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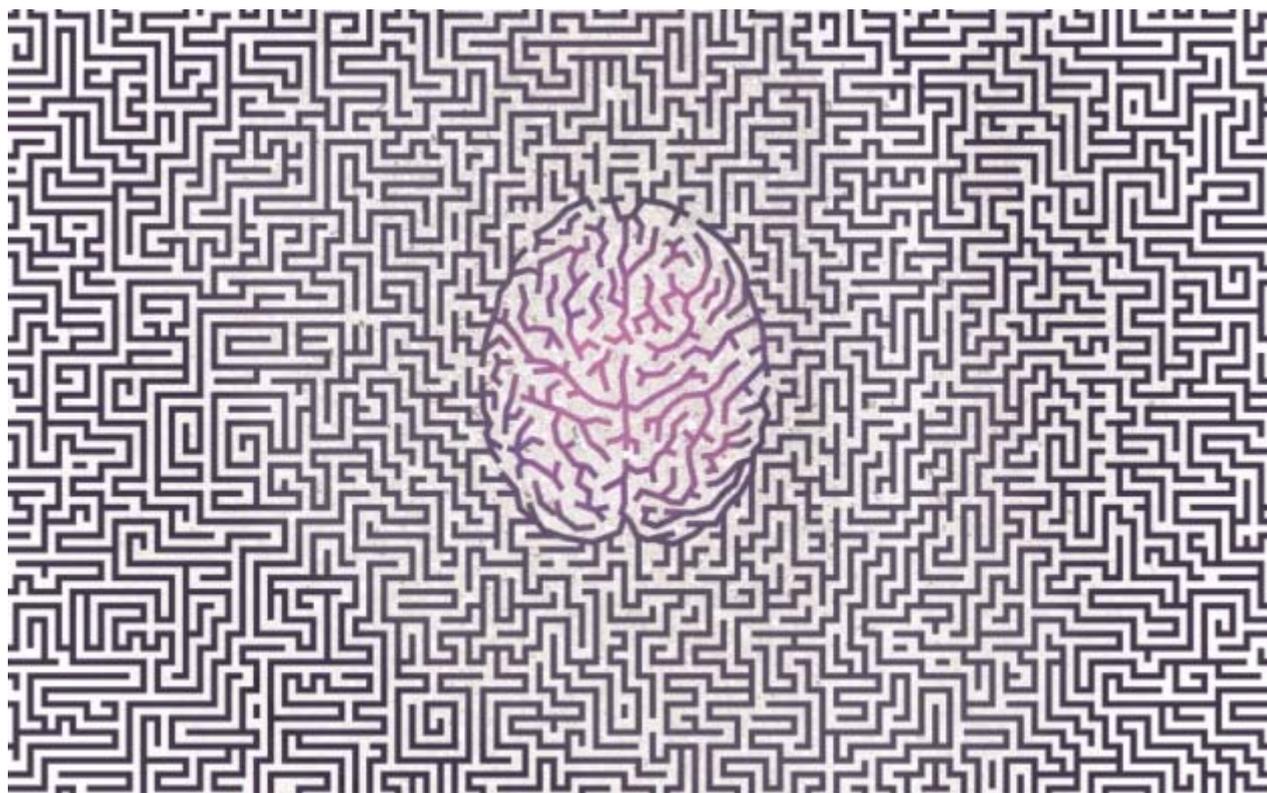
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Neuroscience: Solving the brain

The United States and Europe are both planning billion-dollar investments to understand how the brain works. But the technological challenges are vast.

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When neurobiologist Bill Newsome got a phone call from Francis Collins in March, his first reaction was one of dismay. The director of the US National Institutes of Health had contacted him out of the blue to ask if he would co-chair a rapid planning effort for a ten-year assault on how the brain works. To Newsome, that sounded like the sort of thankless, amorphous and onerous task that would ruin a good summer. But after turning it over in his mind for 24 hours, his dismay gave way to enthusiasm. “The timing is right,” says Newsome, who is based at Stanford University School of Medicine in California. He accepted the task. “The brain is the intellectual excitement for the twenty-first century.”

