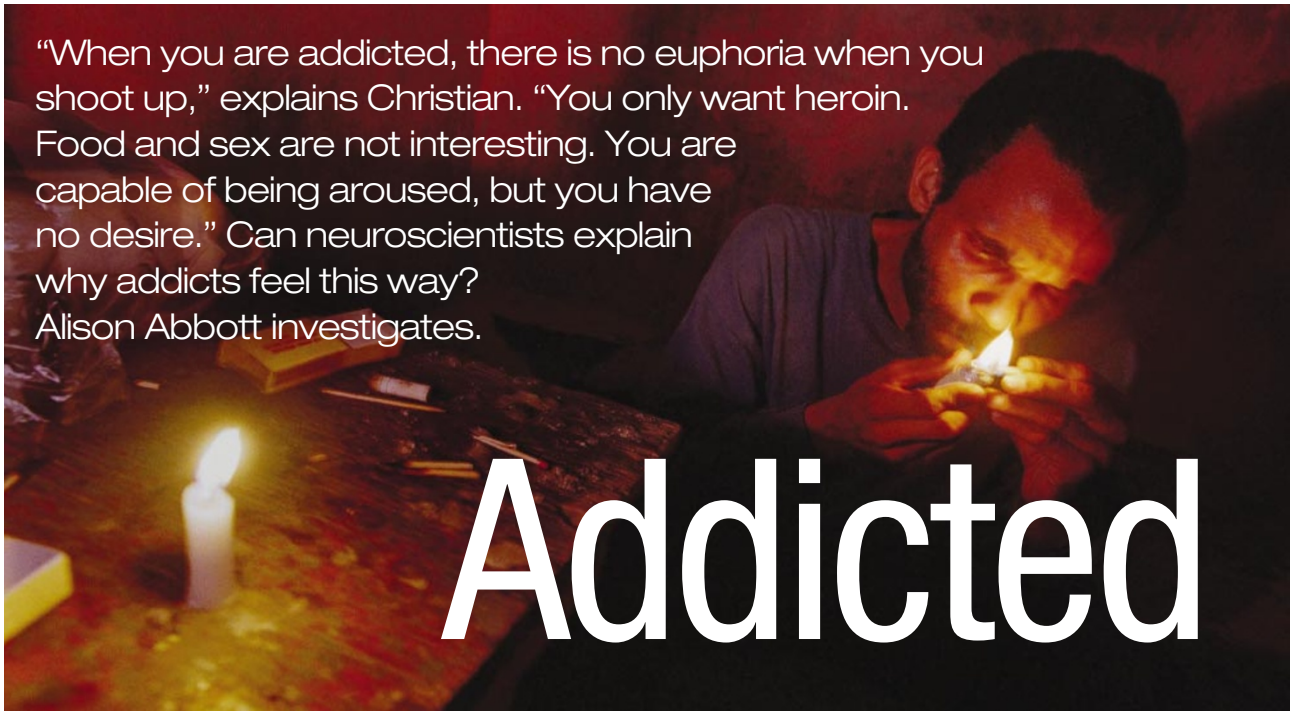


T. VAN HOUTRYVE/AP

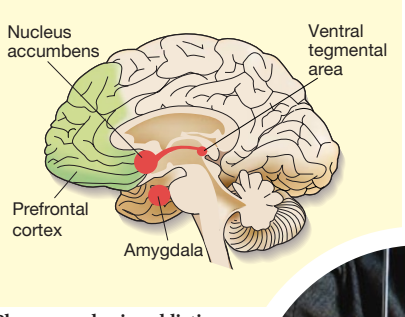
"When you are addicted, there is no euphoria when you shoot up," explains Christian. "You only want heroin. Food and sex are not interesting. You are capable of being aroused, but you have no desire." Can neuroscientists explain why addicts feel this way? Alison Abbott investigates.

Addicted

Christian, a heroin user from Munich, is proud to have been clean for two weeks. Like all reformed addicts, he has a story to tell. Most talk of how drugs are seductively rewarding at first, yet how the craving that follows has little to do with pleasure. But despite these common responses, there are big holes in our knowledge of addiction. Although researchers understand part of the neural circuitry involved, they know little, for example, about what changes in people's brains as they turn from recreational users into addicts.

