ILLUSTRATION BY ADAM NICKEL

THROUGH THE EYES OF A MOUSE

Some brain researchers are increasingly using mice to study visual processing, but others fear the move is short-sighted.

BY MONYA BAKER

When Cris Niell said that he wanted to study how mice see, it did not go over well with more-senior neuroscientists. Mice are nocturnal and navigate largely using their noses and whiskers, so many researchers believed that the nursery rhyme — *Three Blind Mice* — was true enough to make many vision experiments pointless. The obvious alternative model was monkeys, which have large, forward-looking eyes and keen vision. What's more, scientists could rely on decades of established techniques using primates, and it is relatively straightforward to apply the results to the human visual system. "People were saying, 'studying vision in mice, that's crazy,'" Niell recalls.

But he was convinced that the rodents offered unique opportunities. Since the 1960s, researchers have used cats and monkeys to uncover important clues about how the brain turns information from the eyes into images recognized by the mind. But to investigate that process at the cellular level, researchers must be able to manipulate and monitor neurons precisely — difficult in cats and monkeys, much easier in mice. If mice and primates turned out to process visual stimuli similarly, Niell thought, that discovery could unleash a torrent of data about how information is extracted from stimuli — and even, more generally, about how the brain works.

He found a rare supporter in Michael Stryker at the University of California, San Francisco, who had already seen his share of crazy experiments in mouse vision. Stryker offered Niell a postdoctoral position in his lab, and the pair began setting up experiments in 2005.

Nearly a decade later, the two researchers are in better company. At last year's annual meeting of the Society for Neuroscience, Niell attended packed sessions on mouse vision. In March 2012, the Allen Institute for Brain Science in Seattle, Washington, announced a ten-year plan to spend more than US$100 million to map mouse visual areas. And in June this year, the curriculum of a two-week course on vision at Cold Spring Harbor Laboratory in New York featured mice front and centre. More than three-quarters of the 22 students investigating how the visual system works were using mice, says course co-director Andrew Huberman, a neuroscientist at the University of California, San Diego, who has worked on animals from cuttlefish to macaques. In 2001, he says, there may have been a student or two using mice to study how the visual system develops, but no one was studying function. "It's an explosion."

The surge of interest stems largely from advances that give researchers the ability to monitor and control specific mouse neurons using light. Logistical and ethical considerations are also a big draw. Studies with mice are much cheaper, faster and less likely to raise moral concerns than work with monkeys.

But whether they will reveal useful information about human vision is very much an open question, says Huberman. "The mouse visual cortex is like the smartphone of neuroscience," he says. "Everyone feels the need to get one to play with, but it still remains to be seen if it's merely a convenience, a colossal distraction or the greatest thing since the discovery of electricity."

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DRAWN TO RODENTS

Niell wanted to revisit some of the most well-known and seminal experiments in vision science. In the 1950s and 1960s, David Hubel (who died late last month) and Torsten Wiesel pushed electrodes into the backs of cat and monkey brains, and patched the signals to a speaker to track the activity of neurons. The researchers listened in as the animals viewed tilted lines and moving dots; the crackles they heard revealed that organized regions of neurons respond to motion and edges[1]. The results, which later earned Hubel and Wiesel a Nobel prize, became a canonical example of 'cortical computation', in which interconnected neurons transmit and transform information.

It turns out that neurons in the visual cortex process input from the eyes extremely selectively: some respond only to vertical lines, others to horizontal ones, still others to stripes that tilt 40° to the left, to dots creeping up 30° to the right, and so on.

Niell, who now runs a lab at the University of Oregon in Eugene, knew that it would not be easy to discover whether these findings would hold true for mice. The electrodes available at the time often damaged neurons in fragile mouse brains, disrupting activity rather than monitoring it. But after revising their procedures and redesigning their equipment, Niell and Stryker worked out a way to record from individual mouse brain cells using silicon microprobes.

