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Mind's circuit diagram to be revealed by mammoth map

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Our brain is the most complex object in the known universe – so we'll need to map it in formidable detail to track down memory, thought and identity

The greatest map of all (Image: Bruno Vergauwen)

A STRANGE contraption, a cross between a deli meat slicer and a reel-to-reel film projector, sits in a windowless room in Cambridge, Massachusetts. It whirs along unsupervised for days at a time, only visited occasionally by Narayanan Kasthuri, a mop-haired postdoc at Harvard University, who examines the strip of film spewing out.

It may seem unlikely, but what's going on here may revolutionise neuroscience. Spaced every centimetre along the film are tiny dots, each of which is a slice of mouse brain, one-thousandth the thickness of a sheet of aluminium foil. This particular roll of film contains 6000 slices, representing a speck of brain the size of a grain of salt.

The slices of brain will be turned into digital images by an automated electron microscope. A computer will read those images, trace the outlines of nerve cells, and stack the pictures into a 3D reconstruction.

In the jargon, they are building the mouse "connectome", named in line with the term "genome" for the sequence of all of an organism's genes, "proteome" for all its proteins, and so on.

It's an epic undertaking. The full mouse connectome would produce hundreds of times more data than can be found on all of Google's computers, says Jeffrey Lichtman, the neuroanatomist leading the Harvard team. And yet it's just the beginning. Their efforts could be seen as a dry run for a project that is at least four orders of magnitude greater: mapping the human connectome.

With 100 billion neurons, each with up to 10,000 connections, or synapses, the human brain is the most complex object in the known universe. To map the entire thing would arguably be the most ambitious project we have attempted and, for now, lies way out of reach. Yet thanks to the constant acceleration of our computing and biotechnological capabilities, the first steps towards the roughest of drafts are now being taken.

In line with the scale of the challenges, the pay-offs could be huge. Even the most rudimentary blueprint of the brain could reveal how genes and experience shape our wiring, which in turn determines our individual differences. It would advance our understanding of conditions such as autism, schizophrenia and addiction - all of which are increasingly viewed as "connectopathies". It could even shed light on such mysteries as intelligence and consciousness. "Now is the time we're going to answer stuff that we've been waiting half a century to deal with," says Robert Marc, a vision scientist at the University of Utah in Salt Lake City.

It is only in the past few decades that scanning techniques have allowed scientists to peer inside living brains. Magnetic resonance imaging (MRI) provides detailed anatomical images, and an enhanced version called functional MRI measures fluctuations in blood supply to different parts of the brain as people carry out specific mental tasks. On the assumption that blood supply reflects how hard neurons are working, this effectively lets neuroscientists watch the brain in action.

These techniques have led to a wealth of new insights, but they reveal nothing about neural connections. Brain tissue in these images looks more like the filling of a cream cake than the trillions of criss-crossing neural wires that are really there.

To date, those wires have been mapped in just one animal: a millimetre-long, dirt-dwelling worm called *Caenorhabditis elegans*, which turned out to have 302 neurons and 9000 synapses. Incredibly, this work started in the 1970s, with little of today's equipment. The worm was cut into several thousand slices before being imaged under an electron microscope.

In those days, the delicate slices of brain were floated on a bead of water and manipulated using a toothpick with a human eyelash glued to the end. Touching the slices with the eyelash destroyed them, so the team had to gingerly brush the surrounding water to nudge them into place - and for good measure, the slices were almost invisible on the water. Understandably, it took 14 years to assemble the wiring diagram, published in a landmark 446-page paper dubbed "The mind of a worm" (*Philosophical Transactions of the Royal Society B*, vol 314, p 1).

Technology has moved on since the days when an eyelash was part of the laboratory toolkit, and the Harvard team is not alone in coming up with a film-projector-like brain imager. The equipment is improving all the time. A year ago it would have taken 90 years to convert a cubic millimetre of mouse brain into 50,000 images. With their current design it would take just nine years, and further improvements are in the pipeline. Even so, mapping an entire mammal brain is too remote a goal for now. Instead, the focus is on questions that can be answered by mapping discrete areas of the brain.

