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Drugs in focus 19

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Neurobiological research on drugs: ethical and policy implications

Drug addiction is a behaviour characterised by the individual exhibiting a loss of control over their consumption. Addicts may wish to stop, but find it difficult to do so, despite often experiencing negative consequences. Modern developments in neurobiology help us to better understand this process. Moreover, such developments now provide strong scientific grounds for viewing drug addiction as a psychiatric disorder, usually classified as a 'chronic and relapsing brain disease'.

Most neurobiological research on addiction has focused on the role a drug-released neurotransmitter called dopamine has on the repeated activation of the 'reward system'– circuitry made up of a complex set of cerebral structures which act as a barometer, indicating a person's physical and psychological state. Spurred on by recent technological developments occurring rapidly in this field, new models have arisen which take into account the implication of other neurotransmitters in the process, also exploring the role of genetic differences between individuals. By providing a better understanding of how addiction develops, this research may provide the basis for new psychological and pharmacological treatments and prevention strategies. The findings so far are encouraging, but their implications can easily be overstated or misunderstood, and also raise a number of important ethical issues that require careful consideration. This paper provides a summary of the key developments in this area and underlines the fact that any potential new approaches will require rigorous evaluation for safety and efficacy before being introduced into routine practice.

Definitions

Neurotransmitter: a chemical produced and released by neurons. Some of these molecules (GABA, glutamic acid) participate in the communication between neurons; some others (dopamine, noradrenaline, serotonin) modulate (amplify or attenuate) the information.

Reward system: this brain circuit reinforces behaviour when activated. Data indicate that drugs of abuse are pleasurable because they activate this system.

Key issues at a glance

1. Neurobiological research tries to understand how addictive drugs produce neurochemical changes in the brain's reward pathway, making their use appealing and producing a drive to use them repeatedly.
2. A growing body of research suggests that chronic drug use can produce long-term disruptions in the modulation of neurocognitive circuits involved in motivation and attention, decision-making and the ability to inhibit impulses.
3. Neuroimaging and genetic technologies may help to define more precisely intimate mechanisms of addiction and to identify individuals who have a vulnerability to develop addiction, potentially allowing interventions to be targeted at those at greater risk.
4. Novel pharmacotherapies targeted at specific neurotransmitter systems, pharmacological drug implants, drug vaccines or neurological treatments may have the potential to ameliorate addictive behaviours.
5. Neuroscience and genetic research promise to provide a detailed causal explanation in terms of brain processes. However, causal, or over-simplified models of addiction could also potentially lead to more coercive policies towards addicted individuals, the neglect of important social policies, or undermine support for existing proven approaches to drug treatment.
6. There is a pressing need to explore the ethical and policy implications of addiction neuroscience research to ensure that developments are taken forward in ways that adequately safeguard human rights and protect the ethical values of consent, liberty, equality and privacy.

1. Neurobiological research in addiction

Almost all drugs known to induce abuse or addiction in humans increase the release of a neurotransmitter called dopamine in a sub-cortical structure, the nucleus accumbens. The cell bodies of neurons which release dopamine are located in the ventral tegmental area and the substantia nigra (see figure). These dopaminergic neurons form the meso-corticolimbic pathway. They stimulate different cerebral structures, such as the prefrontal cortex, the amygdala and the hippocampus, which are part of a circuitry called the 'reward system'.

Most neurobiological models of addiction argue that, because drugs of abuse release dopamine and activate the reward system, addiction is due to a modification of kinetic reactions and increased dopamine release. This dysregulation would correspond either to an increased reactivity of dopaminergic neurons to specific stimuli linked to the pleasurable and addictive product or to a down-regulation of dopamine signalling and a dampening of activity in the reward pathway. In natural situations, dopamine is released when a rewarding experience is new, better than expected or unanticipated. This release of dopamine helps the individual to memorise signals announcing a reward. Hence, when the dopamine system becomes over-aroused by drug use, pursuit of the repetition of these effects can dominate other important, goal-directed activities.

2. New models in the neurobiology of addiction

Some recent studies suggest that, despite the critical and unquestionable role dopamine plays in reward, drugs of abuse may not necessarily induce addiction via a direct effect on dopaminergic neurons. There is some evidence that dopamine acts downstream to two other neuromodulators, noradrenaline and serotonin, responsible for vigilance and for the control of impulsivity, respectively. Animal studies indicate that noradrenergic and serotonergic neurons are coupled (i.e. limit the activity of each other) and that repeated exposure to drugs of abuse disrupts this regulation. Over time, noradrenergic and serotonergic neurons become autonomous and hyper-reactive to external stimuli and arguably this drug-induced long-term uncoupling explains dysfunctions in motivation and in the ability to inhibit impulses.

