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Compulsive behaviour triggered and treated

Pulses of light start and stop obsessive grooming in mice.

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Compulsive grooming in mice such as is seen here is regulated in part by a region of the cerebral cortex located behind the eyes, optical stimulation has shown.

Researchers have both created and relieved symptoms of obsessive-compulsive disorder (OCD) in genetically modified mice using a technique that turns brain cells on and off with light, known as optogenetics. The work, by two separate teams, confirms the neural circuits that contribute to the condition and points to treatment targets. It also provides insight into how quickly compulsive behaviours can develop — and how quickly they might be soothed. The results of the studies are published in *Science*[1,2].

Brain scanning in humans with OCD has pointed to two areas — the orbitofrontal cortex, just behind the eyes, and the striatum, a hub in the middle of the brain — as being involved in the condition's characteristic repetitive and compulsive behaviours. But “in people we have no way of testing cause and effect”, says Susanne Ahmari, a psychiatrist and neuroscientist at Columbia University in New York who led one of the studies.

It is not clear, for example, whether abnormal brain activity causes the compulsions, or whether the behaviour simply results from the brain trying to hold symptoms at bay by compensating. “There’s been a big debate in the field,” says Satinder Kaur Singh of Yale University in New Haven, Connecticut, who studies molecules involved in OCD-like disorders but was not involved in the new studies. “What the Ahmari paper shows is that it is causative.”

Off switch

Ahmari’s team wanted to see if optogenetics could prompt repetitive grooming in mice — a commonly used equivalent sign of an OCD-like condition in animal models. The team injected viruses into the orbitofrontal cortex carrying genes for light-sensitive proteins. Certain nerve cells then began to produce the protein and became sensitive to light. The researchers then inserted an optical fibre to shine a light on these cells for a few minutes a day. It was only after a few days that they started to see the compulsive behaviour.

“Beforehand, I thought that we would immediately see repetitive behaviours when the light was turned on,” Ahmari says. Rather, it seemed to be chronic activity in these networks that sets off the abnormal grooming. That could have implications for how these patterns of behaviour develop in humans.

In the second study, researchers at the Massachusetts Institute of Technology (MIT) in Cambridge used a mouse model of repetitive behaviour in which the mice carried a mutation in a gene involved in creating neuronal connections. The researchers conditioned both mutant and control mice to groom when water was dripped on their foreheads. After a series of trials, the mutants began to groom even without a water drop.

The team then used optogenetics to stimulate neurons in the orbitofrontal cortex that feed into the striatum. This is a similar but not overlapping group of cells to the neural circuit studied by Ahmari's team.

“Within a matter of a second or two, a behavioural change occurs,” says Ann Graybiel, who co-authored the MIT study. The abnormal grooming disappeared, leaving behind only the normal reaction to the water drop. “It’s phenomenal to watch,” Graybiel says.

She was doubly surprised that the cortex — the area associated with executive, even conscious control of behaviour — could be at the root of such an automatic response. “Everybody has thought that when we get these compulsive behaviours or really strong habits, then these behaviours reel off by themselves,” she says. Instead, the orbitofrontal cortex can send a ‘stop’ signal to other brain regions concerned with more automatic movements.

Such a rapid relief from symptoms contrasts with how long it took the Columbia team to create the symptoms in their mice. This could have been related to the fact that the types of mice used by the two teams were different, Ahmari says, and that they examined slightly different circuits, albeit within the same broad areas.

Graybiel hopes that the results will help to make therapies for OCD, such as deep-brain simulation with electrodes, more precise.

Ahmari thinks that the findings could be harnessed to help vanquish repetitive behaviours more quickly. She says that knowing how the brain changes over time to create repetitive behaviours could lead to better treatments. Nobody is suggesting, though, that humans should have optogenetic-enabling viruses injected into their brains as a therapy. “We’re not quite ready for that,” quips Graybiel.

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References

1. Ahmari, S. M. *et al*. *Science* **340**, 1234–1239 (2013).
2. Burguière, E., Monteiro, P., Feng, G. & Graybiel, A. M. *Science* **340**, 1243–1246 (2013).