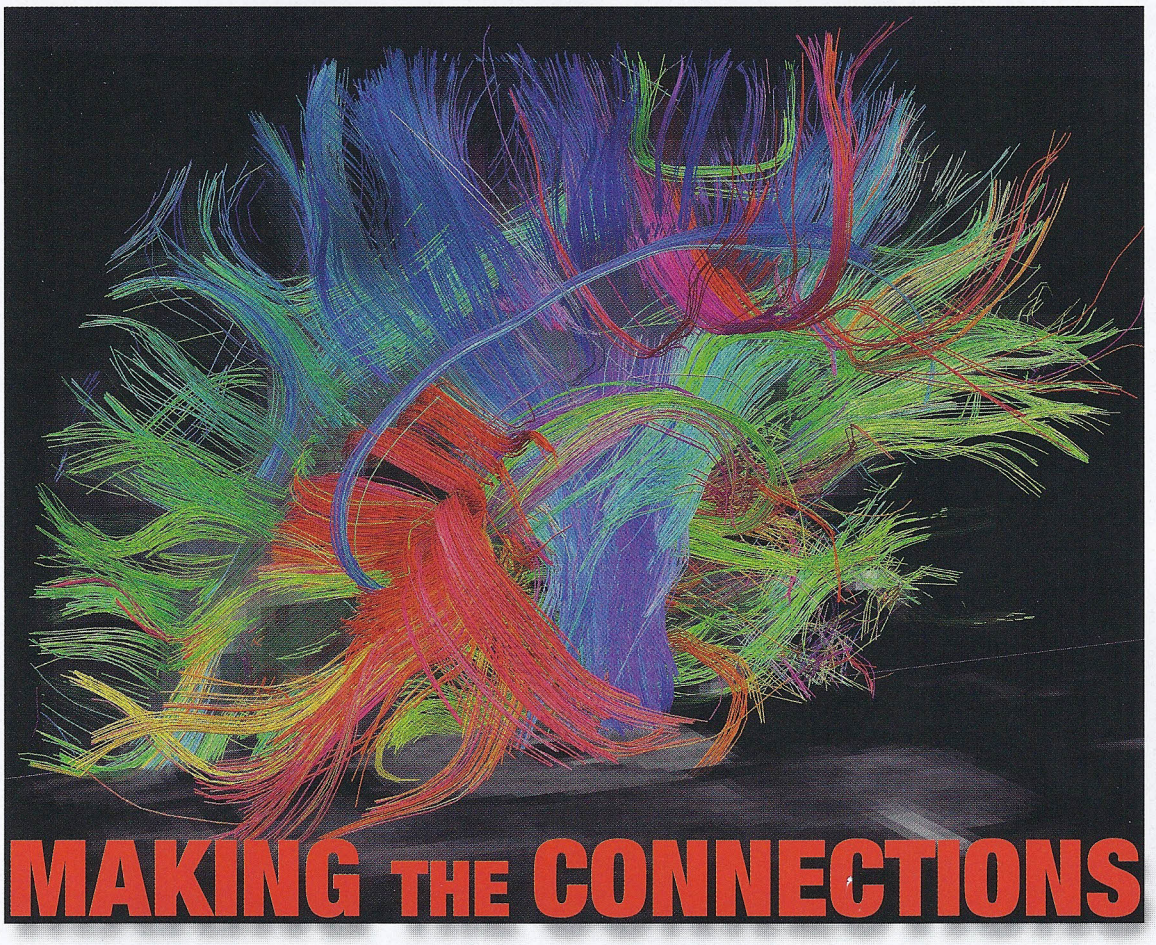
Advantage Business Media

www.BioscienceTechnology.com

October 2010

Bioscience TECHNOLOGY®

THE LIFE SCIENTIST'S SOURCE FOR PRODUCTS & TECHNIQUES



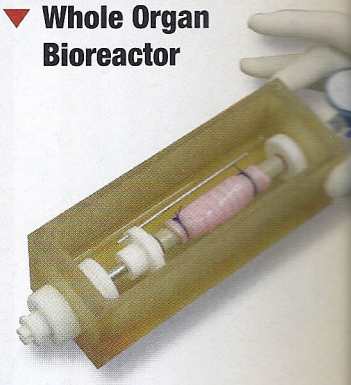
MAKING THE CONNECTIONS

To understand the brain, one must understand its wiring. Connectomics researchers study neural connectivity in order to facilitate this understanding.

