News & views

Neuroscience

A vast brain map links neural activity and wiring

Mariela D. Petkova & Gregor F. P. Schuhknecht

A large consortium of scientists adds functional data to neuronal wiring maps, seeking to crack the computational circuitry of the mouse brain. See pp.435–505

Millions of years of evolution have endowed animals with cognitive abilities that can surpass modern artificial intelligence. Machine learning requires extensive data sets for training, whereas a mouse that explores an unfamiliar maze and randomly stumbles upon a reward can remember the location of the prize after a handful of successful journeys[1]. To shine a light on the computational circuitry of the mouse brain, researchers from institutes across the United States have led the collaborative MICrONS (Machine Intelligence from Cortical Networks) project and created the most comprehensive data set ever assembled that links mammalian brain structure to neuronal function in an active animal[2].

What distinguishes the mammalian brain from that of other vertebrates is a region called the neocortex, which is the largest and evolutionarily newest part of the human brain. The researchers focused on this region because it is generally considered to be the seat of higher cognition and plays a key part in sensory perception, language processing, planning and decision-making. Remarkably, these seemingly different functions are made possible by a blueprint[3] that can be found, with some modifications, in all cortical areas and in all mammals. This makes studying the cortex in some ways similar to working out the principles of a combustion engine by looking at many cars – there are different engine models, but the same fundamental mechanics apply. To understand the engine, it is useful not only to have a description of all its parts, but also to understand how the parts work together. The MICrONS team applied this idea to the brain.

Just as an engine is composed of pistons, cylinders and a fuel system, the brain consists of neurons and synapses – the tiny, specialized connections at which neurons communicate. To reveal these intricate structures, the MICrONS team used a technique called volume electron microscopy, the gold standard for imaging at a nanometre-scale resolution. It captures exceptionally detailed images of synapses and the neurons they belong to, and enables the exact reconstruction of neural circuits. The process involved slicing a portion of the cortex responsible for visual processing into 28,000 extraordinarily thin sections, each only a few tens of nanometres thick – more than one thousand times thinner than a human hair. The sections were then imaged with an electron beam and digitally reassembled into a 3D reconstruction of the brain volume. Machine-learning algorithms subsequently treated this volume like a 3D colouring book, automatically filling in the shapes of neurons and systematically labelling vast numbers of synapses.

This anatomical data set spans a cubic millimetre of mouse cortex, about the size of a small poppy seed. Yet it contains an astonishing 84,000 neurons, half a billion synapses and 5.4 kilometres of neuronal wiring – nearly one and a half times the length of New York City's Central Park (estimated from ref. 4). Although this volume represents a tiny fraction of the mouse brain (and an even tinier fraction of the human brain), it pushes the technological limits of the field of connectomics, which is dedicated to mapping the brain into comprehensive wiring diagrams known

