



Brain gain. A proposed research effort to map brain activity could help make electrode arrays, such as the one shown, finer and more flexible.

in action. “The biggest need in neuroscience is to develop technologies that would allow us to record the activity of many, many neurons in a circuit to understand how the circuit functions through that aggregated activity,” says Story Landis, director of the National Institute of Neurological Disorders and Stroke. “And we just don’t have the tools to do that.”

Neuroscientists arguably can only crudely measure the activity of a brain now. They can turn to PET and MRI imaging that each detect “activation” of broad regions through proxies such as oxygen use, or they can measure the electrical activity of individual or small groups of neurons. However, the brain’s most interesting functions, such as thought and perception, probably incorporate thousands to millions of neurons, says neuroscientist John Donoghue of Brown University, who has participated in planning the new project. To understand “thought disorders” such as schizophrenia, he says, we need to know what level of cellular activity produces thought. “Does it take 1000 cells? 10 million? 100 million?”

In 2011, at a meeting of neuroscientists and nanoscientists in England sponsored by the Kavli, Gatsby, and Allen foundations, a handful of scientists proposed that the two disciplines combine forces to develop tools to answer that question, by recording “every action potential from every neuron within a circuit.” Some naysayers called the idea “ridiculous,” says Rafael Yuste, a Columbia University neuroscientist who has helped plan the BAM project. But George Church, the Harvard University molecular geneticist in charge of the Personal Genome Project, pointed out that nearly every objection had also been raised against the Human Genome Project. “The more questions people asked,” Yuste says, “the stronger the argument became that this could be done.”

After the meeting, Yuste, Church, and three other scientists hashed out a white paper on their idea. Miyoung Chun, the vice president of science programs at the Kavli Foundation, soon became its most vocal and organized advocate, Yuste says. After the group coined the name “Brain Activity Map” for the project, Chun sent the document to the Office of Science and Technology Policy (OSTP) at the White House. Within a few months, Yuste says, they “made the rounds” in Washington, visiting OSTP, NIH, the National Science Founda-

NEUROSCIENCE

Brain Project Draws Presidential Interest, but Mixed Reactions

Shortly after President Barack Obama made a seemingly innocuous pitch for more brain research in his State of the Union address last month, National Institutes of Health (NIH) Director Francis Collins sent out a note to his Twitter followers: “Obama mentions the #NIH Brain Activity Map in #SOTU.”

Few paid heed, however, until a week later when a front-page story in *The New York Times* indicated that the mysterious tweet referred to a soon-to-be announced NIH-led effort rivaling the Human Genome Project in cost and ambition, one that Obama planned to call for in his upcoming annual budget proposal. The initiative aimed to do no less than “build a comprehensive map of [the human brain’s] activity” within a decade, the newspaper reported.

The story stunned and excited many in the scientific community but angered and worried others. Lacking any official declaration of the project’s cost or how it would be funded, some researchers bristled at the prospect of a large new federal initiative that could take money from traditional grants

for individual scientists, especially at a time when NIH faces a massive budget cut (see p. 1020). *The Atlantic*, for example, published online a series of negative tweets, mainly from non-neuroscientists, decrying the Brain Activity Map (BAM) proposal, including this one from biologist Michael Eisen: “someone has to go to congress and explain why basic research is so important, not pander to them with big science crap.”

Even some in the neuroscience community expressed concern. “If this takes away from any of the R01s [individual investigator grants] that would normally be funded by the NIH, it would be bad,” says Eve Marder of Brandeis University in Waltham, Massachusetts, a former president of the Society for Neuroscience, who had attended one of the early planning workshops for BAM. “Right now the community is already so strapped we’re at a breaking point.”

Whatever one’s initial reaction to the new initiative, there is little doubt that researchers, and potentially physicians, would benefit from better ways of observing the brain

tion, and the Defense Advanced Research Projects Agency.

In June 2012, the group published a paper in *Neuron* outlining how three areas of technological development could lead to a better understanding of brain function. First, they envisioned finer, more pliant micro-electrode arrays that mold seamlessly to brain tissue and record from larger groups of neurons. Second, they proposed an effort to advance the field of optogenetics—which has lately revolutionized neuroscience by allowing researchers to manipulate neurons using light (*Science*, 15 December 2006, p. 1674)—by incorporating voltage-sensitive, light-emitting particles such as quantum dots and nanodiamonds into neurons, allowing scientists to track and manipulate neuronal activity on a much larger scale.

Finally, drawing on the growing field known as synthetic biology, they expressed interest in one day inserting artificial DNA-synthesizing enzymes into neurons so that every time the neuron fired, the enzyme would make an error in its DNA assembly, thus recording the cell's activity through a series of mistakes. Whether such molecules could ever be used in humans, or how the data they generate could be recovered is still unknown, the authors said.