Full story on page 10

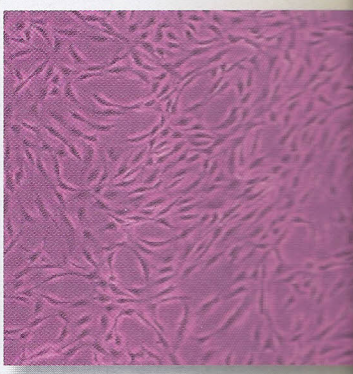
IN THIS ISSUE

▼ Whole Organ Bioreactor



▼ Personal Microarray System

▼ Stem Cell Growth Solutions



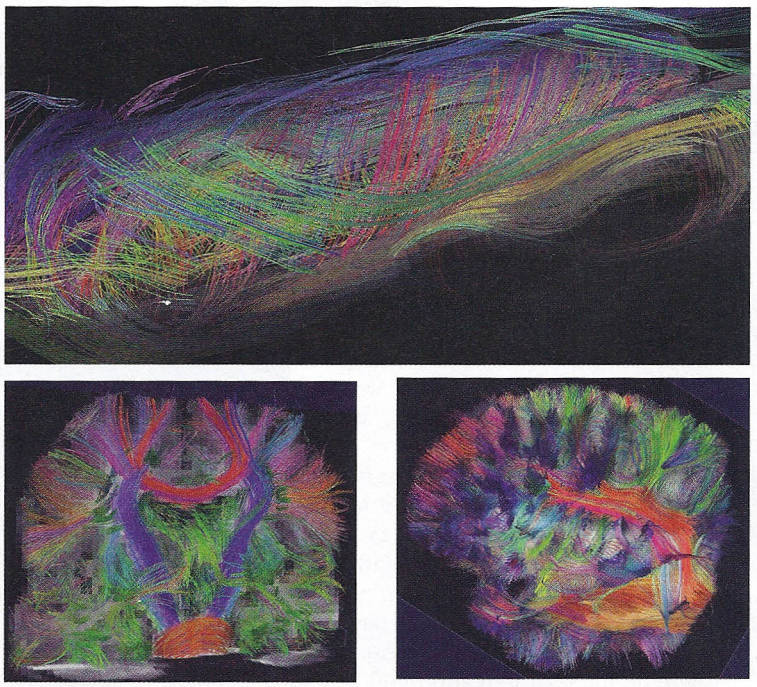
NEXT MONTH IN *BIOSCIENCE TECHNOLOGY*

- 2011 Buyer's Guide
- Cell Biology
- Focus on *in vivo* Imaging
- Focus on Pipettors

Continued from the cover

MAKING THE CONNECTIONS

To understand the brain, one must understand its wiring. Connectomics researchers study neural connectivity in order to facilitate this understanding.



Top: Diffusion spectrum MRI (DSI) tractography of the human hippocampus *ex vivo*. Developed by Van Wedeen, DSI will allow researchers to accurately measure connectivity in human brains for the first time. Bottom: DSI of a normal human brain *in vivo* (L) and *ex vivo* (R).

On the cover: A diffusion spectrum MRI scan of the brain of a normal human subject showing major fiber pathways that produce its large scale connectivity. This, together with functional MRI, is now allowing scientists to map the structural and functional connectivity of the human brain as part of the NIH sponsored Human Connectome Project. (All images courtesy: Van Wedeen, Martinos Center, Massachusetts General Hospital)

By Jeffrey M. Perkel

Imagine you could view your brain on a computer, rotate it with the mouse, and zoom in on some particular cortical fold. Clicking on a single neuron, you trace its path from synapse to synapse, wending your way through the brain like some neurological mashup of Google Earth meets *Fantastic Voyage*.

Sound impossible? For the moment, it is. But, buoyed by new technologies and an influx of cash, researchers in the burgeoning field of neural connectivity, or connectomics, are working to make that vision a reality.

The connectome, according to the 2005 paper that coined the term, is "a comprehensive structural description of the network of elements and connections forming the human brain."[1] The goal, says Olaf Sporns, **Indiana University** neuroscientist and lead author of that paper, is to lay "a theoretical foundation for neuroscience which is based in the idea of networks—anatomical networks of connections that are obviously crucial for shaping what the brain is actually doing."