To provide answers, neuroscientists are embarking on a new generation of experiments. Armed with sophisticated brain-imaging machines, researchers have launched a hunt for the neural signatures of behaviours linked to drug-taking, and are trying to correlate them with specific genes. To do so, they will have to work with much larger numbers of addicts — and their families — than previous studies have done. But if successful, they could help to fill the largest gaps in our understanding, such as why some people become addicted to drugs whereas others don't. They may even shed light on the biggest question of all: will neuroscientists ever be able to offer a cure for addiction?

The anatomy behind the initial drug high is already reasonably well understood, thanks to a series of ground-breaking experiments conducted by psychologist James Olds at McGill University in Montreal and the University of California, Los Angeles, during the 1950s. Olds inserted electrodes into the brains of rats, and allowed the rats to stimulate a particular brain area electrically by pressing a lever. The rodents liked doing it so much that they neglected to eat or drink[1].



Pleasure and pain: addictive drugs administer their effects to different parts of the brain.

The rats were exciting the mesolimbic dopamine system, an area now also known as the 'reward circuit'. This circuit consists of the ventral tegmental area, part of a region at the top of the spinal cord called the brain stem. Cells here send projections to higher emotional and cognitive areas, including the nucleus accumbens, a knot of neurons in the limbic, or emotional, brain (see diagram, above). Neurons throughout the system exchange signals by releasing a chemical called dopamine, which excites neighbouring neurons by binding to receptors on their cell membranes.

The reward circuit is part of the primitive motivational system in mammals, the normal function of which is to ensure that important behaviours such as eating and having sex are perceived as rewarding, thus increasing the likelihood that they will be repeated. Sweet tastes, for example, feed into the circuit through dedicated taste receptors on the tongue, which send signals to the brain stem. A caress activates the system through sensory receptors in the skin.

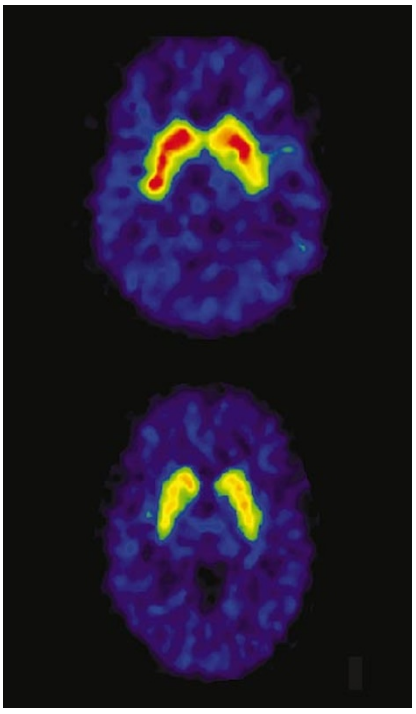
But addictive drugs activate the circuit directly, and with dramatic effect. Cocaine blocks the protein that removes dopamine from the space between neurons, whereas amphetamines stimulate dopamine release. Heroin and nicotine activate the circuit by binding to other, non-dopamine receptors on neurons, although how these receptors interact with the dopamine circuitry has not been worked out in detail. But whichever way they function, all drugs work by raising levels of dopamine in the nucleus accumbens to unnatural highs, and at unnatural speeds.

P. BRONSTEIN/GETTY NEWS

As work in animals has shown, drugs hit the mesolimbic dopamine system like a sledgehammer. "A natural rewarding activity such as sex or food will increase dopamine levels in the nucleus accumbens by 50–100%," says Roy Wise, a psychologist who pioneered research into reward circuitry and is now at the National Institute on Drug Abuse in Bethesda, Maryland. "A dose of cocaine or amphetamine can increase it by up to 1,000-fold."

Imaging studies show that drugs also activate the reward circuit in humans[2], but this is far from being the whole story of addiction. Addicts say that a stubborn craving for their drug develops, which is unrelated to its initial euphoric effects. "Pleasure is not what drives drug intake once addiction has kicked in, as any addict will tell you,"

N. VOLKOW



Nora Volkow, seen at her PET scanner (right), has shown that a methamphetamine addict's brain (above, bottom) has smaller numbers of a specific dopamine receptor than normal.

agrees Nora Volkow, a neuroimaging pioneer at Brookhaven National Laboratory on Long Island, New York, who has worked with addicts for 20 years.

