Mapping the Most Complex Structure in the Universe: Your Brain

Harvard scientists have embarked upon an ambitious program to create a circuit diagram of the human brain, with the help of new machines that automatically turn brain tissue into high-resolution neural maps.

By mapping every synapse in the brain, researchers hope to create a "connectome" -- a diagram that would elucidate the brain's activity at a level of detail far outstripping today's most advanced brain-monitoring tools like fMRI

"You're going to see things you didn't expect," said Jeff Lichtman, a Harvard professor of molecular and cellular biology. "It gives us an opportunity to witness this vast complicated universe that has been largely inaccessible until now."

The effort is part of a new field of scientific research called connectomics. The field is so new that the first course ever taught on it recently ended at MIT. It is to neuroscience what genomics is to genetics. Where genetics looks at individual genes or groups of genes, genomics looks at the entire genetic complement of an organism. Connectomics makes a similar jump in scale and ambition, from studying individual cells to studying swaths of the brain containing millions of cells. A full set of images of the human brain at synapse-level resolution would contain hundreds of petabytes of information, or about the total amount of storage in Google's data centers, Lichtman estimates

A map of the mind's circuitry would allow researchers to see the wiring problems that might underpin disorders like autism and schizophrenia.

"The 'wiring diagram' of the brain could help us understand how the brain computes, how it wires itself up during development and rewires itself in adulthood," said Sebastian Seung, a computational-neuroscience professor at MIT.

But with 100 billion neurons in the human brain, mapping them is an impossibly complex task for humans alone. An early "by hand" connectomics effort by Sydney Brenner of the Salk Institute studied the roundworm and its meager 300 nervous-system cells: It took a decade to complete.

Michael Huerta, associate director of the National Institute of Mental Health for scientific technology research, said that connectomics will fill a key gap in our understanding of the brain.

"You could conceivably know every chemical and every molecule of every cell in the brain, but unless you understand how those cells are connected to each other, you have no idea how information is being processed," Huerta said. "The connectome, in my opinion, is really what it's all about."

Lichtman's lab is creating what could be the equivalent of the genome sequencing machine, which dramatically sped up the race to map the human genome. It's an automated brain peeler and imager they call ATLUM (sidebar, left).

ATLUM uses a lathe and specialized knife to create long, thin strips of brain cells that can be imaged by an electron microscope. Software will eventually montage the images, creating an ultrahigh-resolution 3-D reconstruction of the mouse brain, allowing scientists to see features only 50 nanometers across.

"It works like an apple peeler," Lichtman said. "Our machine takes a brain, peels off a surface layer, and puts it all on tape. These technologies will allow us to get to the finest resolution, where every single synapse is accounted for."

Connectomics differs from other efforts to map the brain not just because of its methods, but also the type of information it seeks. While the Brain Atlas, funded by Paul Allen, maps the genes of a mouse brain, Lichtman's lab is gathering anatomical detail. He's looking at the physical features of cells, like the size of their synaptic vesicles, which store neurotransmitters essential for cell communication.

"My background is in neuroanatomy, and to see (connectomics) data is stunning," Huerta said. "Like the Human Genome Project, this work is giving us a whole new level of information. The neuroscience community in general is very excited about it."

Though he's working on a massive scale, Lichtman's inspiration comes from the desire to understand individual neurons. Specifically, he wants to understand how neurons go from having dozens of connections at birth to having just a few. Each cell pares down many weak connections, keeping just a few strong ones.

"Each baby nerve cell connects to 20 times the amount of nerve cells that it will have as an adult," said Lichtman. "We try to understand what the rules of pruning are. If a nerve cell has 100 connections and needs to prune that down to five, the question is, which five?"

The neurons fight to stay connected, and each competition affects the outcome for the rest of the cells, Lichtman said.

"So to understand the competition's impact on one cell, you have to understand all of the competitions," he said.

The net effect of all that neural "hand-to-hand combat" is what we call brain development, and it's what transforms a baby who can't walk, talk or operate a Blackberry into a modern, adult human being.

While connectomics researchers are very excited, they're still just getting a handle on mouse-sized brains. It could be a decade before data-crunching technology will be available to map the complexity of the human brain.

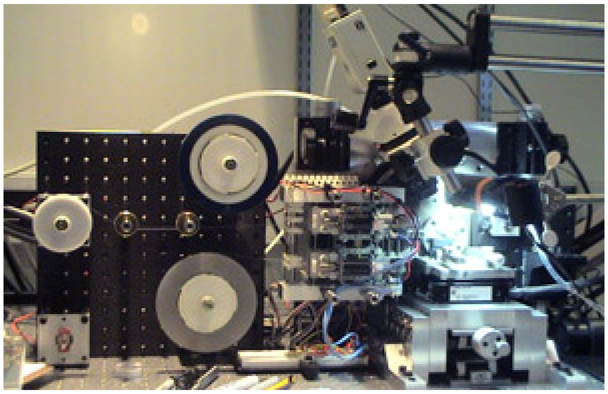
"Some say that the brain is the most complex structure in the universe," said Seung. "Right now it would be an incredible achievement just to find the connectome for a tiny animal like a fly."

But the ATLUM could turn out to be as useful for connectomics researchers as technologies like sequencers turned out to be for genomics researchers. Then

Lichtman and his colleagues would be able to answer some of the most fundamental questions about what happens when you take unprogrammed human beings and release them into the world.

It's the wiring, after all, that provides us with the flexibility that Lichtman calls "the magic of being human."

"When a dragonfly is born, it has to know how to catch a mosquito," Lichtman said. "But for us, none of this is built in. Our brains have to go through this profound education period that lasts until our second decade. What is changing in our brains?"



The ATLUM machine cuts ultrathin slices of mouse brain to prepare them for mapping the connections that link millions of neurons. *Photo credit: Lichtman Lab.*

This article has been written by Alexis Madrigan from www.wired.com.