Stryker, who had trained with Hubel and Wiesel, recalls seeing the first graph that plotted how a neuron responded to a mouse viewing a series of tilting lines. The graph showed sharp, narrow peaks of neural activity at specific orientations[2]. If the lines were tilted just 20° from the preferred angle, the cell fell silent. "I just couldn't believe how pretty it was," says Stryker. "It was like the figure in a book."

The experiments showed that neurons in the mouse visual cortex are about as selective as those in the cat or monkey brain. Niell and Stryker considered that to be strong evidence that the mouse could be used as a model for visual processing in higher animals.

When word got out, the team soon had visitors. Among the earliest were Hillel Adesnik and Bassam Atallah, two neuroscientists then working in the lab of Massimo Scanziani at the University of California, San Diego. Adesnik and Atallah had been studying dissected slices of mouse brain to catalogue how subtypes of neurons were connected. They could test how cells in the freshly dissected tissue responded when stimulated with electricity, but it was hard to know what kind of processing, if any, happens in a brain slice. They really wanted to probe how brain circuits responded to real physiological stimuli — the type delivered by the eyes, ears, nose or skin of a living mouse. When they heard of the results from San Francisco, they hopped on their motorcycles and rode 800 kilometres to learn Niell and Stryker's technique.

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Since that visit, Adesnik, Atallah and others have done experiments that show how neurons interact in intact circuits in the mouse visual cortex. Such work is beginning to reveal how subtypes of neurons cooperate to extract information about the world; it also hints at which stimuli mice notice or ignore. "I consider the mouse visual cortex as the first pillar in a bridge that will link cellular and systems neuroscience," says Scanziani.

It is too early to know how far that bridge will extend, says Edward Callaway, a neurobiologist at the Salk Institute for Biological Sciences in La Jolla, California. "So far, we haven't learned anything fundamentally new from the mouse visual system. And that's not surprising, since we've studied monkeys for the past 40 years."

But the early data are fuelling mouse researchers' hopes that this simple, easily manipulated model could shed light on more-complex brains. For instance, in a sign that mice have sophisticated processing, researchers showed that, like primates, mice have visual areas that receive input beyond the primary visual cortex[3].

Around the same time that Niell and Stryker were learning that mice can see stripes, Matteo Carandini at University College London switched to mice after years of researching vision in monkeys and cats. He wanted to study neural circuitry in the context of behaviour, but for that he had to record from inside individual neurons. That is hard to do in monkeys — and although it can be done in cats, they baulk at the behavioural tasks required. So Carandini began working out training programmes to let him explore what patterns mice perceive as they move around, and how they act on their perceptions.

He and his team developed one task in which mice press a button when they see stripes. The team also monitored mouse visual processing as the animals ran on a treadmill or explored a virtual environment. Carandini now wants to manipulate particular neurons during such experiments to see how the mouse's behaviour changes.

He wants to learn how parts of the brain cooperate: he thinks that work on the mouse's small, flat brain could shed light on processes in higher animals, such as perception and decision-making, and how these are affected by distraction (such as noise) or motivation (such as thirst). "The frontier at this moment is understanding how different parts of the cortex work together," he says. "This is a problem that any animal with a cortex has."

