

# BRAIN STORM

*Barack Obama announced his BRAIN Initiative on 2 April. Ever since, neuroscientists have been scrambling to work out what it actually is.*

BY HELEN SHEN

A mixture of excitement, hope and anxiety made for an electric atmosphere in the crowded hotel ballroom. On a Monday morning in early May, neuroscientists, physicists and engineers packed the room in Arlington, Virginia, to its 150-person capacity, while hundreds more followed by webcast.

Only a month earlier, US President Barack Obama had unveiled the neuroscience equivalent of a Moon shot: a far-reaching programme that could rival Europe's 10-year, €1-billion (US\$1.3-billion) Human Brain Project (see page 5). The US Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative would develop a host of tools to study brain activity, the president promised, and lead to huge breakthroughs in understanding the mind.

But Obama's vague announcement on 2 April had left out key details, such as what the initiative's specific goals would be and how it would be implemented. So at their first opportunity — a workshop convened on 6 May by the National Science Foundation (NSF) and the Kavli Foundation of Oxnard, California — researchers from across the neuroscience spectrum swarmed to fill in the blanks and advocate for their favourite causes.

The result was chaotic, acknowledges Van Wedeen, a neurobiologist at Harvard Medical School in Boston, Massachusetts, and one of the workshop's organizers. Everyone was afraid of being left out of 'the next big thing' in neuroscience — even though no one knew exactly what that might be. "The belief is we're ready for a leap forward," says Wedeen. "Which leap, and in which direction, is still being debated."

Others describe the BRAIN Initiative as a Rorschach test — an indeterminate entity that invited each researcher to project his or her own hopes and insecurities. But as the initiative has evolved, it has also come to resemble a large-scale sociological experiment, as the sprawling neuroscience community struggles to coalesce around a common research plan under intense public scrutiny and tough financial constraints.

## A BIG PICTURE

To the public, Obama's announcement seemed to come from nowhere; the president had never focused much on neuroscience before. In fact, the idea behind it had been spawned some 18 months earlier and almost 6,000 kilometres from the White House. At a meeting in Chicheley, UK, a group of neuroscientists and nanoscientists invited by the Kavli Foundation had developed their vision for the future of neuroscience research: to record electrical

impulses from thousands, or even millions, of neurons at once.

That is the only way in which we might understand how thought emerges from the brain, argues Rafael Yuste, a neuroscientist at

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Columbia University in New York City who spearheaded the idea. Current technology can make recordings from only single neurons or small groups of neurons at a time — which, he says, "is like trying to watch a movie on TV by looking at one pixel".

To do better, the architects of the Kavli plan called for a Brain Activity Map (BAM) project: a technology-development programme that would give researchers the tools to start small,

produce detailed maps of neural activity in simple organisms such as the fruitfly, and then move on to larger, more complex mammalian systems such as the mouse retina. They predicted that, within 15 years, BAM would be able to simultaneously record all of the activity in a mouse cortex — and that primates, and even humans, would be next.

BAM was intended to be provocative. "This is not going to happen if we keep waiting on little labs to do little things," declares Yuste. But, for many outsiders, it was ill-conceived — "a complete work of science fiction", says Markus Meister, a neurobiologist at the California Institute of Technology in Pasadena. Critics argued that the effort would take too long, cost too much and, ultimately, run up against the laws of physics, which limit how densely electrodes can be packed inside the brain. Moreover, creating a full activity map covering an organism's entire lifetime could yield a cripplingly large data set, while distracting from what many saw as the real problem: a dearth of computational and theoretical methods with which to interpret the brain's activity. "We just don't understand the data we have," says Mehrdad Jazayeri, a neuroscientist at the Massachusetts Institute of Technology in Cambridge.

But BAM caught the attention of administrators at the White House, who were on the lookout for a bold presidential initiative (see *Nature* 495, 19; 2013). The first hint of the administration's interest appeared in the president's State of the Union address on 12 February. Few neuroscientists appreciated the significance until five days later, when they were jolted awake by an article on the front page of *The New York Times*, which reported that the White House planned to unveil a ten-year neuroscience initiative





by four private institutions, which had committed to a total of \$122 million over varying lengths of time (see 'Obama's BRAIN').

Thus the crush at the NSF's May workshop: after weeks of uncertainty, researchers were hungry for a chance to weigh in. Participants were asked to submit one-page proposals describing a major obstacle to understanding the brain. Then, in a frenetic pitch-fest, authors took the floor for one minute each to argue their cases.

