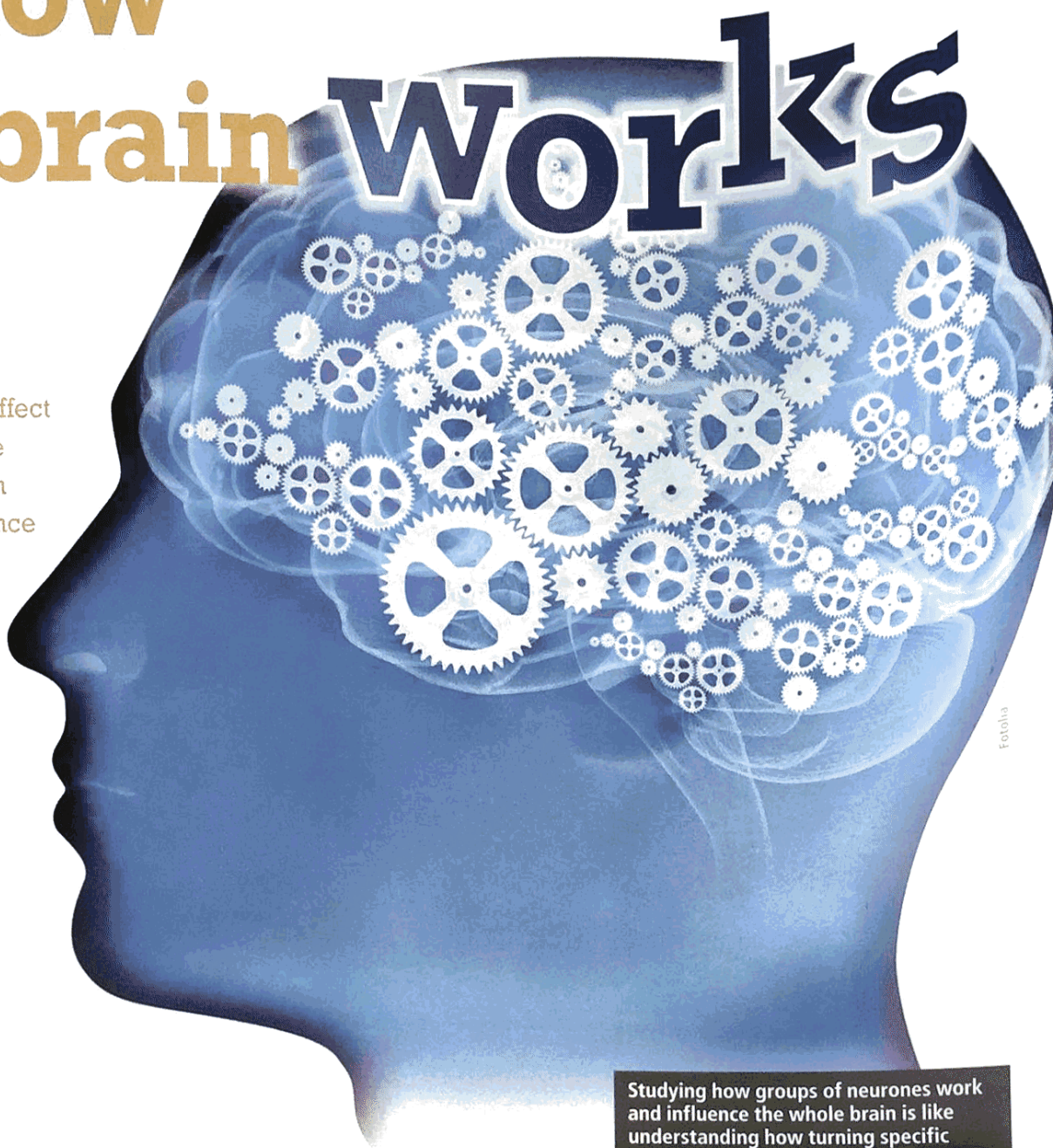
Shedding light on how the brain works

Natasha Bray

Some diseases that affect the brain can change our ability to function normally. Neuroscience researcher Natasha Bray explains how researchers have used revolutionary ways to study neurones to work out how they affect the brain and behaviour



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Studying how groups of neurones work and influence the whole brain is like understanding how turning specific cogs might affect the rest of the system

Key words

Neurone
Depolarise
Action potential
Neurotransmitter
Synapse
Opsin

Everything a person does, says, thinks or feels is thanks to their incredible brain. The human brain is made up of more than 80 billion (80×10^9) specialised cells called neurones. These cells control everything we do, from breathing, walking and talking to even more complicated jobs like socialising, learning and solving problems.

