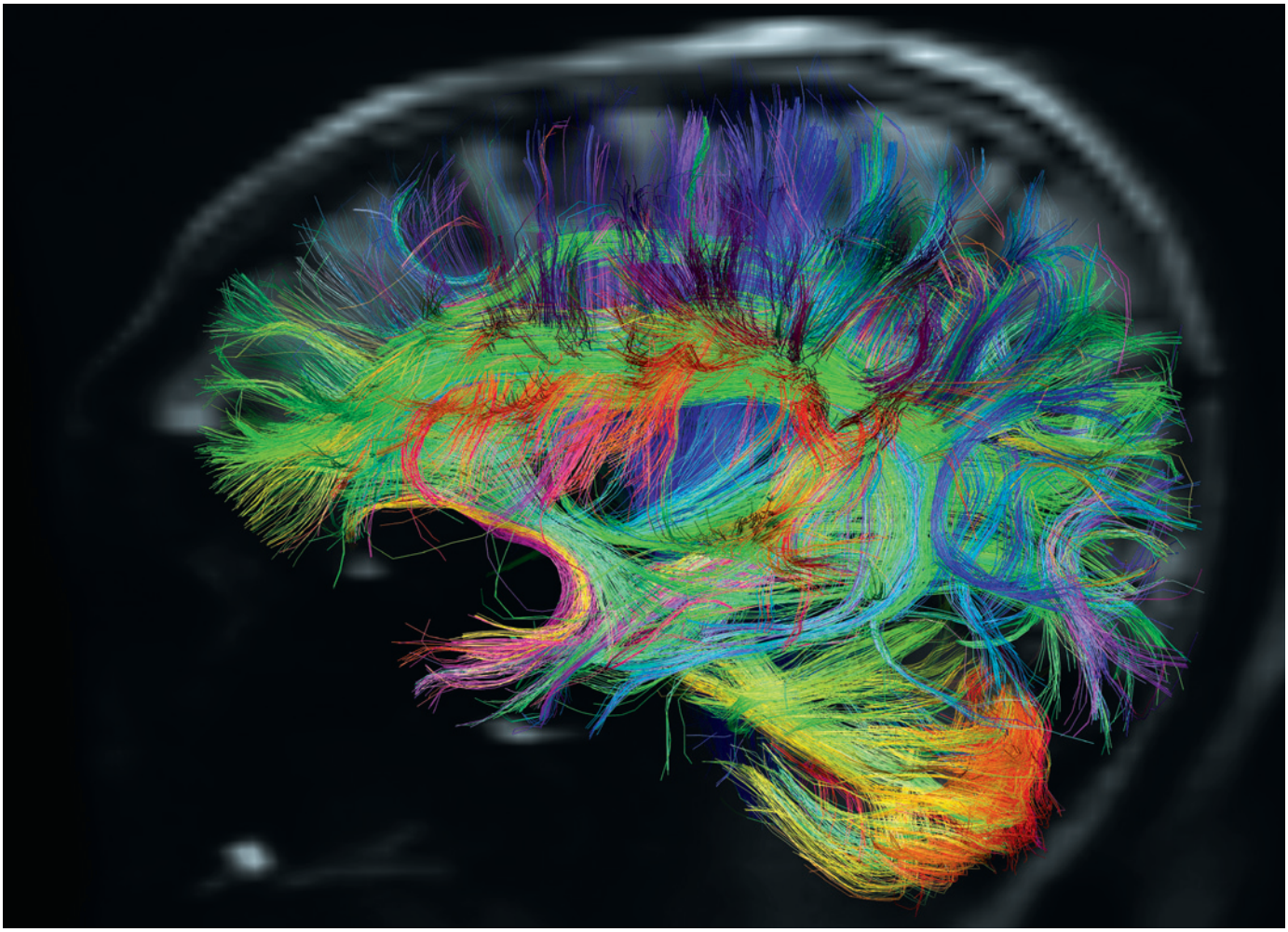


MGH HUMAN CONNECTOME PROJECT ACQUISITION TEAM

Making *connections*

Is a project to map the brain's full communications network worth the money?

BY JON BARDIN

A building that once housed a Second World War torpedo factory seems an unlikely location for a project aiming to map the human brain. But the Martinos Center for Biomedical Imaging — an outpost of the Massachusetts General Hospital in an industrialized stretch of Boston's riverfront — is home to an impressive collection of magnetic resonance imaging machines. In January, I slid into the newest of these, head first. The operator ran a few test sequences to see whether I experienced any side effects from the unusually rapid changes in this machine's magnetic field. And, when I didn't — no involuntary muscle twitches or illusory flashes of light in my peripheral vision — we began. The machine hummed, then started to vibrate. For 90 minutes, I held still as it scanned my brain.