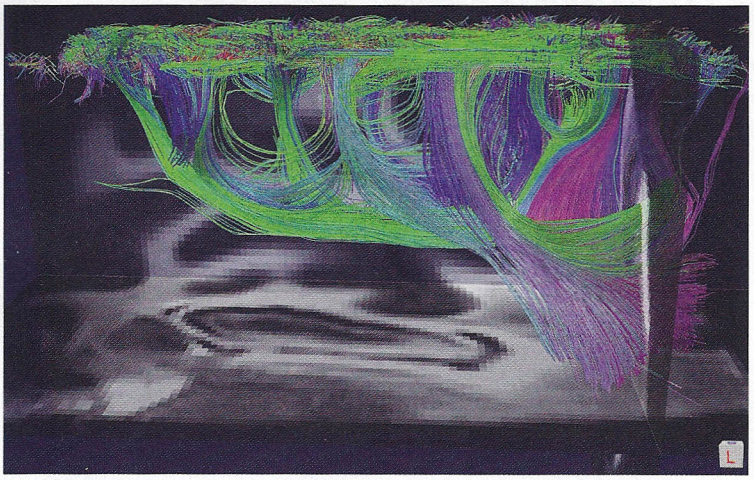
Simply put, to understand the brain, one must understand its wiring. Encoded within the neural connectivity matrix are the basic building blocks of what it means to be human. By plumbing these connections, researchers can begin to address such fundamental questions as the architecture and evolution of the brain and what makes an individual, individual. Learning, memory, and personality all may have a basis in structural connectivity, as do such neuropathologies as schizophrenia, autism, and bipolar disorder.

The shorthand, says **Massachusetts Institute of Technology** computational neuroscientist Sebastian Seung is, "I am my connectome." As Seung told the audience at the TEDGlobal 2010 conference this past July, each individual's connectome is unique, morphing in response to experiences and environment. "The connectome is where nature meets nurture," he said.

Neural circuits are wired with axonal fibers—long cellular processes bundled and tangled like spaghetti in the brain's white matter. Researchers have made progress untangling those circuits in animals, but the problem is daunting, and only the 300-neuron *Caenorhabditis elegans* has been decoded in its entirety. The human connectome is another matter; by one estimate, "each human brain contains an estimated 100 billion neurons connected through 100 thousand miles of axons and between a hundred trillion to one quadrillion synaptic connections."[2]

In a 1993 *Nature* editorial entitled the "Backwardness of Human Neuroanatomy," Francis Crick and Edward Jones decried the "shameful" and "intolerable" lack of even the most basic knowledge of human brain's wiring. "Without [such information]," they wrote, "there is little hope of understanding how our brains work except in the crudest way."[3] The tools of animal neurobiology—genetic manipulation, 3D electron microscopy, and injectable tracer dyes, for instance—are no help; they cannot be used in live humans. "People don't realize how limited our methods have been for finding out what's connected to what," says Seung, a fact that has "held up neuroscience for a century."

Today, though, connectome research is flourishing, at least on a more macroscopic scale. The U.S. **National Institutes of Health** in September awarded $40 million to two separate research teams, one centered at **Washington University in St. Louis** and the **University of Minnesota**, and the other at **Massachusetts General Hospital** (MGH) and the **University of California, Los Angeles**, under the Human Connectome Project (HCP), a five-year effort to noninvasively map structural and functional connections in the live human brain. Last year, the European Union launched the Consortium of Neuroimagers for the Noninvasive Exploration



DSI tractography of a normal human temporal lobe *ex vivo*. This image illustrates the kind of detailed cortical-to-cortical connectivity scientists hope will be obtained in living human subjects in the HCP.

of Brain Connectivity and Tractography with €2.4 million to an international team led by researchers at **Tel Aviv University**. Though they cannot detail specific neuron-to-neuron connections, these efforts can yield a 30,000-foot overview, akin to mapping the highways connecting major cities, says Sporns.

"We have a very deep knowledge about the chemistry of the brain [in general]," says Michael Huerta, Associate Director of the **National Institute of Mental Health** and lead scientific contact for the HCP. "But in terms of the [connectivity of the] human brain we have literally no data in any modern, comprehensive, or systematic sense. And this human connectome project is really going to kick that off in a big way."