Neurones and action potentials

Neurones are like tiny electrical wires that can carry electrochemical impulses. If all the neurones in one human brain were lined up to make one long wire, it would stretch over 600 miles. When a neurone is resting, it has a negative electric charge across its cell membrane of about –70 thousandths of a volt, or –70 mV. When the charge inside the cell

becomes less negative (closer to 0 mV) it is said to be depolarising. If the inside of the cell depolarises to a crucial tipping point, about −55 mV, then the cell 'fires' an action potential.

An action potential is a rapid impulse caused by electrically charged particles moving to and fro across the cell's membrane. First, sodium ions surge in, making the inside of the cell positively charged. The cell's charge reaches about +40 mV, before potassium ions flow out of the cell. This allows the inside of the cell to return to a normal resting potential of −70 mV. An action potential travels in one direction down the length of the cell in a matter of a few thousandths of a second before reaching the gap between two neurones, called the synapse.

Synapses and neurotransmitters

Synapses measure only about 20 millionths of a millimetre across, but they are essential to the way the brain works. They are the junctions between neurones. Each neurone has between 1000 and 10000 synapses with other cells, so we each have around 100 trillion (10^{14}) synapses in our brain. These connections between cells can be strengthened or weakened, created or destroyed — allowing us to store or forget memories in our brain.

When an action potential reaches the synapse, tiny packets of chemical messengers are released from the neurone. These chemical messengers are known as neurotransmitters. Neurotransmitters cross the synapse to the next neurone. Some neurotransmitters attach to large proteins (receptors) on the surface of the cell. When this happens, the receptor opens a pore in the cell membrane. Opening pores in the cell membrane depolarises the cell, which can lead to an action potential. And so the message continues.

Decoding the brain: the problem

Since there are over 100 known neurotransmitters, and many more types of receptor, studying the brain can be a real challenge. Until recently, researchers who studied the brain could only observe what happened to the brain to try to understand how it worked. Controlling the brain could only be done using electric currents or drugs. Electric currents target only a small number of neurones and can damage them, while drugs can take a long time to work. Drugs also act on the whole brain, and can't be targeted at only one section of it. When studying the brain, this is important, because neurotransmitters often have different effects depending on where they are released.

By controlling specific groups of neurones quickly, and with precision, neuroscientists will be able to better understand many brain disorders. This is because, in the brain, activity in one group of cells can cause more or fewer action potentials to fire in a connected group, which may affect another group, and so on. For example, a brain disorder may be characterised by more or less activity in one of the areas downstream of a crucial set of cells. It can be difficult, however, to untangle the neuronal web to know which set of cells has started the disorder. To treat the cause, rather than the symptom, of the disorder, it is important to work out which group of cells needs to be targeted. By switching neurones on or off instantly, scientists can understand how the action of certain cells may cause changes elsewhere in the brain. Changes may even alter behaviour.