Such tools are far from being ready for human use, the scientists caution. Nonetheless, they suggest that over 15 years the field could ramp up from monitoring the equivalent of the whole brain activity of the roundworm *Caenorhabditis elegans*, which has 302 nerve cells, to up to a million nerve cells—equivalent to the entire brain function of a zebrafish or the Etruscan shrew, one of the world's smallest mammals.

"There are people who may say this is not possible, that we are smoking something. But if you look back at the genome project, a lot of people said it was crazy and would never work. There are very few people saying that today," says nanoscientist Paul Alivisatos, director of the Lawrence Berkeley National Laboratory in California and one of the project's planners.

A big unknown is how much pursuing such an initiative would cost. *The New York Times* reported that Yuste and others involved have suggested the cost would be \$300 million annually for a decade, comparable to the \$3.8 billion spent on the Human Genome Project, yet the researchers offered no explanation for that cost estimate when asked by *Science*. And OSTP and NIH have so far declined to address the cost of the project and whether it would draw on existing budgets or new money. Private money

OTHER BIG BETS ON THE BRAIN



- **The Human Connectome Project:** A 5-year, \$38.5 million project funded by the National Institute of Mental Health to map structural connections (above) in the brains of hundreds of healthy adults.
- **The Human Brain Project:** A €1 billion European-led project to build a computer model of the human brain over at least the next 10 years (*Science*, 11 November 2011, p. 748).
- **The Allen Brain Atlases:** Maps of gene expression in the brain. A mouse brain atlas, completed in 2006, cost \$41 million; a human atlas is under way.

might aid the effort, but only the Kavli Foundation has so far made any public commitment, stating it expects to contribute up \$4 million to \$5 million per year of the total. Gerald Rubin, executive director of Howard Hughes Medical Institute's Janelia Farm Research Campus in Ashburn, Virginia, says his facility has already spent more than \$150 million on research relevant to the Brain Activity Map over the past 6 years and will continue to use its yearly budget of \$100 million along those lines.

Beyond the budgetary issue, some researchers have questioned the realism of BAM's stated goals. Partha Mitra, a neuroscientist at Cold Spring Harbor Laboratory in New York, called several of its technological proposals "science fiction." And although he supports the project as a whole, "I flinched when I read the phrase 'every spike from every neuron,'" says David Kleinfeld, a neurophysicist at the University of California (UC), San Diego. Capturing pulses of scattered light from nanodiamonds embedded deep in the brain's intricately folded tissue would require inventing cameras and microscopes that can record photons from all planes in three dimensions at

the millisecond speed that neurons fire—all the while making sure that the method doesn't itself alter brain activity, he notes. Kleinfeld says he has concluded from some rough calculations that such a feat isn't physically achievable in more than a small region of cortex.

Further confusion about the project stems from a discrepancy between its description in the *Neuron* paper, which focused on animal models, and the current iteration, which reflects a "socially responsible," more human-oriented version, Yuste says. During meetings with NIH, he explains, officials said, "This is good that you're going to map the activity of every neuron in the brain, but how about solving schizophrenia? What is this going to do for mankind?" At that point, Yuste says the group invited researchers with more practical links to patient care to join the planning. In the updated version of the project, research with humans will be conducted in parallel with more basic science, says Donoghue. He hopes that BAM will reveal how the brain encodes movement, which would help him build better brain-machine interfaces that allow paralyzed people to mentally operate robotic arms more naturally.

Still, don't expect a complete human brain activity map by 2025. For ethical and safety reasons, most of the techniques described in the group's new proposal are decades away from being applicable to humans, Rubin says. Research proposed in the *Neuron* paper will largely focus on flies, worms, zebrafish, and mice, he says.

The most recent description of the project suggests establishing national "brain observatories" that would "provide access to new technology to all potential users, and serve as a collaborative node for the BAM community." But it is impossible to tell how the project will be administered at this point, says Ralph Greenspan, a systems neuroscientist at UC San Diego and one of the core scientists planning the initiative.

Based on his experience with large research efforts such as the Human Genome Project, Greenspan says new dedicated funding is needed to go ahead with BAM. "In no sense is this something that should replace other basic research" like the connectome project (see box), he says. But that decision is largely out of his hands, Greenspan adds. "Our role was to bring it to the attention of people in Washington, who to our delight seemed to embrace it enthusiastically." Now, he says, "they'll do it the way they see fit."

—EMILY UNDERWOOD

With reporting by Jocelyn Kaiser and Robert F. Service.