So what happens to the brains of drug users as this change takes place? Researchers agree that drugs must cause long-term changes, although the details are far from clear. Some evidence comes from cell-culture experiments and animal studies of several brain areas, including the reward circuit[3]. Both techniques have shown that prolonged administration of drugs alters gene expression, which leads to abnormal protein production. In addition, there is a fall in the density of the neurons' dendritic spines, the protrusions that act as sites for the junctions between cells.

Poor reception

The number of dopamine receptors in the reward circuit also changes. In 1997, Volkow described how she used positron-emission tomography (PET), which traces the movements of molecules tagged with a radioactive isotope, to study dopamine receptors in the reward circuits of methamphetamine and cocaine[4] addicts. She found that the addicts had a lower level of one type of receptor, and that this reduction persisted for up to four months after they stopped taking the drug. "We haven't been able to continue a study for more than four months because addicts have usually relapsed by this time," she notes. Taking cocaine may still elevate an addict's dopamine levels, says Volkow, but the reduced number of receptors prevents the drug from working its magic.

As well as tracking the changes that underlie addiction, researchers are probing the involvement of learning and memory. On the everyday level, we are used to links between memories and rewards. A whiff of cocoa can prompt a craving for chocolate, for example, and addictive drugs can forge stronger associations. Months or years after an addict is clean, craving can be reawakened by the sight of a needle or a visit to old haunts.

But only tentative hints exist about how these associations are learned. Cocaine and nicotine, for example, are known to alter the strength of connections between neurons — a phenomenon associated with learning — in the nucleus accumbens[3]. And several researchers have used imaging studies to show that drugs activate parts of the prefrontal cortex (PFC) — a complex structure at the front of the brain — that are involved in learning and laying down memories.

The involvement of this and other parts of the PFC has led to different theories about the development of addiction. Volkow is one of several researchers who have shown that the orbitofrontal cortex, part of the PFC, is consistently activated by drugs[5]. If a mild stimulant is used to induce craving in addicts, the extent of activation in this area also correlates with the intensity of craving. Volkow points out that the orbitofrontal cortex is dysfunctional in psychiatric disorders that are characterized by obsessive behaviours, and suggests that a similar dysfunction could underlie the obsession that addicts have with drugs. And Edythe London of the University of California, Los Angeles, thinks that problems with the PFC's decision-making function are important in addiction, as addicts seem to lose their ability to weigh up advantages and disadvantages in their drug-seeking and drug-taking behaviours[6].

But if such ideas are to be evaluated, new kinds of experiments will have to be devised. Physiological measures of addictive behaviour need to replace current methods, which rely on asking addicts about their feelings. And to understand why only some drug users become addicted, researchers will have to find a way of getting a handle on the genes involved, which means studying larger numbers of addicts and their families.

Cerebral snapshots

In the United States, new technology provided by the White House's Counterdrug Technology Assessment Center, which oversees the research programmes of the federal drug-control agencies, has kick-started such experiments. The centre is equipping the top US drug-addiction laboratories — about a dozen have so far been selected — with state-of-the-art imaging equipment, including PET and functional magnetic resonance imaging (fMRI) machines. PET machines generally provide the best spatial resolution, but can take up to two hours to complete a reading. Using fMRI, which tracks neural activity by monitoring blood flow in the brain, readings can be taken in minutes.

The machines underpin a new technique that could improve the way in which the mental states of addicts, and of those suffering from other psychiatric disorders, are measured. Over the past couple of years, neuroscientists have used imaging

techniques to search for endophenotypes, standard physiological responses that are observed in subjects carrying out particular mental tasks. The approach has already thrown light on the biology of depression.

Wayne Drevets of the National Institute of Mental Health in Bethesda has studied neural responses to sad faces, which are known to activate the amygdala, a brain area that is involved in processing negative emotions. Using PET scans, Drevets found that the response of the amygdala in depressed people continued unabated after several exposures to the sad face, whereas that of a control group wore off[7]. As the endophenotype — activation of the amygdala — was similar for all depressed subjects, Drevets hopes that it can be used as a potentially more accurate alternative to the standard list of psychiatric criteria that are currently used for diagnosis.

