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NEUROSCIENCE

Rewiring the brain

Neuroscientists are learning how to repair neural circuits damaged by addiction.

BY KATHERINE BOURZAC

Neuroscientist Woody Hopf opens a cabinet in his alcohol research laboratory at the University of California, San Francisco. Inside is a cage containing a rat that is being taught addictive behaviours. The rat has been conditioned to press a lever to release a squirt of alcohol when it hears a beep. Hopf closes the cabinet so that the rat will not be distracted by the sights and sounds of human visitors. Just as it takes time for people to undergo the characteristic brain changes that enforce addiction, he says, it will take time for his rat to become dependent on alcohol.

Researchers such as Hopf view addiction as a disease of the brain circuits responsible for pleasure, stress and decision-making. "Addictive substances come at the brain in different ways," says George Koob, director of the US National Institute on Alcohol Abuse and Alcoholism (NIAAA) in Bethesda, Maryland. "But in the end, they're activating some of the same circuitry and patterns of behaviour."

For decades, researchers have been mapping the electrical and chemical circuits that underlie addiction. Now they are working on strategies for healing these neural pathways. Imaging studies show how the brain rewires during recovery from addiction. When combined with studies of how the brain develops during adolescence, the work could help researchers to understand how the brain changes that are characteristic of addiction occur, as well as who is most vulnerable and why. This work is rapidly being translated into treatments. By using electrodes and fibre-optic cables, researchers can intervene in neural circuits with great precision, causing animals to lose their taste for alcohol or their interest in cocaine, not just for days but for weeks or months. This work is now being tested in people. Researchers hope that therapies to heal damaged brain circuits will improve the odds of people overcoming addictions.

CROSSED WIRES

Koob divides addiction into three stages, each with its own brain circuit — groups of neurons or larger structures that interact in a characteristic way (see page S46). Addiction starts with the feel-good binge stage, which is fuelled by the brain's reward circuit, particularly at the nucleus accumbens. Withdrawal brings stress, centred in the emotional amygdala. Finally, craving and compulsion circuits extending from the prefrontal cortex keep someone using a drug, regardless of negative consequences. Impulsive bingeing leads to habits as the user needs the drug to feel normal.

The changes to the brain's circuitry are long-lasting, so people trying to give up will often relapse. Even years after recovery, people often start using again when some cue, such as the smell of alcohol or the site of an old hangout, retriggers old patterns. But the changes are not permanent. "The brain can enjoy some recovery, probably through remodelling to override the broken parts," says Edith Sullivan, an experimental psychologist at Stanford University in California.

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A film on a new treatment for addiction is at:
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Some of the physical damage caused by alcohol misuse can be undone. For example, says Sullivan, the brains of people who have misused alcohol for a long period shrink, but some of that brain volume can be regained by sustained sobriety. There is also some functional recovery — even if the pathways are not fully restored, the recovering brain starts to find workarounds.

Sullivan's group has been using functional magnetic resonance imaging (fMRI) to study cognition in those recovering from alcoholism. A cognitive skill the researchers focused on is spatial working memory — the thinking that helps you to remember where you parked your car, for example. Poor spatial working memory is characteristic of alcohol misuse.

Sullivan's research suggests that people recovering from alcohol addiction manage to work around brain damage; in other words, their brains find ways of accomplishing tasks by avoiding using damaged areas and they start to regain their working memory[1]. The group found that alcohol-dependent people who had been sober for at least a month performed as well as non-alcohol-dependent controls on spatial working-memory tasks, but used a different part of the brain to do it. Sullivan gave them a more abstract task than looking for a lost object

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or a parked car, but like those tasks it required visual processing, which can take one of two broad neural paths. Patients without brain damage typically rely on a 'where' pathway to do the task, whereas those in recovery from alcohol dependence activate a 'what' pathway, which tends to be used for recognizing and identifying what we see.

"The next step is to find out how to train a person with brain damage to use these new pathways," says Sullivan. Encouraging the natural recovery process could help people who are dependent on alcohol to make faster progress. Sullivan compares the brain damage from alcohol addiction to that caused by stroke. "Recovery won't take three days, it may take three or six months, or a year," she says. It takes time for changes to occur in the brain when someone develops a dependence on alcohol, and it takes time to undo that.

