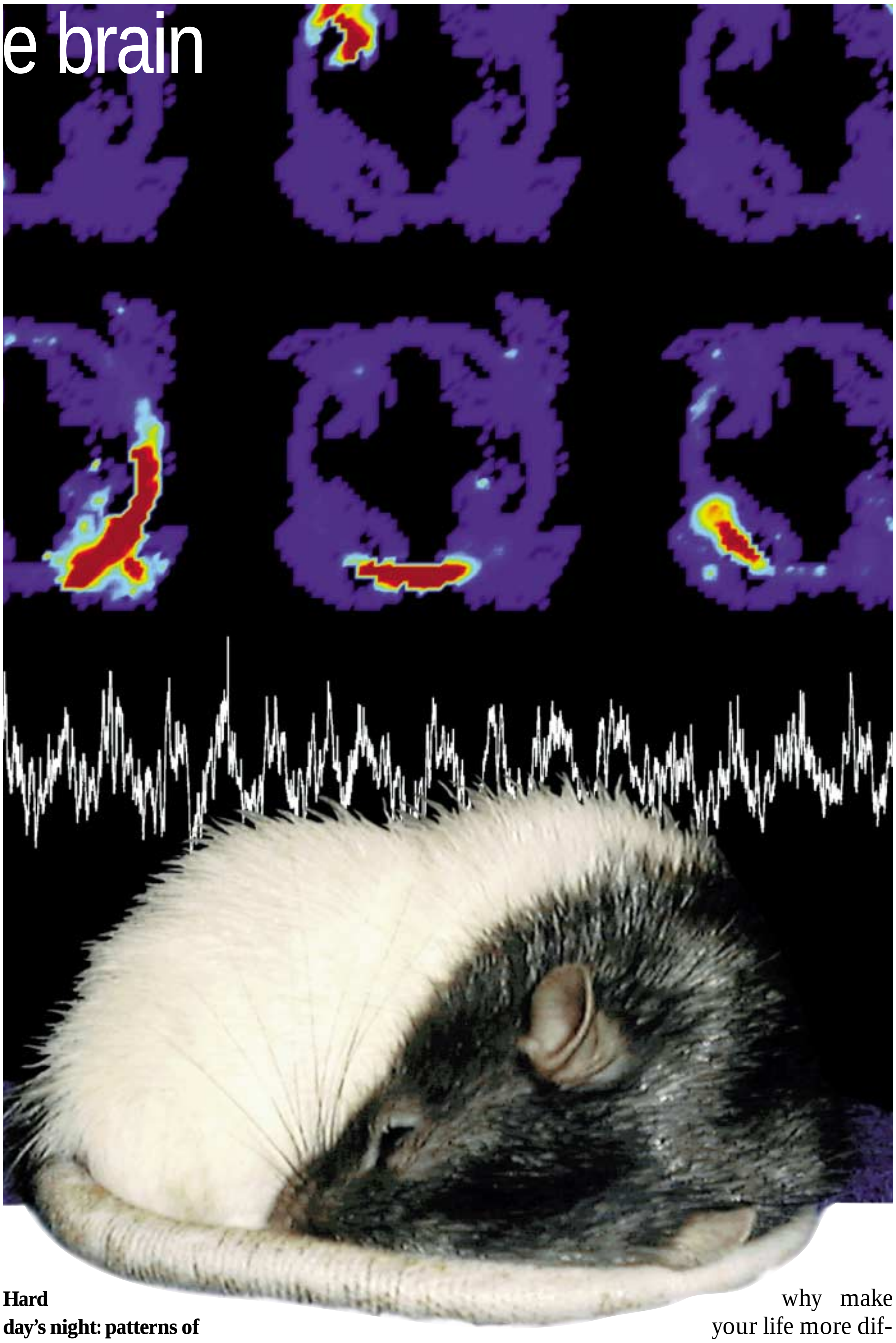
Windows on the brain

By monitoring the activity of up to a hundred brain cells at once, neuroscientists are gaining new insights into brain function and paving the way for fully functioning prosthetic limbs. Marina Chicurel reports.



K. LOUIE & M. A. WILSON

Hard day's night: patterns of neuronal firing recorded as a rat sought food in a track (top) are replayed when the rodent 'dreams'.

A robotic arm flexes as it receives commands from a monkey's neurons. Scientists probe an animal's perceptions and intentions. The dreaming brain comes into view as a rat's memory-traces are shown being replayed during sleep.