The hoped-for precision of endophenotypes could also make it much easier to identify genetic links to mental conditions. Proof of principle has been provided by Daniel Weinberger and Michael Egan, also of the National Institute of Mental Health, who have worked with an endophenotype for one of the cognitive deficits associated with schizophrenia — an abnormal activation observed in the prefrontal cortex of schizophrenics performing a memory test.

Genetic links

Last year, Weinberger and Egan showed that the presence of the endophenotype in schizophrenics and their relatives is linked to the gene that encodes an enzyme — catechol-*O*-methyltransferase, or COMT — that breaks down dopamine. The gene comes in two forms, one of which encodes a more active version of the enzyme. Weinberger and Egan found that subjects who displayed the endophenotype were more likely to have a higher proportion of the gene for the more active enzyme[8]. The effect was slight — equivalent to a 1.5% increase in risk of schizophrenia — but the association had not been picked up in studies that used less precise classical diagnostic criteria, despite the knowledge that schizophrenia is caused by dopamine dysfunction.

Neuroscientists now hope that the same approach could provide a clearer understanding of the genetics and neurobiology of addiction. Hans Breiter of Harvard Medical School, together with Harvard neurogeneticist Greg Gasic, plan to develop addiction-related endophenotypes for tasks associated with reward, for example. Breiter has received a fMRI machine that can produce a very powerful 7-Tesla magnetic field, which improves spatial resolution, from the counterdrug technology programme. "Having a 7-T fMRI machine — the most powerful machine available for human work — will be extremely valuable for this," says Breiter. "The fine resolution will allow us to pinpoint areas of activation in the brain much more accurately."

Greg Gasic (left), Larry Wald and Hans Breiter (at back) plan to seek out genetic clues to addiction.

Breiter and Gasic will begin by focusing on endophenotypes that should shed light on how activity in the reward circuit may be altered in addicts. They will use a series of tasks, which they believe could activate different parts of the reward circuitry[9]. These tasks will measure, for example, evaluation of social stimuli and response to monetary reward. In the latter task, for example, subjects will be scanned while watching a roulette-like wheel spinning and then stopping, and then learning whether they have won or lost a dollar sum. By comparing addicts and non-addicts, the researchers aim to pin down exactly how brain activity in the two groups differs in response to the various outcomes. "Asking drug addicts to report their feelings subjectively is too imprecise," says Breiter. "Endophenotypes are going to be more helpful than subjective description of feelings, or even objective behavioural descriptions."

Daniel Weinberger has found a genetic link to schizophrenia.

In the initial stage of the project, a few hundred nicotine and cocaine addicts will be scanned to validate the endophenotypes. Next, up to 5,000 addicts and non-addicted members of their families will be studied to see whether the endophenotypes are heritable. Finally, a large, multicentre study will be launched, based on these heritable endophenotypes, to identify genes that may predispose people to addiction.

The approach of the collaboration will be very much 'top-down'. Instead of looking for candidate disease genes as in Weinberger's 'bottom-up' approach, the consortium will look for single-nucleotide polymorphisms — changes of a single letter in the genetic codes of different versions of the same genes — that are associated with the addiction endophenotypes. The approach will allow the researchers to search for links to the multiple genes that are expected to be involved in susceptibility to addiction — and also to spot unexpected links to genes that current theories do not flag up as likely to be important.

But it also means that much greater numbers of subjects are likely to be needed if trends are to be spotted amid the normal genetic variation of the population. Tens of thousands of people could eventually be required. "Our strongest challenge will be to scale up the pace at which we do high-throughput neuroimaging," says Breiter. Most fMRI studies have been conducted with a few dozen, not a few thousand, subjects. This means that more computational infrastructure will be needed, as well as a massive step-up in computing power, which Breiter hopes that the counterdrug programme will also support.

The work of Breiter and his colleagues will take many years to deliver answers about susceptibility to addiction. But thanks to the increased availability of high-resolution brain-imaging machines, addiction researchers should, in the meantime, begin to clarify what they mean by terms such as 'reward' and 'craving'. Whether a cure for addiction will follow is anyone's guess, but a better knowledge of the brain mechanisms involved will certainly be an important step towards that goal. As the old adage goes — understand the biology and you'll know where to target your medicine. ■

Alison Abbott is *Nature*'s senior European correspondent.

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White House Counterdrug Technology Assessment Center
www.whitehousedrugpolicy.gov/ctac