Sullivan is currently investigating whether there is a cost to this rewiring. She suspects that people in recovery are performing the cognitive steps needed for these tasks sequentially, so they take longer than people without addictions who do the steps rapidly in parallel. The damaged brain has fewer circuits to use, so the brain finds it harder to multitask.

EARLY START

Our understanding of the addicted brain comes from animal studies and from research on people who are already addicted or are in recovery, such as Sullivan's participants. Researchers can only guess at how these changes develop in people. Henning Tiemeier, a psychiatric epidemiologist at Erasmus Medical Center in Rotterdam, the Netherlands, says that the only way to see these changes is to follow people over time. "There is a lot of debate about how harmful substance abuse is for brain development, and you cannot prove it with one brain image," he says.

Two studies, one planned in the United States and one already underway in the Netherlands, could provide some answers. Both will follow adolescents. The adult brain is already formed, although it is still plastic, which is why alcoholism and drug addiction become so engrained, and why the resulting damage cannot be fully repaired. The worry, says Koob, is that the developing brain may not form properly under the influence of drugs and alcohol. Children do not have the cognitive skills to make good choices, making them particularly vulnerable. "Young people have a well-developed reward system but they don't have a good executive control centre," says Koob. The key part of that centre, in the brain's prefrontal cortex, does not finish developing until about the age of 25.

The US National Institutes of Health (NIH), a federal agency that includes the NIAAA and the National Institute on Drug Abuse (NIDA), is currently accepting proposals for the Adolescent Brain Cognitive Development study, which will enrol 10,000 children aged 10 and follow them into adulthood, using neuropsychological tests, brain imaging and surveys, focused specifically on addiction.

A woman receives transcranial magnetic stimulation, a non-invasive therapy that is being used in Italy to treat cocaine addiction.

Tiemeier is working on the Generation R study in the Netherlands, which has a broader focus on fetal and childhood development and has been following 10,000 children from before birth. The youngest are now aged 9, and the oldest are 12, a stage when some will begin experimenting with cigarettes and alcohol.

Generation R is collecting the first set of brain MRI scans from children in the study, and has about 3,300 so far. By continuing to collect them as the children grow, changes over time will become clear. This is by far the largest brain-imaging study on adolescents in the world, says Tiemeier, so it should provide evidence about how substance use affects the developing organ. He does not expect to see major developmental changes associated with the occasional substance use likely to be found in Generation R because it is a general population study, rather than being focused on people who are addicted to a substance. For this reason, such studies need to be as large as possible if they are to find out what damage drug use does, and how it interacts with puberty, when surges of hormones affect behaviour and brain development.

More information will be available when the Generation R data are combined with results from the NIH study, says Nora Volkow, director of NIDA. These studies will provide a better understanding of the brain changes that reflect what she calls "the skeleton of addictive behaviours". Addiction to cigarettes is different from addiction to heroin, for example, but all addictions have a common neurological framework. These studies will show how it grows. They should also yield insight into who is vulnerable and why, and how they might be helped sooner.

But as further research deepens our understanding of addiction as a disease characterized by changes in the brain, researchers and policymakers need to think about better ways to evaluate medications and therapies, says Volkow. Currently, any pharmaceutical treatment for addiction needs to show that the patient is now completely free of their addiction, which is difficult to prove and takes a long time (see page S53). "Rather than ask for an outcome of complete abstinence, shouldn't we evaluate these treatments on their ability to counteract these brain changes?" she asks.

PAINFUL REALITIES

This focus on reversing changes to the addicted brain is leading to therapy ideas that are showing promising early results in animals. Hopf's rat studies, for example, have led to a potential therapy for alcoholism that is focused on countering the compulsion to use despite negative consequences such as the loss of relationships with family and friends, employment or health. Because rats do not fear these outcomes, Hopf uses simpler analogues. In some experiments, alcohol-dependent rats are given extremely bitter alcohol instead of the expected normal flavour, or in the lever-pressing test they occasionally receive a painful electric shock to their paw. "The rats want the alcohol but they are not happy about it," Hopf says.