A BLURRY PICTURE

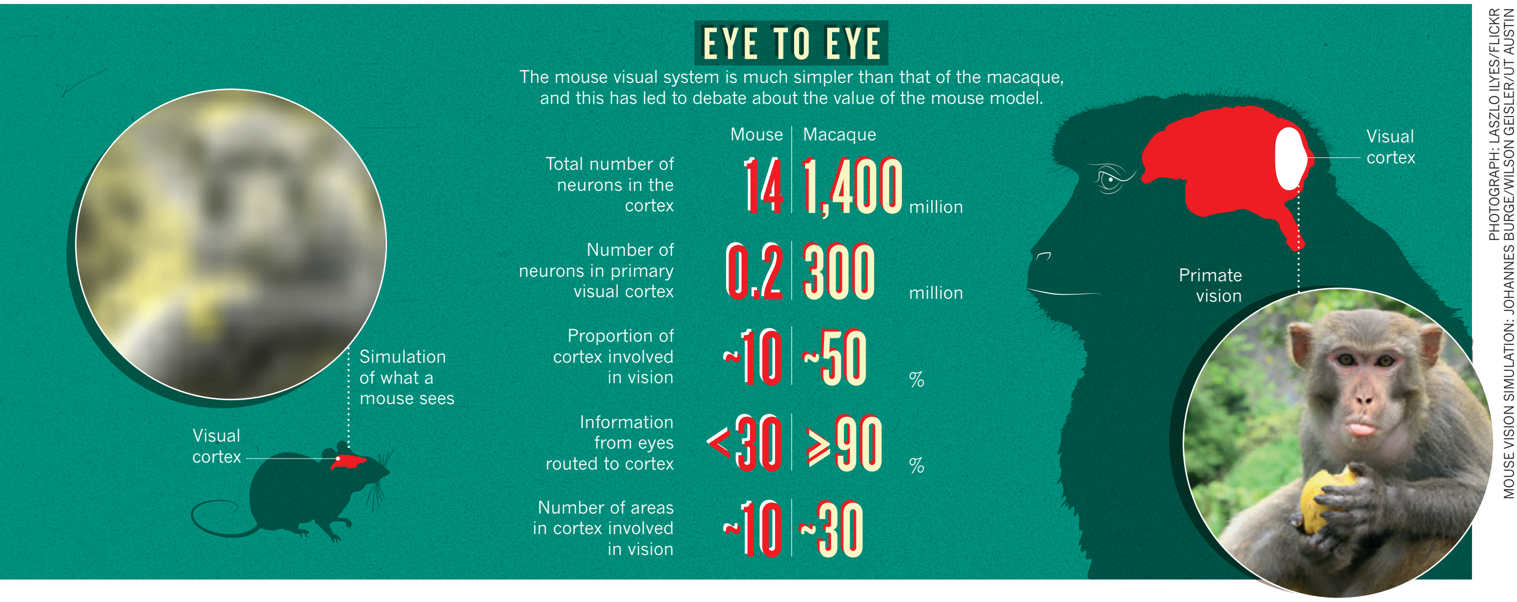
Carandini and others who work on mouse vision all acknowledge that there are limits to this line of research. No one denies that mice see poorly; Niell estimates that they have the equivalent of 20/2,000 human vision (which would qualify them as legally blind). The general rule of thumb is that mouse eyesight is about as good as what humans see in their far-off peripheral vision.

So there will be tasks that rodents will not be able to perform — particularly those related to aspects of facial recognition and visual attention. "To really get to behaviour in a more meaningful way, we'd probably have to use primates," says Callaway, who is working with mice as well as improving genetic tools for studying monkeys.

Still, enthusiasts say, the similarities between mice and humans

EYE TO EYE

The mouse visual system is much simpler than that of the macaque, and this has led to debate about the value of the mouse model.



	Mouse	Macaque	
Total number of neurons in the cortex	14	1,400	million
Number of neurons in primary visual cortex	0.2	300	million
Proportion of cortex involved in vision	~10	~50	%
Information from eyes routed to cortex	<30	>90	%
Number of areas in cortex involved in vision	~10	~30	

PHOTOGRAPH: LASZLO ILYES/FLICKR
MOUSE VISION SIMULATION: JOHANNES BURGE/WILSON GEISLER/UT AUSTIN

outweigh the differences. The mouse visual cortex contains the same neural subtypes as the human visual cortex, in about the same proportions, and the subtypes seem to hook up to each other using the same rules. Evolutionarily, mice are more closely related to humans than are cats. And the fact that a mouse has fewer brain regions than either a primate or a cat, and can distinguish a smaller set of possible images, makes it more experimentally tractable, says Carandini. "The basic rules of computation, I believe, are more general and canonical. Our chances of discovering them are much better in a mouse."

Not all neuroscientists embrace the mouse as a model. "I don't think there's good evidence that mice use the visual cortex the way primates do. Or that the mouse visual cortex is organized the way that primates' are, or that mice are a good model for vision," says Tony Movshon, a neuroscientist at New York University.