Animal studies and other evidence suggest great variability in vulnerability to addiction. New technologies mean that neurobiological research can start to identify neuropsychological and genetic differences in individuals that may influence their chances of developing addiction if they use drugs.

3. New technologies in addiction research

Advances in genomic and molecular biology, such as the ability to clone and sequence receptor subtypes, transporters and endogenous agonists, have enabled scientists to identify and specifically target relevant receptor or transporter sites with drugs that either block (antagonists) or facilitate (agonists or partial agonists) activity. Moreover, genetic manipulation techniques have been used on animal models to increase (i.e. overexpression mutants) or block (i.e. transgenic knockouts of dominant-negative mutants) the activity of a specific molecule under analysis.

In humans, genetic studies have tried to identify specific addiction susceptibility genes. Large-scale linkage and association studies have identified numerous promising candidate genes that confer vulnerability to addiction but, to date, few of these alleles have been consistently replicated and many of the associations are modest.

Neuroimaging, using technologies such as functional magnetic resonance imaging (fMRI), positron tomography (PET), single photon emission computed tomography (SPECT), magnetoencephalograph (MEG), and electroencephalograph (EEG), has provided insight into the way in which drug-induced changes in the brain can produce the type of cognitive deficits seen in people addicted to drugs. These are non-invasive techniques which may help to identify neuropsychological deficits that may be the primary source of an individual's inability to stop using drugs.

'Developments in neuroscience are transforming our understanding of how people become addicted to drugs while opening-up avenues of investigation for new approaches to treatment. We must, however, ensure that such beneficial new approaches are rigorously evaluated prior to implementation to ensure maximum success and financial efficiency.'

Wolfgang Götz,
EMCDDA Director

4. Traditional and new treatments of addiction

Addiction has traditionally been treated by a combination of pharmacological and psychosocial treatments. Usual pharmacological treatments include: (i) drugs that either block the addictive drug from working (e.g. naltrexone as a relapse prevention of heroin dependence) or make it unpleasant (e.g. disulfiram for alcohol dependence) or (ii) drugs that replace the addictive drug with a less harmful version of the drug (e.g. opioid substitution treatment using methadone). Nicotine replacement therapy is a common form of substitution treatment for smoked tobacco but is not particularly effective. Some treatments may also be used for a short period to help wean individuals off all drugs. Psychosocial interventions include cognitive behavioural therapy, motivational interviewing, drug counselling or 12-step support groups. These therapies provide an important adjunct to pharmacological and medical treatments in achieving a long-term successful outcome.

Progress in neurobiological research on addiction has led to the use of drugs which target the dopaminergic system. However, this strategy has not yet proven effective in

treating addiction, possibly because the wrong dopamine receptor has been targeted (i.e. D2) or because other modulatory neurotransmitter systems also require consideration.

A number of other novel treatment approaches are in development or are being researched which may provide new approaches to treating some forms of drug dependence. These include immunotherapies in the form of 'vaccines' against the effects of nicotine, cocaine and heroin that act by binding to the target drug in the bloodstream, thus preventing it from reaching the brain. Neurosurgery is the most invasive and permanent form of experimental treatment, but there exist strong ethical objections to this approach. Less extreme but still raising ethical concerns is deep brain stimulation which involves the insertion of electrical stimulating electrodes into the regions of the brain involved in addiction, such as the insula. A less invasive approach is transcranial magnetic stimulation that involves placing a small magnetic coil against an individual's skull in order to block or enhance neural activity. None of these approaches are currently proven and all bring with them potential costs as well as possible benefits.