That scan would be one of the first carried out by the Human Connectome Project (HCP), a five-year, US$40-million initiative funded by the National Institutes of Health (NIH) in Bethesda, Maryland, to map the brain's long-distance communications network. The network, dubbed the 'connectome', is a web of nerve-fibre bundles that criss-cross the brain in their thousands and form the bulk of the brain's white matter. It relays signals between specialized regions devoted to functions such as sight, hearing, motion and memory, and ties them together into a system that perceives, decides and acts as a unified whole.

The connectome is bewilderingly complex and poorly understood. The HCP proposes to resolve this by using new-generation magnetic resonance imaging (MRI) machines, like that used to scan my brain, to trace the connectomes of more than 1,000 individuals. The hope is that this survey will establish a baseline for what is normal, shed light on what the variations might mean for qualities such as intelligence or sociability, and possibly reveal what

The nerve fibres of the author's brain were traced by diffusion spectrum imaging, and coloured to represent their direction.

happens if the network goes awry. "We increasingly believe that brain disorders — from schizophrenia to depression to post-traumatic stress disorder — are disorders of connectivity," says Thomas Insel, director of the National Institute of Mental Health (NIMH) in Bethesda and a strong supporter of the HCP. "So it is of vital importance that we have ways of detecting and quantifying these connections."

Yet many wonder whether the NIH is making a mistake. Researchers have yet to prove that MRI techniques can produce a reliable picture of normal connectivity, never mind the types of abnormal connection likely to be found in brain disorders, and some researchers argue that the techniques have not been adequately validated. "I would do the basic neuroscience before I started running lots of people through MRI scanners," says David Kleinfeld, a physics and neurobiology researcher at the University of California, San Diego.

THE GRAND CHALLENGE

Proponents counter that the HCP is a calculated risk. "No one thinks this is going to produce a wiring diagram like you might have for the electricity in your house," says Insel. But so little is known about the connectome, he says, that even crude maps would represent a major scientific advance.

The decision to take that risk was made by the NIH's Blueprint for Neuroscience Research, set up in 2004 as a collaboration among the 15 NIH institutes, centres and offices with an interest in nervous-system research. In 2009, after five years of funding smaller projects, the group asked officials from across the NIH to submit ideas for 'grand challenges' in neuroscience: large-scale programmes that, Insel says, "would be both extremely high-impact, and virtually impossible with traditional grant mechanisms".

The Blueprint group received a dozen submissions, including one from Michael Huerta, then a programme officer at the NIMH and a member of a Blueprint subcommittee. Huerta, now at the NIH's National Library of Medicine, began his research career studying the organization of mammalian brains using old-school anatomical and neural-tracing techniques, which typically require the injection of a tracer compound that migrates along nerve fibres and reveals their routes. So he was all too familiar with the barriers to such studies in humans. For ethical reasons, tracers can only be used post-mortem — when they don't migrate far enough to trace a fibre's full length. "The studies just never panned out," says Huerta.

In 2007, Huerta became fascinated by two new non-invasive imaging methods that might finally allow researchers to study the finer details of connectivity in the brains of living humans. The first was diffusion-spectrum imaging (DSI), developed in 2005 by Van Wedeen, a radiologist at the Martinos Center, and his colleagues[1]. DSI is a refinement of the two-decades-old diffusion tensor imaging technique, which exploits MRI's ability to detect the direction in which water molecules are moving at each point in the brain. Because most of those molecules move along the lengths of nerve fibres, like water through a pipe, the data can be used to reconstruct each fibre's location and trajectory. What DSI adds is a more sophisticated form of signal analysis that allows researchers to continue tracing fibre bundles even when one seems to pass behind another, a situation that posed serious problems for the older technique.

> *"We increasingly believe that brain disorders are disorders of connectivity."*

The second method that caught Huerta's attention was resting-state functional MRI (rs-fMRI), in which people think about nothing in particular while their brain activity is measured. This is quite different from conventional functional-imaging studies, in which participants are asked to carry out a specific cognitive task and researchers look for the brain regions that are activated in the process. In rs-fMRI, there is no task, and researchers look for correlations among the activity levels in different areas. The presumption is that any two regions with a consistently high correlation are linked — perhaps by an actual bundle of nerve fibres, but certainly by working together in some way.