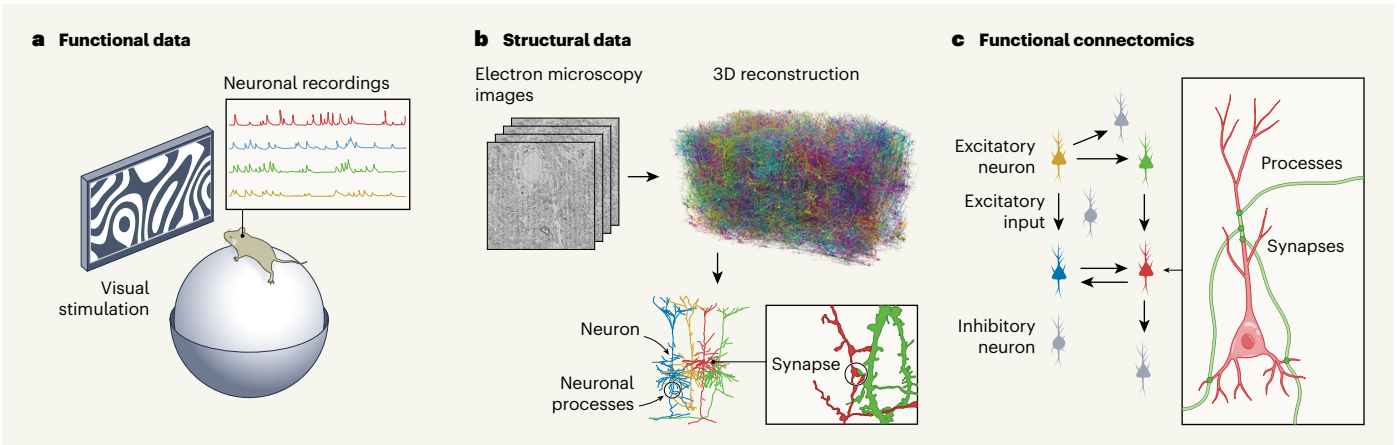


Figure 1 | Large-scale functional connectomics. **a**, The MICrONS Consortium[2,11,13–17] recorded neuronal activity from the brain of an awake and active mouse as it was shown videos to stimulate a brain region called the visual cortex. **b**, Researchers then sliced the same visual cortex tissue into thin sections and imaged them using an electron microscope. Using machine-learning tools, they created a high-resolution 3D map of a cubic millimetre of brain tissue comprising 84,000 neurons and their processes (axons and dendrites), and half a billion neuronal connections (synapses). (Adapted from Fig. 4 of ref. 2 and Fig. 1 of ref. 15.) **c**, By integrating the 3D reconstructions with the neuronal recordings, the authors could trace the connectivity of excitatory and inhibitory neurons, map the positions of individual synapses on neurons and begin to unpick the computational processes that underlie cortical function.

From the archive

Cannabis studies inform fundamental neuroscience, and accessible lectures from Nobel laureate Sir William Bragg.

50 years ago

Marijuana: Effects on Human Behaviour. Edited by Loren L. Miller — In several different scientific areas cannabis research is beginning to have about it a ... feeling of excitement. The range of this research ... is well conveyed in the volume on cannabis which is edited by Dr Loren Miller ... The 14 chapters each either report the contributor's original research with adequate delineation of context, or review a particular sector. The laboratory dissection of the psychological aspects of cannabis is the theme of several different chapters, and one feature of recent work is that experiment on the drug's interference with complex mental functions is providing a useful tool for basic study of those types of function. Chapters on the influence of cannabis on memory and on attention, nicely illustrate this development. Other contributions ... deal with neurophysiological research and possible interference with neurotransmitter mechanisms; again these are not just 'drug studies' but use of a particular substance as an investigating tool.

From *Nature* 10 April 1975

100 years ago

Concerning the Nature of Things: Six Lectures delivered at the Royal Institution. By Sir William Bragg — To deal with the "nature of things" as seen by modern physics in a course of six lectures to a juvenile audience is indeed a formidable task ... It is not so very long since we still regarded the atom and the molecule as more or less theoretical conceptions the real size and weight of which could only be guessed at roughly. Here we see not only the dimensions and weights of the atoms accurately known, but also their exact arrangement in well-defined crystals. [T]he reader — whether juvenile or not ... will share with the scientific world generally a sense of gratitude to Sir William Bragg for having ... done good service in helping to spread the light on "things in general" as physical science now sees them.

From *Nature* 11 April 1925



as connectomes.

By comparison, landmark connectomes such as those of the roundworm *Caenorhabditis elegans* (302 neurons, 5,000 synapses)[5], fruit fly larva (*Drosophila melanogaster*; 3,016 neurons, 548,000 synapses)[6], and the adult fruit fly central brain (25,000 neurons, 20 million synapses)[7] and whole brain (almost 140,000 neurons, 50 million synapses)[8] are a fraction of this volume. An important connectomics study that compared mouse, rhesus macaque (*Macaca mulatta*) and human cortical architecture analysed about 1.6 million synapses across the data sets[9], but the only volume of comparable scale to MICrONS is the one cubic millimetre of human cortex (16,000 neurons, 150 million synapses) that was mapped last year[10]. Together, these two projects define the current technological frontier of large-scale mammalian connectomics.

By itself, a blueprint might be insufficient for understanding how an engine works. Before the group generated their nanometre-scale parts list, they had already observed the components in action. This is where the study truly breaks new ground and transforms structural connectomics, which maps anatomy, into functional connectomics, linking that wiring with neuronal activity, on a large scale (Fig. 1).