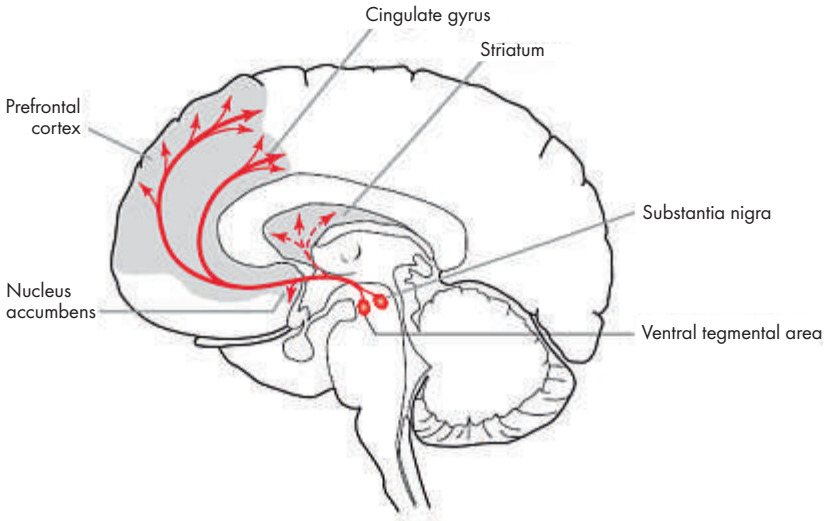
5. Causal models of addiction

How addiction is understood by society is important for deciding which responses are appropriate. The definition of addiction as a disorder in which an individual's control over their drug use is impaired can be contrasted with a historical perspective where drug users were seen as autonomous individuals who voluntarily engaged in illegal activities. Even today, some authors remain sceptical about the existence of addiction, and the extent to which dependent individuals have autonomy over their actions remains a question of fundamental importance. The brain disease model of addiction challenges the view that drug use is always a voluntary choice by arguing that prolonged drug use results in long-lasting changes in the brain structure that undermine voluntary control. Although these brain changes may explain why addicts continue to use drugs despite tolerance to their pleasurable effects and serious adverse consequences, this model may also be used to argue that addicts may lack the autonomy to make informed choices or act upon them. Drug use encompasses a complex set of behaviours and even the autonomy of dependent individuals is variable. One risk of an overly simplified interpretation of the emerging neurobiological evidence is that it could be inappropriately used to justify coerced, highly invasive or even damaging treatments, by proponents overly optimistic about their ability to cure addiction and without showing sufficient concern for broader human rights and ethical implications.

6. Ethical and policy implications

Neurobiological research can make a significant contribution to our understanding of the extent to which addicts are autonomous, and therefore responsible for their actions. The autonomy of addicts in making choices about their drug use is undoubtedly impaired when they are acutely intoxicated or experiencing severe withdrawal symptoms. However, the extent of impairment varies greatly and informed consent, i.e. the process by which individuals agree to treatment in the full knowledge of its possible risks and benefits, and without coercion, can and should be obtained after patient stabilisation. If neurobiological research leads to the development of new treatment approaches, they will join and hopefully complement existing treatments. Patients will need to be given information on different treatment options, and the costs and benefits of any new therapy should be carefully considered along with its potential efficacy. Treatments that are invasive or dangerous are difficult to justify if safer options already exist. Important ethical considerations will surely arise if patients are denied free choices over which treatment they can pursue: these issues are likely to be particularly important for treatments offered within the criminal justice system where some degree of coercion may be present.
A generally accepted ethical principle is that care available in prison settings should be equivalent to that available to the wider community. Ethical concerns would arise if new therapies were disproportionately targeted on those in custody and other treatments of proven efficacy denied.

Dopaminergic projections from midbrain to forebrain



Note: Meso-corticolimbic dopaminergic neurons from the ventral tegmental area and substantia nigra project to an important structure of the reward circuitry, the nucleus accumbens, and to the cortical areas primarily responsible for making decisions, such as whether to use drugs (e.g. the prefrontal cortex, and the cingulate gyrus). Projections from the midbrain also make connections with the caudate and the putamen (labelled Striatum in the figure).
Source: Hyman et al., 2006.

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Conclusions and policy considerations

1. **Neuroscience has the potential to improve our understanding of addiction, possibly leading to new forms of treatment. There is a need to continue supporting studies in this area, whilst reviewing how European research can be encouraged and best organised.**
2. **The assumption that repeated consumption of drugs of abuse induces long-term modifications in cerebral neurotransmission presents a strong argument for research aimed at characterising these modifications and finding ways to reverse them.**
3. **New methodologies such as neuroimaging and genetic research may help to better understand variations in vulnerability to addiction, even if social factors are also clearly important. However, the extent to which this can be used in practice remains questionable.**
4. **The efficacy of novel immunological approaches and neurological techniques will require detailed scrutiny. Some approaches in this area may be used in ways that raise important ethical and social concerns which could offset, or even be greater than potential benefits.**
5. **Neurobiological research provides support for a 'medical model' of addiction. However, many drug issues concern the non-dependent use of illicit substances and the question of which approaches are appropriate to encourage addicted individuals into treatment — particularly those who may not want to be treated — is a critical one.**
6. **A major challenge for policy will be to find ways to educate the public about the neurobiological basis of addiction, whilst acknowledging that individual and social choices also impact on drug use and addiction.**

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