After years of painstaking research and some luck, Hopf found that a particular group of neurons in the reward-centred nucleus accumbens has a key role in promoting compulsive drinking. This year, he found that an approved drug called D-serine binds to receptors on these neurons, causing them to fire less often, leading the alcohol-dependent rats to drink less[2]. It seems to work by disabling the compulsive behaviour — by turning off the power to deny painful realities. Rats that experience bitter or painful consequences drink less when given the drug. Rats have no such negative consequences to fear and are not affected by the drug and drink as normal.

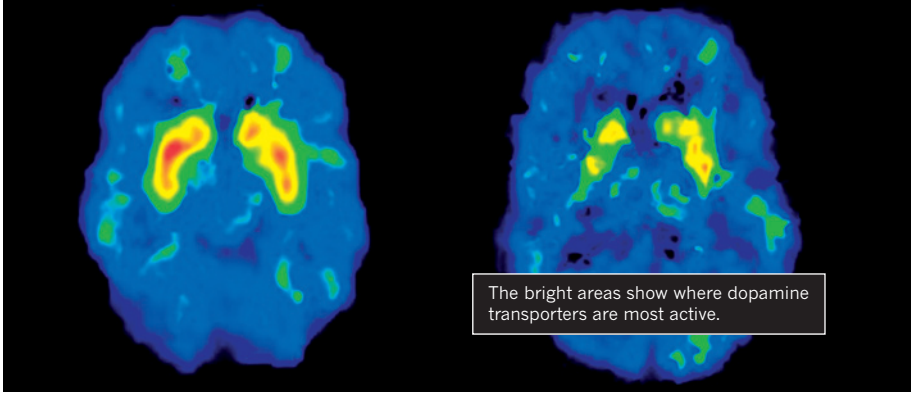
"There is a lot of debate about how harmful substance abuse is for brain development."

The nucleus accumbens and a denial of the reality of the situation are involved in multiple stages of addiction, according to Koob, and have a role in both intoxication and the withdrawal process. Hopf is now writing up a plan for a clinical trial of D-serine.

Other techniques target addiction circuits by using physical interventions, rather than drugs. Researchers at the University of Geneva in Switzerland led by neurologist Christian Lüscher have used a method called optogenetics to target a particular group of cells and receptors involved in cocaine addiction in mice. Optogenetics allows researchers to turn off gene expression precisely by shining light into the brain through implanted optical fibres. When Lüscher's group

METHAMPHETAMINE MISUSE

Brain scans of someone who has never tried the stimulant methamphetamine (left) and of a user (right). Use of the illegal drug affects dopamine transporters in the brain. Eventually, users need more drug to achieve the desired effect. Dopamine is a neurotransmitter that plays a key part in the brain's pleasure pathways.



The bright areas show where dopamine transporters are most active.

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used the method to calm a group of overactive dopamine-receptor neurons in the nucleus accumbens, the mice stopped seeking cocaine[3].

However, optogenetics cannot be used to treat people. The method first requires genetic engineering to render the target cells sensitive to light, and it is not yet possible to safely implant optical fibres in the human brain.

STIMULATING RECOVERY

Instead, Lüscher's team is attempting to emulate the effects of optogenetics by using methods that translate better to the clinic. They are developing a variation on deep-brain stimulation (DBS), a technique that uses an electric current to silence overactive neurons, which is commonly used to treat movement disorders such as Parkinson's disease. By careful placement of the electrodes, clinicians can target DBS to a particular region in the brain. Researchers have tried using it to treat addiction in people, but results have been mixed.

Lüscher is combining DBS with drugs to block particular receptors in the rat brain, making it possible to silence specific cell types. First they implant an electrode in the nucleus accumbens. Then they use a drug that blocks the neurons' dopamine receptors. Finally, they switch on the electrode for ten minutes. The effects of DBS for treating Parkinson's are transient: when the electric field is turned off, the tremor returns. But Lüscher's combined therapy had a longer-lasting effect[4]. After 10 minutes of stimulation, the rats exhibited normal behaviour for the following 21 days. Lüscher thinks this means that the treatment may be repairing part of the circuit that was damaged by addiction. He says that the group's next step will be to test this approach in primates, or possibly take it to clinical trials.