The researchers recorded activity in the cortex from many neurons in parallel, using a genetically modified mouse — the neurons of which produced a fluorescent protein that emitted light when the cells fired. During many sessions over the course of a few days, the mouse viewed an extensive collection of video clips to activate its visual cortex while its head was stabilized under the microscope, but it could still walk on a treadmill. The activity of 76,000 neurons was recorded simultaneously while tracking the mouse's running speed, eye movements and other facial features. This neuronal activity data was then precisely aligned with the electron microscopy volume by matching individual neurons across the functional and electron-microscopy data sets.

In their flagship paper (page 435), the MICrONS Consortium *et al.*[2] introduce this functional connectomics data set to the neuroscience community as an open-access resource. Celii *et al.*[11], in an accompanying methodological paper (page 487), offer tools[12] for browsing, editing, annotation and analysis. In five companion papers, the researchers present scientific use cases. On pages 448 and 478, respectively, Schneider-Mizell *et al.*[13] and Elabbady *et al.*[14] show how different neuron types can be identified, and on page 497 Gamlin *et al.*[15] demonstrate how neuron types can be linked to gene-expression data. Schneider-Mizell *et al.* also show how the data set can be used to generate wiring diagrams. Ding *et al.*[16] (page 459) and Wang *et al.*[17] (page 470) link wiring diagrams to neuronal activity, revealing general circuit motifs (recurring patterns of connectivity between specific neuronal types) in the cortical architecture.

Of course, the work shares some of the common limitations of connectomics. Because connectomic wiring diagrams are inherently incomplete, owing to errors in machine-learning-based neuron reconstructions, they require extensive human editing, which is a formidable challenge at this scale. Alleviating the human editing task with next-generation machine-learning models that are tailored to recognize complete neuron shapes is fertile ground for technological development, and first attempts at this have already aided the fast mapping of network motifs in the cortex[18].

At the same time, studying the cortex poses its own challenges. Before starting to explain an engine, it helps to understand clearly what purpose it fulfils in a vehicle. Even though scientists know a lot about how visual features are represented in the cortex, it is much harder to grasp the nature of the 'higher' computations that underlie cortical function. The visual cortex, for example, processes more than just visual signals, and this might explain some of the neuronal activity that was unrelated to the movies presented to the mouse. Finally, cortical circuits are vast and extend beyond the cubic millimetre imaged here, which means no circuit in the data set is truly complete. Despite these limitations, this work marks a major leap forwards and offers an invaluable community resource for future discoveries in neuroscience.

In a broader context, connectomics is propelling neuroscience into the era of large-scale team science at the intersection of academia and industry, much like the collaborative efforts behind the Large Hadron Collider at CERN, Europe's particle-physics laboratory near Geneva, Switzerland, for particle physics or the Sloan Digital Sky Survey (SDSS) in New Mexico, for astrophysics. These projects demonstrate the power of interdisciplinary, multi-institutional collaborations fuelled by massive data sets. Just as CERN's investigations into fundamental particles and SDSS's cosmic mapping have transformed our understanding of matter and the universe, the investment in MICrONS will help to unravel the complex neural networks underlying cognition and behaviour.

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The authors declare no competing interests.

Medical technology

Wound healing measured by molecular flux

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A non-contact wearable device measures the skin's 'microclimate' for continuous, real-time monitoring of wounds and wound healing. **See p.375**

The skin is the largest organ of the human body, maintaining internal homeostasis – for example by releasing heat through sweating on a hot day – and providing a barrier that protects the body from external threats such as bacteria and other microorganisms. But skin is also highly vulnerable to injury. Chronic, non-healing wounds can increase the susceptibility of the body to infection, increase the complications of elective surgical procedures and greatly add to health-care costs[1]. On page 375, Shin *et al*.[2] present details of a non-contact wearable device that can continuously monitor wounds and wound healing by measuring the flux of molecules into and out of the skin, potentially decreasing treatment costs and improving patient outcomes.

Wearable technologies are seen as having great potential to fill gaps in an often fragmented and disjointed health-care systems. In most modern systems, if a person is ill enough, they will be admitted to a hospital to enable their condition to be monitored continuously, with complex technologies used to diagnose and treat them. But because this is expensive and resource-intensive, there is a great incentive for people to be discharged quickly to reduce the immediate costs of care. Often, this actually increases costs overall: with less frequent monitoring, perhaps weekly or monthly, in a doctor's office or clinic, patients' health can deteriorate, leading to complications and sometimes even re-admission to hospital[3].