Kasthuri, for example, plans to produce a connectome for the mouse cerebellum, a cauliflower-shaped structure at the base of the brain that has fine control over movements. Vision scientist Robert Marc is concentrating on the retina, the patch of nerve-rich tissue at the back of each eyeball that is seen as an extension of the brain, in a bid to understand common causes of blindness such as glaucoma and retinitis pigmentosa. In work his team is preparing to publish, they have mapped connections in a quarter-millimetre-diameter patch of rabbit retina, containing 600 neurons.

Sebastian Seung, a computational neuroscientist at the Massachusetts Institute of Technology who works with Lichtman, is charting part of a zebra finch's brain to try to read the bird's song from its connectome. It may sound like an eccentric goal, but it would be an important proof of concept: that we could one day read a brain's memories.

Projects such as these have attracted the attention of "transhumanists", people who want to harness technology to live forever. They see connectomics as the first step to downloading their brains into computers. The Brain Preservation Foundation has offered a scaled-down version of the X Prize: up to $106,000 for the first lab to develop a way to preserve a whole mammal brain at the moment of death, so that its connectome could be read.

Whether because of the modest nature of the reward - the original X Prize for private space flight was a more attention-grabbing $10 million - or the transhumanists' oddball reputation, most neuroscientists seem indifferent to the prize. "It doesn't motivate me at all," says Kasthuri. "I'm much more interested in using connectomics to understand biology."

The cell-by-cell approach has its critics, though. Charles Gilbert, a neurobiologist also at Rockefeller University in New York, points out that synapses constantly change. He has found that in a mouse cortex, they turn over at the rate of 7 per cent per week. "You may take a snapshot of the connections," he says. "That doesn't necessarily mean that those are the connections that exist all the time."

Another drawback is that a typical speck of brain being mapped will have thousands of neurons coming in from distant areas, which are lopped off at the edge of the sample with no clue to their origin. "Most of the information that a piece of brain processes comes from far away and is shipped off far away," says Anthony Movshon, a neurophysiologist at New York University.

That's why other groups have taken a step back to look at the bigger picture. Instead of trying to map every single nerve cell, they are mapping just the long-distance connections. It's as if they are drawing a map of a country's highways, rather than every local road.

The brain is organised so that the outermost cortex contains the main bodies of the nerve cells and their short branches connecting to nearby cells. Underneath the cortex lie the cells' long projections, or axons, which connect distant areas. Axons are swaddled in a fatty coating called myelin, which improves electrical conduction. As the myelin is pale, the underlying part of the brain is known as the

"white matter", in contrast with the "grey matter" of the cortex.

One technique for mapping axons is over 100 years old: injecting dye into cells in one spot in the brain, and watching as it spreads to distant areas. Partha Mitra of Cold Spring Harbor Laboratory in New York is using an automated version of this technique to inject dye at 500 locations in a mouse brain and trace its course. He says he is likely to produce a draft of the mouse brain later this year and hopes to map the brains of human cadavers in the same way. "We are trying to do the pragmatically defined project that will take us to the whole brain," he says.

But there are newer ways to trace long-distance connections that do not entail injecting harmful dyes or slicing brains into prosciutto. These mean that, finally, we can start to look at living brains.

One method takes advantage of the fact that water molecules can diffuse more freely along axons lengthwise than they can pass through the fatty myelin coating. In 2007, it was reported that a new technique called diffusion MRI could show how the trillions of water molecules in the brain are jostling against one another (see "Mind readers"). Their direction of movement indicates the paths of hundreds of axon bundles in a living brain (*PLoS One*, vol 2, p e597).

