but are afraid of making trouble for themselves."

C.F.C.F.'s main goal was to start persuading the schools closest to the settlement to accept students from Gusev on an individual basis. Getting moms like H. to apply was

only half the solution. And, tough as it could be, it was not the more difficult half.

I waited on the front steps while Suha went in and spoke to the principal of the school into which H. hoped to transfer N. She emerged 40 minutes later, frowning. The principal was actually quite nice, she said. But the school would not be able to accept any students from Gusev. “She said there are already too many Roma kids in this school,” Suha explained. White flight is a common problem in newly integrated schools, and the principal, Suha said, admitted to being worried about what would happen if her school was suddenly flooded with settlement students. “She wants to preserve the quality of education there,” Suha said, as we made our way back to H.’s house. “She thinks, O.K., if I let this kid in, then in the next few weeks two or three more will come. And then the non-Roma parents will start taking their kids out. Her point is, either way, you end up with a segregated school. Because even if you change the law and change the practices, you still haven’t changed people’s minds.”

Bruneau hopes that neural focus groups might help determine which interventions are most likely to succeed. “We would get people in the lab to view a number of different candidate anti-Roma bias campaigns,” he said. “And then see which ones generated the greatest response in predefined brain regions.” Ideally, social scientists working in Hungary would determine which programs to measure, and Bruneau’s research would help evaluate and refine those programs. In psychology experiments he conducted, short narratives about individuals from rival groups proved particularly effective at getting opponents to empathize with one another. He imagined intervention programs that used narratives like these in a variety of ways.

But before any such collaboration could begin, people — not just Roma activists but parents and teachers and school administrators — would have to be persuaded that psychological biases were, in fact, the root of the problem: that they existed in the first place, that they were coloring individual perception and affecting attitudes and behaviors and that science could help change them. Bruneau appreciates how quixotic this sounds. “I get that these are complicated problems,” he told me. “I get that there isn’t going to be any one magic solution. But if you trace even the biggest of these conflicts down to its roots, what you find are entrenched biases, and these sort-of calcified failures of empathy. So I think no matter what, we have to figure out how to root that out.”

*Jeneen Interlandi is a frequent contributor to the magazine. She is at work on an e-book about American-led syphilis experiments in Guatemala.*

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