"What I care most about is reconstructing circuits accurately and fast," declared the first speaker, Albert Cardona. A neuroscientist at the Janelia Farm Research Campus near Ashburn, Virginia, he pushed for improved automated techniques to map the brain's anatomy on a super-fine scale. Others called for equally fine-grained recordings from ever-larger numbers of neurons, in the spirit of BAM. Still others championed their favourite model organisms. And some speakers emphasized the importance of big-data storage, as well as the computational and theoretical advances required to make sense of all that information.

#### BLURRED VISION

To the growing exasperation of audience members, however, there was no convergence towards a coherent agenda for the initiative. No one could even say whether the initiative would be funded with new cash outlays or with money diverted from existing research. By the meeting's end, the hotel lobby had become crowded with restless attendees who had abandoned the talks to check e-mails, make phone calls and run their labs from afar.

Among those who did stay were members of the NIH's BRAIN Initiative advisory committee, a 15-member panel dubbed the 'dream team' — a nickname it has since tried, unsuccessfully, to shake off. Co-chaired by neuroscientists Cornelia Bargmann at the Rockefeller University in New York City and William Newsome of Stanford University in California, the panel's first task was to prepare an interim report outlining the NIH's science goals for the project's first year. Then, once that report had been delivered to the NIH in September, the team would start to develop a long-term implementation plan, due in June 2014.

Shortly after the NSF meeting, the NIH team started on its first order of business: convening a series of four workshops to gather input from the neuroscience community. These covered molecular techniques; large-scale recording technologies; computational and theoretical neuroscience; and human brain studies. The difference in tone was striking. The NSF event had been like a cacophonous town hall meeting, whereas the NIH workshops felt more like an honorary lecture series. Each one began with public presentations by a dozen or so invited speakers, and the proceedings were carefully controlled. Once the open session

based on the Kavli idea. The article suggested that the initiative might receive federal funding on par with the \$3.8 billion spent on the Human Genome Project, and would produce a comprehensive, detailed map of neural activity in the human brain within a decade.

The news alarmed many neuroscientists, who worried that few of them had been consulted, that the money would be made available at the expense of existing programmes and that failure to meet a seemingly impossible goal would undermine public trust in science. "This was a very narrow agenda of a small group of people," recalls Partha Mitra, a neuroscientist at Cold Spring Harbor Laboratory in New York and a vocal critic of BAM.

But the administration was already taking a different tack. By the time of the official announcement on 2 April, the project had been rebranded the BRAIN Initiative and carried a comparatively modest price tag: only \$110 million in federal funding for the 2014 fiscal year. It no longer had a specific lifetime

— although the White House implied that the project could last ten years or longer.

And, unlike BAM, it had no clearly defined goal. Rather than promising to record from any particular number of neurons at once, Obama said simply that new tools were needed to help neuroscientists to develop better pictures of brain circuits in action — and that such technologies could pave the way to treatments for neurological disorders such as epilepsy, autism, Alzheimer's disease and schizophrenia (see *Nature* 499, 272–274; 2013).

Many neuroscientists found the announcement reassuring — at least the BRAIN Initiative wasn't BAM — but puzzlingly vague. All they knew was that the details would be left up to three government agencies: the Defense Advanced Research Projects Agency (DARPA), which would contribute \$50 million in the first year; the National Institutes of Health (NIH), which would pitch in \$40 million; and the NSF, which would add \$20 million. The initiative would be further supported

# OBAMA'S BRAIN

The White House has set lofty objectives for its BRAIN Initiative. Now it is up to the participants (purple) to develop a strategy for the programme.

## PRIVATE RESEARCH

- The Allen Institute for Brain Science **\$60 million annually**
- Howard Hughes Medical Institute **\$30 million annually**
- Kavli Foundation **\$4 million annually for 10 years**
- Salk Institute for Biological Studies **\$28 million**

## FEDERAL AGENCIES

(First year funding)

- Defense Advanced Research Projects Agency **\$50 million**
- National Institutes of Health **\$40 million**
- National Science Foundation **\$20 million**

was over, all of the speakers disappeared into closed discussions with the dream team. One participant likened that experience to being a delegate to the United Nations, with everyone seated around a long oval table behind printed name cards.

Bargmann says that privacy was necessary to allow scientists to speak freely — and sometimes critically — about different experimental approaches. But, in the wider neuroscience community, many felt the selection of invited speakers and topics excluded their interests. The dream team weathered criticism from molecular, cellular and developmental neuroscientists who felt underrepresented, as well as from clinical neuroscientists concerned that there was not enough emphasis on disease research.

