How to make a magnetically-controlled mouse

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Córdoba, Spain, 1963. A neuroscientist steps into the bull ring. His name is José Manuel Rodríguez Delgado and he clutches what to our eyes looks like a clunky Xbox controller. The bull charges. Delgado, defenceless, jabs a button, and the bull dramatically skids to a stop.1

Always one for theatrics, Delgado was a pioneer of remote controlling the nervous system.2 After implanting electrodes into the bull’s caudate putamen, an area of the brain involved in movement, he was able to ‘shut down’ the animal mid-charge. Technology for remote controlling brains has advanced since Delgado’s time, but many of the same technical and ethical problems persist. In March 2016, scientists at the University of Virginia unveiled a revolutionary method to control mouse brains using magnets, which could pave the way in future for human mind control.3 By turning on the magnet, the scientists were able to get the mice to do their bidding and become attracted to the magnet’s location. The critters couldn’t get enough of it, they were hooked, stuck there like at a bar during happy hour.

How do you get mice addicted to a magnet? The mice aren’t wearing Black Sabbath t-shirts or made of metal. Instead – and this is where it gets both creepy and clever – the magnet is activating neurons encoding the feeling of reward in a part of the brain called the striatum, the same neurons activated when you do a line of cocaine. In psychological jargon, the magnetic field is inducing an artificial place preference for the magnet’s location by activating particular cells that encode reward – dopamine receptor type 1-expressing striatal medium spiny neurons. Even this mouthful speaks to how specific the magnetic activation is. Whereas Delgado just blindly shocked and scrambled the bull’s brain, this is precision control, like a surgeon controlling a robotic arm. This ability to magnetically control one defined neuron type to induce a specific behaviour is a feat of molecular engineering whose story deserves to be told.

It starts, surprisingly, with blind Scottish fruit flies. By screening thousands of mutant flies, scientists at the University of Edinburgh in 1969 isolated a few blind flies which did not respond to light.4 The mutated gene responsible for their blindness was pinpointed and shown to encode a channel that lets positively-charged ions into the cell in response to light, causing a short-lasting voltage increase. This was the first transient receptor potential (Trp) channel identified, the founding member of the largest family of ion channels known to science, involved in everything from why chilli peppers taste hot to what turns cells into tumours. The Trpv4 member is a jack-of-all-trades which, among other things, lets calcium ions into the cell in response to physical pressure. For example, when cells swell up with water, the stretching and movement of the membrane opens the Trpv4 channel, activating an anti-swelling response. In effect, Trpv4 is a mechanical motion detector.

Now if you stick an iron filing near a magnet what happens? It moves. A compass needle, it turns. A coil, it spins. It sounds obvious, but magnetic fields can move things. This is where the molecular craftsmanship comes in. What if you could use a magnetic field to tug open the Trpv4 channel and turn on a brain cell? You just need to get metal near the channel, apply a magnetic field to rotate the metal, and so flick Trpv4’s mechanical switch. To do this, the Virginia scientists got hold of some ferritin. Ferritin is an unglamorous protein that binds up iron, to this day used as a marker of blood iron levels to test for anaemia. By attaching two ferritin subunits to the Trpv4 gene, the scientists believed
they could make a magnetically activated channel where ferritin-bound iron would move in response to a magnet, unlock Trpv4 and cause the cell to fire.

And thus they conjoined ferritin to Trpv4 twenty one times, testing the new proteins in cultured human embryonic kidney cells, in brain slices, in zebrafish, tinkering, eliminating and optimizing, until they had a protein they were sure could make neurons in the brain fire with just a magnet. They called the protein Magneto 2.0, a nod to the Marvel X-men villain who could control magnetic fields.

The experimenters used a virus to insert the gene coding for the engineered protein into the reward-controlling neurons in the mouse’s striatum. They targeted these cells because previous work using a technique called optogenetics (where light is used to artificially switch on neurons) suggested that activating striatum neurons wasn’t sufficient to create an addiction-like place preference. However, this result could be attributed to the light not reaching all the cells through the thick porridge of brain tissue. By using their new ‘magnetogenetics’ method, the scientists were able to show that magnetic activation of all the striatum neurons carrying Magneto was sufficient to create a place preference for the magnet. They had shown a causal role for these cells in encoding reward, overcoming the disadvantages of already-existing techniques. And all this, using magnets bought off ebay.