It helped that the request for the brain onslaught was actually coming from Collins's ultimate boss — US President Barack Obama. Just two weeks after that call, on 2 April, Obama announced a US\$100-million initial investment to launch the BRAIN Initiative, a research effort expected to eventually cost perhaps ten times that amount. The European Commission has equal ambitions. On 28 January, it announced that it would launch the flagship Human Brain Project with a 2013 budget of €54 million (US\$69 million), and

contribute to its projected billion-euro funding over the next ten years (see *Nature* **482**, 456–458; 2012).

Although the aims of the two projects differ, both are, in effect, bold bids for the neuroscientist's ultimate challenge: to work out exactly how the billions of neurons and trillions of connections, or synapses, in the human brain organize themselves into working neural circuits that allow us to fall in love, go to war, solve mathematical theorems or write poetry. What's more, researchers want to understand the ways in which brain circuitry changes — through the constant growth and retreat of synapses — as life rolls by.

Reaching this goal will require innovative new technologies, ranging from nanotechnologies to genetics to optics, that can capture the electrical activity coursing through neurons, prod those neurons to find out what they do, map the underlying anatomical circuits in fine detail and process the exabytes of information all this work will spit out. “Think about it,” says neuroscientist Konrad Kording of Northwestern University in Chicago, Illinois. “The human brain produces in 30 seconds as much data as the Hubble Space Telescope has produced in its lifetime.”

Researchers are already chipping away at the problem: the past few years have seen startling advances in techniques that allow the stimulation of precise neurons deep in the brain using light, for example, and the construction of anatomical maps with unprecedented detail. So far, most neuroscientists are using simpler species such as mice or worms to learn basic principles that evolution may have conserved in humans. Here, *Nature* examines some of the technological advances that will be necessary to drive further, and faster, into the brain.

1) Measuring it

If researchers are to make sense of the frenzy of electrical signals coursing through the brain's circuits, they will need to record simultaneously from as many neurons as possible.

Today, they typically gauge neuronal activity by inserting metal electrodes into the brain, but this approach comes with enormous challenges. Each electrode needs its own wire to carry out the measured analogue signal — the voltage change — and the signals can easily be lost or distorted as they travel along the wire to instruments that will convert them into the digital signals needed for analysis. Moreover, the wires must be hair-thin to avoid tissue damage. Advances in electrode technologies have seen the number of neurons that researchers can record from double roughly every seven years over the past five decades, such that probes can now reach a couple of hundred neurons simultaneously¹. But the ultimate challenge will require them to reach many more cells and to record higher-quality signals.

That is becoming possible with a new generation of neuroprobes made from silicon, which allows extreme miniaturization. Instruments such as analogue-to-digital converters can be carved out of the same tiny piece of silicon as the electrodes, so the vulnerable analogue signal does not have to travel. A prototype 'neuroprobe' of this type was unveiled in February at the International Solid-State Circuits Conference in San

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Francisco, California, by imec, a nanoelectronics research organization based in Leuven, Belgium. One-centimetre long and as thin as a dollar bill, the probe packs in 52 thin wires and switches that neuroscientists can flip seamlessly between 456 silicon electrodes.

“The human brain produces in 30 seconds as much data as the Hubble Space Telescope has produced in its lifetime.”

When inserted into a mouse brain, for example, the electrodes dotted across the imec probe can span — and record from — all layers of the animal's brain simultaneously, from the cortex to the thalamus in the brainstem. This could help neuroscientists to unpick the circuitry that connects them. “This prototype can be scaled up,” says Peter Peumans, director of bio- and nanoelectronics at imec. Within three years, he says, the neuroprobes will have up to 2,000 electrodes and

more than 200 wires.

But rather than just passively measuring electrical activity in neural circuits, researchers also want to test what those circuits do by activating them and observing the changes that occur in electrical activity and animal behaviour. Each imec probe includes four stimulating electrodes, and in future models this will be increased to 20 or more. But as recording and stimulating electrodes can interfere with one another, researchers are also trying to stimulate neurons with light instead of electricity. These 'optogenetic' techniques generally involve inserting light-sensitive ion-channel proteins called opsins into neurons, so that a laser light shone into the skull through an optic fibre opens the channels and activates the neurons. One research group recently used optogenetics in mice, for example, to produce repetitive behaviours that are considered to be a model for obsessive-compulsive disorder².

