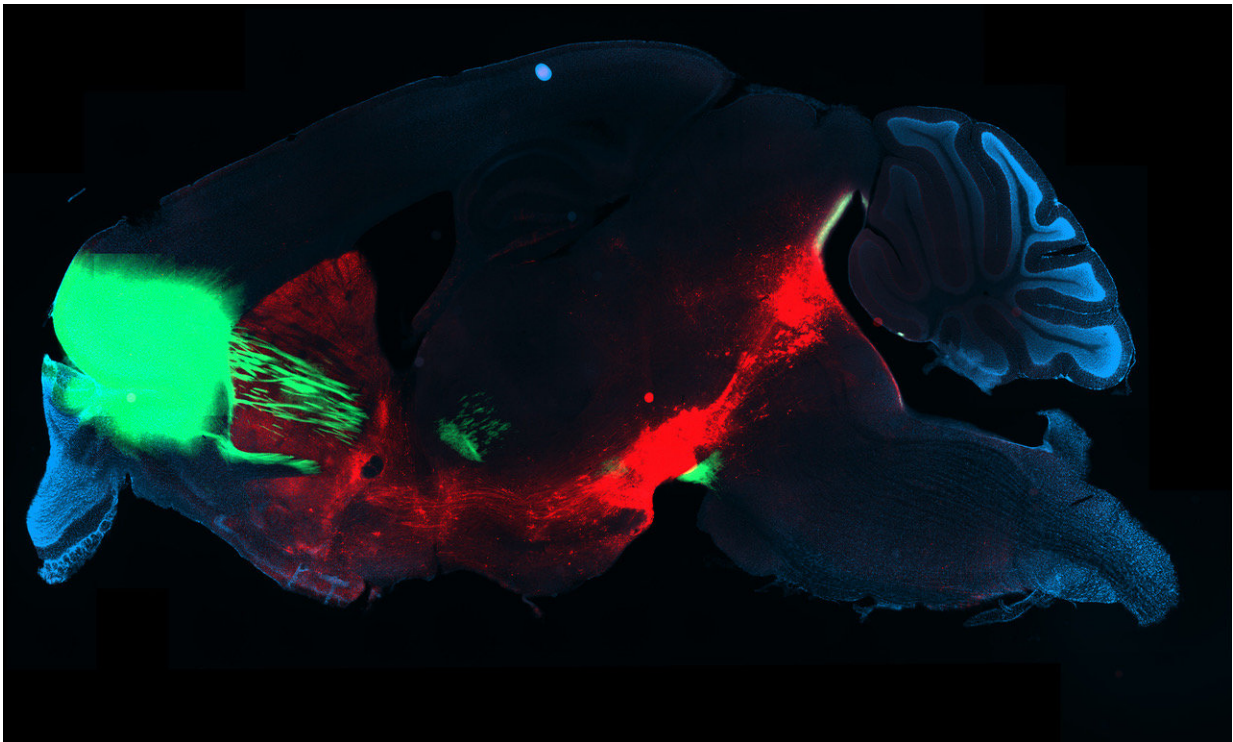


Drugs of abuse: Identifying the addiction circuit

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Section of a mouse brain showing in red the circuit that reinforces the behaviour, in green the circuit that reinforces the decision to continue. If the green projection is very active, the mice self-stimulate their red projection despite negative consequences. They become compulsive. Credit: UNIGE

What happens in the brain of a compulsive drug user? What is the difference in brain function between an addict and a person who takes a

drug in a controlled manner? In an attempt solve this puzzle, neurobiologists at the University of Geneva (UNIGE), Switzerland, have been looking at this difference in a rodent addiction model. They have discovered that the brain circuit connecting the decision-making region to the reward system is stronger in compulsive animals. The researchers also found that decreased activity of this circuit allowed compulsive mice to regain control, and that conversely, by stimulating the connection, a mouse that initially remained in control became addicted. The work is published in this week's edition of the journal *Nature*.

Addiction is a disease that develops in stages. It starts with the initial exposure to a substance followed by a phase where consumption remains controlled. Some individuals, however, will start using drugs compulsively in spite of major negative effects, including mounting debt, social isolation or incarceration. Clinical estimates suggest that only one person in five moves from controlled to compulsive use.

"We do not know why one person becomes addicted to drugs while another doesn't," says Christian Lüscher, senior author and professor at the Departments of Basic and Clinical Neurosciences of the Faculty of Medicine. "But our study identifies the difference in [brain](#) function between the two behaviors."

Negative effects are powerless against addiction

As a model of addiction, the researchers implanted mice with an optic fibre, which enabled the animal to stimulate its reward system, located at the top of the brain stem. Pressing a small lever activated a laser-stimulated molecular switch previously added to nerve cells. These cells are activated by addictive drugs and are responsible for behavioural reinforcement of addiction.

"We then introduce a weak electric shock so that we could observe

which mice continued with the self-stimulation," explains Vincent Pascoli, the study's lead author and researcher in UNIGE's Department of Basic Neurosciences. "This allowed us to identify the mice that had become compulsive." Forty percent of the animals quickly stopped activating the lever following the introduction of the punishment. But 60 percent paid no heed to the negative consequences and continued to stimulate their reward system.

"We used an optical technique to visualize the activity in the brain of freely moving mice. This uncovered a stronger activity in a circuit of addicted mice compared to mice that did not lose control," says professor Lüscher. "The circuit extends from the orbito-frontal cortex to the dorsal striatum, a part of the basal ganglia of the brain." The orbito-frontal cortex, located just above the eyes, is the region responsible for decision-making.

The neurobiologists confirmed that this circuit was responsible for compulsive behaviour by artificially increasing its activity in a mouse that had previously remained in control. The animal quickly developed a compulsive self-stimulation pattern. "Conversely, when we reduced the activity of the circuit in an addicted mouse, she stopped activating the lever," says Pascoli.

Given that the [mice](#) studied in the experiment were all genetically identical, how come the [activity](#) in the [brain circuit](#) was not the same for all of them? "That's the question we'll try to answer in our future research," says professor Lüscher. The researchers present several hypotheses, such as epigenetic contributions based on the [life experiences](#) that make each individual unique and influence the gene and [brain function](#). "Thanks to the present study, we now know which circuit causes the [addiction](#). It will then be easier to find out what causes the disruption in the circuit," says Pascoli by way of conclusion.

More information: Vincent Pascoli et al, Stochastic synaptic plasticity underlying compulsion in a model of addiction, *Nature* (2018). [DOI: 10.1038/s41586-018-0789-4](https://doi.org/10.1038/s41586-018-0789-4)

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