While still in its infancy, diffusion MRI is already leading to important advances. For example, Heidi Johansen-Berg and Timothy Behrens of the University of Oxford are using it to study the effects of stroke, in which a blood clot or bleeding in the brain causes local nerve tissue to die from lack of oxygen. They have found that the death of the area affected by the stroke can have knock-on effects on other areas connected by axon bundles (*Neuroimage*, vol 54, p 161). Seeing those changes is important, since techniques are being developed to strengthen brain connections by applying electric currents or magnetic fields to the skull.

At Harvard, Van Wedeen, one of the original developers of diffusion MRI, has used the technique to reconstruct how the human brain rewires itself over time. His team's results, published in November, show that between toddlerhood and adolescence, the brain becomes more centrally organised around a few major hubs, which might allow signals to criss-cross the brain more rapidly (*Proceedings of the National Academy of Sciences*, vol 107, p 19067).

Rewiring problems may well underlie the tendency of mental illness to arise during adolescence and early adulthood. Diffusion MRI studies have already identified specific axon bundles that are altered in schizophrenia, alcoholism and other conditions. The hope is that miswired brains could be identified and treated years before the symptoms emerge.

The insights are extending beyond medicine. Recent studies show that the strength of specific axon bundles seems to correlate with skills such as arithmetic and rapid word recall. It may also shed light on how experience shapes minds, and how memories form. "My memories, many things that make me an individual, may be encoded in my connectome," says Seung. "The hypothesis is that I am my connectome."

In 2009, Johansen-Berg and Behrens showed that diffusion MRI could detect the effects of just six weeks of juggling practice, for example. Learning the new skill thickened the connections in several axon bundles involved in hand-eye coordination (Nature Neuroscience, vol 12, p 1370).

Another new scanning technique has developed from functional MRI, which was originally designed to see which parts of the brain crank up their workload when people carry out specific mental tasks. It was later found that even when people lie resting in the scanner, the activity of individual brain areas seems to gently fluctuate over a 10 to 30-second cycle. Crucially, many areas known to have strong connections have cycles that are in sync with each other, either in or out of phase. Discovering which areas match up in this way, using a technique known as functional connectivity MRI, is another source of information about the brain's long-distance connections.

It is thanks to developments such as these that the US National Institutes of Health (NIH) has begun what it calls the "human connectome project". In September, it announced grants to two consortia of labs, worth $30 million over the next five years, to roughly map the brains of 1200 people using diffusion MRI, functional connectivity MRI and other techniques. Some will also undergo genetic and psychological tests to measure working memory, arithmetic skills and other mental abilities.

Given the project's name and the amount of cash involved, it is tempting to see it as the successor, in scale and importance, to the human genome project. An NIH press release refers to it as "a grand and critical challenge: to map the wiring diagram of the entire, living human brain".

Some of the researchers involved are more realistic. "At the end of five years it won't be complete," says Behrens, a member of one of the consortia. "I think we will have the macrocircuits pretty good in 20 years."

Perhaps the most relevant lesson from the human genome project is how fast technology can advance. It took 10 years and $3 billion to complete the first draft of the human genome. Now there are firms claiming they will soon be able to read someone's genome in less than a day for $100.

Connectome researchers are convinced this field will generate as yet unimagined rewards. "You will see new hypotheses about how the nervous system works," says Kasthuri. "No one has ever seen data like this before."

Mind readers

Magnetic resonance imaging(MRI) Showing detailed anatomical images, it is like an X-ray for soft tissues

Functional MRI (fMRI) Displays changes in blood supply - assumed to correlate with local nerve activity - to different brain areas during mental tasks such as arithmetic or reading

Diffusion MRI (also called diffusion imaging, tractography) Reveals the brain's long-distance connections; works by tracking water molecules, which can diffuse along the length of axons more freely than escaping out through their fatty coating

Functional connectivity MRI (resting-state MRI) Also shedding light on long-distance connections, it measures spontaneous fluctuations in activity in different brain areas, which reveals the degree to which they communicate

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