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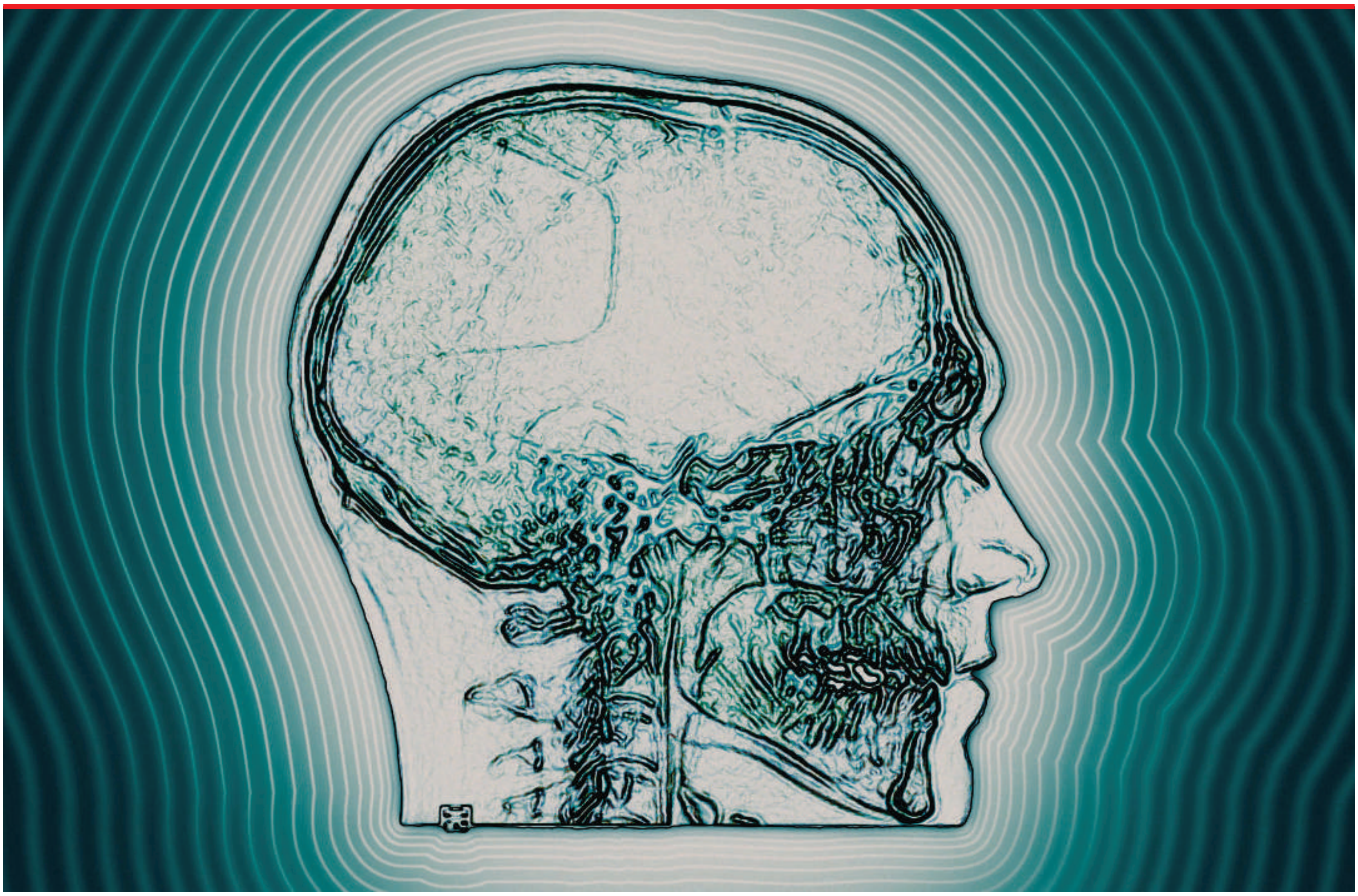


IMAGE SOURCE/CORBIS

BRAIN STORM

A bold scheme to map the entire human brain has become the mission of many scientists from a host of different fields. **Paul Smaglik** tracks the interdisciplinary career implications.