The next generation of optogenetic neuroprobes will include systems that are able to deliver light directly into the brain exactly where it is needed, without the need for cumbersome optical fibres. In April, for example, Michael Bruchas at Washington University in St Louis, Missouri, and his team described their wireless prototype: an optogenetic chip with light-emitting diodes that can be activated by a radio signal to trigger the opsins³. When the team implanted a chip into mice that could stimulate the brain's reward centre, the animals quickly learned to switch it on themselves by poking their noses into a hole — showing that the chip worked and could change behaviour.

The search is on for other natural or genetically engineered opsins that respond to different wavelengths of light and might allow researchers to activate and test various elements of a circuit. Eventually, neuroprobes may not only routinely record from and stimulate hundreds or thousands of neurons in mice and non-human primates, but also include sensors to identify neurotransmitters and measure physiological parameters such as temperature, which can affect neuronal activity.

And the future could bring much more radical methods. Some scientists have proposed the idea of nanometre-scale light-sensitive devices that could embed themselves in the membranes of neurons, power themselves from cellular energy and wirelessly convey the activity of millions of neurons simultaneously⁴.

Another idea is to do away with measuring devices and instead capture the post-mortem trace left by an

action potential as it passes through the brain. Kording is part of a team trying to do this by exploiting DNA polymerase, the enzyme that cells use to build DNA from its component bases. He and his colleagues have designed a synthetic DNA polymerase that, when surrounded by high levels of calcium, inserts the wrong base into the artificial DNA strand it constructs⁵. If this polymerase could be added to neurons, then an action potential, which causes intracellular calcium levels to spike, would trigger errors in the DNA strand, and the time that this occurred could be determined retrospectively from the length and sequence of the DNA. That's the theory, anyway, says Kording. "But we are only getting started."

2) Mapping it

However researchers go about collecting information about neuronal activity and circuitry, it will be essential to map this onto a reliable and highly detailed anatomical atlas of the brain. It is like trying to understand traffic flow in a city: the better the map (the anatomy), the better the predictions of how it will change during rush hour (the active circuits).

For more than a century, the method used to map neuroanatomy has been to slice a brain as thinly as possible, stain the slices to render the cells visible and look at them under the light microscope. But, computationally, it is extremely challenging to align large numbers of slices in order to reconstruct the tangled web of neurons densely packed into a human brain.

Even so, Katrin Amunts of the Research Centre Jülich in Germany and her team announced that they had done it last month, when they published a three-dimensional reconstruction of a human brain in unprecedented detail. To build it, they painstakingly sliced the brain of a 65-year-old woman into 7,400 layers 20 micrometres thick, stained them, imaged them with a light microscope and then used 1,000 hours on two supercomputers to piece the terabyte of data together⁶. The atlas reveals in detail folds of the human brain, which tend to get lost in two-dimensional cross-sections. The whole project took a decade, says Amunts, who has already started work on a second human brain to look at variation between individuals — a project she expects to move a lot faster.

Attempting to take another leap farther, Jeff Lichtman at Harvard University in Cambridge, Massachusetts, and Winfried Denk of the Max Plank Institute for Neurobiology in Munich, Germany, are working with the German optics company Carl Zeiss on a new electron microscope that would image even thinner slices — 25 nanometres, or one-thousandth the thickness of an average cell. "Then you get to see every little damn thing in the brain, from every neuron to every subcellular organelle, from every synapse to every spine neck — everything," says Lichtman.

Using conventional electron microscopes, with their single scanning beam of electrons, researchers have so far been able to reconstruct only a cubic millimetre of brain tissue. It would take many decades to scan a whole mouse brain's worth of ultra-thin slices, says Denk. The new machines, which should be delivered to the two labs next year, will have 61 scanning beams operating in parallel and will shrink this time down to months. Denk estimates that this will allow them to make a computational reconstruction — "a mouse brain in a box", as he puts it — within five years.