Thanks to tools developed to monitor the activity of up to 100 individual neurons simultaneously, these futuristic scenarios are now an everyday reality in some of the world's top neuroscience labs. Such 'multi-unit' recording is poised to transform brain research. "It will mark the transition of neurophysiology from small science to big science," predicts Vernon Mountcastle of Johns Hopkins University in Baltimore, Maryland, whose recordings from single nerve cells helped to underpin present textbook principles of brain function.

For decades, neuroscientists have implanted electrodes into the brain to listen in as neurons talk to one other. When one brain cell sends a signal to another, it fires off a voltage pulse along a fibre leading towards the next neuron. This pulse can be detected by electrodes placed close to the firing neuron.

Head start

Traditionally, researchers have monitored the activity of brain cells one at a time. Such studies have made huge contributions to our understanding of the brain but, ultimately, they cannot lay bare the behaviour of large, interconnected networks of neurons. Searching for a glimpse of this bigger picture, many neuroscientists are now inserting multiple microelectrodes into animals' brains.

The technique first attracted attention in the early 1970s, when researchers mapping connections within the brain began comparing readings taken from pairs of neurons[1]. They noticed that, in some cases, the firing of one neuron preceded the silencing of another, and reasoned that the first neuron was sending signals that, either directly or indirectly, inhibited the second cell. The technique has since been used to map the connections between many different brain areas.

But more ambitious multi-unit studies were slow to take off. "It is more difficult to record from two or more neurons than it is from one," explains Charles Gray of Montana State University in Bozeman. "If you can get a lot of information from one neuron, why make your life more difficult?" Others in the field suggest that researchers were unsure of how to analyse multi-unit data and that many were not even certain what questions the technique could address.

In the late 1980s, Gray, together with Wolf Singer of the Max Planck Institute for Brain Research in Frankfurt, helped to frame one of those questions. Researchers already knew that the rate at which a neuron fires off pulses encodes important information. But Gray and Singer were intrigued by suggestions that the precise timing of the individual pulses might also be important. Theoretical studies[2] had indicated that neurons working on the same problem might fire synchronously.

Gray, Singer and their colleagues examined this idea in 1989, using up to seven electrodes to record the activities of widely distributed neurons in visual areas of cats' brains. When the cats looked at moving bars of light oriented in a particular direction, the researchers saw that neurons specialized to respond to this orientation fired in an oscillating pattern. These oscillations were synchronized even when the cells were far apart from one another and involved in processing information from different areas of the field of view. The researchers suggested that the timing of the neurons' pulses might help to coordinate such distant cells when they are processing similar types of information[3].

All together now

Gray and Singer's experiments motivated many others to turn to multi-unit recordings. The precise significance of the oscillations they saw remains a matter for debate. But dozens of multi-unit studies have since shown that synchronous firing is associated with visual perception and the conscious processing of other types of information[4].

Last year, Singer's team showed anaesthetized cats a checked pattern made up of two different sets of stripes moving at right angles to each other. Varying the brightness of the stripes changes the way the overall pattern is perceived — it is either seen as two individual moving sets of stripes, or a single, checked pattern moving as a whole. Using multi-unit recordings of cells in a visual processing area of the cats' brains, Singer showed that neurons that responded to different sets of stripes fired synchronously when a cat was shown stripes that should have been perceived as a single pattern, but not when the stripes would have appeared to move as two individual sets[5].

Building from the early experiments that used information from pairs of neurons to map connections between different brain areas, some neuroscientists are now finding that cells that are wired together may show strikingly similar behaviour — underlining the precision with which the brain's connectivity can develop. For example, researchers led by José-Manuel Alonso at the University of Connecticut in Storrs and Clay Reid at Harvard Medical School in Boston have recorded simultaneously from connected neurons in two parts of the cat's visual processing pathway — the lateral geniculate nucleus (LGN) and the primary visual cortex.

The LGN is the first relay station in the brain that receives signals from the retina, which it then passes on to the primary visual cortex. Last month, Alonso and Reid reported that the probability of finding a connection between an LGN cell and a cortical cell is highest when the pair share similarities in at least five behaviours[6]. These include the precise timing of their responses and the size of the area in the field of view that they respond to.

Multi-unit experiments can also provide insights into the workings of the sleeping brain. In a study published in January[7], Matthew Wilson and Kenway Louie of the Massachusetts Institute of Technology described how they simultaneously tracked the activities of up to 13 neurons in rats' hippocampi — a brain region involved in spatial learning and memory — while the animals ran around a track to collect food. They then monitored the same neurons as the rats slept.