This demonstration of an apparently long-term reversal of drug-related behaviour is "a miracle", says Jessica Wilden, a neurosurgeon at the Louisiana State University Health Center in Shreveport. Could this lead to a therapy in which you give a patient a pill and a day of brain stimulation and then they are drug free? "In a small way that's what they're showing," she says. But doing it in people will be harder, she warns.

Wilden is investigating whether DBS can be used to treat methamphetamine (meth) addiction. Meth affects dopamine receptors (see 'Methamphetamine misuse') and is a growing problem, particularly in Iran and in the southern United States, often for military veterans. Unlike other drugs, which tend to be misused mostly by men, meth use is equally common in women, and has a burden on children because women tend to be the primary caretakers, says Wilden.

> *"It's up to us to figure out who's getting better and why, and how many sessions it takes."*

"I'm trying to set up a stable model of meth abuse, abstinence and relapse in rats, and then try DBS treatment," says Wilden. It is a huge challenge. The drug is a potent stimulant, with effects lasting for 16–20 hours in the rats; the animals become agitated and stressed, and get tangled up in the equipment used to administer the drug and the cables that connect them to the DBS system.

Although DBS is a helpful research tool, Wilden and Lüscher both doubt whether it can be widely used to treat addiction — and Wilden's work with meth illustrates the difficulties. The therapy is expensive, invasive and requires patients to care for the implants and to return to the clinic for regular follow-ups. Those motivated to overcome alcoholism might be able to do it. But people with more destructive addictions, particularly to meth, are less cooperative and have high rates of homelessness, making the treatment even less suitable. "The deep-brain stimulator is a pacemaker, with wires going under the skin into the chest where they connect to a battery," says Wilden. "That's a lot of metal, especially in people who are fragile. There's no way I can implant this in someone living on the streets."

Lüscher and Wilden plan to validate their interventions with optogenetics and DBS in animals, and then adapt the results to clinically realistic techniques. The most likely candidate is transcranial magnetic stimulation (TMS), which uses a magnetic field to stimulate electrical activity in neurons deep in the brain. One advantage is that TMS is non-invasive: treatment simply involves wearing a magnetic helmet for a few minutes. It is currently used to treat depression and migraines.

So TMS is more patient friendly, but it is also more mysterious — researchers do not know why it works. Furthermore, it has poor spatial precision, which frustrates neuroscientists who want to target specific brain locations. But this might not matter, says Antonello Bonci, a clinical neurologist and scientific director at NIDA.

In 2013, Bonci published a paper describing how his team had used optogenetics to reactivate an area of the prefrontal cortex that was abnormally quiet in cocaine-addicted rats[5]. The treated rats lost interest in pressing a lever to get cocaine. A few months later, Luigi Gallimberti and Alberto Terraneo at the University of Padova in Italy started using TMS to target the equivalent area in the brains of people addicted to cocaine. They have since been successfully using the technique to treat such people.

Bonci says that the results are anecdotal, but exciting: most people who stuck with the treatment for a few weeks have now been clean for several months, and testify that they do not even think about cocaine any more, he says. With this black cloud lifted, they are able to enjoy food, sex, reading, family time and all the other good things in life. Bonci is now working with the Italian group to design a double-blind clinical trial, and is collaborating with another group to work out how the TMS works. "It's up to us now to figure out who's getting better and why, and how many sessions it takes," he says.

In addition to TMS, the Italian patients also received supportive medical care and psychological therapy. Even with brain stimulation or medication, people still need emotional support, as well as therapy "to identify triggering cues and memories, and practise making new grooves of thought", says Hopf. But with tools such as DBS and TMS, neuroscientists' deepening understanding of the circuitry of addiction is now being translated to the clinic much more rapidly than ever before.

"For the first time in the history of neuroscience, we can think about translating basic science to the clinic in months, as opposed to the 15 years it can take for drug development," says Bonci. Thanks to the new technologies, he says, "we're close to a treatment". ■

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