The application of both DSI and rs-fMRI had already led to a number of high-profile publications. But Huerta realized that few groups were applying both methods in the same subjects, and most studies used small samples, limiting their generalizability. So he proposed that the Blueprint group fund a Human Connectome Project that would apply both methods to hundreds of people. This would allow the first large-scale comparison to be made between structural connectivity, as determined by DSI, and functional connectivity, as determined by rs-fMRI. "No single neuroimaging approach would give you the type of gold-standard connectivity data you need," says Huerta, recalling his argument for the dual data sets.

The Blueprint group was intrigued, but was not blind to the problems inherent in these techniques. One obvious issue is DSI's spatial resolution: each fibre bundle in the image contains thousands of neurons, meaning that it would miss a great deal of structure on smaller scales.

Partha Mitra, a neuroscientist at Cold Spring Harbor Laboratory in New York, illustrated the problem to me by displaying a series of high-resolution digital pictures of mouse brain slices, each of which had some of its neurons coloured with a dark brown dye. On one such slice, he showed neurons that originated in the left cortex, then branched out and sent fibres to areas on both the left and the right side of the brain. "The brain is not made up of point-to-point connections," he said. "It's made up of trees."

This level of connectome structure is invisible to even the most advanced diffusion-imaging methods, says Mitra, who heads the Mouse Brain Architecture Project, a parallel version of the HCP, funded by the NIH and the W. M. Keck Foundation of Los Angeles, that seeks to generate a whole-brain wiring diagram for the mouse using staining techniques. And the problem is made even worse when the data are converted into a 'connectivity matrix', which seeks to quantify how much every point in the brain is connected to every other point — but can't tell the difference between, say, two separate fibres and one fibre with two branches.

The Blueprint group was also aware of concerns about resting-state scans. As with the more familiar form of fMRI, what is actually measured isn't neural activity itself, but blood flow. The general presumption is that the two quantities are closely related — that blood flow increases in a region of the brain whenever the neurons there are active and need to be supplied with more oxygen. But recently, Kleinfeld points out, several studies have called that assumption into question, showing that some increases in blood flow in the brain occur without an increase in neuronal activity[2]. "There is no simple one-to-one relationship," he says.

A REMAINING CONCERN

That makes rs-fMRI studies particularly hard to interpret, Kleinfeld adds, if only because the brain's resting-state activity may fluctuate on the same timescales that its blood vessels do. A recent review[3] of rs-fMRI admits that this vascular fluctuation "remains a concern". Other studies show that even something as simple as a subject's pattern of breathing[4] or slight movements of the head[5] can significantly confound rs-fMRI measurements.

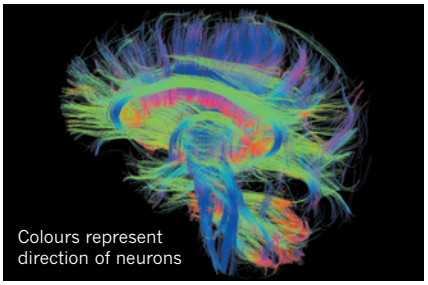
Even leaving the technical challenges aside, there was no assurance that collecting the connectomes of hundreds of individuals would lead to interesting generalizations. "You could certainly imagine situations in which everyone's wiring diagrams are quite different," says Gregory Farber, the programme officer at the NIMH who manages the connectome project. Nonetheless, the Blueprint group was swayed by the argument that imperfect data are better than no data. "The committee asked, 'Will we have better methods in five years?'," recalls Huerta. "I'm sure we would. But if we followed

SCANNING THE CONNECTOME

The Human Connectome Project aims to trace the brain's long-range communication network using two main techniques, both of which rely on magnetic resonance imaging (MRI) to obtain data from living people.

Mapping structure

Diffusion spectrum imaging detects the movement of water molecules that flow along nerve fibres in the brain. The result is a map of the brain's neuronal network.



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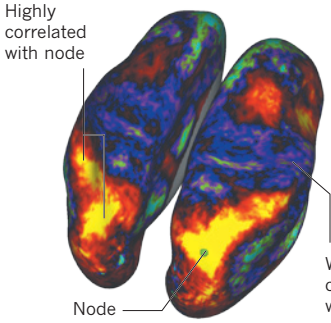
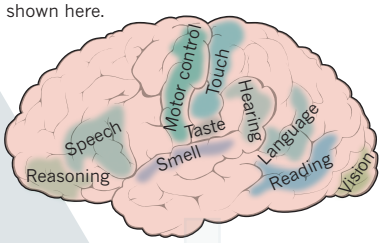
Mapping function

Resting-state functional MRI maps resting brain activity, then looks for correlations between one area and another. Highly correlated areas are thought to have some kind of functional link.