Wilson and Louie spotted patterns of neuronal activity during rapid eye-movement (REM) sleep, some of which lasted for over a minute, that closely matched those recorded when the animals were collecting the food. In humans, at least, REM sleep is a phase in which dreams occur. Wilson believes the patterns he and Louie observed are 'replays' of memories formed earlier in the day, and that they may underpin the rats' dreams.

These observations may shed light on how waking experiences are transformed into memories. Wilson and many others in the field believe that animals use these replays to process information gathered while they are awake, and to lay down long-lasting memories of the day's experiences.

Other researchers, meanwhile, want to put the multi-unit technique to clinical use. They are using multi-unit recordings to develop devices that turn thoughts into actions — a concept that could lead to the development of functional prostheses for paralysed patients.

Out on a limb

As early as 1970, researchers showed that by monitoring the activities of just five neurons in an area of a monkey's brain controlling limb movement, they could predict how the force exerted by the monkey's wrist would change[8]. Subsequent multi-unit experiments have revealed how neurons in such 'motor' areas of the brain encode information about the direction of movement[9], so that it is now possible to predict from such recordings how an animal will move its arm[10]. In the long term, researchers hope that people who have lost the ability to move their limbs may be able to control prosthetic limbs via electrodes implanted into motor areas of their brain.

Researchers have recently made progress towards this goal by using the output of multi-unit recordings to control robotic devices in real time. Last year, a team led by Miguel Nicolelis of Duke University in Durham, North Carolina, monitored neurons in regions of a monkey's brain involved in planning movements as the monkey prepared to move a joystick to the left or the right, or to reach for a piece of food[11].

As the monkey repeated its task, Nicolelis used a computer to develop algorithms that

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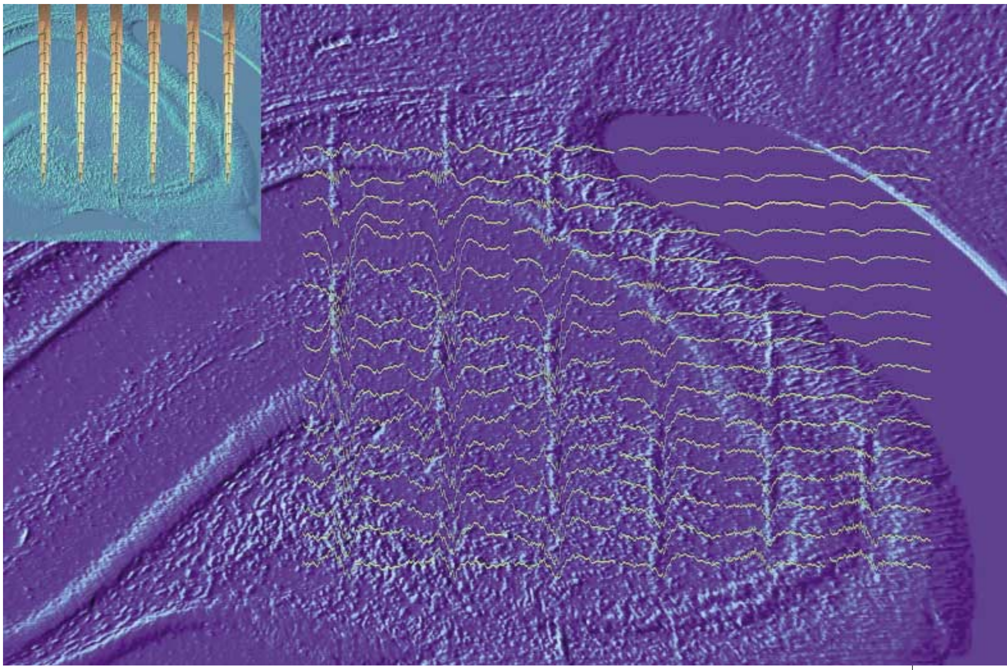

Finely tuned: a 200-millisecond neuronal event captured from 96 brain sites simultaneously using ultrafine silicon probes (inset), each offering 16 independent recording electrodes.

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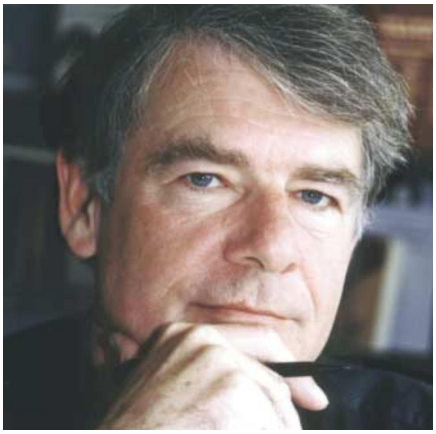

Live link-up: Wolf Singer suggests that neurons synchronize themselves to perform certain tasks.