Wearables – complemented and powered by advances in sensors, robotics and computer vision – are beginning to make possible an alternative approach, in which people with long-term, complex conditions are monitored by technology and autonomously treated without direct involvement of a physician. The skin is an attractive test bed for this approach. Chronic, non-healing wounds – including diabetic foot ulcers, venous leg ulcers and pressure sores – prevent the skin from functioning normally and often lead to disability[4]. These affect more than eight million individuals in the United States alone each year[5,6], costing Medicare, the government insurance scheme for older people and those with disabilities, something between US$28 billion and $97 billion annually[6]. Currently, trained professionals diagnose wound infection in the clinic on the basis of cardinal symptoms of increased pain, redness, swelling and warmth.

Shin *et al*.[2] present a wearable device that creates an enclosed chamber over an area of skin and uses integrated wireless sensors to measure the skin's 'microclimate'. It can robustly detect streams of vaporized molecular substances, including water vapour, carbon dioxide and volatile organic compounds passing into or out of the skin's surface (Fig. 1). This skin flux has long been known to occur, but has proved difficult to measure in a rigorous, controlled and continuous way.

The authors show in studies on human volunteers that their device can detect increased water flux during perspiration. It can also sense increased organic-compound flux when an individual has a build-up of bacteria on their skin, for example when they have not showered or otherwise cleaned themselves. In preclinical animal models, the authors observed a strong correlation between the presence of open wounds and an increased flux of water vapour. They also found that the presence of diabetes, a known risk factor for impaired wound healing, dramatically increased the time needed to re-establish wound-barrier function, as measured by water flux. These findings correlate well with ongoing work measuring water flux in humans with bulky, handheld trans-epidermal water-loss devices[7]. Infected wounds could also be detected through increased organic-compound flux using Shin and co-workers' device.

Such a device could enable remote and continuous wound monitoring when patients are at home, in contrast to conventional methods to monitor skin wounds that require a trained professional to make a reading using

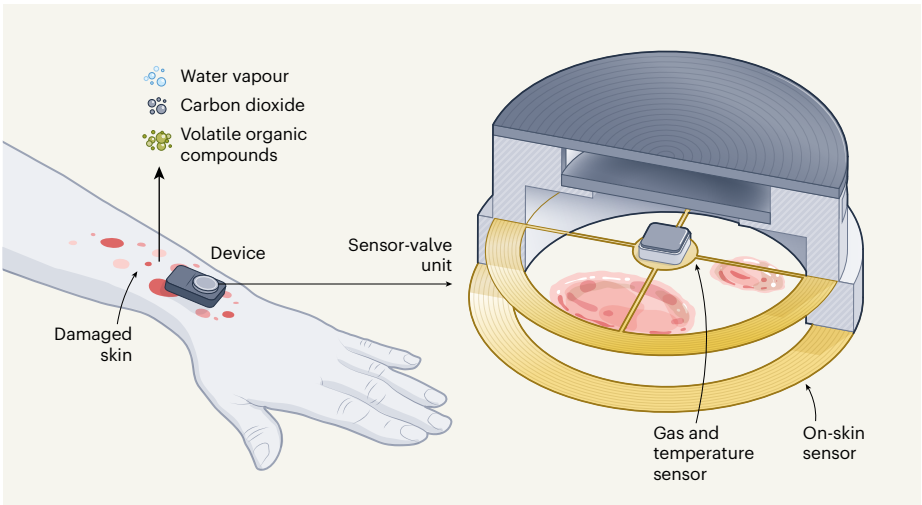


Figure 1 | A non-contact device for real-time monitoring of skin wounds. Skin wounds and unclean skin can produce an elevated flux of water vapour, carbon dioxide and volatile organic compounds (VOCs) in the immediate vicinity of the skin. A wearable device[2] uses wireless gas and temperature sensors, as well as on-skin sensors for temperature, impedance (a measure similar to electrical resistance) and thermal conductivity, to enable remote monitoring of skin health in people with long-term conditions.