A major goal for neuroscientists is to build a complete wiring diagram of the human brain. Such a feat has already been achieved for the nematode worm *Caenorhabditis elegans*. But going from worm to human requires a serious leap: *C. elgans* has 302 neurons connected together through 7,000 synapses; the human brain has an estimated 10 billion neurons, each of which has an average of 10,000 synaptic connections.

Undaunted, many neuroscientists are pursuing at least part of the problem, and funding is following. But with no centralized programme for this effort, there are multiple approaches, ranging from the use of electrophysiology to tease out synaptic connections in specific locations, to building mathematical models of neural networks. As yet there is no consensus on which approach is best, but there is general agreement that building and using different technologies — from the single-cell focus of electrophysiology to the whole brain views captured by functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) — will bring a brain map closer to reality.

Today, neuroimaging and computational neuroscience are akin to genomics in the 1980s, with many groups working in their own niches. Physicists are building better imaging tools; computational experts and statisticians are pondering theoretical frameworks; and neuroscientists are trying new data-gathering methods. The sheer scope means opportunities for scientists from many disciplinary backgrounds. But there is also some professional risk: the field as a whole remains uncertain about whether any single imaging or computational approach can map the trillions of connections that make up the brain's neural network; and the people who build and use the technological tools involved may not be rewarded as directly as those who interpret the data.

Nikos Logothetis is planning data analysis using lots of mathematics.

Perhaps the biggest challenge will be combining myriad images from sources such as electron microscopy, PET and fMRI, says David Van Essen, president of the Society for Neuroscience. Van Essen organized a series of lectures at the society's meeting this week in San Diego to explore this issue and show some examples of how this is being done. He believes that reluctance to adopt an approach that combines multiple kinds of neural imaging with computational techniques goes beyond scientific reasons. "There are challenges to getting integrative and interdisciplinary projects like this funded in a very competitive environment," he says.

Large-scale, team-based approaches should help align images from different sources on top of each other — from single synapse to large-scale data using PET and fMRI. This should help elucidate how the behaviour of individual cells affects broader brain activity.

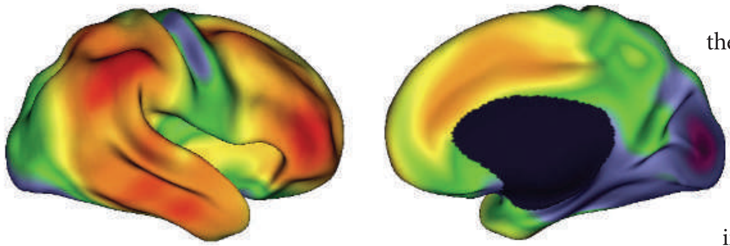
Scientists — from engineers who build better imaging machines to statisticians who will help make sense of the data — will be invaluable. But first, scientists need a better theoretical framework, says Lyle Graham, who leads a group in visual neurophysics and physiology, at France's basic-research agency, the CNRS, in Paris. Graham proposes combining multiple approaches, starting with electrophysiology and computational modelling. Physicists, mathematicians and engineers need to appreciate the nuts and bolts of theory-driven experiments, he notes, and biologists need to understand the role of the computational approach.

Graham says it is not easy recruiting the sort of good experimentalists who are essential for testing hypotheses of brain circuitry and function. "Molecular biology is much more attractive to people doing their PhDs or postdocs," he says. "In electrophysiology, you're not sure it's going to work. It's hard. You have to be a little obsessive." He recommends that people who are considering the field first ground themselves in both the biophysical bench approaches and the theoretical models of how the brain works, so that theory and experiment can inform each other.

