Feature

Small brain, big science

Thanks to the unrivalled arsenal of genetic tools available for mouse studies, the rodent brain is fast becoming a key model system for neuroscience, even in unlikely fields such as vision research. **Michael Gross** reports.

The mouse is a surprising model system to study vision in. It mainly navigates by smell and touch, and doesn't actually see all that well. It doesn't have a fovea — the high performance central area of our visual field that we tend to point in the direction of the things that we are consciously looking at — and the resolution of its retinal image across the visual field resembles our peripheral vision. So a mouse sees the world with as little detail as we see things 'in the corner of our eyes', a type of vision which may occasionally save us from being run over by a bus, but which wouldn't be much use for reading or decoding facial expressions.

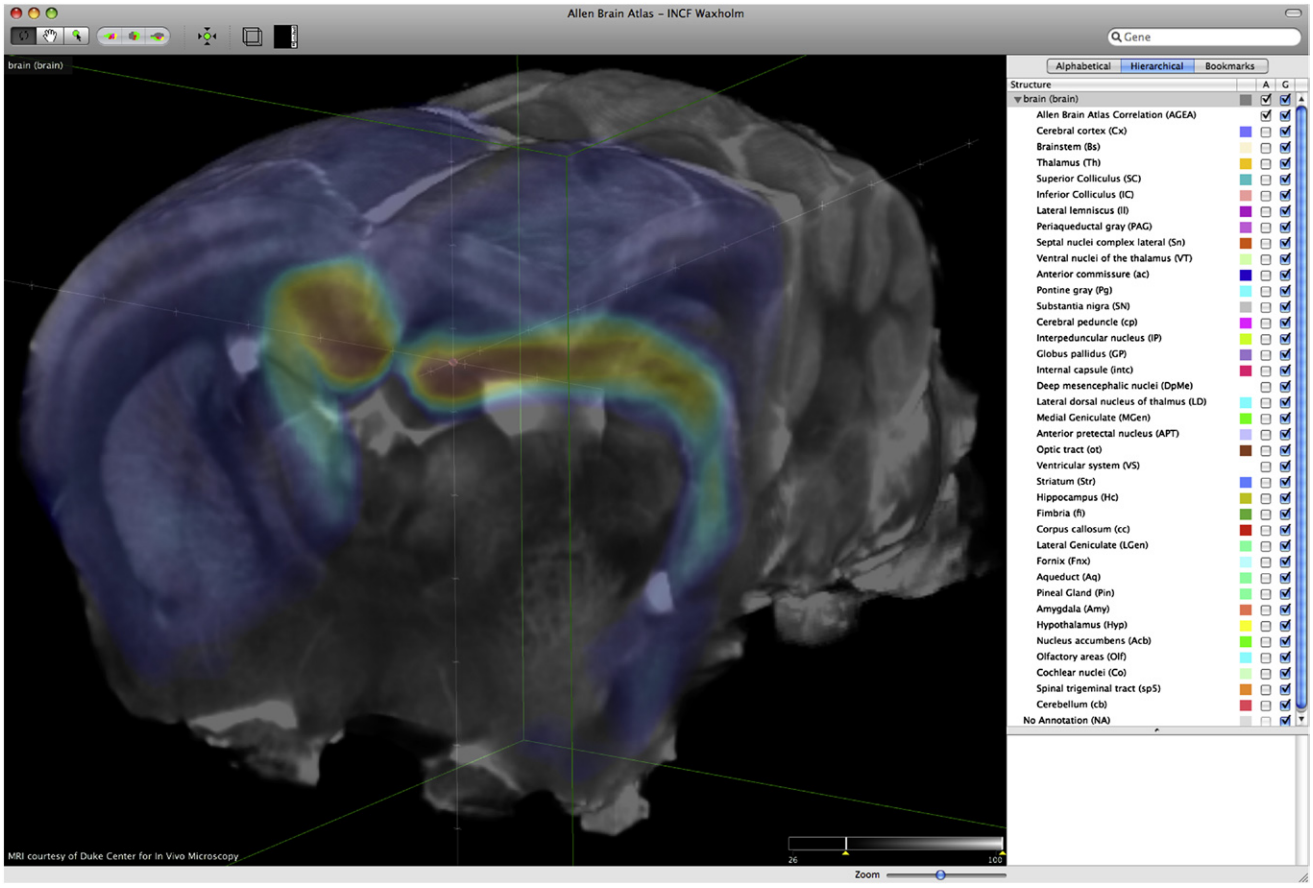
Moreover, mice cones have only two colour pigments, one in the ultraviolet range and one for green light. They are lacking a specific pigment for longer wavelengths (red), so mice wouldn't be able to tell red from green.