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Mechanical mimic: Miguel Nicolelis' robotic arm can copy a monkey's movements in real time.

described the movement in terms of neuronal activity. In both tasks, no more than 10 minutes of repetitions were needed before the algorithm could predict, in real time, how the monkey would move its arm. For the joystick task, Nicolelis then used the algorithm to turn the signals from the monkey's neurons into commands for a robot arm, which simultaneously executed very similar movements to the monkey's own hand.

Andrew Schwartz of Arizona State University in Tempe and the Neurosciences Institute in San Diego, California, is working on the same problem using subtly different methods. "My goal is to make a movement that looks natural," says Schwartz.

He is testing algorithms that use neuronal signals to predict a monkey's arm movements in three dimensions as it interacts with objects in a virtual-reality environment. "The animal sees a series of balls that are floating in space," explains Schwartz. "One of the balls is a cursor that's hooked up to its wrist. What the monkey has to do then is move the cursor to touch one of the other balls."

The picture of a brain network should become crisper if more neurons can be measured.

Thinking small: György Buzsáki wants to gather multi-unit data from tiny volumes of brain tissue.

Once the monkey is trained, the virtual cursor can be unhooked from the monkey's wrist and be guided directly by signals from the animal's neurons. This allows the monkey to observe how its 'thoughts' influence the cursor's movement, and to adjust its responses accordingly. Future users of prosthetic devices will probably use visual feedback in a similar way.

Pump down the volume

Despite the impact of multi-unit experiments on prosthetics and fundamental neuroscience research, some in the field believe that simultaneous recordings from more neurons than the current best of 100 will be needed if the true potential of the technique is to be realized. Just as a computer image becomes sharper with more pixels, the picture of what a brain network is doing should become crisper if the activity of more neurons can be measured. With this in mind, Bruce McNaughton of the University of Arizona at Tucson is now developing techniques to record from several hundred neurons at once.

But for some applications, it is not just a question of sheer numbers, says György Buzsáki of Rutgers University in Newark, New Jersey. The difficulty, he explains, lies in recording from a large number of neurons within a sufficiently small region of the brain. "The big deal is to record many neurons from a very small volume."

Most information processing in the brain is thought to occur within clusters of a few hundreds or thousands of neighbouring cells, which occupy volumes smaller than a cubic millimetre. To understand how these circuits work, Buzsáki thinks it will be necessary to sample the activities of multiple cells within them simultaneously. But the microwires typically used as electrodes cannot be used to record from large numbers of cells in such a small volume, because of the damage their blunt tips would inflict on brain tissue.

The key to getting around this, says Buzsáki, lies in the technology used to build computer chips. Using micromachining and lithography, his team has created slender silicon shafts with up to 16 iridium electrodes positioned along each shaft's length which can be used to record from different neurons independently[12]. In addition to increasing the number of electrodes per implantation site, says Buzsáki, his sharp shafts tend to move through brain tissue without crushing it. His team's latest success is a probe sporting six shafts, yielding a total of 96 electrodes, which span less than a cubic millimetre of brain tissue. And Buzsáki thinks he can do even better. "The currently available industrial technology can produce probes with the same dimensions, but four to five times more recording sites," he says.

Information overload

But the toughest problem for multi-unit studies lies in the analysis of the acquired data. "To my mind, this is the stumbling block," says Moshe Abeles of the Hebrew University in Jerusalem. A single hour of recording from a few dozen cells can produce gigabytes of data, from which researchers must try to extract meaningful information. Many researchers analyse networks of neurons by comparing the activity of each cell to each of the others, one pair at a time. Although these studies provide some clues about how the network functions, they are still far from revealing how tens, hundreds or thousands of neurons behave as a group.

Buzsáki believes the key will be algorithms that can analyse network function by considering many component cells in one go. "Extracting this hidden information requires mathematical tools that are not available anywhere — not in industry, not in academic mathematics departments, nowhere," says Buzsáki. Researchers such as Abeles are now forming multidisciplinary teams, including computer scientists, physicists and mathematicians, to tackle the problem.

If they succeed, neuroscience would be propelled to new heights. But even without a leap forward in data analysis, enthusiasts are convinced that multi-unit recordings are here to stay. "This method is going to be the next revolution in neuroscience, and it's happening right now," says Nicolelis. ■

Marina Chicurel is a writer in Santa Cruz, California.

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