

# BRAIN MECHANISMS OF REWARD AND ADDICTION

TREVOR.W. ROBBINS

Department of Experimental Psychology, University of Cambridge

Many drugs of abuse, including ‘stimulants’ such as amphetamine and cocaine, opiates such as heroin, cannabis and even ‘legal’ drugs such as alcohol and nicotine share common features in their mode of action on ‘brain reward’ mechanisms. Although each of these drugs has a unique molecular target (receptor), and can therefore mimic the actions of several different chemical neurotransmitter systems in the brain, these primary effects of each drug have been shown to influence, directly or indirectly, the activity of a group of nerve cells that use the chemical messenger dopamine. The nerve cells in question are located in the midbrain and send their projections to interconnected forebrain structures including the prefrontal cortex, the so-called ‘limbic system’ and the striatum.

In studies of animals self-administering drugs (which they do in a manner that is indistinguishable from humans), a ventral region of the striatum, the nucleus accumbens, was found to be the key zone for mediating the rewarding effects of drugs such as amphetamine and cocaine, which directly potentiate dopamine neurotransmission in this structure. Depletion of dopamine from the nucleus accumbens in experimental animals lessened the intravenous self-administration of amphetamine and cocaine, presumably because these drugs had lost their rewarding (or reinforcing) properties. Another key finding was that rats would also self-administer morphine directly into the vicinity of the dopamine cell bodies in the midbrain (where there are many opiate receptors) and that this was associated with marked increases in dopamine in the nucleus accumbens. *In fact, a common effect of stimulants, opiates, cannabis, nicotine and alcohol is to increase dopamine levels in the nucleus accumbens, leading to the hypothesis that the mesolimbic dopamine system has a general role in the reinforcing effects of drugs, perhaps stemming from a more general role in mediating natural rewards.*

Recent studies in healthy human subjects using brain-imaging techniques have shown marked changes in blood flow and dopamine receptor activity in the striatum, not only following administration of cocaine or cocaine-like drugs, but also in response to the expectation of monetary reward. Thus, a popular conception of why people first abuse and then become addicted to drugs is that they increase the activity of a common reward system in the brain, the mesolimbic dopamine system: this is often called a positive reinforcement or incentive view of addiction to drugs, which can be contrasted with a negative reinforcement view that focuses on escape from aversive withdrawal symptoms as primary. Our own view is that drug addiction can best be understood as a pathological subversion of normal brain learning and memory processes, strengthened by the motivational impact of drug-associated stimuli, which leads to the establishment of compulsive drug-seeking habits.

## SUMMARY

- Statistics for drug abuse in the UK suggest that cocaine and heroin represent a growing problem. *However, drug abuse is not a simple problem, and abuse of different drugs fluctuates from year to year. It is also difficult to categorise drug abuse precisely because polydrug abuse is the norm.*
- We understand a good deal about how these and other drugs of abuse work in the brain, mainly from experiments with animals.
- In humans the animal data are confirmed by studies using brain-imaging techniques.
- There is probably a common 'reward system' which many, if not all, drugs of abuse appear to influence.
- This reward system includes the nucleus accumbens and the release of the chemical messenger dopamine in this brain structure.
- Drug abuse, addiction and dependence can be considered as aberrant forms of learning, possibly with distinct stages.
- This aberrant learning is controlled by brain structures that interact with the nucleus accumbens such as the amygdala, hippocampus and prefrontal cortex.
- The aberrant learning component of addiction also represents a target for novel treatments (both pharmacological and psychological).

## CONCLUSION

- Some areas of the brain, such as the nucleus accumbens, are sensitive to natural (food, sex), conditioned (money) and artificial (brain stimulation, drugs of abuse) rewards: i.e. drugs may usurp or hijack natural reward mechanisms.
- Drugs with apparently different molecular actions may act on the mesolimbic dopamine pathway for their rewarding effects.
- Central to understanding drug addiction is the question of how chronic drug exposure affects the brain and how it responds to this.
- Conditioning mechanisms contribute importantly to addiction and these recruit and devolve control to other brain regions.

## QUESTIONS & ANSWERS

### **The basis of addiction proposed here is a common neural pathway on which drugs act. Why then do some drugs have more addictive potential than others?**

Drugs vary in their capacity to affect this common system. Nicotine is less active on dopamine pathways than cocaine or amphetamine, but is addictive. All drugs may affect this common system but also have effects on other pathways. While dopamine action is part of it, other brain areas and neurotransmitters certainly mediate as well.