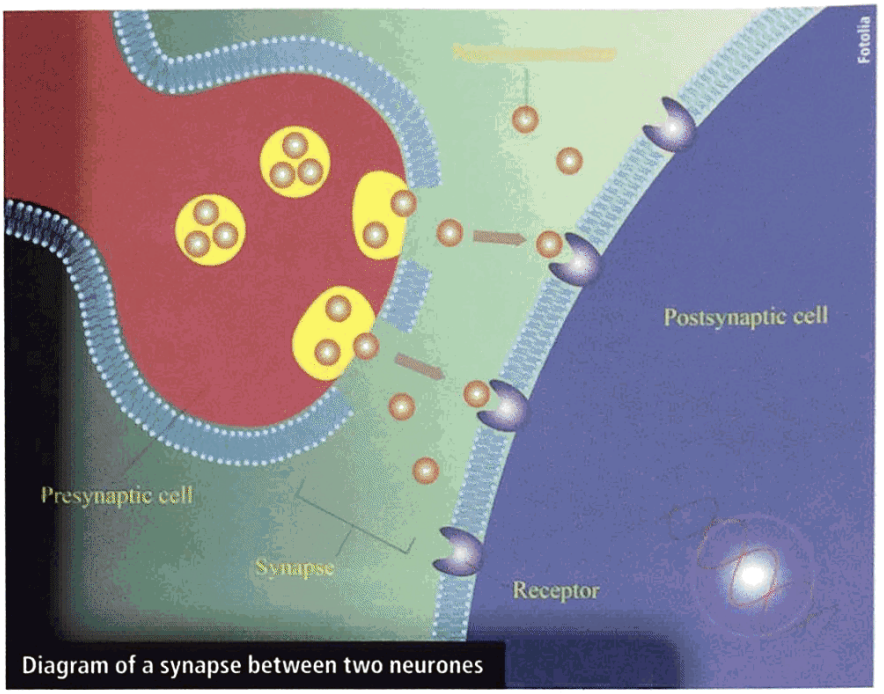

Diagram of a synapse between two neurones

Using a tool from algae

So how can neuroscientists better predict or study what happens when a particular group of neurones becomes active and starts sending neurotransmitter messages? One approach has been developed using algae. Like plants, algae photosynthesise using energy from sunlight. An alga called *Chlamydomonas reinhardtii* lives in fresh water. It uses a clever trick to swim towards sunlight, its source of energy. In the surface membrane of the algal cell is a pore called a channel rhodopsin — a type of opsin. Opsins are light sensitive, so when light shines on the channel rhodopsin, it opens up a channel in the cell membrane. This lets positively charged ions through

Further reading

In 2010, optogenetics was awarded 'Method of the Year' by *Nature* journal. Here is a YouTube video made by *Nature* that illustrates how optogenetics works: **www.youtube.com/watch?v=I64X7vHSHOE**

This is an article from *ScienceDaily* that explains how optogenetics has been used to study motivation: **http://tinyurl.com/d88t7a2**

The humble fruit fly, *Drosophila*, is used to answer many questions in biology

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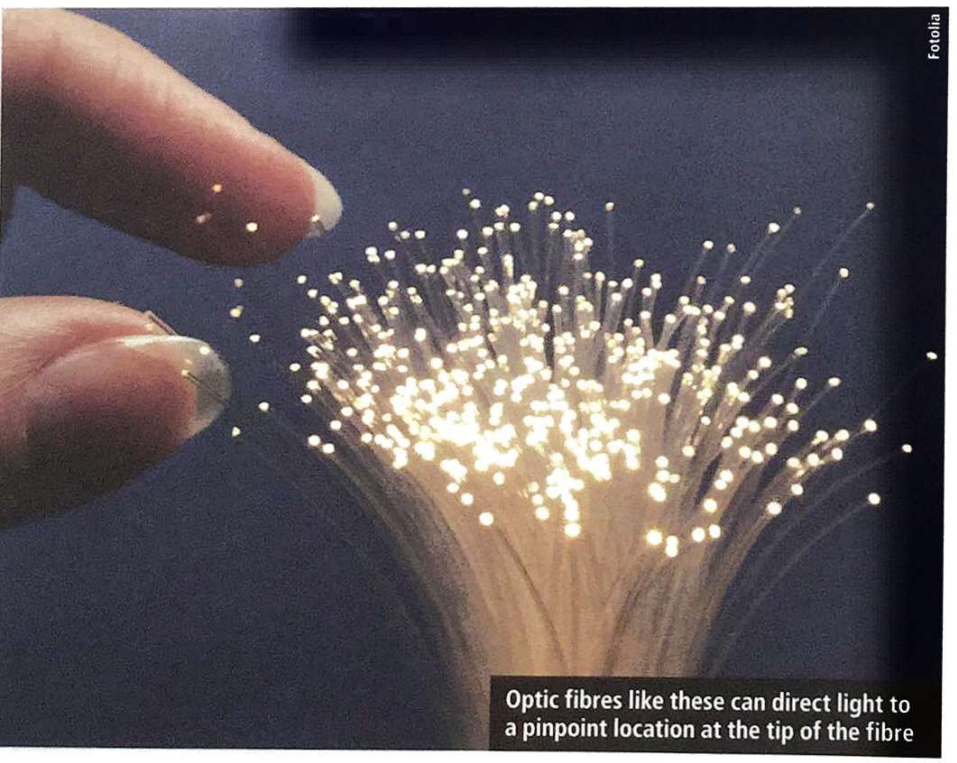
the cell membrane into the cell. These ions inside the cell act like the ignition of a car engine, so the alga can then swim towards the sunlight.

Professor Karl Deisseroth and his colleagues at Massachusetts Institute of Technology (USA) found a way of making neurones produce their own opsin. They isolated the gene from algae that codes for the opsin protein, and using a harmless virus they inserted the gene into neurones in other organisms. If a tiny light is shone onto these neurones, they will switch on, generate an action potential and release neurotransmitter. This technique is called optogenetics: 'opto' meaning 'light' (see *Prospects*, pp. 15–19).