All in the mind

Liam Paninski, a statistician at Columbia University in New York who works on neural codes, is one such person. As an undergraduate, he participated in single-synapse research, but soon discovered he needed a better grasp of statistics to model and validate the data. Although his PhD is in neuroscience, he emphasized statistical methodology as part of his training. That background is helping him make the leap from using electrodes — which provide high-resolution data, but are also highly invasive as they have to be inserted into the living brain — to calcium-sensitive dyes that show electrical activity in the synapses. He is using statistics to 'clean up' the calcium data and to extrapolate them to multiple cells. "You can dump calcium into the brain and look at a whole region," he says.

Paninski believes that multidisciplinary support for learning about the brain's connections is growing. The US National Institutes of Health and National Science Foundation sponsor a grant for collaborative research in computational neuroscience, to bring mathematicians, computational experts and physiologists together. "When I was starting out ten years ago I thought I had to run my own lab and collect my own data," he says. Now he works with a team of neuroscientists and physicists who help him collect the data that he then analyses statistically.



ADAPTED WITH PERMISSION FROM VAN ESSEN AND DIERKER (*NEURON* 2007)

Combined data have been used to create these two views of cortical expansion between monkey and humans. Red patches indicate regions that are likely to have expanded most rapidly in humans.

Winfried Denk of the Max Planck Institute for Medical Research in Heidelberg, Germany, says one approach to building a map is to start small, imaging all the neurons in a very limited section of brain tissue using electron microscopy. "We're trying to develop a method to basically reconstruct detailed circuit diagrams of neural tissues," Denk says. But he suggests that with existing approaches it would take "a billion people a year" to capture all of the synapses in the cortical column alone. "That's not quite practical," he says. Instead, Denk is working with Sebastian Seung's lab at the Massachusetts Institute of Technology in Cambridge. Seung is helping him to generate algorithms that show the result of many synaptic connections, rather than imaging every single one.

Sexy genes

Heidi Johansen-Berg is using diffusion fMRI at the John Radcliffe Hospital in Oxford, UK, to study anatomical connections in the brain. Although it supplies less detail than electron microscopy or electrophysiology, it can still help build a lower-resolution wiring diagram, she says. Such data can then be compared to the human genome and the Allen Brain Atlas, which has mapped out the expression patterns of more than 20,000 genes in the mouse brain.

She anticipates more convergences in imaging and data analysis to come. "It's a very exciting time to enter the field," Johansen-Berg says. "A challenge will be to see how taking a computational approach will help in identifying and describing disease state."

Interdisciplinary groups are trying to combine imaging approaches and analyse them with statistics, and computational and mathematical modelling. Nikos Logothetis, a professor in physiology and cognitive processes at the Max Planck Institute for Biological Cybernetics in Tübingen, Germany, has combined data from fMRI and electrophysiology and wants to do both approaches simultaneously, then use "lots and lots of mathematics" to build circuit diagrams.

Karel Svoboda, a group leader at the Howard Hughes Medical Institute's Janelia Farm campus, says that all 15 neuroscience groups there take a similar approach, but concentrate on specific regions of the cerebral cortex. Janelia plans to add 10–15 more leaders, says Svoboda: investigators examining neural circuits who use imaging tools; physicists, engineers and computational scientists who are building tools; and "eclectic others, who are smart and clever and fun to have around".

To "reverse engineer the brain", more institutes and universities will need to build small multidisciplinary teams like Janelia's, Svoboda says. "This field needs an influx of engineers and applied physicists," he says. Mapping brain structure and function is a broader, deeper problem than sequencing and analysing the genome, he says. For now, that goal will provide plenty of work for multidisciplinary-minded scientists — and could create even greater opportunities if and when the drive to draw up the wiring diagram of the human brain gets the kind of leadership and funding afforded to the Human Genome Project.

Paul Smaglik is a freelance writer based in Milwaukee, Wisconsin.

R. SUSSMAN

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Multitasking: (clockwise from top) Liam Paninski, David Van Essen and Lyle Graham.