### **Why does the use of crack cocaine result in addiction very quickly, whereas long-term use of powder cocaine often does not?**

The rate of access of the drug to the brain is a very important factor in how addictive that substance is. Learning works best when two events happen in close proximity in time. If there is a temporal delay between a stimulus and a reward, the association between the two is much weaker. Crack cocaine has a very fast rewarding action, so there is an extremely strong association between the taking of the drug, the paraphernalia associated with it and the rewarding high. Therefore, because of the immediate feedback, crack cocaine is very potent, enhancing the conditioned stimuli (which become cues for drug-taking) through increases in dopamine in the nucleus accumbens.

### **Is gambling addiction real, or just a sloppy definition?**

All addictive behaviours are likely to activate similar parts of the brain. Often we tend to indulge in one single reward to the exclusion of others, although many drug addicts abuse more than one substance. Other behaviours resemble drug addiction with respect to engaging in repetitive activities, but are not identical. For example, obsessive-compulsive disorder is characterised by an increase in the amount of time spent repeating one activity.

### **Why should the majority of people not seek to maximize their pleasure?**

We all seek to maximize dopamine in the nucleus accumbens. Dopamine is like money, it's a basic reward. However, with most people the realisation of the long-term consequences inhibits the taking of immediate reward.

### **Why do addicts find it so hard to modify their behaviour in the light of its obvious long-term consequences?**

The brain mechanisms underlying addiction involve the uncoupling of immediate reward from longer-term consequences. Rats with lesions of the nucleus accumbens will choose small immediate rewards rather than larger delayed ones. Damage to this mechanism leads to a 'here and now' impulsivity. They have lost the ability to mediate delays via learning, so do not think of long-term consequences when making decisions. Similar damage in human drug addicts may result in them choosing short-term highs and failing to take into account the long-term consequences of their drug taking.

### Why are humans on the whole able to moderate other types of rewarding behaviours, but often cannot control their compulsion to use drugs?

The great majority of people *can* control their drug-taking, as they do with natural rewards. Others have a lack of control even with natural rewards such as food and sex. Individual variability and genetic predisposition help to explain why some lose control. One brain region implicated in addiction is the frontal lobes that help to regulate the action of the nucleus accumbens. If people are impaired in frontal lobe functioning to start with, there may be an increased probability of becoming addicted. However, the toxic effects of drugs may also target frontal areas and, therefore, drugs may further enhance the drug-taking behaviour through degradation of control mechanisms. Amphetamine addicts often have changes in the frontal cortex that are associated with a loss of self-control.

### If both drug and natural reinforcers use the same reward pathways and involve learning, how then can we erase only drug-related memories and not other essential memories?

Reconsolidation is the ability to reactivate memories using reminder cues. It may be possible to activate certain memories using specific cues and then attempt to eliminate these selectively, without damaging an otherwise essential reward system. Protein synthesis encodes and updates memories so we are able to remind a rat of a specific memory and then give protein synthesis inhibitors only when that memory is active. In this way, it is possible to create amnesia for only the specific conditioned stimuli, leaving other reward stimuli intact.

### Could there be therapeutic uses for drug action?

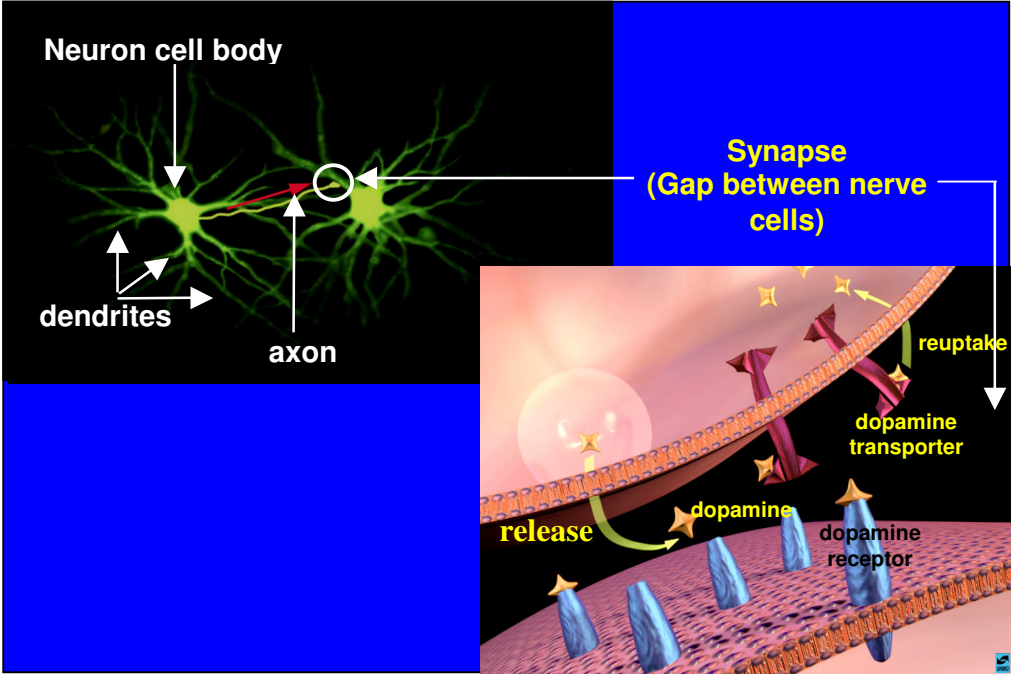
Rehearsing movements can increase plasticity in the brain and cause restitution of damaged areas and/or recruitment of adjacent areas after stroke or head injury. Drugs can strengthen the impact of rehearsed actions, so may be used therapeutically to increase plasticity after damage. There is some evidence that amphetamines can help stroke patients recover, enhancing the rewards gained when movements are rehearsed, and thus reinforcing behaviour.

