NEUROSCIENCE

Scrap of brain seen in full detail

Mouse map is step towards reconstructing human brain.

BY ALISON ABBOTT

Six years might seem like a long time to spend piecing together the structure of a speck of tissue vastly smaller than a bead of sweat. But that is how long it took a team led by cell biologist Jeff Lichtman at Harvard University in Cambridge, Massachusetts, to create the first complete reconstruction of a piece of tissue in the mammalian neocortex.

The reconstruction (N. Kasthuri *et al. Cell* **162,** 648–661; 2015) is essentially a 3D digital map that allows biologists to see the detail and relative positions of every individual cell part in a piece of tissue measuring 1,500 cubic micrometres, helping to reveal how the brain works.

It is a far cry from reconstructing all of the 100 billion or so cells that make up the entire human brain, which is one of neuroscientists' ultimate goals. But Christof Koch, president of the Allen Institute for Brain Science in Seattle, Washington, notes that the various technologies involved will speed up "tremendously" over the next decade: "I would call this a very exciting promissory note."

Lichtman's team has its sights set on a further challenge: reconstructing a cubic millimetre of rodent neocortex — a piece of tissue more than 600,000 times larger than the present achievement. The researchers will do that work as part of a consortium that in July received preliminary approval for funding by the US government agency IARPA (Intelligence Advanced Research Projects Activity), which promotes high-risk, high-pay-off research.

The neocortex is the most recently evolved brain region, and is of particular interest to neuroscientists. As with other brain areas, its function is determined by how individual neurons are connected to each other through structures called synapses. These structures, which can be seen only with an electron microscope, allow chemical or electrical signals to pass between cells and can be pruned or created anew as an animal attunes itself to its environment.

N. KASTHURI *ET AL./CELL* (2015)

Individual cell parts are visible in this 3D map of a tiny piece of mouse brain.

Reconstructing this level of detail required a multistep procedure. A diamond blade shaved a region of mouse neocortex called the somatosensory cortex into several thousand slices, which were continuously rolled onto a single long strip of special plastic tape at a rate of 1,000 sections every 24 hours. The sections were then imaged with a scanning electron microscope powerful enough to capture even the tiny vesicles that contain the chemical signalling molecules in synapses, known as neurotransmitters.

To reconstruct the scrap of tissue, the team homed in at the highest resolution around the finger-like dendrites of two neighbouring neurons. The researchers aligned the relevant digital images so that the parts of each cell in each slice coincided with their positions on adjacent slices. To follow the individual cells through the different slices, they developed computer programs to assign a particular colour to every cell and to trace each one, either automatically or with input from researchers.

The volume of tissue used was too small to contain an entire cell, but large enough to contain fragments of more than 1,600 neurons and of other brain cells of at least six different types, as well as around 1,700 synapses.

One feature revealed by this reconstruction, which is now freely available to the scientific community, was that one neuron does not form synapses with another neuron just because the two happen to be physically close to each other, as some neuroscientists had assumed. Instead, the cells have clear preferences for particular neighbours. This had already been observed in the retina and in the hippocampus, both of which are evolutionarily older than the neocortex. The answer to what confers these preferences may be found in ongoing studies to identify the molecular components of each synapse, says neuroscientist Seth Grant at the University of Edinburgh, UK.

The Lichtman team is now working on similarly sized reconstructions of the cortical tissue from six-day-old mice, to see whether synapses behave the same way in an earlier stage of development, and on reconstructing a piece of human brain acquired during surgery.

As well as improving our understanding of the brain, such reconstructions could inspire new methods of computing. The consortium that is currently negotiating with IARPA is based at Harvard and at the Massachusetts Institute of Technology (MIT) in Cambridge and consists of 13 labs. Under the preliminary contract, the consortium would be part of IARPA's Machine Intelligence from Cortical Networks (MICrONS) programme and would receive tens of millions of dollars over five years, says MICrONS head Jacob Vogelstein. The general goal of the programme, he says, "is to revolutionize machine learning by reverse-engineering from codes discovered in the brain". He adds: "IARPA also invests in neuroscience because we are interested as well in understanding cognition — how people behave and make decisions."■

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