Mouse models

Given the biological background, it is perfectly understandable that a lot of the work on odour perception is conducted on mice, but why would neuroscientists use a 'partially sighted' animal species for vision research? Andrew Huberman from the University of California San Diego and Cristopher Niell from the University of Oregon at Eugene have observed that "a growing number of researchers have begun using mice to parse the mechanisms underlying visual processing." In a recent review of this field, Huberman and Niell list a range of reasons for vision researchers to prefer the little rodents to more conventional models, including humans, macaques, and cats (Trends Neurosci. (2011), *34*, 464–473).

There is the trivial reason that it is a lot easier and cheaper to breed mice in quantity and in diversity than primates. Then, having a small brain is an advantage inasmuch as it gives researchers a better chance to completely survey a given functional area.

However, the key reason is the huge repertoire of genetic variants and tools that already exists in mice and that can be readily expanded and adapted to specific questions. As Huberman and



Mouse clicks: The INCF Digital Atlasing Project aims to establish a framework allowing researchers to share data from a wide range of experimental methods and reference them to a standardised coordinates system, the Waxholm Space (WHS). (Image courtesy of PLoS Comput. Biol.)

Say cheese: Thanks to the unrivalled genetic toolkit and knowledge available for the mouse, it has become a standard model in neurosciences, even in unlikely fields such as vision research.

Niell explain, "modern genetic tools provide the opportunity to see the structure of a defined visual cell type, map its connections, record its activity in response to visual stimulation, and then selectively silence or activate that cell type in a reversible manner." The silencing and activation can, for instance, be achieved with the optogenetic approach, which has found widespread application since the introduction of the easy to use channelrhodopsin photosensors (see Curr. Biol. (2011), *21*, R831–R833).

Another important set of tools are the combinatorial systems for gene expression, including Cre–lox and tetO-tTA. In the former, the *cre* recombinase gene is combined with a cell-type-specific promoter, such that only the cell type of interest will produce the enzyme. Using lox recombination sites, researchers can then introduce reporter or effector genes, which will specifically be turned on in Cre-expressing cells only.

Given the lack of a fovea and a red pigment, studies of the mouse retina can only address some aspects of human vision, including, for instance, peripheral vision and the rod-based night vision. However, there is the intriguing possibility that some of the features that the mouse is lacking can be introduced by genetic manipulation. The only example so far is a study by Gerald Jacobs and colleagues at the University of California at Santa Barbara, who genetically introduced a human red-sensitive cone pigment into mice and could demonstrate that the animals developed trichromatic vision similar to ours (Science (2007), *315*, 1723–1725).

However, the main rewards in mouse vision science will not be gained from the rodents' puny photoreceptors, but from the downstream processing, ranging from the retinal ganglion cells to the primary visual cortex and even to behavioural responses. Despite the relatively impoverished input it receives, Huberman and Niell conclude that "the mouse cortex is indeed performing similar computations as in other species, just at lower spatial resolution."

Visual neurophysiology and psychophysics, which links cellular circuits to both visual input and behavioural output, has traditionally been studied with primates, but this field is now being taken over by mice as well. Researchers are using both reflexive behaviour and trained responses to assess visual perception. For instance, mice trained to receive a reward when responding to the perception of light can help to measure the sensitivity of visual pathways.

In their most recent work, Huberman's and Niell's groups have found that mice have a surprising ability to detect and compare visual stimuli such as bars of different orientations (vertical versus horizontal). "While these abilities are in no way extraordinary, the more we learn about the anatomy, physiology and visual perceptual abilities of mice, the more we realize how similar, as opposed to different, the mouse visual system is," says Huberman. "For example, the eyes and brains of monkeys and cats have long been known to contain cells specialized for detecting very specific kinds of visual stimuli like bars moving in a particular direction. Five years ago, most people considered mice 'blind' let alone sophisticated in terms of visual processing. We now know that mouse eyes and brains contain many of the pathways and functional channels found in other model species."

Mice were also very much in the spotlight at the annual meeting of the Society for Neurosciences (SfN) held in November at Washington, DC. Attending vision neuroscientist Frank Sengpiel from Cardiff University observed that "it's hard to believe how visual neuroscience has come to be dominated by mouse studies in just a few years."

"The mouse model is here to stay. Indeed, use of the mouse for visual neuroscience is growing at an amazing rate," says Huberman. "People working on olfaction, taste, or audition are shifting toward mice as well. At the same time, there is no doubt that other well-established models like the fruit fly, human, and monkey will continue to be used."

Mapping mouse brains

The mouse also features prominently in the neuroscientific research conducted at the Allen Institute for Brain Science, a Seattle-based, non-profit independent research facility launched in 2003 with seed funding from Microsoft co-founder Paul Allen. The institute's inaugural project, the Allen Mouse Brain Atlas, designed as an anatomically and genomically comprehensive public resource, was completed in 2006. Using *in situ* hybridization on an industrial scale, the institute's scientists created a 3D map of the expression of more than 20,000 genes throughout the mouse brain, which is freely available via the institute's Allen Brain Atlas data portal (www.brain-map.org). Approximately 10,000 unique users from around the world visit the Mouse Brain Atlas each month, and it has already been used and cited by hundreds of research papers. With traditional methods, mapping the expression of a single gene of interest would take researchers several months.