The most obvious difference is size: the entire mouse brain is one-fiftieth as big as the part of the macaque brain devoted to vision alone. A macaque's primary visual cortex has more than 1,000 times as many neurons as a mouse's, and a much greater fraction of the macaque brain is devoted to vision (see 'Eye to eye'). Primates have plenty of neurons in dozens of visual areas with targeted purposes, such as recognizing faces and tracking motion. By contrast, the visual regions identified in mouse brains are "tiny little patches of cortex", says Movshon; they extend for micrometres and millimetres, rather than centimetres. The areas are simply too small for the extensive, regional communication observed in primate visual areas, he says. "They can't work the same way."

BUSY BRAINS

Perhaps the biggest problem is that the mouse visual cortex performs many functions besides vision, so the systems that support visual processing could be fundamentally different from those in the primate brain. It is like studying heart function in some alien organ that not only pumps blood but also takes on the respective gas-exchange and electrolyte-balancing functions of the lungs and kidneys.

For all these reasons, instead of switching his vision studies from monkeys to the more tractable mice, Movshon is putting his faith in nascent efforts to take the tools that work so well in mice and adapt them to manipulate subtypes of neurons in monkey brains. "What people are doing now is to pretend that the mouse is a tiny monkey with a pointy noise and whiskers and to hope for the best," he says. Paul Martin, a vision scientist at the University of Sydney in Australia, agrees that scientists could encounter severe problems when they try to relate mouse data to the human experience. "A shopping trolley and a Formula 1 motor car both have wheels and obey Newton's laws of motion. But the motor — what makes them move — is quite different," he says.

Nicholas Priebe at the University of Texas at Austin is advocating more comparative studies to tease out how processing differs between mouse brains and those of other species — and how it is similar. This year, he reported striking differences in how brain regions in cats and mice contribute to selectivity[4]. Discrepancies between mice and primates do not mean that mouse brains have nothing to reveal about human brains, he says, but scientists need to proceed with as much caution as enthusiasm. "If you try to apply everything you learn from the mouse to our brain, then I think there's a serious problem," says Priebe.

For most, the debate is not about whether to study visual processing in the mouse cortex, but about what questions will also apply to higher animals. Many researchers are hopeful that mouse experiments will generate hypotheses for primate research, and that comparable experiments could one day go back and forth between animal systems. But after decades of focusing on primates, researchers have some catching up to do in rodents, says Callaway. "We can't begin to do those things in a mouse until we know more about what they use the visual system to do."

That is part of the aim of the initiative by the Allen Institute for Brain Science to map the mouse visual cortex and visual processing areas. The goal, says Clay Reid, who co-leads the project, is to start at the bottom, building up to big questions about how the brain works. Reid and his team plan to catalogue the cell types and connections in the mouse's visual area, and to monitor what happens as the animals look at, and respond to, a stimulus. Then the team will see how responses change when particular neurons are suppressed or activated. Such experiments are about more than just vision. "We are doing it to try to understand principles of cortical computation and the relationship between cortical activity and behaviour," says Reid. Armed with some clues to those processes, scientists will be able to test these hypotheses in other animals.

Eight years after his initial experiments, Niell is glad to see more researchers embracing what the mouse has to offer. Of course, such a simple system cannot answer every question we have about the human brain, but researchers should learn what they can, says Niell. "You can make so much headway with a mouse that it's silly not to." ■

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1. Hubel, D. H. & Wiesel, T. N. *J. Physiol. Lond.* **160,** 106–154 (1962).
2. Niell, C. M. & Stryker, M. P. *J. Neurosci.* **28,** 7520–7536 (2008).
3. Wang, Q. & Burkhalter, A. *J. Comp. Neurol.* **502,** 339–357 (2007).
4. Scholl, B., Tan, A. Y. Y., Corey, J. & Priebe, N. J. *J. Neurosci.* **33,** 10616–10624 (2013).