#### Illicit Drug Use in the UK: 2000.

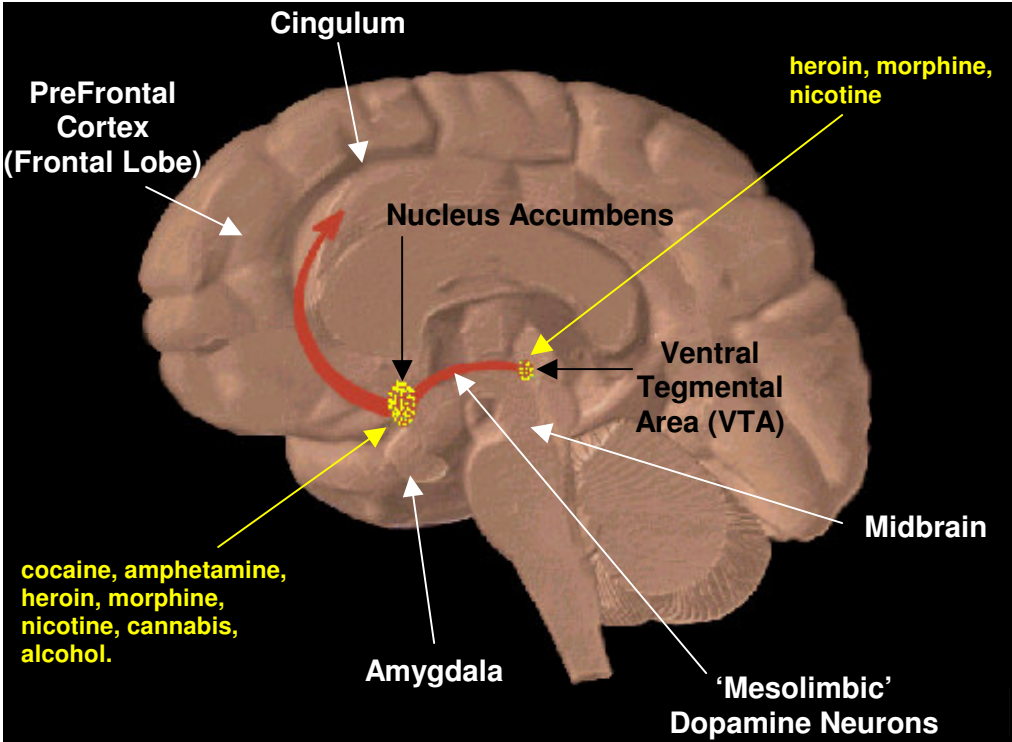
Drug	No. of Users	Annual Value	Popularity
Crack cocaine	210,000	£1,870m	Growing
Heroin	295,000	£2,313m	Growing
Ecstasy	432,000	£294m	Static
Amphetamines	967,000	£258m	Falling
Cocaine*	476,000	£352m	Growing
Cannabis	3,100,000	£1,577m	Static
Total	5,480,000	£6.6bn	

*\*Use of Cocaine, 16-24 Year olds, up from 1 to 5% between 1994-2000*

Source "Drug misuse declared in 2000: Results from British Crime Survey" (Independent 22/9/2001)



Dopamine Action at the Synapse



Dopamine Reward Pathway Common to All Drugs