What Lichtman and Denk have not yet resolved is how to reconstruct a full three-dimensional picture of the tissue from these images. In a trial project using a conventional electron microscope, Denk's lab scanned minuscule volumes of mouse retina, one of the simplest parts of the mammalian brain^{7, 8}. But computing alone was not able to reconstruct the 300 gigabytes of image data the effort generated, so the lab enrolled 230 people to help to trace, by eye, the neurons as they meander through the slices. "It won't be practical to do that sort of crowd-sourcing on a larger scale," says Denk. "We'll have to develop algorithms to get machines to do the job as well as the human eye."

There may be easier ways to carry out brain mapping at lower resolutions. One possibility is a technique called CLARITY, which generated excitement when it was unveiled in April. Karl Deisseroth at Stanford University and his colleagues have developed a way to chemically replace the opaque lipids in the brain with a clear gel, rendering the tissue transparent and allowing the internal arrangements of neurons to be viewed without the need for slicing⁹. Deisseroth has already applied the technique to brain tissue from a boy who had autism spectrum disorder, and found unusual ladder-like arrangements of neurons in his cortex. Other researchers are clamouring to use the method to trace circuitry in normal brains (see *Nature* **497**, 550–552; 2013).

And however efficient the various activity-measuring and anatomy-mapping techniques turn out to be, many researchers hope that it won't be necessary to view — or record from — every individual neuron to get a working picture of the whole brain. "Patterns will emerge from which it will be possible to extrapolate," says Newsome.

3) Making sense of it

Perhaps the most daunting part of the brain challenge lies in storing and handling data. One cubic millimetre of brain tissue will generate an estimated 2,000 terabytes of electron-microscopy information using Lichtman and Denk's new microscope, for example. Denk estimates that an entire mouse brain could produce 60 petabytes and a human brain about 200 exabytes. This amount of data will rival the entire digital content of today's world, "including Facebook and all the big data stores", says Lichtman.

That is just the start. Neuroscientists will eventually want to collect this type of anatomical information for many human brains — each of them unique — and layer onto it information about neuronal activity. They will need to store and organize all these diverse data types so that scientists can interface with them.

Europe's Human Brain Project, which aims to provide a brain simulation that researchers can interact with in real time, adds another level of demand. "One of our challenges is to develop computer languages that allow a supercomputer's capacity to be used efficiently," says Jesus Labarta Mancho of the Barcelona Supercomputing Center in Spain, which is a partner of the Human Brain Project. Current supercomputers would be overwhelmed by experiments requiring different parts of the brain to be simulated in different fractions of a second. So the idea is to develop ways to allow the supercomputer to compress information about some brain areas, freeing up resources for computation on the ones that are relevant to the problem at hand.

Even assuming that the data can be neatly packaged, theorists will have to work out what questions to ask of it. “It is a chicken and egg situation,” says theoretical neuroscientist Christian Machens at the Champalimaud Centre for the Unknown in Lisbon. “Once we know how the brain works, we’ll know how to look at the data.”

Theorists argue about the scale of the task ahead of them; Kording is one of many who think it will be horrendous. “It make's Google's search problems look like child's play,” he says. “There are approximately the same number of neurons as Internet pages, but whereas Internet pages only link to a couple of others in a linear way, each neuron links to thousands of others — and does so in a non-linear way.”

But Partha Mitra, a biomathematician at Cold Spring Harbor Laboratory in New York, thinks that the bigger challenge to knowing the brain will be sociological. “Chasing after the workings of the brain is not like chasing after the Higgs boson, where everyone goes after the same single target,” he says. “It is about the community setting goals in a deliberate manner and working towards them in a disciplined manner.”

Setting those goals is now consuming Newsome's summer, just as he predicted. He is taking part in a series of expert workshops to define the goals of the BRAIN Initiative and shaping a report on it that is due in September. The report won't promise to solve all the challenges of the brain, he says, but it will set a course that, in the long term, just might.

“We'll eventually learn what all the twinkling of the neurons means in terms of our behaviour,” says Newsome, “and that's what really matters.”

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See Editorial page 253

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