HCP researchers will, for more than 1,200 individuals (300 sets of identical twins plus their non-identical siblings), collect genetic and behavioral data, neural activity, and a battery of magnetic resonance scans including resting-state functional magnetic resonance imaging (R-fMRI), task-oriented (T-) fMRI, and diffusion MRI. The result will be a composite dataset against which others may be measured—a comparator against which to identify regions associated with everything from schizophrenia to piano virtuosity.

R-fMRI and T-fMRI use the abundance of deoxygenated hemoglobin, either when the brain is at rest or performing some task, to reveal functional activity and connections—brain regions that act in concert, whether or not they are directly linked. Diffusion MRI uses the movement of water molecules in the brain to trace the physical connections themselves.

Like all magnetic resonance techniques, diffusion MRI lacks the resolution to view individual neurons. Instead, it resolves the brain into "voxels," or 3D pixels, each of which might represent hundreds of thousands of individual cells. But it can reveal the tracks of neural bundles, based on the fact that water molecules in the brain will preferentially travel along axonal fibers rather than perpendicular to them. It sees "a kind of mathematical shadow of the cells," explains MGH scientist and HCP co-PI Van Wedeen.

To collect these MR images, the Washington University/Minnesota team will scan its subjects with a 3-Tesla magnetic field strength clinical instrument "souped up" with the magnetic gradient coil (the device that actually controls the magnetic field pulses in an MR instrument) from a **Siemens** 7T instrument.

"We'll end up with an instrument which has higher performance than a clinical 3T instrument, but still has the routineness and the robustness of a clinical scanner in some ways," says Minnesota HCP co-PI Kamil Ugurbil. Higher field-strength magnets, Ugurbil explains, yield sharper resolution, stronger signals, and better signal-to-noise than their lower-field counterparts. Two hundred subjects will be scanned with a new 7T instrument at Minnesota, and possibly also with a 10.5T instrument, currently in development.

The Massachusetts General Hospital group is taking a slightly riskier approach. With Siemens, Wedeen's team is developing an entirely new gradient coil to install in MGH's 3T instrument. If it works, this "connectome scanner," as Wedeen calls it, "would have gradients five-times more powerful than any gradient that's being used in a human today."

The trick is to collate, integrate, store, and share these data in a way that makes sense and encourages exploration. But the only commonality for all these different datasets is the brain itself. "That's the grand challenge of it all," says Arthur Toga, HCP co-PI at UCLA's Laboratory of Neuro Imaging. It is, he says, "an informatics problem, a visualization problem, a statistical problem, a computational problem, and a biological problem."

For one thing, these datasets could be terabytes in size, raising storage, analysis, and data-transfer issues. Another concern is alignment; datasets must be fit to generic templates that define structural boundaries and facilitate dataset comparisons. But how does one integrate electrophysiology measurements with fiber tracings, or for that matter, with future data, such as gene expression?

"The answers will be complex in many ways, but if we do it right, we'll be letting the field explore a set of issues in ways that have the flavor of what bioinformatics tools allow for data mining the genomes," says Washington University HCP co-PI David Van Essen.

Recent research suggests the payoff could come quickly. In December 2009 Michael Milham, Associate Director of the Institute for Pediatric Neuroscience at the **New York University Medical Center**, and colleagues released 1,414 R-fMRI datasets from 35 institutions around the world as part of the "1000 Functional Connectomes" project. Unlike the HCP, these data were collected neither prospectively nor uniformly; most had already been published. Nevertheless, the data were surprisingly homogeneous across datasets and institutions, revealing previously unknown age- and gender-related differences.

Already, says Milham, thousands of researchers have downloaded the dataset, including NIH researcher Nora Volkow, who in May used the data to identify "functional connectivity hubs in the human brain."

"There are a lot of papers around the world in preparation or in press or in current analysis that are all building on this initial bolus of data," says Milham. It's not synaptic level connectivity, but for connectome researchers, it's a good start.

References

1. O. Sporns *et al.*, "The human connectome: A structural description of the human brain," *PloS Computat Biol*, 1[4]:e42.
2. N. Kasthuri and J.W. Lichtman, "Neurocartography," *Neuropsychopharmacology*, 35:342-3, 2010.
3. F. Crick, E. Jones, "Backwardness of human neuroanatomy," *Nature*, 361:109-10, 1993.