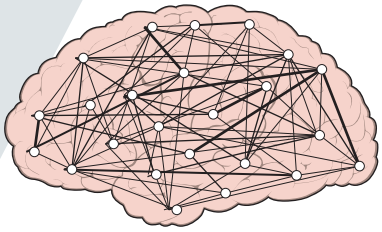


M.F. GLASSER & D.C. VAN ESSEN, THE HUMAN CONNECTOME PROJECT

The brain has many areas specialized for specific functions, some of which are shown here.



Data on structure and function can be combined and analysed using tools such as network theory.



The connectome ties these areas together, allowing the brain to function as a coherent whole. The project's goal is to understand how the connectome works.

that rule, no science would ever get done."

The group also liked the fact that the findings would be broadly applicable to clinical, as well as scientific, questions. "We thought we could do something like what we did with the Human Genome Project," Insel says, "because once you have that map of the brain you can compare it to similar maps across development, or to maps of subjects with different disorders of brain circuitry."

A BLUEPRINT FOR THE BRAIN

In July 2009, the Blueprint group announced its choice of the HCP as one of three grand challenges — the other two focused on pain and on drugs for nervous-system disorders — and simultaneously put out a request for proposals. On 15 September 2010, the NIH announced that it would be funding two HCP proposals.

The larger of the two is a 5-year, $30-million effort led by David Van Essen, a neurobiologist at Washington University in St Louis, Missouri, and Kamil Ugurbil, an fMRI pioneer at the University of Minnesota in Minneapolis. (Another collaborator is Olaf Sporns, a neuroscientist at Indiana University in Bloomington, a co-author on the 2005 review article that coined the term 'connectome'[6].) During phase one, now nearing completion in Minneapolis, this team has developed a scanner that will be able to double the resolution of standard MRI.

Once complete, that scanner will be moved to Washington University, where it will immediately begin high-throughput scanning. The plan is to use both DSI and rs-fMRI (see 'Scanning the connectome') to study 1,200 people: 300 identical twins, 300 non-identical twins and 600 non-twin siblings. This will allow researchers to explore how much of the brain's connectivity is mapped out by genes. Volunteers will also complete behavioural tests and other fMRI, magnetoencephalogram and electroencephalogram protocols, so that brain structure can be further correlated with function. All these data will be made public, allowing unaffiliated researchers to answer their own questions, and Van Essen's group plans to release a set of new data-analysis tools. Connectomics, Van Essen says, "has been a cottage industry. But we expect this project to allow for a much richer, more unified approach".

The smaller HCP project — a 3-year, $8.5-million effort led by Bruce Rosen, a radiologist at the Massachusetts General Hospital, and Arthur Toga, a neurologist at the University of California, Los Angeles — involved building a new fMRI scanner optimized for the collection of fibre-tracking data. The idea was to massively increase the gradient strength of the machine — a measure of how rapidly the MRI's magnetic field varies from point to point in the brain. A more intense gradient is like "a bigger mirror in a telescope", says Wedeen, who is director of connectomics at the Martinos Center. It simultaneously makes the instrument more sensitive to faint signals, and gives it a higher resolution. The machine has now been built — it is the one that collected images of my brain in January — but will require much more tweaking and testing before it is optimized for routine use. But the researchers have already achieved a tenfold increase in sensitivity to the water-diffusion signal, allowing their scanner to trace connections much more precisely than the best off-the-shelf machines.

In a press release announcing the launch of the HCP in July 2009, Insel said that the project would "map the wiring diagram of the entire, living human brain" and that this map could be linked to "the full spectrum of brain function in health and disease". Such lofty ambitions may or may not succeed in five years. But the project still has its place, says Sebastian Seung, a computational neuroscientist at the Massachusetts Institute of Technology in Cambridge, who studies brain connectivity at the cellular level. "I think it is a mistake to think we have to look at every cell in every region of the brain to make scientific progress," says Seung, who is not involved in the HCP.

But he also emphasizes that the HCP's connectivity map will be, at best, a beginning. "That is just going to tell us where to look," he says. "Then we need to study actual cells to learn more", to figure out how the brain's networks actually transmit information.

A week after my visit to the Martinos Center, I received my DSI data. Using free software from the centre, it is easy to explore the architecture of my brain. I can clearly see my hippocampus, and the vast array of fibres projecting from the midbrain sensory hubs up to my cerebral cortex. I am overwhelmed by the visible detail and obvious organization. At present, it is just a pretty picture — a novelty to show friends. But, I wonder: once scientists know what 'average' looks like, and once they understand the variations, what, if anything, will this rainbow-coloured highway map of my brain say about me? ■

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