Other types of opsins have been discovered that switch off neurones in response to light, stopping neurotransmitter being released. Other opsins can react to different colours of light. These opsins can also be put into the same neurones. This is how neuroscientists can use different colours of light to instantly switch neurones on or off.



Optic fibres like these can direct light to a pinpoint location at the tip of the fibre

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Illuminating the fly brain

Light that we can see is unable to travel far through brain cells, so neuroscientists can shine a tiny light in a precise part of the brain without affecting other neurones. They do this by sliding in an optic fibre to the part of the brain where light is wanted. An optic fibre is a hair-thick rod of plastic or glass that carries light like a pipe so that it shines only at the end of the rod at a specific point. The activity of specific groups of neurones can then be controlled instantly, simply by turning the light inside the brain on or off. To switch on or off large numbers of neurones, special opsins that react to invisible light can be used, because this light can travel further through the brain. Putting the optical fibre into the brain doesn't hurt because, unlike the skin, which can sense touch and pain, the brain can't feel pain.

Some of the first experiments using optogenetics were with fruit flies. Fruit flies are relatively simple (see Biological Sciences Review Vol. 23, No. 3, pp. 2–5), having around 200000 neurones, in contrast to the 80 billion neurones of human brains. Critically for optogenetics, because fruit flies are small, a light doesn't need to be put inside them, because visible light can travel through to their neurones from outside. Professor Gero Miesenboeck and his colleagues at the University of Oxford inserted opsin into the two neurones that control the fly's wings in their 'escape reflex'.

When a blue light was shone onto the flies, their wings would start vibrating and the fly would take off. When the blue light was switched off, the fly would return to normal. To check that the flies were not just startled by seeing the flash of light with their eyes, these flies were beheaded, leaving behind just the neurones needed to react to the light. When a blue light was flashed, these headless flies still vibrated their wings.

Discovering the fly's inner psyche

In a different experiment, the same group of neuroscientists injected opsin into random neurones in flies' brains, and then placed each fly into a tube. The tubes were divided into two halves, each filled with a different smell. The flies could walk up and down the length of the whole tube, and didn't show any preference for either of the two smells. Then, one of the halves of the tubes was filled with blue light. This switched on any light-sensitive neurones. Some of the flies avoided crossing into that half of the tube. What was interesting was that these same 'fussy' flies stopped going into that half of the tube even when the blue light was switched off.

These flies were avoiding the smell, even though they didn't have a preference for either smell before the blue light was shone. All the flies that stopped walking in the whole tube shared something in common. Of the random neurones in their brains that reacted to blue light, the 'fussy' flies all had light-sensitive cells in one part of the brain that the 'unfussy' flies didn't. This newly discovered region of the brain, which is made up of only 12 cells, has since been called the flies' 'self-critic' area in the brain. It is thought to have 'nagged' the fussy flies to keep away from the smell in the blue-lit half of the tube. A bad 'feeling' about the smell in that half of the tube had been put into the fly's brain.

What is next for optogenetics?

So far, optogenetics has only been used in animals such as flies, worms, mice and rats. However, it has shed light on many aspects of the way the brain works. In flies it has revealed an 'inner critic' that can make them prefer some smells over others. Optogenetics has also started to unveil how some pieces of the brain can make rats 'social' or 'motivated', which will help us to learn more about conditions such as autism and schizophrenia.

Optogenetics can also be used to investigate possible therapies of sensory system conditions, such as blindness and deafness, through the development of eye or ear implants that communicate with the brain. It is also helping neuroscientists to uncover how drug addiction, epilepsy and Parkinson's disease can be treated. It may be a while before optogenetics can be used to directly treat illnesses like these in people, but in the meantime it is helping us understand our brains and, essentially, ourselves.

Natasha Bray completed her degree in cognitive neuroscience and psychology with industrial/professional experience at the University of Manchester. She returned to Manchester to undertake a PhD in neuroscience. Her research looks into how inflammation, due to illness or injury, affects blood flow in the brain.

Key points

- Neurones carry messages in the form of action potentials.
- Neurones communicate with one another using different neurotransmitters released at synapses.
- Algae use opsin ion channels to react to light.
- Scientists can use opsins to switch specific groups of neurones on or off in response to light.
- Optogenetics is now used to study the brain so that better treatments can be found for disorders.