Adding to researchers' anxiety was the fact that no one knew whether they would have any involvement in the arms of the project being run by the two other federal agencies. The deputy director of DARPA's defence science office, Geoffrey Ling, said in June that his agency would not be releasing any road maps for its BRAIN Initiative efforts; meanwhile, the NSF's lead on the project, biological sciences chief John Wingfield, said in September that the agency intended to wait for the NIH report before issuing its own plan, to avoid duplication. "There are limits to what we can do," he said, contrasting his agency's roughly \$150-million annual expenditure on neuroscience with the NIH's \$5.5-billion budget.

Meanwhile, almost everyone was worried about where the funding would come from — especially as it became clear that Congress would not set aside any new money for the BRAIN Initiative's first year. A modicum of

## OBJECTIVES

- Provide the knowledge for addressing debilitating disorders.
- Develop new imaging technologies and understand how information is stored and processed in neural networks.
- Understand how brain activity leads to perception, decision-making and, ultimately, action.
- Produce a sophisticated understanding of the brain, from individual genes to neuronal circuits to behaviour.

## RESEARCH COMMUNITY

- The National Science Foundation convened workshops to solicit ideas.
- The National Institutes of Health set up a 'dream team' of 15 scientists that is producing reports based on community feedback.

new funding should be forthcoming from the NIH: of the \$40 million it agreed to commit, \$10 million will come from the director's discretionary funds. Officials at the NIH and NSF maintained that the initiative would not derail existing programmes. But the dearth of dedicated new funds meant that the three federal agencies would have to begin, at least in part, by packaging together some ongoing projects. The initiative's private partners, likewise, will mostly stick with existing programmes. The Salk Institute for Biological Studies in La Jolla, California, the Allen Institute for Brain Science in Seattle, Washington, and the Howard Hughes Medical Institute in Chevy Chase, Maryland, were all eager to frame the BRAIN Initiative as a continuation of research they already had under way.

## SOMETHING FOR EVERYONE

By early September, with the private partners determined to do their own thing and two of the three federal agencies all but silent, interest in the NIH report had reached fever pitch: researchers saw it as the de facto national agenda. On 16 September, the advisory committee at last published its interim report on science priorities. Many had feared that it would fail to be sufficiently inclusive, but the document was instead so staggeringly broad that it seemed to encompass all of circuit-based neuroscience. Cataloguing every cell type in the brain, mapping those cells' full anatomical connections, monitoring and manipulating their signals, modelling and simulation — there was something for everyone. "It would be hard to disagree with this report," said Mitra. "It's written, perhaps, with critics in mind."

NIH director Francis Collins tacitly conceded the report's vastness when he formally accepted it. "These areas of research are expansive, and undoubtedly cover more research than NIH can fund with \$40 million in one year," he said; the more ambitious elements could shape funding requests in years to come. And not just a few years, adds Yuste. "This is something you need 15 years and \$3 billion to do."

Tough choices lie ahead as the committee starts work on the long-term report it must deliver next June. The team will need to rank research priorities as short-, medium- and long-term goals, set timelines, estimate costs and define specific deliverable outcomes for the next few years — altogether a daunting task, says Newsome.

"It's much easier to see a year into the future than ten years into the future," agrees Bargmann.

Already, members of the working group are butting heads over questions such as whether ultra-detailed anatomical maps of the brain — painstakingly obtained with electron microscopy (see page 147) — should take priority over lower-resolution maps that can be completed much more quickly using light microscopy.

And then there is the question of management. Although the three government agencies have kept each other informed of their plans, the White House has so far indicated no intention to coordinate the process more formally. This worries researchers such as Yuste, who is urging the creation of 'brain observatories': multi-agency facilities that, like particle accelerators or giant telescopes, could provide community access to technology too large, costly or specialized for individual labs to maintain. Without higher-level planning, he warns, such efforts will be impossible, and the BRAIN Initiative's investment could end up being squandered on many small grants awarded by the individual agencies. "The whole effort will not be more than the sum of its parts," he warns.

But others, including Bargmann, argue against throwing limited resources behind a monolithic, centralized project. "This is not the time to pick one approach and say this is the right approach," she says. Instead, she hopes to foster the strongest and most creative ideas from individuals and groups of researchers — and see where they lead.

The NIH advisory committee hopes to draw on the creativity of the wider neuroscience community at the upcoming annual meeting of the Society for Neuroscience. On 11 November, hundreds of neuroscientists are expected to pile into room 33C at the San Diego Convention Center in California to weigh in on the NIH's interim recommendations. Armed with only a slightly more defined vision than they had six months ago, they will continue to try to define what the BRAIN Initiative can and should mean for their future. ■

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