Expanding the use of the high-throughput methods developed for the Allen Mouse Brain Atlas, including laboratory robots and automatic imaging devices, the institute then created further atlases covering the mouse spinal cord, the developing mouse brain, mouse brain connectivity, and the human brain. With this and with other atlas projects, the institute aims to integrate genomic and anatomic information, together with data mining, visualization and navigation tools, into groundbreaking new online public resources that neuroscientists around the world can use in their research.

In March 2011, the Allen Institute appointed Caltech neuroscientist Christof Koch, who collaborated with the late Francis Crick on the neural basis of consciousness, as Chief Scientific Officer, with the aim to "expand beyond our historic focus on gene expression and into the circuitry and coding of information in the brain," as CEO Allan Jones stated.

Waxholm Fortress: The coordinates system used in the INCF Digital Atlasing Project is named after the island of Waxholm, where a workshop meeting laid the foundations for the system. Previously, the castle featured in a Pippi Longstocking film. (Photo: Wikimedia Commons.)

Wikimouse

Researchers from the Allen Institute are also involved in an international collaborative project that aims to make the step from the stationary atlas of the mouse brain to the mouse brain equivalent of Wikipedia, an online facility where researchers can share their data and connect them to a unified coordinate system making all inputs comparable and easy to reference. The International Neuroinformatics Coordinating Facility (INCF; incf.org), based at the Karolinska Instititute and the Royal Institute of Technology, at Stockholm, Sweden, and supported by 16 member countries, first convened a working group for the digital atlasing project at Waxholm, Sweden, in September 2008. The location lent its name to the geometrical framework the researchers set up for the project, the Waxholm Space or WHS. This space was then clad out with initial MRI data from a single male mouse of the genetically well-characterised strain C57BL/6J, and with matching histological data.

The INCF Digital Atlasing Infrastructure (DAI), as Michael Hawrylycz and colleagues from the Allen Institute, together with collaborators from around the world reported in February (PLoS Comput. Biol. (2011), *7*, e1001065), "is a collection of distributed services that support the publication, discovery, and invocation of heterogeneous atlases and resources." The prototype version for the mouse brain enables linking between the WHS reference space and three existing mouse brain atlases, including the one at the Allen Institute, the Edinburgh Mouse Atlas Project, and the Whole Brain Catalog based at the University of California San Diego.

While the prototype already enables many atlas functions, including the retrieval of images or genetic information for specific sites, its full function will depend on the participation of users and the data they submit and cross-link. Developing standardised input formats is a challenge, as Hawrylycz and colleagues admit, but they hope to establish a standards procedure similar to the one operated by the World Wide Web Consortium (W3C), which has very successfully ensured that websites can normally be viewed by everybody, regardless of what kind of system they were produced on.

As with the visual neurosciences, atlasing projects find the mouse brain big enough to be interesting and small enough to be manageable. "While building such a framework would be considerably more challenging in higher mammals, the benefits in the mouse and rodent in general, are extraordinary, and well worth the effort," Hawrylycz and coworkers conclude.

As more researchers add their data and the system continues to evolve, the authors hope that connecting results from different types of experiments and possibly even comparisons between species may become much more straightforward, and the accumulating information will be easily accessible to all.

"We see 3D spatial data integration as a key strategy for neuroscience research moving forward," says Sean Hill, Executive Director of INCF. "It enables the identification of relationships between structure and function and across scales in the nervous system. In addition, it makes it possible to formally define atlas boundaries rather than relying on the interpretation of several experts — thus creating data-driven atlases."

The top priority, says Hill, is to make it easier for individual researchers to register to the Waxholm Space and share their data. At the recent SfN conference, the INCF held a 'walk-in registration clinic' in order to encourage researchers to join in and share their data using the WHS and associated tools.

Of mice and men

Ultimately, of course, all these mouse studies are preparations for the bigger challenges posed by our own brains. "Multimodal atlasing for the human brain is the next big goal," says INCF's Sean Hill. "We will start in this direction with a workshop to establish standardized techniques for fine-scale alignment and registration of human data. This could form the basis of an open framework to integrate gene expression, cytoarchitecture, immunohistochemical stains, connectivity, DTI and fMRI and other structural and functional data to produce a truly integrated view of the human brain." Gnothi seauton, as the Greeks used to say. Know thyself.

Michael Gross is a science writer based at Oxford. He can be contacted via his web page at www.michaelgross.co.uk