Now unlike Delgado the matador’s remote-controlled bull, magnetogenetics is about more than just the spectacle of mind control. For neuroscientists to understand how the brain works, it’s not enough to just record brain cells and watch the correlated behaviour. They need to ask what behaviours are caused by activating and silencing specific neurons. To control mouse neurons with light using optogenetics required the borrowing and rejigging of a light-activated ion channel from algae, as well as the implanting of fibre optic cables into the brain. But magnetogenetics had long been the Holy Grail, as it would allow for non-invasive control. Some scientists thought they could copy-and-paste a magnetically-sensitive protein from migrating bird species that track the earth’s magnetic field – no such protein was found, however. Early studies built magnetic switches which depended on feeding animals magnetically-responsive particles.
Others focused on intriguing applications outside of neuroscience – using magnets to control insulin release⁶ or the shape of developing cells.⁷

But in Magneto the molecular engineers have finally made a single-component, easy-to-use magnetic switch for mind control (though it cannot turn off neurons, only activate them). The question we mustn’t let slip off our lips then is: how long until Magneto works in humans? The virus needed to introduce the Magneto gene into brain cells means it is risky and unlikely to happen until other forms of gene therapy become common. But the big advantage over optogenetics or electrical deep brain stimulation technology is that magnetogenetics doesn’t require hardcore neurosurgery. For instance: today doctors stick electrodes deep into the base of the brain to treat Parkinson’s disease. Instead of bulky implants, we could non-invasively introduce Magneto to the affected areas and use a magnetic ‘pacemaker’ to retune the disrupted firing patterns responsible for Parkinson’s symptoms.

In contrast to Delgado’s overhyped bull experiments, scientists must be clear about the limitations, dangers and ethical quandaries of this magnetic mind control research. While today it would be tricky to use a virus to get Magneto surreptitiously inside someone’s brain, nanotechnology developments in gene therapy might overcome this obstacle, giving governments and corporations the possibility of covertly controlling people’s brains. Insects mind-controlled via electrical implants have already been created for use as drones – you can even buy them as kitchen-table experiments for kids⁸ – so magnetogenetics might one day be exploited for rescue or, more controversially, military operations. The stuff of science fiction this may be, but magnetogenetics is a fast-moving field straddling fact and future. Just weeks after Magneto’s invention was announced, other scientists reported using a different channel called Trpv1 tethered with ferritin to control food-seeking behaviour in mice – a new weight loss fad, perhaps?⁹

But it is in basic science that magnetogenetics will first prove useful. The invention of optogenetics a decade ago ushered in an era of ‘causal’ neuroscience. Neuroscientists were no longer just listening to the brain, they were talking to it and ordering it around. But optogenetics has suffered from the difficulty of getting light through thick tissue and the need for surgical implants. If Magneto can be expressed by any neuron type, we have a way of testing the function of any desired cell type in a non-invasive way. Experts caution that Magneto is not yet optimized, that it has off-target responses to certain chemicals. But this could be solved with a little molecular tweaking.

Neuroscience began in an age of chemistry, using dyes to stain brain cells and drugs to manipulate the brain. In the mid-20th century, improved amplifiers allowed neuroscience to enter an age of electronics, using electrodes to record from and activate brain cells. In the last few decades we embraced an age of light, using glow-in-the-dark proteins and optogenetics to image and manipulate brain cells. Today, in 2016, through ingenious biomolecular engineering, Magneto has given us true mind control and action-at-a-distance, like his old X-men adversary Charles Xavier. Neuroscience has entered the age of the magnet.

The annual Science Communication Competition is open to talented science communicators who can be undergraduate or postgraduate students; both members of the Society and non-members. Entries to the written and video categories must be original works on a molecular bioscience topic and be targeted at the general public. Full details of the competition, including past winners and terms and conditions are available at http://www.biochemistry.org/GetInvolved/ScienceCommunicationCompetition.aspx

References