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Light-switch magic in the brain

Louise Whiteley, University College London
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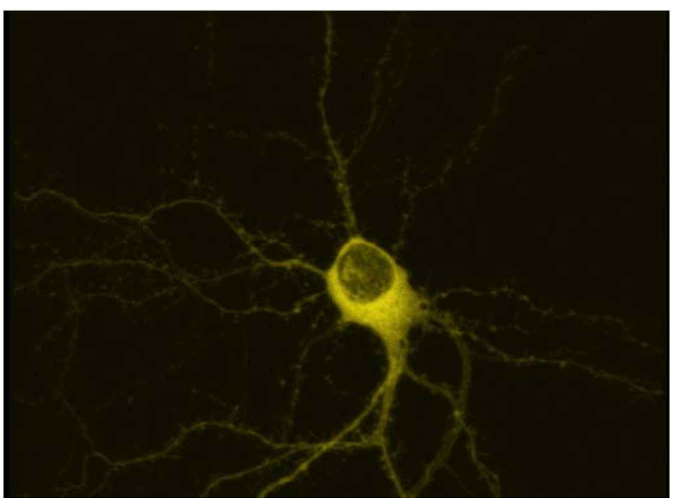
Giving a talk at a scientific conference is a bit like doing a magic trick in front of a bunch of skeptical ten year olds – the audience is constantly trying to spot the invisible strings or the double-sided playing card. At a recent conference in Salt Lake City [1], this skepticism was replaced with 'oohs' and 'aahs', as Professor Ed Boyden revealed a trick that can only be described as scientific magic. He described two protein molecules that can be genetically inserted into brain cells, one which turns cells 'on' when blue light is shone on them, and another which turns cells 'off' when yellow light is shone on them [2,3].

So why was everyone so excited? The brain is a huge interconnected network of neuronal cells, which pass signals to each other in the form of electrical pulses known as 'spikes'. To understand any complex network it really helps to be able to manipulate its components. Imagine trying to understand how the gears of a bike work without being able to shift them up or down, or trying to isolate the broken bulb in a chain of Christmas tree lights – you need to test what happens if you turn the components on and off.

In the brain this is very difficult. Neurons are not only very tiny, but they are all tangled up together and fire patterns of spikes many times a second. In the past, the only way scientists could manipulate neurons rather than just observe them was to stimulate the brain with a metal electrode, encouraging the nearby neurons to fire more spikes. This is fairly imprecise, as it doesn't target individual neurons and is too slow to pick out single spikes.



The new 'light switch' molecules are channels that sit in the membrane of the neuron, opening up when the right kind of light is shone on them to allow specific kinds of charged particles to flow into the cell. The particles that flow in through the 'on' channel cause the neuron to fire a spike, whereas those that flow in through the 'off' channel stop the neuron spiking. Unlike previous advances, this technique is both very specific and extremely quick – the channels can be genetically inserted into individual neurons or types of neuron, and operate in a fraction of a second. Interestingly, these molecules didn't come from a chemistry lab – they were designed by nature. The 'on' channel comes from algae, and the 'off' channel comes from a tiny bacteria-like organism found in the Sahara desert.

One group of researchers who are particularly excited are those trying to understand the 'neural code' – the language of the brain. It's clear that neurons talk to each other via electrical spikes, but we don't really understand what they are saying. Dr Peter Latham, who works on this question, explains; 'One of the reasons it has been so fiendishly difficult to understand the neural code is that all experimental techniques for monitoring the brain are essentially passive: we can observe what the brain is doing, but we can't change the input to local circuits,' This would be a bit like a visitor from outer space trying to learn English just by listening to the radio – unless you can interact with other speakers, it would be pretty much impossible to figure out which bits are words, let alone what the words mean.

Inserting 'light-switch' channels will allow scientists to conduct what Dr. Latham describes as 'dream experiments', in which they can directly manipulate the neural code. For example, one big question is whether *individual*
spikes carry meaning, or whether it's the overall rate of spikes that is important. One 'dream experiment' here would be a game of neural Chinese whispers, in which you use the switches to create a sequence of spikes in one cell, and observe the message it passes on to a different cell. If changing one spike in the original sequence messes up the message that gets passed on, it seems likely that individual spikes carry important information.

The experiments that scientists can do are always restricted by the techniques at their disposal. This new 'light switch' technique promises to open up a whole range of experiments that would have been impossible before, allowing scientists to answer fundamental questions about how the language of neurons is translated into thoughts and actions. Unsurprisingly, intellectual property disputes are already looming – although, unlike magicians, scientists are obliged to reveal their secrets, they still want everyone to know it's *their trick*…

References:
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2. Boyden, E.S. , Zhang, F., Bamberg, E., Nagel, G., & Deisseroth, K. (2005). Millisecond-timescale, genetically targeted optical control of neural activity. Nature Neuroscience, 8, 1263–1268.
3. Zhang, F. et al. (2007). Multimodal fast optical interrogation of neural circuitry. Nature, 446, 633–639.

Louise Whiteley can be contacted at l.whiteley@ucl.ac.uk.

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